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USMLE STEP 1

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Joel S. Goldberg

2
EDITION

SECOND EDITION

LANGE OUTLINE REVIEW™

USMLE STEP 1

Joel S. Goldberg, DO
Assistant Professor of Medicine
Department of Medicine
Drexel University College of Medicine
Philadelphia, Pennsylvania

McGraw-Hill
Medical Publishing Division

New York Chicago San Francisco Lisbon London Madrid Mexico City Milan
New Delhi San Juan Seoul Singapore Sydney Toronto

0-07-148696-8

The material in this eBook also appears in the print version of this title: 0-07-145191-9.

DOI: 10.1036/0071451919

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Contributors

Michael L. Blute, MD
Chair and Professor of Urology
Mayo Clinic
Rochester, Minnesota
Chapter 8, "The Renal System and Urology"

Frank J. Frassica, MD
Chairman and
Robert A. Robinson Chair of Orthopaedic Surgery
Johns Hopkins University
Baltimore, Maryland
Chapter 6, "The Musculoskeletal System"

Ann Honebrink, MD
Assistant Professor
Department of Obstetrics and Gynecology
University of Pennsylvania
Philadelphia, Pennsylvania
Chapter 9, "Reproductive Health"

Serge A. Jabbour, MD, FACP, FACE
Associate Professor of Medicine
Division of Endocrinology, Diabetes & Metabolism
Department of Medicine
Thomas Jefferson Hospital
Philadelphia, Pennsylvania
Chapter 3, "The Endocrine System"

Ramsey Markus, MD
Assistant Professor of Dermatology
Department of Dermatology
Baylor College of Medicine
Houston, Texas
Chapter 11, "The Skin and Related Connective Tissue"

Derek Papp, MD
Resident Physician
Johns Hopkins Hospital of Orthopaedic Surgery
Johns Hopkins University
Baltimore, Maryland
Chapter 6, "The Musculoskeletal System"

Michael Scola, MD
Attending Physician
Division of Hematology/Oncology
Department of Internal Medicine
Morristown Memorial Hospital
Morristown, New Jersey
Chapter 5, "Hematology and Immunology"

Michael Sherman, MD
Associate Professor of Medicine
Pulmonary and Critical Care Medicine
Department of Internal Medicine
Drexel University College of Medicine
Philadelphia, Pennsylvania
Chapter 10, "The Respiratory System"

Paul D. Sponseller, MD
Professor and Vice Chairman
Department of Orthopaedic Surgery
Johns Hopkins School of Medicine
Baltimore, Maryland
Chapter 6, "The Musculoskeletal System"

Cynthia M. Tracy, MD
Associate Chief, Professor of Medicine
Division of Cardiology
Department of Medicine
George Washington University Medical Center
Washington, DC
Chapter 2, "The Cardiovascular System"

Mohammad Wehbi, MD
Assistant Professor of Medicine
Division of Gastroenterology
Department of Internal Medicine
Emory University School of Medicine
Atlanta, Georgia
Chapter 4, "The Gastrointestinal System"

Leon Weisberg, MD
Vice Chairman, Department of Psychiatry and Neurology
Tulane Health Science Center
New Orleans, Louisiana
Chapter 7, "The Central and Peripheral Nervous Systems"

Vincent W. Yang, MD, PhD
Professor and Director
Division of Digestive Diseases
Department of Medicine
Emory University School of Medicine
Atlanta, Georgia
Chapter 4, "The Gastrointestinal System"

Preface

This is the second edition of a comprehensive, yet concise review book for the USMLE Step 1 examination. This text reflects my original concept of maintaining a rapid-reading review book comprised of the key information necessary to ensure exam success. The material is directly based on the most current USMLE guidelines for testing.

For this text I have used the assistance of an exceptional group of clinicians from across the United States. Their collective experience in both teaching and the practice of medicine is without comparison. I hope that you enjoy this text both as an informative work and as an exceptional study aid for the important USMLE Step 1 examination.

Joel S. Goldberg, DO
Philadelphia, Pennsylvania

Acknowledgments

I would like to extend my sincere appreciation to Ms. Marsha Loeb and the publishing staff at McGraw-Hill for their continued assistance in the development and production of this work. I wish to thank my coauthors of this text.

As physicians we know only too well the difficulty of finding time to complete a comprehensive project such as a manuscript. I extend my sincere appreciation to this group of authors who devoted much time and energy to their manuscripts despite their busy teaching and medical practice schedules.

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How to Use This Book

USING THE BOOK AS A STUDY OUTLINE

When you begin to study, turn to the Contents to obtain an overview of this text. Review the material supplied by your school and the National Board of Medical Examiners, including the "Step 1 General Instructions, Content Description, and Sample Items." It is important to have a full understanding of the design of the exam and the type of questions that will be asked.

Once you begin to study, *do not* omit any chapters in this text; instead, start at the beginning and read the book in its entirety. Notice that the outline format is streamlined to allow the rapid assimilation of facts in a minimal amount of reading time. Because extraneous and time-consuming information and phrasing have been omitted, working with *Lange Outline Review: USMLE Step 1* for 1 hour will provide a database equivalent to that procured from several hours' study of any other review text. Because the text is concise, it is vital that you be well rested and in a proper frame of mind for study and concentration. A quiet, comfortable, bright study area without glare is vital (with plenty of snacks nearby, of course!).

USING THE BOOK AS A QUICK REVIEW

In the final several weeks and days prior to your examination, *Lange Outline Review: USMLE Step 1* will serve as a rapid review tool. As in the Step 2 text, this revolutionary new format, which completely covers the "high impact" fact list, will allow the handbook to be read quickly, with successful, easy assimilation of the core facts necessary for exam success.

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Overview of the Basic Sciences

1

I. GENERAL PRINCIPLES

A. Gene Expression

1. DNA Structure, Replication, and Exchange

Deoxyribonucleic acid (DNA), a nucleic acid polymer made of nucleotides (nucleotide is a nucleoside with phosphate groups). Four bases: adenine and guanine (purines) and cytosine and thymine (pyrimidines). DNA may also be double stranded, with two strands having phosphates on the outside and bases inside.

- Watson–Crick pairing: Adenine is paired with thymine and cytosine with guanine. Sequence of bases on one strand known, able to deduce the other.
- Z-DNA: Left-handed double helix.
- A-DNA and B-DNA: Right-handed.
- Negative supercoiling: Fewer base pairs per turn of the helix.
- Positive supercoiling: More base pairs/turn.
- DNA topoisomerase I: Relaxes supercoiled DNA.
- Maxam and Gilbert: Chemical method to determine sequence of bases on DNA.
- Sanger sequencing: Chain termination method to determine DNA base sequencing.
- DNA denaturation or melting: Separating DNA strands by heating or changing the pH.
- Southern blotting: Adding DNA to a denatured chain to determine the sequence.
- Northern blotting: Same but with RNA.

2. Transcription

- Transcription: Conversion of DNA base sequence into RNA base sequence, brought about by an RNA polymerase.
- Enhancers/silencers: DNA sequence that increases transcription.
- Introns: Sequences present in the DNA but absent in the mRNA.
- Exons: Sequences present in the mRNA.

3. Translation

- Translation: RNA bases changed into amino acid side chains.
- Polyribosomes: Large RNA protein complex.

B. Structure and Function of Proteins

- Protein: Linear amino acid polymers joined with peptide bonds, has two ends.
- N-terminus: Free amino group end.
- C-terminus: Carboxylate end.

C. Energy Metabolism

1. Metabolic Sequences and Regulation

- **Metabolism:** The controlled use and aquisition of energy.
- **Catabolism:** Breakdown of molecules.
- **Adenosine triphosphate (ATP)/glutamyl transpeptidase (GTP):** High-energy molecule that stores energy.
- **Anabolism:** Building molecules.

Molecules broken down to make energy: Lipids, amino acids, carbohydrates. Carbohydrates as glucose convert to energy by way of glycolysis and the citric acid cycle. The citric acid cycle (Krebs cycle) generates ATP. The liver can store glucose as glycogen. Amino acid catabolism begins with removal of an amino group and results in creation of ammonia, which enters the urea cycle. Fatty acids are the source of most tissue energy (however, brain can use only glucose). β-Oxidation is the usual method of fatty acid catabolism.

- Oxidative phosphorylation: Production of ATP linked to electron transport.
- Gluconeogenesis: Creation of glucose from noncarbohydrate sources such as pyruvate, amino acids, and lactate.
- Glycogenesis: Creation of glycogen.
- Linoleic acid: Only fatty acid that can't be synthesized by man.
- Triglycerides: How fatty acids are transported.

2. Amino Acids

Essential

Lysine
Arginine
Leucine
Phenylalanine
Valine
Isoleucine
Histidine
Methionine
Threonine
Tryptophan

Nonessential

Serine
Proline
Glycine
Tyrosine
Cystine
Alanine
Asparagine
Glutamine

II. BIOLOGY OF CELLS

- **Cytoskeleton:** Collection of filaments (three types of filaments: microtubules, microfilaments, and intermediate filaments) and other material that determine cell shape and assist with intracellular transport.
- **Nucleus:** Contains nucleoli that contain genes.
- **Histones:** Small proteins.
- **Heterochromatin:** Condensed DNA.
- **Euchromatin:** Scattered DNA
  - Muscle: Striated, smooth, and cardiac.
  - Striated: Thick (made of myosin and attached to the M band) and thin filaments (made of actin and attached to the Z line) Duchenne's muscular dystrophy is an X-linked disorder and defect of the thin filament attachments, resulting in disruption of plasma membranes.
  - Sarcomere: Distance from Z line to Z line.

Cells have an electrical gradient, due to uneven concentration of intra- and extracellular ions, resulting from plasma membrane pumps.

Inside is more negative than the outside as there is increased Na^+ outside and increased K^+ inside.

Collagen is the most common protein in extracellular matrix, composed of three glycoprotein chains. Too little collagen: Ehlers–Danlos syndrome.

- Cell injury: Cells may adapt such as when they atrophy or shrink, or when they enlarge (hypertrophy). Injury may be reversible (brief hypoxia) or irreversible (with prolonged hypoxia).
- Apoptosis: Cell death normally happening in growth and development.

Important organelles found in cell cytoplasm:

- **Mitochondria** "power" the cell.
- **Golgi apparatus** helps to form lysosomes and secretory vesicles.
- **Lysosomes** are the cell's digestive system, contain enzymes.
- **Endoplasmic reticulum** helps with cell metabolism and transporting substances within the cell.
- **Epithelium:** Covers the body and forms gland tissue.
- **Endothelium:** Lining of lymph channels, heart and blood vessels.
- **Mesothelium:** Lines serous membranes of pericardial, pleural, and peritoneal cavities.

III. INFLAMMATION

- Acute inflammation: Vasoconstriction (constriction of smooth muscle cells), then vasodilation, then hyperemia (increased blood in injury area), then transudation (fluid passing through capillaries), and finally edema.
- Inflammation signs: Redness (rubor, from prostaglandins), heat (color, from thromboxanes), pain (dolor), and swelling (tumor, from histamine).
- Chemotaxis: Cells moving toward site of inflammation.
- Phagocytosis: Last stage of the acute cellular response to injury.

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BLOOD CLOTTING FACTORS

Factor	Trivial Name
I	Fibrinogren
II	Prothrombin
III	Tissue factor
IV	Calcium
V	Proaccelerin
VI	Accelerin
VII	Proconvertin
VIII	Antihemophilic factor
IX	Christmas factor
X	Stuart factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Protransglutamidase

IV. GENETICS

A. Embryogenesis

Haploid ovum if fertilized becomes a diploid zygote. Cleavage (mitotic division) becomes a ball of 12–16 cells (morula). Morula becomes a blastocyst with a center area. Embryo forms in the central area.

- Neural tube: Forms brain and spinal cord.
- Allantois: Vestigial growth off of the end of the yolk sac.
- Coelom: Collection of sacs in the mesoderm at week three that form the peritoneum, serous pericardium, and pleura.
- Somites: Segmented blocks of mesodermal cells that form the bones and spine muscles.
- Organogenesis: During the first 8 weeks.

B. Gene Analysis

- Pedigree: Symbolic mapping of the family tree.
- Linkage analysis: A method of gene analysis where two loci that are close to each other are more likely to be transmitted together.

C. Population Genetics

Hardy–Weinberg Law: How the frequency of genotypes relate to the frequency of certain phenotypes.

D. Disease-Producing Mutations

- Includes chromosomal disorders, single gene defects, and mosaicism.
- **Polyploidy:** Extra complete sets of chromosomes.
- **Aneuploidy:** Loss or addition of a single chromosome.
- **Translocations:** Broken genetic fragments move between chromosomes.
- **Inversion:** Reversal of the order of chromatin.
- **Down syndrome:** Trisomy 21, three copies of chromosome 21.
- **Monosomy:** Numerical chromosome abnormality (Turner's syndrome, 45,X monosomy).

Lymphocytes

- Pluripotent hematopoietic stem cells differentiate to form lymphocytes.
- Two major types of lymphocytes:
  - T lymphocytes are processed by the thymus gland to form activated lymphocytes that provide cell-mediated immunity.
  - B lymphocytes are processed by the liver and bone marrow to form antibodies that provide humoral immunity.

Lipids—Substances that are soluble in fat solvents. Includes phospholipids and cholesterol.

V. LIFE CYCLE

Milestones—A child's behavior and skills compared to others in similar grouping.

Stages of Cognitive Development by Piaget—Sensorimotor (to 18 months), preoperational (18 months–7 years), concrete operations (7–12 years), and formal (12 and on).

- 1 month: Lifts head.
- 6–8 months: Sits without support.
- 8–9 months: Stands without support.
- 11 months: Early words (15–18 months, 5–10 words).
- 14 months: Stands alone.
- 15 months: Walks alone.
- 18 months: Throws a ball.
- 24 months: Runs, up and down stairs, vocabulary of 200 words.
- Age 2: Toilet trained.
- Age 3: Copy circle.
- Age 4: Copy cross.
- Age 5: Copy square.

Menarche age 12 in girls on average, puberty ending at age 15. Sexual maturity in boys age 14 with puberty ending at age 17.

VI. NUTRITION

- Water: 60% of body volume and weight (two-thirds intracellular, one-third extracellular).
- Sodium: Major mineral of extracellular fluid.
- Potassium: Major mineral of intracellular fluid.
- Amino acids: The building blocks of proteins—grade I from fish and animals, grade II from plants.
- Vitamins include fat soluble (A, D, E, K) and water soluble (B, C).

A. Functions of Vitamins

- **A (retinol):** Assists with growth and vision (deficiency—night blindness, xerophthalmia [dry cornea and conjunctiva]), reproduction, and maintaining epithelial tissue. Found in yellow and dark green vegatables, fruits, butter, and eggs.
- **B_1 (thiamine):** Carbohydrate metabolism; deficiency leads to beriberi.
- **B_2 (riboflavin):** Deficiency leads to stomatitis, cheilosis, and glossitis.
- **B_6 (pyridoxine):** May have deficiency induced by tuberculosis (TB) treatment drug isoniazid.
- **B_{12} (cobalamin):** Blood formation (deficiency—megaloblastic anemia); present in milk, eggs, shrimp, chicken, pork.
- **C (ascorbic acid):** A coenzyme in hydroxylation reactions, collagen production; deficiency—scurvy, includes loose teeth, swollen joints, and anemia.
- **D:** Sterols that help to regulate levels of calcium and phosphorus; deficiency causes osteomalacia in adults and rickets in children, excess is toxic.
- **Folic acid** (**folate):** Important in purine biosynthesis and blood formation; found in green leafy vegetables, whole-grain cereals, liver; deficiency—megaloblastic anemia and growth failure. Early fetal neural tube development requires folate, so it is vital in women of childbearing age and pregnancy.
- **K:** Clotting. Produced in the gut, also found in spinach, egg yolk, and cabbage. Deficiency may cause hypoprothrombinemia.
- **E:** Antioxidant; deficiency leads to neurologic disorders. Found in vegetable oils and eggs.
- **Niacin (nicotinic acid):** Deficiency leads to pellagra (diarrhea, dementia, and dermatitis). Niacin is used to treat type IIb hyperlipoproteinemia.

- **Biotin:** Deficiency leads to seizures and myalgia. Biotin is a coenzyme in carboxylation reactions, found in milk and eggs. Deficiency rare.
- **Pantothenic acid:** A component of coenzyme A.

B. Other Information

Thiamine deficiency in the United States is mostly seen in alcoholics, from impaired intestinal absorption, that may result in Wernicke–Korsakoff syndrome.

Heavy Metals

- Arsenic leads to nausea, renal and gastrointestinal (GI) disorders; treatment may include penicillamine.
- Iron injures the GI tract; treated with deferoxamine.
- Lead leads to mental retardation; treated with ethylenediaminetetraacetic acid (EDTA).
- Mercury leads to cognitive disorders, depression.
- Silver leads to argyria (blue skin), treated with ferrocyanide and sodium thiosulfate.

C. Eating Disorders

- **Obesity:** Too much fat, body mass index > 25 or body weight 20% over ideal.
- **Bulimia nervosa:** Binge eating followed by induced vomiting.
- **Anorexia nervosa:** Purposeful starvation, distorted body image, amenorrhea.

VII. TEMPERATURE REGULATION

Calorie and Nitrogen Balance

- 1 calorie = the energy it takes to raise 1 g of water 1 degree Centigrade.
- 1,000 calories = 1 kcal.
- 1 kcal = 1 food calorie.
- Direct calorimetry measures energy expenditure by measuring heat output.
- Indirect calorimetry measures oxygen use or CO_2 production and calculates heat output.
- Marasmus: Starvation (wasting of lean tissue).
- Kwashiorkor: Adequate calories but insufficient protein.
- Hypocalcemia: Tetany.
- Low zinc: Growth retardation.
- Radiation: Damages DNA.
- Heavy metals: Multiple disorders with chronic exposure (mercury results in tremor and depression).

VIII. PHARMACODYNAMIC PRINCIPLES

Bioavailability: Amount of active drug dose that reaches the circulation.

Fick's law of diffusion: Motion of drug across a membrane relating to the concentration, dQ/dt = (Diffusion constant)(Area) (dc/dx concentration gradient).

Henderson–Hasselbalch equation: Acid and base ionization ratio where for acids pKa = pH = log AH/A–. For a base pKa = pH + log BH+/B.

Metabolism: May activate or inactivate a drug; liver is the major site of metabolism.
Excretion: Kidneys are main site of excretion.
Zero-order elimination: Constant amount of drug removed per time unit.
First-order elimination: Constant fraction removed per time unit.
LD_{50}: Dose that will kill 50% of those who take it.
ED_{50}: Dose that is effective in 50% of those who take it.
TI: Therapeutic index, a measure of drug's safety, $TI = LD_{50}/ED_{50}$ (higher index is safer).
Drug efficacy: The maximal effect of the drug.
Potency: Amount needed to cause a specific effect.
Agonists: Activate receptors by binding to them.
Antagonists: Interfere with the receptor effect, may be competitive or noncompetitive.
Noncompetitive antagonist: Prevents agonist binding or agonist effect.
Competitive antagonist: Competes with agonist binding site.
Partial agonist: Partially activates the receptor.

Effects of medications may be altered by placebo effect, body weight, kidney or liver function, age, sex, and tolerance.

- **Additive effects:** Effects of two drugs add to each other.
- **Synergy:** Two drugs have effects greater than their additive values.

A. Autacoids

- Autacoids are hormones produced by tissues.
- Four types of autacoids: purines (e.g., adenosine triphosphate), eicosanoids (prostaglandins, leukotrienes), biogenic amines (serotonin, histamine), and polypeptides (angiotensin, bradykinins).

B. Antimicrobials

- Aminoglycosides, tetracyclines, and spectinomycin are protein synthesis inhibitors that affect the 30S bacterial ribosomal subunit.
- Chloramphenicol, erythromycin, and clindamycin are 50S subunit inhibitors.
- Quinolones inhibit the DNA gyrase.
- Penicillins bind at the D-ala-D-ala site on transpeptidase.
- Clavulanic acid: A β-lactamase inhibitor.

C. Antineoplastics

- Methotrexate inhibits dihydrofolate reductase, an antimetabolite.
- Other antimetabolites include cytarabine, 5-fluorouracil, mercaptopurine.
- DNA alkylating agents include cisplatin, cyclophosphamide, melphalan.
- Antibiotic agents include actinomycin D, bleomycin, mitomycin C, doxorubicin.
- Hormonal agents include tamoxifen, estrogen, progestins, leuprolide.

D. Treatment of Heartburn and Gastroesophageal Reflux Disease (GERD)

- Metoclopramide: Stimulates cholinergic receptors and blocks dopaminergic receptors. Increases lower esophageal sphincter (LES) tone (Reglan).

- H_2 antagonists: Inhibit H_2 receptors (less stomach acid) (cimetidine [Tagamet], famotidine [Pepcid], nizatidine [Axid], ranitidine [Zantac]).
- Proton pump inhibitors: Inhibit final pathway of acid secretion (potassium–hydrogen ATPase enzyme). Examples include lansoprazole (Prevacid), omeprazole (Prilosec), esomeprazole (Nexium), pantoprazole (Protonix), rabeprazole (Aciphex).
- Sucralfate: Protects esophageal mucosa.

E. Treatment of Asthma

- Leukotriene modifiers: Zileuton (Zyflo), zafirlukast (Accolate), montelukast (Singulair).
- Bronchodilators: Albuterol (Proventil, Ventolin), metaproterenol (Alupent), terbutaline (Brethine), salmeterol (Serevent).
- Inhaled anti-inflammatory agents (corticosteriods): Beclomethasone (Beclovent, Vanceril), budesonide (Pulmocort), fluticasone (Flovent), triamcinolone acetonide (Azmacort), flunisolide (Aerobid).
- Inhaled anti-inflammatory agents (other types): Cromolyn sodium (Intal), nedocromil sodium (Tilade).

F. Treatment of Migraine

- **Migraine:** Throbbing, unilateral, lasting hours to days, positive nausea, photophobia, family history often positive, more common in females.
- **Tension headache:** Steady pain, bilateral, lasts up to months, more common in females.
- **Cluster headache:** Steady pain, one orbit, severe intensity, lasts 30 minutes to several hours, nasal congestion, tearing eyes, not usually family history, more often in men.

Medications for Treatment

- Triptans: Zomig, Axert, Amerge, Maxalt, Imitrex.
- Vasoconstrictors: ergotamine (Cafergot), dihydroergotamine (DHE), isometheptene (Midrin).
- Nonsteroidal anti-inflammatory drugs (NSAIDs): Many.

Medication for Prevention

- Antiepileptics: Depakote, Neurontin.
- Antiserotonin agents: Cyproheptadine (Periactin), methysergide (Sansert).
- β-blockers: Atenolol, metoprolol, nadolol, propranolol.
- Antidepressants: Fluoxetine (Prozac), Elavil.
- Calcium channel blockers: Diltiazem, nifedipine, nicardipine, verapamil.
- NSAIDs.

IX. BIOTERRORISM AGENTS

A. Anthrax

- Organism is *Bacillus anthracis,* a gram-positive bacterium.
- Disease may be inhalational, cutaneous, or GI.
- Treatment: Ciprofloxacin or doxycycline.

B. Smallpox

- Agent is variola virus, of the genus *Orthopoxvirus.*
- Disease includes maculopapular rash on mucosa of mouth, face, and arms that spreads.

- Treatment is isolation and supportive, vaccination preexposure or within a few days of exposure.

C. Botulism

- Agent is *Clostridium botulinum,* a bacterium.
- Disease may be transmitted via food, wounds, or inhalation, and includes symmetric paralysis, fever, ptosis, nausea, blurred vision.
- Treatment includes support, equine antitoxin, immunoglobulin.

D. Plague

- Agent is *Yersinia pestis,* a gram-negative bacillus.
- Disease is septicemia, disseminated intravascular coagulation (DIC), shock, fever, weakness, swollen lymph nodes (bubo) in groin or axilla, pneumonia.
- Treatment: Streptomycin, gentamicin, doxycycline, ciprofloxacin, or chloramphenicol.
- Postexposure prevention: Doxycycline.

E. Tularemia

- Agent is *Francisella tularensis,* a gram-negative coccobacillus.
- Disease includes fever, headache, aches, cough, weakness, pneumonia.
- Treatment includes gentamicin, streptomycin, or doxycycline.
- Postexposure: Doxycycline.

X. MICROORGANISMS

- Monera (bacteria, mycobacteria, mycoplasma, chlamydia, rickettsia).
- Fungi (yeast, molds).
- Protista (protozoa).

A. Bacteria

- 1–5 µm size.
- Contain cell wall, membrane, ribosomes, cytoplasm, and genetic material.
- May need oxygen (obligate aerobes), tolerate oxygen (facultative anarobes), or not tolerate oxygen (anaerobes).
  - Gram stain: Crystal violet, iodine, acetone, and counterstain (safranin or fuchsin).
  - Gram positive = purple.
  - Gram negative = red.
- Acid-fast stain: Dye (carbolfuchsin), ethanol, and counterstain (green).
- Acid-fast bacteria = red.
- Non-acid-fast bacteria = green.

B. Viruses

All are obligate intracellular parasites that replicate in cells. Six parts of replication: (1) attachment, (2) penetration, (3) uncoating, (4) synthesis, (5) assembly, (6) release.

C. Fungi

- Eukaryotic obligate or facultative aerobes that have cell walls.
- Fungi consist of four phyla: Zygomycetes, Basidiomycetes, and Ascomycetes can sexually reproduce; Deuteromycetes reproduce asexually.
- Mycoses: Infections caused by fungi.

D. Parasites

Includes protozoa (unicellular), helminths (multicellular), and arthropods (jointed).

- Protozoa: Fecal–oral transmission, amebic dysentery, liver abscess.
- *Giardia lamblia:* Fecal–oral transmission, acute or chronic diarrhea.
- *Cryptosporidium:* Fecal–oral transmission, diarrhea, worse for immunosuppressed.
- *Leishmania:* From bite of sandfly, causes kala-azar.
- *Trypanosoma:* Tsetse fly bite, causes sleeping sickness, Chagas' disease.
- *Toxoplasma gondii:* From cat feces, raw meat.
- Nematodes: *Trichinella spiralis* (undercooked pork), *Strongyloides* (directly penetrates skin), *Necator americanus, Ascaris lumbricoides* (diarrhea, pulmonary infiltrates, eosinophilia), *Enterobius vermicularis* (pinworms).

XI. VACCINES

- Live attenuated (live but will not cause disease).
- Whole cell killed (inactivated).
- Recombinant (cloned nucleic acid code, tumor cell vaccine, cytokines).

XII. IMMUNE DISORDERS

Type I (immediate hypersensitivity) is anaphylactic.

Type II (cytotoxic hypersensitivity) from IgG/IgM antibodies and complement.

Type III (immune complex hypersensitivity) results from Ag/Ab complexes and includes Arthus reaction and serum sickness.

Type IV (delayed or cell-mediated hypersensitivity): > 12 hours to take place, resulting from activated T cells and macrophages.

Examples:

Type I: Anaphylactic reaction.

Type II: Drug-induced reaction, incompatible blood transfusion.

Type III: Hypersensitivity pneumonitis.

Type IV: Reaction to PPD test on the skin.

The Cardiovascular System 2

► cram facts

The cardiovascular system is derived from angioblastic tissue that arises in the mesenchyme. Splanchnic mesenchymal cells organize to form the cardiogenic cords. These form endothelial tubes (endocardial heart tubes) that fuse and thicken.

I. NORMAL PROCESSES

A. Embryonic Development, Fetal Maturation, and Perinatal Changes

The cardiovascular system is the first system to function in the embryo, and blood circulation begins by the third week. The blood vessels are derived from angioblastic tissue that arises in the mesenchyme.

Two strands of splanchnic mesenchymal cells organize to form the cardiogenic cords. These form endothelial tubes (endocardial heart tubes) that fuse and thicken. The inner endocardial tube becomes the endocardium. The myoepicardial mantle becomes the myocardium and epicardium. As the tubular heart elongates, dilatations and constrictions develop that become the chambers. As the heart tubes fuse, the mesenchyme around them thickens into the myoepicardial mantle, which differentiates into three layers—outer (epicardium), middle (myocardium), and inner (endocardium).

In the fetus, the pulmonary and systemic circulations run in parallel, and the fetus can survive despite severe cardiac or pulmonary abnormalities. Blood is oxygenated in the placenta and enters the portal venous system. The transition from fetal to neonatal circulation occurs as the lungs take over the function of oxygenation for the placenta (see Figure 2–1).

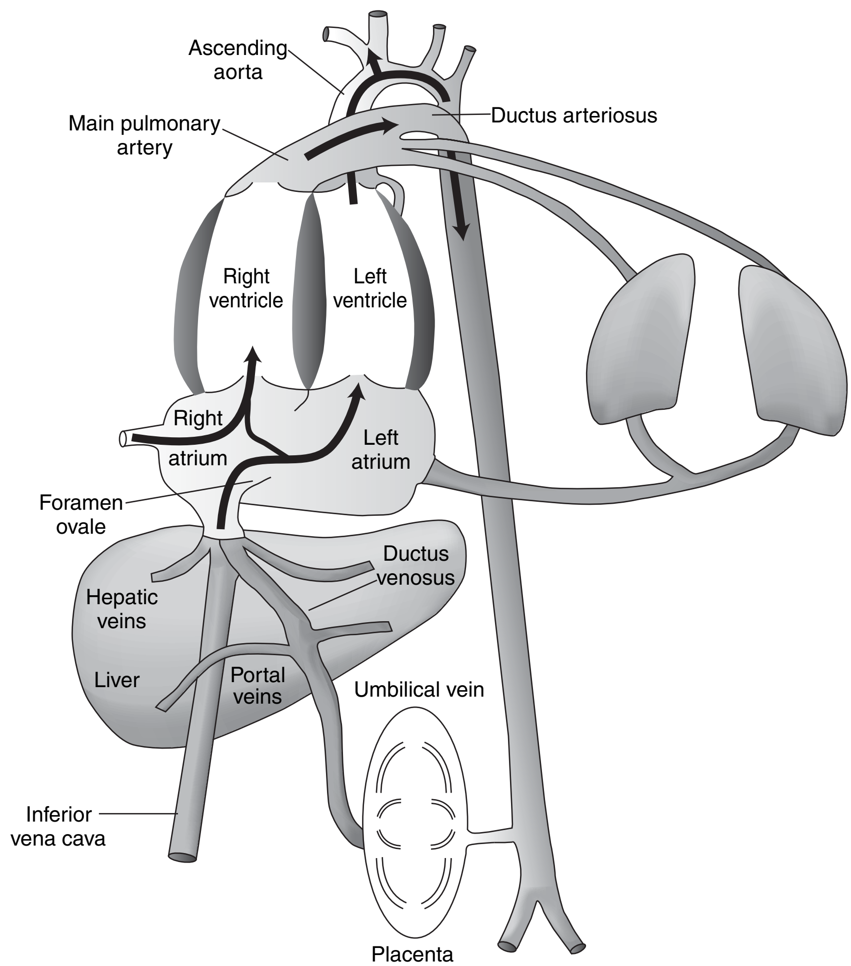

Figure 2–1. Fetal circulation. Arrows indicate direction of flow.

B. Organ Structure and Function

1. Chambers, Valves

The heart is made up of four chambers. The right atrium receives venous blood from the superior vena cava (SVC) and inferior vena cava (IVC). Blood flows from the right atrium through the tricuspid valve to the right ventricle; through the pulmonic valve to the pulmonary artery; and on through the pulmonary vasculature, where it is oxygenated.

The reoxygenated blood passes through the pulmonary veins to the left atrium. There are typically four pulmonary veins. From the left atrium, blood is pumped through the mitral valve to the left ventricle. From the left ventricle, blood is pumped through the aortic valve to the systemic circulation. Blood ultimately makes its way from the arteries to arterioles to capillaries to venules to veins and back to the right atrium.

► cram facts

The heart is made up of four chambers—two atria and two ventricles. Left-sided chambers serve as conduits for oxygenated (arterial) blood and right-sided chambers for deoxygenated (venous) blood.

2. Heart Sounds

The first heart sound has high-frequency sounds related to mitral valve and tricuspid valve closure (M1 and T1). Since the left ventricle begins to contract before the right, it may be possible to hear M1 separate from T1. The second heart sound has high-frequency sounds associated with the closure of the aortic and pulmonary valves (A2 and P2).

The second heart sound may split on inspiration (physiologic splitting) due to increased right heart filling. A third heart sound (S3) is a low-frequency sound heard early in diastole. It can be a normal finding in young adults related to blood in the left ventricle rushing from the base to the apex. More typically, S3 is an abnormal finding and is heard in people with heart failure

The fourth heart sound (S4) is also a low-frequency sound that occurs late in diastole and is associated with atrial contraction. The intensity of S4 increases when the left ventricle has impaired filling (e.g., hypertension, myocardial ischemia, aortic stenosis, and acute myocardial infarction). An S4 is often present in people over age 60 but rare before then.

Ejection sounds related to the aortic and pulmonic valve are best heard with the diaphragm of the stethoscope and if present are heard after the first heart sound. Aortic ejection sounds are usually associated with bicuspid valves. Pulmonic ejection sounds are related to pulmonic stenosis. Midsystolic clicks are high-pitched sounds heard with the diaphragm at the apex and these are produced by prolapse of the mitral valve. An opening snap is heard with the diaphragm at the apex. It is heard in mitral stenosis and relates to valve opening.

► cram facts

The first and second heart sounds are related to mitral valve and tricuspid valve closure (M1 and T1) and closure of the aortic and pulmonary valves (A2 and P2), respectively. It is normal for the first heart sound to split on expiration and the second to split on inspiration. This is typically more noticeable in younger people.

3. Electrical Conduction System

The electrical conduction system is comprised of specialized cells that have the property of spontaneously discharging. The spontaneous discharge of the cells is determined by how quickly certain ions pass from intracellular to extracellular.

The sinus node has the greatest degree of spontaneous activity and is located in the high right atrium near the junction of the SVC. From there, the impulse travels via specialized tissue through the right atrium to the atrioventricular (AV) node, which is localized at the junction of the atrium and ventricle. The AV node serves to control how much of the electrical impulse travels from the atrium to the ventricle. From there, the impulse travels to the ventricle by way

► cram facts

The electrical conduction system is comprised of specialized cells that have the property of spontaneously discharging. The sinus node, which is located near the junction of the SVC and right atrium, has the greatest degree of automaticity (spontaneous discharge).

► **cram facts**

The cardiac cycle has four separate periods, two during the relaxation phase (diastole), and two during contraction phase (systole). The phases are ventricular filling period—diastole; isovolumetric contraction period—systole; ventricular ejection period—systole; and the isovolumetric relaxation period—diastole.

► **cram facts**

Cardiac output is the measure of blood pumped per minute by the heart and is the product of heart rate and stroke volume (CO = HR × SV). The CO is typically normalized for body size (CI = CO/m² BSA). The normal CI = 2.4–4.2 L/min/m².

of the His–Purkinje system. The system divides into right and left bundles and on into smaller branches that carry the impulse throughout the right and left ventricle (see Figure 2–2).

4. Cardiac Cycle

The cardiac cycle is pictured in Figure 2–3. During systole, the ventricular pressure starts to rise rapidly almost immediately after the QRS complex is inscribed. The increase in ventricular pressure creates a pressure gradient between the ventricle and atrium that causes the mitral valve to close. Tricuspid valve closure follows shortly thereafter. As soon as left ventricular pressure rises above the pressure in the aorta, the aortic valve opens. The T wave is inscribed near the end of systole, and the ventricular muscle starts to relax. When the pressure in the left ventricle falls below the aortic pressure, the aortic valve closes and S2 is produced (see Figure 2–3). When pressure inside the relaxing ventricles falls below atrial pressure, the atrioventricular (AV) valves open. A new cycle begins.

5. Cardiac Output

The cardiac output (CO) is the volume of blood pumped by the ventricle per minute. It is the product of heart rate (HR) and stroke volume (SV) (CO= HR × SV). The SV is the amount of blood emptied from the left ventricle on each heartbeat and in the normal adult at rest is between 60 and 80 cc of blood. The resting CO will be between 4.2 and 5.6 L/min. The CO rises with exertion as a result of increases in heart rate and stroke volume. The cardiac index (CI) is the cardiac output normalized for body size. CI = CO/m² BSA (body surface area). The normal CI = 2.4–4.2 L/min/m².

6. Coronary Perfusion

Resting coronary blood flow is usually well preserved until there is severe narrowing (stenosis) of the vessel. With exercise, a normal coronary artery is able to dilate and increase coronary flow four to five times its resting value. When there is a 50% reduction in the diameter of the lumen, there is a reduction in the ability for the vessel to dilate normally and the flow reserve is reduced. The normal coronary anatomy is pictured in Figure 2–4.

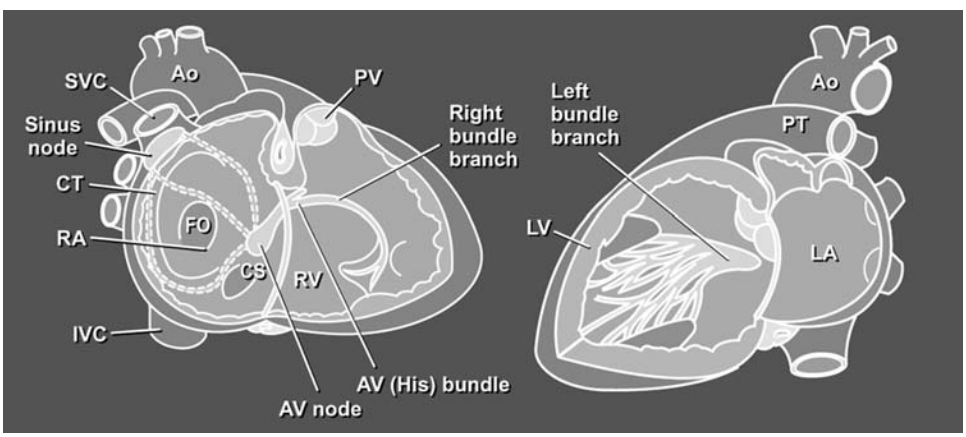

Figure 2–2. Schematic diagram of the cardiac conduction system. The right side of the heart *(left)* showing the sinus node, atrioventricular (AV) node, AV (His) bundle, and right bundle branch. The left side of the heart *(right)* showing incomplete anatomic separation of the left bundle into anterior and posterior fascicles. Ao, ascending aorta; AV, atrioventricular; CS, coronary sinus; CT, crista terminalis; FO, fossa ovalis; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PT, pulmonary trunk; PV, pulmonary valve; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

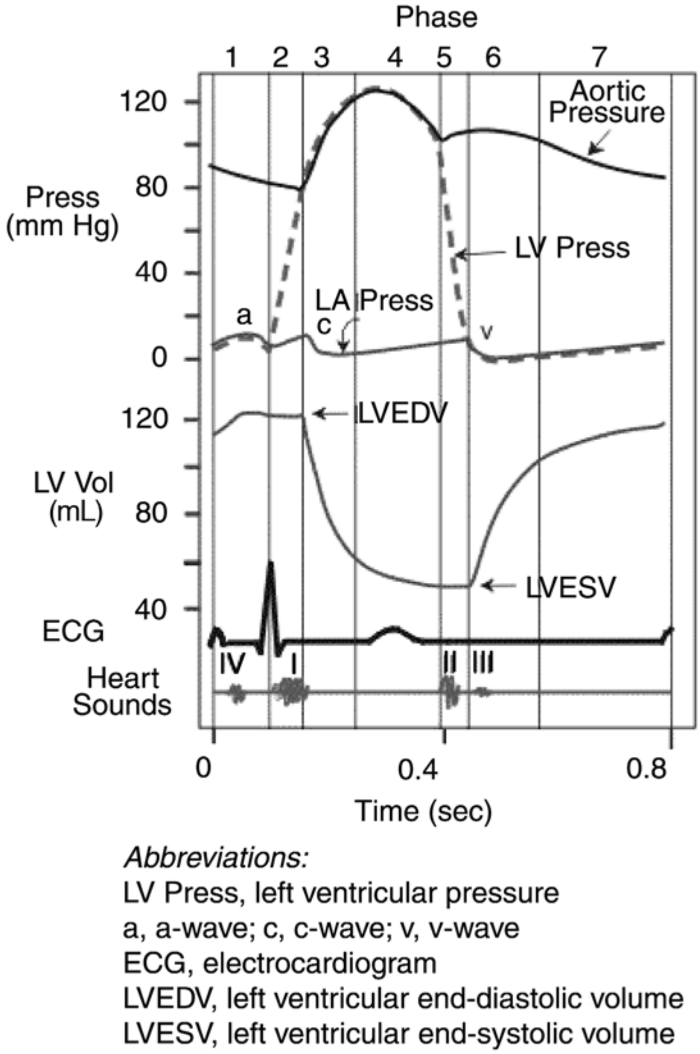

Figure 2–3. The cardiac cycle.

Phase I (Atrial Contraction):

- Phase 1 is initiated by the p wave (represents electrical depolarization of the atria) that causes contraction of the atrial musculature.
- Pressure within the atria increases and a pressure gradient is generated across the atrioventricular (AV) valves causing a rapid flow of blood into the ventricles. Atrial contraction produces a small increase in venous pressure ("a wave" of the jugular pulse) that is followed by the x descent.
- Following atrial contraction, the pressure begins to fall resulting in a pressure gradient reversal across the AV valves. The valves float upward before closure. At this time, the ventricular volumes are maximal, which is termed the end-diastolic volume (EDV).

Phase 2 (Isovolumetric Contraction):

- Phase 2 is initiated by the QRS complex (ventricular depolarization). As the ventricles depolarize, there is a rapid increase in intraventricular pressure. The rate of pressure development is maximal (maximal ventricular dP/dt) early in phase 2.
- The AV valves close as intraventricular pressure exceeds atrial pressure, resulting in the first heart sound (S_1).
- During the time period between the closure of the AV valves and the opening of the semilunar valves, ventricular pressure rises rapidly without a change in ventricular volume (isovolumetric contraction).
- Atrial pressures increase due to venous return and possible bulging of AV valves back into the atrial chambers. The "c-wave" noted in the jugular pulse is thought to occur due to increased right atrial pressure that results from bulging of tricuspid valve leaflets back into right atrium. Just after the peak of the c wave is the x'-descent.

Phase 3 (Rapid Ejection):

- When the intraventricular pressures exceed the pressures within the aorta and pulmonary artery, the aortic and pulmonic valves open and blood is ejected from the ventricles. Maximal outflow velocity is reached early in the ejection phase, and maximal systolic pressures are achieved.
- Atrial pressure initially decreases as the atrial base is pulled downward, expanding the atrial chamber. Blood continues to flow into the atria from their respective venous inflow tracts.

Phase 4 (Reduced Ejection):

- After the QRS complex, ventricular repolarization occurs (T wave). This causes ventricular active tension to decrease and the rate of ejection (ventricular emptying) to fall. Ventricular pressure falls below outflow tract pressure.
- Atrial pressures gradually rise due to venous return.

Phase 5 (Isovolumetric Relaxation):

- The ventricles continue to relax, and intraventricular pressures falls. Ultimately, pressure within the ventricles falls below that in the outflow tracts. The second heart sound (S_2) is created as the aortic and pulmonic valves abruptly close (aortic precedes pulmonic). The dicrotic notch is caused by a small backflow of blood into the ventricles and is seen in the aortic and pulmonary artery pressure tracings.
- Ventricular pressures decrease while volumes remain the same as all valves are closed. The difference between the end-diastolic volume and the end-systolic volume is ~70 mL and represents the stroke volume.
- Atrial pressures continue to rise due to venous return.

Phase 6 (Rapid Filling):

- When ventricular pressures fall below atrial pressures, AV valves open and ventricular filling begins. The ventricles continue to relax despite the inflow, which causes intraventricular pressure to continue to fall.
- The opening of the AV valves causes a rapid fall in atrial pressures and a fall in the jugular pulse. The peak of the jugular pulse just before the valve opens is the v wave. This is followed by the y descent of the jugular pulse.

Phase 7 (Reduced Filling):

- As the ventricles continue to fill with blood and expand, they become less compliant and the intraventricular pressures rise. This reduces the pressure gradient across the AV valves so that the rate of filling falls.
- Aortic pressure (and pulmonary arterial pressure) continues to fall during this period.

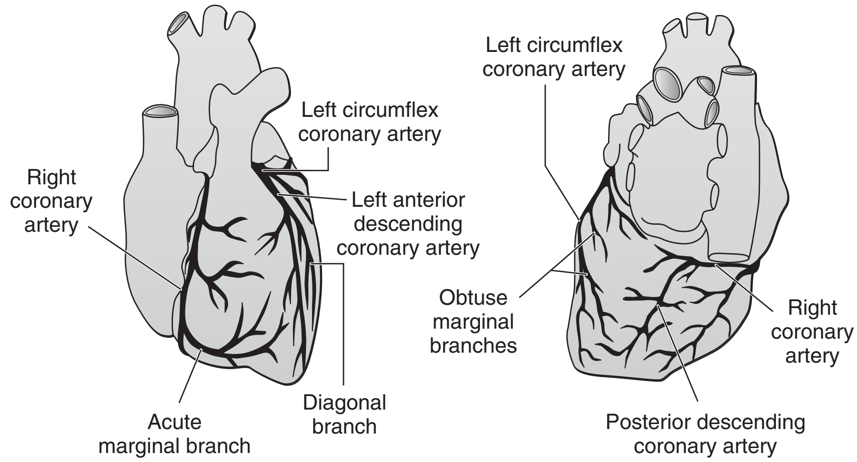

Figure 2–4. Coronary circulation. (Redrawn from L.S. Lilly, ed. *Pathophysiology of Heart Disease.* 2nd ed. Baltimore: Williams and Wilkins, 1988;9.)

C. Cell/Tissue Structure and Function

1. Heart Muscle, Metabolism, Oxygen Consumption, Biochemistry, and Secretory Function

Cardiac muscle metabolism is largely aerobic with little ability to generate energy anaerobically. Cardiac muscle metabolizes fat efficiently.

Heart rate, systolic blood pressure, wall thickness, left ventricular (LV) end-diastolic volume, and contractility determine myocardial oxygen consumption. During exercise, coronary arteriolar resistance decreases, allowing increased coronary flow and increased O_2 consumption. Volume homeostasis is regulated through a complex endocrine system. Hypovolemia stimulates the synthesis and release of renin into the blood. Renin acts to convert angiotensinogen to angiotensin. Angiotensin-converting enzyme (ACE) modifies angiotensin I in the lung to angiotensin II. Angiotensin II, a vasoconstrictor, leads to release of aldosterone from the adrenal cortex. Aldosterone acts on the nephron and causes sodium and water retention. Ultimately, volume, preload, SV, CO, and blood pressure (BP) are increased. Atrial natriuretic peptide (ANP) also participates in volume regulation. As circulating volume is increased, ANP is released by cardiac myocytes. ANP inhibits antidiuretic hormone (ADH) release.

2. Neural and Hormonal Regulation of the Heart, Blood Vessels, and Blood Volume, Including Responses to Change in Posture, Exercise, and Tissue Metabolism

With abrupt positional changes such as standing up quickly, blood pools in the venous capacitance vessels of the legs and trunk. This results in a transient decrease in venous return. As a result, CO and BP fall transiently. Normally, autonomic reflexes are activated through baroreceptors in the aortic arch and carotid bodies. Compensatory changes occur primarily through activation of the sympathetics, which increases the catecholamine levels and augments the vasomotor tone. Sympathetic activation increases myocardial contractility. CO increases and arterial and venous vasoconstriction occurs. Vagal inhibition also increases the heart rate. On more sustained standing, ADH secretion and activation of the renin–angiotensin–aldosterone system occurs, leading to sodium and water retention.

In the presence of abnormalities that affect the autonomic reflex arc, these homeostatic mechanisms may be inadequate to restore the lowered BP. Conditions that can impair autonomics include certain drugs and neurologic disorders. Hypovolemia is the most common cause of symptomatic orthostatic hypotension and is often induced by diuretics.

D. Repair, Regeneration, and Changes Associated with Stage of Life

Cardiac cells have very limited ability to regenerate in response to cell damage since they do not divide. With aging, there is a modest increase in left ventricular hypertrophy (LVH) and increased stiffness or impedance in the central arterial system. There is also a generalized decrease in the ability to augment heart rate and contractility.

E. Cardiovascular Defense Mechanisms

New links have been found between the immune response and diseases of the heart and vasculature. Lymphoid cell infiltration has been shown to be an early event in the development of atherosclerosis.

Abnormal immune response has been implicated in plaque vulnerability, which can contribute to acute ischemic coronary syndromes. Following reperfusion of a coronary vessel in an infarcted area of the heart muscle, there is an intense inflammatory reaction that may extend injury.

II. ABNORMAL PROCESSES

A. Genetic Disorders

Hypertrophic cardiomyopathy (HCM) is a disease of the myocardium resulting in abnormal thickening and decreased compliance (abnormal diastole). In some patients, there is obstruction to LV outflow (obstructive hypertrophic cardiomyopathy). Patients with HCM may experience dyspnea, exertional syncope (mostly in obstructive HCM), and angina-like chest pains and may be at risk for serious arrhythmias. HCM is generally inherited. More than half of the patients inherit it as an autosomal-dominant condition.

Multiple genotypes have been described, and the most common affects the β-myosin heavy chain. Phenotypic expression varies greatly and will determine the course of the disease including age of onset, symptoms, and survival. Spontaneous mutations can comprise up to 40% of cases in the elderly population. People with spontaneous mutations have about a 50% chance of transmitting the disease to each of their offspring. Family screening is recommended for the families of patients presenting with HCM.

The *congenital long QT syndromes* are relatively rare but can lead to torsades de pointes and may lead to sudden death. The genetic basis for at least three congenital long QT syndromes is known. Two involve potassium channels, and the third involves a sodium channel. Patients with the long QT syndrome are at much greater risk if they receive medications that further prolong the QT interval or if they develop hypokalemia. Other genetic disorders affecting the heart are listed in Table 2–1.

► cram facts

Hypertrophic cardiomyopathy (HCM) is a disease of the myocardium resulting in abnormal thickening and decreased compliance (abnormal diastole). It generally has a genetic basis but can arise as a spontaneous mutation. Patients with HCM may be at higher risk for sudden cardiac death.

2-1

COMMON GENETIC DISORDERS AFFECTING THE HEART

Chromosomal disorders
Disorders of cardiac muscle
Disorders of cardiac conduction
Heterotaxy
Marfan's syndrome
Muscular dystrophy
Mitochondrial myopathy
Noonan's syndrome
Turner's syndrome
VCFS/DiGeorge syndrome
Williams syndrome

► cram facts

Congenital heart disease can be divided into those that cause cyanosis (e.g., transposition of the great vessels, total anomalous pulmonary venous return, truncus arteriosus, tricuspid atresia, and tetralogy of Fallot) and noncyanotic (e.g., atrial septal defect, bicuspid aortic valve, ventricular septal defect, pulmonary stenosis, and coarctation of the aorta.

B. Congenital Disorders

Congenital heart disease usually manifests at birth or shortly thereafter. Congenital defects can be classified as cyanotic or noncyanotic. In cyanotic congenital heart disease, the circulation defect results in right-to-left shunting of blood, mixing deoxygenated blood with the systemic circulation, resulting in cyanosis and hypoxemia. Cyanotic defects include transposition of the great vessels (aorta and coronaries arise from the right ventricle), total anomalous pulmonary venous return (oxygenated blood from the lungs enters the right atrium rather than the left), truncus arteriosus (single ventricle with a single great vessel replacing the separate aorta and pulmonary artery), tricuspid atresia (absent tricuspid valve so the right atrium and right ventricle do not connect), and tetralogy of Fallot. Tetralogy of Fallot accounts for about 10% of congenital heart disease and is the most common cause of cyanotic heart diseases in infants. It has four components, including ventricular septal defect (VSD), obstruction to the right ventricular outflow, overriding aorta, and right ventricular hypertrophy (RVH). The classic finding on chest x-ray for tetralogy of Fallot is a boot-shaped heart.

Atrial septal defect (ASD) and bicuspid aortic valve are the two most common congenital heart lesions seen in adults. ASDs can occur near the right atrial junction with the vena cava (sinus venosus defect), low in the right atrial septum (ostium primum defect), or near the fossa ovales (ostium secundum defect).

Shunting can occur across these defects, but patients may remain asymptomatic until adulthood. Long-standing left-to-right shunting can lead to pulmonary hypertension and heart failure. If symptoms are present related to atrial septal defect, they might include dyspnea on exertion, fatigue, and atrial arrhythmias. A VSD is the most common malformation seen in children. Most children who survive to adulthood without surgical correction of the defect will undergo spontaneous closure.

Bicuspid aortic valves generally function normally at birth and can go undetected for many years. Most bicuspid valves eventually undergo some changes. Progressive fibroelastic thickening of the bicuspid valves is a common cause of aortic stenosis in young patients. Bicuspid valves are the most common underlying cause for patients undergoing surgery for isolated valvular aortic regurgitation.

Pulmonary stenosis and coarctation of the aorta are less common congenital lesions seen in the adult. If severe enough, pulmonary stenosis can lead to right heart failure. Coarctation of the aorta is a narrowing of the descending thoracic or abdominal aorta. Usually, the narrowing is distal to the left subclavian artery. It is more common in men than in women. Coarctation is often associated with a bicuspid aortic valve (25% of cases). Coarctation can lead to upper extremity hypertension and lower extremity hypotension. Eisenmenger's complex refers to congenital heart lesions in which shunting occurs and pulmonary hypertension is present and severe enough to reverse flow across the defect. This causes right-to-left shunting and cyanosis, and it can occur as a result of several types of lesions.

Although mitral valve prolapse (MVP) is often associated with congenital heart disease, prolapse itself is not caused by a congenital malformation of the valve. The most common cause of MVP is a myxomatous degeneration of the valve.

Congenital anomalies of the coronary arteries are rare but can lead to serious consequences. For example, if the left coronary artery follows an anomalous course between the aorta and right ventricular outflow track, obstruction of the artery can occur and result in myocardial ischemia or infarction at an early age.

C. Infectious, Inflammatory, and Immunologic Disorders

1. Infectious Disorders

a. Endocarditis—Infectious endocarditis is uncommon in a structurally normal heart. In 60–80% of non–intravenous drug users who develop endocarditis, there is some underlying pathology of the affected valve. The congenital heart lesions associated with increased risk for endocarditis include: aortic coarctation; VSD; bicuspid aortic valve; tetralogy of Fallot; moderate to severe pulmonic stenosis; mitral or tricuspid regurgitation (severe); and patent ductus arteriosus (PDA). Congenital heart disease accounts for the underlying cardiac lesion in about 10–20% of adults with infective endocarditis.

With the declining incidence of rheumatic heart disease, the association between infective endocarditis and rheumatic heart disease has decreased. Today, it is seen as the underlying pathology in about 30% of adults with endocarditis. Intravenous drug users are at high risk for infective endocarditis, which usually affects the tricuspid valve. Bacteremia is common in these patients and most commonly involves *Staphylococcus aureus* (50–60%). Other organisms that are seen with drug abuse and endocarditis include streptococci, enterococci, and gram-negative bacilli (e.g., *Pseudomonas* and *Serratia*) and fungi.

The mortality rates of infective endocarditis have decreased with the use of antibiotics, but the overall incidence of endocarditis has increased somewhat owing to the aging population, greater number of people with prosthetic valves, and increased survival of people with congenital heart disease.

b. Myocarditis—Myocarditis is an inflammatory process involving the myocardium. The major causes of myocarditis include infectious, allergic, toxic, or drug related and postpartum or peripartum. Other causes include systemic diseases such as vasculitis or connective tissue diseases. The infectious agents associated with myocarditis include viral, rickettsial, protozoal, metazoal, and bacterial infections. The viral infections most commonly associated with myocarditis include coxsackie B, Lassa virus, and human immunodeficiency virus (HIV).

The bacterial infections associated with myocarditis include diphtheria, meningococcal, *Clostridium perfringens, Mycoplasma* pneumonia, psittacosis, and spirochetal infections. Alcohol is the most common toxic agent associated with myocarditis.

The most common cause of myocarditis in the United States is viral. The mechanism of injury is thought to be immunological with a viral-related development of cell surface antigen. The resulting antigen–antibody complexes cause cell damage. Patients with myocarditis can present with either minimally or highly symptomatic states. The symptoms are often subclinical when the patient presents for evaluation of the underlying infectious process. If symptoms are present, they may include signs of myocardial dysfunction, including shortness of breath, fatigue, and palpitations. They may also have atypical chest discomfort and tachycardia.

c. Pericarditis—Pericarditis arises as a result of inflammation of the pericardium. Most cases of pericarditis are categorized as idiopathic, but viral infection may well cause some of these cases. Several viruses, including coxsackie A and B, Epstein–Barr virus, HIV, varicella-zoster, influenza, and mumps can lead to pericarditis. Uremia and inflammation post–myocardial infarction can lead to pericarditis (Dressler's syndrome).

Pain associated with pericarditis is often positional in nature and may vary with respiration. A friction rub may be heard unless the amount of fluid is significant, in which case the friction rub will be less noticeable. Electrocardiographic changes of pericarditis include diffuse ST segment changes. Lead aVR will often show ST-segment depression.

The treatment generally involves use of nonsteroidal anti-inflammatory agents (NSAIDs) such as indomethacin. Corticosteroids may be used in patients who do not respond to NSAIDs. Narcotic agents may be needed for pain.

2. Inflammatory Disorders (e.g., Acute Rheumatic Fever)

Acute rheumatic fever is uncommon in the United States today. The acute syndrome is a systemic inflammatory disease secondary to a recent streptococcal soft tissue infection. Rheumatic heart disease is the most common cause of mitral stenosis. The time between the acute infection and the development of mitral stenosis may be as short as 2 years, but more typically will take several years to develop. Rheumatic heart disease can also affect the other valves of the heart in this order: aortic regurgitation, mitral regurgitation, and aortic stenosis. Tricuspid valve disease secondary to rheumatic fever is uncommon.

> **► cram facts**
>
> Valvular heart disease may range from mild to severe. Symptoms can develop as disease progresses, but two-dimensional echocardiogram can be quite useful in monitoring severity and progression of disease. Timing of surgical intervention is important to prevent irreversible damage and will vary depending on the particular valvular lesion.

D. Traumatic and Mechanical

1. Mitral Valve Prolapse

MVP is caused by protrusion or prolapse of a portion of the mitral valve into the left atrium during systole. The MVP syndrome is sometimes referred to as the click murmur or Barlow syndrome. MVP is the most common cardiac valvular abnormality. Its incidence is about 3–5%, with a 2:1 female predominance. Clinical manifestations of MVP can range from completely asymptomatic to atypical chest pains to severe symptoms secondary to mitral regurgitation. Patients may also develop ventricular arrhythmias. In MVP the leaflets may be redundant. Because of abnormal tension on the chordae, cordal rupture can occur, leading to severe mitral regurgitation. Patients with MVP associated with mitral regurgitation are recommended to take antibiotic prophylaxis for procedures potentially associated with bacteremia (e.g., dental procedures).

2. Mitral Regurgitation

Mitral regurgitation can develop as a result of structural abnormalities of the mitral valve leaflets or annulus. It can also develop in dilated cardiomyopathy as a result of dilatation of the mitral annulus. The murmur of mitral regurgitation is holosystolic and is best heard over the apex. The murmur generally radiates toward the axilla and is best heard with the patient lying in the left lateral decubitus position. The LV impulse may be very hyperdynamic. The intensity of the murmur does not always correlate with the severity of the lesion.

3. Mitral Stenosis

In mitral stenosis, the thickened leaflets become noncompliant and partially fused, resulting in obstruction of blood flow from the left atrium to the left ventricle. The left atrial pressure and pulmonary pressures can become elevated. Atrial fibrillation occurs as the left atrium dilates. In atrial fibrillation, blood flow is less brisk and clots can form, and systemic emboli including stroke can occur.

The murmur of mitral stenosis is heard as a diastolic rumble and is best heard directly over the LV apex. An opening snap may be heard, and S1 is accentuated in mild to moderate mitral stenosis. S1 diminishes as the disease progresses. Dyspnea is the classic presenting symptom for a patient with mitral stenosis. The severity of mitral stenosis is determined by the magnitude of the pressure gradient across the mitral valve. During diastole, the pressure in the left atrium will be greater than the pressure in the LV. Echocardiography is an excellent way of determining the severity of mitral stenosis.

4. Aortic Regurgitation

Long-standing hypertension is a common cause of aortic regurgitation because of prolonged increased peripheral resistance. Inflammatory disease of the aortic valve such as rheumatic fever, rheumatoid arthritis, or ankylosing spondylitis can cause aortic regurgitation. Other causes include connective tissue disorders (e.g., Marfan's syndrome or Ehlers–Danlos syndrome), congenitally malformed valves, or prolapse of a leaflet secondary to longstanding VSD, torn cusp from trauma or dissecting aortic aneurysm, and infective endocarditis. Although chronic aortic regurgitation is well tolerated, acute forms are poorly tolerated.

The major symptom of aortic regurgitation is dyspnea. Aortic regurgitation can result in congestive heart failure. Unless it goes undetected and untreated for prolonged periods of time, aortic regurgitation rarely leads to irreversible LV dysfunction.

Findings on physical exam in patients with aortic regurgitation vary depending on the severity of the disease. In general, the murmur is a decrescendo diastolic murmur heard at the right upper sternal border. The murmur is best heard on expiration. A third heart sound (S3) is common. An additional murmur (*Austin Flint murmur*) that resembles the sound of mitral stenosis may be present (results from an interaction between the regurgitant jet and the mitral valve inflow). The pulse pressure may be wide with aortic regurgitation, and the diastolic pressure is often low, giving rise to bounding pulses (Quincke's pulses). The chest x-ray in people with aortic regurgitation will often show LVH and cardiomegaly. Echocardiography is useful in determining the severity and confirming the diagnosis.

5. Aortic Stenosis

The most common cause of aortic stenosis in older patients is senile calcific degeneration. In younger patients, the most common cause is degeneration of a congenital bicuspid aortic valve.

Rheumatic fever is seen as a cause of aortic stenosis less frequently than in the past. Rarely, aortic stenosis can be caused by methysergide, a vasodilator used to treat migraines.

The natural history of aortic stenosis depends on the severity of the lesion. For patients with moderate stenosis (valve area > 1 cm square) the prognosis is excellent. In general, valvular pathology progresses slowly, and the time between diagnosis and surgery may be over a decade. The prognosis is worse in patients with more severe stenosis. In patients with angina, the mean survival is 4–5 months. Those with syncope have a mean survival of 27 months, and those with left heart failure 11 months.

The murmur is a harsh crescendo–decrescendo systolic murmur heard best at the upper right or left sternal border radiating to the carotids. In severe aortic stenosis with LV systolic failure, the murmur may actually decrease in intensity. Assessing the carotid pulsation is important in the diagnosis of the severity of aortic stenosis. As the disease progresses, the carotid upstroke becomes slowed and sustained, and the overall pulse amplitude is small. Precordial examination may show a sustained and forceful apical impulse. The second heart sound is generally diminished in intensity. In aortic stenosis associated with a bicuspid aortic valve, an ejection sound may be present. Findings of congestive heart failure (CHF) will be present in patients with advanced aortic stenosis and systolic dysfunction.

6. Tricuspid Valve Lesions

Tricuspid regurgitation is generally described as a blowing systolic murmur heard at the lower left sternal border. The intensity of the murmur increases with inspiration. Tricuspid regurgitation usually results from right ventricular (RV) dilation and high pressure. The latter is seen as a result of pulmonary hypertension or outflow obstruction to the right ventricle. Other causes of tricuspid regurgitation include infective endocarditis (more typically seen in IV drug abusers), myocardial infarction (MI) (with damage to the papillary muscle), or as a result of a toxic exposure to fenfluramine (a diet medication).

Symptoms of severe tricuspid regurgitation can include those of a low CO (e.g., fatigue, cold skin, dyspnea, and edema). Patients may be aware of pulsations in the neck and their heads may bob back-and-forth manner as though they were indicating “no.” Tricuspid stenosis is almost always rheumatic and usually is accompanied by mitral stenosis.

7. Traumatic Heart Injuries

Traumatic heart injuries result from either penetrating or nonpenetrating trauma. The most common cause of cardiac injury is automobile accidents. Myocardial contusion is a common reversible injury, and if significant, there will be elevation of cardiac enzymes without evidence of coronary artery disease (CAD). Patients may develop reversible wall motion abnormalities on echocardiogram, and cardiac arrhythmias are common. The most common cardiac trauma include RV contusions, aortic valve tearing, tricuspid valve tear, or rupture of the left ventricle or left atrium. Arterial damage that can occur from cardiac trauma include innominate artery avulsion, aortic isthmus rupture, and left subclavian artery traumatic occlusion.

8. Cardiac Tamponade

Cardiac tamponade occurs when fluid accumulation in the pericardial space results in increased pericardial pressure and decreased CO. In tamponade, intrapericardial pressure rises and there is restriction of filling of the heart, with equalization of intracardiac chamber pressures. Ventricular diastolic filling becomes progressively limited and results in decreased SV. The heart rate may increase in an attempt to maintain CO. If left untreated, the compensatory mechanism will be inadequate and the patient may suffer hemodynamic collapse. Signs of tamponade include decreased intensity of heart sounds, narrowed pulse pressure, distention of neck veins, and pulsus paradoxus. Cardiac tamponade can occur as a result of trauma, but is also seen in malignancies, autoimmune disorders, and some viral infections.

> **► cram facts**
>
> Cardiac tamponade occurs when fluid accumulation in the pericardial space results in increased pericardial pressure, which restricts the ability for the heart to fill. Temporizing with fluids and pressors may be helpful, but the only way to relieve tamponade is to remove the fluid from the pericardial space either by tapping the effusion (pericardiocentesis) or through surgery.

E. Neoplastic Disorders

Tumors commonly associated with cardiac metastases include lymphoma, carcinoma of the breast, bronchogenic carcinoma, and leukemia. Tumors spread to the heart by direct extension or hematogenous or lymphatic spread. The most common primary cardiac tumor is the benign myxoma. Myxomas are generally sporadic, but can occur as an autosomal-dominant inherited trait. They generally arise in the left atrium. They may be detectable on physical exam as the tumor plops back in diastole and hits the LV wall.

The most common primary malignant cardiac tumor seen in adults is sarcoma. Sarcomas usually arise in the right atrium. Most of these tumors will have distant metastases by the time the patient presents clinically. The most common benign cardiac tumor seen in children is rhabdomyoma, which arises from either the right or left side of the ventricular septal surface.

F. Metabolic and Regulatory Disorders

1. Dysrhythmias

Premature atrial contractions (PACs) are extremely common and carry no prognostic importance. They may give rise to isolated palpitations or a sensation of skipped beats. They can be worsened by endogenous or exogenous stimulants. Similarly, PVCs are generally benign. Symptomatically, they usually cannot be distinguished from PACs. Neither PACs nor PVCs require treatment, and reassurance is often enough. If a patient is extremely troubled by PACs or PVCs, a β-blocker may be useful.

Atrial fibrillation (AF) is the most common sustained arrhythmia. The incidence and prevalence of this disorder increases with age. By age 85, 15% of people have AF. It is estimated that 1–2 million Americans have AF. It can occur in a structurally normal heart without identifiable precipitants (*lone atrial fibrillation*). Metabolic causes such as hyperthyroidism should be sought and corrected. Most patients with AF have some associated condition like hypertension or CAD. AF can result in blood clot formation in the left atrium due to stasis. The major consequence of this can be stroke. This risk can be reduced to nearly baseline through the use of anticoagulation with coumadin. Risk factors for stroke in patients with AF include hypertension, diabetes, prior stroke or embolic events, and prior MI or chamber enlargement as seen on echocardiogram. Another consequence of AF with rapid ventricular rates can be myocardial dysfunction and heart failure. While many patients experience some degree of effort intolerance with AF, many are asymptomatic.

> **► cram facts**
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> Atrial fibrillation is the most common sustained arrhythmia. When it occurs in the absence of identifiable causes, it is known as lone atrial fibrillation). The major consequences of atrial fibrillation are stroke and tachycardia (rate)-related cardiomyopathy. Patients at risk for stroke are those with a history of hypertension, diabetes, prior stroke or embolic events, and prior MI or chamber enlargement as seen on echocardiogram.

Symptoms are usually greatly reduced with control of the ventricular rate.

There are two treatment strategies for AF. One is rate control using a variety of agents that either directly or indirectly affect the AV node to slow conduction (e.g., β-blockers, calcium channel blockers, or digoxin). The other alternative is rhythm control. This involves use of antiarrhythmic agents to return the heart to and maintain normal sinus rhythm.

All patients, regardless the treatment strategy should be anticoagulated, if they have risk factors for stroke. Recent studies demonstrated no difference in survival or symptom score between rate control and rhythm control strategies in patients with minimal symptoms.

The most common paroxysmal supraventricular arrhythmia is AV nodal reentrant tachycardia. AV nodal reentrant tachycardia, like other forms of reentry, requires the presence of two anatomically and/or functionally distinct pathways. The impulse travels down one of the two pathways (antegrade conduction) but is blocked in this direction on the second pathway. Once the impulse has reached the ventricle, it is able to turn around and come up the pathway that was blocked in the forward direction (retrograde conduction). This sets up a perpetuating cycle.

AV node reentrant tachycardia is common in structurally normal hearts and is generally benign. Treatment strategies may involve use of AV nodal blocking agents or catheter ablation.

Another, somewhat less common form of supraventricular arrhythmia is seen in patients with the Wolff–Parkinson–White (WPW) syndrome and is related to an anomalous electrical connection (accessory pathway) connecting the atrium and the ventricle. There is a small but real risk of sudden death in symptomatic patients with WPW syndrome. These people should be considered for ablation therapy. Other options include antiarrhythmics (Class Ia, Ic, and III). Drugs like digoxin and calcium channel blockers should be avoided as they may make the arrhythmias associated with WPW syndrome unstable.

Although ventricular tachycardia (VT) is the most obvious cause of a wide complex tachycardia, other rhythms should be considered and include supraventricular tachycardia (SVT) with aberration (slow conduction down one of the bundles), SVT with WPW syndrome, and hyperkalemia. The most common underlying cause in VT is CAD. The prognosis of VT is largely dependent on the condition of the heart muscle—those with poor ejection fractions having a worse prognosis than those with normal or near normal function. Treatment options for people with VT and depressed ejection fractions may involve implantation of an internal cardioverter–defibrillator device. Other options may involve the use of antiarrhythmics.

2. Ischemic Heart Disease, Angina, Myocardial Infarction

Angina is an important symptom of ischemic heart disease. Typical angina is described as a pain or pressure in the chest and usually, at least initially, occurs on exertion. It is not relieved or worsened by breathing or positional changes, but may be accompanied by shortness of breath or sweating. Angina is related to an imbalance in oxygen supply and demand. This may be caused by hypoxia or coronary artery spasm but is more commonly related to significant narrowing in one or more of the coronary arteries. Similarly, MI is caused by interruption of blood supply to a segment of the heart muscle. Most typically, this occurs as a result of plaque rupture and clot formation.

Patients with CAD may have recurrent episodes of chest pain with similar levels of exertion. This may occur despite medications and is generally fairly reproducible in terms of precipitating factors. This is referred to as *stable angina.* When a person presents either with their first episode of ischemic chest pain or with a change in the pattern of their angina, this is referred to as *unstable angina* and may be a precursor to MI. This may represent a change in the severity of their CAD or in the stability of the plaques. The symptoms of MI are similar to those of angina but are generally more severe and longer lasting.

Major risk factors for coronary disease include increasing age, family history of coronary disease (< 55 years of age for men or < 65 for women), postmenopausal women, and male gender. These factors are obviously not changeable. However, other factors such as hypertension, lipid profiles, diabetes, and cigarette smoking can be modified significantly. Modification of lifestyle and other treatments are recommended in patients who already have known established coronary disease or who have atherosclerotic disease elsewhere or who are healthy but have major risk factors for development of coronary disease.

The diagnosis of acute MI is made on the basis of clinical symptoms, ECG changes, and elevated serum enzymes. (See Figure 2–5 for timing of abnormal cardiac enzymes after MI.)

The creatine kinase (CK) rises within 6–8 hours after an infarction and peaks at about 24 hours. By 48–96 hours it will have normalized. The specific isoenzyme of CK that is followed is the myocardial band (MB). Factors such as renal failure can interfere with CK measurements. CK and MB may be elevated with severe skeletal muscle damage.

Troponins I and T are more specific for myocardial injury and rise within 3 hours of injury. While troponin I is very sensitive for MI, an increased troponin I in the absence of MI (including renal failure patients) has been shown to be associated with increased mortal-

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Major risk factors for coronary disease include increasing age, family history of coronary disease (< 55 years of age for men or < 65 for women), postmenopausal women, and male gender. These factors cannot be altered, but other factors can be modulated (e.g., hypertension, lipid profiles, diabetes, and cigarette smoking).

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The diagnosis of acute MI is made on the basis of clinical symptoms, ECG changes, and elevated serum enzymes. Early intervention with thrombolytics and/or cardiac catheterization and percuatneous intervention are critical. The earlier the intervention, the greater the degree of myocardial salvage and the better the long-term prognosis. A critical determinant for long-term outcome is ejection fraction.

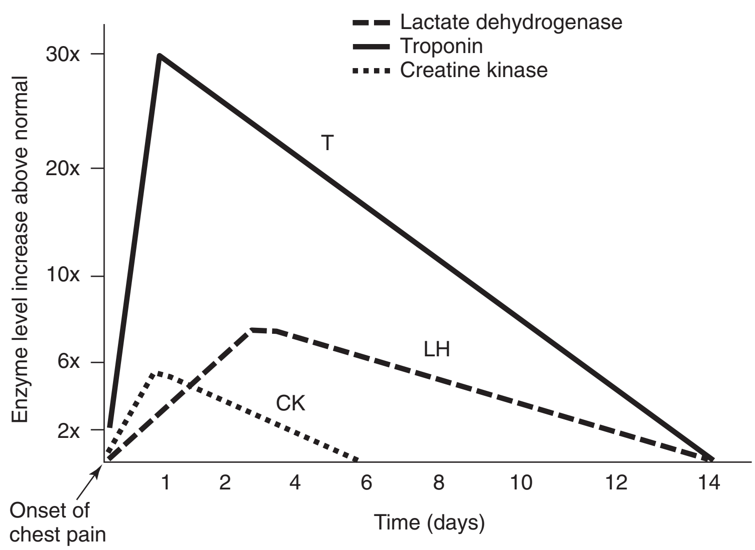

Figure 2–5. Cardiac enzyme changes with MI. (Adapted, with permission, from Kansas University Medical Center.)

ity. LDH is a much less sensitive test. LDH isoenzymes rise in MI beginning around 24–48 hours. LDH peaks in 3–5 days and normalizes in 7–10 days.

Urgent treatment of MI is desirable since the longer the delay in treatment, the greater the myocardial damage and the worse the long-term outlook. Early treatment consists of oxygen, aspirin, heparin (or low-molecular-weight heparin), and nitroglycerin or morphine for pain relief. Thought should be given to the earliest strategy to reperfuse the infarcted vessel. This may include administration of thrombolytics, glycoprotein IIb/IIIa inhibitors, and/or urgent angioplasty. In rare instances, acute coronary bypass surgery may be recommended.

The ECG plays an important role in the diagnosis of MI. The classic ECG findings of an acute Q-wave MI include acute or hyper ST-wave changes with ST-segment elevation in the involved leads. There may be T-wave inversions in the contralateral leads, and ultimately Q waves follow in the involved area.

Hypotension in the setting of an acute MI can have multiple etiologies. Hypovolemia is possible in these patients. In particular, patients with RV involvement may be very volume sensitive. In these patients, the infarct vessel is usually the right coronary artery. Cardiogenic shock is the most serious cause of hypotension in an acute MI and is due to severe LV damage. Findings include a blood pressure of < 90 mm Hg with a decrease in the cardiac index to < 1.8 L/min/m^2. These patients present with clinical signs of hypoperfusion with decreased urine output; altered mental status; pulmonary edema; and cold, clammy skin.

In < 1% of patients, a catastrophic event such as rupture of the ventricular free wall, development of a VSD, or acute papillary muscle rupture with acute mitral regurgitation may complicate an MI. Mortality is extremely high, and, although very risky, surgical treatment is the only option available.

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Shock is defined as the failure of the cardiovascular system to provide adequate blood flow, which can lead to irreversible organ and tissue damage. The determinants of blood flow include blood volume, pump function, and vascular resistance. There are three types of shock: *hypovolemic, vasogenic,* and *cardiogenic*.

3. Shock

Shock is defined as the failure of the cardiovascular system to provide adequate blood flow, which can lead to irreversible organ and tissue damage. The determinants of blood flow include blood volume, pump function, and vascular resistance. There are three types of shock. *Hypovolemic shock* results from profound volume depletion. Causes may include acute blood loss (e.g., gastrointestinal bleeding, trauma, or aortic aneurysm rupture), or other volume depletion such as in diabetic ketoacidosis. *Vasogenic shock* can include septic shock, anaphylactic shock, drug causes, or neurogenic shock. *Cardiogenic shock* was described above and is typically seen with severely decreased cardiac muscle after a large MI. There are some extracardiac causes of cardiogenic shock such as those caused by obstruction of inflow. These causes include tension pneumothorax, cardiac tamponade, and those that cause restriction of outflow such as caused by pulmonary embolism (PE).

4. Systemic Hypertension

Hypertension is defined as an average systolic reading of > 140 on at least two consecutive visits and/or two or more diastolic pressures of > 90 mm Hg on at least two consecutive visits. Measurements of BP should be performed after at least 5 minutes of rest and should be performed in both arms with the patient in a seated as well as standing position. Twenty-four percent of the U.S. population suffers from hypertension. With prolonged poorly controlled hypertension, end-stage renal disease (ESRD) can occur. The fundus serves as a mirror to brain circulation. Changes there may range from minor atherosclerosis to papilledema. The heart is also evaluated for presence of LVH with increased LV mass. This can be seen on ECG or echocardiogram, but the echo is more specific.

In some patients it may be appropriate to look for an underlying cause. However, most cases of hypertension are primary, and only around 5% of patients will have a secondary form of hypertension. Abnormalities that can cause secondary hypertension include renal artery stenosis, adrenal tumor, or coarctation of the aorta. Coarctation of the aorta can lead to rib notching, seen on the chest x-ray.

Treatment of hypertension depends on the individual patient's clinical condition and other factors. Initial treatment usually consists of a β-blocker or diuretic or a combination of the two. Both of these drugs have been shown to decrease mortality. The elderly and African-American patients may especially benefit from diuretics. Loop diuretics are preferred over thiazide diuretics if there is already some degree of renal insufficiency present. Potassium-sparing diuretics such as spironolactone must be used cautiously if there is either renal insufficiency or concomitant use of an ACE inhibitor present. ACE inhibitors are an appropriate initial treatment in patients with proteinuria and diabetes and/or if heart failure is present. ACE inhibitors have been shown to reduce mortality and to reduce progressive renal deterioration. ACE inhibitors must not be used in the second and third trimesters of pregnancy.

5. Heart Failure

Heart failure is a condition in which the heart function is unable to meet the demands of the peripheral circulation. The diagnosis of heart failure is generally made on the basis of clinical findings, physical exam, history, and chest x-ray. Patients with heart failure can progress from initially fairly free of symptoms to severely symptomatic (see Table 2–2). Heart failure can involve both the right and left ventricles, or either ventricle alone. In heart failure, there may be abnormalities in all of the determinants of CO. These include afterload, preload, heart rate, and myocardial contractility.

Heart failure most typically results from systolic dysfunction. The most common cause of systolic dysfunction is coronary artery disease. Systolic dysfunction can also result from valvular lesions (e.g., mitral regurgitation, aortic stenosis, tricuspid regurgitation). Nonischemic causes of ventricular dysfunction include viral or other infectious etiologies. While systolic dysfunction is the most common cause of heart failure, some patients may have diastolic dysfunction.

► cram facts

Most cases of heart failure are related to systolic dysfunction, and the most common cause of systolic dysfunction is ischemic heart disease.

2-2

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION BY SEVERITY OF SYMPTOMS OF HEART FAILURE

- Class I (Mild): Patients with no limitations who can perform normal activities without symptoms.
- Class II (Mild): Patients have mild limitations and symptoms (e.g., occasional swelling). They are somewhat limited in their ability to exercise or do strenuous activities.
- Class III (Moderate): Patients with noticeable limitations in their ability to exercise or perform mildly strenuous activities. They are comfortable at rest.
- Class IV (Severe): Patients who are unable to do any activity without discomfort. They have some heart failure symptoms at rest.

Typically, this results from excessive stiffness of the heart that leads to an inability to fill properly and thus a decrease in CO. These patients may have normal ejection fractions. Pure diastolic heart failure can be defined as present only in patients with normal systolic function.

Conditions associated with diastolic dysfunction and diastolic heart failure include hypertrophic cardiomyopathy, severe hypertrophy secondary to hypertension, and some types of restrictive cardiomyopathies (e.g., endomyocardial fibroelastosis or amyloidosis).

G. Vascular Disorders

1. Peripheral Vascular Occlusive Disease

Peripheral vascular occlusive disease is a subset of atherosclerotic disease. It is characterized by stenosis or occlusion of the arteries and can occur throughout the body. The symptoms of peripheral vascular occlusive disease are determined by where the lesion occurs and what the affected arteries supply. For example, peripheral vascular occlusive disease of the renal arteries may produce hypertension or renal insufficiency. Lower-extremity arterial involvement can produce claudication, but limb-threatening ischemia is possible and is clinically related to the pain occurring at rest. Carotid vascular disease can cause transient ischemic attacks (TIAs) or strokes.

2. Aortic Dissection

Aortic dissection occurs when there is a separation within the media of the aorta. This results in the creation of two lumens: a true lumen and a false lumen. Most patients who develop aortic dissection have underlying disease of the medial layer. Dissections can progress antegrade down the aorta or retrograde (proximally) up the aorta toward the aortic valve. Risk factors for developing aortic dissection include hypertension, advancing age, connective tissue disorders (e.g., Marfan's syndrome), and congenital bicuspid aortic valve. Hormonal changes during pregnancy are also related to the development of aortic dissection in women under the age of 40. Typically, dissections occur in the third trimester, but can occasionally occur in the immediate or early postpartum period.

Acute aortic dissection, particularly of the ascending aorta, has a high mortality rate. Death may be related to tamponade or rupture of the aorta. In many cases, patients describe the pain as tearing and radiating to the back. Diagnostic tests used to look for aortic dissection include magnetic resonance imaging (MRI), computed tomography (CT), transesophageal echocardiography (TEE), and aortography. The sensitivity of MRI and TEE appear to be best. Aortic dissection can be divided into type A and type B. Type A dissections involve the ascending aorta and are generally best treated by emergency surgery. Type B dissections involve the descending aorta distal to the left subclavian artery. These are best treated initially with BP control and long-term medical treatment. If vital organs like the kidneys or the bowel become involved, these patients may require surgery. Lowering the BP is critical in the management of aortic dissections.

3. Aneurysm

Aneurysms are abnormal dilations of a blood vessel. True aneurysms affect all three layers of the vessel wall. Pseudoaneurysms occur when the intima dilates into the media and adventitia. The most common site for an atherosclerotic aneurysm in the aorta is the abdominal aorta. The underlying cause for aneurysm formation in the abdominal aorta is generally atherosclerosis. Aneurysms in the thoracic aorta are often related to connective tissue disease, hypertension, or bicuspid aortic valve. Patients with abdominal aortic aneurysms > 6 cm should be considered for surgical repair. Smaller aneurysms that are symptomatic should also be considered for repair. A number of nonsurgical intra-aortic stents are now available, which may provide a nonsurgical option for some patients.

H. Systemic Diseases Affecting the Cardiovascular System

1. Hemochromatosis

Hereditary hemochromatosis is an inherited disorder that results in total body iron overload. It can also occur as a result of repeated transfusions such as in patients with sickle cell disease. Congestive cardiomyopathy is the most common abnormality associated with hemochromatosis. Other cardiac lesions have been described and include pericarditis, restrictive cardiomyopathy, and chest pain without CAD. Iron can deposit in the conduction system and cause conduction abnormalities. Sudden death can occur as a result of arrhythmias.

2. Amyloidosis

The cause of amyloid production and deposition is unknown. The primary form of amyloidosis typically causes deposits in the heart as well as other tissues (e.g., lung, skin, tongue, thyroid gland, and GI tract). The heart becomes noncompliant as a result of amyloid deposition, and diastolic heart failure can occur. Secondary amyloidosis generally does not involve the heart.

I. Idiopathic Disorders

1. Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a disorder of the heart muscle characterized by inappropriate myocardial thickening (see section II.A above). The natural history of HCM is variable. Many cases remain asymptomatic or mildly symptomatic for years. Two thirds of patients with resting obstruction will develop heart failure over time. The degree of ventricular hypertrophy typically remains stable over time but may increase. About 10% of patients with HCM will go on to develop LV dilatation and a form of dilated cardiomyopathy. Because of elevated end diastolic pressure in these noncompliant ventricles, AF can occur.

AF generally results in a significant clinical deterioration. Mortality in patients with HCM tends to be higher in those with LV obstruction and those with very extensive hypertrophy. The annual mortality for HCM is about 3% in adults and 6% in children. Patients with HCM may be at higher risk for sudden cardiac death (SCD). SCD is most frequent in adolescents and young adults. Historic profiles that suggest a higher risk for SCD in a patient with HCM include prior cardiac arrest or spontaneously occurring and sustained VT, family history of a premature SCD, identification of a high-risk mutant gene, unexplained syncope (particularly when exertional or recurrent), nonsustained VT on ambulatory (Holter) ECG recordings, hypotension during upright exercise, and extreme LVH (> 30 mm) on echo.

2. Dilated Cardiomyopathy

Dilated cardiomyopathy is the most common form of cardiomyopathy. In this condition, generally all chambers of the heart are affected and enlarged. The typical presentation for dilated cardiomyopathy is heart failure and decreased left ventricular ejection fraction (LVEF). Over half of the cases of dilated cardiomyopathy are idiopathic. Other causes include myocarditis (about 9.2% of cases), CAD (about 7.7%), hypertension (about 4.2%), and peripartum cardiomyopathy (about 4.5%). Other causes such as amyloidosis, age, and chronic alcohol use each cause approximately 2–3% of cases.

Several medical options are available for treatment of dilated cardiomyopathy. ACE inhibitors have been shown to reduce mortality in patients with ejection fractions < 40%. When ACE inhibitors cannot be used, vasodilator combinations of nitrates and hydralazine have also been proven to be beneficial (particularly in African Americans). Angiotensin II antagonists are also useful and can be used when ACE inhibitors are not tolerated. Diuretics do not affect mortality but improve the symptoms of volume overload. Spironolactone and β-blockers have been shown to decrease mortality. Digoxin results in fewer hospital admissions but does not alter mortality. Amiodarone may result in some improvement in ejection fraction and decrease the risk of sudden death but does not improve overall mortality. Implantable cardioverter defibrillators can decrease mortality.

III. PRINCIPLES OF THERAPEUTICS

A. Mechanisms of Action and Therapeutic Effects of Drugs for Treatment of Cardiovascular Disorders

1. Antiarrhythmic Drugs

Antiarrhythmic drugs are classified according to their electrophysiologic effect. The Vaughan Williams classification of antiarrhythmic agents is still used commonly because it permits easy communication. The Vaughan Williams classification includes Class I local membrane-stabilizing drugs, which block the fast sodium channel; Class II drugs, which block β-adrenergic receptors; Class III drugs, which prolong duration of the cardiac action potential and repolarization, including those that block potassium channels; and Class IV drugs, which slow calcium channels.

Class Ia agents (e.g., procainamide and quinidine) are not used as frequently as they were in the past. Procainamide has a high rate of intolerable side effects; 40% of the patients must stop the drug within 6 months. A major toxicity to this category of drugs is prolongation of the QT interval, which can result in torsades de pointes. Procainamide can also cause a lupuslike syndrome and agranulocytosis. Quinidine, another Class Ia agent, has been associated with increased mortality in patients who are treated for AF.

Lidocaine is a Class Ib antiarrhythmic, which may decrease the occurrence of ventricular fibrillation (VF) following acute MI, but does not provide any benefit in survival. Class Ic agents are helpful in the setting of AF in patients with structurally normal hearts. The efficacy at 1 year is about 55–60%. Class Ic drugs include flecainide, propafenone, and moricizine.

β-Blockers are Class II drugs and are competitive antagonists of β-adrenergic receptors. There are two β-receptor classes: β_1 and β_2 receptors. β_1 receptors are generally located in the heart. They lead to increased HR and contractility and AV conduction when stimulated. Blockade of the β_1 receptors blunts these increases, particularly during exercise or stress. Several β-blockers produce a small degree of receptor stimulation that offsets the effects of receptor blockade in the resting state but maintains antagonism during exercise. These drugs have what is known as intrinsic sympathomimetic activity. β_2 receptors are more widely spread throughout the body than β_1 receptors. Activation of these receptors results in diverse actions such as bronchodilatation, peripheral vasodilatation, and lipolysis. Many adverse effects of β-blockers such as bronchospasm are secondary to the β_2 receptor blockade. Indications for β-blocker therapy include acute MI, post MI, treatment of supraventricular and ventricular arrhythmias, aortic dissection, HCM, MVP, heart failure, and prolonged QT syndrome. β-Blockers are contraindicated in patients with hypotension or asthma and most patients with chronic obstructive pulmonary disease (COPD).

Amiodarone is a Class III antiarrhythmic, which prolongs refractoriness and duration of cardiac action potential. It also has a β-blocking and vasodilating effect. It is useful in treatment of SVT, as well as VT. Amiodarone is generally well tolerated but can lead to hyper- or hypothyroidism, liver dysfunction, sun sensitivity, skin discoloration, or pulmonary fibrosis. Sotalol is also a Class III antiarrhythmic, and it also has β-blocking effects. It is useful for many supraventricular and ventricular arrhythmias. The side effects of sotalol are largely related to its β-blocking properties and include fatigue, worsening of bronchospasm, and heart failure.

Class IV drugs include the calcium channel blockers. This is a broad category of drugs, and the calcium channel antagonists have several important pharmacologic properties, including an effect on heart rate, AV node conduction, myocardial contractility, and arterial vasodilatation. Not all calcium channel blockers have the same actions.

2. Antimicrobial Drugs

Antimicrobial prophylaxis is recommended for patients at risk for infective endocarditis who are undergoing procedures associated with bacteremia. This remains the practice despite a lack of conclusive evidence of efficacy of prophylaxis. People who are considered to be at high risk for endocarditis are those with prosthetic heart valves, prior bouts of endocarditis, or complex cyanotic congenital heart disease or those who have undergone surgical correction of congenital disease. Moderate-risk patients are those with surgically constructed systemic pulmonary shunts or conduits, significant MVP (murmur and thickened leaflets), HCM, or acquired valvular insufficiency.

3. Coronary and Peripheral Vasodilators

Vasodilators are not the primary treatment in CAD but may be helpful in acute MI to reduce myocardial work. In this setting, a short-acting IV drug is preferable. IV nitroglycerin may be used for the first 24–48 hours. It is particularly helpful in those with large anterior MIs and heart failure. IV nitroglycerin dilates veins, arteries, and arterioles and reduces both preload and afterload, and myocardial work is diminished. While IV nitroglycerin may reduce infarct size and improve mortality in high-risk patients, data do not support its use in low-risk, uncomplicated MI.

Vasodilators are useful in the treatment of CHF due to LV systolic dysfunction. In patients with low CO, the arterial and venous beds are inappropriately constricted as a compensatory mechanism in an attempt to maintain adequate blood flow to vital organs. These compensatory mechanisms result in constriction and increased catecholamine levels and increased sympathetic tone. This results in an increased activity of the renin–angiotensin–aldosterone (RAA) system. These compensatory mechanisms ultimately result in a cycle of decreasing CO and increasing vasoconstriction.

Vasodilators can break the cycle by decreasing the vascular resistance and improving CO. There are different classes of vasodilators, including those that act on the kidney and angiotensin system. Non–ACE inhibitor vasodilators are potent stimulators of the RAA system. They result in the mean lowering of systolic BP and decrease in renal perfusion. ACE inhibitors work directly on the RAA system by blocking the conversion of angiotensin I to angiotensin II. Hyperkalemia can occur with ACE inhibitors, and caution must be taken in patients receiving simultaneous potassium-sparing diuretics.

Angiotensin II receptor blockers do not affect the glomerular filtration rate. They increase renal blood flow and lead to a natriuretic effect. They reduce urinary protein excretion and decrease filtration fraction to reduce urinary albumin excretion.

4. Drugs Affecting Blood Coagulation

The main anticoagulants used for cardiovascular indications are aspirin and Coumadin (warfarin). Intravenously, heparin or low- molecular- weight heparin has been proven to be of benefit in unstable angina. Antiplatelet drugs include aspirin and glycoprotein IIb/IIIa antagonists. The glycoprotein IIb/IIIa antagonists are now standard treatment during coronary intervention. They are of proven benefit in high-risk patients with unstable angina.

Warfarin affects the vitamin K–dependent clotting factors (VII, IX, and X). Warfarin therapy is monitored with a standardized anticoagulation measure called the international normalized ratio (INR). Heparin is a sulfated glycosaminoglycan. Its anticoagulant effects are mediated through antithrombin III, which has a native ability to inhibit thrombin, activated factor X, and activated factor IX. Heparin binds to antithrombin III. Anticoagulation with heparin is almost instantaneous. Low-molecular-weight heparin is smaller in size and has less binding capacity for thrombin, platelets and plasma proteins, and endothelial cells. It inactivates factor X. It has good bioavailability and has a longer plasma half-life than does heparin.

Heparin use is monitored through measurement of the partial thromboplastin time (PTT). Weight-based dosing of low-molecular-weight heparin does not need lab monitoring. Anti–factor Xa activity can be measured and may be useful in patients with renal failure treated with low-molecular-weight heparin since this drug is renally cleared.

Glycoprotein IIb/IIIa receptor antagonists interfere with platelet function. The primary ligand of glycoprotein IIb/IIIa receptor on the platelet membrane is fibrinogen. Fibrinogen simultaneously binds the receptors of two separate platelets. Platelet cross-linking then occurs, leading to aggregation. The glycoprotein IIb/IIIa antagonist occupies the binding site and blunts the pathway of platelet binding.

5. Thrombolytic Agents

Thrombolytic agents can be extremely useful in patients with coronary artery occlusion secondary to ruptured atheromatous plaque. The common pathway in the development of thrombosis is conversion of prothrombin to thrombin. Thrombin subsequently converts fibrinogen into fibrin. Together with red blood cells, platelets, and plasminogen, a thrombus is produced. Because of the critical nature of coronary occlusion and the urgency for revascularization, thrombolytic therapy is often the appropriate choice for patients with presumed MI. Reperfusion therapy with thrombolytics has proven to decrease mortality, improve LV function, and reduce secondary complications. Thrombolytics accelerate conversion of plasminogen to plasmin. Plasmin dissolves fibrin clots and speeds endogenous fibrinolysis. Thrombolytic therapy is effective in approximately 80% of thrombosed vessels. The reocclusion rate is around 15–20%. There are several thrombolytic agents available with specific regimens, but for any thrombolytic the critical factor is time. Therapy within 6 hours of presentation provides the greatest amount of benefit, but it has been shown to be effective up to about 12 hours.

Combining tissue plasminogen activator (TPA) with glycoprotein IIb/IIIa inhibitors has been proven to increase reperfusion rates and may improve outcomes from thrombolysis. Additional treatments after thrombolysis include use of aspirin and heparin to prevent reocclusion. Thrombolytic therapy is reserved for patients who have no evidence of active bleeding elsewhere in their body, no recent noncompressible vessel puncture, no aortic dissection, no history of intracranial malignancy, no recent major surgery, no acute pericarditis, and no known allergies to streptokinase or anisoylated plasminogen streptokinase activator complex (APSAC).

There are several complications associated with the use of thrombolytics. Both streptokinase and APSAC have been associated with severe allergic reactions. Major bleeds occur in about 0.1–0.3% of patients.

6. Immune Suppressants

Patients who undergo cardiac transplantation face a lifetime struggle between rejection and suppression. The regimens used for heart transplant patients are similar to those used in other organ transplants. For patients receiving cyclosporine, the 1-year actuarial survival is about 80%. Early rejection can occur in around 60% of transplant patients.

7. Inotropic Agents

There are two classes of inotropic agents clinically available: glycosides and nonglycosides. The glycosides include digoxin and digoxin-like agents. Nonglycosides are divided into two large groups: sympathomimetic amines and phosphodiesterase inhibitors. The sympathomimetic amines include dopamine, dobutamine, epinephrine, norepinephrine, isoproterenol, and methoxamine. The phosphodiesterase inhibitors include amrinone and milrinone. All of these drugs increase the availability of calcium to the contractile element at the time of excitation/contraction coupling. Glycosides increase inotrope at the cellular level through inhibition of the sodium potassium ATPase pump. The β-adrenergic sympathomimetic drugs result in an increase in cyclic adenosine monophosphate (cAMP). cAMP phosphorylates a protein kinase, which in turn increases the calcium influx through the calcium channel.

8. Lipid-Lowering Agents

Lipid-lowering agents in combination with diet modification can reduce mortality following MI by up to 20%. New guidelines for treatment of low-density lipoprotein (LDL) in primary and secondary prevention vary depending on patient risk stratification. Patients at high risk are those with clinical coronary disease, symptomatic carotid disease, peripheral arterial disease, or abdominal aortic aneurysm. The new guidelines include diabetes as a coronary heart disease risk equivalent.

B. Other Therapeutic Modalities

1. Percutaneous Transluminal Angioplasty (PTCA) and Other Interventions

PTCA is well accepted as a treatment for ischemic heart disease. PTCA is indicated in patients with single-vessel disease if: (a) there is inducible ischemia seen on stress testing while the patient is on medication, (b) the patient continues to have chest pain despite medication, (c) the patient does not tolerate medication, (d) an asymptomatic patient demonstrates significant ischemia on stress testing, (e) the patient survived a cardiac arrest and has coronary disease, (f) an asymptomatic patient has a history of an MI and a positive stress test, or (g) ischemia is documented on a stress test and high-risk noncardiac surgery is planned.

Multivessel angioplasty is often performed in patients with disease involving two major vessels and demonstrable ischemia on stress testing.

PTCA results in an improved lumen diameter mainly by causing plaque rupture and resultant stretching of the media and adventitia and expansion of the outer diameter of the vessel. Other than acute problems, a major concern in PTCA is restenosis or renarrowing of the vessel at the site dilated. Restenosis is radically reduced through the placement of drug-eluting stents (approximately 3%). Such stents contain sirulimus or paclitaxel. Stents are small expandable devices placed at the site of an angioplasty and left in position.

2. Implantable Cardioverter Defibrillator (ICD)

ICDs function by monitoring the cardiac rhythm of the patient. If an arrhythmia is detected, the device can treat in several tiers of therapy. The device can be programmed to provide a pacing treatment to interrupt reentrant loops of VT. If this fails or if the presenting arrhythmia is faster and unstable (ventricular fibrillations), the device can be programmed to provide a shock as a first-line treatment. ICDs are indicated for secondary prevention of cardiac arrest in those who have survived sustained VT or cardiac arrest and for primary prevention of cardiac arrest in those at risk (e.g., post MI or dilated cardiomyopathy with low EF).

3. Pacemakers

Pacemakers are implanted in patients with heart block of any level that causes syncope. They are also indicated in patients with syncope in whom bradyarrhythmias are assumed to be the cause. Pacemakers function by sensing the native cardiac activity. If an appropriate impulse is seen, the output of the pacer is inhibited. If no activity is seen at the appropriate time, the unit delivers a small electrical output and paces the heart.

Pacemakers are comprised of a generator and leads are threaded into the heart. Pacemaker leads can be implanted in either the right atrium or right ventricle, or both. Pacemakers that pace both chambers are used in patients with disrupted AV conduction but whose atria are not fibrillating. Single-chamber atrial pacers are implanted in patients with symptomatic sick sinus syndrome and intact AV conduction. Ventricular-only pacemakers are implanted in patients with AF.

C. Adverse Effects of Drugs on the Cardiovascular System

Several drugs have been shown to induce dilated cardiomyopathy—doxorubicin and cocaine are the most common. Less commonly, interferon, lithium, steroids, and leukotrienes have been shown to cause dilated cardiomyopathy. Doxorubicin cardiac toxicity is felt to be related to myocardial oxidative stress secondary to increased free radical formation.

Drug-induced ischemia and infarction have been associated with 5-fluorouracil, doxorubicin, and vinca alkaloids. Prophylactic treatment with nitrates and calcium channel blockers can be useful in abolishing pain following treatment with vinca alkaloids. The most important factor in the development of cardiomyopathy secondary to anthracycline chemotherapy is the total amount of drug received. The incidence of doxorubicin-induced cardiomyopathy is 1–2% but is dose dependent. It is rare at doses < 450 mg/m^2, but increases to 30–40% in patients who have received up to 700 mg/m^2.

Several drugs have the potential to cause adverse effects on the cardiovascular system. The problems that arise can be serious and potentially life threatening. Some drugs will have fairly predictable potential adverse effects such as arrhythmia induction including tachy- or bradyarrhythmias from cardioactive drugs like digoxin, β-blockers, or antiarrhythmics. However, many reactions are less predictable and may arise from noncardioactive drugs.

IV. PSYCHOSOCIAL, CULTURAL, OCCUPATIONAL, AND ENVIRONMENTAL CONSIDERATIONS

There is growing evidence of a relationship between heart disease and psychosocial and environmental factors. Such factors as social isolation, individual personality traits, and job strain may increase the risk of cardiovascular disease. Depression is also a risk factor for cardiovascular disease.

A. Influence of Emotional and Behavioral Factors on Disease Prevention, Progression, and Treatment

1. Smoking

Tobacco use is an important cause of coronary disease, and smoking is the single most preventable cause of death in the United States. The impact on women is particularly strong, and women who smoke face much higher risks of death from heart disease or stroke than do their nonsmoking counterparts. Secondhand smoke also raises the risk, as does the use of contraceptives in smokers.

2. High Blood Pressure and Obesity

Another modifiable risk for heart disease is hypertension. Hypertension is also the major risk factor for stroke. Women who are overweight by at least 20 pounds have a much higher risk of developing hypertension. Other factors that increase the risk of hypertension include menopause, certain birth control pills, and family history. Among women ages 65–74, 60% have hypertension.

3. Exercise

Several studies have shown a correlation between a sedentary lifestyle and heart disease. This has also been indirectly related to stroke risk. The risk is about twice that of active people.

4. Obesity

Truncal obesity has been associated with an increased risk for heart disease. Obesity also can contribute to other conditions such as hyperlipidemia and diabetes, which further increase the risk of heart disease and stroke.

5. Alcohol

Alcohol in moderate amounts may lower the risk of heart disease. For women, this means about one drink/day. However, excessive drinking or binge drinking can lead to other health problems such as altered lipid metabolism and elevated triglycerides, hypertension, and obesity. In addition, alcohol is a direct myocardial toxin, and binge drinking can cause atrial fibrillation. Prolonged excessive exposure to alcohol can lead to dilated cardiomyopathy.

6. Stress

Stress is the response people describe to a variety of factors, such as emotional, environmental, physical, or chemical. There is growing evidence that stress is related to heart disease. Whether stress is an independent risk factor or a contributor to heart disease is unknown. Stress can lead to behaviors such as overeating, drinking, and inactivity that can contribute to heart disease.

B. Influence of Disease and Treatment on Person, Family, and Society

The population in the United States is aging due to better heath care availability and improved survival of childhood diseases. As a result of this aging population, more health care resources are being used. According to the U.S. Census Bureau's *Statistical Abstract of the United States: 2001*, government expenditures for health services and supplies in 1999 were $524,240,000,000. Although the number of heart transplants has declined since 1990, the numbers of other cardiac procedures for inpatients has increased steadily from 1990 to the present. Rising health care demands impose a financial burden on both government and private sectors.

C. Occupational and Other Environmental Risk Factors for Cardiovascular Disease

Since stress is a risk factor for coronary heart disease, it is appropriate to reduce job and other stress factors in patients with heart disease. A sedentary lifestyle can contribute to heart disease. Similarly, occupations that require little physical activity need to be offset by exercise.

BIBLIOGRAPHY

ACC/AHA 2002 guideline update for management of patients with unstable angina and non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2002;40:366–374.

ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. *J Am Coll Cardiol* 2001;38:1266i–1xx).

ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices. *Circulation* 2002;106:2145–2161.

Alpert JS, Aurigemma GP, Balady GJ, et al. *AHA Clinical Cardiac Consult.* Philadelphia: Lippincott Williams & Wilkins, 2001.

Antman EM, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: Executive summary. *J Am Coll Cardiol* 2004;44:671–719.

Braunwald E, Zipes DP, Peter L, Bonow R (eds.). *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine,* 7th ed. Philadelphia: W.B. Saunders, 2004.

Crawford MH. *Current Diagnosis & Treatment in Cardiology,* 2nd ed. New York: McGraw-Hill, 2004.

Kasper DL, Braunwald E, Fauci A, et al. (eds.). *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill Professional, 2004.

Maron BJ, McKenna WJ, et al. ACC/ESC clinical expert consensus document on hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2003;42(9):1687–1713.

Murphy JG (ed.). *Mayo Clinic Cardiology Review,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 1999.

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The Endocrine System

3

I. NORMAL PROCESSES

A. Thyroid Gland

The thyroid gland secretes thyroid hormones, which are necessary for normal growth and development and metabolic functions such as energy and heat production. The thyroid gland originates as a pouch in the pharyngeal floor and grows inferiorly until it reaches its final position anterior to the trachea. The foramen cecum is the remnant of the thyroid at the base of the tongue; the path of downward migration of the thyroid remains as the thyroglossal duct. The thyroid also contains parafollicular (C) cells, which are neuroendocrine cells that secrete the hormone calcitonin. These cells are derived from the ultimobranchial body, which fuses with the fetal thyroid gland.

The isthmus of the thyroid is located below the cricoid cartilage, and each lobe extends laterally. The thyroid is supplied by the superior thyroid arteries, which originate from the common carotid artery; the inferior thyroid arteries, which originate from the subclavian artery; and the thyroid ima artery, which arises from the brachiocephalic artery. The superior, middle, and inferior thyroid veins provide venous drainage. Microscopically, the thyroid consists of single layers of thyroid epithelial cells surrounding a pink-staining substance called colloid; this structure is called a *thyroid follicle*. These structures are interspersed with calcitonin-producing C cells.

Dietary iodide is transported across the basement membrane of thyroid follicular cells by the Na^+/I^- symporter. A Na^+/K^+/ATPase creates the ion gradient necessary for iodide trapping. Inside of the cell, the iodide is oxidized to iodine, then incorporated into a tyrosine residue of the glycoprotein thyroglobulin. Thyroglobulin is a large molecule with a molecular weight of 660,000 that contains four tyrosyl residues used for thyroid hormone synthesis. Within the thyroglobulin molecule, iodotyrosine residues are coupled to form the thyroid hormones tetraiodothyronine (T_4) and triiodothyronine (T_3). These three steps in thyroid hormone biosynthesis are catalyzed by the enzyme thyroid peroxidase. The thyroglobulin molecule is stored in colloid and is eventually engulfed by the follicular cell; the colloid vesicles are fused with lysosomes and thyroglobulin is hydrolyzed, resulting in the release of T_3 and T_4, which are then released into the circulation.

99.96% of circulating thyroid hormone is bound to plasma proteins. Thyroxine-binding globulin (TBG) binds to about 70% of T_3 and T_4; thyroxine-binding prealbumin (TBPA) binds to about 10% of T_4, and albumin binds to about 15% of T_4 and T_3. About 0.4% of T_3 and 0.04% of T_4 circulate in the unbound state. T_3 is the active form of thyroid hormone. Free T_4 and free T_3 are able to passively diffuse into the target cell cytoplasm. Inside the cell, 5′ deiodinase converts T_4 to T_3. T_3 then enters the nucleus and binds to the thyroid hormone receptor (TR). The activated TR binds to the thyroid hormone response element (TRE) on DNA. T_3 binding may either stimulate or inhibit DNA transcription of specific genes.

Effects of thyroid hormone stimulation on various tissues include fetal brain development and skeletal maturation; increases in oxygen consumption, cardiac contractility, β-adrenergic receptor expression, gut motility, bone turnover, and maintenance of the respiratory drive.

Thyroid hormones are regulated by thyroid-stimulating hormone

(TSH), which in turn is regulated by thyroid-releasing hormone (TRH). TRH is synthesized in the supraoptic and supraventricular nuclei of the hypothalamus. It stimulates the synthesis and secretion of TSH from the pituitary gland in response to decreased levels of T_4 and T_3. TSH stimulates the growth of thyroid cells and the synthesis and release of thyroid hormone. TSH and TRH are both inhibited by increased serum levels of T_4 and T_3.

B. Pancreatic Islets

The islets of Langerhans are located throughout the pancreas. Four cell types are found in the islets: glucagon-secreting A cells, insulin-secreting B cells, somatostatin-secreting D cells and pancreatic polypeptide–secreting F cells. The pancreas develops from endodermal "pancreatic buds," which form tubules. The islets are formed from groups of cells that separate from the tubules.

Insulin is a polypeptide hormone formed from a precursor molecule called preproinsulin, which is converted to proinsulin. Proinsulin is then cleaved into insulin and C peptide. Insulin binds to a membrane-bound glycoprotein receptor composed of an extracellular α subunit and a cytoplasmic β subunit. Tyrosine kinase is activated when the receptor is bound by insulin. This step triggers phosphorylation of various proteins and eventually leads to increased glucose transport. Insulin has various anabolic effects: it increases glycogen synthesis and inhibits its breakdown; it increases protein synthesis; it inhibits ketogenesis and gluconeogenesis; and it stimulates lipoprotein lipase and inhibits hormone sensitive lipase, thus promoting storage of fat. Insulin release is stimulated by glucose and amino acids and is inhibited by catecholamines and somatostatin. In addition, cortisol, growth hormone, and glucagon antagonize the effects of insulin.

The pancreatic A cells secrete glucagon, a polypeptide hormone that protects against hypoglycemia. It binds to a G-protein coupled receptor stimulating intracellular accumulation of cyclic adenosine monophosphate (cAMP). Glucagon stimulates glycogenolysis, gluconeogenesis, and ketogenesis. Its release is stimulated by amino acids and inhibited by glucose, insulin, and somatostatin.

Somatostatin is secreted from the hypothalamus and the gastrointestinal (GI) tract as well as the pancreatic D cells in response to increased blood glucose and protein levels. There are five known somatostatin receptors, SSTR 1–5, all of which are seven-transmembrane spanning G-protein receptors that, when activated, lower cellular cAMP and reduce intracellular calcium levels. SSTR 2 mediates the inhibition of growth hormone and glucagon secretion, whereas SSTR 5 mediates inhibition of insulin release. In addition to inhibiting the release of various hormones, somatostatin also increases gastric emptying time, decreases splanchnic blood flow, and decreases pancreatic exocrine hormone secretion.

Pancreatic polypeptide is secreted from the F cells in response to a mixed meal; however, its function is not yet known.

C. Parathyroid Glands

The parathyroid glands secrete parathyroid hormone (PTH), a hormone important in the regulation of calcium and phosphate metabolism. There are four parathyroid glands: the two inferior glands originate from the third branchial pouch, whereas the two superior glands originate from the fourth branchial pouch. They are ultimately located posterior to the thyroid gland in the anterior neck.

Microscopically, the parathyroids are composed of oxyphil cells and chief cells, both of which contain PTH. The larger oxyphil cells have an eosinophilic cytoplasm packed with mitochondria, whereas chief cells are smaller and have a clear cytoplasm.

PTH is a polypeptide hormone with a half-life of 2–4 minutes. It binds to the PTH receptor, which is a seven-transmembrane spanning receptor located predominantly in the kidney and bone. PTH binding activates the G proteins Gs and Gq. Gs activates adenylate cyclase, leading to cAMP production; Gq activates phospholipase C, which leads to protein kinase C activation and an increase in intracellular calcium.

In the kidney, PTH increases reabsorption of calcium in the renal distal tubule and increases phosphate secretion in the proximal tubule. PTH also stimulates the conversion of 25-hydroxyvitamin D to the active metabolite 1,25-dihydroxyvitamin D, thereby indirectly increasing absorption of calcium from the GI tract. PTH secretion is regulated by calcium levels; high serum calcium levels inhibit its release, and low levels stimulate its release. Calcium binds to the calcium receptor, a G-protein coupled receptor located on the membrane of the parathyroid cell. Calcium binding to the receptor activates protein Gq, which activates phospholipase C, resulting in a rise in intracellular inositol-1,4,5-triphosphate (IP_3) and diacylglycerol. PTH release is also inhibited by hypomagnesemia and high 1,25-dihydroxyvitamin D levels.

PTH is cleaved into an amino-terminal and a carboxy-terminal fragment in the kidney and liver. The carboxy-terminal fragment is predominantly cleared by the kidney and therefore may be elevated in kidney disease.

D. Vitamin D

Vitamin D is a steroid hormone that is important in the regulation of calcium and phosphate homeostasis. It is present in several forms: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol), 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D. Vitamins D_2 and D_3 are formed from the exposure of a precursor molecule (7-dehydrocholesterol) to ultraviolet light. Both vitamin D_2 and D_3 are converted by 25-hydroxylase to 25-hydroxyvitamin D in the liver. 25-Hydroxyvitamin D is then converted to the active form, 1,25-dihydroxyvitamin D, by the enzyme 1α-hydroxylase in the kidney. PTH stimulates the activity of this enzyme.

1,25-Dihydroxyvitamin D enters the target cell and binds to the vitamin D receptor (VDR). The complex binds to DNA to direct the synthesis of specific proteins.

Vitamin D increases intestinal transport of calcium and phosphate and increases the renal tubular reabsorption of calcium. In bone, vitamin D promotes osteoblastic differentiation, leading to adequate bone mineralization; increases osteoclastic bone resorption; and stimulates collagen production.

PTH increases the production of 1,25-dihydroxyvitamin D by activating 1α-hydroxylase. High plasma calcium and phosphate inhibit vitamin D activity.

E. Adrenal Cortex

The adrenal cortex originates from mesoderm and at 2 months' gestation consists of a fetal zone and a definitive zone. The fetal zone produces mainly dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS), whereas the definitive zone produces cortisol and other adrenal steroids. The fetal zone disappears after birth and the definitive zone differentiates into the three adrenocortical layers: the zona glomerulosa, which produces aldosterone, and the zona fasciculata and zona reticularis, which produce cortisol and androgens.

The adrenal gland in the adult is located above the kidneys in the retroperitoneum. It is supplied by the adrenal arteries, which are derived from the aorta, the renal arteries, and the inferior phrenic artery. The left adrenal is drained by the left adrenal vein, which drains into the left renal vein. The right adrenal is drained by the right adrenal vein, which drains directly into the vena cava.

Microscopically, the zona glomerulosa lies just under the adrenal capsule and contains small cells containing scant lipid; it comprises about 15% of the adrenal cortex. The zona fasciculata lies in between the zona glomerulosa and the zona reticularis, and constitutes 75% of the adrenal cortex. These cells are arranged in columns and contain lipid; hence, they are termed *clear cells*. The zona reticularis is the innermost layer of the cortex. These cells are acidophilic and contain lipofucsin granules.

The adrenal cortex secretes primarily aldosterone, cortisol, and androgens. Aldosterone is secreted from the zona glomerulosa, which contains the enzyme aldosterone synthase (P450aldo). The zona fasciculata and zona reticularis lack this enzyme. The zona glomerulosa, on the other hand, does not contain the enzyme 17α-hydroxylase (P450c17) and therefore cannot synthesize cortisol or androgen; this enzyme is present in both the zona fasciculata and the zona reticularis. The latter two zones are regulated by adrenocorticotropic hormone (ACTH), whereas the zona glomerulosa is regulated primarily by the renin–angiotensin system. Steroid synthesis in the adrenal cortex begins with the conversion of cholesterol to pregnenolone in the mitochondria. This reaction is the rate-limiting step in steroidogenesis. See Figure 3–1 for details on the enzymatic pathway.

ACTH is a polypeptide hormone secreted from the anterior pituitary. It activates P450scc and the conversion of cholesterol to pregnenolone. ACTH secretion is stimulated by corticotropin-

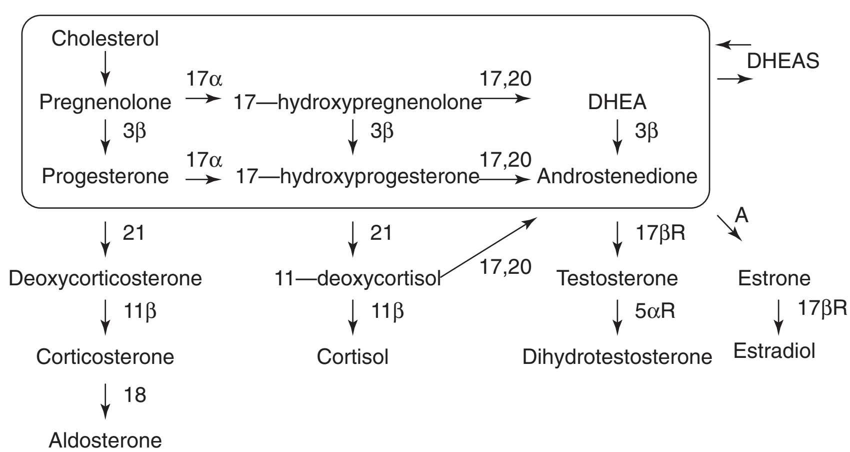

Figure 3–1. Enzymatic pathway in the adrenals, ovaries, and testes. The first step is conversion of cholesterol into pregnenolone. The enzymes mentioned in the figure are the following: 17α = 17α-hydroxylase; 17,20 = 17,20 lyase; 3β = 3β-hydroxysteroid dehydrogenase; 21 = 21 hydroxylase; 11β = 11β-hydroxylase; 17β R = 17β-reductase; 5αR = 5α-reductase; 18 refers to the two-step process of aldosterone synthase, resulting in the addition of a hydroxyl group that is then oxidized to an aldehyde group at the 18-carbon position; A = aromatase.

releasing hormone (CRH), a hormone secreted from the hypothalamus. ACTH release is also stimulated by stress, hypoglycemia, surgery, and depression. High cortisol levels inhibit both CRH and ACTH secretion.

Cortisol circulates in plasma bound to corticosteroid-binding globulin (CBG) and albumin. About 10% circulates in the unbound state. Cortisol enters into the target cell and binds to glucocorticoid receptor proteins. The cortisol-receptor complex enters the nucleus and binds to the DNA-binding domain, initiating transcription of specific proteins.

Cortisol has multiple effects on various tissues. It has catabolic effects on muscle, leading to reduced amino acid uptake and increased protein breakdown. In the liver, cortisol increases hepatic gluconeogenesis by stimulating phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. It inhibits glucose uptake in muscle and adipose tissue and enhances lipolysis in adipose tissue. In the kidney, glucocorticoids enhance water excretion; thus, patients with cortisol deficiency may develop hyponatremia due to free water overload. Cortisol inhibits intestinal calcium absorption and enhances urinary calcium excretion. It stimulates bone resorption, leading to osteoporosis.

Glucocorticoids have profound effects on the immune system. They decrease migration of inflammatory cells to injured tissues, impair antibody production, and decrease lymphocyte production.

Cortisol is metabolized in the liver to inactive metabolites; these are conjugated predominantly with glucuronic acid, and are then excreted in the urine. The adrenal androgens are androstenedione, DHEA, and DHEAS. They have little direct biological effect; however, they are peripherally converted to the more potent androgens testosterone and dihydrotestosterone. Their synthesis is also regulated to some extent by ACTH.

Aldosterone is secreted from the zona glomerulosa and is primarily regulated by the renin–angiotensin system. Renin is an enzyme produced by the juxtaglomerular cells in the glomerulus of the kidney. Its release is stimulated by several factors. Cells of the macula densa, an area located in the thick ascending limb of the loop of Henle, sense reduced sodium levels in renal tubular fluid and stimulate release of renin. Decreases in renal arteriolar pressure are sensed by baroreceptors in the afferent arteriole and also stimulate renin release. In addition, renin release is stimulated by sympathetic nervous system activation. Once released, renin converts angiotensinogen, a protein secreted by the liver, to angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE), a glycoprotein located mostly in the lung, but also present in endothelial cells, brain, and kidney. Angiotensin II is a peptide hormone that binds to seven-transmembrane spanning G protein receptors located on plasma membranes. It activates phospholipase C, inositol triphosphate and diacylglycerol, resulting in increases in intracellular calcium concentration. It causes vasoconstriction of peripheral arterioles in all tissues. It also acts on the adrenal cortex to stimulate the secretion of aldosterone.

Most of aldosterone circulates bound to albumin and weakly bound to CBG; 30–50% circulates in the free state. It crosses the target cell membrane and binds to a mineralocorticoid receptor in the cytoplasm. This complex crosses into the nucleus of the cell where it binds to DNA and influences the synthesis of specific proteins. Aldosterone stimulates sodium channels in the renal collecting duct, enhancing renal sodium reabsorption. It results in a more negative luminal fluid, which leads to increased K^+ and H^+ secretion. Aldosterone is mainly cleared by the liver via conversion to an inactive metabolite.

F. Adrenal Medulla

The adrenal medulla arises from neural crest tissue, which migrates from the spinal ganglia to the adrenal cortex at about 6 weeks' gestation. The arteries that supply the adrenal cortex form a plexus underneath the capsule; some of these vessels pass directly to the adrenal medulla. Venous drainage is the same as that of the adrenal cortex.

The adrenal medulla secretes the catecholamines epinephrine, norepinephrine, and dopamine. The amino acid tyrosine is converted to dihydroxyphenylalanine (dopa) by the enzyme tyrosine hydroxylase, which reaches the adrenal medulla via adrenal medullary nerve axons. Dopa is converted to dopamine by dopa decarboxylase. The enzyme dopamine β-hydroxylase catalyzes the conversion of dopamine to norepinephrine; norepinephrine is then converted by phenylethanolamine-*N*-methyltransferase (PNMT) to epinephrine. PNMT is induced by glucocorticoids. Catecholamines are stored in secretory vesicles and secreted in response to stressful stimuli, such as hypoglycemia, surgery, trauma, acute illness, and exercise. Their release is stimulated by acetylcholine, which is secreted from the nerve terminals resulting in depolarization and an influx of calcium into the nerve cell. The calcium causes the exocytosis of the vesicles.

Catecholamines circulate bound to albumin. Their physiologic effects are initiated by the binding to adrenergic receptors, which are seven-transmembrane spanning proteins coupled to G proteins. There are several different types of adrenergic receptors: α-adrenergic receptors (α_1 and α_2), β-adrenergic receptors (β_1, β_2, and β_3), and dopamine receptors (D_1 and D_2). The α_1 receptors are postsynaptic and cause vasoconstriction and smooth muscle contraction, leading to an increase in blood pressure. They act via activation of Gq protein, stimulating the production of IP_3 and diacylglycerol (DAG). IP_3 increases calcium concentration, and DAG activates protein kinase C.

The α_2 receptors, in contrast, are pre- and postsynaptic. They are found in the nervous system and in smooth muscle. When the α_2 receptor is bound by a catecholamine, Gi α protein inhibits adenylate cyclase and decreases cAMP production.

The β-adrenergic receptors all act via a Gs protein to increase cAMP production, leading to protein kinase A activation and phosphorylation of various proteins. The β_1 receptor is located in cardiac tissue and increases the rate and force of myocardial contraction, leading to an increase in heart rate and cardiac output. The β_2 receptor enhances relaxation of vascular and bronchial smooth muscle.

Dopaminergic receptors are located in various tissues throughout the body, including the brain, heart, kidney, and pituitary. Activated D_1 receptors stimulate adenylate cyclase, leading to increased cAMP levels. D_2 receptors, in contrast, inhibit cAMP production.

Catecholamines are cleared from the circulation by sympathetic nerve reuptake, conjugation, and renal excretion. In addition, they are converted to inactive metabolites by the enzymes catechol-*O*-methyltransferase and monoamine oxidase (MAO).

G. Ovaries

The ovaries are retroperitoneal structures attached to the uterus via the ovarian ligaments and located near the ends of the fallopian tubes. They are derived from the primordial germ cells, which migrate from the yolk sac to enter the genital ridges at around 6 weeks' gestation. At about 20 weeks' gestation, there are about 7 million oocytes; at this point they begin the first meiotic division and become primary oocytes. They remain thus until the first ovulation occurs at puberty. The ovaries are supplied by branches of the ovarian and uterine arteries. Venous drainage is via a venous plexus called the pampiniform plexus which becomes the ovarian vein at the hilum of the ovary.

Histologically, a germinal epithelium surrounds the capsule of the ovary, which is called the tunica albuginea. The outer layer, or cortex, of the ovary contains follicles in various stages of maturity. A follicle consists of an oocyte surrounded by a cavity called an antrum. The antrum is surrounded by two layers of cells: theca cells and granulosa cells. Stromal tissue surrounds the follicles. The inner layer, or medulla, of the ovary contains blood vessels, nerves, and lymphatics.

Ovaries secrete estrogens, progesterone, and androgens. These steroids are derived from cholesterol, which is converted to pregnenolone by side chain cleavage enzyme (P450scc) and then to progesterone by 3β-hydroxysteroid dehydrogenase. Progesterone can be converted to 17-hydroxyprogesterone by 17α-hydroxylase. 17,20-Lyase then converts 17-hydroxyprogesterone to androstenedione, which is converted to testosterone by 17-hydroxysteroid dehydrogenase. Aromatase enzyme converts testosterone to estradiol and androstenedione to estrone.

Circulating ovarian hormones are bound to plasma proteins. Estradiol circulates bound mostly to sex hormone–binding globulin (SHBG) and to albumin, whereas progesterone binds primarily to corticosteroid-binding globulin (CBG) and albumin.

Estradiol can diffuse into the target cell and enter the nucleus, where it binds to an estrogen receptor. The estrogen receptor is present in two forms: α and β. The estrogen-receptor complex then binds to DNA to initiate transcription of specific proteins. Progesterone also diffuses into the cell and binds to progesterone receptors PR-A and PR-B. This hormone receptor complex can bind to specific genes and regulate their transcription.

Estrogens have multiple effects on various human tissues. They are responsible for the development of the uterus, fallopian tubes, and vagina at puberty. They cause growth of breast tissue and they stimulate development of the endometrial lining, which can lead to hyperplasia if unopposed by progestins. Estrogens also cause a growth spurt followed by closure of the epiphyses at puberty. They inhibit bone resorption and increase blood coagulability. They have various effects on plasma lipids: They increase triglycerides, increase high-density lipoprotein (HDL), and reduce total cholesterol levels.

Progesterone is important for the secretory development of the endometrium during the luteal phase of the menstrual cycle, creating conditions necessary for implantation of the embryo. It stimulates glandular growth of breast tissue and causes an increase in body temperature.

Ovarian hormones are regulated by pituitary gonadotropins. Gonadotropin-releasing hormone (GnRH) is secreted in a pulsatile fashion from the hypothalamus and stimulates the secretion of leutinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. These hormones are glycoproteins consisting of an α and β subunit. The α subunit is common to LH, FSH, TSH, and human chorionic gonadotropin (hCG), whereas the β subunit is specific to each hormone. LH receptors are located on theca and granulosa cells; this hormone stimulates the theca cells to synthesize androgens and also stimulates estrogen and progesterone secretion from the corpus luteum. FSH receptors are present only on granulosa cells. FSH stimulates these cells to synthesize aromatase, which converts the androgens to estrogens. It also increases the expression of LH receptors on granulosa cells in the late follicular phase. Estradiol exerts a negative feedback inhibition on LH and FSH.

On day one of the menstrual cycle (defined as the first day of bleeding), estrogen levels are low and FSH levels are therefore high. FSH induces maturation of an ovarian follicle, which begins to secrete estrogen, resulting in inhibition of FSH levels. Estrogen levels eventually peak; paradoxically, high estrogen levels have a stimulatory effect on LH secretion. An LH surge results, initiating the rupture of the mature follicle and resulting in ovulation. The ruptured follicle develops into the corpus luteum, a structure which secretes progesterone. The elevated estrogen and progesterone levels inhibit FSH and LH secretion, leading to degeneration of the corpus luteum in the absence of fertilization. Estrogen and progesterone levels fall; the endometrial lining is no longer maintained and sloughing occurs, reinitiating the menstrual cycle.

Estrogens are converted in the liver to estrone, estriol, and other metabolites. Estrone and estriol are conjugated, then excreted by the kidney. Progesterone is converted to pregnanediol in the liver; it also undergoes conjugation and excretion in the urine.

H. Testes

The adult testes are located in the scrotum. Spermatozoa are transported from seminiferous tubules into a ductal system called the *rete testis.* They are then conducted to the epididymis, the vas deferens, and finally to the ejaculatory ducts. The testes are supplied by the testicular arteries, which branch off of the internal spermatic arteries. Venous drainage occurs via the pampiniform plexus, a network of vessels that merges to form the internal spermatic veins.

Microscopically, the testes are surrounded by a capsule composed of the tunica vaginalis, the tunica albuginea, and the tunica vasculosa. The tunica albuginea forms septae throughout the testis. Within these septae lie the seminiferous tubules, which consist of germ cells in various stages of spermatogenesis surrounded by Sertoli cells and Leydig cells.

Leydig cells secrete testosterone and small quantities of estrogens and progesterone. Testosterone synthesis is initiated by the conversion of cholesterol to pregnenolone (see above). The androgen androstenedione is converted to testosterone via the enzyme 17-hydroxysteroid dehydrogenase. 5α-Reductase converts testosterone to dihydrotestosterone (DHT), a more potent androgen. This conversion occurs primarily in peripheral tissues.

Testosterone circulates primarily bound to sex hormone–binding globulin (SHBG) and to a lesser extent to albumin. It diffuses into the cell membrane and is most often converted to DHT. Both testosterone and DHT associate with the androgen receptor in the cytoplasm. These complexes enter the nucleus and bind to DNA, regulating synthesis of specific proteins.

Androgens are essential for differentiation of the male reproductive tract and external genitalia in the fetus and at puberty. They are responsible for the development of secondary sexual characteristics in males, such as male pattern hair growth, deep voice, and muscle growth. They are also necessary for spermatogenesis to occur.

Androgen secretion is regulated by the hypothalamus and pituitary glands. GnRH is released from the hypothalamus, stimulating release of LH and FSH. LH binds to receptors on Leydig cells, stimulating the secretion of testosterone. Both androgens and estrogens inhibit LH release. FSH binds to Sertoli cell receptors, stimulating the production of hormones necessary for spermatogenesis to occur.

Testosterone is metabolized by the liver into inactive metabolites. These are conjugated and excreted in the urine.

I. Hypothalamus and Pituitary

The hypothalamus and pituitary gland are structures that regulate the function of various endocrine organs, including the thyroid gland, the adrenal gland, the ovaries, and the testes. The hypothalamus lies at the base of the third ventricle and its inferior portion gives rise to the pituitary stalk. It develops from neuroblasts in the diencephalic walls. The pituitary gland lies near the optic chiasm in the *sella turcica,* which is a part of the sphenoid sinus. The pituitary consists of two lobes: anterior and posterior. The posterior pituitary arises from neuroectoderm and is composed of neuronal axons that originate in the supraoptic and paraventricular nuclei of the hypothalamus. The anterior pituitary originates from an evagination of the oropharynx called Rathke's pouch that migrates upward to join the posterior pituitary. It is supplied by the superior, middle, and inferior hypophyseal arteries, which are branches of the internal carotid arteries. The superior hypophyseal artery forms a capillary network in the hypothalamus; it then coalesces into portal veins which drain into the anterior pituitary. The pitutiary is drained by the cavernous sinus.

On histology, multiple cell types are evident in the pituitary gland. Corticotrophs, gonadotrophs, and thyrotrophs are basophilic cells. Corticotrophs secrete ACTH; gonadotrophs secrete LH and FSH; thyrotrophs produce TSH. Somatotrophs and lactotrophs secrete GH and prolactin, respectively, and are acidophilic. Still other cells in the pituitary are chromophobic, but their function is unknown.

The hypothalamus secretes various hormones that regulate the pituitary gland. These include growth hormone–releasing hormone (GHRH), thyrotropin-releasing hormone (TRH), GnRH, CRH, dopamine, and somatostatin. GHRH stimulates GH release from the pituitary; TRH stimulates TSH release; GnRH stimulates LH and FSH release; and CRH stimulates ACTH release. Dopamine inhibits prolactin secretion. If pituitary stalk disruption occurs, therefore, prolactin secretion increases due to release of the inhibitory effect of dopamine. Somatostatin inhibits GH and TSH secretion by reducing cAMP levels.

Anterior pituitary hormones include GH, ACTH, TSH, LH, FSH, and prolactin. GH is a polypeptide hormone important in development of linear growth. Its effects are primarily mediated by insulin-like growth factor 1 (IGF-1), a protein secreted by the liver that stimulates amino acid uptake by skeletal muscle and promotes cell proliferation. GH also antagonizes the effects of insulin by impairing cellular uptake of glucose and stimulating lipolysis. The GH receptor is a single transmembrane spanning protein that interacts with intracellular tyrosine kinases. GH release is stimulated by GHRH, hypoglycemia, and plasma amino acids and inhibited by somatostatin and IGF-1.

ACTH is a polypeptide hormone derived from the precursor molecule pro-opiomelanocortin. ACTH binds to cell membrane receptors in the adrenal cortex, activating adenylate cyclase and increasing intracellular cAMP, which results in activation of P450scc and the conversion of cholesterol to pregnenolone. ACTH is also capable of binding to the melanocyte-stimulating hormone (MSH) receptor and causing hyperpigmentation at high levels. ACTH secretion is stimulated by corticotropin-releasing hormone (CRH), hypoglycemia, surgery, and other stresses. High cortisol levels inhibit both CRH and ACTH secretion.

Thyroid hormones are regulated by TSH, a glycoprotein that consists of an α subunit and a β subunit. The α subunit has homology with FSH, LH, and hCG, whereas the β subunit is unique to each hormone. TSH stimulates the growth of thyroid cells and the synthesis and release of thyroid hormone. It binds to the TSH receptor (TSH-R) located on the thyroid follicular cell membrane and activates a G protein which activates adenylate cyclase, which in turn stimulates the production of the second messenger cAMP. It can also activate the phospholipase C pathway. TSH and TRH are both inhibited by increased serum levels of T_4 and T_3. Somatostatin, glucocorticoids, and significant nonthyroidal illness also inhibit TSH.

LH and FSH are glycoproteins consisting of an α and β subunit. FSH increases production of inhibin by testicular Sertoli cells and estrogen by ovarian granulosa cells. LH stimulates testicular Leydig cells to secrete testosterone and ovarian cells to secrete androgens, estrogens and progesterone. Gonadotropins bind to a G protein–linked seven-transmembrane spanning receptor, leading to activation of adenylate cyclase and increased cAMP levels.

Prolactin is a polypeptide hormone that stimulates lactation in the postpartum state. Its receptor has a single membrane-spanning domain and interacts with other proteins that possess tyrosine kinase activity. Dopamine inhibits its release; TRH stimulates it.

The posterior pituitary secretes two peptide hormones: oxytocin and antidiuretic hormone (ADH). Oxytocin causes smooth muscle contraction, which causes ejection of milk from the mammary ducts. There are two ADH receptors: V1 and V2. Binding to V1 receptors increases vascular smooth muscle contraction through breakdown of phosphatidylinositol. The bound V2 receptor activates a G protein, increasing cAMP levels, and regulates water balance by increasing the permeability of the collecting duct to water. ADH release is stimulated by hypovolemia and increased plasma osmolality.

II. ABNORMAL PROCESSES

A. Hypothyroidism

► Description and Symptoms

Hypothyroidism is a syndrome that results from insufficient thyroid hormone. Nonspecific symptoms may be present such as fatigue, cold intolerance, weight gain, dry skin, depression, constipation, irregular menstrual cycles, paresthesias, muscle cramps, and weakness (see Table 3–1). Untreated hypothyroidism may lead to myxedema coma, a life-threatening condition characterized by hypothermia, hypoventilation, heart failure, bradycardia, and coma. Congenital hypothyroidism is caused by prenatal thyroid hormone deficiency, and is usually asymptomatic at birth. Untreated hypothyroidism in children will lead to mental retardation and short stature.

► Diagnosis

On physical exam, there may be bradycardia and hypertension; puffy, dry skin; and coarse hair. Reflexes exhibit a delayed relaxation phase. The thyroid gland may be small, normal, or enlarged. In primary hypothyroidism, the TSH is elevated and T_4 and/or T_3 levels are low. Thyroid peroxidase antibodies are elevated in Hashimoto's thyroiditis (autoimmune thyroid disease). In secondary (or central) hypothyroidism, the TSH is normal to low and T_4 and T_3 levels are low. All neonates should be screened for congenital hypothyroidism.

► Pathology

Primary hypothyroidism is caused by thyroid gland failure due to autoimmune destruction (Hashimoto's thyroiditis), iodine deficiency, thyroidectomy, or radioactive ablation of the thyroid gland. Secondary hypothyroidism is caused by failure of the pituitary or hypothalamus.

► Treatment Steps

Levothyroxine (T_4) is administered and titrated until the TSH is in the normal range in primary hypothyroidism or until the free T_4 is in the normal range in secondary hypothyroidism.

B. Hyperthyroidism

► Description and Symptoms

Hyperthyroidism is the excess production of thyroid hormone by the thyroid gland. Occasionally, it may result from excessive thyroid hormone intake. Patients present with weight loss, palpitations, tremors, diarrhea, fatigue, nervousness, muscle weakness, and heat intolerance (see Table 3–2). A history of a recent viral syndrome and

> **► cram facts**
>
> In primary hypothyroidism, the TSH is elevated and T_4 and/or T_3 levels are low.
>
> In secondary (or central) hypothyroidism, the TSH is normal to low and T_4 and T_3 levels are low.

3-1

MAJOR SYMPTOMS AND SIGNS OF HYPOTHYROIDISM

Symptoms	
Fatigue and lethargy	Decreased perspiration
Depression	Weight gain
Sleepiness	Decreased appetite
Mental impairment	Constipation
Dry skin	Menstrual disturbances
Cold intolerance	Arthralgia
Hoarseness	Paresthesia
Signs	
Slow movements	Hyporeflexia and delayed relaxation of reflexes
Slow speech	Ascites
Hoarseness	Pleural effusions
Bradycardia	Nonpitting edema (myxedema)
Diastolic hypertension	Puffy face
Dry, coarse skin	Loss of lateral third of eyebrows
Carotenemia	Diffuse or nodular goiter

3-2

MAJOR SYMPTOMS AND SIGNS OF HYPERTHYROIDISM

Symptoms	
Nervousness	Hyperactivity
Fatigue	Palpitation
Weakness	Increased appetite
Increased perspiration	Weight loss
Heat intolerance	Menstrual disturbance
Tremor	Neck pain (subacute thyroiditis)
Signs	
Tachycardia or atrial arrhythmia	Muscle weakness
Systolic hypertension	Ophthalmopathy (Graves')
Warm, moist, smooth skin	Pretibial myxedema, acropachy (Graves')
Stare, lid lag, and eyelid retraction	Diffuse goiter (Graves'), solitary nodule, or multinodular goiter
Tremor and hyperreflexia	Thyroid tenderness (subacute thyroiditis)

neck pain are usually present in subacute thyroiditis. Untreated hyperthyroidism may lead to thyroid storm, which is a medical emergency characterized by tachycardia, fever, mental status changes, and GI symptoms.

► Diagnosis

Physical findings may include tachycardia, tremors, hyperreflexia, and proximal myopathy. Common eye findings in all hyperthyroid patients include stare and lid lag. Patients with Graves' disease (autoimmune thyroid disease) may also have proptosis and diplopia. In Graves' disease, the thyroid gland is usually enlarged and there may be pretibial myxedema (thickening of the skin of the anterior shin) and onycholysis (separation of the nail from its bed—see Figure 3–2). If the patient has a toxic adenoma, a palpable nodule may be present. In primary hyperthyroidism, the TSH will be suppressed to < 0.1 and T_4 and/or T_3 levels will be high. In central hyperthyroidism, the TSH will be normal or high and the T_4 and T_3 levels will be high. A radioactive iodine scan will demonstrate diffusely high uptake of iodine in Graves' disease, focal uptake in toxic adenoma or multinodular goiter (MNG), and low uptake in thyroiditis and exogenous thyroid hormone use.

Figure 3–2. Onycholysis, or separation of the nail from its bed.

► Pathology

Hyperthyroidism is most often caused by Graves' disease, in which activating TSH receptor antibodies result in excess thyroid hormone secretion. In toxic multinodular goiter and toxic adenoma, thyroid nodules develop autonomous function and overproduce thyroid hormone. Subacute thyroiditis is a self-limited disorder caused by an inflammatory destruction of thyroid cells leading to release of excess thyroid hormone. Excess intake of exogenous thyroid hormone may lead to thyrotoxicosis. TSH-secreting pituitary adenoma is a rare cause of thyrotoxicosis.

► Treatment Steps

1. β-Blockers are given to patients with thyrotoxicosis to control heart rate and symptoms of hyperthyroidism.
2. Patients with Graves' disease, toxic multinodular goiter, or toxic adenoma may be treated with radioactive iodine ablation, which leads to destruction of the thyroid gland. This therapy often results in permanent hypothyroidism.
3. Alternatively, patients with Graves' disease may be treated with antithyroid drugs such as propylthiouracil and methimazole, which inhibit the synthesis of thyroid hormone and result in long-term remission of thyrotoxicosis in approximately only 30% of patients. Side effects of these agents may include rash, agranulocytosis, and hepatotoxicity.
4. Surgery (thyroidectomy) is rarely indicated.

► cram facts

In primary hyperthyroidism, The TSH will be suppressed to < 0.1 and T_4 and/or T_3 levels will be high.

In central hyperthyroidism, the TSH will be normal or high and the T_4 and T_3 levels will be high.

A radioactive iodine scan will demonstrate diffusely high uptake of iodine in Graves' disease, focal uptake in toxic adenoma or MNG, and low uptake in thyroiditis and exogenous thyroid hormone use.

C. Thyroid Cancer

► Description and Symptoms

The most common types of thyroid cancer are papillary (70%), follicular (15%), medullary (5%), and anaplastic (3%). Patients may be asymptomatic or may present with a thyroid nodule discovered on exam or on a neck ultrasound. A history of progressive hoarseness, dysphagia, or dyspnea is suggestive of thyroid cancer. Risk factors include a family history of thyroid cancer and a history of head and neck radiation as a child.

► Diagnosis

Diagnosis is made by fine-needle aspiration biopsy of a thyroid nodule. Radioactive iodine scans are not helpful in the evaluation of a thyroid nodule unless the TSH is suppressed; in that case, the iodine scan can allow us to diagnose a toxic nodule (hot nodule with suppressed uptake by the rest of the gland). Toxic nodules do not warrant a biopsy because of the extremely low risk of cancer.

The most common cancer found on a thyroid biopsy is papillary carcinoma. Follicular carcinoma can be distinguished from follicular adenoma only by the presence of capsular or vascular invasion on a surgical specimen; therefore, a biopsy cannot differentiate between the two and the result is reported as "follicular neoplasm." Medullary thyroid cancer is confirmed by immunohistochemical staining for calcitonin.

► Pathology

Microscopically, papillary carcinoma consists of papillary projections of enlarged cells that often contain nuclear inclusions and powdery chromatin. Follicular cancer is characterized by small thyroid follicles with scant colloid. It is indistinguishable from follicular adenoma except for the presence of capsular or vascular invasion.

Medullary cancer is derived from parafollicular cells and appears as sheets of cells with amyloid. Anaplastic carcinoma consists of undifferentiated tumor cells.

► cram facts

The most common cancer found on a thyroid biopsy is papillary carcinoma. Follicular carcinoma can be distinguished from follicular adenoma only by the presence of capsular or vascular invasion on a surgical specimen; therefore, a biopsy cannot differentiate between the two and the result is reported as "follicular neoplasm." Medullary thyroid cancer is confirmed by immunohistochemical staining for calcitonin.

► Treatment Steps

1. Total thyroidectomy is performed on all patients with clinically significant thyroid carcinoma, followed by radioactive iodine ablation in the case of papillary and follicular cancers, in order to destroy any residual tumor cells.
2. Following radioactive iodine ablation, patients with papillary and follicular thyroid carcinomas are treated with doses of levothyroxine that cause TSH suppression.
3. Anaplastic cancer can be treated with palliative radiotherapy in addition to total thyroidectomy (mainly in order to relieve compressive symptoms). Chemotherapy has not been shown to be of much benefit.
4. Medullary carcinoma is also treated with total thyroidectomy. Palliative radiotherapy and chemotherapy may be tried in selected cases.

Papillary and follicular thyroid carcinomas usually have an excellent prognosis if discovered and treated in the early stages. Medullary thyroid cancer is more aggressive. Anaplastic thyroid cancer has a very poor prognosis in spite of treatment; death usually occurs within a year of diagnosis.

D. Euthyroid Goiter and Thyroid Nodules

► Description and Symptoms

A euthyroid (nontoxic) goiter is a diffuse enlargement of the thyroid gland not associated with hypothyroidism or hyperthyroidism. Patients who have either goiter or nodules may present with an awareness of an enlarged thyroid, or may complain of local compressive symptoms such as dyspnea, dysphasia, and hoarseness.

► Diagnosis

A thyroid goiter is diagnosed on physical exam. Palpable nodules and nodules > 1 cm on ultrasound should undergo fine-needle aspiration to exclude thyroid cancer. Every patient with a goiter or a thyroid nodule should have a TSH level to rule out hypothyroidism or hyperthyroidism.

► Pathology

Hashimoto's thyroiditis is the most common cause of thyroid goiter in the United States. Goiters can also be caused by iodine deficiency, which is rare in the United States. Genetic enzyme defects may be responsible for some euthyroid goiters.

Ninety-five percent of thyroid nodules are benign. The differential diagnosis of a benign thyroid nodule includes follicular adenoma, colloid nodule, thyroid cyst, and chronic lymphocytic thyroiditis (Hashimoto's). Follicular adenoma cannot be distinguished from follicular carcinoma on the basis of fine-needle cytology.

► cram facts

Palpable nodules and nodules > 1 cm on ultrasound should undergo fine-needle aspiration to exclude thyroid cancer.

Hashimoto's thyroiditis is the most common cause of thyroid goiter in the United States.

► Treatment Steps

Patients with benign nodules and goiters are evaluated at biannual or annual intervals for a change in symptoms or a change in the size of the nodule or goiter. Such changes require reevaluation. Thyroid nodules that are suspicious for malignancy (including follicular adenomas) must be removed. Goiters or nodules that cause compressive symptoms also require surgical resection. Thyroid hormone suppressive therapy has not been found to be significantly effective in shrinking thyroid nodules or goiter.

E. Thyroiditis

► Description and Symptoms

Thyroiditis refers to an inflammatory condition of the thyroid gland. Subtypes include granulomatous or de Quervain's thyroiditis, silent thyroiditis, postpartum thyroiditis, and acute infectious thyroiditis. Patients with de Quervain's thyroiditis characteristically present with neck pain and symptoms of hyperthyroidism following a viral illness. Silent thyroiditis results in symptoms of hyperthyroidism without neck pain. Postpartum thyroiditis is also painless and occurs within 1 year after delivery. Patients with acute thyroiditis present with a painful thyroid gland associated with fever and local redness, warmth and swelling.

The natural course of thyroiditis follows several clinical stages. Initially, patients may present with symptoms of hyperthyroidism. This stage is followed by symptoms of hypothyroidism, followed by spontaneous resolution in most cases.

► Diagnosis

Laboratory findings vary according to the clinical stage at presentation. If the patient presents in the hyperthyroid stage, TSH will be low and T_4 and/or T_3 will be elevated. Conversely, if the patient presents in the hypothyroid stage, the TSH will be elevated and the T_4 and/or T_3 will be low. The sedimentation rate is elevated in subacute thyroiditis. Antithyroid antibodies may be elevated in silent thyroiditis and postpartum thyroiditis. A 24-hour radioiodine uptake and scan is helpful in distinguishing thyroiditis from other forms of thyrotoxicosis. The iodine uptake will be very low in the hyperthyroid stage of thyroiditis. Iodine uptake will increase during the subsequent stages of thyroiditis. Acute infectious thyroiditis requires needle aspiration of the thyroid to identify the causative organism.

► cram facts

Patients with de Quervain's thyroiditis characteristically present with neck pain and symptoms of hyperthyroidism following a viral illness.

A 24-hour radioiodine uptake and scan is helpful in distinguishing thyroiditis from other forms of thyrotoxicosis. The iodine uptake will be very low in the hyperthyroid stage of thyroiditis, but high in Graves' disease and toxic nodule(s).

Patients with thyroiditis who present with symptoms of hyperthyroidism may be treated with a β-blocker. No further treatment (antithyroid drugs) is necessary in subacute, silent or postpartum thyroiditis.

► Pathology

A granulomatous inflammatory pattern is seen in patients with subacute thyroiditis. In contrast, silent thyroiditis and postpartum thyroiditis are characterized by lymphocytic infiltration of the thyroid gland. Acute infectious thyroiditis may be caused by bacterial, fungal, or protozoal infection of the thyroid gland.

► Treatment Steps

Patients with thyroiditis who present with symptoms of hyperthyroidism may be treated with a β-blocker. No further treatment is necessary in subacute, silent, or postpartum thyroiditis. Patients are followed every 4–6 weeks until resolution of thyroid function abnormalities occurs.

Infectious thyroiditis is treated with systemic antibiotics. Surgical drainage is required for abscesses.

F. Diabetes Mellitus

► Description and Symptoms

Type 1 diabetes is characterized by insulin deficiency caused by β-cell destruction. This disorder most commonly affects young patients.

Type 2 diabetes, in contrast, is the result of insulin resistance and β-cell failure, leading to hyperglycemia. This disorder is more common in older obese patients. Patients with diabetes may be asymptomatic or may present with polyuria, polydipsia, polyphagia, and weight loss. Patients may also present in diabetic ketoacidosis or hyperosmolar coma (see topics). Chronic complications of diabetes include retinopathy, neuropathy, nephropathy, and coronary artery disease (CAD), which occur over the course of years in poorly treated patients (see Table 3–3).

► Diagnosis

A fasting plasma glucose ≥ 126 mg/dL or a random blood glucose ≥ 200 mg/dL (with symptoms of hyperglycemia) on more than one occasion establishes the diagnosis of diabetes. Occasionally, a 2-hour glucose tolerance test can be used for diagnosis. In type 2 diabetes, evidence of the dysmetabolic syndrome (syndrome X) is often present. Features of this syndrome include abdominal obesity, hyperinsulinemia, increased triglycerides, decreased high-density lipoprotein (HDL) cholesterol, and hypertension.

► Pathology

Type 1 diabetes is caused by an autoimmune process in over 95% of cases. Type 2 diabetes is caused by insulin resistance, leading to increased insulin levels and progressive β-cell failure.

► Treatment Steps

The goal of therapy for all diabetics is to reduce the glycohemoglobin to < 7%. This therapy has been shown to reduce the incidence of chronic complications.

1. All patients with type 1 diabetes require insulin therapy. Available intermediate or long-acting insulins include NPH, Lente, Ultralente, and glargine. Short-acting insulins include regular insulin, and the new insulin analogues such as aspart or lispro, which are administered with meals. Insulin pumps are beneficial in selected patients with type 1 diabetes.
2. Patients with type 2 diabetes have multiple therapeutic options:
   - Metformin is an agent that inhibits hepatic gluconeogenesis, with some insulin-sensitizing effects. It can rarely lead to lactic acidosis when given to patients with renal insufficiency, cardiac

3-3

CLINICAL MANIFESTATIONS IN DIABETES

Polyuria, polydipsia, polyphagia
Unexplained weight loss
Vaginitis (usually due to monilial infection)
Intertriginous candidiasis (common in the obese) and oral candidiasis (uncommon)
Skin lesions and infections
Retinopathy (blurred vision, decreased visual acuity, visual loss)
Atherosclerotic heart disease (myocardial infarction, heart failure) and peripheral vascular disease (lower-extremity amputation); stroke
Neuropathic foot ulcers with secondary infections and diabetic Charcot's foot (degenerative change of the bony structure of the foot)
Peripheral neuropathy (sensory deficit, burning and tingling sensations)
Autonomic neuropathy (postural hypotension, gastroparesis, diarrhea, neurogenic bladder, sexual dysfunction)
Renal failure

failure, liver disease, or severe infections. Diarrhea is the most common side effect with this agent.

- Sulfonylureas (glimepiride, glipizide, glyburide) are a class of antihyperglycemic agents that stimulate the pancreas to secrete insulin. These drugs may lead to hypoglycemia, especially in older patients with borderline kidney function.
- Meglitinides (repaglinide) and nateglinide also induce insulin secretion from the pancreas. They are very short acting and must be taken with each meal. They may also cause hypoglycemia, but less than sulfonylureas.
- Thiazolidinediones (pioglitazone, rosiglitazone) are PPARγ agonists that improve tissue sensitivity to insulin. These agents can rarely cause hepatotoxicity and therefore are contraindicated in patients with hepatic disease. Liver function tests must be monitored periodically on these agents. These drugs may also result in fluid overload and should be avoided in patients with cardiac failure. Weight gain is another common side effect.
- α-Glucosidase inhibitors (acarbose and miglitol) slow the absorption of glucose by inhibiting the gastrointestinal enzymes (α-glucosidases). The main side effects are flatulence and diarrhea.
- Insulin therapy may be required in patients with type 2 diabetes who fail to achieve the glycohemoglobin goal on multiple oral agents.

Patients with diabetes require periodic screening for early kidney damage (microalbuminuria), retinopathy, and neuropathy. Cholesterol levels are also followed, and the LDL cholesterol should be maintained below 100 mg/dL.

G. Diabetic Ketoacidosis (DKA)

► Description and Symptoms

Untreated insulin deficiency leads to DKA. This disorder is characterized by hyperglycemia, ketosis, and metabolic acidosis. It is most common in patients with type 1 diabetes. Patients present with polyuria, polydipsia, generalized abdominal pain, nausea, vomiting, and mental status changes. There is usually a precipitating factor such as infection, trauma, myocardial infarction, or failure to take insulin.

► Diagnosis

On physical exam, the patient's mental status may range from lethargic to comatose. Respirations may be deep and rapid (Kussmaul's). The breath has a fruity odor caused by ketosis. Mucous membranes are dry and the abdomen is tender. Blood glucose is usually > 250 mg/dL. Serum β-hydroxybutyrate and urine ketones are elevated, the bicarbonate is low, and the anion gap is elevated. The arterial blood pH is usually < 7.35. The potassium may be normal or elevated, though there is a total body potassium depletion.

► Pathology

Insulin is required to suppress ketogenesis. When insulin is deficient, counterregulatory hormones (glucagon, epinephrine, cortisol, and growth hormone) rise, causing increased lipolysis and elevated fatty acids. The fatty acids are converted to ketone bodies and result in a metabolic acidosis. Elevated blood glucose causes an osmotic diuresis and leads to dehydration and loss of electrolytes in

► cram facts

A fasting plasma glucose ≥ 126 mg/dL or a random blood glucose ≥ 200 mg/dL (with symptoms of hyperglycemia) on more than one occasion establishes the diagnosis of diabetes.

Metformin can rarely lead to lactic acidosis when given to patients with renal insufficiency, cardiac failure, liver disease, or severe infections. Diarrhea is the most common side effect with this agent.

Sulfonylureas may lead to hypoglycemia, especially in older patients with borderline kidney function.

Thiazolidinediones are contraindicated in patients with hepatic disease. These drugs may also result in fluid overload and should be avoided in patients with cardiac failure. Weight gain is another common side effect.

► cram facts

Untreated insulin deficiency leads to diabetic ketoacidosis.

In the treatment of DKA, shock may result if insulin is given prior to normal saline (due to entry of glucose and water inside the cells, leading to more volume depletion).

The insulin infusion should be maintained until the β-hydroxybutyrate is in the normal range and the patient is able to eat.

the urine. Insulin deficiency inhibits potassium influx into cells; therefore, there is a total body potassium depletion in spite of normal serum levels.

► Treatment Steps

1. Vigorous hydration with at least 2 L of normal saline is required initially. Shock may result if insulin is given prior to normal saline (due to entry of glucose and water inside the cells, leading to more volume depletion).
2. Insulin is then initiated with a bolus of 0.1 U/kg followed by an insulin infusion at 0.1 mg/kg/hr, titrated to lower blood glucose by 75–100 mg/hr. Too rapid blood glucose lowering can cause cerebral edema. When the patient's blood glucose reaches 200–250 mg/dL, the fluids are changed to 5% dextrose in half normal saline. The insulin infusion should be maintained until the β-hydroxybutyrate is in the normal range and the patient is able to eat. Subcutaneous insulin can then be initiated prior to discontinuation of the insulin infusion.
3. Electrolytes should be monitored every 2–4 hours until stable. Potassium is supplemented in spite of normal serum levels.
4. Precipitating factors such as infections should be sought and treated.

H. Hyperosmolar Coma

► Description and Symptoms

This condition is characterized by severe hyperglycemia, hyperosmolarity, and dehydration. It is distinguished from diabetic ketoacidosis by the lack of significant ketosis or acidosis. Patients present initially with polyuria and polydipsia, followed by mental status changes ranging from lethargy to coma. There is usually a precipitating factor such as infection, myocardial infarction, stroke, or recent surgery.

► Diagnosis

There is evidence of severe dehydration on physical exam, including dry mucous membranes and orthostatic hypotension. There may be focal neurological deficits. Serum glucose is > 600 mg/dL and serum osmolarity is usually elevated to > 330 mOsm/kg. Ketosis and metabolic acidosis are usually absent or mild. Acute renal failure is often present.

► Pathology

Untreated hyperglycemia with a relative insulin deficiency initially leads to an osmotic diuresis. If there is inadequate access to fluids or if there is excessive fluid loss due to illness, severe dehydration results. Prerenal failure then follows, with reduced renal excretion of glucose and a resulting rise in serum osmolarity. It is thought that the small amount of insulin present in these patients is sufficient to prevent ketosis.

► cram facts

Hyperosmolar coma is distinguished from diabetic ketoacidosis by the lack of significant ketosis or acidosis. As in diabetic ketoacidosis, fluids should be given prior to insulin.

► Treatment Steps

1. As in diabetic ketoacidosis, fluids should be given prior to insulin. Normal saline is given initially, followed by half normal saline. The free water deficit is usually 9–12 L; half of this deficit should be replaced in the first 12 hours.
2. Insulin infusion is initiated as in diabetic ketoacidosis. When the blood glucose reaches 250 mg/dL, 5% dextrose in half normal

saline should be initiated. When the patient's mental status improves and the patient is able to tolerate oral fluid intake, subcutaneous insulin is initiated.

I. Hypoglycemia and Insulinoma

► Description and Symptoms

Hypoglycemia is defined as a low serum blood glucose associated with hypoglycemic symptoms and resolution of symptoms with normalization of blood glucose levels (Whipple's triad). The most common cause of hypoglycemia is overtreatment of diabetes mellitus with insulin or insulin secretagogues. Other causes include insulinoma, severe kidney and liver disease, and glucocorticoid or GH deficiency. Classic hypoglycemic symptoms are either adrenergic (palpitations, tremors, sweats, headaches) or neuroglycopenic (lethargy, confusion, seizures, coma).

► Diagnosis

The diagnosis of hypoglycemia is made by establishing Whipple's triad. Glucose levels are checked during symptoms of hypoglycemia. If the glucose is < 45, blood tests for insulin, C peptide, cortisol, GH, and sulfonylureas are done. Patients with insulinoma have elevated insulin and C peptide levels. In surreptitious insulin use, insulin levels will be very high and C peptide levels will be low. Patients taking sulfonylureas will have a picture similar to that of insulinoma in addition to a positive blood sulfonylurea screen.

► Pathology

Insulinomas are tumors that secrete insulin autonomously. They are benign in 90% of cases. They are usually solitary tumors, and they may be associated with multiple endocrine neoplasia type 1 (MEN-1), where the patient may have associated hyperparathyroidism and pituitary tumors as well. Patients with severe liver disease have diminished glycogen stores and reduced gluconeogenesis and may develop clinical hypoglycemia. Patients with kidney disease also have diminished gluconeogenesis as well as reduced insulin clearance. GH and cortisol are insulin counterregulatory hormones and aid in the recovery of hypoglycemia in normal patients, and the absence of these hormones may lead to inadequate resolution of hypoglycemia.

> **► cram facts**
>
> Patients with insulinoma have elevated insulin and C peptide levels. In surreptitious insulin use, insulin levels will be very high and C peptide levels will be low.
>
> Patients taking sulfonylureas will have a picture similar to that of insulinoma in addition to a positive blood sulfonylurea screen.

► Treatment Steps

Acute hypoglycemia is treated with a carbohydrate snack or with IV glucose. Severe hypoglycemia is treated with glucagon, 1 mg IM, which takes effect in about 10–15 minutes. Glucagon may cause nausea and vomiting. The treatment of insulinoma is surgical resection.

J. Hypocalcemia

► Description and Symptoms

Hypocalcemia is defined as a serum calcium that is below the range of normal. Causes include hypoparathyroidism and pseudohypoparathyroidism, vitamin D deficiency, hypomagnesemia, and renal disease. Patients often present with numbness and tingling of the extremities, and muscle cramps. Seizures and tetany may occur in severe cases (see Table 3–4).

► Diagnosis

Possible physical findings include: Chvostek's sign (facial twitch elicited by tapping below the zygomatic arch) and Trousseau's sign

3-4

CLINICAL MANIFESTATION OF HYPOCALCEMIA
Paresthesias
Chvostek's sign (twitching of the circumoral muscles in response to tapping the facial nerve, just anterior to the ear)
Trousseau's sign (carpal spasm elicited by inflation of a blood pressure cuff to 20 mm Hg above the patient's systolic pressure for 3 minutes)
Laryngospasm and bronchospasm
Dry, rough skin; coarse, brittle hair; alopecia
Abnormal dentition; cataracts
Extrapyramidal signs; pseudopapilledema
Prolonged QT interval on electrocardiogram

(hand cramps after blood pressure cuff on upper arm is inflated above systolic pressure for 3 minutes). Cardiac arrhythmias and cardiac failure occur in severe cases. The diagnosis of hypocalcemia is confirmed by a low serum calcium level. In hypoparathyroidism caused by surgery or autoimmune destruction, the phosphate will be high and PTH levels will be low. In pseudohypoparathyroidism, where there is resistance to PTH, phosphate and PTH levels will both be high. Vitamin D deficiency results in low calcium and phosphate levels, high PTH, and low 25-hydroxyvitamin D levels.

► cram facts

Possible physical findings of hypocalcemia include Chvostek's and Trousseau's signs.

In pseudohypoparathyroidism, where there is resistance to parathyroid hormone, both phosphate and PTH levels will be high. This disorder is often associated with a characteristic phenotype called Albright's hereditary osteodystrophy.

Hypomagnesemia impairs release of PTH from the parathyroid glands and causes target-organ resistance to PTH.

► Pathology

Thyroidectomy often results in hypoparathyroidism because of the proximity of the parathyroid glands to the thyroid. Hypoparathyroidism can also be caused by autoimmune destruction of the parathyroid glands. This disorder may occur as part of the type 1 polyglandular autoimmune syndrome, in which case other autoimmune diseases may be present. Hypomagnesemia impairs release of PTH from the parathyroid glands and causes target organ resistance to PTH. Patients with severe renal disease have reduced levels of 1α-hydroxylase, the enzyme that converts 25-hydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D. Pseudohypoparathyroidism results from target organ resistance to PTH. This disorder is often associated with a characteristic phenotype called Albright's hereditary osteodystrophy; phenotypic findings include short stature, shortening of the fourth and fifth metacarpals (see Figure 3–3), short digits, and a round face.

► Treatment Steps

Oral calcium is administered to maintain serum calcium levels at 8–9 mg/dL. Intravenous calcium may be required in more severe

Figure 3–3. Shortening of the fourth and fifth metacarpals in pseudohypoparathyroidism.

cases. Vitamin D is supplemented in patients with vitamin D deficiency. Patients with hypoparathyroidism and renal insufficiency will require calcitriol (1,25-dihydroxyvitamin D) supplementation. The reason for this is that PTH stimulates the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Therefore, when PTH is deficient, 1,25-dihydroxyvitamin D must be supplemented.

K. Hypercalcemia

► Description and Symptoms

Hypercalcemia is defined by a calcium level above the upper limit of normal. The main causes include hyperparathyroidism, hypercalcemia of malignancy, and vitamin D excess. Presenting symptoms may include polyuria, polydipsia, kidney stones, constipation, nausea, weakness, myalgias, and mental status changes ranging from lethargy to coma.

► Diagnosis

Total and ionized calcium levels are elevated. There may be evidence of dehydration and altered mentation on physical exam. PTH levels are elevated and phosphate levels are low in primary hyperparathyroidism. In hypercalcemia of malignancy, PTH- related peptide (PTHrp) may be elevated, and PTH is suppressed. Vitamin D excess results in elevated calcium and phosphate levels, high vitamin D levels, and low PTH levels.

► Pathology

Hyperparathyroidism is a common cause of hypercalcemia. PTH increases calcium resorption from bone as well as renal tubular reabsorption of calcium. Hyperparathyroidism is most commonly caused by a single parathyroid adenoma, but four-gland hyperplasia also occurs. There are two types of malignancy-associated hypercalcemia: humoral hypercalcemia of malignancy (HHM) and local osteolytic hypercalcemia (LOH). Squamous cell carcinomas are the most common causes of HHM. In this condition, the tumor secretes PTHrp, a protein that has structural similarity to PTH and increases bone resorption and decreases renal excretion of calcium. In LOH, osteoclast-stimulating factors are released directly onto bone. LOH occurs more commonly in breast cancer, lymphoma, and multiple myeloma.

► Treatment Steps

1. Severe hypercalcemia is treated initially with normal saline. This treatment serves to rehydrate the patient and to increase the urinary excretion of calcium.
2. After the patient is sufficiently hydrated, diuretics (furosemide) may be administered in order to increase the renal excretion of calcium.
3. Bisphosphonates such as intravenous pamidronate effectively reduce calcium levels by inhibition of bone resorption. However, the effect may be delayed up to 2 days. The duration of action of pamidronate is 2–8 weeks.
4. Calcitonin also inhibits bone resorption. Its onset of action is more rapid than that of the bisphosphonates; it usually lowers calcium levels within 2–4 hours and lasts 2–3 days. However, tachyphylaxis usually develops.

► cram facts

PTH levels are elevated and phosphate levels are low in primary hyperparathyroidism.

In hypercalcemia of malignancy, PTH-related peptide (PTHrp) may be elevated, and PTH is suppressed.

Vitamin D excess results in elevated calcium and phosphate levels, high vitamin D levels, and low PTH levels.

L. Hyperparathyroidism

► Description and Symptoms

There are three types of hyperparathyroidism: primary, secondary, and tertiary. Primary hyperparathyroidism is caused by excess PTH release from the parathyroid glands. Secondary hyperparathyroidism is characterized by elevated PTH levels in response to hypocalcemia, hyperphosphatemia, or vitamin D deficiency. In tertiary hyperparathyroidism, usually seen in patients with long-standing renal insufficiency, prolonged hypocalcemia leads to autonomous secretion of PTH from the parathyroid glands. Patients with hyperparathyroidism may be asymptomatic or may present with symptoms of hypercalcemia (see section II.K).

► Diagnosis

In primary hyperparathyroidism, PTH is normal to high, with high calcium and low phosphate levels. Bone mineral density may reveal osteopenia or osteoporosis. Renal calcification or nephrolithiasis may be seen on abdominal films. In secondary hyperparathyroidism, PTH is also elevated, but calcium levels are normal to low and phosphate levels may be low, normal, or high. Vitamin D levels may also be low.

PTH levels may be markedly elevated in tertiary hyperparathyroidism, and hypercalcemia is present.

► Pathology

- Primary hyperparathyroidism is most often caused by a single parathyroid adenoma.
- Four-gland parathyroid hyperplasia is seen more commonly in familial syndromes such as MEN.

► Treatment Steps

- Patients with primary hyperparathyroidism who have no associated complications may be followed with serial calcium levels.
- The definitive treatment for primary hyperparathyroidism is removal of the parathyroid adenoma. If the patient has hyperplasia of all four glands, 3½ glands are removed.
- In secondary hyperparathyroidism, the underlying cause must be sought and treated (e.g., vitamin D deficiency).
- In tertiary hyperparathyroidism with hypercalcemia, 3½ parathyroid glands are surgically removed.

► cram facts

In primary hyperparathyroidism, PTH is normal to high with high calcium and low phosphate levels.

In secondary hyperparathyroidism, PTH is also elevated, but calcium levels are normal to low and phosphate levels may be low, normal, or high.

PTH levels are markedly elevated in tertiary hyperparathyroidism, and hypercalcemia is present.

Primary hyperparathyroidism is most often caused by a single parathyroid adenoma. Four-gland parathyroid hyperplasia is seen more commonly in familial syndromes such as multiple endocrine neoplasia.

M. Osteomalacia/Rickets

► Description and Symptoms

Osteomalacia refers to a defect in the mineralization of bone matrix. The primary cause of this disorder is a deficiency of vitamin D or a defect in its metabolism. Osteomalacia occurs in adult bone, whereas rickets occurs in growing bone. Children with rickets present with weakness, hypotonia, poor growth, and occasionally with fractures. They may display bone deformities such as bowing of the tibia and fibula, "rachitic rosary" (thickening of the costochondral junctions), and swelling at the ends of long bones. Adults with osteomalacia may be asymptomatic or may present with bone pain and proximal muscle weakness.

► Diagnosis

Patients with vitamin D deficiency will have low 25-hydroxyvitamin D levels, low calcium and phosphate levels, and elevated PTH levels.

Radiologic findings of osteomalacia and rickets include osteopenia, pseudofractures (Looser zones or Milkman fractures), widening of the epiphyses, and subperiosteal resorption in the phalanges.

► Pathology

Vitamin D promotes osteoblastic formation and mineralization of the bone matrix. In its absence, these processes do not adequately occur. Vitamin D also promotes the gastrointestinal reabsorption of calcium and phosphate, and both these minerals are deficient in vitamin D deficiency. Phosphate deficiency syndromes also lead to osteomalacia.

► Treatment Steps

Patients with vitamin D deficiency are treated with high doses of vitamin D for several months, followed by maintenance doses of 400–800 IU/day. If the patient has malabsorption, higher doses may be required. Calcium is also supplemented at 1,000–3,000 mg/day.

► cram facts

Osteomalacia occurs in adult bone, whereas rickets occurs in growing bone.

Patients with vitamin D deficiency will have low 25-hydroxyvitamin D levels, low calcium and phosphate levels, and elevated PTH levels.

N. Osteoporosis

► Description and Symptoms

Low bone mass with microarchitectural disruption and low-trauma fractures characterize osteoporosis. This condition occurs most commonly in postmenopausal women. Other risk factors include glucocorticoid use, excess thyroid hormone intake, tobacco or alcohol use, family history, and small body habitus. A patient with osteoporosis is asymptomatic until a fracture occurs. Vertebral compression fractures are the most common type of osteoporotic fracture, and may be painful or asymptomatic, and may result in height loss and kyphosis. The wrist and hip are also common sites for osteoporotic fracture.

► Diagnosis

The diagnosis of osteoporosis is established using dual-energy x-ray absorptiometry (DEXA). The bone density reading obtained is compared to the bone density of a 30-year-old normal subject. A "T-score" refers to the number of standard deviations from the bone mass of a 30-year-old subject. A T-score of < −2.5 establishes the diagnosis of osteoporosis, while a T-score between −1 and −2.5 indicates osteopenia. A "Z-score" is the number of standard deviations from the bone mass of age-matched subjects. This number is not used in the diagnosis of osteoporosis.

► Pathology

Osteoporosis commonly occurs in postmenopausal women when levels of estrogen decline. Estrogen inhibits osteoblast-mediated osteoclastic proliferation, primarily by inhibiting interleukin-6 (IL-6) production by osteoblasts. Chronic glucocorticoid excess (such as exogenous steroid intake or Cushing's syndrome) causes osteoporosis by inhibiting bone formation and stimulating bone resorption. Other causes of osteoporosis include hyperparathyroidism, hyperthyroidism, hypogonadism, multiple myeloma, renal failure, liver failure, and malabsorption.

► cram facts

A T-score of < −2.5 establishes the diagnosis of osteoporosis, while a T-score between −1 and −2.5 indicates osteopenia.

Bisphosphonates such as alendronate and risedronate may cause esophagitis and esophageal ulceration and must be taken on an empty stomach with water.

► Treatment Steps

1. Calcium (1,000–1,500 mg/day) and vitamin D (400–800 IU/day) should be initiated in all patients.
2. Bisphosphonates such as alendronate and risedronate inhibit bone resorption and are effective in reducing the risk of osteo-

porotic fracture by up to 50%. These drugs may cause esophagitis and esophageal ulceration and must be taken on an empty stomach with water.

3. Estrogen also inhibits bone resorption and improves bone density but is controversial in the treatment of osteoporosis due to its effects on other organ systems.
4. Selective estrogen receptor modulators such as raloxifene also reduce osteoclastic bone resorption. Raloxifene has been shown to reduce the risk of vertebral fractures in postmenopausal women.
5. Patients on therapy should be monitored every 1–2 years with DEXA scans.

O. Obesity

► Description and Symptoms

Obesity is defined as a body mass index (BMI = kg/m^2) ≥ 30. It is a condition that is associated with many adverse health consequences, including diabetes, hypertension, high cholesterol, arthritis, obstructive sleep apnea, coronary artery disease (CAD), gallstones, and certain neoplasms such as endometrial cancer.

► Diagnosis

Overweight is defined by a BMI ≥ 25, obesity by a BMI ≥ 30, and morbid obesity by a BMI ≥ 40.

► Pathology

The causes of obesity are poorly understood. Leptin is a hormone that is secreted by adipose tissue and is involved in regulation of satiety and energy expenditure. Leptin deficiency is rarely a cause of obesity; however, leptin resistance has been demonstrated in obese patients. Other hormonal associations with obesity are under investigation.

► cram facts

Obesity is defined as a body mass index (BMI = kg/m^2) > 30.

Sibutramine is a serotonin and norepinephrine uptake inhibitor that leads to appetite suppression. Side effects may include blood pressure elevation.

Orlistat inhibits pancreatic lipase, an enzyme responsible for fat absorption in the GI tract. It is not systemically absorbed, but it often causes bloating and diarrhea, limiting its tolerability.

► Treatment Steps

Caloric intake restriction and aerobic exercise are the mainstays of treatment. When these methods are unsuccessful, pharmacological therapy may be required. There are three agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of obesity. Sibutramine is a serotonin and norepinephrine uptake inhibitor and leads to appetite suppression. It may result in an 8–10% weight loss. Side effects may include headaches, palpitations, and blood pressure elevation. Orlistat inhibits pancreatic lipase, an enzyme responsible for fat absorption in the GI tract. Average weight loss seen with this agent is 7–8%. It is not systemically absorbed, but it often causes bloating and diarrhea, limiting its tolerability. Phentermine is a sympathomimetic agent approved only for short-term treatment of obesity. Gastric surgery such as gastric bypass or gastric banding is indicated in patients who have a BMI > 40 or a BMI > 37 with associated obesity-related morbidity.

P. Cushing's Syndrome

► Description and Symptoms

Cushing's syndrome is a complex of symptoms and signs caused by excess cortisol. The most common cause of this syndrome is excess glucocorticoid intake. The most common cause of endogenous cortisol excess is Cushing's *disease*, which refers to an ACTH-secreting pituitary adenoma. Other causes include hyperfunctioning adrenal adenomas, adrenal carcinomas, and ectopic ACTH-secreting tumors. Symptoms and signs may be subtle and include weight gain with truncal obesity, hypertension, diabetes mellitus, abdominal striae (see Figure 3–4), thin skin, easy bruising, dorsocervical and supraclavicular fat pads, and depression (see Table 3–5).

► cram facts

The most common cause of Cushing's syndrome is excess glucocorticoid intake. The most common cause of endogenous cortisol excess is Cushing's disease, which refers to an ACTH-secreting pituitary adenoma.

There are two screening tests for the diagnosis of Cushing's syndrome: 24-hour urine free cortisol and 1-mg overnight dexamethasone suppression test. An abnormal 1-mg test needs to be confirmed by a 24-hour urine free cortisol. If the 24-hour urine free cortisol is diagnostic of Cushing's, the next step is to obtain an ACTH level.

► Diagnosis

There are two screening tests for the diagnosis of Cushing's syndrome: 24-hour urine free cortisol and 1-mg overnight dexa-methasone suppression test. The 24-hour urine is abnormal if the cortisol level is more than three times the upper limit of normal, whereas the 1-mg overnight dexamethasone suppression test is abnormal if the morning cortisol is not suppressed to < 3 μg/dL after 1 mg dexamethasone the night before. The 1-mg test carries some false positives (in the case of depression, alcoholism, and severe obesity); therefore, an abnormal 1-mg test needs to be confirmed by a 24-hour urine free cortisol. If the 24-hour urine free cortisol is diagnostic of Cushing's, the next step is to obtain an ACTH level. If the ACTH is low, the source of excess cortisol is either an adrenal adenoma or adrenal carcinoma. If the ACTH is normal or high, then the differential diagnosis includes an ACTH-secreting pituitary adenoma or an ectopic ACTH-secreting tumor. To distinguish between the latter two disorders, a high-dose dexamethasone suppression test may be performed. If the cortisol level is suppressed after this test, the likely source is a pituitary adenoma. A magnetic resonance imaging (MRI) scan of the pituitary is then obtained. If the cortisol is not suppressed, there is most likely an ectopic source of ACTH secre-

Figure 3–4. Abdominal striae seen in Cushing's syndrome.

3-5

SYMPTOMS AND SIGNS OF CUSHING'S SYNDROME

Symptom or Sign
Centripetal obesity; facial plethora
Weakness, proximal myopathy
Hypertension
Psychological changes
Easy bruisability; striae; hyperpigmentation; acne, oily skin; hirsutism
Oligomenorrhea or amenorrhea; impotence
Ankle edema
Backache, vertebral collapse, fracture
Polydipsia, polyuria
Renal calculi
Headache
Glucose intolerance

tion. Further imaging (e.g., computed tomography [CT]/MRI of the chest) is then required to find the tumor.

► Pathology

ACTH-secreting pituitary tumors are almost always benign. The most common causes of ectopic ACTH are carcinoid tumors and small-cell lung cancers. Other causes include tumors of the pancreatic islets and medullary thyroid cancer.

► Treatment Steps

If a patient has a pituitary adenoma, it must be surgically removed. If the blood work suggests a pituitary adenoma but no adenoma is identified on imaging, inferior petrosal vein sampling is indicated to localize the tumor. Adrenal adenomas and carcinomas are also surgically removed. The source of ectopic ACTH secretion is often difficult to find, or the tumor may not be surgically resectable due to extensive disease. In this case, bilateral adrenalectomy may be indicated.

Q. Adrenocortical Insufficiency

► Description and Symptoms

Adrenocortical insufficiency refers to an absence or a deficiency of cortisol. This condition may be primary (Addison's disease) in the case of direct adrenal damage, or secondary in pituitary or hypothalamic dysfunction. The most common cause of this syndrome is secondary adrenal insufficiency resulting from chronic glucocorticoid use and withdrawal. The most common cause of primary adrenal insufficiency in the United States is autoimmune adrenalitis; worldwide, it is tuberculosis. The presentation of adrenal insufficiency includes symptoms of fatigue, weight loss, orthostatic dizziness, nausea, diarrhea, and abdominal pain. Patients with primary adrenal insufficiency may have hyperpigmentation due to ACTH excess (see Figure 3–5). If a patient undergoes an acute stress such as infection or trauma, shock may occur (see Table 3–6).

► Diagnosis

Adrenal insufficiency should be suspected in anyone presenting with shock of unknown cause. Sodium levels classically are low. Potassium levels are elevated in primary adrenal insufficiency due to concurrent aldosterone deficiency. A corticotropin stimulation test is the diagnostic study of choice. Baseline cortisol levels are drawn, then

Figure 3–5. Hyperpigmentation due to ACTH excess. On the right is a hyperpigmented hand of a patient with Addison's disease; on the left is the hand of the patient's mother, who has normal adrenals.

250 μg of corticotropin is administered IV or IM. Another cortisol level is obtained 30–60 minutes later. If this level is < 18–20 μg/dL, the patient has adrenal insufficiency. An ACTH is then obtained. If this level is high, it indicates primary adrenal insufficiency. A CT of the abdomen is then done to rule out hemorrhage or metastatic infiltration of the adrenals.

If the ACTH is low or normal, the patient has secondary adrenal insufficiency. Pituitary function tests as well as an MRI of the pituitary are then obtained to assess pituitary morphology and function.

► Pathology

Patients who chronically take glucocorticoids may exhibit signs and symptoms of adrenal insufficiency when the dose is reduced. This occurs because of ACTH suppression and adrenal atrophy. This condition may take many months to resolve. Other causes of secondary adrenal insufficiency include pituitary tumors compressing or infiltrating the ACTH-secreting cells.

Autoimmune destruction of the adrenal glands may be an isolated condition or may occur in association with polyglandular autoimmune syndromes type 1 or 2, in which case other autoimmune conditions will be present.

Other causes of primary adrenal insufficiency include hemorrhage, various infections, and infiltration (e.g., metastases) of both glands.

► Treatment Steps

Acute adrenal insufficiency is a medical emergency that must be treated immediately with stress-dose glucocorticoids (e.g., hydrocorti-

3-6

CLINICAL MANIFESTATIONS OF ADRENAL INSUFFICIENCY

Tiredness and weakness
Anorexia and weight loss
Nausea, vomiting, and diarrhea
Myalgias and arthralgias
Psychiatric manifestations
Hypotension
Hypoglycemia
Hyponatremia, hyperkalemia, and acidosis
Mild normocytic anemia; lymphocytosis, eosinophilia
Hyperpigmentation
Decreased axillary and pubic hair
Loss of libido; amenorrhea
Associated autoimmune disorders (e.g., vitiligo, Hashimoto's)

► cram facts

The most common cause of this syndrome is secondary adrenal insufficiency resulting from chronic glucocorticoid use and withdrawal. The most common cause of primary adrenal insufficiency in the United States is autoimmune adrenalitis.

A corticotropin stimulation test is the study of choice to diagnose adrenal insufficiency.

Acute adrenal insufficiency is a medical emergency that must be treated immediately with stress-dose glucocorticoids (e.g., hydrocortisone 100 mg every 8 hours) and aggressive volume replacement using normal saline.

Patients who have primary adrenal insufficiency will also have aldosterone deficiency and will therefore require replacement of this hormone in the form of fludrocortisone.

sone 100 mg every 8 hours) and aggressive volume replacement using normal saline. Chronic adrenal insufficiency is treated with maintenance-dose steroids, such as prednisone 5 mg/day or hydrocortisone 20–30 mg in divided doses. The steroid dose should be doubled or tripled if the patient develops an acute illness; stress doses should be given if the patient undergoes major surgery or if the patient becomes critically ill. Patients who have primary adrenal insufficiency will also have aldosterone deficiency and will therefore require replacement of this hormone in the form of fludrocortisone.

R. Primary Hyperaldosteronism

► Description and Symptoms

Primary hyperaldosteronism refers to autonomous secretion of aldosterone by the adrenal cortex. It is distinguished from secondary aldosteronism by the lack of renin excess. Primary hyperaldosteronism may be caused by either an autonomous aldosterone-secreting adenoma or by bilateral adrenal hyperplasia. Patients present with hypertension, which is often resistant to multiple drug therapies. Spontaneous hypokalemia is also present and may cause symptoms such as muscle weakness and cramps, paresthesias, palpitations, polyuria, and polydipsia.

► cram facts

Primary hyperaldosteronism refers to the autonomous secretion of aldosterone by the adrenal cortex. It is distinguished from secondary aldosteronism by the lack of renin excess.

A useful screening test for primary hyperaldosteronism is a plasma aldosterone-to-plasma renin ratio. If this ratio is > 20, further tests should be done.

The definitive treatment for a unilateral aldosterone-secreting adenoma is surgical resection.

In the case of bilateral adrenal hyperplasia, surgical resection is not effective and the patient must be managed medically with potassium supplements and antihypertensives such as spironolactone or eplerenone.

► Diagnosis

A useful screening test for primary hyperaldosteronism is a plasma aldosterone-to-plasma renin ratio. If this ratio is > 20, further tests should be done. A 24-hour urine aldosterone collected while on a high-sodium diet is another diagnostic test. A 24-hour urine aldosterone > 12–14 μg indicates primary hyperaldosteronism. Once hyperaldosteronism is documented, a CT of the adrenal glands is done. If an adrenal nodule > 1 cm appears on CT, surgical resection is indicated. If there are no nodules of this size in either gland, adrenal vein sampling must be performed. For this study, catheters are inserted into both adrenal veins and aldosterone levels in each vein are measured and compared. If the patient has a unilateral aldosterone-producing adenoma, the aldosterone level will be higher on the side of the affected adrenal gland. If the patient has bilateral adrenal hyperplasia, the aldosterone levels will be almost the same on both sides.

► Pathology

Excess aldosterone levels result in sodium and water retention and plasma expansion, leading to hypertension. Aldosterone increases renal excretion of potassium and thus can lead to hypokalemia.

► Treatment Steps

The definitive treatment for a unilateral aldosterone-secreting adenoma is surgical resection. Hypokalemia usually resolves, and hypertension improves or resolves after removal of the adenoma. In the case of bilateral adrenal hyperplasia, surgical resection is not effective and the patient must be managed medically with potassium supplements and antihypertensives such as spironolactone or eplerenone.

S. Congenital Adrenal Hyperplasia (CAH)

► Description and Symptoms

CAH is a group of autosomal recessive syndromes of adrenal enzyme deficiency. The most common cause is 21α-hydroxylase deficiency. Deficiencies can also occur in the enzymes 11β-hydroxylase, 17α-hydroxylase, and 3β-hydroxysteroid dehydrogenase (see Figure 3–1). Symptoms will depend on the enzyme deficiency involved. 21α-Hydroxylase deficiency may be congenital or adult onset, partial or complete. Findings may include ambiguous genitalia or later-onset virilization in females. Salt wasting and adrenal crisis may also occur. In 11β-hydroxylase deficiency, females have ambiguous genitalia at birth; hypertension is also present. 3β-Hydroxysteroid dehydrogenase deficiency and 17α-hydroxylase deficiency cause ambiguous genitalia in male infants. 3β-Hydroxysteroid dehydrogenase deficiency is also associated with salt wasting; 17α-hydroxylase deficiency causes hypertension.

► Diagnosis

1. Plasma levels of 17-hydroxyprogesterone will be elevated in patients with 21α-hydroxylase deficiency. ACTH and adrenal androgen levels will also be elevated. In the salt-losing variant, hyponatremia and hyperkalemia will occur.
2. In 11β-hydroxylase deficiency, plasma levels of 11-deoxycorticosterone and 11-deoxycortisol will be elevated in addition to ACTH and adrenal androgens.
3. In 3β-hydroxysteroid dehydrogenase deficiency, levels of pregnenolone and 17-hydroxypregnenolone will be increased. DHEA and DHEAS will also be increased.
4. 17α-Hydroxylase deficiency is diagnosed by demonstrating elevated plasma levels of progesterone, pregnenolone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone.

► Pathology

Adrenal enzyme deficiencies result in an increase in ACTH secretion from the pituitary gland because of loss of negative feedback inhibition. Elevated ACTH levels cause hyperplasia of the adrenal glands. In certain enzyme deficiencies, precursor hormones accumulate and are diverted to alternate enzyme pathways, resulting in elevated adrenal androgens such as DHEA, DHEAS, and androstenedione. This androgen excess is responsible for ambiguous genitalia in female newborns but does not affect male infants. Excess levels of 11-deoxycorticosterone that occur in 11β-hydroxylase and 17α-hydroxylase deficiencies cause hypertension because this enzyme has mineralocorticoid properties.

► Treatment Steps

Adrenal crisis in the newborn period is treated with glucocorticoids and mineralocorticoids.

Chronic treatment consists of glucocorticoid treatment in the form of hydrocortisone or prednisone. This therapy replaces deficient cortisol and inhibits ACTH secretion, thereby diminishing adrenal androgen production. Mineralocorticoid replacement is necessary in patients with the salt-wasting varieties of CAH. Plastic surgery can be performed on children with ambiguous genitalia.

► cram facts

The most common cause of CAH is 21α-hydroxylase deficiency.

Plasma levels of 17-hydroxyprogesterone will be elevated in patients with 21α-hydroxylase deficiency. ACTH and adrenal androgen levels will also be elevated. In the salt-losing variant, hyponatremia and hyperkalemia will occur.

T. Pheochromocytoma

► Description and Symptoms

A pheochromocytoma is a tumor of the adrenal medullary cells that secretes epinephrine, norepinephrine, and dopamine. Patients present with episodes (“spells”) that classically consist of headache, palpitations, and perspiration. Other symptoms include pallor, ortho-

► cram facts

The classic test is a 24-hour urine for catecholamines and metanephrines. A newer test, the plasma free metanephrines, is now the test of choice but can lead to many false positives.

Ten percent of pheochromocytomas are extra-adrenal (paragangliomas); however, the majority of these are intra-abdominal.

Preoperative preparation is of the utmost importance to prevent serious perioperative complications such as arrhythmias and hypertensive crisis. Patients are treated with an α-adrenergic blocker (e.g., phenoxybenzamine) for about 2 weeks until the patient is normotensive and symptoms are controlled.

β-Blockers must not be given prior to α-blockers because unopposed α-receptor activation will result, with worsening of hypertension.

static dizziness, and anxiety. Hypertension is present in over 90% of cases and may be paroxysmal or sustained.

► Diagnosis

The diagnosis of pheochromocytoma is established by demonstrating elevated levels of catecholamines and their metabolites in the urine or plasma. The test of choice is a 24-hour urine for catecholamines and metanephrines. A CT scan of the abdomen should reveal an adrenal mass 90% of the time. Ten percent of pheochromocytomas are extra-adrenal; however, the majority of these are intra-abdominal. M-I^{131} iodobenzylguanidine (MIBG) can be used in scintigraphy because it is concentrated in sympathomedullary tissue and is 100% specific for pheochromocytoma; however, it lacks sufficient sensitivity (78%) to be used as a screening test.

► Pathology

Pheochromocytomas follow a "rule of 10s": 10% are extra-adrenal, 10% are bilateral, 10% are familial, 10% are malignant, and 10% can recur after resection. Histologically, benign tumors are not distinguishable from malignant tumors except for the presence of significant local infiltration or metastases. Familial associations of pheochromocytoma include MEN-2a and -2b, von Hippel–Lindau, and type I neurofibromatosis.

► Treatment Steps

Surgical resection is the definitive treatment for pheochromocytoma. Preoperative preparation is of the utmost importance to prevent serious perioperative complications such as arrhythmias and hypertensive crisis. Patients are treated with an α-adrenergic blocker (e.g., phenoxybenzamine) for about 2 weeks until the patient is normotensive and symptoms are controlled. β Blockade may be instituted if significant tachycardia is present. However, β-blockers must not be given prior to α-blockers because unopposed α-receptor activation will result, with worsening of hypertension.

U. Hypopituitarism

► Description and Symptoms

Hypopituitarism refers to a deficiency or absence of one or more pituitary hormones. It may be caused by pituitary destruction or by hypothalamic dysfunction. Symptoms are varied and depend on the hormone deficiency. ACTH deficiency causes adrenal insufficiency and symptoms of weakness, weight loss, dizziness, nausea, and vomiting.

Hypotension and hypernatremia may be present, but hyperkalemia is not a feature of secondary adrenal insufficiency because aldosterone is not deficient in this condition. Gonadotropin deficiency causes oligomenorrhea or amenorrhea in women and decreased libido and erectile dysfunction in males. GH deficiency causes growth delay in children. TSH deficiency results in hypothyroid symptoms, such as weight gain, fatigue, cold intolerance, and menstrual irregularities. There are no symptoms of prolactin insufficiency. If a tumor or hemorrhage is present, the patient may complain of a headache or vision changes, such as visual field deficits or diplopia.

► Diagnosis

If hypopituitarism is suspected, pituitary hormone levels should be measured. These include ACTH, cortisol, TSH, and free T_4, and in males FSH, LH, and testosterone. An MRI of the pituitary is required to identify any tumor, hemorrhage, or other pituitary abnormality that may be present.

► Pathology

Causes of hypopituitarism include tumors (e.g., pituitary adenomas, craniopharyngiomas, and metastases), infarction (Sheehan's syndrome, pituitary apoplexy), trauma, infiltrative processes (e.g., sarcoid, hemochromatosis), and idiopathic causes. GH and gonadotropins are usually the first hormones to be affected, followed by TSH, ACTH, and prolactin.

► Treatment Steps

Treatment depends on the cause of the hypopituitarism and on the hormone deficiencies present. If the MRI reveals a large tumor in the area of the pituitary gland, surgical resection is indicated. In pituitary apoplexy, surgical decompression of the pituitary is usually necessary. ACTH deficiency is treated with hydrocortisone or prednisone, as discussed previously. TSH deficiency is treated with levothyroxine (T_4), which is titrated to keep the serum free T_4 in the normal range. Gonadotropin deficiency may be treated with oral contraceptives or hormone replacement therapy in women, and with testosterone in men. GH treatment is controversial at this time in adults; in children, GH injections must be given to prevent or arrest growth retardation.

► cram facts

Hyperkalemia is not a feature of secondary adrenal insufficiency because aldosterone is not deficient in this condition.

If a tumor or hemorrhage is present, the patient may complain of a headache or vision changes, such as visual field deficits or diplopia.

V. Prolactinoma

► Description and Symptoms

Prolactinomas are pituitary adenomas that secrete excess prolactin. Macroprolactinomas refer to tumors > 1 cm in diameter; microprolactinomas are < 1 cm in diameter. Patients with prolactinomas may present with galactorrhea, headaches, and vision changes. Women may have oligomenorrhea or amenorrhea and infertility, whereas men may have impaired libido or erectile dysfunction.

► Diagnosis

An elevated prolactin level establishes the diagnosis of hyperprolactinemia. The differential diagnosis of an elevated prolactin also includes pregnancy, primary hypothyroidism, renal failure, antipsychotic drug therapy, and other tumors that cause pituitary stalk compression. An MRI of the pituitary is obtained if prolactin levels are high. The increase in prolactin level corresponds to the size of the pituitary tumor; tumors > 1 cm are usually accompanied by prolactin levels > 200 ng/mL.

► Pathology

Prolactin stimulates lactation in the postpartum state. Hyperprolactinemia leads to hypogonadism by altering the pulsatile secretion of LH and FSH. Other than prolactinomas, tumors that compress the pituitary stalk may also lead to high prolactin levels. Stalk compression suppresses the inhibitory effect of dopamine release; dopamine inhibits prolactin release; therefore, prolactin levels will rise. However, the elevation in prolactin seen in this condition will be less than that seen in prolactinomas.

► cram facts

The increase in prolactin level correlates with the size of the pituitary tumor; tumors > 1 cm are usually accompanied by prolactin levels > 200 ng/mL.

The initial treatment for prolactinomas is medical therapy with dopamine agonists.

► Treatment Steps

The initial treatment for prolactinomas is medical therapy with dopamine agonists. Bromocriptine and cabergoline are the most commonly used agents. These drugs bind to D2 receptors on the cell membranes of prolactin-secreting cells and inhibit activation of cAMP. This leads to a decrease in prolactin secretion. Both drugs are effective in reducing prolactin levels and reducing tumor size. They may cause nausea and dizziness. Rarely, pituitary surgery is required in cases of drug failure or drug intolerance.

Y. Acromegaly/Gigantism

► Description and Symptoms

Acromegaly is caused by excess growth hormone secretion in adults. The clinical features of acromegaly include hypertrophy of soft tissue and cartilage, enlarged hands and feet, enlargement of mandibular and maxillary bones, frontal bossing, cardiac hypertrophy, skin tags, colon polyps, and diabetes mellitus, but no linear growth. Gigantism occurs with excess GH secretion in children. In contrast to adults with acromegaly, children with gigantism display accelerated linear growth because their epiphyses have not yet closed (see Table 3–7).

► Diagnosis

The best screening test for acromegaly is an insulin-like growth factor type 1 (IGF-1) level. This hormone is secreted predominantly by the liver in response to GH. The serum IGF-1 is very specific for acromegaly in nonpregnant adults. If the IGF-1 is normal but clinical suspicion is high, a glucose suppression test is performed. This test is based on the inhibition of GH by glucose in normal patients and the absence of inhibition in patients with acromegaly. Following biochemical confirmation of GH excess, an MRI of the brain is obtained to look for a pituitary tumor.

► cram facts

The best screening test for acromegaly is IGF-1 level.

The treatment of acromegaly is transsphenoidal removal of the pituitary tumor.

If surgery is not effective, octreotide, a somatostatin analogue, may be administered.

► Pathology

Acromegaly and gigantism are almost always caused by excess GH-secreting pituitary adenomas. Rarely, it may be caused by ectopic GHRH secretion. Most of the clinical effects of acromegaly are caused by excess IGF-1 effects on bone, cartilage, and soft tissue.

► Treatment Steps

1. The treatment of acromegaly and gigantism is transsphenoidal removal of the pituitary tumor. Surgery is effective in reducing GH levels in about 70% of patients, but only 50% of patients who have tumors > 1 cm.
2. If surgery is not effective, octreotide, a somatostatin analogue, may be administered. Octreotide suppresses GH secretion by the pituitary. It is available as a monthly injection. Side effects may include gallstones and other GI symptoms such as diarrhea.

3-7

CLINICAL MANIFESTATIONS OF ACROMEGALY
Acral overgrowth (enlarged hands and feet); skin tags
Macrognathia, enlargement of nose and frontal bones
Macroglossia; malocclusion
Deepening of the voice; excessive sweating
Arthralgias; carpal tunnel syndrome
Sleep apnea; hypertension
Cardiomyopathy, left ventricular hypertrophy, arrhythmias
Amenorrhea in females, impotence and loss of libido in males
Osteoporosis (if hypogonadism present)
Increased risk of colonic polyps and gastrointestinal malignancies
Glucose intolerance; hyperphosphatemia

3. Radiation therapy may be necessary to control GH levels. However, this treatment may take 5–10 years to be effective. In addition, hypopituitarism is a common consequence of radiotherapy to the pituitary gland.

X. Diabetes Insipidus (DI)

► Description and Symptoms

DI is characterized by an insufficiency of ADH or a defect in its action resulting in an inability to concentrate the urine. Causes of this syndrome include central DI, which is a defect in ADH secretion by the cells in the posterior pituitary; and nephrogenic DI, where the kidney is resistant to the effects of ADH. Primary polydipsia is caused by disorders in thirst regulation or by psychogenic disorders. The presenting symptoms are polyuria, nocturia, and polydipsia.

► Diagnosis

A urinalysis will show a specific gravity of < 1.005. Serum osmolality may be elevated in DI depending on the hydration status, whereas urine osmolality will be inappropriately low. If the patient has inadequate access to water, the serum sodium will be elevated. Patients wih primary polydipsia, in contrast, will have both dilute plasma and dilute urine.

A water deprivation test is often necessary to confirm the diagnosis of DI. For this test, the patient avoids drinking water until urine osmolality plateaus. Patients with complete diabetes insipidus will continue to have a high urine output and a low urine osmolality. In contrast, urine osmolality will rise to levels greater than plasma osmolality in patients with primary polydipsia.

If diabetes insipidus is diagnosed, ADH is then given as an injection to distinguish central from nephrogenic DI. If the urine olsmolality rises to > 50%, the patient has central DI. If it remains stable, the patient has nephrogenic DI.

> **► cram facts**
>
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> If DI is diagnosed, ADH is then given as an injection to distinguish central from nephrogenic DI. If the urine olsmolality rises to > 50%, the patient has central DI. If it remains stable, the patient has nephrogenic DI.
>
> Causes of nephrogenic DI include chronic renal disease, hypercalcemia and hypokalemia, drugs such as lithium and demeclocycline, and sickle cell anemia.

► Pathology

ADH is secreted by the posterior pituitary in response to hypovolemia and increased serum osmolality. It acts on the renal collecting duct, increasing water permeability. Damage to the ADH-secreting cells in the posterior pituitary can be caused by pituitary surgery, brain tumors such as craniopharyngiomas, infiltrative processes such as sarcoidosis, and autoimmune destruction. Causes of nephrogenic DI include chronic renal disease, hypercalcemia and hypokalemia, drugs such as lithium and demeclocycline, and sickle cell anemia.

► Treatment Steps

Central DI is treated with desmopressin acetate (DDAVP), a synthetic ADH analogue, which is available as a nasal spray, an oral tablet, or an injection. This medication is effective in controlling symptoms of polyuria and polydipsia. Excessive use of this drug may cause water intoxication and hyponatremia. Nephrogenic DI does not respond to this agent; diuretics (like thiazides) may be helpful.

Y. Syndrome of Inappropriate ADH Secretion (SIADH)

► Description and Symptoms

SIADH refers to a condition in which ADH levels are inappropriately high in the face of low plasma osmolality and hyponatremia.

Patients may present with symptoms of hyponatremia, including nausea, vomiting, agitation, lethargy, or confusion. In severe cases, seizures, coma, or death may occur.

► Diagnosis

The diagnostic criteria for SIADH include hyponatremia, low plasma osmolality with high urine osmolality, and euvolemia on physical exam. Adrenal insufficiency, hypothyroidism, and renal insufficiency must be excluded to make the diagnosis.

> **► cram facts**
>
> The diagnostic criteria for SIADH include hyponatremia, low plasma osmolality with high urine osmolality, and euvolemia on physical exam. Adrenal insufficiency, hypothyroidism, and renal insufficiency must be excluded to make the diagnosis.

► Pathology

Causes of SIADH include tumors (e.g., small cell lung cancer, lymphoma, and brain tumors), central nervous system disorders (e.g., meningitis, trauma, hemorrhage), and pulmonary disorders (e.g., pneumonia, tuberculosis). Tumors cause SIADH by secreting ADH independent of serum osmolality or volemic status. Many drugs can also cause SIADH, such as chlorpropamide, phenothiazines, tricyclic antidepressants, cyclophosphamide, and selective serotonin reuptake inhibitors.

► Treatment Steps

Treatment of SIADH begins with treatment of the underlying cause, if possible. Offending drugs should be discontinued and infections treated. Often, as in the case of tumors, the underlying cause cannot be treated. In severe acute hyponatremia, treatment with 3% (hypertonic) saline is indicated. The sodium level should be raised slowly (i.e., not more than 1–2 mEq/L/h) to avoid the complication of central pontine myelinolysis. Fluid restriction is the first step in management of mild, chronic SIADH; however, patients often do not adhere to this regimen due to excessive thirst. Demeclocycline is an agent that induces nephrogenic diabetes insipidus and is effective in raising sodium levels. Nephrotoxicity may complicate treatment with demeclocycline.

BIBLIOGRAPHY

Braverman LE, Utiger RD (eds.). *Werner and Ingbar's The Thyroid,* 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2000.

Favus MJ (ed.). *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism,* 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2005.

Greenspan FS, Gardner DG (eds.). *Basic and Clinical Endocrinology,* 6th ed. New York: McGraw-Hill, 2001.

Larsen PR, Kronenberg HM, Melmed S, Polonsky KS (eds.). *Williams Textbook of Endocrinology,* 10th ed. Philadelphia: W.B. Saunders, 2002.

Müller-Wieland D, Goldstein BJ (eds.). *Textbook of Type 2 Diabetes.* London: Martin Dunitz, 2003.

4 The Gastrointestinal System

I. NORMAL PROCESSES

A. Embryonic and Fetal Development

1. Gut

Formation of the Primary Gut Tube

- The gut forms as a result of folding of the embryo during the third and fourth weeks of gestation.
- The endoderm of the embryo forms the primary gut tube.
- The primary gut tube consists of foregut, midgut, and hindgut.
- The foregut leads to the pharynx, esophagus, stomach, liver, pancreas, and gallbladder and the first half of the duodenum.
- The midgut leads to the second half of the duodenum, jejunum, ileum, and colon proximal to the level of mid-transverse colon.
- The hindgut leads to the colon distal to mid-transverse colon and rectum.

Rotation of the Gut

- The rapid growth and elongation of the gut tube allows it to rotate in the abdominal cavity. The rotation of the gut allows the respective structures (stomach, small, large intestine, etc.) to assume their appropriate orientation in the adult.

2. Liver and Gallbladder

The liver parenchyma, gallbladder, and their ducts are derived from the duodenal endoderm beginning at the fourth week of gestation.

3. Pancreas

- Two pancreatic buds, dorsal and ventral, are first formed at the fourth week of gestation.
- The ventral pancreatic bud migrates posteriorly and fuses with the dorsal pancreatic bud by the sixth week of gestation. Failure of the buds to fuse results in pancreas divisum.
- The dorsal pancreatic bud gives rise to the head, body, and tail of the pancreas.
- The ventral pancreatic bud gives rise to the other part of the pancreatic head, uncinate process, and the main pancreatic duct.
- After fusion of the two buds, the ventral pancreatic bud becomes the main pancreatic duct.

B. Organ Structure

The gastrointestinal (GI) tract is a hollow organ that consists of four layers throughout the body (from the outside in): serosa, muscularis, submucosa, and mucosa (see Figure 4–1).

1. Esophagus

- A muscular tube (striated and smooth muscle layers) that is lined by squamous epithelium. It lacks a serosal layer.
- It has an upper sphincter (consists of cricopharyngeus muscle and the inferior pharyngeal constrictor muscle), which relaxes with swallowing, and terminates in a physiologic lower esophageal sphincter (LES)

2. Stomach

- A muscular organ with a lesser and a greater curvature.
- It is anatomically divided into several regions: cardia, fundus (above the gastroesophageal junction), body, antrum (begins at the incisura angularis), and pylorus (sphincter controls movement of food outside the stomach).

► cram facts

Abnormal rotation of the ventral pancreatic duct around the second portion of the duodenum results in the annular pancreas and consequent obstruction. Patients present with projectile vomiting in the first few days of life.

► cram facts

The main pancreatic duct and the common bile duct meet and empty their secretions into the second portion of the duodenum at the major duodenal papilla or ampulla of Vater.

► cram facts

An enlarged left atrium and bronchogenic carcinoma can both cause esophageal constriction due to the close anatomic relations among these structures.

► cram facts

Esophageal diverticula, localized dilation of the lumen due to wall defects, include Zenker's (upper esophagus) and traction (midesophagus) diverticulum.

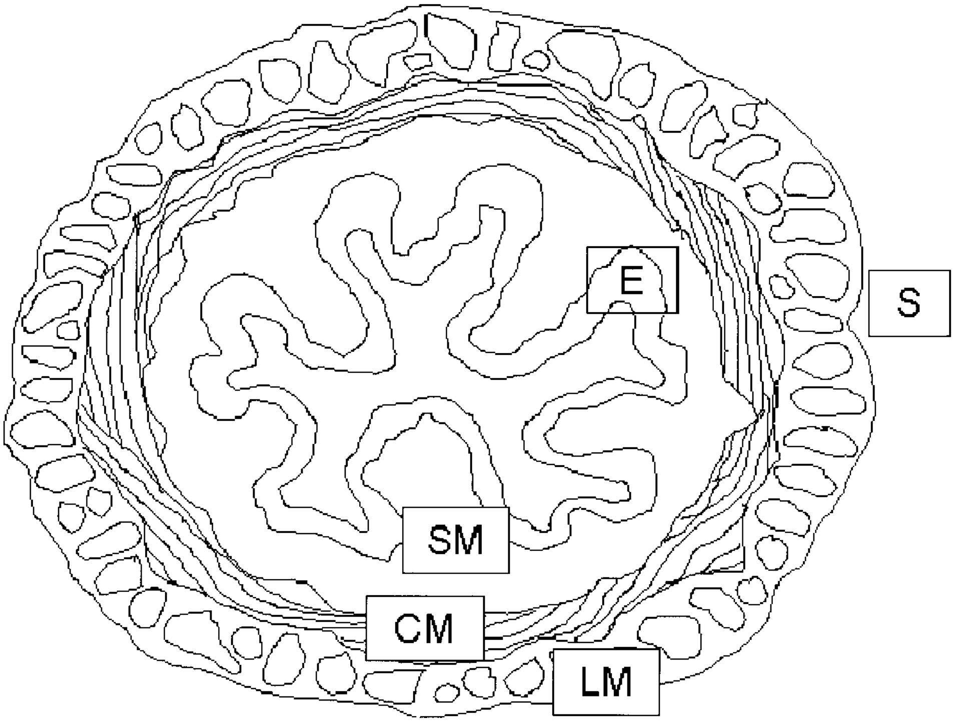


Figure 4–1. The basic organization of the intestinal tract. Illustrated is a cross-section of the intestine showing the various layers. S, serosa; LM, longitudinal muscle; CM, circular muscle; SM, submucosa; E, epithelium; L, lumen. The mucosal layer consists of the epithelium, lamina propria, and muscularis submucosa.

- The surface is lined by simple columnar epithelium that is glandular in nature. It can be divided into several types: cardiac, oxyntic or fundic, and antral or pyloric.
- The cells in the oxyntic glands include surface mucous cells, parietal cells (which secrete hydrochloric acid and intrinsic factor), chief cells (which secrete pepsinogen), and endocrine cells.
- Antral glands contain many endocrine cells called enterochromaffin (EC) cells that secret gastrin (G cells), and somatostatin (D cells).

3. Duodenum

- The duodenum is C shaped and lined by submucosal glands called Brunner's glands.
- It is fixed in a retroperitoneal position.

4. Jejunum and Ileum

- Has circumferential or spiral folds called *plicae circulares*.
- The mucosa contains the epithelium, lamina propria, and muscularis submucosa.
- Throughout the small intestine (including the duodenum) the surface is covered with fingerlike projections (villi), which are further covered by microvilli. This constitutes the brush border, which is essential for terminal digestion (proteins and carbohydrates) and absorption of nutrients.
- The epithelium is columnar and contains several cell types, including Paneth cells, absorptive cells, goblet cells, and enteroendocrine cells.

5. Large Intestine

- Consists of cecum, appendix, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anus.

► cram facts

In pernicious anemia, the resultant absence of parietal cells causes failure to secret intrinsic factor (results in vitamin B_{12} deficiency) and hydrochloric acid (achlorhydria).

► cram facts

Diseases resulting in the loss of the brush border or micovilli/villi (infections, inflammation) result in malabsorption and diarrhea.

- The mucosa is flat (i.e., does not have any villi).
- The muscular layer of the large intestine consists of longitudinal and circular fibers.
- The longitudinal fibers are concentrated into three flat bands called taeniae coli.
- In the anal canal, the circular layer forms the internal anal sphincter.
- Overlapping and distal to the internal anal sphincter are layers of striated muscle, which make up the external anal sphincter.
- The colon is also divided into segments called haustra or haustrations.

► cram facts

The acinar cells are loaded with zymogen granules (which contain inactive enzymes) whose premature activation in the pancreas is one of the causes of acute pancreatitis.

6. Pancreas

- The pancreas is a mixed gland, of which approximately 80% is exocrine and 2% is endocrine. The remaining 18% is blood vessels, lymphatics, and excretory ducts.
- The endocrine glands are present in the islet of Langerhans.
- The exocrine glands are arranged in the form of acini, which drain into the excretory ducts.
- The acinar cells synthesize and secrete major enzymes for the digestion of all three primary foodstuffs (protein, fat, and carbohydrate).

7. Liver

- The liver parenchymal cells, the hepatocytes, are divided into lobules.
- The angle of each lobule is called the portal tract or portal triad (containing the hepatic artery, portal vein, and bile duct).
- The central portion of the lobule is occupied by the hepatic vein.
- The blood flows from the portal triad to the central hepatic vein through sinusoids, which are separated by plates of hepatocytes.

8. The Biliary System

- Bile secretion begins at the level of the bile canaliculus, the smallest branch of the biliary tree.
- These small ducts coalesce into larger ducts, which eventually form the right and left intrahepatic ducts.
- The two intrahepatic ducts form the common hepatic duct.
- After the cystic duct (duct draining the gallbladder) joins the common hepatic duct, the duct becomes the common bile duct.
- The common bile duct joins the pancreatic duct at the level of the ampulla of Vater, at which point the smooth muscle layers are thickened to form the sphincter of Oddi (Figure 4–2).

► cram facts

Proton pump inhibitors are a class of drugs that block the H-K ATPase pump mediating the secretion of hydrochloric acid by the parietal cells and hence reduce the stomach acidity. Histamine 2 receptor (H_2) antagonists and resection of the vagus nerve (decreases Ach) also result in decreased acidity.

C. Organ/Tissue/Cell Physiology

1. Gastrointestinal Secretory Products/Hormones

a. Stomach

Acid (HCl)—Produced and Secreted by Parietal Cells or Oxyntic Cells

- Stimulation of acid secretion is mediated by histamine, gastrin, and acetylcholine (ACh).
- Inhibition of acid secretion is mediated by hormones, including somatostatin, secretin, and gastric inhibitory peptide (GIP).

Pepsinogen—Produced by Chief or Peptic Cells

- Pepsinogen is secreted by the chief cells and is converted to pepsin in the gastric juice when the pH falls below 5.

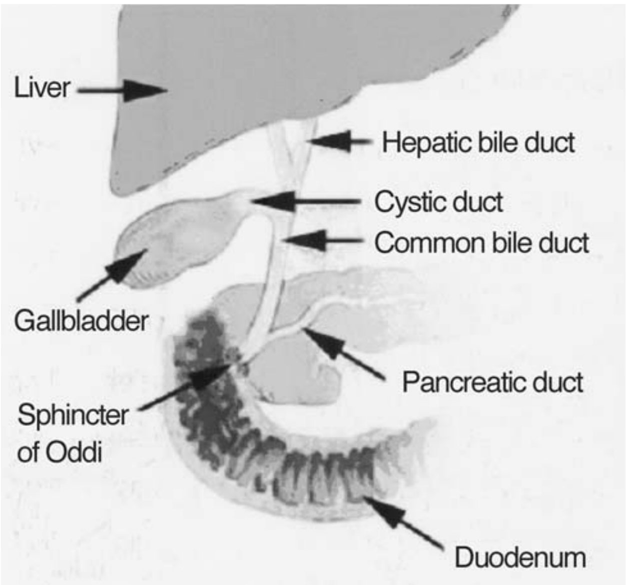


Figure 4–2. This graph depicts the pancreaticobiliary system.

- Pepsin begins the digestion of proteins by splitting interior peptide bonds.

Intrinsic Factor (IF)—Produced and Secreted by the Parietal Cells

IF forms a complex with vitamin B_{12} in the stomach, which is necessary for the absorption of the vitamin in the ileum.

Gastrin—Produced and Secreted by G Cells in the Antrum and Duodenum

- Primary effect is to stimulate acid secretion.
- Release is stimulated by protein in the stomach and inhibited by the presence of acid.

► **cram facts**

Hypergastrinemia is seen in pernicious anemia due to achlorohydria.

b. Duodenum, Jejunum, and Ileum

Cholecystokinin (CCK)—Secreted by the Duodenum, Jejunum, and Some Ileum

- Primary effect is the stimulation of pancreatic enzyme secretion.
- Can also stimulate gallbladder contraction, sphincter of Oddi relaxation, and decreased stomach emptying.
- Release is stimulated by fatty acids, peptides, or amino acids in the intestinal lumen.

► **cram facts**

The function of CCK is to facilitate the presence of pancreatic enzymes and bile in the duodenum to ensure fat digestion.

Secretin—Secreted by the Duodenum Only

- Most important function is to stimulate pancreatic and bile HCO_3^- secretion.
- Secretion is primarily mediated by acid in the small duodenum.

Gastric Inhibitory Peptide (GIP)—Secreted by the Duodenum and Jejunum

- Functions to inhibit gastric acid secretion.
- Release is stimulated by protein, fat, and carbohydrate in the small intestine.

Motilin—Secreted by the Duodenum and Jejunum

Increases gastric and intestinal motility.

c. Pancreas

Exocrine

- Fluid and electrolytes.
  - Composition of the pancreatic fluid is predominantly HCO_3^- and Na^+.

- Enzymes.
  - The proteases (e.g., trypsin, chymotrypsin) are secreted as inactive enzyme precursors and converted to active forms in the lumen of the intestine.
  - Pancreatic amylase and lipase are secreted in active forms.

Endocrine

Insulin and glucagon.

> **► cram facts**
>
> Pancreatitis with loss of exocrine function results in malabsorption and diarrhea due to the lack of pancreatic enzymes necessary for digestion. Loss of the endocrine function results in diabetes due to decreased insulin production.

2. Digestion and Absorption

a. Carbohydrates

Principal Dietary Forms

Carbohydrates, mainly in the form of starch, account for approximately 50% of ingested calories of average daily intake.

Digestion

- Digestion of carbohydrates occurs in the small intestine (pancreatic amylase).
- Further digestion is carried out by the brush border carbohydrases including glucoamylase, sucrase, isomaltase, trehalase, and lactase.
- The products of digestion include glucose (from starch), galactose (from lactose), and fructose (from sucrose).

Absorption

- Fructose is transported into the cells by facilitated diffusion in the apical membrane.
- Glucose and galactose are transported by an active transport system in an Na^+-dependent manner.

Abnormalities in Carbohydrate Digestion and Absorption—Lactase Deficiency

- Caused by a reduction or absence of lactase in the brush border causing lactose intolerance.
- Symptoms are diarrhea, bloating, and abdominal cramps.
- Treatment is lactose-free diet or lactase enzyme supplementation.

> **► cram facts**
>
> A large percentage of individuals of most races, other than those of northern European descent, lose lactase activity later in life.

b. Protein

Digestion

- Digestion of protein begins in the stomach with the action of pepsin and continues in the small intestine by pancreatic proteases excreted as inactive precursors (endopeptidases and exopeptidases).
- Endopeptidases include trypsin, chymotrypsin, and elastase. Trypsinogen is activated by enterokinase, a brush border enzyme. The activated enzyme, trypsin, can then convert all other inactive forms of proteases into active forms.
- Exopeptidases include carboxypeptidases A and B.
- The products of protein digestion include free amino acids, dipeptides, tripeptides, and larger peptides.

Absorption

The absorption of protein digestion products occurs at the level of the brush border.

c. Lipids

Digestion

- Dietary lipids first undergo emulsification in the duodenum with the action of bile salts, which are released in response to CCK.

- Emulsified lipids can then be digested by pancreatic lipase (also released in response to CCK) with the help of co-lipase, into monoglycerides and free fatty acids.

Absorption

- The digested fatty acids and bile salts first form mixed micelles prior to their delivery to the brush border for uptake.
- The bile salts remaining behind are reabsorbed by the terminal ileum and transported back to the liver. This process is called the enterohepatic circulation.
- Once in the cell, the free fatty acids and monoglycerides are reassembled back into triglycerides. Together with reassembled phospholipids and cholesterol, the triglycerides assemble into a large lipoprotein particle called chylomicron.
- Chylomicrons are secreted through the basolateral membrane into the lymphatic system (lacteal) for transport to the rest of the body.

3. Neural Regulatory Functions

a. Innervation of the GI System—The GI tract is innervated by the autonomic nervous system (ANS), which is divided into two systems:

- The extrinsic nervous system, which can be divided into two branches:
  - Parasympathetic innervation:
    - Supplied primarily by the vagus nerve and pelvic nerves; mainly excitatory.
  - Sympathetic innervation:
    - Supplied by nerves that run between the spinal cord and the prevertebral ganglia and between these ganglia and the organs of the gut.
- The intrinsic nervous system, also called the enteric nervous system (ENS) (Figure 4–3):

► cram facts

Anything interfering with the appropriate digestion/absorption of fats results in diarrhea with high fat content (steatorrhea).

► cram facts

Terminal ileal disease processes like Crohn's disease or surgical resection interfere with the enterohepatic circulation reducing the bile salts necessary for fat digestion/absorption and hence resultant steatorrhea.

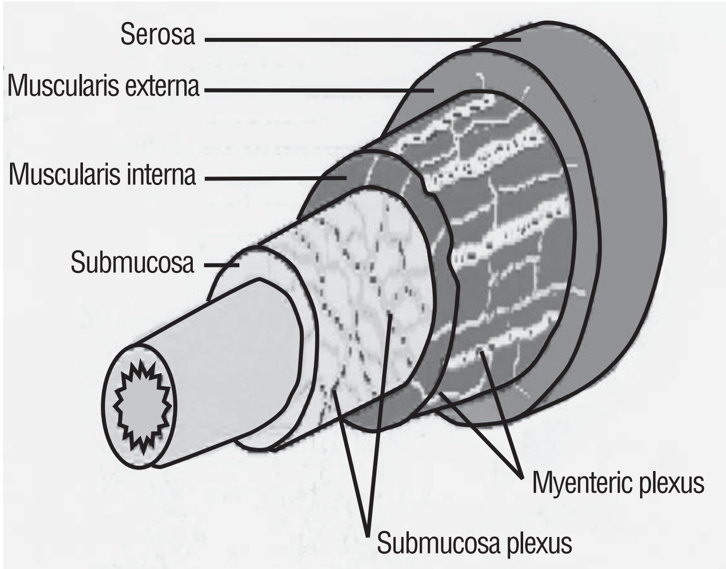


Figure 4–3. The basic organization of the enteric nervous system. The submucosal plexus and the myenteric (Auerbach's) plexus (between the circular and longitudinal muscle layers).

- The myenteric (Auerbach's) plexus, located between the longitudinal and circular layers of muscle in the tunica muscularis, and the submucosal (Meissner's) plexus.
- The myenteric plexus controls digestive tract motility, and the submucosal plexus regulates GI blood flow and controls epithelial cell function.

b. Neurotransmitters (Neurocrines) of the GI ANS

- ACh.
  - The primary function is excitatory, stimulating smooth muscle contraction, increasing intestinal secretions, releasing enteric hormones, and promoting dilation of blood vessels.
  - It derives from extrinsic parasympathetic and enteric nervous system neurons.
- Norepinephrine.
  - The effect of norepinephrine is almost always inhibitory and opposite that of acetylcholine.
  - It derives from extrinsic sympathetic neurons and exerts its primary effect on the ENS.
  - Neurocrines of the ENS include ACh, serotonin, vasoactive intestinal peptide (VIP), nitric oxide (NO), substance P, and somatostatin.

4. Gastrointestinal Motility

a. Esophageal Motility (Swallowing)

- The process of swallowing involves the integrated activities of the oral cavity, pharynx, and esophagus.
- As food is propelled from the pharynx (pharyngeal phase), the upper esophageal sphincter (UES) is relaxed, allowing the food to pass into the esophagus.
- The esophagus propels material from the pharynx to the stomach by coordinated contractions (peristalsis) of the muscle.
- When esophageal peristalsis is preceded by a pharyngeal phase, it is called *primary peristalsis.*
- When esophageal contractions occur in the absence of oral and pharyngeal phases, it is called *secondary peristalsis.*
- The lower esophageal sphincter (LES) transiently relaxes as the food bolus passes through this region.

► cram facts

Difficulty swallowing (dysphagia) can be caused by narrowing of the esophageal lumen (tumors or fibrotic strictures such as with reflux) or due to diseases affecting the esophageal muscular activity (scleroderma, achalasia, stroke).

b. Gastric Emptying

- The predominant motor activity of the cephalic region (fundus) of the stomach is the accommodation of ingested material. Little mixing of ingested material occurs in this region of the stomach due to minimal contractile activity.
- Peristaltic contractions begin in the midstomach and move forward to the gastroduodenal junction, increasing in both velocity and intensity. This activity in the caudal region allows for appropriate mixing of the food contents.
- Gastric emptying is regulated in a manner that allows for optimal intestinal digestion and absorption of foodstuffs: solids empty only after a lag period, during which time they are reduced in size by the repulsive activity of the stomach; liquids begin to empty almost immediately.

► cram facts

Delayed gastric emptying, or gastroparesis, causes symptoms of postprandial fullness sensation, nausea, and, rarely, abdominal pain. It is most commonly idiopathic but can be caused by diabetes.

c. Motility of the Small Intestine

- Motility of the small intestine is organized to optimize the processes of digestion and absorption of nutrients and the forward propulsion of undigested material.

- The migrating motor complex (MMC) is characteristically present in the fasting phase. It begins in the stomach and sweeps through the rest of the small intestine.
- The MMC cycles at intervals of about 1.5 hours and is designed to maintain a clean small intestine with low bacterial counts.

d. Motility of the Large Intestine

- Segmental contractions of the longitudinal and circular muscle layers lead to propulsion of material.

5. Physiology of Bile

a. Constituents of Bile

- Bile acids are the major organic constituents of bile. They are derived from cholesterol and are amphipathic (both hydrophilic and hydrophobic). They exist as conjugates of taurine or glycine.
- The other organic components of bile include phospholipids, cholesterol, and bile pigments (porphyrin derived).

b. Bile Secretion

- Bile acids are secreted by the liver.
- Primary bile acids include cholic and chenodeoxycholic acids, and secondary bile acids include deoxycholic and lithocholic acids. The secondary bile acids are produced in the intestine by bacterial action on primary bile acids.
- Both primary and secondary acids are secreted in the intestine, reabsorbed by the ileum, taken up by the hepatocytes, conjugated with taurine and glycine, and resecreted in the bile. This process is called the enterohepatic circulation.

c. Bile Storage and Transport to the Intestine

- Bile is usually stored in the gallbladder during fasting.
- Shortly after eating, the gallbladder contracts and gradually empties. The stimulus for its contraction is primarily mediated by CCK.

II. ABNORMAL PROCESSES

A. Congenital Disorders and Abnormalities of Gastrointestinal Development

1. Tracheoesophageal Fistula

- Results from failure of the gut and respiratory tubes to separate completely during development.
- Manifested by coughing spells or aspiration typically with breastfeeding as the milk passes through the fistula to the lungs.
- Diagnosed with barium swallow.
- Corrected by surgery.

> ► **cram facts**
>
> Esophageal atresia is a disorder in which the esophagus ends as a blind pouch. It is also associated with episodes of coughing and cyanosis as the food regurgitates back from the blind pouch into the lungs.

2. Congenital Hypertrophic Pyloric Stenosis

- A congenital obstructing lesion caused by hypertrophy of the smooth muscle layer of the pylorus.
- Manifested by nonbilious projectile vomiting beginning at 3–4 weeks of age.
- Can be diagnosed with ultrasonography, and treatment is usually surgical.

> ► **cram facts**
>
> Congenital hypertrophic pyloric stenosis is the most common disorder requiring abdominal surgery during the first 6 months of life. It is more common in males.

3. Omphalocele

- Results from failure of the umbilicus to close completely.
- Manifested by the protrusion of GI structures through an unclosed umbilical ring in a newborn.

► cram facts

Rule of the three "2s" for Meckel's diverticulum: affects 2% of the population, 2 inches long, and around 2 feet from the ileocecal valve.

4. Gastroschisis

A defect in the ventral abdominal wall that leads to herniation of GI structures.

5. Meckel's Diverticulum

- Results from failure of complete regression of the vitelline duct.
- Most patients are asymptomatic. Symptoms include intestinal obstruction, GI bleeding (due to gastric tissue), or sepsis.

6. Hirschsprung's Disease (Congenital Megacolon)

- Manifested as severe constipation in a newborn or infant.
- Characterized by the absence of the enteric nervous system in the distal colon due to failure of the neural crest cells forming the myenteric plexus from migrating into the colon. As a result, the involved area exhibits increased tone, has a narrow lumen, and is devoid of propulsive activity.
- The internal anal sphincter is always involved.
- The colon proximal to the diseased segment becomes dilated, producing a megacolon.
- Treated with surgical removal of the diseased segment.

B. Infectious, Inflammatory, and Immunologic Disorders

1. Infectious Disorders

a. Peptic Ulcer Disease (PUD)

► cram facts

Cushing ulcers are associated with intracranial hemorrhage, and curling ulcers are associated with severe burns.

► cram facts

Multiple ulcers, abnormal location such as jejunum, and failure to respond to therapy suggests Zollinger–Ellison syndrome (gastrin-producing tumor/gastrinoma with consequent increased acid production).

► cram facts

H. pylori and NSAIDs are the most common causes of PUD.

► Symptoms

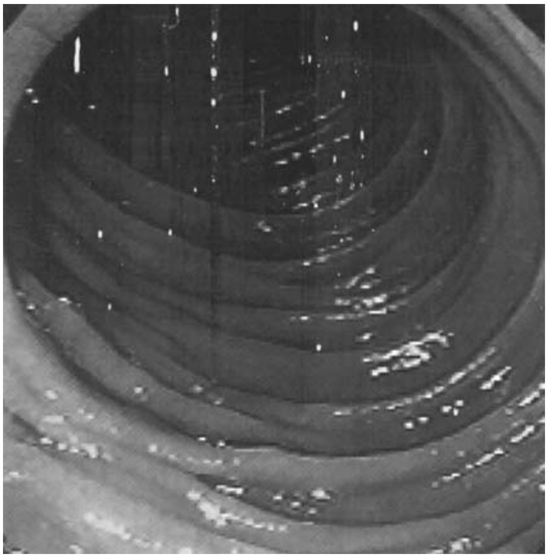
- Main manifestation is abdominal pain, often described as burning and gnawing in character and is located in the epigastric area. Pain usually occurs 2–3 hours after a meal and is relieved by ingestion of food or antacids. Patients can be awakened by the pain in the middle of the night.
- Other symptoms include nausea, vomiting, weight loss, bleeding, obstruction, and perforation.

► Diagnosis

Duodenal ulcers (DUs) and gastric ulcers (GUs) can be diagnosed with either upper GI endoscopy (esophagogastroduodenal endoscopy [EGD]) (see Figure 4–4) or an upper GI x-ray series.

► Pathology

- Ulcers are mucosal defects that extend through the muscularis mucosae and into the submucosa or even deeper layer.
- Pathophysiologic factors of PUD include *Helicobacter pylori* (HP) infection, defective epithelial defense mechanisms, abnormal gastric acid secretion and motility, and the use of ulcerogenic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs).
- > 80% of DUs and < 60% of GUs are associated with HP infection.
- *H. pylori* produces the enzyme urease, which breaks down urea into ammonia and CO_2.
- Diagnostic tests for HP (detect the urease or the produced CO_2) can be divided into those that do and those that do not require samples of gastric tissues. Histologic examination of biopsied specimens and rapid urease tests such as the CLO test and Pylori Tek require gastric samples. Urea breath test and serology tests do not.
- Eradication of HP infection significantly decreases recurrence rate for both DUs and GUs.



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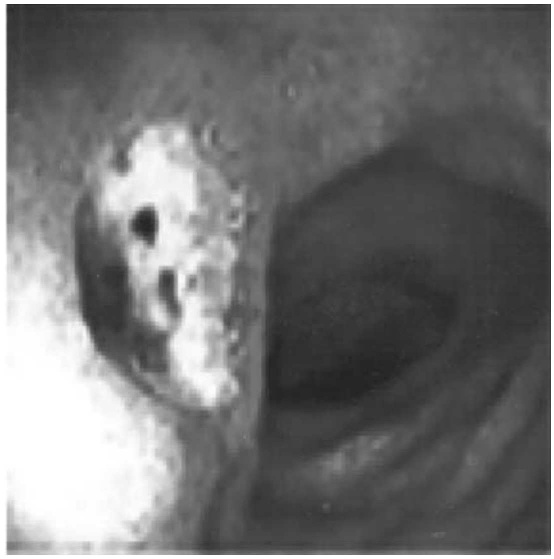


B

Figure 4–4. Endoscopic appearance of a duodenal ulcer. A. The appearance of a normal duodenum during endoscopy. **B.** The presence of a large, deep-based ulcer in the duodenal bulb.

► Treatment Steps

1. If HP is present: Triple antibiotic therapy in conjunction with the use of a proton pump inhibitor (PPI) or H_2 receptor antagonist.
2. If HP is absent: Treatment should be directed at avoidance of all ulcerogenic drugs, in conjunction with the use of a PPI or H_2 receptor antagonist.

b. Infectious Esophagitis

Candidal Esophagitis

► Symptoms

- Difficulty in swallowing (dysphagia) or painful swallowing (odynophagia).
- Chest pain and heartburn.

► Diagnosis

- Upper endoscopy with tissue biopsies and brushing for culture.
- Lesions usually appear plaque-like.

► Pathology

Occurs primarily in immunocompromised hosts, including acquired immune deficiency syndrome (AIDS) patients and patients receiving immunosuppressive medications.

► Treatment Steps

Topical agents (nystatin or clotrimazole), oral agents such as fluconazole or itraconazole, or parenteral agents such as amphotericin B depending on severity of the infection.

Viral (Herpes Simplex Virus and Cytomegalovirus) Esophagitis

- Lesions appear as linear superficial or deep ulcerations.

- Histology shows the presence of multinucleated giant cells with intranuclear inclusion bodies. Cytomegalovirus (CMV)-infected cells can also have cytoplasmic inclusion bodies.

► Treatment Steps

1. Herpes simplex virus (HSV) esophagitis is treated with IV acyclovir.
2. CMV esophagitis is treated with IV ganciclovir.

c. Infectious Diarrhea

Bacterial Diarrhea

- Toxigenic pathogens/noninvasive:
  - *Vibrio cholerae*
    - Causes severe diarrhea that leads to rapid dehydration.
    - Cholera toxin increases the cellular level of cyclic adenosine monophosphate (cAMP) via increasing adenylate cyclase activity. This in turn stimulates fluid secretion.
    - Fluid and electrolyte replacement is the mainstay of treatment.
  - Enterotoxigenic *E. coli* (ETEC):
    - Acquired by consuming contaminated food and liquids.
    - Secretes two types of toxins: heat-labile toxin (LT) and heat-stable toxin (ST).
    - Clinical manifestation is watery diarrhea, which is usually self-limited and does not require antibiotic treatment.
  - Other *E. coli* intestinal pathogens:
    - Enteropathogenic *E. coli* (EPEC)
    - Enteroinvasive *E. coli* (EIEC)
    - Enterohemorrhagic *E. coli* (EHEC)
    - Diffusely adhering *E. coli* (DAEC)
- Invasive pathogens:
  - *Shigella:*
    - A major cause of bacillary dysentery (abdominal pain, fever, bloody diarrhea).
    - Typically causes diarrhea containing an inflammatory exudate composed of polymorphonuclear leukocytes and blood.
    - Transmission is oral–fecal route through person-to-person contact.
    - Treatment includes rehydration and antibiotics (ampicillin, trimethoprim–sulfamethoxazole, and fluoroquinolone).
  - *Salmonella:*
    - Salmonellosis is a common foodborne infection. Foods that commonly transmit salmonellosis include poultry, meat, eggs, and dairy products.
    - Disease typically involves the terminal ileum, with mild mucosal ulcerations, and has systemic involvement.
    - Clinical syndromes include (1) gastroenteritis, (2) bacteremia, (3) enteric or typhoid fever, (4) localized infections to the bones or joints, and (5) a carrier state.
    - Treatment with antibiotics is usually not indicated in gastroenteritis caused by *Salmonella* due to the possibility of prolonging the intestinal carriage of the organisms.
    - Typhoid fever needs to be treated with antibiotics such as chloramphenicol.

► **cram facts**

ETEC is the most common cause of traveler's diarrhea.

- *Clostridium difficile:*
  - Toxin secreted by *C. difficile* causes pseudomembranous enterocolitis/antibiotic-associated diarrhea.
  - Usually involves the presence of pseudomembranes on the intestinal mucosa, which can be located in the small bowel, colon, or both.
  - Typical symptoms include watery diarrhea, abdominal pain, fever, and occasional bleeding.
  - Diagnosis can be established by a positive *C. difficile* toxin assay or by endoscopy with histopathology.
  - Treatment includes discontinuation of antibiotics and the use of antimicrobials directed against *C. difficile* such as vancomycin and metronidazole.

► **cram facts**

Clostridium difficile produces two toxins: A and B. It can cause severe infection of the colon resulting in megacolon (similar to ulcerative colitis).

Parasitic Diarrhea

- *Entamoeba histolytica:*
  - Infection can be either asymptomatic or result in dysentery and extraintestinal diseases (such as amebic liver abscesses).
  - Diagnosis can be established by examination of the stool for the presence of trophozoites or by upper endoscopy with mucosal biopsy.
- *Giardia lamblia:*
  - *Giardia* causes a watery diarrhea that is malabsorptive in nature along with bloating and abdominal cramps.
  - Does not cause any invasion of the intestinal mucosa but can lead to villous atrophy.
  - Diagnosis is established by examination of the stool for the presence of cysts or trophozoites or by upper endoscopy with mucosal biopsy.
  - Treatment of choice is metronidazole.

d. Viral Hepatitis (Table 4–1)

Hepatitis A Virus (HAV)

- Accounts for most hepatic infections.
- Can be acute or chronic. Drugs (such as acetaminophen) are to be considered in the differential diagnosis of viral hepatitis.
- Chronic hepatitis is associated with cirrhosis and hepatocellular carcinoma.

► Symptoms

- Incubation period varies for each virus.
- Prodromal symptoms include fatigue, weakness, anorexia, nausea, vomiting, and abdominal pain followed by jaundice and dark urine, which develop within 1–2 weeks of the prodromal symptoms.
  - Bilirubin is produced in an unconjugated (indirect) form as a result of the breakdown of the heme moiety in red blood cells.

► **cram facts**

Jaundice or yellowish discoloration of the skin is the result of both conjugated and unconjugated hyperbilirubinemia.

4-1

VIRAL HEPATITIS

Viral Hepatitis	Transmission	Type	Chronicity
Hepatitis A	Oral–fecal route	Single-stranded (ss) RNA	No
Hepatitis B	Parenteral Perinatal	Double-stranded (ds) DNA	Yes
Hepatitis C	Parenteral Perinatal	dsDNA	Yes
Hepatitis D	Parenteral	RNA containing	Yes
Hepatitis E	Oral–fecal	ssRNA	No

It is bound to albumin, taken up by hepatocytes and conjugated (direct form, which is water soluble), and then released into bile. It is reabsorbed in the terminal ileum. The part remaining admixed with the stool gives it the characteristic brownish color.

- Serum transaminase levels increase during the prodrome, followed by a rise in bilirubin level.

> ► **cram facts**
>
> Clay-colored stools are the result of any disorder interfering with the delivery of bilirubin into the intestinal lumen (cholestasis or obstruction of the common bile duct interfering with the flow of bile).

► Diagnosis

Detection of antibody against respective viruses, usually immunoglobulin M (IgM) variety, or detecting the virus particles.

► Treatment Steps

1. Prevention of infection with attention to public and personal health measures.
2. Passive immunoprophylaxis with immune globulin before exposure or after exposure for hepatitis A and B.
3. Medications including interferon and antiviral agents such as ribavirin. Pegylated interferon is now available.

> ► **cram facts**
>
> Hepatitis C is the most common cause of post-transfusion hepatitis.

2. Inflammatory Disorders

a. Gastritis

► Symptoms

- Abdominal pain and nausea with or without vomiting.
- Acute usually caused by *H. pylori* or drugs/toxins like NSAIDs or alcohol or severe physical stress.
- Chronic of two types: Type A is autoimmune due to the destruction of the parietal cells, and type B is caused by *H. pylori*.

> ► **cram facts**
>
> Vaccines are available only for hepatitis A and B.

b. Pancreatitis

Acute or chronic.

► Symptoms

- Acute: Severe epigastric abdominal pain, nausea, vomiting, and fever.
- Chronic: Abdominal pain and steatorrhea (due to loss of enzyme production).

> ► **cram facts**
>
> The most common cause of chronic pancreatitis is alcohol.

► Diagnosis

- Elevation of pancreatic amylase and lipase (more specific).
- Computed tomography (CT) scan, magnetic resonance imaging (MRI), or abdominal ultrasound.
- Endoscopic retrograde cholangiopancreatography (ERCP).
- Differential diagnosis includes acute cholecystitis, bowel perforation, mesenteric ischemia, intestinal obstruction, and dissecting aortic aneurysm (see Figure 4–5).

> ► **cram facts**
>
> Pseudocyst with superimposed bleeding or infection is a complication of acute pancreatitis. Obstruction of the common bile duct by the scar tissue as it traverses the pancreatic head is a complication of chronic pancreatitis.

► Pathology

- Predisposing conditions for acute pancreatitis include gallstones (most common), alcohol, hypertriglyceridemia, hypercalcemia, drugs, infections, trauma, structural abnormalities, and heredity.
- Most causes of acute pancreatitis involve initial injury to peripheral acinar cells. This results in the conversion of trypsinogen to trypsin within acinar cells. Trypsin, in turn, converts proenzymes into active enzymes with consequent autodigestion of the pancreas and fat necrosis.

► Treatment Steps

1. Mild pancreatitis is treated with supportive measures, including rehydration, pain control, and fasting.

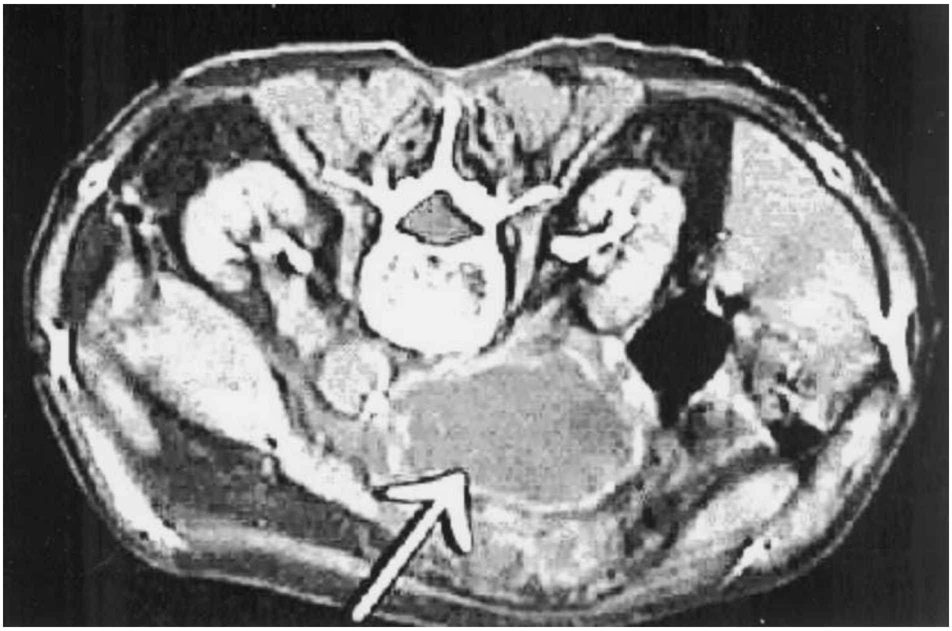


Figure 4–5. CT scan appearance of a pancreatic pseudocyst. The head of the pancreas is enlarged with the presence of a pseudocyst in the center. This is a complication of acute pancreatitis.

2. Severe pancreatitis requires intensive care unit admission because it can be associated with multiple organ failure (lungs, kidneys most commonly).

b. Acute Cholecystitis and Cholangitis

► Symptoms

Most common symptoms include right upper quadrant (RUQ) abdominal pain, fever, nausea, vomiting, and jaundice.

► Diagnosis

- Usually diagnosed by clinical history and presentation.
- Leukocytosis and elevation of liver enzymes and bilirubin.
- Abdominal ultrasound or CT scan.
- ERCP is sometimes used to diagnose common bile duct stones.

► Pathology

Caused by obstruction of the cystic duct (cholecystitis) and common bile duct (cholangitis), respectively, by gallstones.

► Treatment Steps

Replacement of fluids and electrolytes, pain control, antibiotics. ERCP with stone extraction in the common bile duct (for cholangitis), and cholecystectomy (for cholecystitis).

3. Immunologic Disorders

a. Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) includes both Crohn's disease and ulcerative colitis (see Table 4–2).

► Diagnosis

- CT scan and contrast radiogram (small bowel series or barium enema).

> **► cram facts**
>
> Charcot's triad is fever, RUQ pain, and jaundice. It is present in 50% of patients with cholangitis.

> **► cram facts**
>
> In acute pancreatitis, the pancreas is swollen and edematous. In chronic pancreatitis, the pancreas is small, firm, and shrunken, with calcifications (can be seen on a regular abdominal x-ray or CT scan).

► cram facts

Crohn's diseases involving the terminal ileum can result in fat-soluble volume deficiency (vitamins A, D, E, and K). This is due to the fact that these require bile salts, which will be deficient due to impaired enterohepatic circulation.

► cram facts

IBD is associated with a number of extraintestinal manifestations involving the joints, the eye, the liver (primary sclerosing cholangitis), and the skin (erythema nodosum and pyoderma gangrenosum).

► cram facts

Celiac sprue can be associated with dermatitis herpetiformis, IgA deficiency, thyroid disease, lymphocytic colitis, and rheumatoid arthritis.

4-2

INFLAMMATORY BOWEL DISEASES

Differences/Similarities	Ulcerative Colitis	Crohn's Disease
Site of involvement	Rectum always involved, continuous proximal spread with only colonic involvement	Any segment of the GI tract, usually ileocolonic. Can be only smalll intestinal or colonic.
Pattern of involvement	Continuous	Skip fashion
Gross appearance	Shallow ulcers, pseudopolyps	Deep ulcers, strictures, "cobblestone mucosa"
Microscopic findings	Crypt abscesses, mucosal inflammation, no granulomas and no fibrosis	Crypt abscesses, transmural inflammation, granulomas (45–50%), and fibrosis
Diarrhea	Bloody	Usually nonbloody
Abdominal pain	Only when disease is severe	Frequent
Perianal disease	No	Yes, in 30% of cases
Complications	Megacolon and colon cancer (more than Crohn's disease)	Fistulas, adhesions, strictures, and cancer of the small and large intestine

- Endoscopy with biopsy of tissues.
- Differential diagnosis includes neoplastic disorders and drug-induced injuries.

► Pathology
- Represents a state of sustained and heightened immune response.
- The initiating event could be bacterial.
- Genetic and environmental factors are important.

► Treatment Steps
Aminosalicylates such as 5-aminosalicylate; antibiotics, including metronidazole and ciprofloxacin; glucocorticoids; immunosuppressants, including thiopurine such as 6-mercaptopurine and methotrexate; and other immune modulators such as infliximab. Other treatment options include bowel rest, parenteral nutrition, and surgeries (should be considered as a last resort).

b. Celiac Disease (Sprue)

► Symptoms
Symptoms are caused by malabsorption, including diarrhea, steatorrhea, weight loss, abdominal bloating, anemia, fatigue, and easy bruisability.

► Diagnosis
- Presence of fat in the stool and abnormal D-xylose absorption (test showing decreased absorption of this sugar, signifying a mucosal problem).
- Serological tests include IgA endomyseal antibodies, antigliadin antibodies, and anti–tissue transglutaminase antibodies.
- Small intestine biopsy and gluten challenge.

► Pathology
- Caused by hypersensitivity to gluten (present in wheat, rye, and barley).
- Involves only the mucosa of the small intestine with villous atrophy and increased number of intraepithelial lymphocytes.

► Treatment Steps
Gluten-free diet with possible glucocorticoids in refractory cases.

c. Autoimmune Hepatitis (AIH)

► Symptoms
- Fatigue, jaundice, abdominal discomfort, mild pruritus.
- Symptoms due to liver cirrhosis such as altered mentation (encephalopathy) and ascites.

► Diagnosis
- Elevated liver transaminase levels, hypergammaglobulinemia, and hyperbilirubinemia.
- Serological markers include anti–smooth muscle antibody (SMA), antinuclear antibody (ANA), and anti–liver kidney microsomal (LKM1) antibody.

► Pathology
Characterized by autoantibodies attacking the hepatocytes with interface hepatitis on histologic examination, hypergammaglobulinemia, and autoantibodies in serum.

► Treatment Steps
Medications to modulate the immune response (corticosteroids, azathioprine).

e. Primary Biliary Cirrhosis (PBC)

► Symptoms
Fatigue, jaundice, and pruritus are common.

► Diagnosis
- Liver biochemical tests are cholestatic in nature (elevated alkaline phosphatase and gamma-glutamyl transferase levels). Serum amino transaminase levels mildly elevated.
- Antimitochondrial antibody (AMA) is present in approximately 90% of patients with PBC.

► Pathology
- An autoimmune liver disease that commonly affects middle-aged women.
- Characterized by ongoing inflammatory destruction of the intrahepatic bile ducts.

► Treatment Steps
Symptomatic with anti-inflammatory medications (corticosteroids, colchicines, and azathioprine), ursochenodeoxycholic acid (UDCA) for itching. Liver transplantation may be necessary.

► cram facts

Primary biliary cirrhosis is associated with other diseases such as arthritis or arthropathy, scleroderma, autoimmune thyroiditis, and keratoconjunctivitis.

► cram facts

As in Crohn's disease, there is decreased absorption of lipid-soluble vitamins due to the decreased bile resulting from the destruction of the bile ducts.

C. Motility Disorders

1. Gastroesophageal Reflux Disease (GERD) or Noninfectious Esophagitis

► Symptoms
Most common symptoms are heartburn, acid regurgitation, and dysphagia.

► Diagnosis
Upper endoscopy; radiological studies, including an upper GI series, 24-hour pH probe monitor, and assessing the motility of the esophagus (esophageal manometry).

► cram facts

Atypical symptoms include asthma, cough, laryngeal irritation, and noncardiac chest pain.

► Pathology

- Caused by reflux of gastric and/or duodenal content.
- Etiology of GERD is multiple and includes an incompetent LES, transient LES relaxation, a sliding and not a paraesophageal hiatal hernia, delayed gastric emptying, and impairments of esophageal emptying.

► Treatment Steps

1. Lifestyle modification including weight loss, avoidance of certain foods, smoking cessation, and elevation of the head of the bed; and drugs to reduce the acidity of the stomach (antacids and H_2 receptor antagonists, PPIs, and prokinetic agents).
2. Antireflux surgery may be required.

► cram facts

Complications of GERD include fibrotic strictures causing dysphagia, and bleeding due to severe esophagitis.

2. Achalasia

► Symptoms

- Dysphagia, mainly to solids, is the most common symptom.
- Chest pain is seen in about half of the patients.
- Weight loss is common, and pulmonary symptoms can develop due to aspiration.

► Diagnosis

- Barium study shows a dilated esophagus with a narrowed gastroesophageal (GE) junction that resembles a bird's beak.
- Endoscopy.
- Manometry shows the absence of esophageal peristalsis and elevated LES pressure with incomplete relaxation after a swallow.

► Pathology

Physiologic studies demonstrate the presence of denervation of the smooth muscle segment of the esophagus. This results in the failure of peristalsis in the esophagus with consequent dilation. The LES fails to relax normally after a swallow.

► Treatment Steps

Measures to relax the LES using calcium channel blockers, injection of botulinum toxin, or endoscopic dilatation, and as a last resort, esophagomyotomy.

► cram facts

Achalasia is associated with increased risk for esophageal cancer.

3. Irritable Bowel Syndrome (IBS)

► Symptoms

Abdominal pain, bloating, and constipation or diarrhea, or both.

► Diagnosis

Primarily by clinical presentation but need to rule out other organic etiology.

► Pathology

A chronic disease characterized by frequent unexplained symptoms of abdominal pain, bloating, and bowel disturbances, which may be either predominantly diarrhea or predominantly constipation or alternating. Often associated with emotional distress.

► Treatment Steps

Lifestyle modification, including stress reduction, and pharmacologic agents (antispasmodics for pain, antidiarrheals, anticonstipating agents, and antidepressants).

4. Intestinal Pseudo-Obstruction

► Symptoms

- Usually manifested as abdominal pain, distention, and vomiting.
- Constipation or fecal impaction is common.

► Diagnosis

Radiologic studies such as barium enema.

► Pathology

A syndrome that is caused by ineffective propulsion and characterized by symptoms and signs of intestinal obstruction in the absence of an occluding lesion of the intestinal lumen.

► Treatment Steps

Correct underlying disease, prokinetic agents (to facilitatae normal propulsion), and palliative surgery.

► cram facts

Intestinal pseudo-obstruction can be caused by electrolyte abnormalities (hypokalemia, hypocalcemia), use of medications that slow the GI tract (anticholinergic agents), and diseases that affect the muscles or the enteric nervous system.

D. Metabolic Disorders

1. Hepatic Encephalopathy

► Symptoms

- Symptoms include impaired intellectual functions such as impaired attention, depression, personality change, sleep disorder, confusion, disorientation, somnolence, and coma.
- Impaired neuromuscular functions such as tremor, incoordination, asterixis, ataxia, decreased reflexes, and absent response to stimuli.

► Diagnosis

- Often based on clinical diagnosis.
- Conditions that precipitate hepatic encephalopathy include infection, GI bleeding, excessive dietary protein, dehydration, and uremia.

► Pathology

- Hepatic encephalopathy, or portosystemic encephalopathy, represents a reversible decrease in neurologic functions caused by liver disease.
- Occurs most notably in patients with portal hypertension. It is associated with elevated ammonia levels without any causal relationship. Fetor hepaticus is the sweet odor of the breath associated with increased ammonia levels.

► Treatment Steps

Identify and treat the precipitating cause and initiate ammonia-lowering treatments such as lactulose or neomycin.

2. Malabsorption

► Symptoms

- GI symptoms include diarrhea, steatorrhea, flatulence, and abdominal distention.
- Musculoskeletal symptoms include weakness, paresthesias, osteomalacia, and fractures.
- Skin and mucous membrane symptoms include easy bruisability, dermatitis, stomatitis, ecchymoses, petechiae, and edema.
- Weight loss, growth retardation, anemia, and neuropathy are common.

► cram facts

Diarrhea can be acute or chronic. In addition, it can be classified into osmotic or secretory. Osmotic diarrhea is due to malabsorption such as with lactose intolerance. Secretory is due to the active secretion of fluids by the mucosa as with cholera.

► Diagnosis

- Stool studies to rule out infectious etiology (most important step).
- 72-hour fecal fat determination to examine the integrity of fat absorption.
- D-xylose test to determine the integrity of the intestinal mucosa.
- Radiologic studies can detect anatomic abnormalities.
- Endoscopic evaluation with mucosal biopsy can detect mucosal abnormalities.

► Pathology

- Mechanisms of malabsorption can be divided into premucosal (lumenal), mucosal, and postmucosal (vascular and lymphatic).
- Causes include pancreatic diseases with decreased enzyme secretion (pancreatic insufficiency due to chronic pancreatitis or cystic fibrosis), liver diseases (cirrhosis), biliary obstruction with decreased bile salt concentration in the duodenum, and intestinal diseases with resultant decreased absorption of nutrients (celiac sprue, amyloidosis, IBD, giardiasis, or bacterial overgrowth).
- Fat absorption is often affected by these disorders.

► Treatment Steps

Correct underlying etiology if a specific cause of malabsorption can be determined.

E. Neoplastic Disorders

1. Barrett's Esophagus and Esophageal Cancer

► Symptoms

Dysphagia or weight loss.

► Diagnosis

Upper GI endoscopy with biopsy of the Barrett's segment.

► Pathology

- Barrett's metaplasia, intestinal metaplasia (change from squamous to columnar epithelium) with villous architecture and goblet cells, is a consequence of chronic GERD.
- A premalignant condition for adenocarcinoma of the esophagus.

► Treatment Steps

Treat GERD; if Barrett's metaplasia is present, then periodic (every 1–2 years) endoscopic examination (surveillance) should be performed, with biopsy of the Barrett's segment to detect dysplasia early.

> **► cram facts**
>
> Trousseau's syndrome, migrating thrombophlebitis, is associated with pancreatic cancer.

> **► cram facts**
>
> Chronic pancreatitis is a risk factor for pancreatic cancer.

2. Pancreatic Cancer

► Symptoms

- Symptoms usually develop late in the disease and mainly in the form of painless jaundice.
- A nontender and palpable gallbladder, depression, weight loss, and diabetes can occur.

► Diagnosis

CT scan, ERCP, endoscopic ultrasonography (EUS), and MRI.

► Pathology

- The second most common GI malignancy.

- Genetic factors may play a role.
- Majority of pancreatic cancer is derived from exocrine (ductal and acinar) elements.

► Treatment Steps
1. Pancreaticoduodenectomy or the "Whipple procedure."
2. Palliative measures include endoscopic stenting, radiation, and chemotherapy.

3. Colon Polyps and Cancer (Figure 4–6)

► Symptoms

Polyps are common and usually asymptomatic.

► Diagnosis

Colonoscopy (see Figure 4–7) or barium enema.

► Pathology
- Colon cancer is the most common GI cancer.
- Polyp (adenoma) is the precursor to cancer. Adenoma can be tubular, villous, or mixed.

► Treatment Steps
1. Screening of colon cancer in average-risk individuals (those without family or personal history) should take place after age 50.
2. Adenomatous polyps can often be removed during colonoscopy (polypectomy).
3. Colon cancer is usually treated with surgery, but radiation or chemotherapy may be necessary.

► cram facts

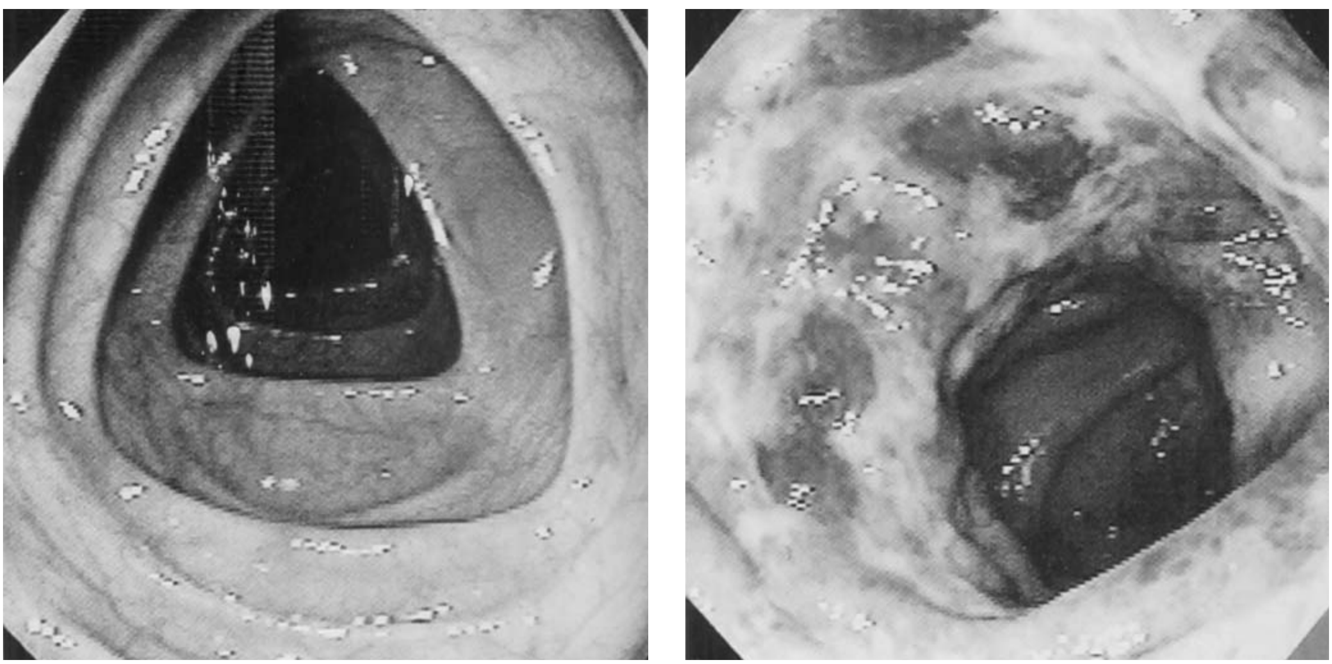
Larger polyps and cancer can cause bleeding, anemia, or obstruction.

► cram facts

Right-sided or cecal cancer is usually flat and presents with bleeding.

► cram facts

Left-sided or rectosigmoid cancer is usually circumferential and presents with obstruction.



A B

Figure 4–6. Colonoscopic appearance of a normal colon (A) and a colon with ulcerative colitis (B). Note the presence of diffuse ulcerations, exudates, edema, and bleeding in ulcerative colitis.

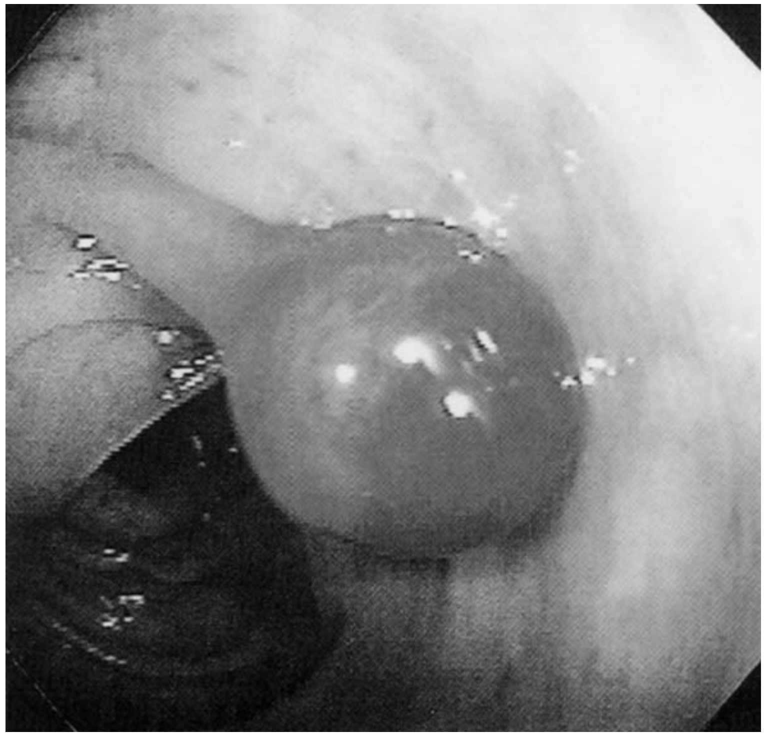


Figure 4–7. Colonoscopic appearance of a polyp. Note that this pedunculated polyp is supported by a stalk.

F. Vascular Disorders

1. Mesenteric Ischemia

► Symptoms

- Development of sudden abdominal pain in patients with predisposing factors such as congestive heart failure, cardiac arrhythmias, recent myocardial infarction (MI), or hypotension should raise the suspicion for acute mesenteric ischemia.
- Abdominal distention or bleeding can occur.

► Diagnosis

- Plain x-ray reveals “thumbprinting” of the small bowel.
- CT scan.
- Selective mesenteric angiography.

► Pathology

- Ischemic injury of the intestine results from deprivation of oxygen and nutrients necessary for cellular integrity. Can be caused by occlusion of blood vessels either by a thrombus or embolus. Can also be caused by hypoperfusion such as a hypotensive episode.
- Acute mesenteric ischemia is more common than chronic mesenteric ischemia, and arterial disease is more frequent than venous disease. Acute mesenteric ischemia is usually due to occlusion of the superior mesenteric artery. Chronic mesenteric ischemia is usually associated with hypercoagulable conditions, cancer, cirrhosis, or following abdominal surgery.

► Treatment Steps

Supportive, correct underlying disease, and surgery may be necessary.

G. Systemic Disorders Affecting the Gastrointestinal System

1. Human Immunodeficiency Virus (HIV) Infection

► Symptoms

Diarrhea, odynophagia and dysphagia, abdominal pain, GI bleeding, and anorectal diseases.

► Diagnosis

Endoscopic evaluation and biopsy.

► Pathology

- GI system is often involved due to HIV infection.
- Diarrhea is common and is mostly caused by protozoal infection. Esophageal symptoms include dysphagia and odynophagia and are often caused by candidal or herpetic esophagitis.

► Treatment Steps

Based on specific causes of symptoms.

► cram facts

Hairy cell leukoplakia is whitish plaques on the tongue in HIV patients.

2. Diabetes Mellitus

► Symptoms

- Dysphagia from esophageal dysfunction.
- Nausea, vomiting, and abdominal pain from delayed gastric emptying (gastroparesis).
- Diarrhea and other intestinal conditions including fecal incontinence and constipation.

► Diagnosis

- Clinical history.
- Diarrhea due to neuropathy is also common.

► Pathology

Diabetic autonomic neuropathy is a common cause of GI symptoms associated with diabetes mellitus.

► Treatment Steps

Prokinetic agents for esophageal and gastric dysmotility, and clonidine may be effective in diabetic diarrhea.

H. Genetic Disorders

1. Hereditary Hemachromatosis (HH)

► Symptoms

- Symptomatic patients experience lethargy, weakness, arthralgia, abdominal pain, and loss of potency in men.
- Hepatomegaly and skin pigmentation are common.

► cram facts

Hemochromatosis can also be acquired through blood transfusions.

► Diagnosis

- Abnormal liver function tests.
- Elevated iron saturation and increased hepatic iron content.
- Mutational analysis of the homozygote for the hemochromatosis (HFE) gene.

► Pathology

- *HH* is the term used for the autosomal recessive disorder of iron overload caused by mutations in the HFE gene and is characterized by an inappropriately elevated rate of intestinal iron absorption.

► **cram facts**

Females are less susceptible to hemochromatosis effects due to the blood loss (autophlebotomy) they sustain with menstruation.

► **cram facts**

Kayser–Fleischer rings are yellow-brown corneal deposits seen with a slit lamp examination.

- Disease is manifested by iron overload of important organs, such as the liver with consequent cirrhosis, the skin with bronze color, the joints with arthralgias, the pancreas with consequent pancreatic insufficiency and diabetes, and the hypothalamus with consequent impotence.

► Treatment Steps

Periodic phlebotomy to reduce the body iron stores, and liver transplantation may be required if cirrhosis is evident.

2. Wilson's Disease (Hepatolenticular Degeneration)

► Symptoms

Symptoms include hepatic, neurologic (Parkinson-like symptoms), and psychiatric.

► Diagnosis

- Abnormal liver function tests.
- Patients have increased urinary copper output and decreased serum copper content and ceruloplasmin level.

► Pathology

- An autosomal recessive disorder that causes copper overload/deposition in the liver, lenticular nuclei, cornea, and other sites.
- Can cause chronic active hepatitis and liver cirrhosis.

► Treatment Steps

Treatments include copper chelation with lifelong use of D-penicillamine, trientine hydrochloride (both remove copper from the tissues), and zinc (competes with copper for intestinal absorption).

3. Cystic Fibrosis

► Symptoms

Recurrent respiratory infection, malabsorption of nutrients, and intestinal motility disorder are common.

► Diagnosis

Mutational analysis of the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

► Pathology

- The most common genetic disorder of the Caucasian populations.
- An autosomal recessive disease caused by mutation of the CFTR gene, causing an abnormal chloride secretion.
- Frequently causes disease of the pancreas (exocrine dysfunction), lung (recurrent infection), and intestine (paralytic ileus).

► Treatment Steps

Pancreatic enzyme replacement.

4. α_1-Antitrypsin (AT1) Deficiency

► Symptoms

- Liver disease including cholestasis is common.
- Emphysema is the major manifestation of involved lung.

► Diagnosis

- Serum AT1 level.
- Phenotypic determination by protein electrophoresis.

► Pathology

- The most common metabolic disorder of the liver.
- Autosomal recessive with codominant expression.
- The PiZZ variant of AT1 is associated with liver and lung disease.

► Treatment Steps

Symptomatic measures, and liver transplantation may be necessary.

► **cram facts**

In all the liver disorders resulting in cirrhosis or end-stage liver disease, decreased albumin levels result in ascites and reduced production of coagulation factors increases the risk for bleeding.

BIBLIOGRAPHY

Cotran RS, Robbins SL, Kumar V (eds.). *Robbins Basic Pathology,* 7th ed. Philadelphia: W.B. Saunders, 2002.

Drake RL, Vogl W, Mitchell A. *Gray's Anatomy for Students.* New York: Churchill Livingstone, 2004.

Fawcett DW (ed.). *Bloom and Fawcett: A Textbook of Histology,* 12th ed. New York: Chapman & Hall, 1994.

Ganong WF (ed.). *Review of Medical Physiology,* 20th ed. New York: McGraw-Hill, 2001.

Goldman L, Ausiello D (eds.). *Cecil Textbook of Medicine,* 22nd ed. Philadelphia: W.B. Saunders, 2003.

Tortora GJ, Grabowski SR (eds.). *Principles of Anatomy and Physiology,* 10th ed. New York: Wiley, 2002.

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Hematology and Immunology

5

I. NORMAL PROCESSES

A. Hematopoiesis

During early fetal development, hematopoiesis occurs in “blood islands” found within the yolk sac. Hematopoiesis shifts to the liver after 4 months and to the bone marrow in late gestation. By adolescence, hematopoiesis is limited to the proximal long bones, pelvis, and axial skeleton. Blood cells are derived from pleuripotent and progenitor stem cells capable of both self-renewal and further differentiation along myeloid and lymphoid lines (Figure 5–1). Normal adult blood cell counts are listed in Tables 5–1 and 5–2.

B. Erythrocytes

1. Erythropoiesis

Stages of erythropoiesis recognizable by light microscopy are the pronormoblast (large nucleus with prominent nucleoli), basophilic

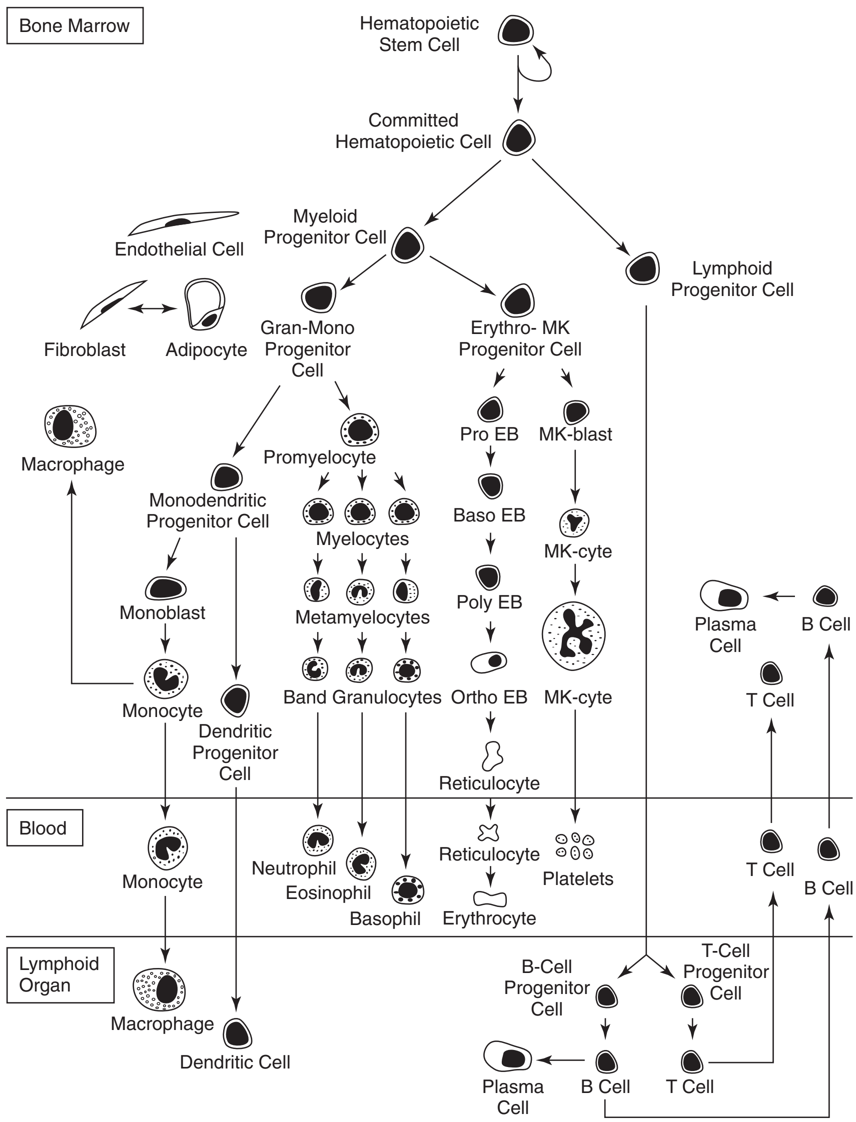


Figure 5–1. Hematopoiesis. (Reproduced, with permission, from Lee GR, Foerster J, et al. *Wintrobes Clinical Hematology.* Baltimore, MD: Lippincott Williams & Wilkins, 1999:147.)

5-1

NORMAL ADULT HEMATOLOGY REFERENCE VALUES

Hemoglobin	13–18 g/dL
Hematocrit	40–52%
Red blood cell count	$4.4–5.9 \times 10^6/mm^3$
White blood cell count	$4.0–10 \times 10^3/mm^3$
MCV	80–100 fL
MCH	26–34 pg
MCNC	32–36 g/dL
Platelet count	$150–450 \times 10^3/mm^3$
Reticulocyte count	0.8–2.5%

normoblast, polychromatic normoblast (last stage capable of mitosis), and orthochromatic normoblast. With each stage, the red cell decreases in size, the nuclear-to-cytoplasmic ratio decreases, the cytoplasm assumes a less blue and more pinkish appearance (decreasing ribosomal RNA/increasing hemoglobin concentration), and the nucleus becomes increasingly pyknotic. Following extrusion of the nucleus, the erythrocyte circulates as a reticulocyte (1% of circulating erythrocytes), fully maturing in 1–2 days. Erythropoiesis is stimulated by erythropoietin, a cytokine produced principally by renal cortical interstitial cells.

2. Erythrocyte Destruction

After 100–120 days, most senescent erythrocytes are removed from circulation by splenic macrophages. Liberated iron binds to transferrin for transport to the bone marrow for reincorporation into erythroid precursors. Heme is converted by a series of enzymes into biliverdin and subsequently bilirubin. Bilirubin requires hepatic conjugation with glucuronic acid for water solubility. Conjugated bilirubin is excreted in bile and converted by enteric bacteria to urobilinogen. Some urobilinogen is reabsorbed (10–20%) and either excreted in urine or recirculated by the liver. A few erythrocytes (15%) are destroyed intravascularly. Released hemoglobin binds to haptoglobin and is removed from circulation by hepatocytes.

3. Hemoglobin Structure

a. Globin—A single hemoglobin unit is a tetramer of polypeptide globin chains, each chain containing a heme moiety (Figure 5–2). Two α globin chains couple noncovalently with two non-α chains (β, γ, or δ). The pairing of α and β globin chains is referred to as hemoglobin A; α and γ as hemoglobin F (fetal hemoglobin); and α and δ as hemoglobin A_2. After birth, γ globin production is gradually replaced by β globin production. By 6 months of life, hemoglobin A is the predominant form of hemoglobin (97%), with smaller quanti-

5-2

WHITE BLOOD CELL DIFFERENTIAL COUNT IN ADULTS

	Percentage	Absolute
Segmented neutrophils	50–70%	$2,400–7,500/mm^3$
Bands	2–5%	$96–648/mm^3$
Lymphocytes	20–40%	$950–4,750/mm^3$
Monocytes	2–9%	$100–950/mm^3$
Eosinophils	0–5%	$0–450/mm^3$
Basophils	0–2%	$0–215/mm^3$

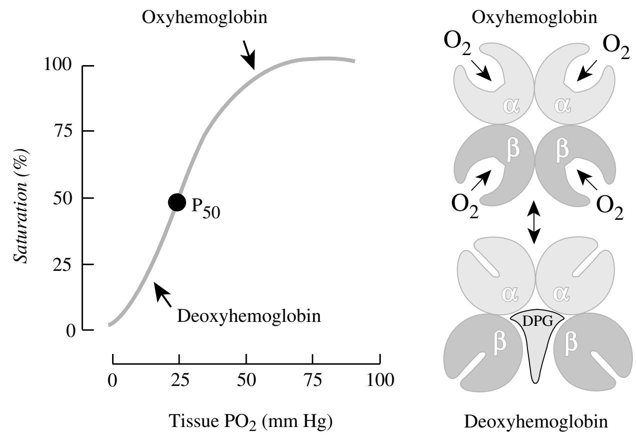


Figure 5–2. Hemoglobin-oxygen dissociation curve. Hemoglobin is capable of a respiratory motion where oxygen loaded at the lung is unloaded at the tissue level. To accept oxygen, 2,3-DPG and carbon dioxide are expelled, salt bridges are ruptured, and each of the four heme groups opens to receive a molecule of oxygen. Oxygen release to tissues reverses the process; salt bridges are reestablished and both 2,3-DPG and carbon dioxide are accepted. The complex interaction of the four heme groups is responsible for the sigmoid shape of the hemoglobin-oxygen dissociation curve. (Redrawn from Hillman RS, Ault AA, Rinder HM. *Hematology in Clinical Practice,* 4th ed. New York, NY: McGraw-Hill, 2005:4.)

ties of hemoglobin A_2 (2%), and residual hemoglobin F (1%). Two α globin genes are found on each chromosome 16 and one β globin gene on each chromsome 11.

b. Heme—Heme consists of a reduced ferrous ion, surrounded by a protoporphyrin ring. The first step of protophorphyrin biosynthesis is rate limiting and irreversible, and involves the conversion of glycine and succinyl coenzyme A (CoA) to 5-amino-levulinic acid by the enzyme S-aminolevulinic acid synthetase.

4. Hemoglobin Function

a. Oxygen Transport—Most oxygen (98.5%) is transported bound to hemoglobin (oxyhemoglobin). The relationship between the PO_2 (partial pressure of oxygen) and hemoglobin oxygen saturation is illustrated by the oxygen dissociation curve (Figure 5–3). Oxygen binding at one heme site facilitates binding at other heme sights within a he-

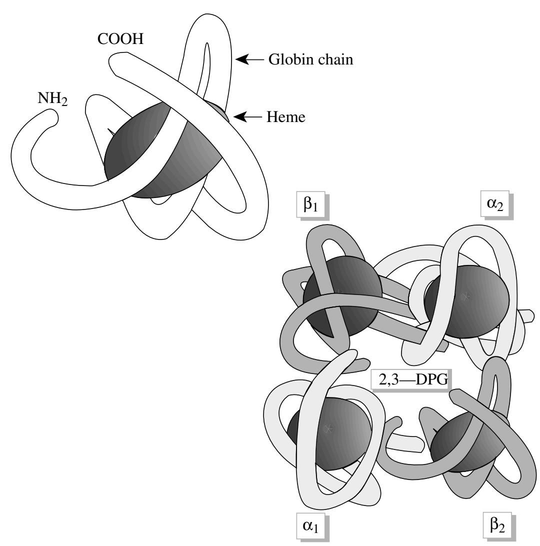


Figure 5–3. Hemoglobin–oxygen dissociation curve. (Redrawn from Hillman RS, Ault AA, Rinder HM. *Hematology in Clinical Practice,* 4th ed. New York, NY: McGraw-Hill, 2005:81.)

moglobin unit, resulting in a "sigmoid-shaped" curve. The steep portion of the curve allows greater release of oxygen at tissue sites where oxygen tension (i.e., PO_2) is low. A low pH (Bohr effect), high temperature, and increased red blood cell concentrations of 2,3-diphosphoglycerate (2,3-DPG) shift the curve to the right (allowing greater O_2 release at any given PO_2). Hypoxia increases 2,3-DPG production.

b. Carbon Dioxide Transport—Most carbon dioxide (70%) is transported in blood as bicarbonate (HCO_3^-) and hydrogen ions (H^+). Carbonic anhydrase, a cytoplasmic enzyme, is responsible for the conversion of CO_2 and H_2O to H_2CO_3 and subsequently H^+ and HCO_3^-. At the tissue level, where CO_2 is abundant, the reaction is driven toward HCO_3^- and H^+ production.

In the lungs, CO_2 is reconstituted and expired. Five to 10% of carbon dioxide is transported dissolved in plasma, and 20–30% is bound to the N-terminal end of hemoglobin (carbaminohemoglobin).

Hemoglobin CO_2 saturation has a fairly linear relationship with the P_{CO_2} (partial pressure of carbon dioxide). The carbon dioxide dissociation curve shifts according to oxygen tension (high PO_2, to the right; low, to the left), referred to as the *Haldane effect.*

5. Nutritional Requirements

a. Vitamin B_{12} (Cobalamin)—Cobalamin is derived from microorganisms and obtained by the ingestion of animal products. The daily requirement is 2–3 μg, and normal total body store is 4 mg. In the stomach cobalamin binds R-binder protein (produced in saliva) for transport to the duodenum, where it then binds intrinsic factor (produced by gastric parietal cells). Cobalamin is absorbed in the terminal ileum, transported in the blood by transcobalamin II, and stored within the liver. Cobalamin is a cofactor in the conversion of methylmalonyl CoA to succinyl CoA. It also serves as a methyl donor in the conversion of homocysteine to methionine. In this reaction, cobalamin is regenerated by accepting a methyl group from *N*5-methyltetrahydrofolate. Cobalamin deficiency affects DNA synthesis by "trapping" tetrahydrofolate as *N*5-methyltetrahydrofolate.

b. Folate (Folic Acid)—Daily requirement is 150–300 μg of folate, and normal total body store is 5–20 mg. Folate is present as polyglutamates in a variety of foods, including green vegetables and organ meats. Intestinal enzymes convert folate polymers to *N*5-methyltetrahydrofolate monoglutamate, the principal transport form of folate. *N*5-methyltetrahydrofolate is either polyglutamated and stored within hepatocytes or undergoes enterohepatic recirculation. Folate is a cofactor for the transfer of one-carbon fragments (e.g., methyl, formyl, and methylene). Folate-dependent reactions include (1) the de-novo synthesis of purines; (2) the conversion of deoxyuridylate monophosphate (dUMP) to deoxythymidylate monophosphate (dTMP); and (3) the synthesis of methionine (which also requires B_{12}, as described above). The conversion of dUMP to dTMP is catalyzed by the enzyme thymidylate synthetase and is rate limiting in DNA synthesis. *N*5,10-methylenetetrahydrofolate (derived from tetrahydrofolate) serves as a one-carbon donor in the reaction, and in the process is oxidized to dihydrofolate. Dihydrofolate is then reduced to tetrahydrofolate by dihydrofolate reductase (see Figure 5–4).

c. Iron—Total body iron for adults is 3–4 g, most contained within hemoglobin, myoglobin, and various enzymes (e.g., cytochrome P-450), with the remaining iron in storage as either ferritin or hemosiderin. Daily iron requirement is roughly 1 mg for men and post-

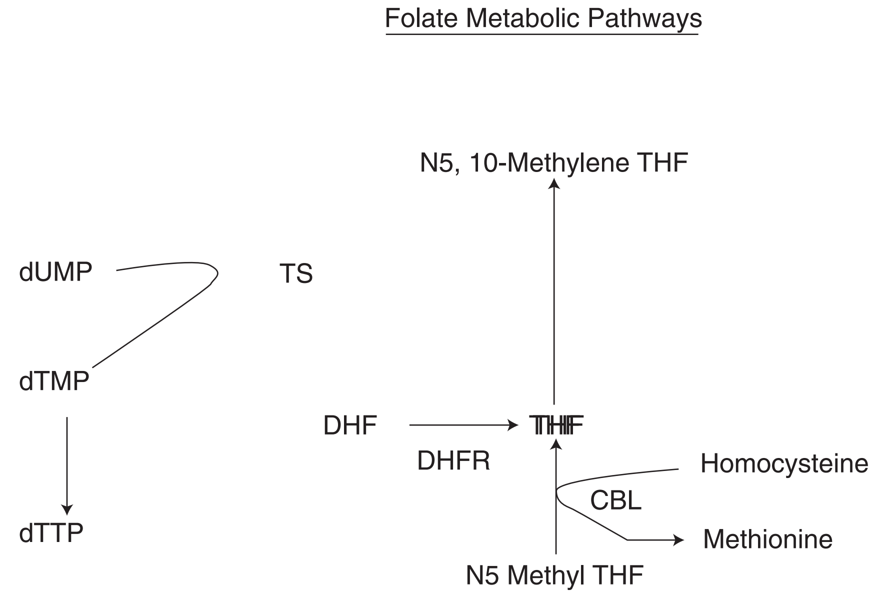


Figure 5–4. Folate metabolic pathways. dTMP, deoxythymidylate monophosphate; dUMP, deoxyuridylate monophosphate; dTTP, deoxythymidylate triphosphate; THF, tetrahydrofolate; DHF, dihydrofolate; DHFR, dihydrofolate reductase; TS, thymidylate synthetase; CBL, cobalamin.

menopausal women; premenopausal and pregnant women require more. The typical Western diet contains 10–20 mg of iron per day. Absorption varies from 5 to 10% but can increase 3–5-fold in states of deficiency or increased erythropoiesis. Animal-derived (heme) iron is more efficiently absorbed than plant-derived (nonheme) iron. Heme is taken up intact by proximal intestinal enterocytes, where iron is liberated. Nonheme iron is mostly in the nonabsorbable ferric state, reduced to the ferrous state in acid environments (gastric acidity, ascorbic/citric acid). Amino acids also complex with and increase nonheme iron absorption. Iron is either transported directly into portal circulation or remains within enterocytes as ferritin depending on requirements.

Transferrin—Transferrin is a hepatically synthesized iron transport protein. Transferrin binds to specific cell-surface receptors. The rate of both transferrin and transferrin receptor synthesis is affected by iron stores. Transferrin is ordinarily one third saturated with iron (measured as the transferrin saturation). The total iron-binding capacity reflects both the bound and unbound ability of transferrin.

Ferritin—Ferritin is the principal storage form of iron, found within hepatocytes, mononuclear phagocytic cells, and maturing erythrocytes. The concentration of ferritin increases in states of systemic inflammation (i.e., “acute phase reactant”). Synthesis of apoferritin (unoccupied ferritin) increases in iron-deplete states, promoting iron storage. Lysosomal degradation and denaturation of intracellular ferritin results in an iron-containing, Prussian blue–staining protein called *hemosiderin.*

6. Erythrocyte Cytoskeleton (Figure 5–5)

Spectrin is the most abundant cytoskeletal protein. It exists as a dimer of intertwined alpha and beta chains. The ends of spectrin form tetramers by head-to-head association with other spectrin

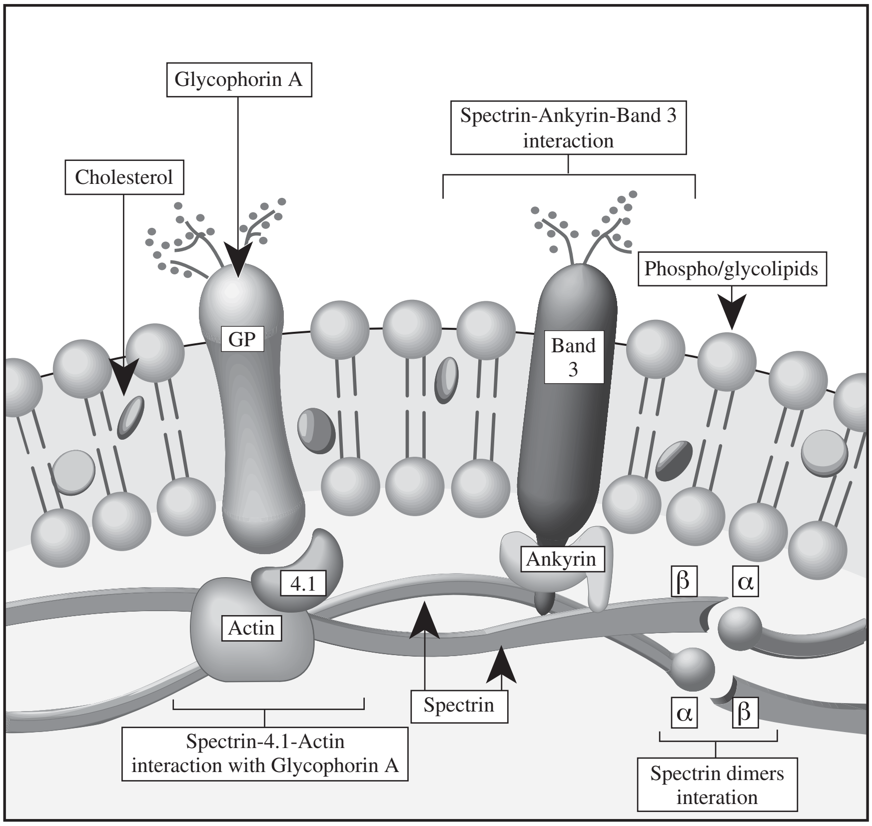


Figure 5–5. Red blood cell cytoskeleton. (Reproduced, with permission, from Hillman RS, Autt KA. *Hematology in Clinical Practice.* New York: McGraw-Hill, 2002:3.)

dimers. This association is reinforced by the presence of both actin and protein 4.1. Spectrin is tethered to the lipid bilayer membrane by ankyrin (protein 4.2), which binds directly to the transmembrane ion transporter, band 3. Protein 4.1 also has a binding site for the transmembrane protein glycophorin.

7. Erythrocyte Energy Metabolism and Utilization

Anaerobic metabolism generates energy to maintain charge balance and prevent oxidation. Glucose freely enters erythrocytes and is metabolized preferentially via glycolysis. It can be selectively shifted into the hexose-monophosphate pathway during oxidative stress. Glycolysis generates adenosine triphosphate (ATP), nicotinamide adenine dinucleotide (NADH), and 2,3-DPG. Sodium/potassium/ATP pumps require ATP to maintain electrolyte balance and prevent osmotic swelling. The hexose-monophosphate shunt generates nicotinamide adenine dinucleotide phosphate (NADPH), via glucose-6-phosphate dehydrogenase (G6PD). NADPH maintains a reduced glutathione, protecting erythrocytes from oxygen-derived free radical injury.

C. Platelets

Platelets are anucleate fragments of megakaryocyte cytoplasm. Megakaryocytes are large cells with abundant cytoplasm and hyperlobulated, polyploid nuclei. Thrombopoietin, produced by hepatocytes, is the principal cytokine responsible for thrombocytopoiesis. Platelet alpha and dense granules contain various factors important for clotting (e.g., platelet factor 4, thrombospondin, von Willebrand factor, fibrinogen, serotonin, and adenosine diphosphate [ADP]). Platelets survive approximately 10 days and are removed primarily by the spleen.

D. Granulocytes

1. Granulocytopoiesis

Granulocytes are derived from myeloid progenitor stem cells. The neutrophil (polymorphonuclear leukocyte [PMN]) is the most abundant and clinically important granulocyte. Stages of neutrophil maturation include myeloblast, promyelocyte, myelocyte, metamyelocyte, band, and segmented neutrophil. Myeloblasts have large nuclei with many nucleoli, and scant agranular cytoplasm. Azurophilic (primary) and specific (secondary) granules appear during the promyelocyte and myelocyte stage, respectively (see Table 5–3). With further maturation, chromatin condenses; the nucleus loses nucleoli, becomes ovoid, and segments; and protein synthesis ceases. A mature neutrophil has a characteristic hyperlobed nucleus and purple-staining, cytoplasmic azurophilic granules (Wright–Giemsa stain). Neutrophil production, maturation, and release are controlled by several cytokines, including granulocyte colony–stimulating factor (G-CSF) and granulocyte/monocyte colony–stimulating factor (GM-CSF). Steroids and endotoxin stimulate neutrophil release from the marrow storage compartment into circulation.

2. Neutrophil Function

a. Circulation, Diapedesis, Chemotaxis—Neutrophils in circulation are in equilibrium with neutrophils adherent to endothelial cells (marginating compartment). Exercise or epinephrine causes a rapid, transient demargination of neutrophils. Neutrophils remain in circulation for 6–8 hours. Selectins are glycoproteins found on neutrophils (L-selectin) and endothelial cells (E-selectin) that allow for neutrophil migration by loose binding to specific glycoprotein ligands (i.e., binding molecules). Chemoattractants (complement fragment C5a, leukotriene B4, bacterial products, etc.) stimulate neutrophil expression of integrins, cell-surface glycoproteins with an increased affinity for specific endothelial ligands. Neutrophils enter the extravascular space by extending pseudopods (an actin- and myosin-dependent process) between endothelial cells (diapedesis). *Chemotaxis* is the term for the chemoattractant-directed movement of neutrophils toward sites of tissue injury. Survival in tissue is measured in days.

b. Phagocytosis/Bacterial Killing—Opsonization (antibody and/or complement fragment targeting of antigen for phagocytosis). Neutrophils have specific receptors for the Fc portion of immunoglobulin G (IgG), C3b, and C3d complement fragment, but are capable of phagocytizing nonopsonized antigen. Phagocytized

5-3

POLYMORPHONUCLEAR (PMN) CELL GRANULE CONTENT

Cell Type	Content
Azurophilic	Myeloperoxidase, lysozyme, defensins, lytic enzymes (i.e., elastase, proteinase, glucuronidase, glucosiminidase, mannosidase, etc.)
Specific	Lactoferrin, lysosyme, lytic enzymes (e.g., gelatinase, collagenase, heparanase, histaminase), vitamin B_{12} binding protein

particles fuse with specific and azurophilic granules. Effective microbial killing relies on the generation of potent reactive oxygen molecules. Following phagocytosis, oxygen consumption increases ("oxidative burst"), and NADPH-dependent oxidase enzymes assemble on the cell membrane. NADPH serves as the electron donor in the reduction of oxygen to superoxide (O_2^-), which is then converted by superoxide dismutase to hydrogen peroxide (H_2O_2). Hydrogen peroxide reacts with halide ion (Cl^-) in the presence of myeloperoxidase to form hypochlorite, a potent antimicrobial.

E. Eosinophils

Maturation is similar to that of neutrophils. Eosinophils have bilobed nuclei and distinct granules that appear yellow-red with Wright–Giemsa stain. The granules contain preformed substances, including major basic protein, cationic protein, and eosinophil peroxidase. When activated, eosinophils generate leukotrienes and numerous proinflammatory cytokines. Like neutrophils, eosinophils are capable of migration, adhesion, pseudopod formation, and limited phagocytosis. They play an important role in allergic disease (type 1 hypersensitivity reactions) and in antiparastic (helminthic) immunity.

F. Basophils

Maturation is similar to that of neutrophils. Basophils are structurally and functionally similar to tissue-based mast cells. They possess a single large (usually hypersegmented) nucleus and numerous histamine-containing granules that appear dark purple with Wright–Giemsa stain. Receptors for the Fc portion of immunoglobulin E (IgE) are found on the cell membrane. Basophils are important in allergic inflammation (e.g., type 1 hypersensitivity responses).

G. Monocytes/Macrophages

1. Monocytopoiesis, Monocyte/Macrophage Circulation

Monocytes/macrophages (i.e., mononuclear cells) are part of the reticuloendothelial system. Monocytes originate from monoblasts and subsequently promonocytes. Monocytes are distinguished by their large size and large, oblong nuclei. Monocyte growth and differentiation is mediated by monocyte colony-stimulating factor (M-CSF), GM-CSF, G-CSF, and interleukin 3. After circulating for a few hours, monocytes enter tissue where they differentiate into macrophages (liver, Kupffer cells; lung, alveolar macrophages; skin, Langerhans' cells; brain, microglial cells; spleen, splenic macrophages; bone, osteoclasts). Monocyte/macrophage locomotion is via pseudopod extension in the direction of chemotactic signals.

2. Macrophage Function

Macrophage cell surface molecules include class 1 and 2 major histocompatibility complex (MHC) for antigen presentation, and binding receptors for various ligands (e.g., the Fc portion of immunoglobulin, complement C3b/C4b, transferrin, low-density lipoprotein [LDL] cholesterol). Macrophages are capable of chemotaxis and phagocytosis, further amplified by T-lymphocyte cytokines (e.g., tumor necrosis factor gamma [TNF-γ]). Unlike neutrophils, macrophages arrive at sites of inflammation late (24–72 hours), undergo mitosis, and survive for several months. In addition to their role in inflammation, macrophages are effector cells in many immune and nonimmune reactions (see Table 5–4).

H. Lymphocytes

1. General

All lymphocytes are derived from lymphoid progenitor cells. Sixty to 80% of circulating lymphocytes are T cells, 10–20% B cells, and 5–10% natural killer (NK) cells (null cells or large granular lymphocytes). NK cells have prominent azurophilic granules (Wright–Giemsa stain). Immunophenotyping directed at unique cell-surface antigen proteins (i.e., CD or “cluster of differentiation” antigens) is necessary to differentiate T and B lymphocytes.

2. B Lymphocytes

In the process of bone marrow maturation, autoreactive B lymphocytes are eliminated. Each mature B lymphocyte expresses cell-surface immunoglobulin M (IgM) with a unique, antigen-specific binding site (i.e., the idiotype). Idiotype specificity results from rearrangement of the V, J, D genes coding for heavy- and light-chain components of the antigen-binding site. The mature B lymphocyte circulates between lymphatic tissue (i.e., lymph nodes, spleen, Peyer’s patch, etc.). Antigen binding to the B-cell immunoglobulin receptor (with $CD4^+$ T-lymphocyte “help”) initiates transformation of the B lymphocyte into either an immunoglobulin-producing plasma cell or a memory cell (primary immune response). Plasma cells actively synthesize idiotype-specific IgM (i.e., humeral immune response). Memory B cells are capable of a rapid amnestic response (secondary immune response) on reexposure to antigen or prolonged primary exposure. Heavy-chain class switch alters the isotype (e.g., IgG, IgE, and IgA) while preserving antibody idiotype. A secondary immune response is more rapid, specific, and of greater magnitude than a primary response.

3. T Lymphocytes

T lymphocytes are derived from bone marrow progenitor cells that mature in the thymus gland. During maturation, autoreactive T lymphocytes are deleted. The T-cell receptor gene undergoes rearrangement similar to that of the B-lymphocyte immunoglobulin gene. A T-cell receptor consists of α- and β-chain subunits, associated with a group of proteins (called CD3 complex), important for transmem-

5-4

FUNCTIONS OF MACROPHAGES

Inflammation	Granules contain lytic enzymes similar to PMNs, including myeloperoxidase. They can generate an “oxygen burst” and remove opsonized antigen.
Immune modulation	1. Produce cytokines important in cell recruitment and propagation of an inflammatory/immune response. Interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α) activate lymphocytes and stimulate division, initiate synthesis of hepatic acute phase reactants, induce hyperthermia (via direct effect on the hypothalamus), stimulate neutrophils, and enhance neutrophil–endothelial adhesions. TNF-α contributes to the cachexia (wasting) seen in many chronic illnesses. 2. Present antigen, initiating immune response. 3. Produce complement proteins, tissue factor, and some coagulation proteins. 4. Form giant cells and granulomas, eradicating and/or limiting dissemination of intracellular and other fastidioius microorganisms (e.g., mycobacterium, fungi, syphilis).
Scavenging/phagocytosis	Splenic and hepatic macrophages remove opsonized circulating antigen as well as senescent blood cells.
Iron metabolism	Store iron with increased activity during acute and chronic inflammation.
Lipid metabolism	Take up LDL, becoming foam cells.

brane signal conduction. The end of the α and β chains forms the idiotypic variable antigen-binding region, and the base forms the constant region. T cells subdivide into populations of $CD8^+$ suppressor cells, $CD8^+$ cytotoxic cells, or $CD4^+$ helper cells. $CD4^+$ helper T cells are critical for initiating and coordinating an immune response. T-helper cells are subdivided into two distinct populations: T_H1 and T_H2. T_H1 produce interleukin-2 (IL-2) and interferon-γ (IFN-γ), which play a role in autocrine T-helper stimulation, delayed hypersensitivity reactions, CD8+ T-cell cytotoxicity, and macrophage activation. T_H2 produce IL-4, IL-5, and IL-6, important in providing B-cell help (e.g., isotype switching, proliferation, and differentiation into plasma/memory cells) and activating eosinophils and mast cells. Mature T lymphocytes circulate between lymphatic tissues. $CD8^+$ cytotoxic T lymphocytes recognize viral antigen or unique cancer antigens expressed on host cells in conjunction with class 1 MHC. Cytotoxic T cells (with "help" from $CD4^+$ T lymphocytes) produce "perforins" capable of lysing altered host cells. Cell-mediated immunity refers to the coordinated response by macrophages, NK cells, T-helper cells, and cytotoxic lymphocytes. Memory T cells remain once antigen is cleared.

4. NK Lymphocytes

NK lymphocytes directly attack host cells altered by virus or neoplasia without formal antigen presentation. They do not have cell-surface immunoglobulin or receptors but do have Fc receptors that bind and directly destroy opsonized targets (referred to as *antibody-dependent cellular cytotoxicity* [ADCC]).

I. Aspects of Normal Immunity

Immune mechanisms are classified as either innate or adaptive. Innate immunity includes cellular components as well as mechanical and chemical barriers to infection. Innate immunity is patterned, nonspecific, and without memory. Conversely, adaptive immunity is highly specific and capable of recalling previous antigen encounters with a rapid, amplified immune response (see Table 5–5).

1. Antigen

Since antigen is almost always presented in conjunction with MHC, the immunogenicity of an antigen is partially determined by a host's unique human leukocyte antigen (HLA) haplotype (see below). A large antigen may consist of multiple immunogenic sites, or *epitopes*. Haptens are small molecules that must bind to larger carrier proteins for recognition by the immune system.

2. Antibodies (Immunoglobulins)

The prototypical antibody consists of two light chains noncovalently bound to two heavy chains. The amino terminal end of the light and heavy chain forms the antigen-binding Fab region; the carboxyl-terminal heavy-chain ends form the non-antigen-binding Fc region. The Fc region of the antibody determines the specific antibody class or isotype (IgM, IgG, IgA, IgE, or IgD), and is responsible for antibody–cell and antibody–complement interactions. Antibody can bind antigen forming circulating immune complex, opsonize large antigen (e.g., bacteria), or agglutinate (i.e., "clump together") multiple adjacent antigen. The process of antibody–antigen binding prevents antigen from reaching its intended target, permits Fc recognition by phagocytic/NK cells, and initiates inflammation (via complement activation).

5-5

COMPONENTS OF INNATE AND ADAPTIVE IMMUNITY

Innate	
	Phacocytic cells Cytokines NK cells Complement Mechanical barriers (e.g., skin, mucous membranes, cerumen, cilia of respiratory passages) Chemical barriers (e.g., lysozyme in tears, lactoferrin in several secretions, gastric acidity)
Adaptive	
	Antigen-induced immune response Transferred immunity (e.g., placental maternal–fetal IgG transfer, immune globulin infusion) Vaccinations
Classes of immunoglobulins	
IgM	Circulates as a pentamer with 10 antigen-binding sites and a joining "J" chain. It is produced early in the primary response and has a half-life of 5 days. It efficiently agglutinates antigen and activates complement.
IgG	The most abundant antibody produced during the secondary immune response. The half-life of circulating IgG is approximately 3 weeks. It is less efficient at activating complement but readily binds to Fc receptors. It can pass from maternal to fetal circulation.
IgA	A dimer secreted primarily at mucosal barriers. It contains both a joining J chain and a secretory piece. IgA's primary function is limiting bacterial and viral binding to mucosal surfaces, neutralizing surface toxins, and preventing bacterial colonization.
IgE	The important immunoglobulin in allergic and antiparasitic immune responses. It binds to specific Fc receptors found on mast cells and basophils.
IgD	Has a limited role in immunity.

3. Major Histocompatibility Complex (Human Leukocyte Antigen)

MHC refers to the cell-surface proteins that allow the immune system to distinguish self from nonself antigen. MHC is subdivided into class 1 (present on all cells) and class 2 (present on antigen-presenting cells, B lymphocytes, and activated T lymphocytes). Class 1 and 2 MHC consist of several proteins, the genes of which are found on chromosome 6. The coding region is divided into loci designated HLA-A, -B, and -C (class 1) and HLA-DP, -DQ, and -DR (class 2). Within the population, there are many alleles for each HLA locus, generating substantial genetic diversity. The alleles at the six different loci are closely linked (haplotype). One of two potential haplotypes from each parent is passed to each offspring, resulting in a roughly 25% chance that nonidentical siblings will be HLA matched. Identifying HLA-matched donors is important for successful bone marrow transplantation.

4. Antigen-Presenting Cells (APCs)

With few exceptions (e.g., virally infected cells, NK cells), antigen must be formally presented to lymphocytes to initiate an immune response. Antigen is "processed" by macrophages, Langerhans' cells, dendritic cells, and other APCs and presented in conjunction with class 2 MHC (T-helper cell recognition) or class 1 MHC (cytotoxic and suppressor T-cell recognition).

5. Complement

Complement consists of 24 serum proteins circulating in an inactive state. Activation occurs via the "classic" or "alternate" pathways and eventuates in the formation of C3 convertase (C4bC2a or C3bBb), a protease capable of splitting C3 into C3a and C3b. C3b can combine directly with C3 convertase, forming a new protease, C5 convertase. C5 convertase cleaves C5 into C5a and C5b. C5b, in combination with C6, C7, and C8, promotes polymerization of C9 into a membrane attack complex, capable of lysing target cells. In the "classic" pathway, antibody–antigen immune complex directly activates complement, the cleavage products of which assemble into C4bC2a (C3 convertase). The "alternate" pathway does not require the presence of antibody. Tissue damage or certain microorganisms generate a low level of C3b, which is either inactivated (via complement factor H) or combines with complement factors B and D to form C3bBb (C3 convertase). The more C3 convertase present, the more C3b generated (i.e., feedback amplification). The primary inflammatory mediators generated by complement activation include C3a, C4a, C5a (anaphylatoxins); C3b (opsonin); and C5bC6,7,8,9 (membrane attack complex).

6. Lymph Nodes

Lymph nodes function as "immunologic filters" along draining lymphatic pathways. A lymph node consists of a fibrous capsule, a subcapsular sinus, an outer cortex, and an inner medulla. Large numbers of B lymphocytes, some T lymphocytes, dendritic cells, and macrophages form aggregates within the cortex (lymphoid follicles). Primary follicles stain homogeneously and contain mostly unstimulated B lymphocytes. Secondary follicles contain lighter-staining "germinal" centers rich in activated, antigen-stimulated lymphocytes (immunoblasts), capable of further differentiation into plasma cells or memory cells. The outermost area of the follicle is the mantle zone. Plasma cells are found mostly in the more centralized medulla. The area between the cortex and medulla (paracortical region) contains predominantly T lymphocytes and APCs.

7. Thymus

The thymus gland is found in the anterior mediastinum of children and undergoes atrophy after adolescence. It is derived embryologically from the third and fourth pharyngeal pouches. The outer cortex is rich in dividing immature T lymphocytes originating in the bone marrow. As T lymphocytes migrate toward the central medulla, surface antigen is acquired (i.e., CD3 and CD4 or CD8), receptor genes undergo rearrangement, and autoreactive cells are deleted.

8. Spleen

The spleen serves as an immunologic and mechanical filter for the blood. The parenchyma, or red pulp, consists of splenic cords (of Billroth) and open venous sinusoids. Aggregates of lymphocytes ("white pulp") are found throughout the red pulp. The splenic artery branches into smaller central arteries that penetrate the white pulp and terminate in the red pulp. The area of the white pulp surrounding the central arteries is rich in T cells (periarterial lymphatic sheaths). B cells are located more peripherally in follicular aggregates capable of forming germinal centers. Branches off the central artery terminate in a macrophage- and B-cell-rich "marginal zone," located between the white and red pulp.

J. Hemostasis

Hemostasis refers to normal mechanisms of clot formation. Primary hemostasis involves vasoconstriction of the injured vessel and formation of an occlusive platelet plug. Secondary hemostasis describes the processes leading to generation of a fibrin-based thrombus.

Thrombus dissolution (fibrinolysis) follows, coincident with repair of vascular injury. Secondary hemostasis is antagonized by anticoagulant mechanisms. Clotting factors and anticoagulant proteins are synthesized in the liver. The liver also removes products of fibrinolysis (fibrin degradation products, thrombin–antithrombin, and tissue plasminogen activator–plasminogen activator inhibitor complexes) and activated clotting factors from circulation.

1. Primary Hemostasis

Resting vascular endothelial cells produce substances such as prostacyclin and nitrous oxide that inhibit platelet aggregation and promote vasorelaxation. Vascular injury results in vasoconstriction (mediated by endothelial cell–derived endothelin and platelet-derived thromboxane A_2), and exposes platelets to subendothelial collagen, a potent platelet agonist. High sheer stress (e.g., as generated by disrupted vascular endothelium) can activate platelets directly, independent of collagen binding. Platelets do not bind directly to collagen, but are bridged by von Willebrand factor (vWF), a large multimeric protein produced by endothelial cells and platelets. Platelet surface glycoprotein GP 1bIX serves as the vWF binding site. Platelet activation alters platelet shape, exposes surface GPIIbIIIa receptor, initiates synthesis of thromboxane A_2, and triggers the release of platelet granules (the "release reaction"). In the process, negatively charged inner membrane phospholipid is exposed. The platelet membrane–derived fatty acid, arachidonic acid, is converted by the sequential action of platelet enzymes cyclooxygenase and thromboxane synthetase to thromboxane A_2. ADP, released from platelet α granules, and other platelet agonists (such as epinephrine, collagen, thrombin, thromboxane A_2) recruit and activate additional platelets. Activated platelets aggregate by fibrinogen binding to exposed platelet surface receptor GPIIbIIIa.

2. Secondary Hemostasis

The sequential, amplified activation of glycoproteins ("clotting factors") culminates in the formation of a fibrin-based thrombus (Figure 5–6). Activated clotting factors (designated by the subscript "a")

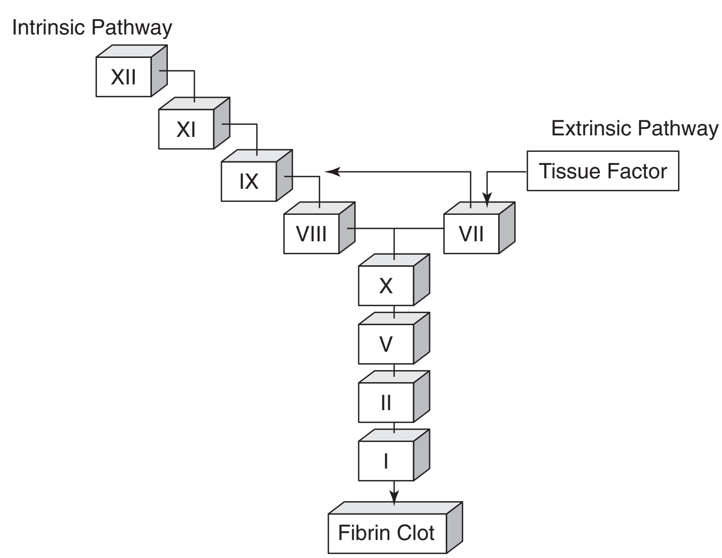


Figure 5–6. Coagulation cascade.

function as either enzymes or cofactors. Clotting factors II, VII, IX, and X require vitamin K for full activity ("vitamin K–dependent clotting factors").

a. The Extrinsic Pathway—Tissue factor (thromboplastin) is a cell membrane lipoprotein found abundantly in certain tissues (e.g., the adventitia of vessels, brain, bowel and respiratory epithelium, renal glomeruli, placenta, etc.). Endothelial cells and monocytes express tissue factor during systemic inflammation. Factor VII binds to tissue factor and undergoes autoactivation to VIIa. VIIa complexed with tissue factor converts X to Xa (also IX to IXa).

b. The Intrinsic Pathway—In vitro activation of the intrinsic pathway begins with the assembly of factor XII, factor XI, prekallikrein, and high-molecular-weight kininogen (HMWK) on a negatively charged surface (e.g., glass, kaolin, diatomaceous earth, heparin, collagen, chondroitin sulfate). Factor XII is activated to XIIa (contact activation) and prekallikrein to kallikrein. Factor XIIa converts HMWK to bradykinin (a mediator of inflammation) and factor XI to XIa. Factor XIa converts factor IX to IXa, which in turn converts X to Xa. This reaction is greatly accelerated by the cofactor VIIIa. Factor VIII circulates bound to vWF and is converted to VIIIa by thrombin. In vivo, normal hemostasis does not require factor XII, prekallikrein, or HMWK (i.e., individuals congenitally deficient in these do not bleed). In vivo, thrombin, not XIIa, is the principal activator of factor XI.

c. The Common Pathway—Both the extrinsic and intrinsic pathways converge on prothrombin (factor II), which is converted to thrombin (factor IIa) by factor Xa. This reaction is accelerated by the presence of cofactor Va. Thrombin converts fibrinogen (factor I) to fibrin, which self-polymerizes. Factor XIIIa strengthens fibrin by catalyzing the formation of covalent bonds between adjacent fibrin molecules.

d. Laboratory Testing—The prothrombin time (PT) and partial thromboplastin time (PTT) are in vitro assays used to assess the function of the extrinsic and intrinsic pathways, respectively. The PT measures the time required for plasma to form a fibrin clot following the addition of thromboplastin and calcium. Variable interlaboratory sensitivity of thromboplastin led to creation of the international normalized ratio (INR), which compares thromboplastin activity to an established World Health Organization standard. The PTT is the time necessary for plasma to form a fibrin clot following the addition of a negatively charged reactant (e.g., diatomaceous earth), calcium, and phospholipid (partial thromboplastin).

3. Fibrinolysis

Tissue plasminogen activator (t-PA), an endothelium-derived plasminogen activator, converts plasminogen to plasmin. Plasmin cleaves fibrin into fibrin degradation products and D-dimers (circulating covalently linked fragments of fibrin). Urokinase is another endogenous plasminogen activator produced by epithelial cells within the genitourinary tract. Streptokinase is a plasminogen activator derived from β-hemolytic streptococci. The enzymatic activity of plasminogen activators and plasmin is antagonized by endothelial cell-derived plasminogen activator inhibitor-I (PAI-I) and α-plasmin inhibitor, respectively.

4. Anticoagulant Pathways

Antithrombin-mediated proteolysis of thrombin is greatly amplified by heparin, a glycosaminoglycan cofactor produced by endothelial cells. Protein C is a vitamin K–dependent anticoagulant that inhibits factor Va and VIIIa. Protein C requires activation by thrombin and the presence of protein S (also vitamin K dependent) as a cofactor. Tissue factor pathway inhibitor (TFPI) is an anticoagulant that binds to Xa and then to the VIIa–tissue factor complex, antagonizing extrinsic pathway activation.

5. Vitamin K

Vitamin K is found abundantly in green, leafy vegetables and produced in smaller quantities by endogenous intestinal flora. It is a fat-soluble vitamin that is absorbed in the terminal ileum and undergoes extensive enterohepatic recirculation. Vitamin K functions as a cofactor in the carboxylation of certain glutamic acid molecules of clotting factors II, VII, IX, and X and proteins C and S. The negatively charged, carboxylated protein binds calcium, which serves as a bridge between the clotting protein and negatively charged, platelet-derived phospholipid. In the process of carboxylation, vitamin K is oxidized to a nonfunctional vitamin K epoxide. Epoxide reductase, the target enzyme of the anticoagulant medication warfarin, reduces vitamin K epoxide back to vitamin K.

II. ABNORMAL PROCESSES

A. Evaluation

Evaluation of any blood disorder begins with an instrument-derived complete blood count (CBC) with leukocyte differential count. Reported values include the white blood cell count (WBC); red blood cell count (RBC); red cell mean corpuscular volume (MCV); hemoglobin concentration; hematocrit (HCT—packed red cell percent volume); red cell mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC); red cell distribution of width (RDW—index of red cell size variation); and platelet count. A review of the peripheral blood smear (PBS) allows one to accurately determine the type and morphology of all cells (Figure 5–7). The following red cell descriptive terms are used: *microcytic, macrocytic, normocytic* (small, large, normal erythrocytes—reflected by the MCV), *anisocytosis, poikilocytosis* (heterogeneity in erythrocyte size and shape—reflected by an elevation in the RDW); *hypochromic, normochromic* (reduced, normal intensity of color—reflected by the MCHC). A bone marrow biopsy may be necessary to assess the adequacy of hematopoiesis and determine marrow cell type and distribution.

► cram facts

Disorders of blood cells are divided into disorders of either cellular excess or insufficiency. Cellular excess results from either a normal physiologic increase in marrow production to some extrinsic stimulus (e.g., sepsis-induced leukocytosis) or from an intrinsic marrow disorder (e.g., chronic myelocytic leukemia). Cellular insufficiency results from either consumption/destruction/loss (e.g., idiopathic thrombocytopenic purpura) or from an intrinsic marrow disorder (e.g., myelodysplasia).

B. Anemias

Anemia is defined as a decrease in the red cell or hemoglobin mass. It results from either impaired erythroid production or shortened erythrocyte survival. The severity of signs and symptoms (pallor, fatigue, malaise, exertional dyspnea, light-headedness) varies depending on the rate and degree of red cell mass reduction, as well as presence or absence of underlying cardiopulmonary disease. With extremely rapid falls in hemoglobin, symptoms of shock predominate.

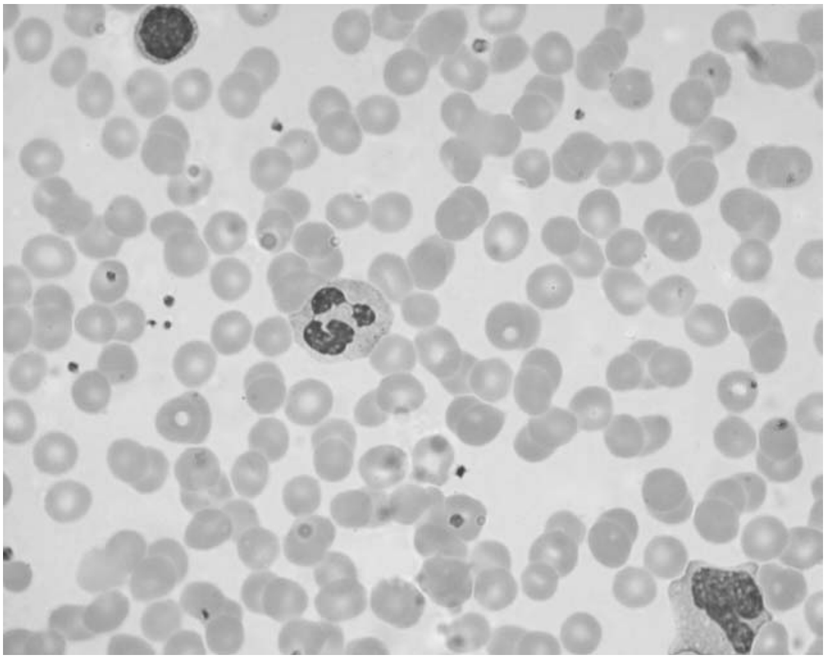


Figure 5–7. Normal peripheral blood smear.

1. Anemias of Decreased Production

a. Iron Deficiency Anemia

► Description and Symptoms

Iron deficiency is the most common cause of anemia. In addition to general symptoms related to anemia, iron deficiency also affects epithelial cell production, occasionally resulting in mouth sores, atrophic tongue, intestinal malabsorption, and fragile or "spoon-shaped" nails (koilonychia). Some patients develop abnormal cravings (pica) for ice or other substances.

► Diagnosis

Mild anisocytosis (e.g., elevated RDW) may be the only early finding. Once storage iron is depleted, anemia develops. The cells become microcytic and progressively hypochromic (i.e., low MCV, MCHC) (Figure 5–8). Circulating target cells are seen. Laboratory findings include a low serum ferritin, low serum iron, elevated total iron-binding capacity (TIBC) and increased soluble transferrin receptor. Since ferritin is an acute-phase reactant, normal or near-normal values may be seen with concurrent inflammation. Reduced bone marrow hemosiderin staining reflects a depleted storage state.

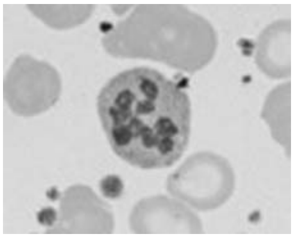


Figure 5–8. Iron deficiency anemia.

► Pathology

The most common cause is chronic blood loss. In men and postmenopausal women, the gastrointestinal tract is the most frequent site (e.g., colon/gastric cancer, peptic ulcer disease, gastritis). In premenopausal women, menometrorrhagia is very common. Rarely is impaired absorption (e.g., celiac sprue) a primary cause. Modifying factors include increased iron requirement (e.g., pregnancy, infancy, adolescence) and decreased intake (elderly, alcoholism, poverty, vegetarians).

► Treatment Steps

1. Correct the underlying cause of deficiency (usually bleeding).
2. Iron replacement, oral route preferred. Alternatively, iron can be given IM or IV.
3. Dyspepsia and constipation are common with oral administration; anaphylaxis, muscle aches, joint pain, adenopathy, and fevers occasionally occur with IV.

b. Megaloblastic Anemia

A group of anemias characterized by impaired DNA synthesis, unusually large blood cells and blood cell precursors, and hypersegmented neutrophils. The most common cause of megaloblastic anemia is B_{12} or folate deficiency.

Vitamin B_{12} (Cobalamin) Deficiency

► Description and Symptoms

Due to abundant stores of B_{12}, megaloblastic anemia requires years to manifest. Common findings include insidious anemia, progressive neurologic compromise (sensory and motor deficits, ataxia), and an inflamed tongue (glossitis). The disease is fatal if left untreated. The most common cause is pernicious anemia (PA). In addition to the above findings, PA is associated with a loss of gastric acid production (achlorhydria) and an increased risk of gastric cancer. Other causes of B_{12} deficiency include resection of the terminal ileum (impaired absorption), gastric resection (loss of intrinsic factor production), bacterial overgrowth and fish tapeworm disease (competitive loss of cobalamin), inadequate intake (strict vegan vegetarians), and nitrous oxide exposure (inactivation of cobalamin).

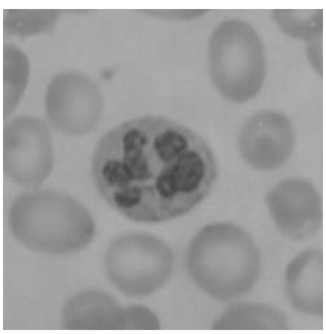


Figure 5–9. Megaloblastic anemia.

► Diagnosis

Routine labs reveal a macrocytic anemia, reduced cobalamin concentration, and elevated methylmalonyl CoA and homocysteine levels. In severe cases, leukopenia and thrombocytopenia develop, and lactic dehydrogenase (LDH) and bilirubin are increased due to red cell hemolysis. Specific anti–intrinsic factor antibodies are often measurable in PA. Macrocytic erythrocytes and hypersegmented neutrophils are seen on PBS review (see Figure 5–9). The bone marrow is hypercellular with megaloblastic erythroid and granulocytic precursors. Although rarely done nowadays, the Schilling test can assist in identifying the cause by measuring urinary excretion of orally ingested radioactive B_{12}.

► Pathology

Cobalamin is necessary for normal DNA replication. Transcription and translation proceed without associated cell division, resulting in disproportionate cytoplasmic enlargement (i.e., nuclear-cytoplasmic dysynchrony). Surviving erythrocytes are unstable and hemolyze prematurely. Neurologic symptoms reflect progressive demyelination of the dorsal lateral columns and cerebral cortex. Pernicious anemia is the result of autoimmune injury to gastric mucosa. Specific antibodies are directed at parietal cells and intrinsic factor, blocking the subsequent binding of cobalamin.

► Treatment Steps

1. Cobalamin (1 mg), usually by regular IM injections.
2. Hematologic abnormalities normalize promptly (heralded by a rising reticulocyte count). Neurologic deficits may not improve.

Folate Deficiency

► Description and Symptoms

Dietary deficiency (alcoholics, elderly, homeless) is the most common cause of folate deficiency. Increased requirement is seen during pregnancy, infancy, dialysis, and with some hemolytic anemias. Malabsorption may occur with celiac sprue and certain drugs (e.g., Dilantin). Methotrexate (an immune suppressant/chemotherapy agent) irreversibly inhibits dihydrofolate reductase, inducing a functional folate deficiency. Megaloblastic anemia develops after 4–5 months of folate deficiency. Symptoms are similar to those seen with B_{12} deficiency, with the notable absence of neurologic deficits.

► Diagnosis

Peripheral blood and laboratory features of severe folate deficiency are identical to those of B_{12} deficiency, except methylmalonyl CoA levels are normal. Serum folate concentration is reduced.

► Treatment Steps

Prompt resolution of abnormalities is expected following oral/parenteral folate replacement.

c. Anemia of Chronic Disease (ACD)

► Description and Symptoms

ACD is the most common cause of anemia in hospitalized patients. It occurs in the setting of chronic infection or inflammation (e.g., rheumatoid arthritis, tuberculosis, osteomyelitis, human immunodeficiency virus [HIV], endocarditis) or neoplasia. Degree of anemia usually parallels severity of disease. Symptoms from the underlying chronic disease generally dominate the clinical picture.

► Diagnosis

ACD is associated with a moderately severe normocytic, normochromic anemia that may become hypochromic and microcytic with progression of the underlying disease. Iron studies reveal a low serum iron, a suppressed TIBC, and elevated serum ferritin (acute-phase reactant). Bone marrow may show increased stainable iron.

► Pathology

Hemoglobin production is decreased as a result of iron sequestration within macrophage ferritin and away from transferrin. Contributing mechanisms include the systemic inhibitory effects of inflammatory cytokines on erythropoiesis, relative reduction in erythropoietin level for the degree of anemia, and shortened erythrocyte survival.

► Treatment Steps

1. If possible, control the underlying chronic disease.
2. The use of synthetic, recombinant erythropoietin in large pharmacologic doses is often effective (e.g., epoetin alfa, darbepoetin alfa).

d. Renal Disease

► Description and Symptoms

Anemia is common in chronic renal disease. Severity parallels worsening renal function. Symptoms stem from the anemia and uremia.

► Diagnosis
Normocytic, normochromic anemia occurring in a patient with renal impairment PBS may reveal cells with many thin, cytoplasmic projections (burr cells) as renal failure progresses.

► Pathology
The primary mechanism is inadequate erythropoietin production due to loss of renal epithelial cells.

► Treatment Steps
1. If possible, correction of renal impairment.
2. Patients usually respond to injections of synthetic erythropoietin.

e. Aplastic Anemia (AA) and Pure Red Cell Aplasia (PRA)

► Description and Symptoms
Bone marrow failure states may be limited to the erythroid line (pure red cell aplasia) or affect all three cell lines, causing pancytopenia. Potential etiologies of AA include medications and toxins (e.g., radiation, gold, nonsteroidal anti-inflammatories, antiepileptics, benzene, and chloramphenicol) and viral exposure (non-A, -B, or -C viral hepatitis; HIV; Epstein–Barr virus). In certain individuals, infection with parvovirus can cause PRA. Many cases of PRA and AA are idiopathic (unknown cause). Signs/symptoms (dyspnea, infection, bleeding, etc.) reflect degree/severity of cytopenias. Fifteen percent of patients with idiopathic PRA have an associated thymoma.

► Diagnosis
Usually a profound normocytic/normochromic anemia. With aplastic anemia, platelets and granulocytes are also decreased. Blood cells usually appear morphologically normal on PBS. Bone marrow shows absence of all blood cell precursors (AA) or selectively erythroid precursors (PRA).

► Pathology
Parvovirus B-19 infects early erythroblasts and transiently interrupts erythropoiesis. Individuals highly dependent on uninterrupted erythropoiesis (e.g., chronic hemolytic anemias) or those unable to effectively eradicate infections (e.g., immune compromised) may develop a profound anemia. Idiopathic PRA is a rare disorder, believed to arise from immune dysregulation. Most cases of AA result from T lymphocyte–derived cytokine suppression of antigenically altered early myeloid stem cells.

► Treatment Steps
1. Treatment of AA involves discontinuation of implicated medications, transfusion support, and treatment of infections.
2. Anti–T-cell immunoglobulin (ATG) obtained from horse sera, given in conjunction with cyclosporin, or allogeneic bone marrow transplantation are potentially curative options.
3. Treatment for PRA usually involves steroids, immune suppressants, IV immunoglobulin, or ATG. Parvovirus aplasia often responds to infusions of IV immunoglobulin. Removal of the thymus, in patients with or without thymoma, may induce remissions.

f. Myelodysplastic Syndrome (MDS)

► Description and Symptoms
MDS is a common, acquired, usually idiopathic bone marrow failure state primarily affecting the elderly. Patients previously exposed to

chemotherapy or radiation therapy are at increased risk (see section II.G.1). MDS may cause anemia (most common) or pancytopenia. Circulating cells are morphologically and functionally abnormal. Signs/symptoms reflect degree/severity of cytopenia. MDS evolves into acute myelogenous leukemia in 30% of patients.

► Diagnosis

Anemia (usually macrocytic) is present as an isolated finding or as part of pancytopenia. Mature and precursor blood cells appear morphologically abnormal (i.e., dysplastic). Marrow review is usually diagnostic and may reveal ringed sideroblasts (early erythrocytes with perinuclear, iron-containing mitochondria). Cytogenetic (i.e., chromosome) abnormalities are frequently present. The number and type of abnormalities have prognostic significance. The World Health Organization (WHO) classification (Table 5–6) has replaced the original French–American–British (FAB) system.

► Pathology

MDS results from the mutation of genes controlling growth and differentiation of early myeloid stem cells. Cells differentiate but undergo apoptosis prior to marrow release. Levels of pro-apoptotic cytokines (e.g., TNF, transforming growth factor-α [TGF-α]) are increased.

► Treatment Steps

1. Transfusions represent the cornerstone of management for most.
2. Responses occasionally seen with use of high-dose growth factor (e.g., erythropoietin, G-CSF).
3. Azacitadine is a newer drug that can increase counts and reduce transfusion requirements.
4. Other treatment options include immune suppression, chemotherapy, and allogeneic bone marrow transplantation.

► **cram facts**

The reticulocyte count helps to differentiate anemias of premature destruction (e.g., hemolytic, bleeding) from anemias of marrow failure (e.g., iron deficiency, anemia of chronic disease): It is usually elevated with premature destruction but normal or low in marrow failure.

2. Anemias of Increased/Premature Destruction (Hemolytic Anemia)

a. General—The common feature of all hemolytic anemias is premature destruction of erythrocytes. Hemolytic anemias are subclassified as congenital (i.e., due to abnormalities in red cell structural proteins, hemoglobin, or metabolic pathways) or acquired. With most hemolytic anemias, the reticulocyte count, serum indirect (un-

5-6

WORLD HEALTH ORGANIZATION CLASSIFICATION OF MDS

Type	Bone Marrow Findings
Refractory anemia (RA)	Anemia with dysplastic erythrocytes; < 15% sideroblasts; no excess marrow blasts
RA with ringed sideroblasts (RARS)	Anemia with dysplastic erythrocytes; ≥ 15% sideroblasts, no excess blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia and dysplasia in > 2 lines (i.e., erythroid, platelets, granulocytes); no excess blasts
RCMD with ringed sideroblasts	Cytopenia and dysplasia in > 2 lines (i.e., erythroid, platelets, granulocytes); ≥ 15% sideroblasts; no excess blasts
RA with excess blasts	Cytopenia and dysplasia in ≥ 1 line; blasts 5–19% of marrow cellularity
MDS 5q-	Normal or increased dysplastic megakaryocytes; no excess blasts; isolated deletion long-arm 5th chromosome (5q-)
MDS unclassified	

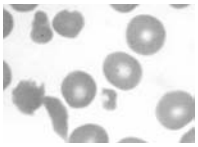


Figure 5–10. Schistocytes.

conjugated) bilirubin, and serum LDH concentration are elevated; the haptoglobin level is reduced; and hemoglobin/hemosiderin are detectable in the urine (i.e., hemoglobinuria/hemosidinuria). The primary site of hemolysis is often specified as either intravascular (i.e., within the vascular space) or extravascular (i.e., primarily within the spleen/liver). Schistocytes and other erythrocyte fragments are commonly seen on PBS in the setting of intravascular hemolysis (Figure 5–10).

b. Acquired Hemolytic Anemias by Mechanical/Physical/Infectious Destruction

► Description and Symptoms

A group of related disorders characterized by intravascular hemolysis, thrombocytopenia, and thrombosis of small vessels. Included in this group are hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), and (pre)eclampsia. All of these disorders have in common intravascular thrombosis (either platelet or fibrin based) resulting in tissue ischemia and intravascular fragmentation of erythrocytes. Additionally, patients with TTP and HUS may have fever, mental status changes, and loss of renal function (more pronounced with HUS). Most cases of TTP/HUS are idiopathic. Occasionally occurs in the setting of infection (enterohemorrhagic *Enterobacteriaceae coli, Shigella dysenteriae,* HIV most common), allogeneic bone marrow transplantation, or some medications (cyclosporin, ticlopidine). Preeclampsia affects women late in the third trimester of pregnancy and causes severe hypertension, peripheral edema, and tonic–clonic seizures (eclampsia). (DIC is described in a later section).

► Diagnosis

In the appropriate clinical setting, findings of intravascular hemolysis, thrombocytopenia, and vessel thrombosis, leading to tissue ischemia/organ dysfunction.

► Treatment Steps

1. TTP/HUS often responds to daily plasma exchange (i.e., plasmapharesis) +/– glucocorticoids. The mechanism may include replacement of the missing vWF protease in TTP.
2. When feasible, the treatment of (pre)eclampsia is delivery of the fetus. IV magnesium prevents seizures and relieves vasoconstriction.

Malaria

► Description and Symptoms

Malaria is a protozoal infection (*Plasmodium*) that causes febrile hemolytic disease. *Plasmodium* parasite is transmitted via the *Anopheles* mosquito. Four species have been identified: *P. ovale, P. vivax, P. malariae,* and *P. falciparum*. Symptomatic patients have recurrent (or sustained) chills and fevers, vomiting, headaches, and lassitude. Splenomegaly, anemia, and jaundice are common. *P. falciparum* is associated with greatest degree of parasitemia, risk of organ failure, central nervous system (CNS) disease (cerebral malaria), and malignant hyperthermia. Severe hemolytic anemia with renal failure and high fevers (black water fever) is an uncommon complication. Death rate of *P. falciparum* approaches 10%. Malaria is responsible for 2 million deaths a year (mostly children and mostly falciparum). Endemic malaria has been eradicated from the United States, Russia, and Europe, but remains a major health problem in tropical countries.

► Diagnosis

Suspected in a febrile patient with a potential exposure history and findings of hemolysis. Both thick and thin PBSs are examined for parasitic erythrocytes (greatest with *P. falciparum*). Antibody-based diagnostic test cards are available for *P. falciparum*.

► Pathology

Plasmodium's life cycle is complex, with multiple stages. Hemoglobin is consumed as a source of nutrition. Hemolyzed and infected erythrocytes are removed by the spleen. *P. vivax* and *P. ovale* invade only reticulocytes (i.e., 1% of peripheral erythrocytes), *P. malariae* only mature erythrocytes, and *P. falciparum* all stages.

► Treatment Steps

1. Prevention involves the use of anti-mosquito techniques and chemoprophylaxis.
2. Chloroquine is safe and effective against most plasmodia.
3. Mefloquine is used as chemoprophylaxis against resistant falciparum.
4. Chloroquine is the preferred treatment for non-falciprum plasmodia, usually followed by several weeks of primaquine to eradicate hepatic disease.
5. Treatment of falciprum varies depending on severity: quinidine, quinine, or artemether/artesunate parenterally for severe infection; quinine + tetracycline/doxycylcine or mefloquine for less severe infection. Exchange transfusion can be used.
6. Research for an effective vaccine is ongoing.

C. Acquired Autoimmune Hemolytic Anemias (AIHAs)

Warm AIHA

► Description and Symptoms

The most common type of AIHA. May be idiopathic or associated with other autoimmune disorders, lymphomas, or leukemias (e.g., chronic lymphocytic leukemia). Symptoms vary depending on degree of hemolysis. Jaundice and splenomegaly are common.

► Diagnosis

Laboratory findings of hemolytic anemia. Positive Coombs' test detects the presence of antierythrocyte IgG antibody or C3 complement fragment on surface of erythrocyte (direct Coombs') or unbound antibody in serum (indirect Coombs'). Spherocytes are seen on PBS (Figure 5–11).

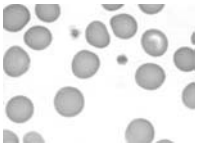


Figure 5–11. Spherocytes.

► Pathology

Antibody (IgG) binds to erythrocytes optimally at 37°C (98.6°F). Antibody targets an epitope of Rh blood group antigen. Spherocytosis results from progressive phagocytic loss of erythrocyte cell membrane as opsonized erythrocytes pass splenic macrophages (e.g., extravascular hemolysis).

► Treatment Steps

1. First-line treatment is corticosteroids, tapered over months in responding patients.

2. Patients failing steroids undergo splenectomy.
3. Other treatments include IV gamma-globulin (inhibits splenic macrophage removal), immune-suppressant drugs (e.g., cyclophosphamide) or use of anti-CD20 monoclonal antibody (e.g., rituximab).

Cold AIHA (Cold Agglutinin Disease)

► Description and Symptoms

Represents 10–20% of AIHA. Often idiopathic. May occur following *Mycoplasma* or Epstein–Barr virus infections, or in association with lymphoma/chronic lymphocytic leukemia. Findings include cutaneous mottling; cyanosis of the nose, fingers, ears, toes, etc.; signs/symptoms of anemia.

► Diagnosis

Laboratory features of hemolytic anemia. Fewer spherocytes than warm AIHA. Agglutinated erythrocytes on PBS review. Cold agglutinins are measurable, reported as a titer. Direct Coombs' test positive for the presence of erythrocyte-bound complement.

► Pathology

Antibody, usually IgM, targets erythrocyte "I/I" blood group antigen optimally in the cooler extremities. IgM agglutinates erythrocytes, occluding small vessels. Complement is activated. IgM dissociates as the erythrocyte returns to core body temperature, leaving complement intact. The presence of complement initiates formation of the membrane attack complex (intravascular hemolysis) and facilitates removal by hepatic macrophage (extravascular hemolysis).

► Treatment Steps

1. Generally supportive, keeping patient warm, as episodes are often self-limited.
2. Plasmapharesis (more effective than in warm AIHA, gives IgMs predominant intravascular concentration), alkylating agents (e.g., cyclophosphamide), and rituximab have been used.

Paroxysmal Cold Hemoglobinuria

► Description and Symptoms

The most common cause of AIHA in children (< 5% of all AIHA). Acute intravascular hemolysis, usually following a viral or other infection (originally described in patients with syphilis). Hemoglubinuria and flulike symptoms (backache, fever, etc.) are common.

► Diagnosis

In the appropriate clinical setting, findings of intravascular hemolysis (hemoglobinuria, high LDH, and bilirubin) and a positive test for Donath–Landsteiner antibody.

► Pathology

At cold temperature, a polyclonal IgG antibody capable of activating complement (Donath–Landsteiner antibody) binds to the "P" blood group antigen, activating complement, causing cell lysis.

► Treatment Steps

Generally supportive, keeping patient warm, as episodes are usually self-limited.

d. Congenital Hemolytic Anemias: Hemoglobinopathies

Sickle Cell Anemia (SCA)

► Description and Symptoms

SCA is a congenital hemoglobinopathy that primarily affects individuals of African descent. May have evolved as a protective mechanism (i.e., sickle trait confers protection against severe anemia of malaria). Symptoms stem from premature erythrocyte hemolysis and from sickle erythrocyte occlusion of the microvasculature (vaso-occlusive ischemia) (Table 5–7). Early pigmented (bilirubin) cholelithiasis is common. Clinical severity varies substantially among affected individuals. For severely affected patients, life expectancy is shortened. Infection (pneumococcal, other encapsulated organisms) is the most common cause of death during childhood; acute chest crisis and chronic organ failure in adults. Heterozygotes (i.e., those with sickle cell trait) have a mild anemia but are otherwise asymptomatic.

► Diagnosis

Homozygotes have a moderately severe anemia (baseline hematocrit 18–25%), reticulocytosis, and hyperbilirubinemia. PBS reveals sickled erythrocytes. Confirmation is made by hemoglobin electrophoresis (homozygotes: 90% hemoglobin S with characteristic mobility pattern).

► Pathology

A point mutation in the β globin gene results in a substitution of valine for glutamate at the sixth position of the β globin chain (hemoglobin S). Polymerization of hemoglobin S induces erythrocyte sickling. Initially reversible, erythrocyte sickling becomes fixed. Sickle erythrocytes are poorly deformable and obstruct the microvasculature. Hypoxia, acidosis, and dehydration increase hemoglobin S polymerization and sickling.

► Treatment Steps

1. Most patients need no or infrequent treatment.
2. Bony crises and other vasoocclusive manifestations are treated with IV hydration, rest, analgesics, oxygen (if patient is hypoxic), and occasionally transfusions (simple or exchange).
3. Hydroxyurea reduces hospitalizations, reduces frequency of bone crises, and improves survival. It may work by increasing the production of fetal hemoglobin.
4. Many patients are dependent on chronic analgesics.

5-7

CLINICAL MANIFESTATIONS OF SICKLE CELL VASO-OCCLUSION

Site	Manifestation
Bone	Infarctions resulting in painful “bony crises”; aseptic necrosis (mostly hips); sclerotic areas on x-ray
Lung	Chest crisis (chest pain, fever, hypoxia with progressive respiratory failure); pulmonary hypertension, cor pulmonale
Spleen	“Auto infarction,” with premature loss of splenic function
Brain	Childhood stroke
Penile vasculature	Priapism
Skin	Nonhealing lower extremity ulcers
Kidney	Papillary necrosis with isosthenuria (loss of urine-concentrating ability)
Fingers/toes	Dactylitis (painful fingers/toes, mostly children)

5. Children are vaccinated against encapsulated organisms and take prophylactic penicillin.
6. Bone marrow transplant is a potentially curative therapy.

Thalassemia

► Description and Symptoms

Thalassemias are divided into α and β, depending on which globin chain gene is deficient. α-Thalassemia is common among Asians and African-Americans; β-thalassemia among individuals of Mediterranean descent. Several different mutations have been described. Symptoms of thalassemia stem from anemia and the resulting increased, compensatory, erythropoietic response. Disease severity varies depending on the number of genes mutated and the degree of impaired globin production. The clinical features of thalassemia are summarized in Table 5–8.

► Diagnosis

Individuals with thalassemia minor have an asymptomatic, mild but markedly microcytic, hypochromic anemia. Target cells and basophilic stippling are seen on PBS. Those with thalassemia major have a severe anemia and associated reticulocytosis. PBS reveals severely microcytic, hypochromic, poikilocytic red cells; circulating immature erythrocytes; target cells; and basophilic stippling. In β-thalassemia, the concentration of hemoglobin F (fetal) and hemoglobin A_2 is found to be abnormally increased by hemoglobin electrophoresis. Electrophoresis shows a normal pattern in α-thalassemia trait but precipitated β chains (i.e., hemoglobin H) in patients with hemoglobin H disease.

► Pathology

Diminished production of either α or β globin chains results in a relative imbalance of the unaffected globin chain. Uncoupled chains (α in β-thalassemia; γ or β in α-thalassemia) self-couple into inherently unstable hemoglobin tetramers that precipitate out and damage the erythrocyte. Erythrocytes undergo premature apoptosis within the marrow. Surviving erythrocytes are removed prematurely by splenic macrophages. High erythropoietin levels drive erythropoiesis in a compensatory effort, causing marrow hyperplasia (bone expansion) and extramedullary hematopoiesis (i.e., hematopoiesis within the spleen and liver).

► Treatment Steps

1. Patients with β-thalassemia major (and possibly hemoglobin H, β-thalassemia intermedia) are dependent on red cell trans-

5-8

CLINICAL FEATURES OF THALASSEMIA	
β-Thalassemia	Heterozygous β-thalassemia (β-thalassemia trait or minor) causes clinically insignificant anemia. Homozygous patients are classified as β-thalassemia major (absent β globin chain production) or β-thalassemia intermedia (markedly reduced β globin chain production). β-Thalassemia major results in severe, life-threatening, transfusion-dependent anemia after 6 months of age. Other findings include bone thickening and distortion, hepatosplenomegaly, and growth retardation. Anemia is moderately severe in β-thalassemia intermedia.
α-Thalassemia	Mutation of a single gene is clinically silent. Mutation affecting two genes gives rise to a clinically insignificant anemia (α-thalassemia minor). Mutations affecting three genes (hemoglobin H disease) cause a moderately severe anemia (similar to β-thalassemia intermedia). "Hydrops fetalis" (in utero death) results when all four α globin genes are mutated.

fusions for survival and normal growth. Transfusions correct the anemia and suppress hematopoiesis. Chronic transfusions eventually result in iron overload and organ damage.
2. Nocturnal, subcutaneous infusion of an iron chelator (e.g., deferoxamine) is used to remove excess iron.
3. Bone marrow transplantation is a potentially curative option.
4. Newer therapies for patients with β-thalassemia major are directed at "switching on" γ globin genes. γ Globin chains form tetramers (hemoglobin F) with otherwise uncoupled α chains.

e. Congenital Hemolytic Anemias: Enzymatic and Structural Protein Abnormalities

G6PD Deficiency

► Description and Symptoms
X-linked genetic disorder affecting African-Americans (~10%) and individuals of Mediterranean descent. Erythrocytes sustain oxidative injury following exposure to certain drugs (e.g., antimalarials, sulfonamides, nitrofurantoin), foods (fava beans), and/or infections. The African-American subtype results in a moderately severe, self-limited hemolytic anemia. Other subtypes may cause severe hemolysis requiring transfusion.

► Diagnosis
Suspect when acute hemolysis develops in an otherwise healthy male. PBS may reveal Heinz bodies (on crystal violet staining) and "bite cells." Qualitative and quantitative assays are available to determine erythrocyte G6PD levels. These assays may be normal in the African-American subtype *during* a hemolytic episode.

► Pathology
G6PD is an enzyme in the hexose-monophosphate pathway, required for the generation of NADPH. NADPH reduces glutathione, required to prevent oxidative injury to hemoglobin. Oxidized hemoglobin precipitates as Heinz bodies, damaging red cells. In the spleen, Heinz bodies are phagocytized, leaving residual bite cells. Eventually, the cell is removed from circulation.

► Treatment Steps
Avoid implicated drugs and aggressively treat infections. Transfusion is rarely indicated.

Pyruvate Kinase (PK) Deficiency

► Description and Symptoms
Most common hemolytic disorder related to a deficiency of a glycolytic enzyme. Autosomal recessive. Heterozygosity in the United States estimated at 1%. Chronic hemolysis. Splenomegaly and pigmented (bilirubin) cholelithiasis are common. Variable clinical severity.

► Diagnosis
Moderately severe hemolytic anemia. A specific quantitative enzyme assay is available.

► Pathology
Several mutations have been described. Reduced concentration of functional PK limits ATP generation, necessary for maintaining electrolyte balance (via Na^+/K^+/ATP pump), resulting in an

accumulation of 2,3-DPG. A resulting right shift of the oxygen dissociation curve mitigates the effects of the anemia. The spleen is the primary site of erythrocyte removal.

► Treatment Steps

1. Red cell transfusions if necessary.
2. Splenectomy increases erythrocyte survival.

Hereditary Spherocytosis (HS)

► Description and Symptoms

Deficiency/abnormality of erythrocyte skeletal protein spectrin. Generally a disorder of Caucasians, inherited in an autosomal dominant fashion. Chronic hemolysis. Splenomegaly and pigmented (bilirubin) cholelithiasis are common. Variable clinical severity.

► cram facts

Microcytic anemia (i.e., reduced MCV)—think: iron deficiency, anemia of chronic disease, thalassemia, lead toxicity.

Macrocytic anemia (i.e., increased MCV)—think: megaloblastic anemia, increased number of reticulocytes, agglutination, myelodysplasia, alcohol, liver disease, thyroid dysfunction.

Normocytic anemia (i.e., normal MCV)—think: anemia of chronic disease, renal disease, acute blood loss, multiple myeloma, aplastic anemia, bone marrow.

► Diagnosis

Chronic, mild-to-moderate, mostly extravascular hemolytic anemia. Spherocytes on PBS. Positive “osmotic fragility test” (spherocytic erythrocytes bathed in salt solution of increasing osmolarity prematurely hemolyze).

► Pathology

Spectrin deficiency results in loss of erythrocyte membrane, creating poorly deformable spherocytes. During passage through the spleen, erythrocytes undergo progressive phagocytosis.

► Treatment Steps

1. Splenectomy increases erythrocyte circulation time, improving anemia.
2. Patients with cholelithiasis usually undergo elective cholecystectomy.

C. Bleeding Disorders

Bleeding from altered primary hemostasis is immediate and slow (“oozing”) and involves skin (petechiae, ecchymoses) and mucous membranes. Bleeding from altered secondary hemostasis is delayed but often severe. Extensive ecchymoses; hematomas; intramuscular, articular, and/or cerebral bleeds are common.

1. Platelet Disorders (Altered Primary Hemostasis)

a. Quantitative Platelet Disorders (Thrombocytopenia)

► Description and Symptoms

Thrombocytopenia is defined as a platelet count $< 150 \times 10^3/\text{mm}^3$. Risk of bleeding increases with platelet count $< 50 \times 10^3/\text{mm}^3$. Results from either impaired bone marrow production (e.g., aplastic anemia, myelodysplasia, chemotherapy, ethanol, infections) or from increased consumption/loss (immune thrombocytopenic purpura, DIC, TTP, some infections).

► Diagnosis

Small platelets on PBS and a reduced number of megakaryocytes suggest impaired marrow production; large platelets and an increased number of megakaryocytes suggest increased consumption/loss.

► Treatment Steps

Treatment is directed at the underlying cause.

Immune Thrombocytopenic Purpura (ITP)

► Description and Symptoms

Results from autoimmune, antibody-mediated platelet destruction. In children, it often follows a viral infection. In adults, it is usually idiopathic, primarily in young females, or in a setting of preexisting immune dysregulation (e.g., lymphoma, leukemia, AIDS, lupus, etc.). May result following exposure to certain drugs (e.g., heparin, valproate, quinidine, phenytoin, trimethoprim–sulfamethoxazole). Heparin (heparin-induced thrombocytopenia [HIT]) is the most commonly implicated drug (5% of exposed patients, less with low-molecular-weight heparin). HIT may cause arterial and/or venous thrombosis.

► Diagnosis

Antiplatelet antibody assays are often positive but nonspecific for ITP. Platelets are noted to be large on PBS. Marrow shows an increased number of megakaryocytes. HIT requires demonstration of specific antiheparin antibodies.

► Pathology

Antibodies are directed at surface glycoproteins. Opsonized platelets are removed by splenic macrophages. In HIT, antibodies target heparin/platelet factor 4 (a platelet granular protein) conjugates.

► Treatment Steps

1. Durable remission with corticosteroids in 25%.
2. For those failing steroids, 75% achieve remission following splenectomy.
3. Other effective treatments include RhoGAM (antibody directed at "D" locus of Rh red cell surface antigen), IV immunoglobulin (IVIG), and rituximab. Proposed mechanisms for Rho-GAM and IVIG include "tying up" splenic macrophage Fc receptors and inhibiting macrophage function.
4. Failure/relapses difficult to treat. Immune suppressants (e.g., cyclophosphamide, azathioprine), vincristine, androgens, are all used.
5. Drug-induced ITP resolves after discontinuing the implicated medication.
6. For HIT, an alternative nonheparin anticoagulant (e.g., lepirudin, argatroban—both direct thrombin inhibitors) is required

b. Acquired Qualitative Platelet Disorders

Drug Induced

► Description and Symptoms

Many drugs inhibit platelet function. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common. The inhibitory effect of aspirin lasts 5–7 days. Usually minor bleeding.

► Diagnosis

Requires a high index of suspicion, since aspirin is found in many over-the-counter products. The bleeding time is often prolonged. Aspirin results in abnormal platelet aggregation studies with an absent second wave of aggregation.

► Pathology

Aspirin *irreversibly* inhibits the enzyme cyclooxygenase (COX), responsible for the conversion of arachidonic acid to thromboxane, a potent platelet agonist. Platelet inhibition lasts for the life of the platelet. Other NSAIDs *reversibly* inhibit thromboxane. COX-2 inhibitors (e.g., celecoxib) selectively spare platelet COX (type 1).

► Treatment

1. Usually no treatment necessary.
2. Transfusing a small quantity of normal platelets, or desmopressin (DDAVP) (stimulates endothelial release of vWF multimers) can be used.

Uremia

► Description and Symptoms

Patients with chronic renal failure are at risk of bleeding due to uremic-induced platelet dysfunction. Anemia (low erythropoietin) is concomitantly present.

► Diagnosis

Based on clinical grounds. Bleeding time and platelet aggregation studies are usually impaired.

► Pathology

Uremia impairs platelet activation and adhesion. Concomitant anemia alters normal peripheral vascular platelet flow (i.e., platelets no longer at vessel wall surface).

► Treatment Steps

1. Dialysis.
2. Increase hematocrit by red cell transfusion and/or use of synthetic erythropoietin.
3. DDAVP and conjugated estrogens are effective in transiently reversing uremic platelet defect.

Congenital Qualitative Platelet Disorders: Bernard–Soulier and Glanzmann's Thrombasthenia

► Description and Symptoms

Bernard–Soulier and Glanzmann's thrombasthenia are rare, congenital disorders characterized by deficiency in GP IbIX (receptor for vWF) and IIbIIIa (receptor for fibrinogen), respectively. Patients develop moderately severe mucocutaneous bleeding, usually beginning early in life.

► Diagnosis

Platelets are reduced in number; they are large in Bernard–Soulier, normal in Glanzmann's. Both are characterized by impaired platelet aggregation studies.

► Treatment Steps

Transfusion of platelets during bleeding episodes and high-risk situations (e.g., surgery).

Congenital Qualitative Platelet Disorders: von Willebrand's disease (vWD)

► Description and Symptoms

vWD is the most common congenital bleeding disorder. Type 1 and type 2 follow autosomal dominant inheritance. Type 1 vWd (~90% of cases) represents a quantitative deficiency of von Willebrand factor. Type 2 results from a functional impairment in the most hemostatically active, high-molecular-weight von Willebrand multimers. Variable clinical severity. Most severely affected patients have a lifelong history of easy bruising, epistaxis, dental bleeding, menorrhagia, etc.

► Diagnosis

Von Willebrand factor (vWF) concentration is decreased in type 1. The highest-molecular-weight vWF proteins are selectively decreased in type 2. The bleeding time is usually prolonged. Factor VIII concentration/activity is reduced, prolonging the PTT. Diminished aggregation seen with ristocetin agonist (ristocetin normally promotes vWF binding to the GP1bIX platelet receptor).

► Pathology

Type 1 vWD results from impaired RNA transcription; type 2 is a qualitative disorder in which the largest multimers fail to undergo assembly or are catabolized shortly after synthesis. Many different mutations have been described.

► Treatment Steps

1. DDAVP used for type 1 vWD with minor bleeding or prior to small surgical procedures (less effective in type 2 disease).
2. Purified factor VIII concentrates containing abundant vWF are used for substantial bleeds and prior to major surgery.
3. Cryoprecipitate, rich in vWF, is rarely used due to potential viral contamination.

2. Coagulation Disorders (Coagulopathies)

a. Congenital Disorders

Hemophilia

► Description and Symptoms

A congenital X-linked bleeding disorder due to deficient production of clotting factor VIII (classic hemophilia, hemophilia A) or factor IX (Christmas disease, hemophilia B). Clinical manifestations vary depending on the amount of intact protein produced. Severely affected patients (< 1% normal protein) have lifelong recurrent, often spontaneous bleeds. Recurrent joint bleeds result in permanent arthritic deformity. Patients with mild hemophilia (≥ 5% protein) experience rare, trauma/surgical-induced bleeds.

► Diagnosis

Based on clinical picture and family history (spontaneous mutations can arise). The PTT is prolonged. Reduced factor level is demonstrated by qualitative (clotting based) or quantitative assays.

► Pathology

Many different mutations have been described affecting gene transcription.

► Treatment Steps

1. DDAVP transiently increases plasma concentration of factor VIII (by increasing vWF) and is used prior to minor surgical procedures in patients with mild hemophilia A.
2. Major surgery and bleeds (and minor/surgery bleed in patients with severe hemophilia) require factor VIII replacement. Highly purified and recombinant factor VIII and IX products are available.
3. ε-Aminocaproic acid inhibits plasmin-mediated fibrinolysis and is often used as an adjunct for dental surgery.
4. Following transfusion, some patients with severe hemophilia A develop anti–factor VIII alloantibodies (i.e., "inhibitor"), limiting further infusions.
6. Treatment options for patients with inhibitor include the use of porcine factor VIII, prothrombin complex (i.e., isolated vitamin K–dependent clotting factors), recombinant factor VIIa, and/or desensitization.

b. Acquired Disorders

Vitamin K Deficiency

► Description and Symptoms

Represents the most common acquired clotting factor abnormality. At-risk patients are those with compromised dietary intake, especially if taking antibiotics; those with fat malabsorption; and those with impaired enterohepatic circulation. Warfarin, a therapeutic anticoagulant, works by inhibiting hepatic enzymes necessary for reconstituting vitamin K.

► Diagnosis

Prolonged INR +/– PTT. A 1:1 mix with normal plasma corrects coagulopathy. Decreased concentration and activity of specific vitamin K–dependent clotting factors.

► Pathology

Improperly carboxylated (e.g., decarboxylated) vitamin K–dependent clotting factors are incapable of normal assembly on negatively charged phospholipid surfaces.

► Treatment Steps

1. Vitamin K replacement usually results in normalization of clotting tests within 12 hours.
2. Rare anaphylaxis described following administration of IV vitamin K.
3. Intentional or accidental warfarin overdose responds to vitamin K +/– fresh-frozen plasma.

Liver Disease

► Description and Symptoms

Acute or chronic liver disease is a common cause of coagulopathy and potential bleeding. Symptoms of underlying liver disease usually dominate clinical picture.

► Diagnosis

INR and PTT are prolonged, and clotting factor concentration/activity is reduced. A 1:1 mix with normal plasma corrects coagulopathy. Liver enzyme abnormalities present. Pancytopenia is common.

► Pathology

The liver is the primary site of synthesis and removal of coagulant and anticoagulant factors. Pancytopenia results from the sequestration of platelets within an enlarged spleen.

► Treatment Steps

1. Nonbleeding patients do not require treatment.
2. If patient is bleeding or surgery is planned, clotting factors, fibrinogen, and platelets can be replaced using fresh-frozen plasma, cryoprecipitate, and platelets, respectively.

Disseminated Intravascular Coagulation (DIC)

► Description and Symptoms

Acute DIC can present as hypercoagulability and/or bleeding. DIC usually occurs in hospitalized individuals with an underlying severe illness (gram-negative sepsis, severe burns, trauma, cancer, promyelocytic leukemia, retained dead fetus, abruptio placentae, etc.).

► Diagnosis

In the appropriate clinical setting, DIC is suggested by the presence of a mild hemolytic anemia, thrombocytopenia, prolonged INR and PTT, low fibrinogen, circulating fibrin degradation products, and D-dimers. Protamine sulfate assay (gelification of circulating fibrin monomers) is positive. PBS may reveal fragmented erythrocytes.

► Pathology

Inappropriate release/production of tissue factor activates the clotting cascade. Fibrinolysis follows. Diffuse occlusive intravascular thrombi cause organ dysfunction, tissue ischemia, and red cell hemolysis. Bleeding develops from eventual consumption of clotting factors and platelets.

► Treatment Steps

1. Reverse/treat the underlying cause of the DIC (e.g., infection, cancer) and general supportive measures.
2. Fresh-frozen plasma, cryoprecipitate, and platelets are sometimes necessary in bleeding patients.
3. Heparin may interrupt ongoing thrombin generation.

D. Thrombotic Disorders

The term *thrombosis* implies inappropriate, pathological arterial or venous clot formation.

1. Arterial

The risk factors for arterial thrombosis are generally the established risk factors for atherosclerosis. Treatment generally involves risk factor modification and antiplatelet agents (NSAIDs, abciximab, clopidogrel).

2. Venous

► Description and Symptoms

Venous thrombosis usually affects the deep veins of the lower extremities (deep vein thrombosis [DVT]). Calf vein DVTs are usually asymptomatic, but propagation into more proximal veins can induce symptoms including edema, pain, discoloration, and dilation of superficial veins. Over time, chronic venous stasis may develop (chronic edema, pain, hemosiderin-induced skin discoloration, and ulceration). Pulmonary embolism (PE) occurs when a part or all of a proximal DVT embolizes, obstructing pulmonary arterial vessels. Lung infarction (dyspnea, chest pain, hemoptysis), syncope, acute right heart failure, or sudden death ensue. *Venous thromboembolism* (VTE) is the term used to describe DVT +/– PE.

► Diagnosis

Diagnosis of VTE requires objective testing, usually with duplex compression ultrasonography. Ventilation–perfusion scan (looking for mismatch) and spiral CT scan (pulmonary arterial filling defect) are used for PE. Angiography is necessary if diagnostic uncertainty remains. An increased concentration of circulating D-dimers is a sensitive but nonspecific assay for VTE.

► Pathology

The risk of VTE increases in sitations of vessel injury, blood stasis, and thrombophilia (together referred to as "Virchow's triad"). Hypercoagulable conditions are categorized as either congenital or acquired (Table 5–9).

► Treatment Steps

1. Anticoagulants (heparin, warfarin) are used to prevent further propagation and possible embolism.
2. Unfractionated heparin is administered as a weight-based IV bolus, followed by continuous IV infusion, maintaining PTT at 1.5–2 times control. Heparin binds to antithrombin and inhibits clotting enzymes, mostly thrombin and factor Xa.
3. Protamine sulfate can be used to rapidly reverse unfractionated heparin effect.

5-9

HYPERCOAGULABLE CONDITIONS

Congenital	Description
Factor V Leiden mutation	Point mutation in factor V gene renders protein resistant to anticoagulant effect of activated protein C. Heterozygous mutation found in 5% of the Caucasian population (rare in non-Caucasians), majority asymptomatic and don't require treatment. Found in 20–50% of patients with idiopathic VTE.
Prothrombin gene mutation	Point mutation in the promotor region of the prothrombin (factor II) gene increases prothrombin concentration. Heterozygosity found in 3% of the Caucasian population. 15–20% of patients with idiopathic VTE.
Protein C, S, antithrombin 3 deficiency	Rare disorders of anticoagulant proteins. Several mutations described resulting in both functional abnormalities and antigenic deficiciency. Accounts for 5–15% of idopathic VTE.
Acquired	
Antiphospholipid antibody syndrome (APS)	An acquired, circulating nonspecific antibody inhibitor, referred to as lupus anticoagulant. Found in 5–10% of the general population; patients with AIDS (most asymptomatic), other autoimmunity (e.g., lupus), and/or taking certain meds (procainamide, quinidine, chlorpromazine). Most individuals with APS are asymptomatic. Symptomatic patients develop arterial/venous thromboses, recurrent miscarriages. Antibodies bind to protein–phospholipid units, prolonging in vitro clotting times (PT, PTT), which persists after performing 1:1 mix with normal plasma (inhibitor effect). Presence of anticardiolipin/antiphospholipid antibody can be directly assayed.
Exogenous estrogen (e.g., birth control pills, estrogen replacement, tamoxifen), malignancy (particularly adenocarcinoma), pregnancy, myeloproliferative disorders, surgery, CHF, paralysis	The mechanisms vary but include tissue injury (surgery, malignancy), altered coagulant-to-anticoagulant ratio (estrogen, pregnancy, malignancy), and stasis (pregnancy, surgery).

4. Low-molecular-weight heparins have a longer half-life and more specific binding to antithrombin. They preferentially inhibit clotting factor Xa over thrombin. These features allow once- or twice-daily subcutaneous dosing, without monitoring PTT.
5. Fondaparinux is a new, ultra-low-molecular-weight heparin, retaining only the active pentasaccharide moiety of the heparin molecule. Activity is specific for Xa.
6. Warfarin is the preferred anticoagulant for long-term anticoagulation. Dose is adjusted to achieve a therapeutic INR of 2–3. Many medications alter hepatic warfarin metabolism. Vitamin K antagonizes warfarin effect.

E. Leukocyte Disorders

1. Qualitative Leukocyte Disorders

Defects in virtually every aspect of leukocyte function have been described: adhesion, phagocytosis, oxidative burst, etc.

a. Chediak–Higashi Syndrome (CHS)

► Description and Symptoms

A rare, autosomal recessive disorder affecting leukocytes and other cells. Patients develop recurrent bacterial and fungal infections, neutropenia, albinism, peripheral neuropathies, and bleeding. Symptoms stem from the accumulation of abnormal granules in many different cells. Surviving patients enter an “accelerated phase” (lymphocyte proliferation, lymphadenopathy, hepatosplenomegaly, and pancytopenia), a consequence of secondary Epstein–Barr virus infection. Accelerated phase is usually fatal without marrow transplantation.

► Diagnosis

Suspect in an individual with recurrent infections beginning early in life and associated other findings. Granulocytes and bone marrow myeloid cells with giant peroxidase-staining granules.

► Pathology

CHS is believed to result from a mutation in a gene controlling normal granule development and trafficking. The presence of giant, fused azurophilic and specific granules in neutrophils affects normal neutrophil maturation and function (phagocytosis, chemotaxis, granule release, etc.). Abnormal granules present in other cells including melanocytes, platelets, Schwann cells, etc.

► Treatment Steps

1. Efforts are directed at both the prevention (prophylactic trimethoprin–sulfamethoxazole, vaccinations, good hygiene, etc.) and aggressive, prompt treatment of infections.
2. The use of high-dose ascorbic acid and G-CSF growth factor may reduce infections.
3. Allogeneic bone marrow transplantation is the only potentially curative therapy.

b. Chronic Granulomatous Disorder

► Description and Symptoms

A rare, clinically heterogeneous disorder, usually inherited in X-linked fashion. Patients develop recurrent, severe bacterial and fungal infections beginning early in life. Diffuse granuloma formation (occasionally causing organ dysfunction), hepatosplenomegaly, lymphadenopathy, anemia (of chronic disease), and wasting reflect the inability to completely eradicate infections.

► Diagnosis

Diagnosis confirmed by demonstrating absent neutrophil and monocyte staining using nitroblue tetrazolium (NBT). Flow cytometric assays of oxidase activity also useful.

► Pathology

Mutations occur in genes coding for the various protein subunits of the NADPH oxidase system, required for generation of a "respiratory burst" (superoxide synthesis).

► Treatment Steps

1. Prevention and treatment of infections as described above.
2. Prophylactic antimicrobials (trimethoprin–sulfamethoxazole, itraconazole) and thrice weekly injections of interferon-γ (enhances phagocytic function) reduce infections.
3. Allogeneic bone marrow transplantation is potentially curative.

2. Quantitative Leukocyte Disorders

a. Neutropenia (Agranulocytosis)

► Description and Symptoms

In adults defined as an absolute neutrophil count (ANC) $< 1.5 \times 103/mm^3$. Etiology may be acquired or congenital (Table 5–10). Risk of life-threatening bacterial infection increases with ANC $< 500 \times 10^3/mm^3$. Source of infection is usually endogenous flora (skin, gastrointestinal tract).

► Diagnosis

Cause is usually evident by history of recent medication exposure, selective labs (antinuclear antibody [ANA], folate, B_{12}, etc.), review of the PBS +/– bone marrow biopsy.

► Pathology

Drugs, myelodysplasia, some infections, B_{12}, and folate deficiency interfere with normal myeloid maturation. Autoimmunity shortens normal survival.

5-10

CAUSES OF NEUTROPENIA

Acquired	
	Drug induced (e.g., chemotherapy, some antibiotics, antiepileptics, propylthiouracil, clozapine)
	Infection (e.g., postviral, HIV, erlichia, rickettsia, brucella, tuberculosis, some staphylococcal)
	Autoimmune (in isolation or part of systemic disorder)
	Splenic sequestration
	B_{12}/folate deficiency
	Myelodysplasia
	Marrow infiltration
Congenital	
	Ethnic neutropenia (African-Americans, African blacks, Yemenite Jews)
	Severe/benign congenital
	Cyclical neutropenia

► Treatment Steps

1. Patients with neutropenia and fever require prompt hospital admission and antibiotics.
2. Underlying potentiating causes (e.g., medications) are also addressed.
3. Granulocyte growth factor (eg, G-CSF, GM-CSF) is occasionally used to prevent and treat neutropenia.

b. Lymphocytopenia

► Description and Symptoms

Defined as an absolute lymphocyte count (ALC) $< 1.0 \times 10^3/\text{mm}^3$. Acquired causes include malnutrition, acquired immune deficiency syndrome (AIDS), autoimmunity (component of rheumatoid arthritis, lupus), medications (e.g., purine analogs, glucocorticoids), and radiation. Congenital causes are rare (see section II.H.1.b). Susceptibility to infection varies depending on duration, severity, and lymphocyte subset affected. T-cell deficiency predisposes to parasitic, viral, and fungal opportunistic infections (e.g., *Pneumocystis jiroveci*); B-cell deficiency to encapsulated bacterial and some viral infections.

► Diagnosis

The cause is usually evident by history, examination, and performing select tests (e.g., HIV antibody, ANA, quantitative immunoglobulins, bone marrow biopsy). Immunophenotyping (histochemical staining, flow cytometry) is useful to determine lymphocyte distribution.

► Treatment Steps

Treatment is directed at reversing the underlying cause.

c. Monocytosis/Lymphocytosis

► Description and Symptoms

Reactive monocytosis is seen in association with chronic inflammatory states (rheumatoid arthritis, osteomyelitis, and other chronic infections) and malignancy. The most common cause of reactive lymphocytosis is Epstein–Barr virus (EBV)-induced mononucleosis (self- limited exudative pharyngitis, cervical lymphadenopathy, splenomegaly, mild hepatitis). Other infections (e.g., cytomegalovirus, toxoplasmosis, hepatitis, pertussis, acute HIV) can also cause lymphocytosis.

► Diagnosis

The etiology is usually determined by history and examination. Lymphocytosis, neutropenia, and mild thrombocytopenia are common with mononucleosis. Many atypical-appearing lymphocytes (abundant cytoplasm, azurophilic granules) are seen on PBS (Figure 5–12). The presence of heterophil IgM antibodies confirms the diagnosis. Anti-EBV serologies are available.

► Pathology

EBV is transmitted by saliva and enters host epithelial and B lymphocytes. An immune response follows. EBV remains dormant as a nuclear episome in immune-competent hosts.

► Treatment Steps

Treatment for reactive mono/lymphocytosis is directed at the underlying cause. Mononucleosis is self-limited without treatment.

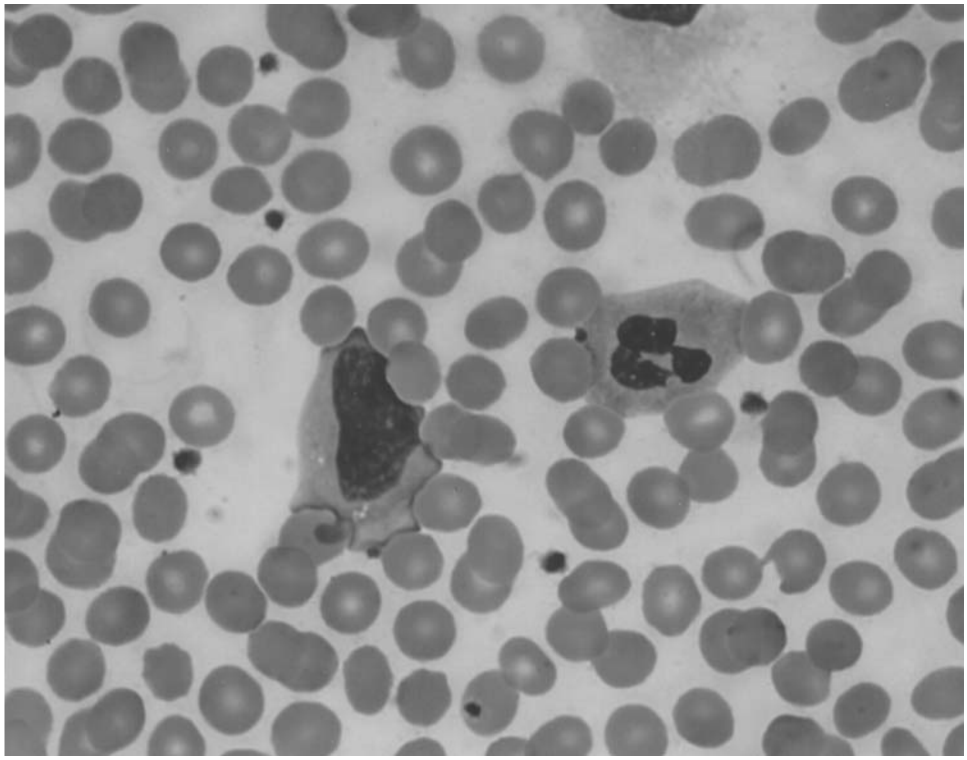


Figure 5–12. Atypical lymphocyte and PMN in EBV infection.

F. Proliferative Disorders

An increase in mostly mature-appearing blood cells without evidence of an underlying associated nonhematologic disorder is referred to as a primary *proliferative disorder.*

1. Myeloproliferative Disorders

a. Polycythemia Vera

► Description and Symptoms

The hallmark of polycythemia vera is an increased red cell mass. Symptoms include headaches, tinnitus, visual changes, and generalized pruritus. Facial “rubor”/plethora, splenomegaly, and hypertension are common. Greatest morbidity and mortality come from bleeding (usually gastrointestinal) and/or thromboses (mostly venous). Approximately 10% of patients with polycythemia vera evolve into acute myelogenous leukemia (AML), and another 25% develop myelofibrosis with myeloid metaplasia.

► Diagnosis

The hematocrit, hemoglobin, and red blood cell count are usually markedly elevated. Platelets and granulocytes may be modestly elevated. Serum erythropoietin concentration is usually low from suppression. Bone marrow is hypercellular. One must exclude reactive erythrocytosis from chronic tissue hypoxia (e.g., high-altitude living, pulmonary disease, etc.) or inappropriate erythropoiten production from liver/renal tumors. Surreptitious erythropoietin use (“blood doping”) should also be considered.

► Pathology

The cause of polycythemia vera is unknown. Mutations may render early erythroid precursors ultrasensitive to low-dose erythropoietin and other cytokines. Symptoms, including thrombosis and bleeding, are a consequence of dysfunctional platelets and increased serum viscosity.

► Treatment Steps

1. Phlebotomy to reduce red cell mass is the cornerstone of therapy.
2. Myelosuppressive therapy (e.g., hydroxyurea) and low-dose aspirin are often used as adjuncts to phlebotomy (see Table 5–11).
3. Anagrelide selectively inhibits megakaryopoiesis and is useful for patients with more marked thrombocytosis.

b. Essential Thrombocythemia (ET)

► Description and Symptoms

The hallmark of ET is expansion of platelet mass. Symptoms stem from thrombosis (usually arterial and microvascular) and bleeding. Thrombosis of the small vessel in the fingers and toes causes painful

5-11

CHEMOTHERAPY USED IN HEMATOLOGICAL DISORDERS

Drug Class	Examples	Mechanism	Toxicities
Alkylating agent	Cyclophosphamide Melphalan Chlorambucil	Electrophilic aklyl side chain binds DNA residues, inhibits DNA synthesis	Myelosuppression, alopecia, mucositis, hemorrhagic cystitis (cyclophosphamide)
Vinca alkaloid	Vincristine	Inhibits microtubule assembly	Constipation, neurotoxicity, vesicant (if leaks)
Antibiotic	Daunorubicin Doxorubicin	Intercalates in DNA and inhibits DNA/RNA synthesis	Myelosuppression, nausea/vomiting, cardiotoxicity, alopecia, radiosensitizer, vesicant
Antimetabolites			
Purine/pyrimidine synthesis inhibitor	Hydroxyurea	Inhibits ribonucleotide reductase	Myelosuppression, nausea
Pyrimidine analog	Cytarabine	Analog of 2'-deoxycitidine Inhibits DNA polymerase Incorporated into DNA, inhibiting replication	Myelosuppression, nausea/vomiting, mucositis, neurotoxicity (high doses)
	5-Azacytidine	Cytidine analog; incorporated into RNA, interfering with protein synthesis. Hypomethylates DNA.	Myelosuppression, nausea
Purine analog	Fludarabine	Metabolite (2-fluoro-ara-A) inhibits DNA primase, polymerase, ribonucleotide reductase	Myelosuppression, cell-mediated immune suppression
	Cladribine	Blocks adenosine deaminase	
Antifolate	Methotrexate	Competitive inhibitor of dihydrofolate reductase	Myelosuppression, diarrhea, rash, mucositis, liver toxicity (hepatitis, cirrhosis), pneumonitis
Purine antagonist	Mercaptopurine	Inhibits purine synthesis, incorporated into DNA as abnormal purine	Myelosuppression, cholestatic liver failure
Monoclonal antibodies	Rituximab	Anti-CD20 monoclonal antibody, opsonizes CD20 expressing B lymphocytes	Anaphylaxis, lymphopenia
	Ibritumomab Tositumomab	Anti-CD20 monoclonal antibody conjugated with a radioisotope	Anaphylaxis, myelosuppression
	Gemtuzumab	Anti-CD33 monoclonal antibody conjugated with cytotoxic molecule, calicheamicin	Anaphylaxis, myelosuppression
	Alemtuzumab	Anti-CD52 antibody, expressed on all lymphocytes	Anaphylaxis, myelosuppression
Proteasome inhibitor	Bortezomib	Inhibits proteasome, allowing cell to undergo apoptosis	Neuropathy, nausea, thrombocytopenia
Tyrosine kinase inhibitor	Imatinib	Inhibits "abl" tyrosine kinase, overexpressed in CML	Rash, myalgias, edema, dyspepsia, liver toxicity

burning and redness (*erythromelalgia*). Splenomegaly is common. There is a small risk of transformation to AML and/or myelofibrosis.

► Diagnosis

ET is differentiated from a reactive thrombocytosis (acute/chronic inflammation, post-splenectomy, iron deficiency) and other myeloproliferative disorders. The platelet count is usually > 600×10^3/mm^3. Bone marrow shows increased, abnormal-appearing megakaryocytes.

► Pathology

Platelet production is 2–15 times normal, and megakaryocyte colonies increase spontaneously. May represent increased sensitivity to normal cytokine signals. Platelets are dysfunctional.

► Treatment Steps

1. Treatment is generally reserved for symptomatic patients (thrombotic/hemorrhage).
2. Anagrelide is platelet specific. May cause fluid retention, palpitations, diarrhea. Other myelosuppressive agents (hydroxyurea, interferon-α) are non–platelet specific.
3. Aspirin is very effective in treating small-vessel thrombosis (e.g., erythromelalgia, transient ischemic attacks).

c. Myelofibrosis with Myeloid Metaplasia (MMM)

► Description and Symptoms

Progressive marrow space fibrosis resulting in extramedullary hematopoiesis, usually involving spleen and liver. Symptoms of anemia often dominate. Abdominal discomfort (from enlarged spleen), sweats, and weight loss (from increased hematopoietic metabolism) are common. Most cases of MMM arise de novo. May follow radiation, benzene, or toluene exposure. Other myeloproliferative disorders can evolve into MMM (especially polycythemia vera). Survival is generally 5–10 years. Approximately 10% evolve into AML.

► Diagnosis

Usually pancytopenia. Anemia can be severe. PBS shows a leukoerythroblastic picture ("teardrop"-shaped erythrocytes, circulating immature myeloid and erythroid precursors; see Figure 5–13). Bone marrow shows prominent reticulin fibrosis.

► Pathology

Increased marrow fibroblast activity secondary to abnormal megakaryocyte proliferation and cytokine signaling.

► Treatment Steps

Therapeutic options are limited:

1. Anemia may respond to recombinant erythropoietin, corticosteroids, and/or androgens (e.g., danazol).
2. Splenectomy, splenic irradiation, and/or myelosuppressive chemotherapy are used for symptomatic splenomegaly (e.g., refractory cytopenias, pain, early satiety).
3. Allogeneic bone marrow transplantation for select patients.

d. Chronic Myelogenous Leukemia (CML)

► Description and Symptoms

CML is a proliferative disorder characterized by clonal expansion of mostly neutrophilic granulocytes. Symptoms usually stem from splenomegaly (discomfort/early satiety), hypermetabolism (sweats,

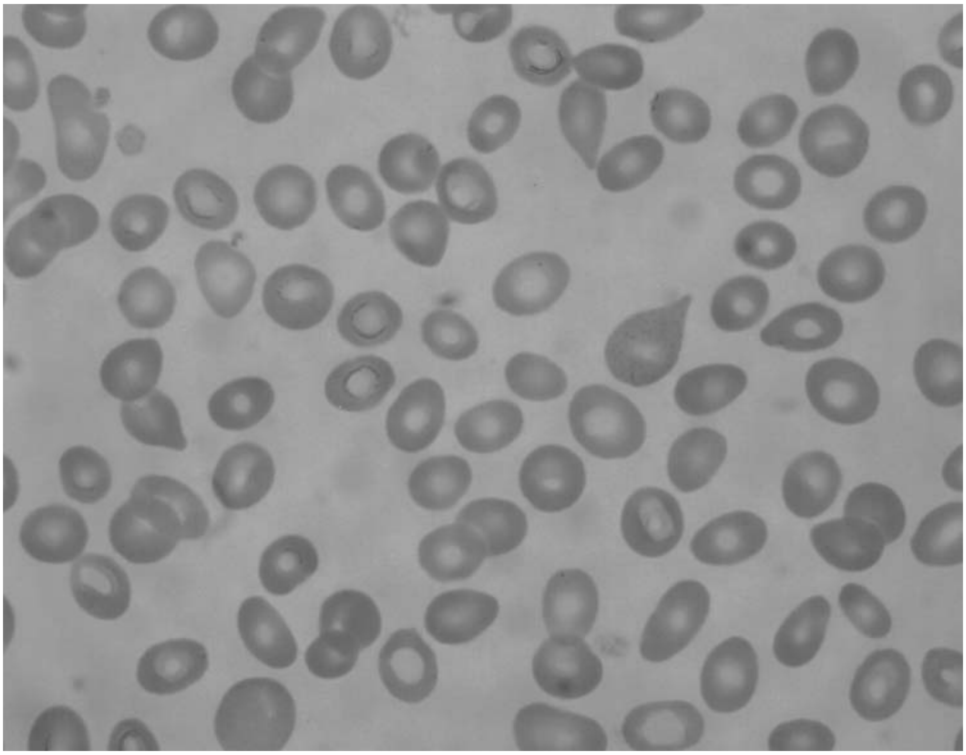


Figure 5–13. Myelofibrosis with "teardrop" RBIs.

fever, weight loss), and/or anemia. Many patients are asymptomatic. Early chronic-phase CML evolves into a more aggressive accelerated phase within 2–10 years of diagnosis, and eventually into acute leukemia ("blast crisis").

► Diagnosis

Variable degree of granulocytosis. Many immature granulocytic forms (e.g., metamyelocytes, myelocytes) are noted on PBS review (Figure 5–14). Anemia and thrombocytosis are common. The Philadelphia (Ph) chromosome (reciprocal translocation between the long arms of chromosomes 9 and 22) is detected by bone marrow cytogenetics (or fluorescent in-situ hybridization [FISH] analysis) in 95% of patients. Differential diagnosis includes reactive leukocytosis secondary to inflammation, corticosteroids, adrenaline, etc.

► Pathology

The cause is unknown. Radiation exposure is a risk factor. The "abl" gene found on chromosome 9 codes for a tyrosine kinase. Translocation juxtaposes "abl" and "bcr" (chromosome 22), disrupting tyrosine kinase-mediated, transcellular membrane signal transduction.

► Treatment Steps

1. Imatinib is a well-tolerated, specific tyrosine kinase inhibitor that effectively induces hematologic and cytogenetic remissions. Although duration of effect is currently unknown, imatinib is the treatment of choice for patients in chronic phase (see Table 5–11).
2. Allogeneic bone marrow transplantation is a potentially curative therapy for some patients intolerant or unresponsive to imatinib.

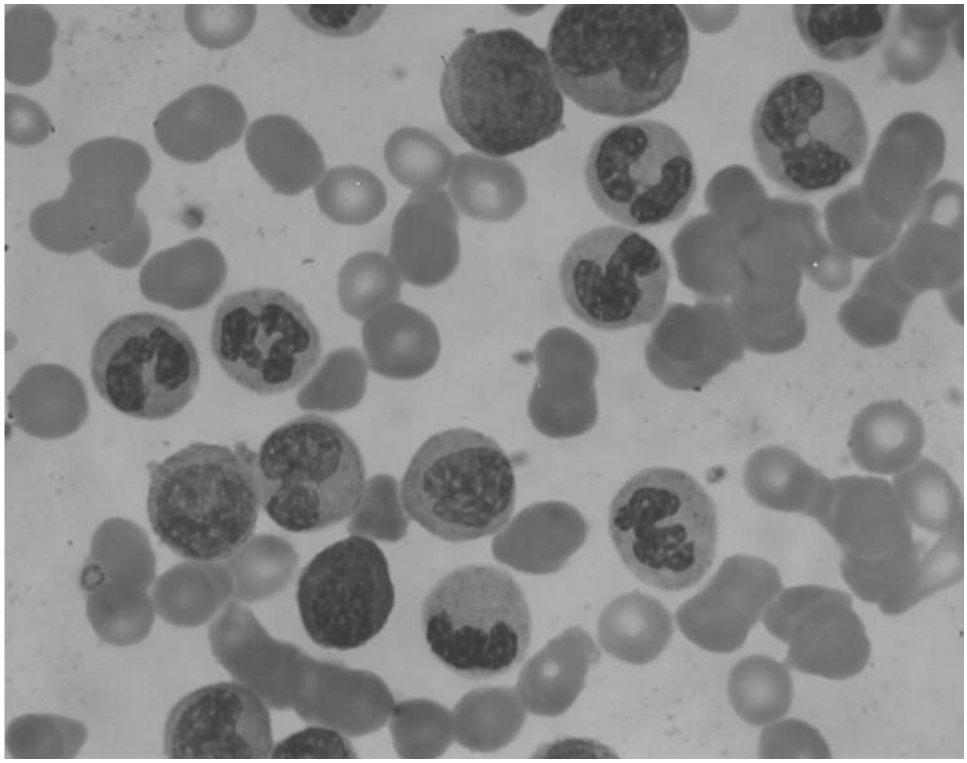


Figure 5–14. Chronic myelogenous leukemia.

3. Hydroxyurea and interferon-α are sometimes used to control blood counts.
4. Treatment options for “blast”-phase CML are limited.

2. Lymphoproliferative Disorders

a. Hodgkin’s Lymphoma (Hodgkin’s Disease)

► Description and Symptoms

Rare compared to NHL. Occurs in a bimodal distribution: young adults and the elderly. Familial clustering seen. Patients present with lymphadenopathy, usually contiguous lymph node sites. Systemic symptoms (fevers, night sweats, and/or weight loss), referred to as “B” symptoms, confers a worse prognosis. The lymph node in HD is comprised mostly of reactive lymphoreticular cells and scant, clonally malignant Reed–Sternberg (RS) lymphocytes. The classification of Hodgkin’s disease (HD) is summarized in Table 5–12.

5-12

CLASSIFICATION OF HODGKIN’S DISEASE (HD)

Classic HD	
Nodular sclerosis	Most common subtype. Lymph node with abundant sclerotic collagen tissue, women > men, usually early stage at presentation, mediastinal nodal involvement common.
Mixed cellularity	Second most common, men > women, often older and advanced stage, most common subtype in HIV positive, lymph nodes richly cellular.
Lymphocyte depletion	Rare (< 1%), older, advanced stage.
Nodular lymphocyte predominant	Recognized as entity distinct from classic HD. Rare (< 5%), young males, early stage, abundant lymphocytes, L & H (“popcorn) cells found instead of RS cells. Often chronic, relapsing.

► Diagnosis

Requires a biopsy of an involved lymph node. In classical Hodgkins, RS cells give a characteristic immunohistochemical staining pattern. Staging requires complete body imaging, usually positron emission tomography (PET) or gallium scan, and a bone marrow biopsy. Ann Arbor staging is based on number of lymph node sites (stage I or II) on one side or both sides (stage III) of the diaphragm. Extranodal disease is stage IV. Laparotomy for splenic sampling is no longer done.

► Pathology

In most cases, the RS cell represents a malignantly transformed B lymphocyte. Remaining cells are polyclonal, reactive lymphocytes, macrophages, granulocytes, eosinophils. An association between EBV infection and HD exists, particularly mixed cellularity and HIV associated subtypes.

► Treatment Steps

1. Stage I disease (e.g., one lymph node site) is frequently treated with radiation alone.
2. Stage II disease is usually treated with radiation and several cycles of chemotherapy (see Table 5–11).
3. Stage III and IV disease are generally treated with chemotherapy alone (see Table 5–13).
4. Cure rate is 70–90% for early/intermediate stage, 50–60% for advanced stage. Relapse may be salvaged with additional treatment (e.g., autologous/allogeneic bone marrow transplantation).

b. Non-Hodgkin's Lymphoma (NHL)—NHL includes many different lymphocytic neoplasms, usually presenting as diffuse, nontender lymph node swelling (i.e., "diffuse lymphadenopathy"). Commonly involves the blood, bone marrow, and extranodal sites (liver, intestinal tract, central nervous system, skin). Ann Arbor staging is used. The classification of lymphoid malignancies is based on clinical/pathological features (Table 5–14). Diagnosis is usually made by immunohistochemical and flow cytometric immunophenotyping of a sampled lymph node. Most lymphomas represent transformation of a normal germinal center cell. Treatment varies depending on subtype. Treatment for less aggressive NHL (i.e., "low grade") is reserved for symptomatic patients (i.e., "watchful waiting"). Aggressive (i.e., "high grade") NHLs are treated at diagnosis using combination regimens. Stem cell transplantation (both allogeneic and autologous) is reserved for relapsed/refractory disease. The most important subtypes of NHL are described in Table 5–15.

► **cram facts**

NHLs are often classified based on predicted clinical behavior as "low" (e.g., follicular), "intermediate" (e.g., diffuse large cell), and "high" (e.g., Burkitt's) grade. Intermediate and high-grade NHL are rapidly prolific, but potentially curable; low-grade NHL progresses slowly, but is generally incurable. Since low-grade NHL and CLL are not curable in most instances, treatment is usually deferred until patients are symptomatic.

5-13

COMMON CHEMOTHERAPY REGIMENS FOR HEMATOLOGICAL MALIGNANCIES

Hodgkin's lymphoma	Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD)
Follicular (non-Hodgkin's) lymphoma	Rituximab, Fludarabine (alone or in combination); cyclophosphamide, vincristine, prednisone, rituximab (CVP-R); cyclophosphamide, Adriamycin, vincristine, prednisone, rituximab (CHOP-R)
Large B cell (non-Hodgkin's) lymphoma	CHOP-R
Acute myeloid leukemia	Daunorubicin, continuous infusion cytarabine ("7&3")
Chronic lymphocytic leukemia	Fludarabine, cyclophosphamide, rituximab, chlorambucil, prednisone (alone or in combination); alemtuzumab
Multiple myeloma	Thalidomide, dexamethasone; arsenic trioxide; bortezomib; melphalan, prednisone

5-14

WHO CLASSIFICATION OF LYMPHOID MALIGNANCIES

B-Cell Neoplasm	T-Cell Neoplasm
Precursor B cell	Precursor T cell
B lymhoblastic lymphoma	T lymphoblastic lymphoma
Mature (peripheral) B cell	Mature (peripheral) T cell
CLL/SLL	T-cell granular lymphocytic
Prolymphocytic leukemia	Prolymphocytic
Lymphoplasmacytic (Waldenström's)	NK-cell leukemia
Splenic marginal zone	Adult T-cell lymphoma (HTLV-1)
Hairy cell leukemia	Extranodal T cell/NK cell
Plasma cell myeloma	Enteropathic T cell
Nodal/extranodal marginal zone	Hepatosplenic T cell
Follicular	Subcutaneous panniculitis
Diffuse large B cell	Mycosis fungoides
Burkitt's	Anaplastic large cell
Hodgkin's disease	Peripheral T-cell lymphoma

C. Multiple Myeloma

► Description and Symptoms

Belongs to a group of disorders referred to as *plasma cell dyscrasias*. Accumulation of neoplastic plasma cells causes bone lysis/fracture, hypercalcemia, and excessive monoclonal immunoglobulin production (M-protein). Excessive immunoglobulin and/or light-chain fragments (Bence Jones proteins) can injure the kidneys, cause serum hyperviscosity (see macroglobulinemia below), peripheral neuropathy, and suppression of normal immunoglobulin production. Cytopenias and infections are common. Survival is usually measured in years. Infection is the leading cause of death. Cause is largely unknown. Familial clustering evident. Higher incidence following radiation exposure and in metal workers.

► Diagnosis

Monoclonal protein (immunoglobulin and/or light chain) is detected by urine and serum protein electrophoresis (SPEP). Serum immunoelectrophoresis (SIEP) uses specific antisera to identify the type

5-15

COMMON SUBTYPES OF NHL

Follicular lymphoma	The most common lymphoma in the United States (45% of adult NHL). Low grade. Usually diffuse lymphadenopathy, +/– "B" symptoms. Growth is generally slow and unpredictable, but usually progressive over years. Early-stage disease may be curable, but more typical course is treatment-induced remission with eventual relapse and progression. Translocation between the immunoglobulin heavy-chain gene (chromosome 14) and the BCL2 gene (chromosome 18), results in constitutive expression of BCL2, an anti-apoptotic protein. Occasionally transforms into a more aggressive (usually large B-cell) lymphoma (Richter transformation).
Diffuse large B-cell lymphoma	Common (~40%) subtype of adult NHL. Intermediate grade. Often arises in immune-compromised host (e.g., post-organ transplant, AIDS). Usually presents as a rapidly increasing lymphadenopathy. Extranodal involvement and "B" symptoms common. Fatal without treatment. EBV pathogenic immune-compromised host. Treatment consists of CHOP-R chemotherapy.
Burkitt's lymphoma	Rapidly growing high-grade NHL occurring as both an endemic (African) and nonendemic (sporadic) form. The endemic form affects children residing in certain regions of Africa. Typical presentation is bulky peripheral lymphadenopathy and jaw involvement. Nonendemic Burkitt's occurs in varied geographic locations. High incidence in patients with advanced AIDS. Abdominal/intestinal involvement common. Biopsy reveals a population of mitotic small, noncleaved cells with sporadic macrophages creating a "starry sky" appearance. A characteristic translocation between chromosomes 8 (c-myc gene) and 14 (immunoglobulin heavy-chain gene) causes overexpression of oncoprotein c-myc. Latent EBV infection is believed pathogenic in endemic and many (20%) nonendemic Burkitt's. Cure possible using aggressive combination chemotherapy.

of M-protein. Erythrocytes are agglutinated (rouleaux formation) on PBS. Bone marrow reveals increased plasma cells. Osteopenia and discrete "punched-out" lytic bone lesions are seen on plain-film x-ray.

► Pathology

Plasma cell proliferation and survival is supported by cytokines (e.g., IL-6) produced by malignant plasma cells and marrow stromal cells. Many patients are infected with human herpesvirus 8, known to produce an IL-6 homologue. Osteoclast activation is cytokine (IL-1, IL-6) mediated. Cytogenetic abnormalities, including translocation between the fibroblast growth factor receptor (chromosome 4) and the immunoglobulin heavy chain (chromosome 14) common.

► Treatment Steps

1. Initial therapy usually consists of corticosteroids +/– thalidomide.
2. Melphalan (alkylating agent) +/– corticosteroid is an established alternative regimen.
3. Newer treatments include bortezomib (proteasome inhibitor) and arsenic trioxide.
4. Autologous bone marrow transplant prolongs remissions and improves survival. Allogeneic transplant may be curative.
5. Radiation therapy is effective for relieving focal bone pain.
6. Bisphosphonates (e.g., zoledronate) decrease the incidence of skeletal events (e.g., fracture, pain).

d. Monoclonal Gammopathy of Uncertain Significance (MGUS)—M-protein in the blood that remains stable over years, without other findings of myeloma. Common in the elderly (10% over age 70). Twenty-five percent will progress to frank myeloma over time. No treatment is necessary.

e. Waldenström's Macroglobulinemia (Lymphoplasmacytic Lymphoma)

► Description and Symptoms

A plasma cell dyscrasia characterized by excessive production of IgM (macroglobulin), hepatosplenomegaly, and lymphadenopathy. Symptoms stem from hyperviscosity (blurred vision, tinnitus, dizziness, heart failure, thrombosis), interference with normal clotting protein function (bleeding), cytopenias, and peripheral neuropathy (imbalance, pain).

► Diagnosis

Lymphoplasmacytic cells (i.e., transition between lymphocyte and plasma cell) often seen on PBS and abundantly evident on bone marrow examination. Rouleaux formation is common finding. SPEP confirms the presence of a monoclonal IgM paraprotein.

► Pathology

The cause of Waldenström's is unknown. Hyperviscosity is a consequence of increased plasma concentration of IgM (large macromolecule). Anemia reflects marrow involvement by malignant cells and plasma volume expansion. Occasionally, IgM acts as a cold agglutinin or cryoglobulin.

► Treatment Steps

1. Treat only if symptomatic.
2. Treatment is similar to that of other low-grade lymphomas (e.g., follicular lymphoma).
3. Plasmapheresis effective for hyperviscosity.

f. Primary (AL Amyloid) Amyloidosis

► Description and Symptoms

A rare plasma cell dyscrasia. Tissue infiltration by insoluble, light chain–derived amyloid fibril. Occasionally arises in the setting of myeloma (20%), but more commonly associated with an MGUS. Organ infiltration results in insidious development of hepatomegaly with liver failure, nephrotic syndrome leading to renal failure, malabsorption, tongue enlargement, autonomic neuropathy, and restrictive cardiomyopathy. Congestive failure may predominate. Without treatment, life expectancy is 1–2 years.

► Diagnosis

Monoclonal plasma cells evident on bone marrow examination. Monoclonal light chains, +/– intact immunoglobulin, detected by serum and/or urine immunoelectrophoresis. Congo red staining of subcutaneous fat pad biopsy produces characteristic "apple-green" birefringence under polarized light (90% sensitive).

► Pathology

Affected individuals may have a defect in normal light-chain degradation or production of an amyloidogenic light chain, resistant to proteolysis.

► Treatment Steps

Treatment is directed at the plasma cell dyscrasia. Alkylating agent–based chemotherapy (e.g., alkeran) followed by autologous stem cell transplantation can result in long-term remission with gradual improvement in organ dysfunction.

g. Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

► Description and Symptoms

Nomenclature depends on degree of blood (CLL) and/or lymphoid (SLL) involvement. Most common leukemia in Western countries. Highest incidence is in elderly men. Natural history is highly variable, from indolent to aggressive disease. Progressive disease marked by increasing peripheral lymphocytosis, marrow involvement (causing pancytopenia), lymphadenopathy, hepatosplenomegaly, and the development of "B" symptoms. Frequent complications include hypogammaglobulinemia (increasing risk of infection), autoimmune hematologic disorders (e.g., AIHA, ITP), and late transformation to more aggressive NHL (e.g., Richter's transformation).

► Diagnosis

A monoclonal population of small, round B cells (2–5% T cell) demonstrated in peripheral blood, marrow, and/or lymph node biopsy. Flow cytometric immunophenotyping reveals characteristic, aberrant cell-surface expression of CD5 antigen (normally expressed on T cells). Lymphocytes easily fragment on blood smear preparation giving rise to "smudge cells." In the United States, the RAI staging system is most commonly used (Table 5–16).

► Pathology

No clear association with radiation, medication, or other environmental exposure. Neoplastic transformation of a subpopulation of $CD5^+$ expressing B lymphocytes. Cytogenetic abnormalities fre-

5-16

RAI STAGING SYSTEM FOR CLL

Stage	Clinical Features
0	Lymphocytosis in blood
1	*plus* lymphadenopathy
2	*plus* splenomegaly (+/– hepatomegaly)
3	*plus* anemia
4	*plus* thrombocytopenia

quently found by FISH, and BCL-2 overexpression common (i.e., impaired apoptosis).

► Treatment Steps

1. Treatment reserved for symptomatic patients.
2. See Table 5–13.
3. Alemtuzumab, a monoclonal antibody for CD52 (present on most B/T cells), used in relapsed disease.
4. Intravenous gamma globulin reserved for hypogammaglobulinemia and recurrent infections.
5. Autoimmune disease (e.g., ITP) treated in standard fashion.
6. Allogeneic transplantation is a consideration for select, younger patients.

G. Acute Leukemias

The acute leukemias (acute myelogenous leukemia [AML], acute lymphoblastic/cytic leukemia [ALL]) are a group of disorders arising from neoplastic transformation and progressive accumulation of early hematopoietic myeloid (AML) or lymphoid (ALL) stem cells ("blasts"). Blast cells fail to mature properly, overpopulate the bone marrow, and eventually invade peripheral blood and other tissues. Normal hematopoiesis is disrupted, usually causing profound cytopenias. Life expectancy without treatment is usually only a few months. Most cases arise de novo; however, secondary AML (and to a lesser degree ALL) can arise from preexisting blood disorders (MDS, myeloproliferative disorders), prior exposure to chemotherapy (alkylating agents, topoisomerase II inhibitors), benzene, tobacco, radiation, and some congenital syndromes (i.e., Fanconi's anemia, Bloom syndrome, Down syndrome). Familial clustering of AML and ALL seen.

1. AML

► Description and Symptoms

Generally a disease of adults (80%); highest incidence in the elderly. Fever, bleeding, fatigue, and dyspnea common presenting symptoms. Acute promyelocytic leukemia (APML) uniquely associated with DIC (i.e., bleeding and thrombosis). Treatment of young adults associated with high complete remission (70–80%), but relapse common (30–40% cure). Prognosis is generally worse for AML occurring in the elderly and those with secondary AML (10–15% long-term cure). Cytogenetic data has prognostic significance and is useful in stratifying patients and making treatment decisions.

► Diagnosis

Confirmed by ≥ 20% blasts present on bone marrow biopsy (Figure 5–15). The proposed WHO classification incorporates and expands the original FAB classification (Tables 5–17 and 5–18). The presence

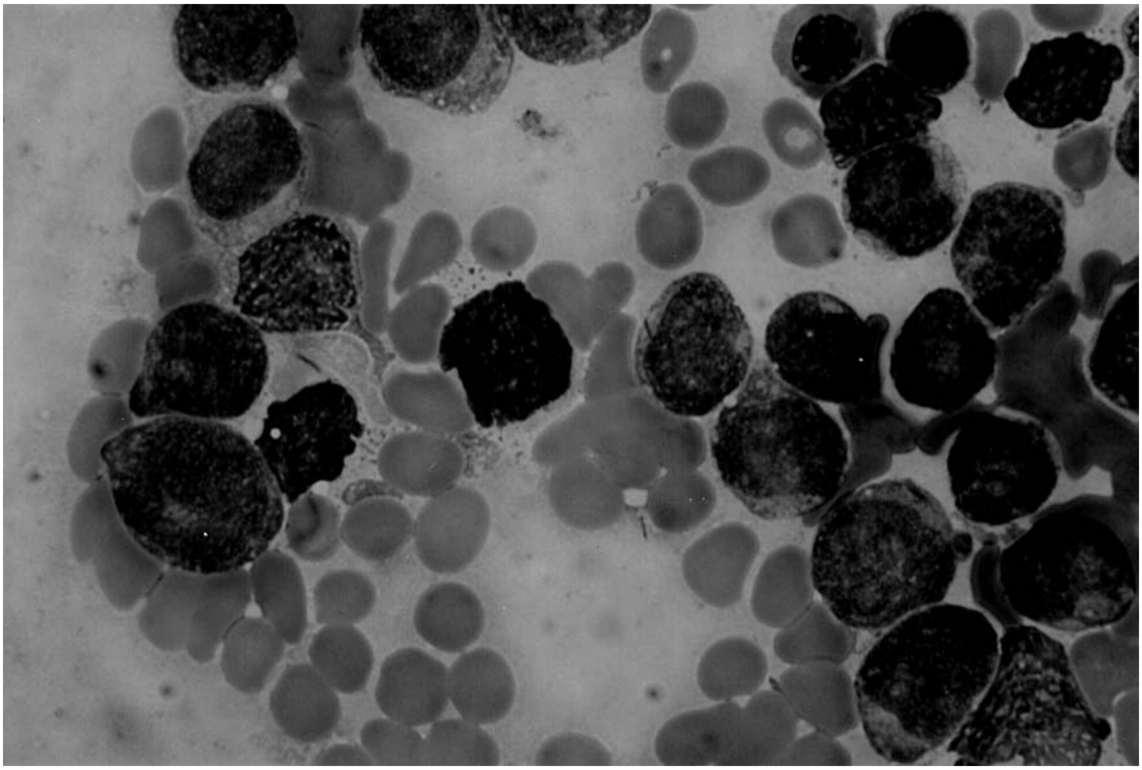


Figure 5–15. Acute myelogenous leukemia.

of cytoplasmic granules (e.g., Auer rods), staining for myeloperoxidase, Sudan black, and/or specific esterase assist in differentiating AML from ALL. Immunophenotyping of blasts is instrumental for precise classification. Some cases of AML show features of both ALL and AML (biphenotypic).

► Pathology

Mutations in genes that control cell cycling, maturation, survival, and adhesion of an early myeloid progenitor stem cell. A translocation of the retinoic acid receptor gene on chromosome 17 and the PML gene on chromosome 15 [t(15:17)] is pathognomonic in APML.

► Treatment Steps

1. Consist of the "induction phase" (3 days of IV anthracycline/7 days of continuous infusion cytarabine) to induce remission and

5-17

FRENCH–AMERICAN–BRITISH (FAB) CLASSIFICATION OF ACUTE MYELOID LEUKEMIA (AML)

M0	Myeloblastic leukemia, minimally differentiated
M1	Myeloblastic leukemia, without maturation
M2	Myeloblastic leukemia, with maturation
M3	Promyelocytic leukemia
M4	Myelomonocytic leukemia
M5	Monocytic leukemia
M6	Erythroleukemia
M7	Megakaryoblastic leukemia

5-18

WHO CLASSIFICATION OF AML

AML with recurrent genetic abnormalities (e.g., 8:21 traslocation, inversion 16, acute promyelocytic with 15:17 trasnlocation)
AML with multilineage dysplasia
AML, therapy related
AML, minimally differentiated
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Acute erythroid leukemias
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
AML not otherwise categorized
Acute leukemias with ambiguous lineage (i.e., bilineage, biphenotypic, undifferentiated leukemia)

the "consolidation phase" (several cycles of high-dose cytarabine and/or bone marrow transplantation) to maintain remission.

2. Allogeneic transplant is reserved for younger patients with either relapsed disease or in first remission with a high likelihood of relapse (i.e., poor-risk disease).
3. Gemtuzamab can prolong survival in relapsed disease.
4. APML represents a prognostically favorable subtype. All-trans retinoic acid (ATRA), in combination with chemotherapy, and arsenic trioxide are both active regimens for this subtype.

2. ALL

► Description and Symptoms

ALL is the most common childhood malignancy (peak age 2–5) in the United States. Fifteen percent of cases occur in adults. Presentation is similar to AML; however, lymphadenopathy, hepatosplenomegaly, bone pain (sometimes misdiagnosed as juvenile rheumatoid arthritis), and CNS involvement (headaches, neurologic symptoms) more common in ALL. Prognosis favorable for childhood ALL (cure 90%), less favorable for adults, particularly if Philadelphia chromosome present (3% childhood, 25% adults). T-cell ALL is uncommon, usually young adults, presenting with large mediastinal mass, and a favorable overall prognosis.

► Diagnosis

Bone marrow reveals increased lymphoblasts, classified by the FAB system as L1–3 based on morphologic features (Table 5–19). Most childhood ALL is L1 and most adult, L2. L3 subtype is equivalent to Burkitt's lymphoma. Lack of cytoplasmic granules, periodic acid-Shiff (PAS)-positive staining, and the presence of TdT (terminal

5-19

FRENCH–AMERICAN–BRITISH (FAB) CLASSIFICATION OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

L1	Small cells, round nuclei, rare nucleoli, scant cytoplasm (most childhood ALL)
L2	Large cells, irregular nuclei, one or more nucleoli, abundant cytoplasm (adult ALL)
L3	Large cells, round nuclei, one or more nucleoli, abundant cytoplasm with vacuoles (identical to Burkitt's lymphoma cells, rare ALL subtype)

deoxytransferase) favor diagnosis of ALL over AML. Chromosomal abnormalities are common in ALL.

► Pathology

Genetic and environmental factors result in transformation, by progressive accumulation of mutations, of early lymphoid progenitor stem cell. Most are of B lineage (85%), less commonly (15%) of T lineage (i.e., T-cell ALL). Several cytogenetic abnormalities have been identified with prognostic significance. These can be detected by traditional metaphase karyotyping or using interphase PCR and/or FISH to identify specific translocations.

► Treatment Steps

1. Treatment consists of induction, consolidation, and maintenance extending over 2–3-year period.
2. Each phase uses high-dose, combination chemotherapy.
3. Prophylactic intrathecal chemotherapy, with or without cranial irradiation, to eradicate a potential CSF sanctuary of disease.
4. Allogeneic transplant is used for select, high-risk patients in first remission or at relapse.

H. Immune Disorders

1. Immune Deficiency

Both acquired and congenital causes (Table 5–20). Congenital immune deficiencies usually manifest after 6 months, as levels of maternal antibodies wane.

a. AIDS

► Description and Symptoms

First recognized in the early 1980s in homosexual males, with wasting, immune deficiency, and pneumonia. Forty million cases estimated worldwide, most (95%) occurring in adults living in the developing world (two thirds in sub-Saharan Africa), acquired via heterosexual transmission. In the United States, homosexual and bisexual men most affected, although incidence decreasing; increasing among IV drug users, heterosexuals, and women. Flulike symptoms common following initial infection (i.e., acute HIV infection), marked by transient fall in $CD4^+$ T-lymphocyte count and high viral load. Symptoms resolve with immune response and antibody production. A latent phase follows, lasting 5–10 years, with low viremia but gradual loss of $CD4^+$ T lymphocytes. Risk of opportunistic infections (OIs) and some neoplasms increases, as T-cell count declines. Disease entities include: pneumonia (bacterial, *Mycobacterium tuberculosis, Pneumocystis jiroveci* (formerly *carinii*), *Mycobacterium avium-*

5-20

EXAMPLES OF ACQUIRED IMMUNE DEFICIENCY

Acquired immune deficiency syndrome (AIDS)
Malnutrition
Age extremes (e.g., infancy and old age)
Post-splenectomy
Medications (e.g., corticosteroids, chemotherapy, immune suppressants)
Neoplasia
Leukemia/lymphoma
Hypogammaglobulinemia
Systemic diseases (e.g., diabetes, renal failure, cirrhosis)

intracellulare [MAI]), oral disease (candidiasis, oral hairy leukoplakia), gastrointestinal disease (*Cryptosporidium, Isospora* diarrhea; CMV colitis, hepatitis), neurologic infections (cerebral toxoplasmosis, CMV retinitis, progressive multifocal leukoencephalopathy, cryptococcal pneumonia), tumors (Hodgkin's/non-Hodgkin's lymphoma, Kaposi's sarcoma), and HIV wasting syndrome. AIDS is the leading cause of death among young adults. Mortality rate in the United States is decreasing with new therapies.

► Diagnosis

Enzyme-linked immunosorbent assay (ELISA) for anti-HIV antibodies (sensitive). Positive results confirmed by Western blot (specific). Viral RNA transcripts ("viral load") by polymerase chain reaction (PCR) correlates with disease severity. AIDS is defined as a $CD4^+$ T-lymphocyte count of $< 200 \times 103/mm^3$; or HIV infection and any opportunistic infection, malignancy, tuberculosis, wasting syndrome, recurrent bacterial pneumonia, or thrush.

► Pathology

AIDS is caused by HIV, an RNA retrovirus that binds to host T-helper lymphocytes via $CD4^+$ cell-surface antigen. Viral genome encodes "reverse transcriptase" used to transcribe DNA from viral RNA. DNA is incorporated into host genome and remains latent. Upon reactivation, host nuclear transcription machinery is used to synthesize new virions, resulting in cell lysis and death. Progressive decline in T-helper cell concentration causes a primary deficiency in cell-mediated immunity. The time from infection to development of AIDS ranges from months to years (median 10 years).

► Treatment Steps

1. Prevention of infection and preservation of $CD4^+$ lymphocytes using combinations of nucleoside and non-nucleoside reverse transcriptase inhibitors (inhibit reverse transcriptase) with protease inhibitors (prevent cleavage of translated protein into final products). Effect of therapy monitored by following HIV RNA load and $CD4^+$ cell count.
2. Prophylaxis against OIs using trimethoprim–sulfamethoxzole (*Pneumocystis, Toxoplasma*), azithromycin or clarithromycin (MAI), isoniazid/pyridoxine (patients with positive purified protein derivative [PPD]) initiated as $CD4^+$ count falls below 200×103 cells/mm^3.
3. Treatment of specific OIs/neoplasms generally less successful than immune competent host, requiring more extensive/longer duration of treatment and chronic suppressive therapy.

b. Congenital Immune Deficiency

Summarized in Table 5–21.

2. Hypersensitivity

Hypersensitivity reactions are severe immunologic reactions to foreign or self-antigen causing tissue damage. There are four recognized hypersensitivity reactions, classified according to the prevailing immune mechanism.

a. Type 1 "Immediate" Hypersensitivity

► Description and Symptoms

Includes many common allergic reactions such as asthma, allergic rhinitis, urticaria, atopic dermatitis, anaphylaxis, and angioedema.

5-21

CONGENITAL IMMUNE DEFICIENCIES	
Bruton's (X-linked) agammaglobulinemia	An X-linked disorder predisposing to recurrent bacterial infections after 6 months of age (following the attenuation of passively acquired maternal immunoglobulin) and a lifelong increased risk of autoimmune disorders and type 1 hypersensitivity. A mutation of a gene on X chromosome that codes for a tyrosine kinase necessary for normal B-cell maturation results in the loss of mature B lymphocytes, follicle formation, and plasma cells. Patients are agammaglobulinemic. Treatment is with regular infusions of intravenous immunoglobulin (IVIG).
IgA deficiency	The most common immune deficiency in Caucasion population (1/700). No clear pattern of inheritance. Patients develop recurrent sinopulmonary and gastrointestinal infections due to diminished IgA production. Associated with a high incidence of autoimmunity (lupus, rheumatoid arthritis), allergy, and inflammatory bowel disease. Anaphylaxis may occur following erythrocyte or plasma transfusions (IgE directed against "foreign" IgA). Treatment is with IVIG.
Common variable immune deficiency (CVID)	A heterogeneous disorder characterized by hypo/agammaglobulinemia, normal B-lymphocyte concentration, and normal follicle formation. Plasma cells are absent. No clear pattern of inheritance and no gender predilection. Familial clustering noted. Precise cause unclear. Clinical manifestations and treatment similar to Bruton's; however, usually later onset of symptoms (adults). Increased frequency of autoimmune disorders, celiac sprue–like syndrome, lymphomas, pernicious anemia, and gastric cancer.
Severe combined immune deficiency (SCID)	Profound immune deficiency due to absence of both T and B lymphocytes. Without treatment, patients with SCID usually die early in life from recurrrent microbial infections. Most cases of SCID (60%) involve X-linked mutations in gene coding for a protein component of many cytokine receptors. Lack of cytokine signaling blocks normal lymphocyte maturation. Most non-X-linked SCID are autosomal recessive and result from a deficiency of the enzyme adenosine deaminase. Bone marrow transplant is the preferred treatment. Gene therapy replacing the missing adenosine deaminase gene has been used in patients with autosomal recessive SCID variant.
DiGeorge syndrome	Absent T-cell maturation due to thymic aplasia/hypoplasia. Developmental failure of the third and fourth pharyngeal pouch (origin of parathyroids, thymus, heart and vessels, facial structures) results in a loss of cell-mediated immunity, cardiac and facial deformities, and hypocalcemia. For most patients, immunologic deficits improve with time. Severe, persistent T-cell immune deficiency may respond to fetal thymic transplantation. Other efforts are directed at treating hypocalcemia and cardiac abnormalities.

Vasodilation, smooth muscle contraction, mucous and edema formation occur during the immediate phase. A cutaneous "wheal-and-flare" reaction is seen. Hypotension is a consequence of systemic vasodilation with extensive fluid loss. The second phase (slow response of anaphylaxis) continues for hours to days and involves recruitment of other inflammatory cells (neutrophils, lymphocytes, monocytes, and eosinophils).

► Diagnosis

Mostly a clinical diagnosis. Usually a personal or familial history of similar reactions (atopic history). Sputum and blood eosinophil concentration and serum IgE levels may be increased in asthma. Provocative testing with allergen (skin injection, inhalation) may elicit positive reaction.

► Pathology

Specific antigens (allergens) stimulate B cells to produce IgE (reagin) that binds to mast cells and basophil Fc receptors. Upon reexposure, allergen binds to IgE and triggers cell degranulation, releasing preformed mediators (histamine, serotonin), chemotactic factors, and proteases. Activated mast cells/basophils synthesize other mediators, including cytokines (IL-1, -4, and -5; TNF), bradykinin, leukotrienes, and prostaglandins.

► Treatment Steps

1. Treatment consists of antihistamines, bronchodilators (β_2-agonists, anticholinergics), leukotriene inhibitors, and/or corticosteroids depending on the severity/frequency. Severe, acute episodes may require blood pressure support (IV fluids, epinephrine).

2. Cromolyn is used in childhood asthma as a mast cell stabilizer.
3. Theophylline (increases cAMP) is occasionally used in adult asthma.
4. Allergen desensitization is occasionally pursued.

b. Type 2 Hypersensitivity

► Description and Symptoms

Autoimmune reactions in which antibody targets specific tissue-based antigen. Graves' disease, Hashimoto's thyroiditis, myasthenia gravis, Goodpasture syndrome, and ITP are included in this category.

► Diagnosis

Mostly a clinical diagnosis. Assays for specific antibodies may be available to assist with the diagnosis (e.g., pernicious anemia: anti-parietal cell antibodies).

► Pathology

Multiple mechanisms leading to autoimmunity have been proposed. Foreign antigen resembling self-antigen may lead to cross-immune reactivity ("molecular mimicry"). Self-antigen may become antigenic by chemical, viral, or other modification; or enhanced, aberrant antigen presentation. Normally anergic, but autoreactive circulating lymphocytes become activated by various nontraditional means. $CD8^+$ suppressor T-lymphocyte function may be lost. Genetic predisposition and hormonal status clearly important (highest incidence of many autoimmune disorders in young females with positive family history). Antibody binding to antigen may activate (Graves' disease) or inhibit (myasthenia gravis) the target, or cause complement activation. This in turn causes localized damage by inflammation or removal of opsonized antigen by phagocytosis.

► Treatment Steps

Treatment varies according to disease. May consist of replacing the substance lost by tissue damage (e.g., thyroid replacement for Hashimoto's hypothyroidism; B_{12} in pernicious anemia) or suppressing the immune system (e.g., corticosteroids, azathioprine, cyclophosphamide, cyclosporin) to prevent further tissue damage.

c. Type 3 Hypersensitivity

► Description and Symptoms

Antibody targets circulating antigen which is subsequently deposited in tissue as immune complex. Target antigen can be exogenous (e.g., medications, microbes) or endogenous (some autoimmune disorders). Examples of type 3 hypersensitivity include systemic lupus erythematosus, rheumatoid arthritis, and poststreptococcal glomerulonephritis. Years ago, systemic manifestations of immune complex deposition commonly occurred following infusion of horse-derived antisera ("acute serum sickness").

► Diagnosis

Mostly a clinical diagnosis. Assays for circulating immune complex may assist in diagnosis. For example, IgM directed against IgG (rheumatoid factor) is often found in rheumatoid arthritis. Anti-streptococcal antibodies (ASO titer) are found in patients with suspected poststreptoccocal glomerulonephritis.

► Pathology

Immune complex is deposited in various tissues (skin, glomeruli, vessels, joints, etc.), resulting in complement activation and inflammation. Highest incidence when immune complexes are small and formed in the setting of excess antigen (particularly if the reticuloendothelial system is impaired or overloaded).

► Treatment Steps

1. Many episodes resolve with time (serum sickness, poststreptococcal glomerulonephritis).
2. Other chronic autoimmune disorders (e.g., lupus) may require immune-suppressant medication.

d. Type 4 (Delayed or Cell-Mediated) Hypersensitivity

► Description and Symptoms

Includes both cytotoxic (i.e., involving $CD8^+$ cytotoxic T lymphocytes) and classic delayed hypersensitivity reactions (i.e., mediated by $CD4^+$ T-helper lymphocytes). Type 4 reactions are important in the eradication of virally infected cells (classic $CD8^+$ cytotoxic reaction); immune attack against mycobacterial, protozoal, and fungal infections; transplant graft rejection; and contact dermatitis (e.g., gold, latex, and poison ivy hypersensitivity reactions). Other reactions include the purified protein derivative (PPD) tuberculin skin reaction and granuloma formation.

► Diagnosis

The diagnosis is usually clinical, but may involve provocative testing (e.g., PPD, contact allergen).

► Pathology

Type 4 hypersensitivity reactions involve mostly mononuclear cells. $CD4^+$ T-helper lymphocytes produce cytokines that recruit and activate $CD8^+$ cytotoxic T lymphocytes and macrophages. Granulomas form when the immune system attempts to contain or eradicate certain fastidious antigen (e.g., *Mycobacterium,* foreign body, sarcoidosis). Contact dermatitis results from the binding of "haptens" (perfumes, detergents, poison ivy) to carrier proteins in skin, forming an antigenic stimulus that sufficiently elicits an immune response. Transplant graft rejection involves both type 4 cell-mediated and humoral immune responses. Both host- and donor tissue–based APCs present allogeneic MHC molecules as antigen, triggering a rejection response. Preformed antibodies against donor tissue antigen cause hyperacute graft rejection.

► Treatment Steps

1. Treatment of graft rejection consists of immune suppression (cyclosporin, corticosteroids, tacrolimus, etc.).
2. Contact dermatitis is treated with corticosteroids and avoidance of the precipitating allergen.

I. Transfusion and Transfusion Reactions

1. Erythrocytes

The appropriate threshold for transfusion is not clearly defined and must be individualized. Normal pretransfusion evaluation involves "typing" recipient erythrocyte and "screening" recipient serum for the presence of alloantibodies against certain erythrocyte antigens. Typing uses antisera directed against "A," "B," and "D" (Rh) erythrocyte surface antigens. Absence of A and B is designated "O." Each unit of transfused packed red blood cells contains approximately 200 cc of erythrocytes.

2. Platelet Transfusions

Risk of spontaneous bleeding low with platelet count > $20 \times 10^3/mm^3$; $10 \times 10^3/mm^3$ is a reasonable transfusion threshold if low bleeding risk (i.e., no NSAID use, coagulopathy, fever). Invasive procedures require platelet count > $50 \times 103\ mm^3$. Typical rise in platelets is 5,000–10,000/mm^3 per unit transfused.

3. Plasma Therapy

Fresh-frozen plasma (FFP) is used to treat bleeding due to deficient clotting factor (e.g., vitamin K deficiency, coumadin induced, congenital deficiency, liver disease, etc.). Each unit of FFP contains 200–250 cc of plasma. Generally, 4–6 units are required, which raises clotting factor level by > 30%. Solvent–detergent methods are used to inactivate enveloped viruses (HIV, hepatitis B and C). Cryoprecipitate is prepared by allowing frozen plasma to thaw at 4°C (39.2°F). The resulting precipitate is rich in fibrinogen, factor VIII, and vWF.

Common transfusion reactions are summarized in Table 5–22.

5-22

TRANSFUSION REACTIONS

Erythrocyte Reactions	
Acute hemolytic transfusion reaction	Rare (1/250,000–1,000,000) nowadays but potentially life threatening, resulting from ABO incompatibility, virtually always from human error. Patients develop immediate hypotension, fever, nausea, back/chest pain, and hemoglobinuria. DIC, renal failure, and shock can follow. Treatment is mostly supportive (IV fluids, pressure support, etc.).
Delayed transfusion reaction	Relatively common (1/1,000). Occurs a week or more after transfusion. Erythrocytes are hemolyzed by IgG antibody developing de novo or anamnestically against non-ABO erythrocyte antigens. Increased frequency in multiparous women and/or pretransfused individuals. Suspected by inadequate post-transfusion rise in hemoglobin, with evidence of hemolysis. New antibody is detected by repeat screen.
Febrile transfusion reaction	Common reaction (2% of transfusions), particularly in multiparous women and/or heavily transfused recipients. Symptoms include fever and chills and occasionally rigors late in the transfusion. Recipient antibodies are directed against donor leukocytes and proteins. Treatment is with acetaminophen and diphenhydramine (meperidol for rigors). Often given prophylactically pretransfusion. Filters that deplete leukocytes reduce the incidence.
Anaphylaxis	Rare. Seen in some individuals with congenital IgA deficiency, receiving IgA-containing blood. Transfusion-related lung injury occurs in 1/5,000 transfusions from high-titer, anti-HLA antibody in the donor blood (e.g., multiparous donor) directed against recipient leukocytes. Patients develop noncardiogenic pulmonary edema. Treatment is supportive (oxygen, diuretics).
Volume overload/pulmonary edema	Seen most frequently in patients with impaired cardiac function.
Viral infection	Rarely seen with current screening methods. Risk of hepatitis C is 1/1,600,000, hepatitis B 1/100,000, and HIV 1/2,000,000. Roughly 50% of the population seropositive for CMV, which can be transmitted via transfused leukocytes. CMV causes life-threatening infections in seronegative, immune-compromised recipients. Leukoreduction filters reduce risk of transmission. CMV-negative blood products are generally used for CMV-negative transplant recipients.
Platelet reactions	
Transfusion refractoriness	Heavily transfused patients develop refractoriness, attributed to sensitization of recipient to HLA platelet antigens. Leukoreduction (to reduce sensitization) may delay development. Treatment options include using single-donor, HLA-matched platelets. "Crossmatching" platelets allows identification of compatible units.
Febrile transfusion reactions	Occur more commonly following platelet (18%) than erythrocyte transfusion. Highest incidence is in heavily transfused patients. Pretransfusion diphenhydramine and acetaminophen reduce risk.
Bacterial contamination	More common with platelets than erythrocytes since platelets are stored at room temperature. The shelf life of donated platelets is limited to 5 days to minimize risk.
Plasma reactions	
Febrile transfusion reactions	
Volume overload	

J. Cultural, Occupational, and Environmental Considerations

1. Supportive Care

The appropriate management of patients with a hematologic malignancy involves a multidisciplinary team approach (pharmacist, social worker, mental health specialist, nurse, dietitian, etc.). Supportive care includes the assessment and management of disease-related symptoms (pain, cancer-related fatigue, depression/anxiety, malnutrition, immobility, etc.), as well as treatment-related symptoms (diarrhea, vomiting, constipation, mucositis, skin breakdown, alopecia, etc.). Supportive care also involves addressing issues of resuscitation, health care proxy, the patient's living situation, patient–family relationship, etc.

2. Nutritional Support

Anorexia and weight loss are common in patients with malignancies—a direct effect of both the tumor and the treatment. Assessment of a patient's nutritional status begins with a detailed history and examination, with attention to weight, muscle mass, fat stores, and edema. Serum protein measurement (albumin, total protein, transferrin) and cholesterol concentration are commonly used markers of nutritional status. A trained dietitian can assist in calculating daily calorie intake and deficits, the choice of appropriate diets, and the need for nutritional supplementation. Enteral feeding is preferred to parenteral. In certain situations (e.g., bowel obstruction, postoperative, bone marrow transplantation) when resumption of enteral feeding is not expected for 10–14 days, parenteral feeding (e.g., total parenteral nutrition [TPN]) may be required. TPN for an individual with a terminal malignancy and expected short survival is neither beneficial nor appropriate. Appetite stimulants (e.g., megestrol acetate, corticosteroids, dronabinol) are occasionally appropriate for short-term use.

3. Psychosocial Support

Psychosocial support is important for patients with a malignancy or other chronic debilitating disorder (e.g., sickle cell disease). Depression is estimated to affect 25% of patients with malignancy. Anxiety and sleep disturbance are equally common. Management requires a multidisciplinary approach and incorporates pharmacologic and nonpharmacologic (support groups, individual/family counseling) interventions.

4. Hospice Care

Hospice provides care for patients with a life expectancy of ≤ 6 months. Hospice consists of a team of providers (physician, social worker, nurse, nursing assistant, bereavement counselor, chaplain, volunteers) who address all aspects of care pertinent to the dying patient and his or her family. The cost of hospice is covered by both Medicare and Medicaid. Care is usually provided at home but can be provided in specialized, institutional settings.

BIBLIOGRAPHY

Hoffman R. *Hematology: Basic Principles and Practice.* Philadelphia: Elsevier, 2005.

Kasper DL, et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005.

Lee GR, et al. *Wintrobe's Clinical Hematology,* 10th ed. Baltimore: Williams & Wilkins, 1999.

The Musculoskeletal System

6

I. NORMAL PROCESSES

A. Embryonic Development

The musculoskeletal system develops from the mesoderm. The mesenchyme comes from the mesoderm, and within, there are pluripotential cells that are capable of forming bone, cartilage, ligament, tendon, and fascia. At the sixth week of fetal life, the limb bud forms. The first trimester is a critical period as infections, such as rubella, or medications may disturb normal development. As an example, the ingestion of thalidomide during this period results in severe upper limb deficiencies.

Bone often forms on a cartilage template and this is called *enchondral ossification*. Enchondral ossification occurs primarily at the growth plate, which separates the epiphysis and metaphysis. Secondarily, it occurs at the actual articular cartilage, which covers the epiphysis. Long bones grow through enchondral ossification with a growth plate at both ends of the bone. In contrast, flat bones such as the skull or the scapula do not have growth plates and increase in size by appositional growth or intramembranous ossification. The growth plate is weaker than cortical and metaphyseal bone. While adults often sustain fractures through the bone or dislocations of their joints, children often fracture through the weaker growth plate. These injuries are called *physeal injuries,* and significant injury to the growth plate may result in either a growth arrest with a shortened limb or an angular deformity when a portion of the growth plate closes prematurely.

Long bones are composed of three regions, the diaphysis, epiphysis, and metaphysis.The diaphysis develops from the primary ossification center and is also called the shaft of the bone. At each end of the diaphysis, an epiphysis serves as the end of the long bone and the articular cartilage covers the bone to act as one half of the articulation for the joint. The metaphysis serves as the transition between the diaphysis and the epiphysis. In the diaphysis, there is thick cortical bone with relatively little trabecular bone, while in the metaphysis the cortical bone is thin and the trabecular bone becomes very dense.

B. Organ Structure and Function

1. Bone

On a microscopic level, bone is composed of cortical and trabecular bone. Long bones are tubular in design with an outer cortex and a central medullary cavity. The cortical bone is dense and strong. The trabecular bone is composed of thin plates, and the hematopoietic marrow is interspersed between the spicules of trabecular bone. Bone remodeling occurs at a rapid rate in the young child and then achieves a steady state in the adult. Bone resorption and bone formation are two processes coupled such that osteoclastic bone resorption and osteoblastic bone deposition occur at an equal rate. Resorption and formation can become uncoupled in a number of disease states including Paget's disease, osteoporosis, and hyperparathyroidism (Table 6–1).

2. Cartilage

Articular cartilage covers the ends of long bones and provides the gliding surfaces for synovial joints. Articular cartilage is composed of water, chondrocytes, and a matrix, which is composed principally of proteoglycans and collagen. Cartilage has no blood supply and it re-

6-1

COMMON METABOLIC BONE DISEASES

	Diagnosis/Pathology	CA	PO	PTH	AP
Osteoporosis	BMD < 2.5 SD Below age-matched control	Normal	Normal	Normal	Normal
Osteomalacia	Unmineralized osteoid seams on bone biopsy	Low or normal	Low	Elevated[a]	Elevated
Hyperparathyroidism	Solitary parathyroid adenoma in 80%; from gland hyperplasia 10–20%	Elevated	Low	Elevated	Normal or elevated
Paget's disease	Increased bone remodeling and turnover secondary to osteoclastic bone resorption	Normal	Normal	Normal	Elevated

[a]Elevated when calcium level is low.

ceives its nourishment from the synovial fluid. The chondrocytes produce a matrix, which is composed of Type II collagen and the sulfated proteoglycans. The proteglycans have a large number of negative charges, and these aggregates generate a high osmotic pressure. The articular cartilage is able to withstand high loads secondary to the relationship among collagen, proteoglycans, and water.

3. Joints

A joint connects two bones together, and there are several types. Synovial joints allow motion between two bones. The joint is lined by synovial cells, which produce synovial fluid that lubricates the joint. The synovial membrane has two types of cells. Type A synoviocytes are similar to macrophages, and they clear the joint of waste materials. The Type B cells manufacture hyaluronate, which is the main lubricant of the joint. The synovial fluid acts as both a lubricant and a source of nutrition for the articular cartilage. Normal synovial fluid contains < 200 cells/mm^3. The cell count rises dramatically in inflammatory conditions such as infections, gout, and rheumatoid arthritis.

A symphysis is a second type of joint in which two bones are connected by very strong ligments and the joint is joined by fibrocartilage. The adjacent ends of the bone are covered by hyaline cartilage. A symphysis is very stable, with little motion and excellent stability. The pubic symphysis is a rigid joint; however, during childbirth, the ligaments soften and the joint expands.

4. Ligaments

Ligaments connect two bones together, and they serve to stabilize joints. Ligaments are composed predominately of Type I collagen. As an example, anterior cruciate ligament loss often results in severe knee instability, with buckling of the knee and damage to the menisci and the articular cartilage. Compromise of the inferior glenohumeral ligament in shoulder dislocation may result in chronic anterior shoulder instability.

5. Muscle–Tendon Units

Muscle–tendon units allow coordinated skeletal motion. The muscle exerts its action by contracting. There are several types of muscle action:

- ***Isotonic contraction***—The muscle shortens and allows motion.
- ***Isometric contraction***—The muscle resists lengthening without shortening.
- ***Eccentric contraction***—The muscle allows lengthening while maintaining tension.

Muscles are composed of muscle fibers that vary in length and may have many nuclei. Approximately 50% of body weight is skeletal muscle. A single motor unit is composed of the anterior motor horn cell in the spinal cord, its axon, the nerve muscle junction, and the muscle fiber. Muscles have a connective tissue layer through which the nerves and blood vessels travel.

- ***Epimysium***—Surrounds the entire muscle.
- ***Perimysium***—Surrounds bundles of muscle fibers.
- ***Endomysium***—Surrounds each individual muscle fiber.

C. Cell Tissue Structure and Function

There are a number of important cells in the musculoskeletal system.

1. Bone

Osteoblasts cover the bone surface, and they are very active metabolically. They manufacture the bone's matrix (osteoid). Osteoblasts have receptors for parathyroid hormone, and when activated the osteoblasts release a messenger (RANKL), which signals the osteoclast progenitor cells to differentiate into osteoclasts. Osteocytes are osteoblasts that have become embedded in the bone matrix. They are inactive metabolically. They receive electric signals and control the remodeling of bone and mineral homeostasis. Osteoclasts are the bone-resorbing cells. Once activated, they attach to the bone surface and resorb the bone by secreting several enzymes into a zone between the osteoclast and the bone.

2. Cartilage

The chondrocyte is the principal cartilage cell. The chondrocyte maintains the cartilage matrix by secreting Type II collagen and proteoglycans.

3. Fibrous Tissue

Fibroblasts manufacture and secrete Type I collagen, and they are present in ligaments, tendons, joint capsules, and other connective tissue structure.

IV. ABNORMAL PROCESSES

A. Genetic Disorders

There are a number of genetic disorders that occur in the musculoskeletal system. Some of the most common are discussed in this section.

1. Osteogenesis Imperfecta

► Description and Symptoms

A connective tissue disorder with fragile bones characterized by multiple fractures. Patients have bone fragility, short stature, often have blue sclera, middle ear deafness, and defective dentinogenesis.

► Diagnosis

In classic cases the diagnosis is made through radiographs and a genetic history. A dermal puncture biopsy and fibroblast culture can be performed to establish a definitive diagnosis.

► Pathology

There is a defect in Type I collagen synthesis.

► Treatment Steps

Measures to prevent fracture and prevent osteoporosis. Bisphosphonates have also been shown to improve bone density. Most fractures are treated closed. When internal fixation is necessary, intramedullary rods are used.

2. Marfan's Syndrome

► Description and Symptoms

A familial connective tissue disorder characterized by tall stature, aortic root dilatation, scoliosis, kyphosis, lens dislocation, and arachnodactyly.

► Diagnosis

Clinical (Ghent criteria). Genetic testing for the fibrillin gene is also available but is only about 80% sensitive.

► Pathology

Multiple connective tissue problems including aortic dissection, joint hypermobility, lens dislocation, and skeletal deformities.

► Treatment Steps

Composite replacement of the aortic valve and root; spinal fusion when necessary.

3. Muscular Dystrophy

► Description and Symptoms

A group of noninflammatory inherited disorders of muscle with progressive muscle degeneration. Duchenne's muscular dystrophy (X-linked, boys only) is the most common. Children present with delayed walking, waddling, lordotic gait, toe walking, frequent tripping and falling, and inability to hop or jump. Calf pseudohypertrophy is commonly described. Gower's sign (starting on all fours and standing by slowly working hands toward body to prop self up) often present.

► Diagnosis

Serum creatinine phosphatase is markedly elevated.

► Pathology

Single-gene defect for the protein dystrophin. Muscle degeneration occurs, with loss of muscle fibers and proliferation of connective tissue.

► Treatment Steps

There is no specific treatment, and death usually occurs in the second or third decade. Scoliosis is treated with fusion, and bracing of the lower extremities is sometimes necessary.

4. Neurofibromatosis

► Description and Symptoms

The most common single-gene disorder, characterized by multiple neurofibromas and café au lait spots. The condition has an autosomal dominant pattern. One half of patients present as spontaneous mutations.

► Diagnosis

Based on two or more of the following: six café au lait spots, one optic glioma, two or more Lisch nodules on the iris, one bone lesion (vertebral scalloping or tibial pseudoarthrosis), a first-degree relative, axillary or inguinal freckling, cutaneous or plexiform neurofibroma.

► Pathology

This is a disorder of the neural crest cells.

► Treatment Steps

Fusion is sometimes necessary, and patients should be monitored for the development of neurofibrosarcomas (occurs in about 5–20% of patients).

B. Congenital Disorders

1. Brachial Plexus Birth Injury

► Description and Symptoms

Brachial plexus injury occurs in about 1 in 1,000 births and is usually caused by downward traction (Erb's palsy) on the arm. Upward traction injuries are much less common (Klumpke's palsy). Risk factors are fetal malposition, shoulder dystocia, cephalopelvic distortion, high birth weight, and the use of forceps.

► Diagnosis

Inability to move the arm and shoulder after birth. Arm typically adducted at the shoulder and in extension in Erb's palsy with wrist functional or in flexion.

► Pathology

Varies from stretch to disruption of the brachial plexus. Erb's, C5–6; Klumpke's, C8–T1.

► Treatment Steps

While 80% of patients recover spontaneously, some require repair of the injured nerves, tendon transfers, and occasionally humeral osteotomy.

2. Developmental Hip Dysplasia

► Description and Symptoms

A condition in which the femoral head is not normally placed in the acetabulum, and there is deficient formation of the acetabulum. Four times as common in females, and full dislocations occur in about 1 in 1,000 births. May go undetected and result in significant hip disease.

► Diagnosis

Physical exam is the mainstay of screening. In the first few months of life, the examiner can subluxate the hip or reduce the dislocated hip. In older children, there is simply loss of abduction range. Plain radiographs are preferred for imaging only after 5–6 months of age. Ultrasound is more sensitive in the younger child.

► Pathology

Shallow or flattened acetabulum and increased femoral head anteversion.

► Treatment Steps

Young children < 3 months of age can be treated with bracing (Pavlik harness), while older children often require closed or open reduction or rotational osteotomies.

3. Torticollis

► Description and Symptoms

Also called *wryneck*. The head is held in a tilted position. The condition may occur after a difficult delivery or an upper respiratory infection.

► Diagnosis

The head appears laterally flexed (with the ear closer to one shoulder) and rotated (with the chin closer to the other shoulder).

► Pathology

Contracture or spasm of the sternocleidomastoid muscle. Torticollis may also be caused by upper cervical bony abnormalities.

► Treatment Steps

Over 90% of patients are successfully treated with stretching exercises. Release of the sternocleidomastoid muscle or fusion of the upper spine is necessary to correct a bony abnormality.

4. Cerebral Palsy

► Description and Symptoms

A nonchanging central neurologic injury, which becomes apparent in the first 3 years of life, characterized by hypotonia followed by spasticity. There are many different causes, including maternal infections, fetal hypoxia and brain injury, encephalitis, and metabolic disorders. One should remember that children with diplegic cerebral palsy often have normal intelligence.

► Diagnosis

The diagnosis is made by the characteristic postural and movement disorders.

► Pathology

No specific test or biopsies are performed. The injury is to the neural tissue of the central nervous system (CNS).

► Treatment Steps

Surgical treatment is aimed at correcting deformities with techniques such as spinal fusions and release of ankle and knee deformities. Injections and dorsal rhizotomy to control spasticity are also used.

C. Infections

1. Septic Arthritis

► Description and Symptoms

Occurs in children and adults. Joint infections may occur in children with no predisposing symptoms; however, adult patients are usually immunocompromised or have preexisting joint pathology. IV drug use increases risk. Severe pain with any joint movement is the hallmark. Patients will refuse to bear weight or perform any activities with the involved joint. Fever may be present.

► Diagnosis

Definitive diagnosis is made with joint aspiration. Analysis of synovial fluid will show > 50,000 white blood cells/mm^3, and there will be a high proportion (90%) of polymorpholeukocytes. Normal synovial fluid looks pale yellow and clear, while infected fluid looks cloudy and turbid. Immunocompromised patients (HIV, chemotherapy patients, etc.) may have low cell counts. Approximately 80% of patients who have not been on previous antibiotics will have a positive culture.

► Pathology
The synovial tissue is inflamed, with an infiltration of inflammatory cells (polymorpholeukocytes, lymphocytes, plasma cells, macrophages). Adults and children are most commonly infected with *Staphylococcus aureus.* Sexually active adolescents are at risk to present with *Neisseria gonorrhoeae.* IV drug users are more likely to have infection by *Escherichia coli, Pseudomonas,* or *Klebsiella.* Patients with sickle cell disease are more likely to have *Salmonella* infection than other individuals.

► Treatment Steps
Selected patients can be treated with IV antibiotics and serial joint aspiration. The majority of patients undergo arthrotomy and irrigation of the joint. Antibiotics are given for 3–6 weeks.

2. Osteomyelitis

► Description and Symptoms
Infection within the medullary cavity. The infection may be developed hematogenously, following surgical procedures or open fractures, or by direct extension in patients with diabetic ulcers or decubiti. Patients present with pain, tenderness over the bone, and, in some long-standing cases, a draining sinus. Fever may or may not be present.

► Diagnosis
Radiographs will show bone destruction in acute cases, and chronic cases have both bone destruction and bone formation. The diagnosis is definitively made by culture of the bone.

► Pathology
The normal marrow is replaced by an infiltration of inflammatory cells, edema, and varying amounts of fibrosis. Most common pathogens are the same as those discussed in septic arthritis.

► Treatment Steps
Debridement of necrotic bone and the inflammatory process followed by at least 6 weeks of antibiotics.

3. Lyme Disease

► Description and Symptoms
Carried to humans through deer ticks (*Ixodes dammini*). Both children and adults may contract the disease, and patients present with a targetoid rash or rash with central clearing, arthritis, synovitis, and even carditis. There are three geographic areas where the disease clusters: upper mid-Atlantic, upper Midwest, and some Western states.

► Diagnosis
Serum tests are performed. Enzyme-linked immunosorbent assay (ELISA) is sensitive, and titers of 1:80 are considered positive. The positive ELISA test is confirmed with Western blot analysis. CNS fluid can be tested in patients with neurologic symptoms.

► Pathology

The disease is a reaction to the spirochete *Borrelia burgdorferi*.

► Treatment Steps

Tetracycline is the drug of choice for individuals > 8 years of age. Chronic arthritis, atrioventricular conduction blocks, and encephalitis may occur in untreated cases. Amoxicillin may be used in children under age 8.

D. Inflammatory Conditions

1. Rheumatoid Arthritis

► Description and Symptoms

Autoimmune disorder of synovial joints characterized by arthritis and deformity. Patients present with morning stiffness and swelling. Joint symptoms occur, with swelling and pain. The disease is symmetric and involves both large and small joints. The hypertrophic synovium (or pannus) destroys ligaments and capsular structures, leading to ulnar deviation of the digits and instability of the first and second vertebrae in many patients.

► Diagnosis

Serum rheumatoid factor is positive in many patients, and all have an increased serum erythrocyte sedimentation rate (ESR).

► Pathology

Severe infiltration of the synovium with pannus formation. The articular cartilage is destroyed in a symmetric fashion, and there is periarticular bone resorption. Cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) play an important role in joint destruction.

► Treatment Steps

Anti-inflammatory medications (combinations of nonsteroidals, steroids, gold, methotrexate) and physical therapy are the mainstays of treatment. More recently, TNF antagonists such as etanercept (a soluble TNF receptor) and infliximab (anti-TNF antibody) have been used for treatment and will hopefully markedly decrease the need for surgical intervention. Joint reconstruction of the knee, hip, shoulder, elbow, and small joints of the hand is very effective. Fusion of the first and second vertebrae of the spine is sometimes necessary if atlantoaxial instability exists.

E. Traumatic Disorders

1. Fractures

► Description and Symptoms

Occur in normal bone from excessive loading (such as a motor vehicle accident, falls from heights, etc.) or in abnormal bone secondary to very minor loading (as in metastatic bone disease, multiple myeloma, or severe osteoporosis). In most fractures, patients have severe pain and restrict use of the limb. (See Table 6–2).

► Diagnosis

Point tenderness will be present over the bone; the diagnosis is made with plain radiographs. Magnetic resonance imaging (MRI) is an excellent modality to detect occult fractures.

6-2

FRACTURES WITH IMPORTANT ASSOCIATED INJURIES OR COMPLICATIONS

	Associated Injury/Complication
Tibial shaft	Compartment syndrome—may develop in first 48 hours
Pelvic	Life-threatening hemorrhagic—occurs within first 6 hours
Scapula	Ipsilateral pneumothorax
Elbow supracondylar (pediatric)	Forearm compartment syndrome
Cervical spine in patient with ankylosing spondylitis	Epidural hematoma

► Pathology

A crack or fracture line through the cortical bone.

► Treatment Steps

Stable fractures in acceptable alignment are treated nonoperatively with a cast, while unstable or displaced fractures are treated operatively (internal or external fixation).

2. Stress Fractures

► Description and Symptoms

May occur through normal or abnormal bone. Athletes and military recruits often develop a stress fracture following intense and repetitive activity such as running or marching. Patients with osteoporosis are also prone to stress fractures, especially after a minor fall. Pain with activity is the hallmark. In accessible areas, there will also be pain over the affected bone.

► Diagnosis

Plain radiographs show periosteal new bone in many patients. Technetium bone scans are very sensitive and will show increased uptake. MRI scans are very useful to detect occult fractures.

► Pathology

There are microfractures in the cortical bone.

► Treatment Steps

Protected weight bearing for 4–6 weeks is effective for most stress fractures.

3. Growth Plate Injury

► Description and Symptoms

Children often sustain a fracture through the growth plate rather than a dislocation or intra-articular fracture, which occurs in the adult. Growth plate injuries are graded from I to V. A grade I injury occurs through and parallel to the physis alone, while a grade II injury occurs through the physis with the fracture line exiting through bone before the physis ends. A grade III or IV injury is more severe as the joint is involved, and a grade V injury crushes the growth plate. A growth arrest with either shortening of the limb or an angular deformity may occur after grade III–V injuries.

► Diagnosis

Plain radiographs in two orthogonal planes will allow detection and grading of the injury.

► Pathology

The fracture line occurs through the cartilage hypertrophic zone.

► Treatment Steps

Grade I and II injuries are treated with closed reduction and casting, while grades III and IV usually require open reduction and internal fixation.

4. Dislocations

► Description and Symptoms

Occur when the articulating joint surfaces completely separate. There is no contact. Dislocations are almost always traumatic in nature from falls, motor vehicle accidents, and contact sports. Dislocations most commonly occur in the shoulder, elbow, proximal interphalangeal joint of the finger, hip, and knee (Table 6–3).

► Diagnosis

Visual inspection will show severe deformity, and radiographs demonstrate separation of the joint surfaces.

► Pathology

Tearing or avulsion of the ligaments and joint capsules.

► Treatment Steps

Reduction with conscious sedation or general anesthesia.

6-3

COMMON DISLOCATIONS

Joint	Type	Mechanism	Associated Injury	Treatment	Prognosis
Shoulder	Anterior	Usually traumatic injury with the arm abducted and externally rotated	1. Axillary nerve 2. Inferior glenohumeral ligament	Reduction, 3–4 weeks of immobilization, strengthening exercises	High incidence of recurrent dislocation (10–50%)
	Posterior	Often secondary to a seizure	1. Lesser tuberosity of humerus 2. Posterior glenoid rim		Low risk of recurrent dislocation
Elbow	Posterior	Fall on an outstretched arm	Periarticular fractures	Reduction, 1 week of immobilization, range of motion exercises	Very low risk of recurrent dislocation, small loss of elbow extension
Proximal interphalangeal joint	Dorsal	Direct blow to finger, hypertension to the finger	Avulsion of volar plate	Immobilization for 2–4 weeks, range of motion exercises	Low risk of recurrent dislocation; chronic swelling and reduced range of motion (mild)
Hip	Posterior	Force to the knee with the hip flexed (dashboard injury)	1. Fracture of the posterior rim of the acetabular 2. Sciatic nerve palsy 3. Femoral head osteonecrosis	Reduction, removal of any loose fragments in the joint	Good if there is no cartilage damage to femoral head
Knee	Posterior	Severe or minor trauma to the knee; motor vehicle accidents, auto–pedestrian, sports injuries	Popliteal artery injury in 10–20%	1. Multiple knee ligament reconstruction 2. Vessel repair when necessary	Good with ligament reconstruction

5. Compartment Syndrome

► Description and Symptoms

Swelling of a closed compartment results in increased pressure with compromise of the microvascular circulation of nerve and muscle cells. Permanent nerve damage may occur, and muscle necrosis is often irreversible. Compartment syndrome may occur following closed and open tibial fractures, penetrating injuries, prolonged recumbency from drug or alcohol overdoses, and revascularization procedures. Patients present with pain out of proportion to injury, pain on passive range of motion, and tense compartments.

► Diagnosis

The diagnosis can be made from the clinical findings alone; however, most surgeons measure the compartment pressures. Pressures > 40–50 mm Hg or pressures within 30–40 mm Hg of the diastolic pressure are suggestive of the diagnosis.

► Pathology

Increased pressure in a closed space.

► Treatment

Fasciotomy should release the compartment, with secondary closure at a later date.

6. Cauda Equina Syndrome

► Description and Symptoms

Occurs when there is compression of the nerve roots of the cauda equina, resulting in a combination of bowel and bladder dysfunction and lower-extremity weakness. The syndrome can be caused by a tumor, prolapsed intervertebral disk, or a hematoma. Back pain, urinary retention with overflow incontinence, and decreased rectal tone are found. In addition, patients have a loss of perianal sensation or "saddle anesthesia" (S2–4 dermatomes).

► Diagnosis

The diagnosis is made based on the clinical findings and cross-sectional imaging such as computed tomography (CT) or MRI.

► Pathology

Compression of the nerve roots in the spinal canal.

► Treatment Steps

Surgical decompression, often as soon as possible.

7. Sprain/Strain

► Description and Symptoms

Strains and sprains are common ligament injuries. Ankle sprains (anterior talofibular ligament) are the most common of all the ligament injuries. A grade 1 sprain occurs when the ligament is stretched without an increase in laxity of the joint. A grade 2 sprain is a stretching of the ligament with some tearing of the fibers but only mild laxity of the joint. A grade 3 injury implies complete tearing of the ligament and laxity of the joint. With ankle sprains, if the patient can bear weight, most are graded as a first- or second-degree sprain and can be treated with early range of motion. Grade 3 injuries require casting or bracing and a period of non–weight bearing.

► Diagnosis

Physical examination shows tenderness over the ligament +/– joint laxity.

► Pathology

Hemorrhage and tearing of ligament fibers.

► Treatment Steps

Virtually all strains are treated nonoperatively. Bracing or casts are used in selected grade 2 and 3 injuries.

8. Tendon Rupture

► Description and Symptoms

Tendons may rupture from acute overloading or from attritional or degenerative processes. Tendon ruptures are usually not detected by plain radiographs, so one must have a high degree of suspicion in the trauma patient.

- ***Achilles tendon rupture***—Often occurs in middle-aged athletes during tennis or racquetball. The Thompson test (squeezing the gastrocnemius muscle with the patient prone and observing for plantar flexion) will be positive (no plantar flexion).
- ***Jersey finger***—Occurs in football players when they tear their finger flexor tendons while trying to grab the football jersey while making a tackle.
- ***Posterior tibial tendon rupture***—Occurs commonly in the older patient from chronic attrition and results in an acquired flatfoot deformity.
- ***Patellar tendon rupture***—May occur spontaneously or with very little trauma in patients taking oral steroids or patients with rheumatoid diseases. Patients are unable to extend the knee from the flexed position.

► Diagnosis

Testing of the musculotendinous unit shows a complete lack of function. In patellar tendon ruptures, one will see a high-riding patella (patella alta).

► Pathology

Complete disruption of the tendon fibers.

► Treatment Steps

Open tendon repair with a period of immobilization to allow tendon healing.

9. Slipped Capital Femoral Epiphysis

► Description and Symptoms

Occurs in adolescents (boys 10–16 years, girls 10–14 years) and is characterized by displacement of the femoral head relative to the physis. Children present with pain and a limp. The pain is often referred to the thigh or the knee.

► Diagnosis

Plain radiographs show posterior and inferior displacement of the femoral head relative to the physis.

► Pathology

Radiographs may show an abnormally wide growth plate, and the slip occurs through the hypertrophic cartilage zone.

► Treatment Steps

In situ pinning of the slip with a single screw is the best method of treatment. Screw fixation causes closure of the growth plate and stabilization of the slip.

F. Neoplastic Disorders

1. Metastatic Bone Disease

► Description and Symptoms

Bone is the third most common site of metastases and the most common cause of a destructive lesion in the adult skeleton (patients > 40 years of age) (Table 6–4). The most common carcinomas to metastasize to bone are breast, prostate, lung, and kidney. Patients present with pain, inability to walk, and fractures. Lung and kidney carcinomas often present with a bone metastasis (sentinel metastasis).

► Diagnosis

Radiographs will show a bone lesion. Most metastases are lytic and very destructive. Breast and prostate metastases may be sclerotic and show increased bone deposition.

► Pathology

Clusters of epithelial cells in a fibrous stroma are seen inside the medullary cavity.

► Treatment Steps

External beam irradiation is used for painful lesions, and surgery for fractures and bone lesions that meet the criteria of impending fracture.

2. Multiple Myeloma

► Description and Symptoms

A form of plasma cell dyscrasia in which the bone marrow becomes dominated by plasma cells and the skeleton has numerous

6-4

BONE TUMORS COMMON IN ADULTS

Tumor	Age Group	Sites	Presentation	Pathology	Treatment
Metastatic bone disease	45–80+	Vertebrae, pelvis, proximal femur, femoral shaft, humerus	Pain at rest and at night Activity-related pain	Epithelioid cells in a fibrous background	External beam irradiation for painful lesions, internal fixation for fracture and impending fracture
Multiple myeloma	50–80+	Skull, vertebrae, pelvis, long bones	Pain following fracture	Plasma cells	Chemotherapy, external beam irradiation for painful and/or progressive lesions, internal fixation for fractures
Lymphoma	40–80+	Pelvis, long bones	Pain of variable intensity and duration	Small and large blue lymphoid cells	External beam irradiation
Chondrosarcoma	40–80	Long bones, pelvis	Pain that may be mild in nature	Chondrocytes with atypical nuclei	Resection and reconstruction
Malignant fibrous histiocytoma	40–80	Long bones, pelvis	Pain at rest and at night	Storiform pattern of pleomorphic fibroblasts and histiocytes	Chemotherapy and resection/reconstruction
Chordoma	40–80	Sphenoid, sacrum	Diffuse pelvic pain	Physaliferous cells in a lobulus growth pattern	Resection and radiation

"punched-out," purely lytic lesions. Patients present with bone pain, fractures, and anemia.

► Diagnosis

Serum protein electrophoresis will show a monoclonal gammopathy in > 95% of patients. The serum hemoglobin will be low and the ESR elevated in over two thirds of patients. Urine protein electrophoresis may also show a monoclonal gammopathy.

► Pathology

The bone marrow has a plasmacytosis that is > 30%. The plasma cells are monoclonal.

► Treatment Steps

Systemic chemotherapy is the mainstay of treatment. Radiation is used for progressive and painful lesions, while surgery is reserved for fractures.

3. Osteosarcoma

► Description and Symptoms

The most common primary bone sarcoma. While the disease may occur in all decades of life, it is most common in the second and third decades (Table 6–5). Children present with pain and swelling. Fractures occur in about 5% of patients.

► Diagnosis

Plain radiographs usually suggest the diagnosis of destructive metaphyseal lesions with areas of bone formation.

6-5

BONE TUMORS COMMON IN CHILDREN AND YOUNG ADULTS

Tumor	Age Group	Sites	Presentation	Pathology	Treatment
Osteosarcoma	10–25	Distal femur, proximal tibia, proximal humerus, proximal femur	Severe pain at rest and with activity, night pain	Pleomorphic spindle cells producing osteoid	Preoperative chemotherapy followed by resection and reconstruction (5-year survival 60–70%)
Ewing's tumor	10–25	Femur, pelvis, virtually any bone	Severe pain and a mass; may have fevers	Small blue cells with no matrix production	Chemotherapy/radiation; surgical resection in selected patients
Osteochondroma	10–25	Distal femur, proximal tibia, pelvis, humerus	Bony mass, mechanical symptoms	Thin cartilage cap	Simple removal in selected patients
Nonossifying fibroma	5–20	Distal femur, proximal tibia, distal tibia	Usually incidental finding; may fracture with minor trauma	Storiform pattern of fibroblasts, histiocytes, giant cells	Observation in most patients, curettage and bone grafting in selected patients
Osteoid osteoma	5–35	Femur, tibia, pelvis	Severe, dull pain, completely relieved by aspirin	5–10-mm haphazard nidus of osteoid and osteoblasts	Nonsteroidal agents for up to 2 years or radiofrequency ablation
Eosinophilic granuloma	5–40	Femur, scapula, pelvis, skull	Dull pain	Langerhans' histiocytes and eosinophils	Variable—corticosteroid injection, curettage, low-dose radiation
Giant cell tumor	20–45	Distal femur, proximal tibia, distal radius, pelvis	Pain with activity, articular symptoms	Mononuclear cells and a uniform distribution of multinucleated giant cells	Curettage and cement augmentation

► Pathology

Needle or open biopsy is performed showing a spindle cell sarcoma in which the cells produce osteoid.

► Treatment Steps

Preoperative chemotherapy is followed by surgical resection. Modern treatment yields cure in two thirds of children.

4. Ewing's Tumor

► Description and Symptoms

A small blue-cell tumor that occurs in children. Patients present with pain, swelling, and occasionally fevers. Pathologic fracture occurs in about 5%.

► Diagnosis

Plain radiographs show a lytic destructive lesion that can be confused with osteomyelitis.

► Pathology

Biopsy shows a monotonous infiltration of small blue cells. Cytogenetic analysis shows a chromosomal translocation between the chromosomes 11 and 22.

► Treatment Steps

Combinations of chemotherapy and radiation therapy are used. Resection of the involved bone is performed in selected patients. Modern treatment yields cures in two out of three patients.

5. Osteochondroma

► Description and Symptoms

Exostosis that arises on the surface of a bone. It has a thin cap of hyaline cartilage and grows by the process of enchondral ossification in a similar manner to the growth plate. Osteochondromas are common in children, and they may increase in size as the child grows. Pain may occur from mechanical trauma or muscle irritation.

► Diagnosis

Plain radiographs show the characteristic lesion on the surface of the bone with either a narrow stalk (pedunculated osteochondroma) or a shallow broad attachment (sessile osteochondroma). There is often altered growth of the involved bone(s).

► Pathology

The cap of cartilage shows a linear arrangement of the chondrocytes that resembles the physis.

► Treatment Steps

Symptomatic lesions are simply excised, while asymptomatic lesions are treated with observation.

6. Soft Tissue Tumors

a. Lipoma

► Description and Symptoms

Subcutaneous lipomas are the most common soft tissue tumor and occur in older patients. They may be located on the arms, chest wall, back, or legs. Their growth is slow, and they are usually asymptomatic.

► Diagnosis

By history and physical examination in most patients, MRI for selected patients. MRI will show a mass that exactly matches the subcutaneous fat on all sequences.

► Pathology

Mature fat cells with a lobular growth pattern.

► Treatment Steps

Observation (rapidly growing lesions may signify liposarcoma) or simple excision.

b. Liposarcoma

► Description and Symptoms

The second most common soft tissue sarcoma in adults. Most patients are > 40 years of age. The tumors are located below the fascia, and the thigh is the most common location. In contrast to most other sarcomas, liposarcomas have malignant behavior ranging from low- to medium- to high-grade sarcomas.

► Diagnosis

Needle or open biopsy is necessary. MRI usually shows a deep-seated mass that has low signal on T1-weighted images and high signal on T2-weighted images.

► Pathology

Low-grade tumors show well-differentiated fat with lipoblasts, while the higher-grade sarcomas are very anaplastic with marked pleomorphism.

► Treatment

Multimodality treatment is performed with radiation, chemotherapy, and surgical resection. High-grade, large tumors have a poor prognosis (40–60% mortality).

c. Malignant Fibrous Histiocytoma

► Description and Symptoms

The most common soft tissue sarcoma in adults. The most common location is the thigh. Patients present with a rapidly growing mass that may or may not be painful.

► Diagnosis

Needle or open biopsy is necessary. MRI usually shows a deep-seated mass that has low signal on T1-weighted images and high signal on T2-weighted images.

► Pathology

A “storiform pattern” with marked pleomorphism and nuclear atypia is present.

► Treatment

Multimodality treatment is performed with radiation, chemotherapy and surgical resection.

d. Rhabdomyosarcoma

► Description and Symptoms

The most common childhood sarcoma. About 15% of rhabdomyosarcomas occur on the upper and lower extremities. Children present with either a small nodule or a rapidly growing mass.

► Diagnosis

Small tumors are often excised without prior imaging, while large tumors show the typical features of a sarcoma on MRI: low signal on T1-weighted images and high signal on T2-weighted images.

► Pathology

Rhabdomyosarcoma is a small blue cell tumor. There may or not be rhabdomyoblasts present. The alveolar subtype is more common in the extremities. Immunostains are important in the diagnosis (desmin, muscle specific actin, MyoD1, and MIC2). Many tumors have a characteristic translocation between chromosomes 2 and 13.

► Treatment Steps

Children are treated with multiagent chemotherapy and radiation. Surgical resection is used in a large percentage of patients.

G. Metabolic and Regulatory Disorders

1. Osteoporosis

► Description and Symptoms

The most common metabolic bone disease, characterized by low bone mass and microarchitectural deterioration of bone tissue, which leads to bone fragility and an increased fracture risk. Bone remodeling is uncoupled with increased resorption (especially in women during the first 6 postmenopausal years). Fractures of the hip (femoral neck and intertrochanteric region), vertebrae, and wrist are the most common.

► Diagnosis

Osteoporosis is usually identified by bone density measurement (dual-energy x-ray absorptiometry [DEXA] scan). The diagnosis is definitively made when the bone density is 2.5 standard deviations (SD) below the value for a young adult. Values between 1.0 and 2.5 SD suggest osteopenia.

► Pathology

There is a normal ratio between the mineral content and collagen. The bone is normal (there is just too little).

► Treatment Steps

Osteoporosis is treated with a combination of vitamin D, calcium, exercise, and bisphosphonates. The bisphosphonates prevent the osteoclasts from removing the bone.

2. Osteomalacia or Rickets

► Description and Symptoms

A disorder characterized by poorly mineralized bone. The bone is thus softer and less able to support normal physiologic loading. Patients have diffuse bone pain and fractures, and may have bowing of their legs. Children may have prominence of their costochondral junctions (rachitic rosary). Other characteristic findings include frontal bossing, Harrison's groove, and flaring of the metaphyses on radiograph. Osteomalacia may have many etiologies and can be broadly classified as vitamin D deficiency, calcium deficiency, and phosphate deficiency. *Rickets* is the term given to osteomalacia in the growing skeleton.

► Diagnosis

Serum studies show low or normal serum calcium, low levels of phosphorus, and a markedly elevated alkaline phosphatase level.

► Pathology

Wide unmineralized osteoid seams are present when an iliac crest biopsy is performed. With vitamin D deficiency, intestinal calcium and phosphate absorption is reduced, causing hypocalcemia. The parathyroid glands respond to the hypocalcemia by increasing production of serum parathyroid hormone (PTH). PTH then increases osteoclast resorption of bone.

► Treatment Steps

Treatment is tailored to the specific cause of the osteomalacia. Vitamin D–deficiency rickets is treated with vitamin D_2 supplementation (1,500–5,000 IU/day PO). Calcium deficiency is treated by oral calcium supplementation.

H. Vascular Disorders

1. Legg–Calvé–Perthes Disease

► Description and Symptoms

A hip disorder in which there is avascular necrosis of the immature femoral head. There is flattening of the femoral head and extrusion of the head laterally. Males are much more commonly affected (4–5:1), and children are usually 4–8 years old. Children present with pain, limp, and decreased range of motion.

► Diagnosis

Plain radiographs show fragmentation and irregularity of the femoral head.

► Pathology

Following the osteonecrosis, a reparative process results in weakening of the bone, which leads to fragmentation and collapse. Finally, remodeling replaces the avascular bone and restores a degree of normal spherical shape.

► Treatment Steps

Restoration of joint motion through protected weight bearing or braces is important. The femoral head must be contained within the acetabulum. Corrective osteotomy of the proximal femur or acetabulum is sometimes necessary. The best prognostic factor is young age (≤ 6 years).

I. Degenerative Disorders

1. Degenerative Disk Disease

► Description and Symptoms

Degenerative disk disease is common and occurs with aging. The cervical and lumbar spine are commonly involved. Pain and limitation of movement are the hallmark symptoms. The prevalence of this condition is extremely common, and 80–90% of the population will experience an episode of significant pain.

► Diagnosis

Plain radiographs show loss of intervertebral disk height and osteophytes.

► Pathology

Degeneration of the gelatinous material of the intervertebral disk is the first event, followed by thinning of the peripheral annulus fibrosus. The posterior facet joints also become arthritic, with narrowing and osteophyte formation.

► Treatment Steps

Physical therapy, weight reduction, and nonsteroidal anti-inflammatory drugs (NSAIDs) ameliorate the condition in most patients. Fusion is used in selected patients.

2. Herniated Intervertebral Disk

► Description and Symptoms

Herniation of disk material with subsequent compression of a nerve root results in severe and agonizing low back pain. After a short time, the low back pain is replaced by radicular pain, which follows the distribution of the involved nerve. Patients may have motor weakness, numbness, and a diminished or absent reflex. The straight leg–raising test will be positive.

► Diagnosis

The presentation suggests the diagnosis, and the disk herniation can be localized with MRI.

► Pathology

The disk material herniates posteriorly through the annulus fibrosus and impinges on the nearby nerve root.

► Treatment Steps

Most patients can be treated nonoperatively with rest, NSAIDs, and physical therapy. Decompression with removal of the offending disk is reserved for patients with unrelenting pain and progressing neurologic deficits.

3. Osteoarthritis (Degenerative Joint Disease)

► Description and Symptoms

The most common form of arthritis. May involve many different joints, including the hip, knee, shoulder, intervertebral joint and facet, and finger joints. Pain, stiffness, and decreased function are the hallmark symptoms.

► Diagnosis

Plain radiographs show loss of the articular cartilage, subchondral sclerosis and cysts, and osteophytes.

► Pathology

The condition begins with loss of the articular cartilage, with hypertrophy and remodeling of the subchondral bone and secondary inflammation of the synovial membrane.

► Treatment Steps
Initial treatment is NSAIDs, weight reduction, activity modification, and the use of a cane to reduce loads across the hip and knee. Intra-articular corticosteroid injections may provide temporary or long-lasting relief. Joint replacement surgery is effective in the hip, knee, shoulder, and elbow.

4. Rotator Cuff Tendinitis Tear

► Description and Symptoms
Degeneration of the rotator cuff tendons is common in middle-aged patients. The rotator cuff becomes thinned and can completely tear. Patients present with discomfort with overhead activities and pain at night. Shoulder motion is limited and painful. The limitation of shoulder motion can progress to severe adhesive capsulitis or a frozen shoulder. The rotator cuff can completely tear with minor trauma or the activities of daily living.

► Diagnosis
Plain radiographs are usually normal, and an MRI may show normal tendons, tendinosis (increased signal), partial-thickness tear, or complete tear.

► Pathology
Tendon degeneration is the primary process.

► Treatment Steps
Physical therapy, NSAIDs, and subacromial cortisone injections are effective in > 90% of patients. Decompression of the subacromial space is occasionally necessary. Rotator cuff tears are treated with decompression and suture repair of the tendons.

J. Systemic Disorders Affecting the Musculoskeletal System

1. Hemophilia

► Description and Symptoms
Hemophilia is a clotting disorder characterized by severe bleeding. Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are both inherited as sex-linked recessive disorders. Males are affected almost exclusively. Severe hemophilia occurs when there is < 1% clotting factor, moderate hemophilia when there is 1–5% clotting activity, and mild when there is > 5% clotting activity. With severe hemophilia, patients may bleed with the mildest trauma, while major trauma or surgery is necessary for significant bleeding with the milder forms. Patients may bleed into joints such as the knee, elbow, ankle, and shoulder. Following a hemarthrosis, the joint is more susceptible to repeat episodes of bleeding (target joint). Patients may also experience muscle bleeds. Femoral nerve palsy can occur following psoas muscle bleeding.

► Diagnosis
Factor levels are measured to both detect the condition and grade the severity.

► Pathology

There is a genetic defect for the gene for factor VIII (hemophilia A) and factor IX (hemophilia B). Affected joints show hypertrophic synovium, and there is erosion of the articular cartilage.

► Treatment Steps

Hemarthroses are treated with factor replacement and rest. Synovectomy may prevent bleeds into target joints. Arthroplasty is necessary for joints that are destroyed.

2. Sickle Cell Disease

► Description and Symptoms

A red blood cell disorder in which sickling of the erythrocytes causes microvascular occlusion. Patients have painful "crises," osteonecrosis, and osteomyelitis. Marrow and trabecular infarction occurs. Skeletal manifestations include sickle cell dactylitis, "bone within bone" appearance of cortical infarction, and femoral head osteonecrosis. Osteomyelitis may occur secondary to organisms such as *Staphylococcus aureus* and *Salmonella*.

► Diagnosis

Serum studies show a high level of hemoglobin S.

► Pathology

A genetic defect leads to a substitution of valine for glutamic acid in the β globulin chain (hemoglobin S).

► Treatment Steps

Osteonecrosis and joint collapse can be treated with arthroplasty in selected patients. Osteomyelitis requires identification of the causative organism, debridement, and antibiotics. Prophylactic transfusions are necessary before elective surgery.

K. Idiopathic Disorders

1. Scoliosis

► Description and Symptoms

Curvature of the spine > 10 degrees. Curve progression may occur in adolescents during the growth spurt. Progressive curves may require bracing or fusion. Females are more likely to progress than males.

► Diagnosis

Curvature of the spine can be suspected on physical examination (forward bending) and confirmed with radiographs.

► Pathology

There is no known cause for idiopathic scoliosis.

► Treatment Steps

Observation is performed until curves progress beyond 25 degrees. Bracing is used to prevent progression of curves > 25 degrees in growing patients. Surgical correction and fusion is necessary in some patients with curves > 45 degrees.

2. Paget's Disease

► Description and Symptoms

A condition in which bone remodeling becomes uncoupled, causing excessive remodeling of bone. The condition occurs more commonly in northern Europe and in patients of Anglo-Saxon descent. Osteoclasts resorb the normal bone, and the bone is remodeled into a mosaic architecture that is weaker than normal bone. Patients may develop arthritis, bowing deformities, and fractures.

► Diagnosis

Plain radiographs show cortical thickening and coarsened trabeculae. The serum alkaline phosphatase level (a marker of osteoblastic deposition of osteoid) is elevated in 95% of patients, and technetium bone scan shows increased uptake in the involved bones.

► Pathology

The osteoclasts show increased activity. A "mosaic pattern" of bone is present. Electron microscopy shows intranuclear inclusion bodies. Slow virus infection with a paramyxovirus may be responsible for the condition.

► Treatment Steps

Symptomatic patients are treated with bisphosphonates. Arthroplasty is often necessary in patients with severe arthrosis.

BIBLIOGRAPHY

Favus MJ. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism,* 4th ed. Philadelphia: Lippincott Williams & Wilkins, 1999.

Klippel JH. *Primer on the Rheumatic Diseases,* 11th ed. Atlanta: Arthritis Foundation, 1997.

Kumar V, Abbas AK, Fausto N. *Pathologic Basis of Disease,* 7th ed. Philadelphia: Elsevier Saunders, 2005.

Salter RB. *Textbook of Disorders and Injuries of the Musculoskeletal System,* 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999.

The Central and Peripheral Nervous Systems

7

I. NORMAL PROCESSES

A. Development of the Nervous System (NS)

The brain stem and spinal cord are divided into:

1. *Alar plate:* Sensory neurons.
2. *Basal plate:* Motor neurons.
3. *Primary vesicles* (forebrain, midbrain, hindbrain) split into secondary vesicles (telencephalon, diencephalon, mesencephalon, metencephalon, myelencephalon).

α-Fetoprotein is an indicator of neural tube defects (spina bifida, anencephaly) and may be detected in maternal blood or amniotic fluid.

B. Neurocytology

NS contains:

- *Neurons* (derived from neuroectoderm).
- *Glial cells* (derived from mesoderm):
  - *Astrocytes:* Support cells.
  - *Oligodendrocytes:* Form myelin in central nervous system (CNS).
  - *Schwann cells*: Form myelin in peripheral nervous system (PNS).
  - *Microglia:* Scavenger cells of CNS.
  - *Ependymal cells:* Form lining of ventricles and spinal central canal.

1. Types of Neurons

- Betz cells: Upper motor neurons.
- Motor neurons of spinal cord (ventral horn cells): Lower motor neurons.
- Purkinje cells: Cells of cerebellum.

2. Oligodendroglia

- Form myelin sheath (composed of lipid and protein) in CNS.
- Target organ of damage in immune-mediated attack in multiple sclerosis.

3. Schwann Cells

Similar to astrocytes and oligodendrocytes. Located in the PNS and produce myelin.

C. Cerebral Circulation

Brain is 2% of body weight in adults but receives 20% of cardiac output and utilizes 20% of oxygen content.

1. Anterior Circulation

- Internal carotid artery (ICA).
- Ophthalmic artery.
- Anterior cerebral artery (ACA).
- Middle cerebral artery (MCA).

2. Posterior Circulation

- Vertebral arteries.
- Basilar artery.
- Posterior cerebral arteries.

To image the cerebral circulation, the most definitive study is *conventional catheter contrast angiography.*

D. Blood–Brain Barrier (BBB)

Capillaries are lined by endothelial cells and contain a continuous array of astrocytic extensions. Endothelial cells contain tight junctions. With most pathological conditions, there is breakdown of BBB.

► **cram facts**

Blood–brain barrier is characterized by tight endothelial capillary junctions to keep toxic substances out of CNS.

► cram facts

To diagnose meningitis and SAH, the most sensitive test is lumbar puncture with CSF analysis.

E. Cerebrospinal Fluid (CSF)

Colorless, acellular fluid with low protein content (< 45 mg/dL) and sugar content (two-thirds of blood sugar). Formed by choroid plexus. Absorption through arachnoid granulation and venous sinus. Rate of formation is 0.35 mL/min.

F. CSF Spaces and Leptomeninges

Consist of *arachnoid* and *pia mater* and surround brain and spinal cord. The arachnoid and pia mater become separated by subarachnoid space containing CSF. Meninges consist of the following:

1. Dura mater:
   - Subdural space: Outer layer. Contains bridging veins, which may be lacerated to result in subdural hematoma.
   - Epidural space: Potential space contains arteries. Rupture of middle meningeal artery may result in epidural hematoma.
2. Pia mater: Inner layer directly covering brain and spinal cord.

The contents of CSF can be sampled by *lumbar puncture*. Diagnosis of meningitis and subarachnoid hemorrhage (SAH) can be established by CSF analysis.

G. Ventricles

Two lateral ventricles (anterior frontal horns, bodies, atria, occipital horns). Communicate with third ventricle through interventricular foramina (Monro). Third ventricle communicates with fourth ventricle through aqueduct of Sylvius. Fourth ventricle communicates with basal cistern through median (Magendie) and paired lateral (Luschka) foramina.

H. Cerebral Cortex

► cram facts

Frontal lobe injury causes personality and behavior, not cognitive, disorders.

1. Frontal Lobe

a. Prefrontal—Associated with inability to initiate activities, inhibit socially inappropriate behavior, sustain concentration, shift from one mental task to another. Lesions result in the "Phineas Gage" type of disorder (this man had crowbar lodged in frontal lobes following an explosion) with marked change in personality and behavior but no cognitive impairment. Lesions result in changes in concentration, abstracting capability, judgment, and problem-solving capacity.

b. Motor and Premotor Cortex—Somatotopic organization, with representation of face, hand, and arm located on lateral convexity; and hip, leg, and foot located medially. Injury to motor cortex leads to contralateral motor deficit and Babinski sign.

c. Frontal Eye Fields—Injury causes horizontal deviation to ipsilateral side; stimulation causes eye deviation to contralateral side.

d. Broca Area—Located in posterior–inferior frontal region of dominant hemisphere. Injury results in inability to express written and spoken language.

2. Parietal Lobe

a. Sensory Cortex—Lesions cause contralateral hemianesthesia and impaired ability of the patient to recognize size, shape, weight, and form of objects placed in the hand.

b. Supramarginal and Angular Cortex—Lesion in the dominant hemisphere results in Gerstmann syndrome, which consists of finger agnosia, agraphia, acalculia, right–left confusion.

c. Inferior Parietal Lobule—Injury results in contralateral astereognosis (denial of deficit, which is usually left motor impairment), neglect, or inattention. Patient may not recognize left side of body; this leads to failure to dress left side (dressing apraxia). Also, patient may be inattentive to left hemiplegia (anosagnosia of Babinski). Patient may have constructional apraxia such that when asked to draw a clock, all the numbers are placed on the right side.

3. Temporal Lobe

a. Primary Auditory Cortex—Bilateral loss results in cortical deafness.

b. Wernicke Area—Located along the posterior Sylvian region of superior temporal gyrus. Injury results in receptive aphasia with impaired comprehension.

c. Meyers Loop—Visual radiation fibers projecting to inferior portion of visual calcarine cortex. Injury results in superior homonymous quadrantanopia.

d. Olfactory Cortex—Fibers of olfactory tract project to this region; lesions result in anosmia (loss of smell). Irritative lesions may cause olfactory hallucinations. A “bad taste or smell” is characteristic aura of psychomotor seizure.

e. Hippocampal Cortex—Bilateral lesions result in *recent* memory disturbances; however, *remote* memory remains intact.

f. Anterior Temporal Lobe—Injury results in Kluver–Bucy syndrome. This includes visual agnosia or inability to visually recognize objects, hypersexual behavior, and oral behavior or placing objects in the mouth (including dangerous objects).

g. Occipital Cortex—Calcarine region. This is primary visual cortex; lesions cause contralateral hemianopsia.

I. Limbic System

Anatomic system that subserves emotional expression. Major components include orbitofrontal cortex, medial–dorsal and anterior thalamus, septal region, limbic lobe, hippocampal formation, amygdala, and mammillary body. Papez system includes hippocampus projecting to mammillary body, anterior thalamus, cingulate gyrus, enterorhinal cortex, and fibers returning to hippocampus. Major neurotransmitters in this system include dopamine (ventral tegmentum), serotonin (raphe nucleus), and norepinephrine (locus ceruleus).

J. Extrapyramidal Motor System

Components are caudate, putamen, globus pallidus (GP), subthalamic nucleus (STN), substantia nigra (SN), thalamus, and neocortex. Major connections include striatum (caudate, putamen), which receives input from thalamus, neocortex, and SN. Projects to GP and SN. GP projects to striatum, thalamus, and STN. SN projects to thalamus. Major neurotransmitters include gamma-aminobutyric acid (GABA) within striatum, globus pallidus, and pars reticularis of SN; dopamine (DA) within pars compacta of SN; acetylcholine with in the striatum; glutamate is excitatory within fibers of STN projecting to globus pallidus. The basal ganglia initiate and execute motor activity, which is involved in automatic postural and reflex motor activity. Clinical disorders include the following:

1. *Parkinsonism.* Clinical features include 3-cycle-per-second (cps) *resting* pill-rolling hand tremor, impaired postural reflexes, bradykine-

► cram facts

Parkinson’s disease is a hypokinetic disorder due to dopamine insufficiency.

sia, cogwheel rigidity, masklike facies, shuffling gait with stooped posture, sialorrhea, and seborrhea. Most commonly due to adverse effect of major neuroleptics (high potency); mechanism is dopamine receptor blockade. If neuroleptic medication is discontinued, clinical features of Parkinson's disease (PD) disappear. Treatment of idiopathic PD includes levodopa replacement (Sinemet) or utilization of dopamine receptor agonist medication.

2. *Huntington's disease.* Inherited as autosomal dominant disorder due to defect on chromosome 4 with abnormal trinucleotide repeats. Clinical features include behavioral disorders (psychosis, hallucinations), dementia, and chorea (rapid jerklike semipurposeful motor movements). Mechanism involves effect of glutamate excitotoxicity; there is degeneration of striatal cholinergic and GABA neurons. CT/MRI usually shows *caudate nucleus* atrophy.
3. *Hemiballism.* This is violent flailing movement, usually occurring unilaterally. It is due to damage (infarct, hemorrhage, neoplasm) of contralateral STN.
4. *Neuroleptic-induced movement disorder.* This includes:
   - *Acute:* Dystonic neck or mouth movements. Treatment includes Benadryl.
   - *Subacute:* Akathisia (motor restlessness) or parkinsonism. Responds to anticholinergic medication.
   - *Delayed* (tardive): Oral–facial–lingual or shoulder movements. Tardive dyskinesia occurs when neuroleptic medication dose is decreased or discontinued. This is caused by hypersensitivity to dopamine receptors.
5. *Hepatolenticular degeneration (Wilson's disease):* Inherited as autosomal recessive disorder. Copper accumulates in the liver, resulting in cirrhosis. Also, copper accumulates in cornea to cause blue pigment rim (Kayser–Fleischer ring); this is seen best with slit lamp. Copper toxicity causes necrotic basal ganglionic and cortical (frontal) lesions. Patient presents with dyskinesia and hepatic dysfunction. Diagnosis is established by low serum ceruloplasmin; liver biopsy shows excessive copper. Treatment with penicillamine decreases burden of copper.

K. Thalamus

Group of nuclei located in third ventricular wall. Integrate and relay information concerning motor, sensory, consciousness, cognitive, and behavioral systems. The *ventral posterior* nucleus (lateral, representing extremities and trunk and is termination of medial lemniscus and lateral spinothalamic tract; medial, representing face) relays information to sensory parietal cortex.

L. Midbrain

Region of brain stem located above pons; extends to diencephalon.

► cram facts

Midbrain is center for vertical eye movements.

1. Structures

- Cerebral aqueduct.
- Inferior and superior colliculus (located dorsally) and referred to as *quadrigeminal plate.*
- Inferior collicus is relay for auditory fibers.
- Superior colliculus is related to eye movement control.

2. Fiber Tracts

- Cerebral peduncles representing corticospinal tract (ventral).
- Spinothalamic tract.
- Lateral lemniscus.

- Medial lemniscus.
- Superior cerebellar peduncle (brachium conjunctivum).

3. Nuclei

- Red nucleus—receives fibers from cerebellum; sends efferent fibers to olivary nuclei (rubrospinal tract).
- *Substantia nigra*—source of dopaminergic cells.
- *Cranial nerves:*
  - Trochlear—motor nerve to superior oblique muscle.
  - Oculomotor—motor nerve to medial, superior, and inferior recti muscles; levator palpebrae of eyelid and pupillary constrictors.

4. Neurologic Syndromes

The midbrain is supplied by superior cerebellar artery.

5. Paramedian Syndromes

- Oculomotor nerve dysfunction causes ipsilateral ptosis, dilated pupil (mydriasis), and diplopia, in both horizontal (due to medial rectus weakness) and vertical (due to superior and inferior recti) directions.
- Lesion of cerebral peduncle causes contralateral hemiparesis.
- Lesion of red nucleus and brachium conjunctivum causes contralateral ataxia.

M. Pons

1. Structures

a. Basis Pontis

- Pontocerebellar fibers of middle cerebellar peduncle (laterally located).
- Corticobulbar and corticospinal tract (medially located).

► cram facts

Pons is center for horizontal eye movements.

b. Pontine Tegmentum

- Floor of fourth ventricle.
- Spinothalamic tract.
- Medial lemniscus.
- Medial longitudinal fasciculus (controls horizontal eye movements).
- Reticular formation (controls consciousness).
- Cranial nerves:
  - *Vestibular* and *cochlear* control balance, equilibrium, and hearing.
  - *Facial*—motor nerve to facial muscles and taste from anterior tongue.
  - *Abducens*—motor nerve to lateral rectus muscle.
  - *Trigeminal*—sensory nerve from face and muscles of mastication (chewing).

2. Neurologic Syndromes

a. Paramedian Structures and Dysfunction

Arterial supply is the paramedian penetrating branch of the basilar artery:

- Abducens nucleus: Ipsilateral impairment of lateral gaze.
- Facial nerve: Ipsilateral facial weakness (both upper and lower portions).
- Corticospinal tract (CST): Contralateral hemiparesis.
- Medial lemniscus: Contralateral impaired proprioception.
- Parapontine gaze center: Impaired horizontal gaze toward the lesion.

b. Lateral

Anterior inferior cerebellar artery supplies this region.

- *Facial nucleus:* Ipsilateral facial weakness involving both upper and lower face.
- Sensory trigeminal tract: Impaired ipsilateral facial pain and temperature.
- Spinothalamic tract: Impaired contralateral pain and temperature on the trunk and extremities.
- *Cochlear–vestibular nucleus:* Ipsilateral hearing loss and vertigo.
- Middle cerebellar peduncle: Ipsilateral ataxia.
- Descending sympathetic fibers: Ipsilateral Horner syndrome (ptosis, miosis, anhidrosis).

► cram facts

Medulla contains cardiovascular and respiratory autonomic centers.

N. Medulla

Continuation of the spinal cord above the foramen magnum.

1. Structures

- Medullary pyramids and decussation located medially and ventrally.
- Termination of fasciculus gracilis and cuneatus and origin of second-order neurons in medial lemniscus (dorsal–medial).
- Descending tract of trigeminal nerve and nucleus of spinal tract (laterally located).
- Fourth ventricle (midline).
- Cranial nerves:
  - *Hypoglossal:* Motor nerve to tongue.
  - *Spinal accessory:* Motor nerve to sternocleidomastoid and trapezius muscles.
  - *Glossopharyngeal:* Sensory nerve from pharynx and tongue and taste from posterior tongue.
- Descending sympathetic fibers.
- Inferior cerebellar peduncle—located in dorsolateral region.
- Inferior olivary nucleus—located ventrolaterally and receives fibers from cerebellum.

2. Neurologic Syndromes

a. Paramedian

Arterial supply is the anterior spinal artery. If there is vascular occlusion, structures involved and signs include:

- Medullary pyramid—contralateral hemiparesis.
- Median lemniscus—contralateral impaired proprioception.
- Hypoglossal nerve—ipsilateral tongue weakness.

b. Lateral (Wallenberg) Syndrome

This region is supplied by vertebral and posterior inferior cerebellar arteries. Structures involved and neurologic dysfunction:

- Nucleus ambiguus: Dysarthria, dysphagia and dysphonia.
- Descending trigeminal tract and trigeminal nucleus: *Ipsilateral* loss of facial pinprick and temperature sensation.
- Spinothalamic tract: Contralateral impaired pain and temperature in trunk and extremities.
- Inferior cerebellar peduncle: Ipsilateral limb ataxia.
- Vestibular system: Vertigo.
- Descending sympathetic fibers: Ipsilateral Horner syndrome.

► cram facts

Cerebellum controls rapid alternating movements; corticospinal tract controls rapid successive movements.

O. Cerebellum

Composed of two lateral hemispheres (representing upper extremities) and midline vermis (representing head, neck, trunk, and lower extremities).

1. Midline

Vermis has spinocerebellar afferent fibers and is involved in balance and walking.

2. Lateral

Represents cerebellar hemispheres and has corticopontine pathway afferents and involved in coordination of upper extremity movements.

P. Spinal Cord

Originates at foramen magnum and terminates at first lumbar vertebra.

1. Levels

► cram facts

Cervical cord controls arms and legs; thoracic cord controls legs.

a. Cervical

Contains fibers that supply upper and lower extremities and trunk. Lesions cause quadriplegia or quadriparesis, incontinence, and sensory impairment below lesion level.

b. Thoracic

Supplies trunk and lower extremities. Lesions cause paraplegia or paraparesis with incontinence and sensory impairment.

c. Conus Medullaris

Termination of spinal cord at first lumbar vertebra. Compressive lesions cause sensory impairment in saddle distribution; buttock region (S2–4) and bottom of foot (S1); bilateral Babinski signs; incontinence and sexual dysfunction; absent ankle reflex; intact knee jerk; and mild motor dysfunction with prominent gastrocnemius weakness, but more proximal muscles not involved.

d. Cauda Equina

Involves the nerve roots from L3 to sacral region. Compressive lesions cause unilateral radicular pain; unilateral sensory loss involving saddle region; unilateral muscle weakness and wasting involving knee, ankle, and foot; absent knee and ankle reflexes; negative Babinski sign (spinal cord not affected); no incontinence or impaired sexual function.

2. Sensory Tract

Dorsal columns (medial lemniscus).

► cram facts

Spinal cord lesions cause motor, sensory dysfunction; motor system causes only motor dysfunction.

Function—Mediates vibration, proprioception, touch discrimination.

Pathway—Receptors include muscle spindles, Golgi tendon organs, tactile corpuscles. First-order neurons are located in *dorsal root ganglia.* These project to gracile fasciculus (located medially) from lower extremities and cuneate fasciculus from upper extremities. Second-order neurons are located in gracile and cuneate nucleus in the medulla. This gives rise to medial lemniscus, which *decussates* in medulla and terminates in ventral posterolateral thalamic nucleus. Third-order neurons project from thalamus to somatosensory parietal cortex.

3. Lateral Spinothalamic Tract

Function—Mediates pinprick, temperature, and nondiscrimatory light touch. These are more primary sensory modalities and have survival value.

***Pathway*—**Receptors include free nerve endings with input from both fast- (A-delta) and slow-conducting (C) pain fibers. First-order neurons are located in dorsal root ganglia. They project axons through dorsolateral tract of Lissauer in the spinal cord. Second-order neurons are located in the dorsal horn, and axons *decussate* through central white matter and terminate in ventral–posterior lateral thalamic nucleus. Third-order neurons project to parietal sensory cortex.

4. Motor Tract

Lateral corticospinal tract (LCST).

***Function*—**Mediates voluntary, skilled, coordinated motor tasks. Lesion results in paresis or plegia with positive Babinski sigm (plantar extensor response).

***Pathway*—**LCST originates primarily from premotor and primary motor cortex cells (Betz cells) and from cells in primary sensory cortex. There is somatotopic organization, with leg and foot located medially along paracentral lobule and face and upper extremity represented along lateral convexity. LCST descends through internal capsule and extends into ventral brian stem to decussate in medulla. LCST terminates through interneurons on anterior (ventral) horn neurons.

Q. Visual System

The visual system consists of visual apparatus (including rods and cones), optic nerve, optic chiasm, optic tract, optic radiations (parietal portion and temporal portion), and primary occipital (calcarine) cortex.

1. Visual Apparatus

Includes retina containing rods and cones. These are necessary for visual processing system.

- Rods mediate sight under conditions of dim illumination; visual pigment is rhodopsin-containing retinene, derived from vitamin A. Cones mediate color vision.
- *Amaurosis fugax* is sudden unilateral blindness due to ischemic disorder of ophthalmic and central retinal artery due to ipsilateral carotid artery stenosis.

> **► cram facts**
>
> If lesion is anterior to optic chiasm, visual loss occurs in one eye only; if chiasmal loss occurs in bitemporal fields; if posterior to chiasm, loss is contralateral to lesion.

2. Optic Nerve

Thickly myelinated fibers. May undergo *demyelination* as in MS. Symptoms include visual acuity loss in involved eye with *scotoma* (area of central blindness) surrounded by normal peripheral vision. When optic disc is visualized with ophthalmoscope, it appears *pale* due to loss of myelinated fibers. Papilledema involves swelling of optic nerve head and is due to increased intracranial pressure.

3. Optic Chiasm

Temporal fields decussate in central region. Lesion causes bitemporal hemianopsia. Most common lesion is compression from undersurface by pituitary adenoma (Figure 7–1).

4. Optic Tract

Lesion causes contralateral homonymous hemianopsia.

5. Optic Radiations

Lesions pass through the temporal (inferior fibers representing superior temporal visual fields) to cause contralateral superior

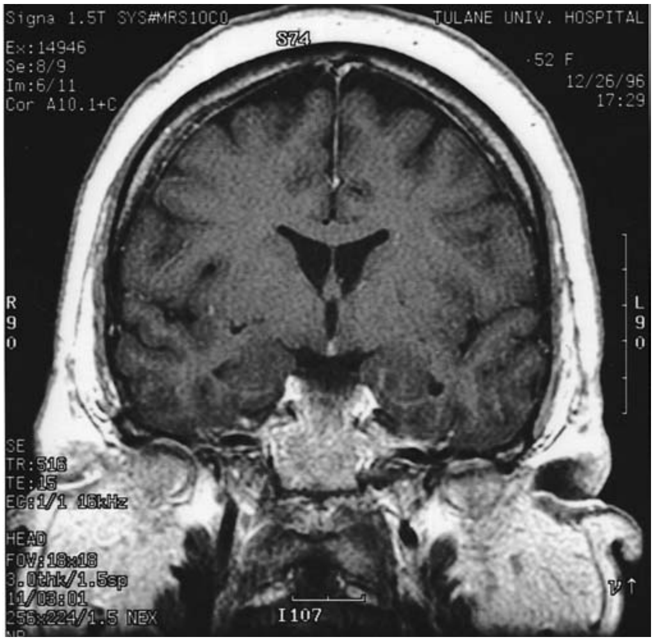


Figure 7–1. Pituitary suprasellar tumor. Coronal MRI shows intrasuprasellar extension of pituitary tumor.

homonymous hemianopsia; whereas those passing through the parietal (superior fibers representing inferior visual fields) cause inferior contralateral homonymous hemianopsia.

6. Primary Occipital Cortex

Lesion causes a contralateral homonymous hemianopsia usually with sparing of the central (macular) region.

R. Neurotransmitters

1. Acetylcholine

Involved in the neuromuscular junction (nicotinic receptors), parasympathetic nerves, preganglionic sympathetic fibers, postganglionic sympathetic fibers (innervating sweat glands and muscle blood vessels), spinal cord, basal nucleus of Meynert (memory system that degenerates in Alzheimer's disease), and neostriatum (involved in motor dysfunction in PD).

2. Dopamine

Major dopamine pathways arise in midbrain: nigrostriatal from substantia nigra to neostriatum; mesolimbic from ventral tegmental to septal region. Also found in arcuate nucleus of hypothalamus and projects to infundibulum. Dopamine deficiency characterizes PD. Dopamine receptor abnormality in schizophrenia. Dopamine involved in neuroendocrine hypothalamic pituitary hormones. Neuroleptics are dopamine blockers and elevate prolactin level due to blockage of prolactin-inhibiting factor. Dopamine receptors:

- D_1 are excitatory, postsynaptic, and activate adenylate cyclase.
- D_2 are inhibitory, inhibit adenylate cyclase, and are both pre- and postsynaptic.

3. Norepinephrine

Transmitter of postganglionic sympathetic neurons. Norepinephrine neurons are located in locus ceruleus and activate adenylate cyclase.

4. Serotonin

Neurons located in raphe nucleus of brain stem.

5. Opioid Peptides

Endorphins are localized to hypothalamus. Enkephalins are widely distributed. Involved in pain system.

6. Nonopioid Peptides

Substance P has role in pain transmission (found in spinal cord dorsal root ganglion).

7. Gamma-aminobutyric Acid (GABA)

Major brain inhibitory neurotransmitter. Localization—neocortical glutamate neurons project to striatum, subthalamic nucleus, and thalamus.

8. Glycine

Major inhibitory transmitter of spinal cord.

9. Glutamate

Major brain excitatory neurotransmitter. Localization—neocortical glutamate neurons project to striatum, STN, and thalamus.

S. Neuroimaging Studies

1. Shadow Radiography

Plain skull radiogram delineates the distribution of ionized calcium. It shows bone discontinuity and delineates skull fracture. It may show osteolytic or osteoblastic bone lesions in cancer or multiple myeloma patients or intracranial tumor calcification.

2. CSF Examination

Measure opening pressure (patient must be in relaxed recumbent position with legs extended); this is < 200 mm H_2O. Fluid should appear clear and colorless. Cloudy fluid indicates white blood cells; red, pink, or xanthochromic indicates intracranial blood. If BBB is intact, protein is < 45 mg/dL and sugar is 66% of blood sugar. CSF should be sterile, and all cultures, serologic studies, and stains should be negative.

3. Electroencephalogram (EEG)

Measures cerebral cortical surface brain electrical activity. There is symmetrical activity with rate of 10 cps in the awake state. If consciousness is impaired by pathological conditions such as toxic metabolic encephalopathy, EEG pattern slows in symmetrical pattern. EEG may show abnormal discharges such as spikes, slow waves, spike-and-slow waves in epilepsy. EEG must show abnormal discharge during a seizure unless episode is psychogenic in origin.

► cram facts

CT is best to show brain hemorrhage; MRI is best to show ischemia–infarction.

4. Computed Tomography (CT)

Visualizes intracranial and spinal structures based on differences in electron densities. Calcification and blood appear hyperdense. Infarction and demyelination may be seen as hypodense lesions, but MRI is more sensitive for these lesions.

5. Magnetic Resonance Imaging (MRI)

Visualizes intracranial and spinal structures based on distribution of proton content of water. In T1-weighted images, the image appears similar to CT with CSF appearing dark; whereas in T2- weighted images, CSF appears white. MRI is very sensitive to visualize ischemia–infarction and demyelination; however, it is less sensitive to detect hemorrhage. MRI is most sensitive to detect spinal pathology and cord.

6. Conventional Catheter Angiography

Iodinated contrast material is injected into arteries to visualize arterial (stenosis, occlusion, aneurysm, arteriovenous malformation) and venous disease. Arterioles are *not* visualized.

7. Nerve Conduction Velocity and Electromyogram (NCV/EMG)

By stimulating over superficial peripheral nerve and recording with skin electrodes over the muscle, nerve conduction velocities are determined. NCV is dependent on integrity of myelin sheath. By inserting needle electrode into muscle, electrical properties of muscle can be determined.

II. ABNORMAL PROCESSES

A. Nervous System Malformations

- *Anencephaly:* Failure of anterior neuropore to close.
- *Spina bifida:* Failure of posterior neuropore to close.
- *Holoprosencephaly:* Single ventricle with failed forebrain cleavage.
- *Hydrocephalus*: Enlarged ventricles with obstruction usually due to cerebral aqueduct stenosis.
- *Fetal alcohol syndrome:* Includes microcephaly (small brain), holoprosencephaly, and congenital heart disease.

Skin and NS are both derived from the ectoderm; therefore, there are genetic neurocutaneous disorders.

Common Syndromes	**Skin**	**NS**
Von Recklinghausen	Neurofibroma Café au lait	Schwannoma Glioma
Tuberous sclerosis	Adenoma sebaceum	Periventricular tumors, lesion
Sturge–Weber	Port-wine nevus	Occipital vascular

B. Cerebral Edema

Types:

- *Cytotoxic:* Cell swelling with influx of sodium and water.
- *Vasogenic:* Plasma filtrate exudes into extracellular space due to breakdown of BBB.
- *Interstitial:* Cerebrospinal fluid (CSF) infiltrates through ventricular walls into white matter.

C. Neuronal Pathological Reaction

1. Ischemia/Infarction

May be *focal* (cerebral infarction) or global (hypoxic–ischemic encephalopathy). Brain requires aerobic metabolism and survives utilizing oxygen and glucose. With energy failure, brain switches to inefficient anaerobic metabolism.

2. Other Neuronal Injury Mechanisms

- *Central chromatolysis:* Swelling of cell body and loss of Nissl granules.
- *Wallerian degeneration:* Occurs in axon when neuron is destroyed. This occurs in distal axon when cell body is separated from axon.
- *Neurofibrillary degeneration:* Formation of clumped neurofibrils within neuronal cytoplasm. Most common in Alzheimer's disease.
- *Inclusion bodies:* Abnormal deposits in neurons: Lewy bodies seen in Parkinson disease; Negri bodies in rabies.

- *Amyloid plaque:* Consists of protein precipitate, which is seen in gray matter of patients with Alzheimer's disease.

D. Abnormalities of CSF Circulation

1. Hydrocephalus

Dilation of ventricles due to obstruction of CSF flow. Two variants of impaired CSF circulation or hydrocephalus:

1. *Normal pressure hydrocephalus* (NPH):
   - A form of communicating hydrocephalus.
   - Enlarged ventricles with nonvisualized cisterns and nonvisualized sulcal spaces.
   - Symptoms are cognitive impairment, urinary incontinence, gait impairment.
   - Diagnosis established by CT/MRI showing enlargement of all ventricular chambers and nonvisualized cisterns and sulcal spaces.
   - Treatment of communicating or noncommunicating hydrocephalus is diversionary shunt.
2. *Idiopathic intracranial hypertension* (pseudotumor cerebri):
   - Impaired resistance to CSF absorption.
   - Symptoms are headache, diplopia, visual loss; sign is papilledema.
   - Diagnosis made if CT/MRI are normal and CSF is abnormal *only* for elevated pressure.

► cram facts

Hydrocephalus is diagnosed by CT or MRI and treatment is diversionary shunt.

E. Herniation

The cranium is a closed space consisting of brain parenchyma (gray and white matter), CSF, and blood vessels. It does not have elasticity to accommodate volume changes without causing resultant CSF pressure increase. Expanding mass lesions cause increased intracranial pressure, which subsequently leads to shifts in position of tissue (herniation).

1. Transtentorial (Uncal)

Supratentorial mass shifts uncus of hippocampus over free edge of tentorium, compressing ipsilateral midbrain. Structures affected:

- Ipsilateral oculomotor nerve, resulting in fixed dilated pupil.
- Ipsilateral cerebral peduncle, resulting in contralateral hemiparesis.
- Ipsilateral posterior cerebral artery, resulting in contralateral homonymous hemianopsia.

2. Cerebellar Tonsillar

Usually due to posterior fossa mass expanding in downward vector such that tonsils extend through foramen magnum and compress medulla. Symptoms include neck stiffness and autonomic change (Cushing reflex), which results in slowed pulse, respiratory irregularity, and increased blood pressure.

F. Aphasia

Impaired language (written and spoken) and communication difficulty due to lesion in the *dominant* hemisphere.

Three Major Types of Aphasia:

1. *Broca aphasia:* Lesion located in inferior frontal gyrus. Characterized by nonfluent, dysarthric, telegraphic, effortful speech with poor repetition but normal comprehension.
2. *Wernicke aphasia:* Lesion located in posterior superior temporal gyrus and characterized by impaired comprehension, impaired repetition, and fluent nonsensical speech.

► cram facts

Aphasia is language communication disorder; dysarthria is motor speech impairment.

► cram facts

Wernicke aphasia is due to focal temporal lesion; confusion is due to bilateral hemispheric dysfunction.

3. *Conduction aphasia:* Lesion located in arcuate fasciculus (connects Broca and Wernicke regions), characterized by impaired repetition, fluent speech, and normal comprehension.

G. Spinal Cord Lesions

Upper motor dysfunction is caused by injury to cortical motor cells or LCST located in internal capsule, brain stem, or spinal cord. Weakness is cardinal symptom, and pattern of weakness depends on lesion localization (internal capsule causes contralateral hemiparesis, cervical spinal cord causes quadriparesis) with Babinski sign. Immediately after the injury, motor tone is *flaccid* (hypotonic), and this evolves to *spasticity* (hypertonic) with hyperreflexia and positive Babinski sign.

a. Lower Motor Neuron (LMN) Dysfunction

Caused by damage to anterior horn cell. Findings include *weakness, wasting, atrophy, fasciculations,* and *reduced reflexes* (consistent with severity of weakness). There is *no* positive Babinski sign.

b. Combination of Upper Motor Neuron (UMN) and LMN Findings

Amyotrophic lateral sclerosis (ALS—Lou Gehrig's disease) is a progressive degenerative disorder. Clinical features represent combination of UMN and LMN impairments. Bulbar muscles may be involved to cause dysarthria, dysphagia, and dysphonia.

H. Sensory System Disorders

1. Tabes Dorsalis

Due to neurosyphilis. Results from impairment of posterior nerve roots as they enter the spinal cord. Symptoms are impaired proprioception and vibration (sensory ataxia), lightning-like radicular pain, absent reflexes, and positive Babinski signs.

2. Hemisection (Brown–Séquard Syndrome)

Due to compression of one side of the spinal cord. Findings include ipsilateral impairment of proprioception and vibration due to dorsal column dysfunction below lesion level, ipsilateral impairment of UMN function due to LCST dysfunction below lesion level, and contralateral loss of pain and temperature one to two levels below lesion due to decussation of lateral spinothalamic tract within spinal cord.

3. Anterior Spinal Artery Syndrome

Occlusion of this artery causes infarction of both sides of anterior and lateral spinal cord with sparing of posterior (dorsal columns). Clinical features include weakness due to LCST involvement below lesion, bilateral loss of pinprick and temperature below lesion, incontinence due to LCST and sacral parasympathetic center, and intact vibration sensation and proprioception. This region is supplied by posterior spinal artery.

4. Subacute Combined System Degeneration

Caused by vitamin B_{12} deficiency. These patients have hematologic (megaloblastic anemia) and neurologic dysfunction, including impaired proprioception and vibration sensation, UMN findings, and evidence of peripheral nerve dysfunction. Diagnosis is established by complete blood count (CBC) showing macrocytic anemia, visualization of abnormalities on peripheral blood smear and bone marrow (megaloblasts), and reduced B_{12} level.

► cram facts

Syrinx is cavity in cord showing fluid on MRI.

5. Syringomyelia

Cavity in spinal cord. This usually occurs at midcervical region. Findings include bilateral loss of pain and temperature in a shawl (C4–6) distribution, with uncomfortable dysesthetic pain in this region; flaccid paralysis of LMN type in the hands, and UMN findings below lesion level. Diagnosis is established by spinal MRI, which shows fluid in the central spinal cord (Figure 7–2).

6. Transverse Myelitis

Inflammatory demyelinating disorder. Usually affects white matter of cervical or thoracic region. Findings include UMN impairment below lesion, impaired sensation below lesion, and incontinence and sexual dysfunction.

I. Clinical Disorders Involving Neurotransmitters

1. Dopamine

Deficiency occurs in PD.

2. Acetylcholine (ACh)

- Deficiency in basal nucleus of Meynert impacts memory system in Alzheimer's disease.
- Antibodies to ACh receptors produced in thymus block postsynaptic binding site in muscle in myasthenia gravis. In myasthenic syndrome and botulism, there is a presynaptic defect preventing ACh release. Skeletal muscle weakness is consequence of these disorders.

3. GABA-Containing Neurons

In Huntington's disease, there is loss of striatal GABA-containing neurons.

Figure 7–2. Syringomyelia. Hypointense (black) area within the spinal cord indicating fluid-filled cavity imaged with MRI.

4. Glutamate Excitotoxicity

This hypothesis suggests that glutamate activates *N*-methyl-D-aspartate receptor. This leads to calcium influx and neuronal death in certain neurodegenerative disorders (e.g., Huntington's disease, ALS).

J. Infectious/Inflammatory Disorders

1. Meningitis

May be acute (viral, bacterial) or chronic (syphilitic, tuberculous, fungal, neoplastic). Symptoms include:

- New and different type of headache.
- Systemic signs (fever, myalgia, rash).
- Neck stiffness and rigidity.
- Presence of the following neurologic abnormalities indicates complicating pathological process:
  - Seizures.
  - Papilledema.
  - Altered consciousness.
  - Focal neurologic deficit.

> **► cram facts**
>
> In acute meningitis, lymphocytes in CSF indicates viral etiology and polymorphonuclear leukocytes indicate bacterial etiology.

Complicating pathological processes include:

- Encephalitis.
- Cerebritis.
- Brain abscess.
- Subdural empyema.
- Epidural empyema.
- Vasculitis with ischemia–infarction.
- Venous sinus thrombosis.
- Hydrocephalus.

Diagnosis of *uncomplicated* meningitis is established by CSF analysis. If bacterial meningitis suspected, delay in diagnosis worsens outcome; therefore, immediate LP must be done.

CSF Findings in Acute Meningitis

	Viral	**Bacterial**
Pressure	Normal	Elevated
White blood cells	Lymphocytes	Neutrophils
Glucose	Normal	Decreased
Protein	Mild elevation	Marked elevation
Gram stain	Negative	Positive
Bacterial culture	Negative	Positive

If patient has received prior antibiotics, consider partially treated bacterial meningitis and perform *latex* agglutination and polymerase chain reaction (PCR) for bacterial DNA or RNA. CSF may show mixed pleocytosis, normal sugar, and negative bacterial stain and culture. If etiology of meningitis is in doubt, initiate antibiotics until cultures are complete. Treat bacterial meningitis with *intravenous* antibiotics to allow CSF penetration for 10–14 days. Etiologies:

- *Streptococcus pneumoniae* most common in adults.
- *Neisseria meningitidis* less common.

a. Acute Viral Meningitis

► Description

Enterovirus most common, especially in summer months.

► Symptoms

Headache, fever, meningeal irritation.

► Diagnosis

- CSF shows lymphocytic pleocytosis.
- PCR analysis and viral culture.

b. Acute Viral Encephalitis

► Description

Herpes simplex type I and adenovirus most common etiologies.

► Symptoms

Meningeal irritation and fever with altered consciousness and/or focal neurologic deficit.

► Diagnosis

CSF shows lymphocytic pleocytosis. PCR analysis and viral culture.

► Treatment Steps

Acyclovir is treatment for herpes simplex encephalitis.

c. Chronic Meningitis

Initial consideration is whether the patient is immunocompromised. If so, consider:

- HIV positive.
- Utilizing immunosuppressive medication.
- Transplant recipient.
- Neoplastic treatment.
- Diabetes mellitus.

Etiologies for chronic meningitis include:

- Bacterial—syphilis, Lyme disease, tuberculous, *Listeria.*
- Fungal—cryptococcal, *Candida,* aspergillosis.
- Neoplastic—leukemia, lymphoma.
- Inflammatory noninfectious—sarcoid.

Diagnosis established by CSF findings, but determining etiology may require *meningeal biopsy.*

2. HIV Neurologic Manifestations

a. Direct Viral Effect

- Aseptic (lymphocytic) meningitis.
- AIDS motor–dementia complex.
- Peripheral neuropathy.

b. Effect of Immunosuppression on Nervous System

Opportunistic Infections

- Toxoplasmosis—multiple gray matter parenchymal lesions. Enhancing CT/MRI lesions.
- Progressive multifocal leukoencephalopathy. Nonenhancing CT/MRI lesions.

Other Multiple Parenchymal Lesions

- Cryptococcal meningitis.
- *Mycobacterium* meningitis.
- Neurosyphilis.

Neoplasms
- Primary CNS lymphoma.
- Kaposi's sarcoma.

K. Epilepsy

Seizures are paroxysmal disorders caused by abnormal hypersynchronous electrical brain discharges. Abnormal brain electrical discharges are recorded with EEG. In the interictal period (between episodes when the patient is having no clinical manifestations), EEG is still usually abnormal but *may* be normal.

1. Definitions

- **Epilepsy:** Recurrent seizures due to abnormal brain electrical activity.
- **Syncope:** Passing out spells in which there is no abnormal brain activity. Not neurologic disturbance and usually due to brain hypoperfusion.
- **Aura:** Beginning of seizure.
- **Ictus:** Clinical episode.
- **Postictus:** Clinical features after the episode.

2. Classification

a. Generalized Seizures

Abnormal discharges begin in both hemispheres simultaneously.

- Generalized tonic–clonic (grand mal) may be genetically based.
- Abnormalities of paroxysmal shifts (perhaps due to sodium, chloride, or calcium channels):
  - No aura.
  - Initial phase—tonic muscle contractions, loss of consciousness.
  - Later replaced by rhythmical clonic jerking.
  - Episode lasts 2–5 minutes.
  - Patient is postictally confused and returns to normal in the interictal state.
  - EEG shows generalized spike discharges (Figure 7–3).

► cram facts

In immunosuppressed patients, CNS pathologies are very different than in immunocomponent patients.

► cram facts

Epilepsy is recurrent seizures with EEG abnormalities.

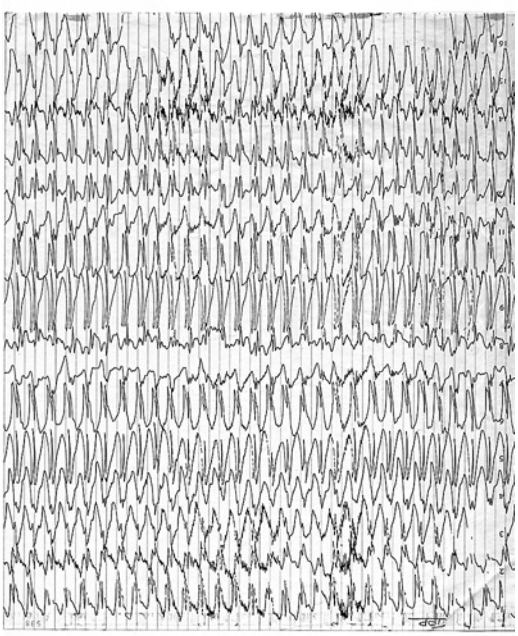


Figure 7–3. EEG shows symmetrical, 3-cycle-per-second spike-and-slow wave activity seen in patients with absence seizures.

b. Absence Seizures (Petit Mal)

- Sudden brief periods of loss of awareness.
- No loss of postural tone—may be accompanied by eyelid blinking.
- Rapid recovery of awareness. No postictal confusion.
- EEG shows symmetrical 3-cps spike-and-wave discharges.

c. Partial (Focal) Seizures

Begin in one focal area of the brain and may stop or *secondarily* generalize to tonic–clonic seizure. They are due to structural brain disease. If *macroscopic,* CT/MRI usually shows an abnormality. If *microscopic,* CT/MRI is negative.

d. Simple (Partial) Seizures

Cause abnormal motor, sensory, autonomic, or psychic symptoms *without* alteration in consciousness.

e. Complex Partial (Psychomotor, Temporal Lobe) Seizures

Focal seizures in which the patient loses contact with his or her surroundings and does not respond appropriately. Following episode, patient may appear briefly dazed. EEG usually shows spikes arising from temporal lobe. In some cases, complex partial seizure secondarily generalizes to major motor seizure. Patients frequently report *aura* of "bad taste or smell" or other autonomic phenomena (e.g., rising feeling in epigastrium or chest).

► cram facts

If seizures do not respond to anti-epileptic drugs, consider psychogenic seizures.

3. Management of Seizures

- Avoid events that may precipitate seizures (medications affecting CNS excitability, alcohol use and withdrawal, metabolic derangements, fever in a child).
- Utilize antiepileptic drugs in patients with recurrent nonprovoked seizures.

L. Demyelinating Disorders of the CNS

- Multiple sclerosis is most common.
- Lesions are spread out *temporally* and *spatially.*
- Involves thickly myelinated tracts of CNS and *never* involves PNS.

1. Clinical Patterns

Include optic neuritis, transverse myelitis, ataxia, diplopia with internuclear ophthalmoplegia, sensory impairment, vertigo, and neurogenic bladder.

2. Pathogenesis

Immune-mediated disorder in genetically susceptible individual.

3. Diagnostic Studies

a. Most Sensitive—MRI shows *multiple* brain and spinal cord abnormalities (high-signal-intensity lesions on T2-weighted images and gadolinium-enhancing lesions on T1-weighted images [Figure 7–4]).

b. Most Specific—CSF abnormalities including presence of myelin basic protein and increased levels of intrathecally produced γ globulin.

c. Course

- Relapsing–remitting.
- Relapsing–remitting with secondary progression.
- Primary progressive.

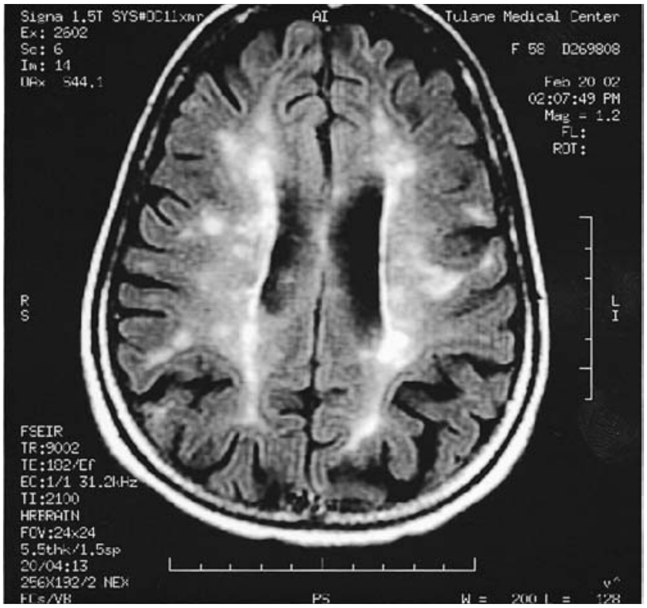


Figure 7–4. Multiple sclerosis. MRI shows periventricular hyperintense (white) lesions consistent with demyelination.

d. Disease-Modifying Therapies

- Interferon.
- Glatiramer.
- Methylprednisolone.
- Most effective in relapsing–remitting and least effective in primary or secondary progressive MS.

M. Neoplasms

1. Pediatric

Common in posterior fossa to compress brain stem, cerebellum, aqueduct, or fourth ventricle. Include medulloblastoma, cerebellar astrocytoma, ependymoma, and brain stem glioma. Also suprasellar–hypothalamic tumor arising from remnant of Rathke pouch—craniopharyngioma.

2. Adult

a. Extracerebral (Axial) Tumors

Meningiomas

- Arise from arachnoid granulation. They compress but do not invade brain. They contain dispersed psammoma body calcification.
- Diagnosis: CT or MRI.
- Management: Surgical excision of slow-growing benign tumor.

Pituitary Adenoma

- Arise within sella turcica. This may cause:
  - Endocrine symptoms: Hyperpituitarism—increased prolactin (amenorrhea–galactorrhea), growth hormone (gigantism, acromegaly), adrenocorticotropic hormone (Cushing's syndrome); hypopituitarism.
  - Visual symptoms: Bitemporal hemianopsia due to optic chiasm compression.

► cram facts

MS is demyelinating disease of CNS characterized by symptoms disseminated in time and space.

Tumors in children usually occur in posterior fossa.

- Diagnosis: CT/MRI.
- Management:
  - Surgical decompression of optic chiasm.
  - Radiotherapy.

b. Intracerebral Tumors

Metastatic

- Invading tumor nodule with surrounding vasogenic edema.
- Diagnosis: CT/MRI (must utilize contrast).
- Management: Corticosteroids to reduce vasogenic edema, radiotherapy.

Glioma (Astrocytoma, Oligodendroglioma)

- Infiltrating tumors that grow along white matter pathways.
- Diagnosis: CT/MRI.
- Management: Surgical debulking, radiotherapy, chemotherapy.

N. Neuromuscular Disorders

Major neurologic disorders that cause *gait impairment.*

> **► cram facts**
>
> Nerve disease causes distal weakness; muscle disease causes proximal weakness.

1. Weakness

- Upper motor neuron lesion.
- Lower motor neuron lesion.
  - Anterior horn cell (distal weakness, fasciculations, normal sensation).
  - Peripheral nerve disorder (neuropathy) (distal weakness, absent reflexes, sensory loss in distal distribution).
  - Neuromuscular disorder (proximal weakness and fatigue).
  - Muscle disorder (myopathy) (proximal weakness, normal sensation).

2. Cerebellar Disorder

- Ataxia.
- Dysmetria.
- Intention tremor.

3. Proprioceptive Disorder (Peripheral Neuropathy or Spinal Cord Lesion)

Positive Romberg sign (gait and station *mildly* impaired with eyes open and *marked* deterioration of balance with eyes closed.

4. Vestibular Disorder

- Vertigo present.
- Hearing loss and tinnitus may be present.

5. Parkinson's Disease

Associated shuffling, festinating gait; stooped posture; resting pill-rolling *hand* tremor; and bradykinesia.

6. Normal Pressure Hydrocephalus

- Gait apraxia.
- Dementia.
- Incontinence.

7. Patterns of Neuromuscular Disease

a. Nerve Disease (Neuropathy)

- *Distal* weakness and sensory impairment.
- Absent ankle jerks.
- Weakness in feet (and later hands).
- Sensory impairment in feet (and later hands).

b. Motor Neuron Disease

- Distal weakness.
- Fasciculations.
- Normal sensation.
- Normal reflexes (unless upper motor neuron also involved as in ALS).

c. Muscle Disease (Myopathy)

- Proximal weakness.
- No fasciculations.
- Reflexes dependent on severity of weakness.
- Normal sensation.

> ► **cram facts**
>
> Muscle disease causes elevated enzyme CK levels.

d. Myopathy Types

- Polymyositis (inflammatory myopathy).
- Dystrophy (congenital abnormality of muscle, most common in boys—Duchenne muscular dystrophy due to absence of *dystrophin*).

8. Diagnostic Tests

- Serum creatine kinase (CK) elevated in myopathy.
- Nerve conduction velocity slowed in neuropathy.
- Electromyogram shows characteristic pattern in neuropathy, myopathy, anterior horn cell disease.
- Definite diagnosis of nerve or muscle disease: Muscle biopsy, nerve biopsy.

O. Traumatic Brain Injuries

Neurobehavioral injuries may occur when trauma initially causes impaired consciousness or amnesia. This pattern defines brain concussion:

- All imaging studies normal.
- Pathology—diffuse axonal shearing injury.
- Symptoms (headache, vertigo, visual blurring, difficulty concentrating and thinking).
- Symptoms usually resolve in several weeks.

1. Types of Injuries

a. Bone Fracture

- *Linear:* Detected by skull radiogram.
- *Basilar:*
  - Causes leakage of CSF (otorrhea, rhinorrhea).
  - Risk of bacterial meningitis due to dural tear.
  - Periorbital ecchymosis (raccoon eyes).
  - Ecchymosis over mastoid (Battle sign).

Skull radiogram may be negative in basilar fracture and may require tomograms of skull base and diagnosis suspected by clinical signs.

b. Depressed Fracture

- Tears dura.
- Bone fragment may bruise brain.

c. Contusion

Brain bruise. These occur in superficial brain regions. There may be coup (direct) and contrecoup (indirect) injury. CT/MRI shows edema, hemorrhage, necrosis.

► cram facts

Lucid interval indicates epidural hematoma.

d. Traumatic Brain Hemorrhage

- Subarachnoid.
- Epidural:
  - Fracture across middle meningeal artery groove.
  - Arterial bleeding.
  - Initial loss of consciousness followed by "lucid interval" and subsequent delayed neurologic deterioration.

e. Subdural Hematoma

May be acute or chronic (delayed) venous bleeding. Diagnosis of traumatic hematoma best established by CT. Following trauma in which patient develops hemiparesis with pupillary abnormality (dilated and nonreactive pupil) contralateral to hemiparesis, think traumatic hematoma *ipsilateral* to pupillary abnormality (e.g., subdural or epidural hematoma).

2. Management of Traumatic Brain Lesions

- Control intracranial hypertension.
- Hyperventilate.
- Mannitol.
- Hypertonic saline.
- Corticosteroids (presently not believed effective).
- Emergency CT.
- Surgical hematoma evacuation.

► cram facts

Bell's palsy causes both upper and lower facial weakness.

P. Common Nerve Injury Syndromes

1. Bell's Palsy

Idiopathic lower motor neuron facial nerve palsy (paralysis of upper and lower face).

Symptoms
- Pain behind ear.
- Inability to close one eye.
- Inability to draw back corner of mouth.

Signs—Weakness of muscles of upper and lower face.

2. Radial Nerve

May be compressed at axilla.

Symptoms—Weak hand and cannot extend wrist.

Signs—Weak wrist extensors, which makes it difficult to put hand in position of function and cannot use intrinsic hand.

3. Ulnar Nerve

Usually compressed at wrist.

Symptoms—Weak hand.

Signs
- Weak intrinsic hand muscles with exception of thumb.
- Decreased sensation on ulnar side of fourth and fifth fingers.

4. Median Nerve

Usually compressed at wrist (carpal tunnel syndrome).

Symptoms
- Pain at wrist and hand.
- Difficulty holding objects.

Signs
- Weakness of thumb flexor.
- Sensory impairment of thumb and index and middle fingers.

5. Peroneal Nerve

Usually compressed at popliteal fossa.

Symptoms—Foot drop.

Signs
- Weakness of foot dorsiflexor and inverters.
- Sensory loss over top of foot.

6. Posterior Tibial Nerve

Symptoms—Difficulty standing on toes.

Signs
- Weakness of foot dorsiflexors and inverters.
- Sensory loss on bottom of foot.

7. Sciatic Nerve

Symptoms—Flail useless foot.

Signs—Combined peroneal and tibial injury.

Q. Headache

1. Primary Headache Disorders
- Migraine with aura (classic migraine).
- Migraine without aura (common migraine).
- Cluster.
- Tension.

a. Migraine with Aura
- Sensory (usually visual) symptoms precede headache.
- Aura lasts 20–30 minutes and headache develops on contralateral side to visual symptoms.
- Buildup of pain is gradual over 4–6 hours.
- Activity worsens pain.
- Nausea and vomiting common.
- Patient is photo- and sonophobic.
- Women more likely to have migraine than men.

b. Migraine Without Aura

No sensory symptoms precede headache.

c. Cluster
- Occur in bursts or cluster. Patient may be asymptomatic for years and suddenly headache recurs.
- Awakens patient from sleep.
- Rapidly reaches maximal severity.
- No nausea or vomiting.
- Activity may reduce headache.
- Male predominance.
- Ipsilateral conjunctival redness, lacrimation, rhinorrhea, Horner syndrome.

d. Tension
- Bilateral with occurrence in frontal, temporal, or occipital–neck region.
- Aching pain.
- Relieved by rest or sleep.
- Minimal nausea or vomiting.

► cram facts

In migraine, the aura is usually sensory and neurological disturbance precedes the headache.

► cram facts

Migraine builds up over several hours; thunderclap onset is highly suggestive of brain bleed.

2. Secondary Headache Disorders

Those due to underlying neurologic (meningitis, subdural hematoma, SAH), systemic, or contiguous (eyes, ears, sinus, neck, temporomandibular disorders) structures.

The following suggest a serious underlying condition that requires diagnostic tests:

- New-onset headache.
- Thunderclap in onset (maximal severity at onset).
- "Worst" headache in severity.
- Systemically ill.
- Altered consciousness or seizure.
- Neurologic impairment.
- Visual disturbance (consider temporal arteritis) in *any* patient, especially those older than 60.
- Precipitating factors absent (stress, menses, alcohol, food with high tyramine content).
- Associated elevated blood pressure.

3. Other Head Pains

a. Trigeminal Neuralgia

Paroxysmal 15–30-second burst of pain in distribution of trigeminal nerve (usually in maxillary or mandibular region). Manage with antiepileptic agents.

> **cram facts**
>
> New-onset headache in elderly patient requires ESR. Ipsilateral visual loss and contralateral neurological deficit indicates extracranial carotid disease.

b. Temporal Arteritis

- May begin with jaw claudication or polymyalgia rheumatica.
- Temporal pain.
- May cause vascular ischemia or blindness.
- Diagnosis—elevated erythrocyte sedimentation rate (ESR), temporal artery biopsy.
- Management—corticosteroids.

R. Cerebrovascular Disease

1. Stroke

Stroke is defined as sudden onset of focal neurologic impairment due to cerebrovascular disease. Usually due to arterial or arteriolar disease, but less commonly, may involve veins (venous sinus thrombosis).

Major Risk Factors for Stroke

- Hypertension.
- Cardiac disease.
- Dyslipidemia.
- Diabetes mellitus
- Bad lifestyle—smoking, alcohol, tobacco, illicit drugs.

Mechanisms of Stroke

Hemorrhagic

- Intracerebral.
- Subarachnoid.

Ischemic

- Cardiogenic cerebral embolism.
- Lacunar stroke.
- Atherothrombotic—extracranial, intracranial.
- Coagulopathy.
- Cryptogenic (no etiology identified).

When evaluating mechanism of cerebrovascular disease, consider Virchow's triad and vascular thrombosis.

- Abnormality of blood vessel wall (stenosis and plaque formation).
- Abnormality of blood flow (cardiac disturbance such as atrial fibrillation).
- Coagulation disorder (hypo- or hypercoagulable state).

In evaluating patients with sudden transient or persistent focal neurologic disorder, consider these mechanisms:

Vascular
- Hemorrhagic.
- Ischemic.

Electrical
- Epileptic—enhanced excitatory activity.
- Migraine—spreading cortical depression.

In stroke, there is sudden impairment of focal neurologic function, which rapidly reaches maximal severity.

Hemorrhagic Stroke

Symptoms
- Prominent headache.
- Vomiting.
- Seizure.
- Altered consciousness.

Etiology
- Hypertension most common.
- Berry aneurysm—causes SAH (Figure 7–5).
- Arteriovenous malformation (AVM).
- Coagulopathy (anticoagulant, thrombolytic agents).

► cram facts

Hypertension causes arteriolar disease and may lead to infarction or hemorrhage.

2. Hypertension

Lipohyalinosis and *fibrinoid degeneration* of arteriolar wall. Bleeding occurs from Charcot–Bouchard arteriolar aneurysms, *not* visualized by angiography.

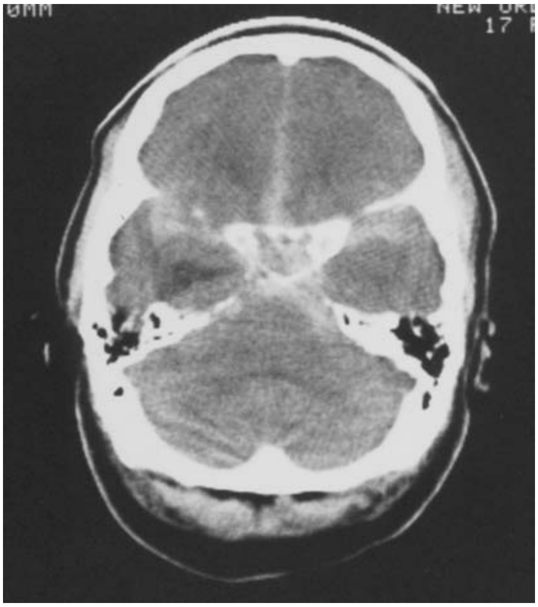


Figure 7–5. Subarachnoid hemorrhage. Blood is seen in the basal subarachnoid space.

Hypertensive Bleeding Locations

Putamen

- Hemiplegia > hemianesthesia.
- Horizontal gaze preference *away* from hemiplegia.

Thalamus

- Hemianesthesia may be more or equally prominent compared to hemiplegia.
- Visual field defect.
- Vertical gaze paresis.

Pons

- Coma.
- Central neurogenic hyperventilation.
- Quadriplegia with bilateral Babinski signs.
- Miotic but reactive pupils.
- Absent horizontal eye movements.
- Gait ataxia.
- Dysmetria.

► cram facts

CT is most definitive study to demonstrate intracerebral hemorrhage.

Diagnosis of intracerebral hemorrhage (ICH) is definitively established by CT. MRI is best for ischemia and diffusion weight imaging MRI can determine if ischemia is acute (Figure 7–6). If patient is not hypertensive, angiography is necessary to try to demonstrate aneurysm or vascular malformation.

3. Berry Aneurysm

- Due to *congenital* weakness in media of blood vessel wall.
- Location occurs at arterial branching points:
  - Anterior cerebral–anterior communicating.
  - Internal carotid–posterior communicating.
  - Vertebral–basilar junction.
  - Trifurcation of middle cerebral artery.
- Symptoms of ruptured aneurysm:
  - Sudden severe, new-onset headache.
  - Thunderclap (sudden headache of maximal severity at onset).
  - Meningeal irritation: Stiff neck, Kernig's sign, Brudzinski's sign, focal neurologic sign (occur only if hemorrhage extends into brain parenchyma or compresses neural structures, e.g., cranial nerves)
- If internal carotid–posterior communicating artery (ICA-PCoA) aneurysm enlarges, it may compress oculomotor nerve.

Symptoms of ICA-PCoA Aneurysm

- Droopy eyelid.
- Diplopia.

Signs

- Ptosis.
- Impaired medial, superior, and inferior eye movement.
- Fixed and dilated pupil.

Diagnosis of Ruptured Aneurysm

- CT may show blood in subarachnoid space.
- MRI rarely positive for blood.
- LP always shows red blood cells or xanthochromic.
- Angiogram shows arterial aneurysm sac.

Treatment

- Surgical clipping of aneurysm to prevent bleeding recurrences.
- Twenty percent of patients have multiple aneurysms.

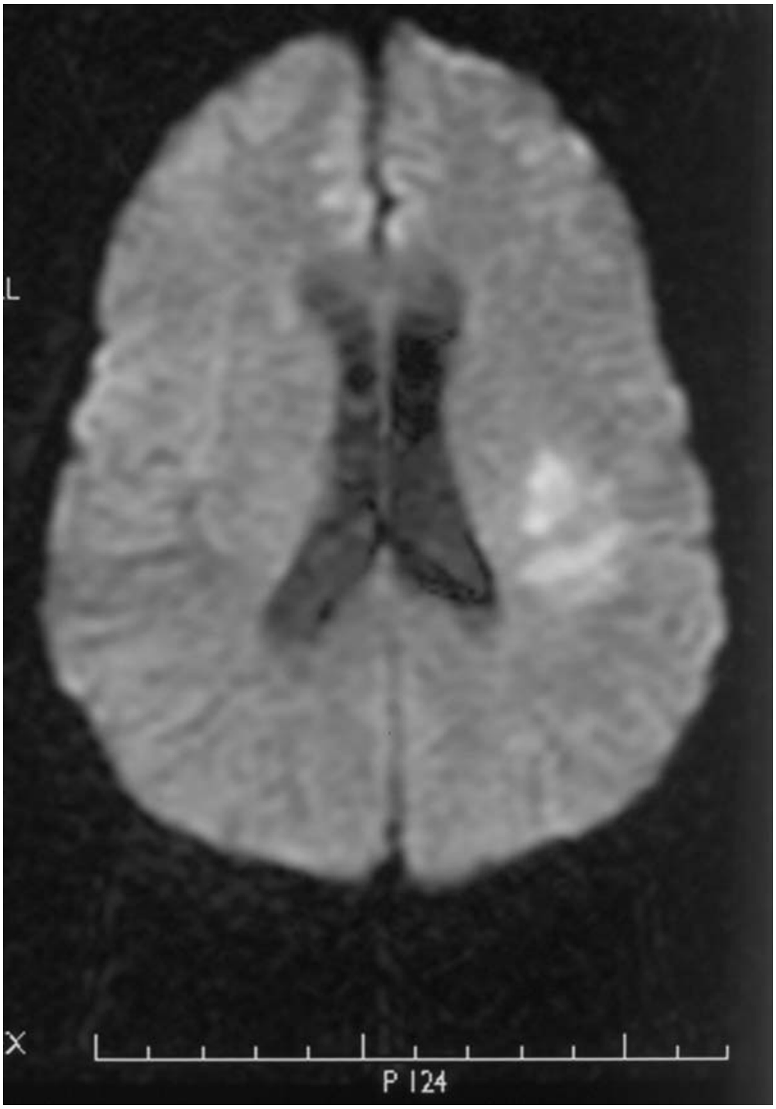


Figure 7–6. Acute ischemic lesion. Diffusion-weighted MRI shows hyperacute left subcortical bright ischemic lesion.

S. Arteriovenous Malformation

- Congenital.
- Abnormal arteries and veins with poorly formed capillary network.
- Bleed into subarachnoid or intracerebral space.
- Present as hemorrhagic stroke with symptoms and signs dependent on location.

Diagnosis

- CT shows bleeding if ICH or SAH occurred.
- LP positive if bleeding has occurred.
- Angiography shows abnormal vessels.

Treatment—Excision of abnormal blood vessels to prevent further bleeding.

► cram facts

Hypertension leads to arteriolar aneurysm; berry aneurysms cause SAH.

T. Stroke

1. Ischemic Stroke

- Asymptomatic as determined by presence of cervical bruit.

- Transient reversible defect as indicated by TIA (transient ischemic attack).
- Persistent fixed major stroke.

2. Asymptomatic

By auscultating over carotid artery in neck, abnormal sound (bruit, murmur) may be appreciated. This indicates flow is turbulent and not laminar. Carotid duplex is necessary to determine if turbulent flow is due to carotid stenosis. The degree of stenosis is best determined by conventional catheter angiogram. If stenosis is 60%, carotid endarterectomy is warranted.

3. Transient Ischemic Attack (TIA)

Sudden onset of *focal* neurologic *deficit,* which resolves within 24 hours; however, 90% resolve within 60 minutes. This "mini-stroke" may be harbinger of major stroke. Clinician must delineate the cause of focal reduction in blood flow to prevent fixed major disabling stroke.

If there is atheroma and stenosis of extracranial carotid, carotid endarterectomy (CEA) is warranted, or treatment with antiplatelet agents is initiated. If there is arteriolar disease (lipohyalinosis, fibrinoid degeneration) due to hypertension, characteristic clinical syndrome (pure motor hemiparesis, pure sensory stroke, dysarthria, clumsy hand syndrome) with small deep infarct visualized by CT/MRI and *negative* angiogram (arterioles are beyond resolving capability of angiogram), diagnosis is established and this indicates hypertensive vascular disease. If there is "red clot" originating from the heart (e.g., atrial fibrillation), anticoagulation is warranted.

4. Acute Stroke

If focal deficit does not resolve in 60 minutes, and CT shows no evidence of hemorrhage or nonvascular lesion, consider thrombolytic (tPA) therapy. This must be administered within 3 *hours* of *onset* of neurologic deficit. Blood pressure must be carefully controlled or brain hemorrhage may be precipitated by thrombolytic agents; therefore, initial and immediate noncontrast CT scan is necessary as are laboratory studies to exclude hypocoagulable state (hemoglobin, platelet count, prothrombin time). If CT shows no hemorrhage and there are no laboratory abnormalities and stroke features are not resolving, intravenous tPA should be administered. Thrombolytics should not be combined with other antiplatelet or antithrombotic (anticoagulant) medication for initial 24 hours. The goal of treatment is to reperfuse the tissue supplied by the occluded vessel. Neuroprotection strategies to prevent the triggering of the ischemic cascade are not helpful; however, avoidance of seizures, hyperglycemia, hyperthermia, low oxygen, and elevated carbon dioxide tensions may prevent further neurologic deterioration. Because the brain swelling is due to cytotoxic edema (energy failure), this is not likely to respond to conventional therapy for cerebral edema. If the patient does not meet the temporal profile for tPA, anticoagulation or antiplatelet medication should be considered to prevent recurrent stroke. Blood pressure lowering in acute ischemic stroke is controversial, as this may lower perfusion pressure and worsen neurologic deficit. If atrial fibrillation is the cause of the stroke, anticoagulation should be initiated.

If CT shows ICH, these steps should be initiated:

- If hemorrhage occurs in cerebral cortex, consider nonhypertensive etiology including vascular malformation (aneurysm, AVM) or medical–hematologic disorder.

► cram facts

Thrombolytic therapy is utilized in ischemia stroke if patient has been symptomatic less than 3 hours.

- If lesion occurs in cerebellum, hematoma evacuation is indicated to prevent secondary brain stem compression. Hematomas at other sites of hypertensive etiology may be evacuated but these usually recur.
- Treatment of surrounding *vasogenic* edema (due to impaired blood–brain barrier) may be effective and lowering of elevated blood pressure may limit hematoma size.

U. Hypertensive Encephalopathy

When the upper limit of cerebral autoregulation is exceeded and systolic blood pressure exceeds 240 mm Hg and diastolic exceeds 140 mm Hg, encephalopathy with signs of nonfocal generalized neurologic dysfunction (confusion, seizures) occur. CT shows no signs of hemorrhage or ischemia infarction. Treatment mandates lowering of blood pressure with parenteral, short-acting, and easily controllable agents, such as sympathetic blocking agent (labetalol) or blood vessel dilating agent (nitroprusside).

The Renal System and Urology

8

I. NORMAL PROCESSES

A. Embryonic Development, Fetal Maturation, and Perinatal Changes

1. General

- Genitourinary (GU) system arises from mesoderm and endoderm (see Table 8–1).
- Genital and urinary systems are closely related embryologically.

2. Kidney

- Develops progressively as three distinct entities: pronephros, mesonephros, and metanephros.
- Ipsilateral vas and kidney both arise from the mesonephric duct.
- Fetal kidney can reliably be detected at 15 weeks of gestation.
- Renal agenesis results in pulmonary hypoplasia with decreased airway branching.
- Glomeruli and tubules arise from metanephric blastema.
- Ureter, pelvis, and collecting ducts arise from the mesonephric duct.

a. Pronephros

- Earliest stage in humans.
- Consists of 6–10 pairs of tubules.
- Connects to pair of ducts that open into cloaca.
- Vestigial structure—disappears by 4th week of embryonic life.

8-1

MALE AND FEMALE GENITOURINARY ANALOGS

Embryonic Structure	Male	Female
Mesonephric (wolffian) duct	Ureter	Ureter
	Renal pelvis	Renal pelvis
	Collecting duct	Collecting duct
	Epididymis	Epoophoron
	Vas deferens	Gartner's duct
	Seminal vesicles	
	Ejaculatory ducts	
	Appendix epididymis	Vesicular appendage
	Paradidymis	
Paramesonephric (müllerian) duct	Appendix testis	Uterine tubes
	Prostatic utricle	Uterus
		Upper vagina
Müller's tubercle	Verumontanum	Hymen
Junction of sinovaginal bulb with UG sinus	Posterior urethral valves (when present)	Hymen
Urogenital sinus		
Ventral	Bladder	Bladder
	Supramontanal urethra not including the trigone	Entire urethra not including the trigone
Phallic	Inframontanal urethra	Vaginal vestibule
	Membranous urethra	
Genital tubercle	Penis	Clitoris
Urethral folds	Penile urethra	Labia minora
Genital swellings	Scrotum	Labia majora
Gubernaculum	Gubernaculum testicle	Ovarian ligament
		Round ligament
Genital glands	Testis	Ovary
Genital cords	Seminiferous tubules	Pfuger's tubes
	Prostate	Glands of Skene
	Cowper's glands	Bartholin's glands

b. Mesonephros

- Principal excretory organ during early embryonic life (4–8 weeks).
- Mesonephric tubules form Bowman's capsule.
- Distal ends connect to primary nephric duct (mesonephric duct), which connects to cloaca.
- Mesonephric duct forms male gonadal structures (see below).

c. Metanephros

- Originates from intermediate mesoderm and mesonephric duct.
- Development begins with a budlike outgrowth from the mesonephric duct (ureteral bud).
- Ureteral bud grows cephalad and into mesoderm (nephrogenic cord).
- Distal end of the metanephric duct connects to cloaca.
- Cephalic end of the ureteral bud becomes renal pelvis.
- Metanephric tissue forms increasing numbers of tubules that eventually form the nephron.
- Glomeruli are fully formed by 36th week.

3. Bladder and Urethra

- Blind end of the hindgut forms cloaca.
- Urorectal fold divides cloaca into ventral (urogenital [UG] sinus) and dorsal (rectum) portions—completed by 7th week.
- UG sinus connects to mesonephric ducts.
- Trigone develops from mesoderm, the rest of the bladder from endoderm.
- UG sinus is divided at Müller's tubercle into a ventral (bladder) portion and a urethral (phallic) portion; ventral portion forms bladder, proximal urethra in males, and entire urethra in females; phallic portion forms part of the male urethra, lower one third of vagina, and the vestibule in the female.
- Bladder originally extends to the umbilicus, where it is connected to the allantois.
- By 15th week, allantois is obliterated at the level of the umbilicus.

4. Prostate

- Develops as multiple solid outgrowths of the urethral epithelium above and below the entrance of the mesonephric duct.
- Prostate glandular structures are endodermal (UG sinus), stroma is mesodermal.

5. Gonads

- Testis descends from the retroperitoneum into the scrotum guided by the gubernaculum; it carries the peritoneum with it as it descends, forming processus vaginalis.
- Ovary descends from the retroperitoneum into the pelvis; gubernaculum becomes the round ligament.
- Primordial germ cells: Endodermal in origin.

6. External Genitalia

- Genitalia are unisex (potential for either sex) until week 7–8.
- By 3 months, genitalia become recognizable as male or female.
- DHT (dihydrotestosterone) mediates male differentiation of the UG sinus structures.
- Testosterone mediates differentiation of wolffian structures.
- Male: Genital tubercle elongates to become phallus, urethral folds fuse forming penile urethra, genital swellings migrate caudally, meet and fuse forming scrotum.

- Female: Genital tubercle becomes the clitoris; urethral folds do not fuse, remaining separate and forming labia minora; genital swellings become labia majora.

B. Organ Structure and Function

1. Kidney

a. Anatomy

- Retroperitoneal organ surrounded by Gerota's fascia.
- From front to back, structures entering renal pelvis are renal vein, renal artery, and renal pelvis.
- Renal arteries are end arteries.
- Grossly divided into cortex, medulla, calyces, and pelvis.
- Nephron is the functional unit (consisting of glomerulus with its afferent and efferent arteries, Bowman's capsule, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting duct).

> **► cram facts**
>
> Renal arteries are end arteries.

b. Function

- Excretion of wastes.
- Acid–base balance.
- Fluid/free water balance.
- Regulation of blood pressure.
- Vitamin D metabolism.
- Erythropoetin production.

2. Ureters

a. Anatomy

- Paired retroperitoneal organs connecting renal pelvis to bladder.
- Lined by transitional epithelium.
- Blood supply arises from (proximal to distal) renal, internal spermatic/ovarian, common iliac, internal iliac, and vesical arteries.

> **► cram facts**
>
> Sympathetics promote storage; parasympathetics promote emptying,

b. Function—Drainage of urine from kidney to bladder.

3. Bladder

a. Anatomy

- Hollow organ divided into several parts: Dome, body, neck, and trigone.
- Median umbilical ligament (obliterated urachus) connects the dome of the bladder to the umbilicus.
- Lined with transitional cell epithelium.
- Blood supply: Superior, middle, and inferior vesical arteries.
- Sympathetic fibers promote storage; parasympathetics promote emptying.

b. Function—Storage and release of urine.

4. Urethra

a. Male Urethra

- Divided into four segments: Pendulous, bulbar, membranous, and prostatic.
- Distal portion is covered by squamous epithelium, the rest by transitional epithelium.
- Blood supply: Internal pudendal artery.
- Lymphatic drainage: Inguinal lymph nodes (distal urethra) and pelvic lymph nodes (proximal urethra).

b. Female Urethra

- Squamous epithelium lines the distal one third, transitional lines the rest.
- Blood supply: Internal pudendal, inferior vesical, and vaginal arteries.
- Lymphatic drainage: Inguinal (distal urethra) and pelvic (proximal urethra) lymph nodes.

5. Testis

a. Anatomy

- Surrounded by tunica vaginalis.
- Seminiferous tubules converge at the mediastinum and drain into the epididymis.
- Histology: Sertoli cells, Leydig cells, spermatogenic cells, stroma.

b. Function—Testosterone production and spermatogenesis.

6. Prostate

a. Anatomy

- Divided into four zones (peripheral, central, transitional, and anterior).
- Supported by puboprostatic ligaments.
- Perforated posteriorly by ejaculatory ducts, which empty through the veru montanum.
- Separated from rectum by Denonvilliers' fascia.
- Blood supply: Inferior vesical, internal pudendal, and middle rectal arteries.

b. Function—Seminal fluid production.

C. Renal Physiology

1. Glomerular Filtration and Hemodynamics

- Blood flow to kidneys is approximately 20% of cardiac output.
- Autoregulation occurs at 80–200 mm Hg—changes in blood pressure (BP) within this range produce only trivial changes in glomerular filtration rate (GFR).
- Approximately 20% of the plasma reaching the glomeruli is filtered into tubules.
- GFR is dependent on glomerular capillary pressure, Bowman's space pressure, glomerular colloid osmotic pressure, and colloid osmotic pressure of the filtrate.
- Normally, proteins are not filtered—colloid osmotic pressure of the filtrate negligible.
- Inulin is cleared solely by GFR; therefore, inulin clearance = GFR.

> **► cram facts**
>
> Inulin clearance = GFR.

2. Tubular Reabsorption and Secretion

- Ninety-nine percent of glomerular filtrate (180 L/day) is reabsorbed in the renal tubules.
- "Fine-tuning" of urine composition occurs in the distal nephron.

a. Proximal Convoluted Tubule

- Reabsorbs approximately 60–70% of the glomerular filtrate.
- Reabsorption is isosmotic and is driven primarily by Na-K-ATPase pump.
- Almost all filtered glucose and amino acids and 70% of Na are reabsorbed in this segment.

b. Loop of Henle

- Fluid entering the loop is isotonic to plasma.
- The ascending loop is impermeable to water.
- Sodium is reabsorbed in the ascending loop by the Na-K-Cl co-transporter, leading to a decrease in fluid osmolality as it exits the loop and accumulation of solute in the medulla.

c. Collecting Duct

- Composed of two types of cells: Principal and intercalated.
- Arginine vasopressin (AVP) increases the permeability of principal cells to water.
- Reabsorption of Na occurs via Na-K-ATPase.
- Aldosterone increases Na absorption and K secretion in the collecting duct.
- Atrial natriuretic peptide (ANP) decreases Na reabsorption in this segment by decreasing the number of open Na channels.

3. Urinary Concentration and Dilution

- Vasopressin increases permeability of the collecting duct to water.
- Isosmotic absorption of solute occurs in the proximal tubule.
- Descending limb of loop of Henle: H_2O diffuses from the lumen into hypertonic interstitium.
- Ascending limb of loop of Henle: Low permeability to H_2O and active transport of Na, K, and Cl out of the lumen.

4. Renal Mechanisms in Acid–Base Balance

- Majority of filtered HCO_3 (80%) is reabsorbed in the proximal convoluted tubule.
- Carbonic anhydrase catalyzes breakdown of H_2CO_3 into H_2O and CO_2, which is then reabsorbed.
- For each H^+ ion secreted with urinary buffers, a new HCO_3 ion is generated and reabsorbed.
- Mechanisms of H^+ excretion into tubular lumen: Exchange of H^+ for Na^+ and H^+-ATPase .
- Majority of H^+ is secreted in the proximal tubule.
- In the collecting tubule, H^+ is excreted via the H^+ pump.
- Net acid excretion = titratable acidity + urinary NH_4 − urinary HCO_3.
- Titratable acid = 80% phosphate and 20% urate, citrate, etc.
- NH_4 participates in acid excretion, NH_3 combines with H^+ in the lumen.

► cram facts

Net acid excretion = titratable acidity + urinary NH_0 - urinary HCO_3

5. Renal Mechanisms in Body Fluid Homeostasis

- Osmoreceptors sense serum osmolality and regulate antidiuretic hormone (ADH) production.
- ADH increases water reabsorption in the collecting duct, leading to water conservation.
- Aldosterone increases Na absorption in the kidney, leading to concomitant water resorption.
- Aldosterone production is regulated via the renin–angiotensin system.

6. Micturition

- Afferent fibers from bladder wall activate the sacral center in response to filling.
- Sacral micturition center controls detrusor contraction, bladder neck opening, and sphincteric relaxation.
- Micturition reflex is an automatic spinal cord reflex, but it can be facilitated or inhibited by the pontine micturition center and cerebral cortex centers.

7. Renal Metabolism and Oxygen Consumption

- Kidney exhibits aerobic metabolism.
- Metabolic substrates: Lactate, glutamine, glucose, free fatty acids, citrate, and ketone bodies.
- Cortex utilizes aerobic metabolism, medulla—anaerobic or aerobic glycolysis.
- Active ion transport is mediated by membrane ATPases—mitochondrial oxidative phosphorylation is used to generate ATP.

8. Hormones Produced by the Kidney

Renin, erythropoietin, calcitriol.

9. Hormones Acting on the Kidney

a. Renal Vasoconstrictors—Angiotensin II, norepinephrine, endothelin, ADH, leukotrienes, lipoxins, platelet-activating factor, growth factors.

b. Renal Vasodilators—Endothelium-derived relaxing factor (NO), prostaglandins, histamine, bradykinin, acetylcholine, glucocorticoids, insulin, insulin-like growth factor, calcitonin gene–related peptide, cyclic adenosine monophosphate (AMP).

c. Other Hormones and Vasoactive Substances—Natriuretic peptides, parathyroid hormone, purine nucleotides.

II. ABNORMAL PROCESSES

A. Genetic Disorders

1. Alport's Disease (Hereditary Nephritis)

► Description and Symptoms

- Most common form—X-linked dominant.
- Characterized by hematuria, impaired renal function, sensorineural deafness, and ocular abnormalities (cataracts most common).
- Females usually asymptomatic; most males develop renal insufficiency between 20 and 30 years of age.

► Diagnosis

Urinalysis (hematuria), strong family history, audiometry (positive in 50%), creatinine elevated, renal biopsy, and immunofluorescent microscopy.

► Pathology

Involves mutation of a gene encoding the α_5 chain of type IV collagen.

► Treatment Steps

1. Supportive care.
2. Renal transplantation if renal failure occurs.

2. Thin Basement Membrane Disease (Benign Familial Hematuria)

► Description and Symptoms

- Autosomal dominant inheritance.
- Most patients asymptomatic, no extrarenal manifestations.
- Benign course; very few patients develop renal failure.

► cram facts

Thin basement membrane disease: no extrarenal manifestations.

► Diagnosis
Family history, urinalysis (hematuria), renal biopsy (rule out other causes).

► Pathology
Diffuse thinning of the glomerular basement membrane.

► Treatment Steps
No therapy required.

3. Polycystic Kidney Disease (PKD)
Can be autosomal recessive (ARPKD) or autosomal dominant (ADPKD).

► cram facts

ARPKD—neonates
ADPKD—adults

► cram facts

ADPKD—cerebral ("berry") aneurysms

a. ARPKD (Figure 8–1)

► Description and Symptoms
- More severe than ADPKD.
- Patients diagnosed prenatally or neonatally.
- Usually results in early renal failure and death in infancy.
- Symptoms related to large kidney size and renal insufficiency.

► Diagnosis
Renal ultrasound (US) reveals massively enlarged kidneys with many tiny cysts.

► Pathology
Diffuse cystic dilatation of collecting tubules.

► Treatment Steps
Treat complications, supportive care only.

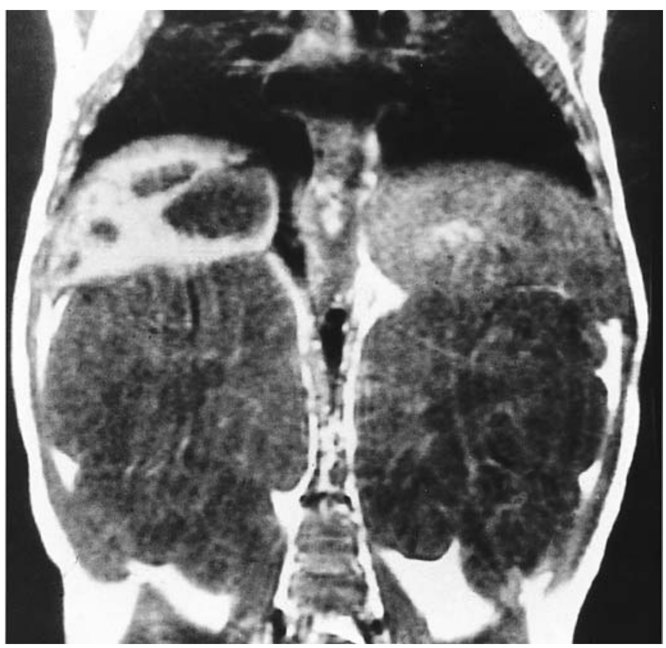


Figure 8–1. CT appearance of autosomal recessive polycystic kidney disease (ARPKD). Note the presence of dramatically enlarged kidneys and multiple tiny cysts.

b. ADPKD (Figure 8–2)

► Description and Symptoms
- Most common form of cystic kidney disease.
- Symptoms and signs: Hypertension (HTN), hematuria, bilateral flank masses, early satiety, and urinary tract infections (UTIs).
- Forty to fifty percent will have coexistent cerebral (“berry”) aneurysms prone to rupture.
- One third will have hepatic cysts.

► Diagnosis

Renal US, abdominal computed tomography (CT).

► Pathology

Diffuse bilateral progressive cystic degeneration of renal parenchyma.

► Treatment Steps

Medical management of complications with eventual dialysis and/or renal transplantation.

B. Congenital Disorders

1. Horseshoe Kidney (Figure 8–3)

► Description and Symptoms
- Most common type of renal fusion.
- Often associated with other urogenital anomalies.
- One third of patients asymptomatic.
- Symptoms related to hydronephrosis, infection, and stones, not horseshoe kidney per se.

► Diagnosis

CT, intravenous pyelogram (IVP).

► Pathology

Crossed fusion of two kidneys.

► Treatment Steps

Treatment not necessary in asymptomatic individuals unless evidence of significant obstruction is present.

Figure 8–2. CT appearance of autosomal dominant polycystic kidney disease (ADPKD). Multiple bilateral large cysts are appreciated.

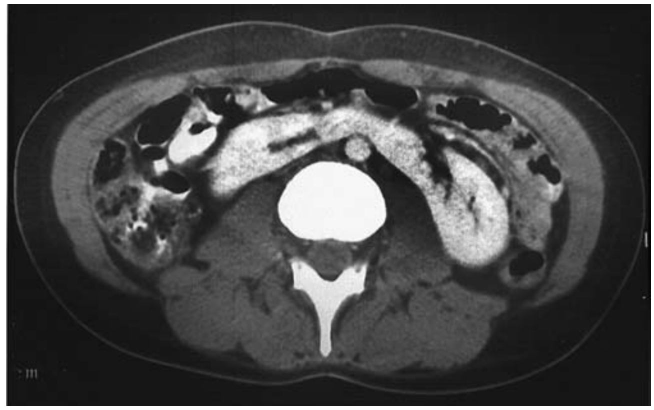


Figure 8–3. CT appearance of a horseshoe kidney. A bridge of tissue (isthmus) connecting the lower poles of both kidneys over the spine is visualized.

2. Medullary Sponge Kidney

► Description and Symptoms

- Congenital dilatation of the renal collecting ducts due to tubular ectasia or dysplasia.
- Leads to urinary stasis and nephrocalcinosis; increases likelihood of UTIs.
- Usually asymptomatic, unless renal colic due to urolithiasis.

► Diagnosis

IVP (shows pyramidal cavities filled with contrast material and/or stone material).

► Pathology

Ectasia and dysplasia of the collecting ducts leading to urinary stasis.

► Treatment Steps

Treatment indicated only for UTIs and urolithiasis.

C. Infectious Disorders

► **cram facts**

Bacterial cystitis: *Escherichia coli* most common pathogen.

1. Bacterial Cystitis

► Description and Symptoms

- Can be chronic (persistent or recurrent) or acute.
- More common in females.
- *Escherichia coli* is the most common pathogen.
- Symptoms: Frequency, urgency, dysuria, malodorous/cloudy urine, low back/suprapubic pain.

► Diagnosis

- Urinalysis and urine culture (gold standard).

► Pathology

Ascent of bacteria from distal urethra.

► Treatment Steps

Antibiotics (empiric or directed).

2. Urethritis

► Description and Symptoms

- Usually sexually transmitted.
- Symptoms: Urethral discharge, dysuria, frequency, urgency.

► Diagnosis

History, Gram stain and culture of urethral swab or discharge.

► Pathology

Inoculation of organisms into urethra during sexual intercourse. Most common pathogens: *Chlamydia trachomatis* (40%), *Ureaplasma urealyticum* (30%), *Neisseria gonorrhoeae* (25%), *Trichomonas vaginalis* (5%).

► Treatment Steps

Antibiotics (empiric or directed).

3. Acute Pyelonephritis (Figure 8–4)

► Description and Symptoms

- Bacterial infection of renal parenchyma.
- Symptoms: Chills, fever, flank pain, malaise, dysuria, pyuria, frequency, urgency.

► Diagnosis

Physical exam (costovertebral tenderness), urinalysis (pyuria), urine cultures, and complete blood count (CBC) (increased WBC with a left shift).

► Pathology

- Usually results from bacterial ascent from the lower urinary tract, hematogenous route is rare; *E. coli* and other Enterobacteriaceae account for over 90% of ascending infections; *Staphylococcus aureus* is more common in hematogenous infections.

► Treatment Steps

Intravenous and oral antibiotics (adjust according to sensitivities).

4. Acute Bacterial Prostatitis

► Symptoms

High fever, chills, low back and perineal pain, frequency, urgency, dysuria, urinary retention; malaise, myalgias, and arthralgias.

► cram facts

Acute pyelonephritis: *E. coli* and other Enterobacteriaceae more common in ascending infections; *Staphylococcus aureus* in hematogenous infections.

Figure 8–4. CT appearance of acute pyelonephritis involving the left kidney. The left kidney appears enlarged and shows decreased contrast enhancement as compared to the normal right kidney.

► Diagnosis
Tender, swollen prostate on digital rectal examination (DRE); urinalysis (increased WBC), urine culture, and blood culture.

► Pathology
Most commonly secondary to ascent of bacteria from urethra; hematogenous route is rare; *E. coli* most common organism.

► Treatment Steps
Quinolone antibiotics for 4–6 weeks (adjust according to sensitivities).

D. Inflammatory Disorders

Interstitial Nephritis (IN)

► Description and Symptoms
- Inflammatory disorder of renal interstitium and tubules that may result in acute renal failure.
- Can be secondary to infection, drug use (analgesics, antibiotics, etc.), metabolic causes (oxalate nephropathy, hypercalcemic nephropathy), heavy metal ingestion, obstructive uropathy, etc.
- Early stages are asymptomatic, late stages manifest with fever, maculopapular rash (in drug-induced IN), arthralgias, HTN, malaise, nausea, vomiting, and other uremic symptoms.

► Diagnosis
- Clinical history (history of drug ingestion, etc), urinalysis (WBC, RBC, WBC casts, eosinophils, proteinuria), CBC (peripheral eosinophilia), serum creatinine (elevated), and kidney biopsy in select patients.

► Pathology
Results from both humoral and cell-mediated hypersensitivity reactions mounted against a hapten–protein complex; microscopy: interstitial infiltrates of mononuclear cells, edema, and eosinophils.

► Treatment Steps
Withdraw causative agent, acute dialysis if necessary; supportive care and metabolite management; corticosteroids.

E. Immunologic Disorders

1. Acute Transplant Rejection

► Description and Symptoms
- Most frequent in the first 3 months following transplant.
- Both cellular and humoral components are responsible, but T-cell response is the most important factor.
- Twenty-five to thirty percent of patients will have at least one episode of acute rejection following transplantation.
- Symptoms: Fever, graft tenderness, malaise; can be completely asymptomatic.

► Diagnosis
Physical exam (graft tenderness), serum creatinine (elevated), graft biopsy, renal US (to rule out other causes).

► Pathology
- Helper T cells are stimulated by allograft's foreign antigens (HLA).
- Interleukin-2 (IL-2) production.

- CD8+ cytotoxic T-cell stimulation.
- Graft destruction; histologic changes: infiltration of the interstitium with mononuclear cells and invasion of the tubular basement membrane and vessels with lymphocytes.

► Treatment Steps

High-dose steroids, OKT3 (murine monoclonal antibody specific for the CD3 portion of the T lymphocyte–receptor complex).

2. Chronic Transplant Rejection

► Description and Symptoms

- Gradual, progressive loss of renal function (usually occurs over a period of years).
- Usually asymptomatic, signs include HTN, proteinuria, worsening azotemia.

► Diagnosis

Urinalysis (proteinuria), serum creatinine (elevated), renal biopsy.

► Pathology

Most likely secondary to combination of immunologic (repetitive subclinical acute rejection) and nonimmunologic (hyperfiltration injury) factors; microscopy: glomerulosclerosis, tubular atrophy, interstitial fibrosis, and small vessel obliteration.

► Treatment Steps

No specific therapy at present; optimize immunosuppression and manage HTN.

3. Immunoglobulin A (IgA) Nephropathy (Berger's Disease)

► Description and Symptoms

- Most common form of glomerulonephritis (GN).
- Occurs most frequently in the second or third decade with 3:1 male predominance.
- Typically occurs following an upper respiratory infection.
- No symptoms.
- Progresses slowly to chronic renal failure (CRF).

► Diagnosis

Urinalysis (microscopic hematuria and proteinuria), renal biopsy.

► Pathology

Immunofluorescent microscopy: Deposition of IgA in the glomerular mesangium.

► Treatment Steps

Corticosteroids for patients in ARF, no effective treatment for slowly progressive disease.

4. Goodpasture's Disease

► Description and Symptoms

- Immune hypersensitivity disorder—cause unknown.
- Lung involvement common.
- Symptoms and signs: Hemoptysis, dyspnea, renal failure, hematuria, proteinuria.

► cram facts

IgA nephropathy occurs after upper respiratory infection.

► cram facts

IgA nephropathy: deposition of IgA in glomerular mesangium.

► cram facts

Goodpasture's disease: antibody-mediated (type II hypersensitivity) renal disease; linear antibody deposition in GBM.

► Diagnosis

Renal biopsy, antiglomerular basement membrane antibodies, urinalysis (hematuria), CXR.

► Pathology

- Cytotoxic antibody-mediated (type II hypersensitivity) renal disease.
- Renal damage caused by linear deposition of antibody specific for type IV collagen of the glomerular basement membrane (GBM).
- Microscopy: Epithelial cell crescents, glomerular adhesions, interstitial inflammatory exudates.
- Immunofluorescence: Linear deposition of immunoglobulin and complement in the GBM.

► Treatment Steps

1. Supportive respiratory measures.
2. Hemodialysis.
3. High-dose corticosteroids.
4. Cyclophosphamide.
5. Plasmapheresis to remove circulating antibodies.

F. Glomerular Disorders

1. Nephrotic Syndrome

► cram facts

Nephrotic syndrome = increased glomerular permeability to protein. Nephritic syndrome = hematuria.

► Description and Symptoms

- Results from increased glomerular permeability to protein.
- More prevalent in children.
- Characterized by proteinuria (> 3.5 g/24 hr), hypoalbuminemia, hypercholesterolemia, and peripheral edema (with or without anasarca).
- Symptoms: Frothy urine, anorexia, malaise, edema, and muscle wasting.

► Diagnosis

Urine dipstick (proteinuria), 24-hour urine collection (> 3.5 g of protein/24 hr is diagnostic), serum albumin (< 3.5 g/dL), renal biopsy.

► Pathology

Failure of size- and charge-selective barrier leading to leakage of protein molecules.

► Treatment Steps

1. Supportive therapy.
2. High-protein, low-fat, and low-cholesterol diet.
3. Hypolipidemic drugs.
4. Angiotensin-converting enzyme (ACE) inhibitors.
5. Salt restriction with or without diuretics.

2. Nephritic Syndrome

► Description and Symptoms

- Characterized by hematuria, HTN, renal insufficiency, and edema.
- Progresses to nephrotic syndrome and/or ESRD in 30–80% depending on etiology.

► Diagnosis

Urinalysis and urine microscopy (RBC casts, proteinuria), renal biopsy, serum antistreptolysin-O (elevated in postinfectious GN), blood urea nitrogen (BUN) and creatinine (elevated).

► Pathology

Diffuse inflammatory changes in the glomeruli; epithelial cell hyperplasia and epithelial crescents; immunofluorescence may show immune complex deposition (in postinfectious GN).

► Treatment Steps

1. Antimicrobial therapy if infectious etiology present.
2. Treat HTN and hypervolemia if present.
3. Dialysis.

G. Traumatic and Mechanical Disorders

Obstructive Uropathy

► Description and Symptoms

- Acute obstruction produces pain; chronic, slowly progressing obstruction may be completely asymptomatic.
- Etiologies: Kidney stones, strictures (urethral or ureteral), benign prostatic hypertrophy, prostate cancer, etc.
- Decreased urine output present in cases of bilateral upper tract or bladder outlet obstruction.
- Symptoms related to renal failure/insufficiency (malaise, nausea, HTN, etc.).

► Diagnosis

- Clinical history (anuria, flank pain).
- Urethral catheter passage (to rule out or treat bladder outlet obstruction).
- Serum creatinine (elevated).
- Imaging (renal US, IVP, CT scan, retrograde pyelography).

► Pathology

Obstruction leads to cellular atrophy, necrosis, and renal injury.

► Treatment Steps

Identification and relief of obstruction.

H. Neoplastic Disorders

1. Renal Malignancies (Figures 8–5 through 8–7)

► Description and Symptoms

- Types: Metastatic cancer, transitional cell carcinoma (TCC), renal cell carcinoma (RCC), sarcoma, etc.
- Tumors typically asymptomatic until large.
- Symptoms may include abdominal or flank pain, hematuria, weight loss, HTN, etc.
- Eighty percent of solid masses in the kidney are malignant.

► cram facts

Renal malignancies: Renal cell carcinoma most common.

► Diagnosis

CT scan.

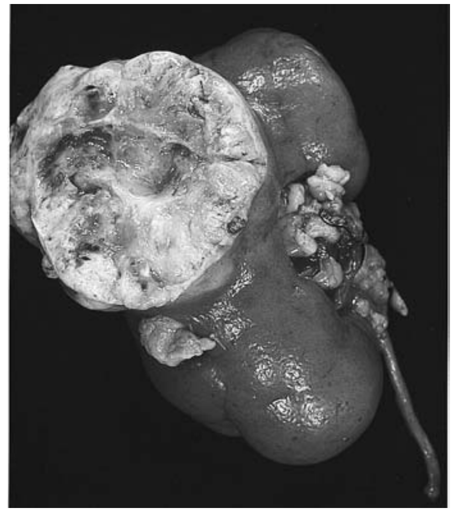
► Pathology

Microscopic appearance depends on cell type; RCC is the most common solid renal malignancy (90%).

► Treatment Steps

Surgical excision.

Figure 8–5. Surgical specimen of renal cell carcinoma of clear cell type.



2. Bladder Cancer (Figure 8–8)

► Description and Symptoms

- Second most common urologic malignancy (after prostate cancer).
- Predisposing factors: Smoking, occupational exposure to dyes, rubber industry, schistosomiasis, etc.
- Symptoms: Gross or microscopic painless hematuria and irritative voiding symptoms.

► Diagnosis

Urinalysis (hematuria), urine cytology (cancer cells), cystoscopy.

► Pathology

TCC most common (90%), followed by squamous cell carcinoma (8%), and adenocarcinoma (2%); as the depth of tumor invasion increases, the likelihood of metastatic disease increases as well.

► Treatment Steps

Surgical resection, chemotherapy for high-stage and metastatic cancers.

Figure 8–6. Filling defect in the right collecting system produced by transitional cell carcinoma of the right renal pelvis.

Figure 8–7. Gross pathologic appearance of transitional cell carcinoma of the upper pole of the kidney.

3. Prostate Cancer

► Description and Symptoms

- Most common cancer in American men; more common in African-Americans.
- Second most common cause of cancer death in males in the United States (after lung cancer).
- High-fat diet and cigarette smoking are predisposing factors.
- Most patients asymptomatic at diagnosis; symptoms frequently portend advanced disease.

► Diagnosis

DRE, prostate-specific antigen (PSA), prostate biopsy.

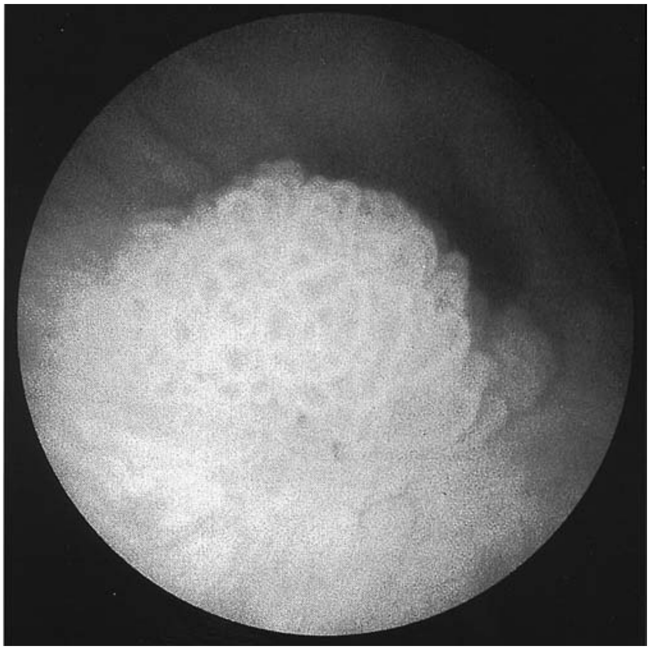


Figure 8–8. Cystoscopic appearance of transitional cell carcinoma of the urinary bladder. Note the characteristic papillary appearance.

► Pathology
Ninety-five percent are adenocarcinomas.

► Treatment Steps
External beam radiation therapy vs. brachytherapy (radioactive seed implantation) vs. hormonal therapy vs. cryotherapy vs. surgical removal.

4. Urethral Cancer

► cram facts

Urethral cancer: Chronic irritation and indwelling catheters—risk factors; SCC most common histologic subtype.

► Description and Symptoms
- More frequent in females.
- Chronic irritation, indwelling catheters, and infection are risk factors.
- Symptoms: Pain, hematuria, frequency, urgency, obstructive voiding symptoms, dyspareunia.

► Diagnosis
Retrograde urethrogram, urethroscopy, and biopsy.

► Pathology
Squamous cell carcinoma (SCC) is the most common histologic subtype.

► Treatment Steps
Surgical excision followed by chemotherapy if advanced disease.

5. Penile Cancer (Figure 8–9)

► Description and Symptoms
- Risk factors: Chronic inflammation, infection, human papillomavirus (HPV) infection, phimosis, smoking.
- Circumcision in infancy is protective.
- Symptoms: Penile pain, nonhealing penile ulcer/mass.

► Diagnosis
Physical exam (ulcerated fungating mass, ulcer) and biopsy.

► Pathology
> 95% of penile cancers are SCCs.

Figure 8–9. Invasive squamous cell carcinoma of the penis. Note the yellowish solid appearance of the tumor (right). On the left side normal corporal tissue is present.

► Treatment Steps

Surgical excision, laser therapy, fulguration, or chemotherapy with topical 5-fluorouracil.

6. Testicular Cancer (Figure 8–10)

► Description and Symptoms

- Most common solid tumor in young adult males.
- Ten percent of patients have a history of undescended testis (cryptorchidism).
- Symptoms: Testicular mass and/or testicular pain (uncommon).

► cram facts

Testicular cancer: Most common solid tumor in young adult males.

► Diagnosis

Physical examination and testicular ultrasound.

► Pathology

- Divided into germ cell (seminoma, embryonal cell carcinoma, teratoma, choriocarcinoma) and non–germ cell (Leydig cell, Sertoli cell, gonadoblastoma, and lymphoma) tumors.
- Seminoma is the most common subtype in young adults.
- Testicular lymphoma is more common in older adults (> 60 years old).

► Treatment Steps

Inguinal orchiectomy followed by watchful waiting, radiation therapy, or chemotherapy depending on cell type and stage of the tumor.

I. Metabolic and Regulatory Disorders

1. Acute Renal Failure (ARF)

► Description and Symptoms

- Abrupt decrease in the ability of the kidney to excrete waste products resulting in azotemia.
- Etiology may be prerenal (e.g., hemorrhage, dehydration, cardiogenic shock, hypotension), renal (e.g., acute tubular necrosis, acute interstitial nephritis), and postrenal (bilateral ureteral obstruction, bladder outlet obstruction).
- Symptoms: None in early stages; symptoms are secondary to azotemia and fluid overload in later stages.

► cram facts

Etiologies of ARF: Prerenal, renal, and postrenal.

Figure 8–10. Seminoma of the testicle surrounded by normal testicular tissue.

► Diagnosis

- History and physical.
- Serum creatinine, BUN (elevated).
- Urinalysis (eosinophils, WBCs, RBCs, casts).
- FENA (fractional excretion of sodium).
- Bladder catheterization if bladder outlet obstruction is suspected.
- Renal US (to rule out hydronephrosis).

► Pathology

Depends on etiology.

► Treatment Steps

1. Treat underlying condition.
2. Provide supportive care.
3. Dialyze as needed.

2. Chronic Renal Failure (CRF)

► Description and Symptoms

- Refers to progressive chronic irreversible loss of functioning nephrons, ultimately leading to ESRD.
- Most common etiologies: Diabetes mellitus, HTN, primary glomerular diseases (eg, glomerulonephritis), hereditary renal disease, and chronic infections.
- Symptoms: None in early stages; symptoms are secondary to azotemia in later stages.

► Diagnosis

- History and physical.
- Serum creatine and BUN (elevated).
- Renal US.
- Twenty-four-hour urine collection.
- Renal biopsy.

► Pathology

Depends on etiology.

► Treatment Steps

1. Correct reversible causes and electrolyte abnormalities.
2. Avoid nephrotoxic drugs.
3. Treat uremic symptoms.
4. Dietary measures.
5. Hemodialysis and transplantation in later stages.

J. Tubular Disorders

1. Fanconi's Syndrome

► Description and Symptoms

- Autosomal recessive tubular transport disorder.
- Combination of aminoaciduria, glucosuria, salt wasting, hypercalciuria, hypophosphatemia, proximal renal tubular acidosis (RTA), hypouricemia, and tubular proteinuria.
- No abnormalities apparent at birth—dwarfism and hypophosphatemic rickets later in life.
- Renal failure is rare.

► Diagnosis

Urinalysis, 24-hour urine collection, serum electrolytes and glucose, renal biopsy.

► Pathology

- Constellation of transport defects in the proximal tubule involving amino acids, monosaccharides, sodium, potassium, calcium, phosphate, bicarbonate, uric acid, and protein.
- Microscopy: "Swan-neck" deformity and cellular atrophy of the proximal tubule.

► Treatment Steps

Replace electrolytes (sodium, potassium, phosphate)and free water; correct acidosis.

2. Renal Tubular Acidosis (RTA)

► Description and Symptoms

- Impaired secretion of H^+ or resorption of bicarbonate ions leading to metabolic acidosis.
- Four subtypes exists (see below).

a. Types 1–3

- Associated with hypokalemia.
- Symptoms: Muscle weakness, hyporeflexia, paralysis, osteopenia, kidney stones.

b. Type 4

- Associated with hyperkalemia.
- Usually asymptomatic.

► Diagnosis

- Blood gas, serum electrolytes, and aldosterone.
- Acid load test: In type 1 RTA when ammonium chloride given PO, urine pH remains > 5.5.
- HCO_3 titration test: When HCO_3 is infused IV, in type 2 RTA HCO_3 will appear in the urine (pH > 6.5) before plasma HCO_3 reaches normal range.

► Pathology

- Type 1 (distal)—impaired hydrogen secretion in the distal nephron, urine pH is never < 5.5.
- Type 2 (proximal)—impaired reabsorption of HCO_3 in the proximal tubule.
- Type 3—combination of types 1 and 2—very rare.
- Type 4—aldosterone deficiency or unresponsiveness of the distal tubule to aldosterone.

► Treatment Steps

- Sodium bicarbonate or citrate salts, potassium supplementation.
- Type 4 RTA: Volume expansion and K-wasting diuretics; mineralocorticoid therapy if needed.

> ► **cram facts**
>
> Type 4 RTA is the only RTA type associated with hyperkalemia.

3. Nephrogenic Diabetes Insipidus

► Description and Symptoms

- Inability to concentrate urine due to lack of response of the renal tubules to ADH.
- Can be X-linked recessive or acquired.
- Symptoms: Polyuria, polydipsia, and severe dehydration.

► Diagnosis

Urine osmolality (usually 50–100 mOsm/kg)—hypotonic to serum; water deprivation test.

► Pathology

Normal production of ADH by pituitary, but nephron unresponsive.

► Treatment Steps

1. Increase free water intake.
2. Restrict Na.
3. Thiazide diuretics.

K. Disorders of the Collecting System

Urolithiasis (Figures 8–11 and 8–12)

► Description and Symptoms

- Calcium-containing stones are the most common (70%) followed by infectious stones (struvite) at 15–20%, uric acid stones at 5–10%, and cysteine stones at 1–5%.
- Symptoms: Sharp, intermittent colicky flank pain, hematuria, nausea, vomiting, fevers, chills, irritative voiding symptoms.

► Diagnosis

Plain x-ray, IVP, or noncontrast CT.

► Pathology

Crystal formation and aggregation when stone components in urine reach supersaturation levels; dehydration, obstruction, or foreign bodies promote stone formation; citrate and magnesium inhibit stone formation.

► Treatment Steps

Small stones (< 5–6 mm) should be managed conservatively (pain control, fluids); larger stones need surgical removal.

L. Vascular Disorders

Renal Artery Stenosis

► Description and Symptoms

- Atherosclerosis is the most common cause overall.
- Fibrous dysplasia is more common in younger women.
- Usually leads to renal insufficciency and/or HTN.
- Lumen must be decreased by 70% before stenosis will be hemodynamically significant.
- Usually asymptomatic.

► Diagnosis

- Physical examination (abdominal bruit).
- Captopril renal scan.

Figure 8–11. Radiographic appearance of bilateral renal calculi.

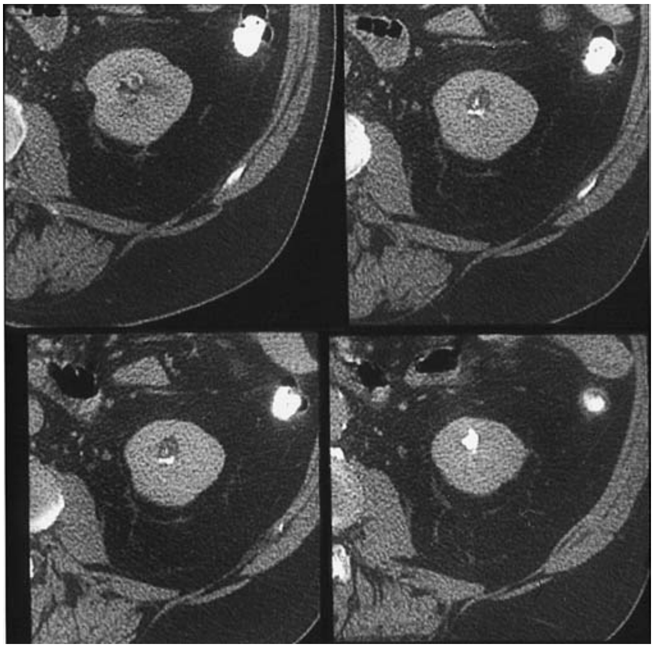


Figure 8–12. Noncontrast CT scan of a left renal calculus. Note its hyperdense (bright) appearance, which is similar to bone.

- Doppler US (duplex scan).
- Arteriography or CT angiography.

► Pathology

Stenosis lead to decreased blood flow and perfusion pressure within the kidney, which leads to stimulation of the renin–angiotensin system, resulting in HTN.

► Treatment Steps

Percutaneous angioplasty with or without stent placement; surgical bypass grafting.

M. Effects of Systemic Disease on the Kidney

1. Diabetes Mellitus (DM)

► Description and Symptoms

- Nephropathy is a common complication of DM, often resulting in ESRD.
- Poor DM control is a significant risk factor.
- Symptoms: None in early stages; uremic symptoms in late stages.

► Diagnosis

Urinalysis, 24-hour urine collection for protein, renal biopsy.

► Pathology

- Histology: Nodular intercapillary glomerulosclerosis.
- Pathogenesis: Hyperfiltration injury, intraglomerular HTN, and increased blood glucose.

► Treatment Steps

1. Control HTN.
2. Control blood sugar.
3. Treat UTI.
4. Transplant and dialysis for ESRD.

2. Hypertensive Nephropathy

► Description and Symptoms
- Progressive renal insufficiency/failure associated with chronic HTN.
- Symptoms: none.

► Diagnosis
- History and physical (HTN).
- Serum creatinine (elevated).
- Urinalysis.
- Twenty-four-hour urine collection (proteinuria).
- Renal US (small kidneys).
- Renal biopsy.

► Pathology
- Medial hypertrophy and fibroblastic intimal thickening cause vascular lumen narrowing, hyaline-like material deposition follows in the afferent arterioles.
- Microscopy: Global and segmental glomerulosclerosis.

► Treatment Steps

Tight control of blood pressure (keep diastolic BP < 90 mm Hg).

3. Systemic Lupus Erythematosus (SLE)

► Description and Symptoms
- Autoimmune disease; renal involvement common.
- More common in middle-aged females.
- Symptoms: Fevers, arthralgias, malar (butterfly) rash, photosensitivity, alopecia, serositis, etc.

► Diagnosis

Urinalysis (proteinuria, hematuria) and renal biopsy.

► Pathology
- Disease results from deposition of immune complexes in the kidney.
- Hematoxylin bodies (basophilic amorphous substance found in areas of necrosis).
- Immunoglobulin and complement deposits on immunofluorescent microscopy.

► Treatment Steps
1. Control blood pressure.
2. Corticosteriods.
3. IV cyclophosphamide.

III. PRINCIPLES OF THERAPEUTICS

A. Mechanisms of Action and Effects of Drugs Used for Treatment of Renal and Urinary System Disorders

► cram facts

Urolithiasis: Citrate and magnesium inhibit stone formation.

1. Diuretics

a. Carbonic Anhydrase Inhibitors (Prototype: Acetazolamide)
- Inhibit carbonic anhydrase in the proximal convoluted tubule.
- Diuresis is self-limiting secondary to bicarbonate depletion and decreased excretion.
- May lead to significant potassium wasting.

b. Osmotic Diuretics (Prototype: Mannitol)

- Filtered in the glomerulus but poorly reabsorbed.
- Osmotically prevent water from being reabsorbed.
- Most of the effect occurs in the proximal convoluted tubule.

C. Loop Diuretics (Prototype: Furosemide)

- Reduce or inhibit transport of Na, K, and Cl in the loop of Henle (ascending limb).
- Also induce Ca diuresis (useful in hypercalcemia).

d. Thiazide Diuretics (Prototype: Hydrochlorothiazide)

- Decrease NaCl transport in the distal convoluted tubule.
- Result in potassium wasting and increased reabsorption of calcium.

e. Potassium-Sparing Diuretics

Spironolactone

- Pharmacologic antagonist of aldosterone in the collecting duct.
- Causes increase in Na excretion and K reabsorption.
- May cause hyperchloremic metabolic acidosis and hyperkalemia.

Triamterene, Amiloride

- Inhibit Na influx and promote K reabsorption in the collecting tubule.
- Independent of aldosterone.
- May cause hyperkalemia.

2. Antidiuretics (Prototype: ADH, Desmopressin)

Facilitate water reabsorption in the collecting tubule by increasing its permeability to water.

3. Other Therapeutic Modalities

a. Dialysis

- Process of removing toxins directly from the blood (hemodialysis) or across the peritoneum (peritoneal dialysis) using diffusion across a semipermeable membrane or ultrafiltration.
- Helps excrete wastes but does not correct erythropoietin and calcitriol production.
- Indications for urgent dialysis: Uremic symptoms and signs, uremic encephalopathy, pericarditis, intractable metabolic acidosis, fluid overload, and life-threatening hyperkalemia.

b. Peritoneal Dialysis

- Dialysate is instilled into the peritoneal space and periodically drained and replenished.
- Readily adaptable to home use.
- Substance clearance is a function of peritoneal contact time.
- Major complication of peritoneal dialysis: Peritonitis.

c. Hemodialysis

- Blood is removed from the patient via a suitable vascular access and pumped to the membrane units.
- Most CRF patients require hemodialysis three times a week.
- Most membranes are made of cuprophane (regenerated cellulose).
- Dialysate delivery system mixes purified water with an electrolyte concentrate to approximate the chemical composition of extracel-

lular fluid (ECF), warms it to body temperature, and checks the conductivity to ensure that it is isotonic to the patient's blood.
- Treatment typically takes 3–5 hours and results in significant fluid shifts

d. Renal Transplantation

- Best treatment for renal failure.
- Restores metabolic functions (e.g., erythropoietic stimulation and calcium homeostasis).
- Offers excellent graft and patient survival rates.
- Kidney allografts are obtained from living relatives or cadavers.
- Tissue typing is performed prior to transplant to maximize success and graft survival.
- Lymphotoxic crossmatches are performed between donor lymphocytes and recipient sera to detect preformed cytotoxic antibodies.
- Chronic multidrug immunosuppression is required.

B. Effects of Drugs and Other Exogenous Substances on Renal Function

1. Drugs

- Human kidney has the highest blood supply/g and the largest endothelial surface area/g of all tissues; circulating agents are delivered at 50 times the rate as for other tissues
- Patients of advanced age, those with dehydration, or concomitant exposure to other nephrotoxins are particularly susceptible.
- Most common nephrotoxic agents: Aminoglycosides, amphotericin B, cyclosporine, cisplatin, methotrexate, etc.
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use can also negatively affect renal function.
- Salicylates have direct nephrotoxicity in overdose and a synergistic role in mixed analgesic nephropathy

2. Radiologic Contrast Agents

- Can cause acute tubular necrosis (ATN) or ARF.
- Chronic renal insufficiency/failure, advanced age, dehydration, DM, myeloma, CHF, solitary kidney are risk factors for renal complications.
- Renal failure usually occurs 1–2 days after exposure.
- Treatment is usually supportive.

3. Occupational and Other Environmental Risk Factors

- Heavy metals (arsenic, lead, mercury, bismuth) can cause ATN and ARF.
- Most heavy metals accumulate in the proximal nephron secondary to the presence of transport or binding sites.
- Cadmium, copper, gold, uranium, arsenic, and iron nephrotoxicity are prevalent.
- Lead poisoning most common.
- Chronic lead syndrome includes shrunken kidneys, uremia, hypertension, anemia with basophilic stippling, encephalopathy, peripheral neuropathy, and Fanconi's syndrome.

C. Psychosocial, Cultural, Occupational, and Environmental Considerations

1. Kidney Transplantation

- Recipients may have significant psychological issues (e.g., depression, anxiety).

- Pretransplant dialysis may trigger extreme mood swings secondary to electrolyte shifts.
- Donor should be carefully screened—rule out monetary or other financial gain.
- Cost of transplantation and dialysis to society is very high.
- There is a significant shortage of cadaveric organs.
- Transplant recipients require lifelong high-intensity care—compliance is key.

2. Chronic Renal Disease

- Chronic renal diseases span many years.
- Psychological/psychiatric problems common (e.g., depression, suicidality, etc.).
- Chronic renal conditions frequently require years of therapeutic, dietary, and lifestyle measures—compliance is paramount.

3. Environmental and Occupational Exposure

- Smoking is one of the biggest risk factors for TCC, RCC, and SCC of the penis.
- Exposure to heavy metals may cause renal failure.
- Industrial dyes, farm chemicals, and employment in rubber industry increase the risk of TCC.

Reproductive Health

9

I. NORMAL PROCESSES

A. Embryonic and Fetal Development, Conception to Delivery

1. Conventional Pregnancy Dating and Definitions

By convention and for practical purposes, menstrual or gestational age is computed as the number of weeks that have passed since the first day of the last menstrual period (LMP), assuming that the pregnant woman has a 28-day menstrual cycle length. Pregnancy is also frequently divided into **trimesters.** The normal human gestational period is around 40 weeks (280 days) from the last menstrual period, or 38 weeks (266 days) from fertilization (Table 9–1).

2. Fertilization

Day 1 occurs in the ampullary portion of the fallopian tube when a capacitated sperm penetrates the oocyte that has been extruded (ovulation) from a mature graafian follicle on the ovary's surface. The remaining graafian follicle becomes the corpus luteum. **Capacitation** causes changes in the sperm's surface characteristics that allow it to penetrate the oocyte's **corona radiata** and **zona pellucida.**

The oocyte and sperm cells form the male and female pronuclei, each with 23 chromosomes. These pronuclei duplicate their haploid DNA and combine their chromosomal material with each other to restore a full diploid compliment of DNA (46,XY or 46,XX) when the two-cell-stage zygote is formed (Day 2). Via a process termed *cleavage*, a series of mitotic divisions take place, causing a rapid increase in the number and decrease in the size of the cells in the zygote. The **morula** stage is reached after three to four divisions, at about 3 days postfertilization, when the zygote is about to enter the uterus. The morula has an inner cell mass (which will become the embryo) and an outer cell mass (which will become the placenta).

> ► **cram facts**
>
> Pregnancy tests detect the beta subunit of hCG (β-hCG) in the serum or urine.
>
> Because β-hCG is not produced until 6 days postfertilization, pregnancy is not detectable before more than 6 days postfertilization.

3. Week 1

At the time of entry into the uterus, the **blastocyst** is being formed from the morula, consisting of the **embryoblast** at one pole and the **trophoblast** (future placenta) flattened out to form the epithelial wall of the blastocyst. At this time, implantation into the endometrium (the inner surface of the uterus) begins. The blastocyst begins to produce **human chorionic gonadotropin (hCG)** around 6 days after fertilization.

4. Week 2

The cells of the embryoblast quickly differentiate into the embryonic disc, which consists of two layers, the endodermal germ layer and the ectodermal germ layer. The trophoblast differentiates into the inner cytotrophoblast layer (facing the embryoblast) and an outer syncytium layer (which becomes contiguous with the maternal endometrium at the beginning of implantation). The amniotic cavity begins to form between the embryonic disc and the trophoblast.

9-1

GESTATIONAL PERIODS
Zygote—fertilization to end of first week postfertilization
Embryo—first week to end of seventh week postfertilization
Fetus—eighth week to birth

During this time, the blastocyst continues implantation into the decidualized endometrium (decidua), and by the 11th to 12th day after fertilization it is completely embedded in the endometrial stroma. Trophoblasts invade the blood supply of the endometrium over the decidua basalis, forming lacunae of maternal blood, which go on to develop into the placenta. The blastocyst cavity, between the embryonic disc and the overlying cytotrophoblasts, lined by the extraembryonic endoderm, is called the *primitive yolk sac* (Figure 9–1). As the pregnancy grows, the decidua vera and the decidua capsularis join, eventually forming the fetal membranes. The uterine cavity is eventually obliterated (weeks 14–16).

5. Week 3

By day 16, the mesodermal layer of the embryonic disc has developed from the primitive streak between the endo- and ectodermal layers of the embryonic disc. It is from these three germ layers that all organs of the developing embryo eventually arise (Table 9–2). By the end of the third week after fertilization, the cephalic (head) and caudal (tail) ends of the embryo become distinct. The **notochord,** an extension of the primitive streak, develops and becomes the early support structure in vertebrates.

Neural folds develop from the ectoderm, while the underlying mesoderm develops into somites. In addition, the mesenchymal cells around the embryo condense to form the connecting stalk (future

► **cram facts**

Once the cephalad and caudad ends of the embryo have been formed at about 5 weeks after the LMP, they are detectable on ultrasound. The ultrasonic measurement between the cephalad and caudad ends of the embryo is called the crown–rump length; this measurement is used in the ultrasonic dating of early pregnancy.

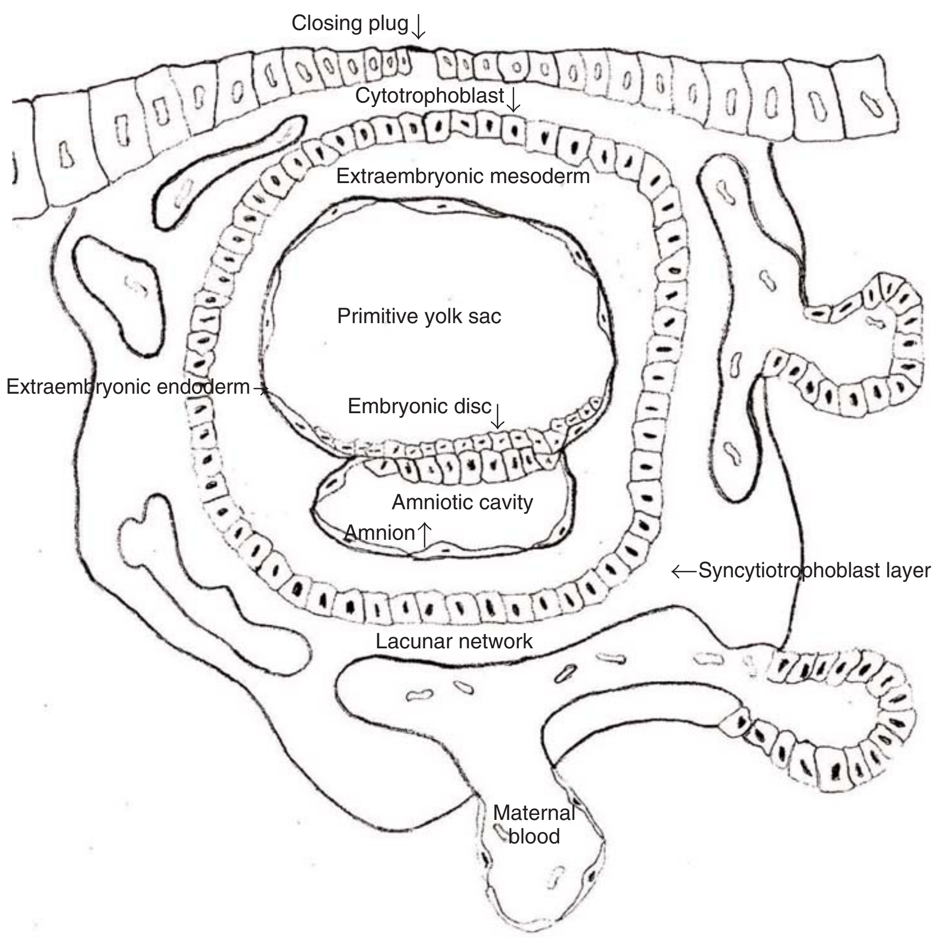


Figure 9–1. Embryo 12 days postfertilization.

9-2

GERM LAYER EVOLUTION

Endoderm	Mesoderm	Ectoderm
Gastrointestinal tract lining	Dermis	Nervous system
Liver	Skeleton	Epidermis
Pancreas	Connective tissue	
Thyroid	Vascular system	
	Urogenital system	
	Majority of skeletal and smooth muscle	

umbilical cord), which joins the developing embryo to the mesodermal layer (soon to be called the chorion) above the developing placenta.

► cram facts

Folic acid deficiency is related to neural tube defects. Since the neural tube forms very early in pregnancy, it is recommended that women who may become pregnant start to take folic acid supplementation prior to pregnancy to prevent neural tube defects.

6. Weeks 4–8

The neural groove closes at the beginning of the fourth week to form the neural tube. Somites continue to develop from the mesodermal layer and develop into the cardiovascular, urogenital, musculoskeletal, and subcutaneous skin tissues. The endodermal germ layer becomes the epithelial lining of the respiratory and gastrointestinal tracts and the bladder. Also, the endodermal layer forms the parenchyma of many glands including the pancreas, thymus, liver, tonsils, and thyroid and parathyroid glands.

While the cephalic end of the embryo is still far larger than the caudal end at the end of this period, by the end of week 8 (the end of the embryonic period) the body has developed to the point where the embryo (now known as a fetus) is identifiable as a human. Arms, legs, fingers, and toes are fully developed. By the end of the eighth week, all organ systems are formed and while the fetus grows in size, changes in shape are much less obvious.

7. The First Trimester

The first trimester is completed by the end of 12 weeks' gestation (10 weeks postfertilization). At this time the crown–rump length of the fetus is about 7 cm, and the uterus is palpable just above the symphysis pubis. By the end of the first trimester, the fetal head is about one-half of the crown–rump length. The early fetal bones are becoming calcified, and nails are present on fingers and toes. Fetal movement can be seen on ultrasound by the mid first trimester, and external sexual organ differentiation can begin to be seen at the end of the first trimester.

8. The Second Trimester

By the end of 20 weeks' gestation the fetus has grown rapidly in length, reaching about 15 cm crown–rump length (which is roughly half to one-third of the average length of a full-term newborn). However, the weight of the fetus is only about 500 g (less than one-sixth of the average 3,400-g weight of a normal full-term fetus). By 20 weeks, "quickening" or sensation of fetal movement by the mother has occurred. The fetal body continues to catch up with the head in size (by 20 weeks the head is only one-third of the crown–rump length), and early in the second trimester arms and legs have reached their proportional size in relationship to the fetal body. The fetal skin is covered with fine hair called *lanugo*, and some scalp hair is visible. The uterus is at the level of the maternal umbilicus.

After 20 weeks, the uterine size is measured as the number of centimeters between the maternal symphysis and the top of the fundus. In a normal pregnancy, this measurement in centimeters roughly corresponds to the number of weeks of gestation completed. With current neonatal technology, approximately 40–50% of babies born prematurely at 24 weeks survive.

9. The Third Trimester

During the last 3 months of pregnancy, the fetus gains weight at the most rapid rate, approximately 700 g/month. This allows the 28-week fetus weighing only about 1,100 g to achieve the average full-term weight of around 3,200–3,400 g. The fetal eyes, until now covered with a papillary membrane, open by the end of the 28th week. Lung, brain, and gastrointestinal tract maturation continues to occur. During the last months of pregnancy, the fetus becomes rounder and the fetal skin less wrinkled due to the addition of subcutaneous fat.

10. Perinatal Period

At the time of delivery, the fetal head and maternal pelvis must adapt to each other to allow the passage of one through the other. The fetal skull is comprised of the occipital bone and the two parietal bones. The junction of the sagittal and lambdoidal sutures form the roughly triangular-shaped posterior fontanelle, an important obstetric landmark in *determining the position of the fetal head during labor.* The junction of the frontal coronal sutures and sagittal sutures forms the roughly diamond-shaped anterior fontanelle, another important obstetric landmark. Because the skull bones meet in these flexible sutures and are not rigidly connected, the fetal skull can adapt to passage through the maternal pelvis (Figure 9–2).

While ultrasound has shown us that shallow respiratory movements occur periodically in utero, the baby must initiate regular deep inspiration very soon after birth, replacing the fluid that filled the lungs in utero with air. It is crucial that surfactant (surface active material in the pulmonary alveoli that lowers the surface tension in the alveoli and prevents lung collapse with expiration) be present at birth. The relative absence of surfactant in the lungs of babies delivered prematurely causes respiratory distress syndrome. When alveoli are filled with air instead of fluid soon after birth, a fall in pulmonary arterial pressure occurs and causes the closure of the ductus arteriosus. During fetal life, the ductus arteriosus shunts venous blood from the pulmonary trunk into the descending aorta. Its closure ensures circulation of venous blood through the pulmonary circulation. In the immediate newborn period, the APGAR scoring system is used to evaluate the appearance of expected physiologic signs at 1 and 5 minutes after birth (Table 9–3).

B. Reproductive Organ Structure and Function

1. Female Breast

a. Embryology—The mammary glands derive embryologically from ectodermal tissue. While multiple pairs of mammary buds initially are formed, most of these regress and disappear, leaving one pair that goes on to become the breasts. Breast tissue is characterized as breast buds covered by areolar tissue before puberty. At the time of puberty, estrogen causes growth of both mammary ducts, *glands,* as well as deposition of fat tissue between these ducts.

b. Anatomy—At maturity, the mammary gland is made up of up to 25 lobes that arise from the mammary buds. The lobes, which are

► cram facts

Accessory breast tissue and nipple buds, left over from incomplete regression of auxiliary breast buds, is often found under the arms or along the chest wall. This tissue often will enlarge with pregnancy.

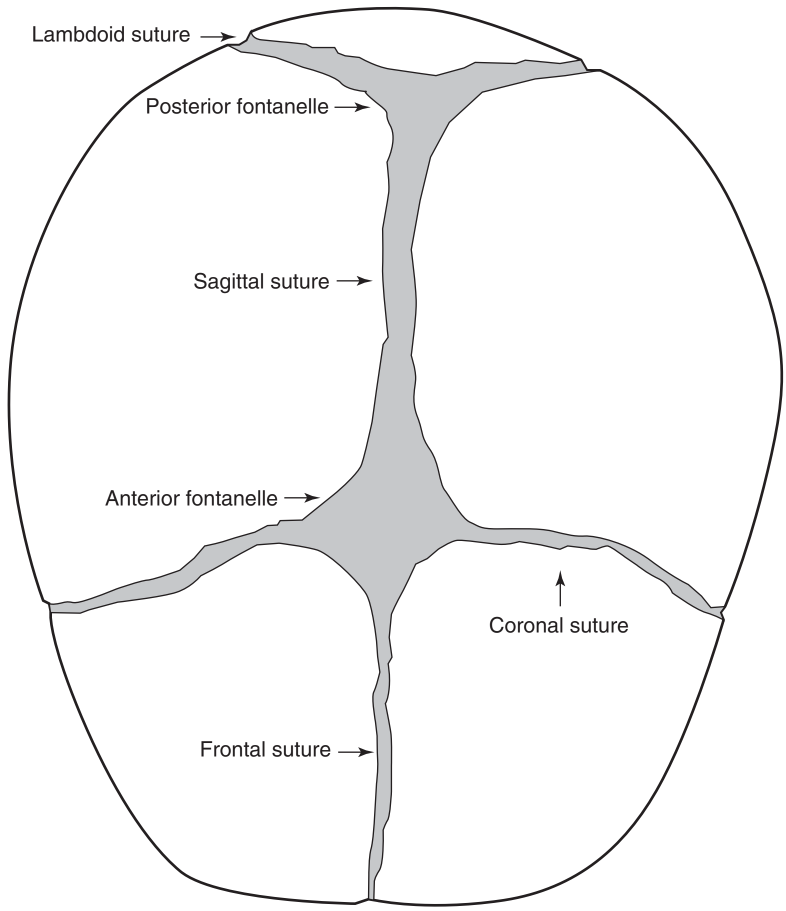


Figure 9–2. Fetal head sutures.

separated by fat, are divided into lobules, which are further divided into alveoli. Each alveolus joins to a small duct, and these ducts join to form a network of larger and larger ducts, eventually forming a single duct for each lobe. Each lobe's duct opens onto the nipple as a lactiferous duct.

c. Function—During lactation, the alveoli secrete milk, which is transported out of the breast by the duct system. In the immediate postpartum period, colostrum is produced for the first 5 days, and after this milk production is established in a breast-feeding woman. Colostrum is richer in minerals and protein and has less sugar and fat than more mature breast milk. In addition to nutrients, maternal immunologic factors such as immune globulins, complement, lymphocytes, and macrophages are found in both colostrum and breast

9-3

APGAR SCORING

Sign	0	1	2
Heart rate	Absent	Below 100	Over 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Flaccid	Some flexion of extremities	Active motion
Reflex irritability	No response	Grimace	Vigorous cry
Color	Blue, pale	Body pink, extremities blue	Completely pink

milk. Lactation is initiated by the fall in estrogen and progesterone levels at delivery. This removes inhibition at the level of the breast alveoli and allows lactose production. Once established, the baby's sucking also stimulates milk ejection from the ducts secondary to the release of oxytocin from the neurohypophysis. This elegant reflex release of oxytocin also contributes to contraction of the uterus and decrease in postpartum blood loss.

2. Female Genital Tract

a. Embryology—The female genital tract consists of the ovaries and the genital ducts. The ovaries are formed in a genetically female embryo when primordial germ cells migrate to the genital ridge after development among the endodermal cells in the inner wall of the yolk sac prior to the sixth week postfertilization. By the sixth week, the primordial germ cells invade the genital ridge, and together these form the primitive sex cords and, along with the second generation of cortical cords, give rise to epithelial cell clusters surrounding primordial germ cells. The germ cells become oocytes, and the surrounding epithelial cells become follicular cells. Development of male or female genital duct systems is influenced by hormones secreted during fetal life. In males, the fetal testes produce a substance that causes the development of the mesonephric duct system into male genitalia and inhibits the development of the paramesonephric or müllerian duct system. In the absence of this substance, the müllerian ducts go on to develop the fallopian tubes, uterus, and upper third of the vagina, and the mesonephric duct system regresses. Therefore, ovaries are not necessary for the development of female sexual organs. The external female genitalia derive from the genital tubercle, which goes on to become the clitoris, while urethral folds and the genital swellings go on to become the labia minora and majora, respectively. The urogenital groove goes on to become the outer opening of the vagina.

► **cram facts**

Testicular feminization is an example of how ovaries are not needed for the development of the uterus, ovaries, and tubes. In this condition, a genetically male fetus develops into a phenotypical female with uterus, tubes, and a vagina secondary to congenital absence of testosterone receptors.

b. Anatomy—Female reproductive anatomy can be divided into the external genitalia and internal organs of reproduction. The external genitalia are diagrammed in Figure 9–3. The internal reproductive organs include the uterus and cervix, fallopian tubes, and ovaries. The cervix forms the lower cylindrical portion of the uterus and provides communication with the vagina. The cervix is lined on its interior canal by columnar epithelium and on its vaginal surface by squamous epithelium. The body of the uterus sits above the cervix and may assume an anteverted, mid, or retroverted position with relationship to the longitudinal axis of the body. While the uterus is primarily a muscular organ (the myometrium), its external surface is covered by peritoneum and its interior surface is lined with endometrium (see section I.B.3.b).

► **cram facts**

The junction between the squamous cells lining the ectocervix and the columnar cells lining the endocervix is a dymanic area called the transformation zone. It is in this zone of active metaplasia where cervical neoplasia, which can lead to cervical cancers, arise.

The normal mature uterus is about the size and shape of a medium-sized pear. It sits in the pelvis between the bladder and the rectum. The fallopian tubes communicate with cornua, the meeting of the lateral and superior margins of the uterus. The interstitial portion of the tube implants into the uterus. The next portion of the tube distal to the uterus is the isthmus, followed by the ampulla and ending in the infundibulum. The ends of the fallopian tubes are fimbriated, facilitating capture of the ovum by the tube. The rest of the tube is lined by columnar cells, some of which are ciliated, again facilitating tubal transport of the egg into the uterus. The tube is also lined with two layers of musculature, which undergoes rhyth-

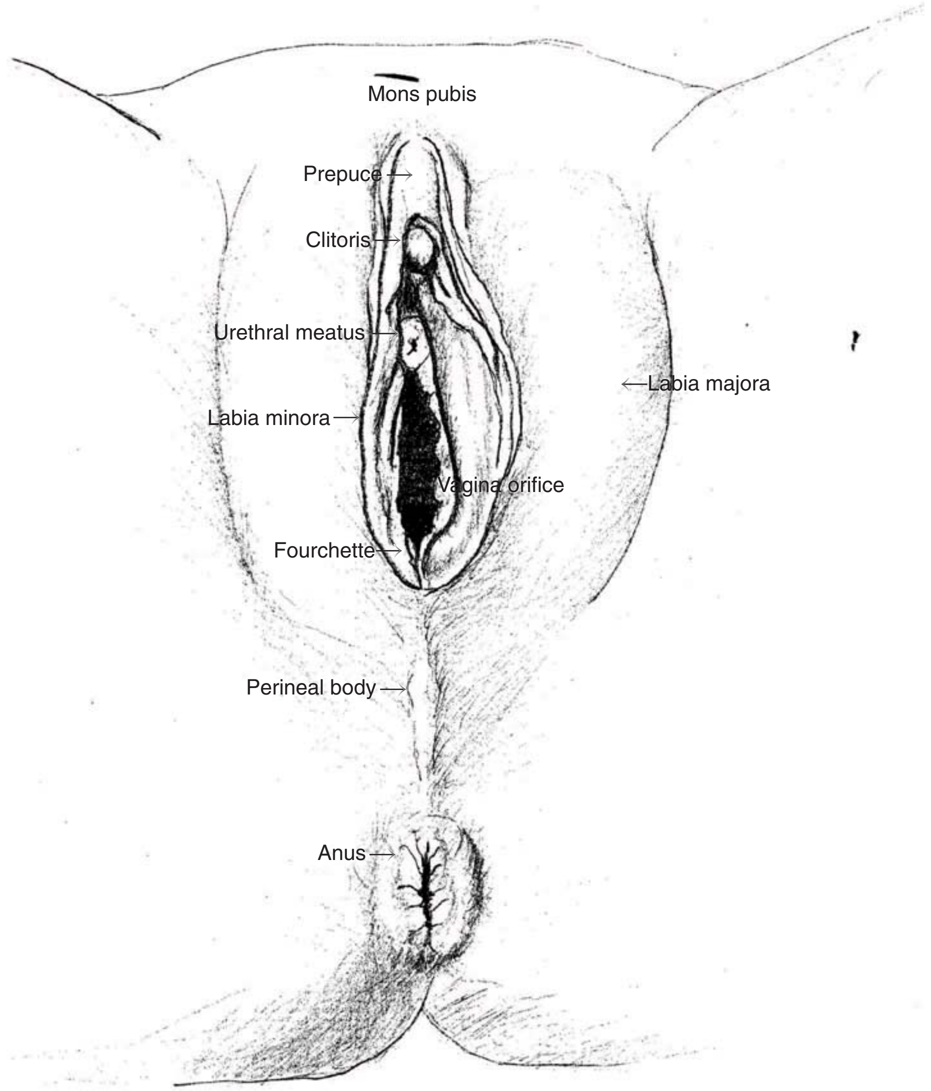


Figure 9–3. Female external genitalia.

mic contractions regulated by hormonal fluctuations during the menstrual cycle. The uterus is held in place in the pelvis by the round, broad, and uterosacral ligaments. The broad ligament also surrounds the blood supply to the uterus, the uterine artery as well as the utero-ovarian artery, after it leaves the ovary.

3. Female Reproductive Function—Birth Through Menopause

a. Birth to Puberty—While estrogen levels in female fetuses at term and newborns immediately after birth are high, shortly after birth, female pituitary gonadotropin and ovarian sex steroid levels are low and remain low until around 8 years of age. Both central inhibition of pulsatile gonodotropin-releasing hormone (GnRH) secretion as well as exquisite pituitary sensitivity to negative feedback from very low levels of estrogen are thought to be responsible. Since the hypothalamic–pituitary–ovarian axis controls activity in the female reproductive tract, development of secondary sex characteristics and reproductive tract function do not occur until puberty, the transition between immature and mature functioning of the reproductive tract. The earliest age for normal pubertal changes to occur is 8, and the normal range of age at menarche in the United States is 9–17.7 years. The main factor influencing the timing of puberty seems to be genetic, but general health and nutrition, as well as geographic location, light exposure, and psychological factors, are also contributing factors. As puberty begins, a growth spurt is initiated, which is under the control of both growth hormone and estrogen. Around the same time, breast development (thelarche) is initiated by increased ovarian secretion of estrogen. In addition, the vaginal mucosa becomes cornified under the influence of estrogen, and increased vaginal secretions are observed. The uterus also enlarges as puberty approaches, and female fat distribution becomes more apparent. In both boys and girls, adrenarche occurs when the adrenal glands increase secretion of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS). The initiator of adrenarche remains uncertain.

Increased adrenal secretion of these hormones leads to the development of axillary and pubic hair. While adrenarche and thelarche are under separate hormonal influences, in general, thelarche precedes adrenarche. The sequence of events leading to increased ovarian function (gonadarche) and the remaining events of puberty are initiated by the release of GnRH produced by the hypothalamus from inhibition. In addition, the pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) become less sensitive to estrogen's negative feedback. This allows pulsatile release of GnRH, which results in increased levels of pituitary-secreted LH and FSH, which in turn influence ovarian release of sex steroids and eventual menarche (the initiation of the first menstrual period). While the first several menstrual cycles a girl experiences are usually anovulatory, fertility is possible from menarche on.

The sequence of accelerated growth, followed by thelarche, adrenarche, and finally menarche, takes an average of 4.5 years to complete. Tanner staging (Table 9–4) is a commonly accepted method of objectively assessing the normal development of secondary sex characteristics.

b. Menstrual Cycle—After menarche, menstrual cycle length becomes more regular as the hypothalamic–pituitary–ovarian axis matures. As the menstrual cycle begins, the follicle destined to ovulate is recruited. Continued follicular growth is stimulated by FSH and its stimulation of estrogen production by granulosa cells.

In the first half of the menstrual cycle (preovulatory or follicular phase), estrogen is the predominant hormone produced by the

9-4

TANNER STAGING

	Breast	Pubic Hair
Stage 1	Isolated papillary elevation	Absence of pubic hair
Stage 2	Elevation of breast and papillae as small mound, enlargement of areola	Hair sparingly present on labia majora, long and pigmented
Stage 3	Continued enlargement of breast and areola	Increased dark and coarser and curlier hair, spreading to mons
Stage 4	Areolar and papillary mound separating from breast	Increased hair, limited to mons
Stage 5	Areola blends with breast contour	Increase in adult-type hair and adult distribution

► **cram facts**

While the time from menstruation to ovulation (the follicular phase) can vary, the duration of the luteal phase is a fairly constant 14 days. Therefore, differences in cycle length are more likely caused by differences in length of the follicular phase, an important factor to take into account when dating a pregnancy from the last menstrual period.

granulosa cells that line the ovarian follicle, causing the endometrium to proliferate. At midcycle, elevated levels of estrogen cause a surge in LH, which causes leutinization and production of progesterone in the granulosa cells. In addition, the LH surge stimulates resumption of reduction division in the oocyte. Finally, the oocyte is released from the follicle (ovulation), and the follicle remaining becomes the corpus luteum. Progesterone is the dominant hormone produced by the corpus luteum in the second half of the menstrual cycle (the luteal phase) following ovulation (Figure 9–4).

c. Menopause—While many oocytes are lost to ovulation, the great majority are lost by simple attrition. Once the ovarian supply of follicles is depleted, menopause occurs. *Perimenopause* refers to the time before and immediately after menopause, encompassing the gradual decline in ovarian function and the symptoms derived from this decline such as variation in menstrual cycles, decreased fertility secondary to increasingly anovulatory cycles, and symptoms of relative estrogen deficiency such as vaginal dryness and vasomotor symptoms (hot flashes and night sweats). The median age at menopause is 50–52. Perimenopausal symptoms can occur for several years prior to menopause, while the average age of onset of irregularities in cycle length is 47.5. Smoking, malnutrition, and lower body weight are factors that have been associated with earlier menopause. When no follicles are left, estrogen levels are low, with elevated FSH and LH levels. Certain common health problems have been shown to accelerate in postmenopausal women, most notably heart disease and osteoporosis.

4. Male Reproductive Tract

a. Embryology and Structure—Migration of primordial germ cells to the genital ridge and formation of primitive sex cords occur similarly in female ovaries and male testes in early embryonic life. In males, under the influence of the Y chromosome, the primitive sex cords become the testes, which are covered by the tunica albuginea, a layer of connective tissue. The fetal testes produce an inducer substance that causes the growth of the mesonephric system and the de-

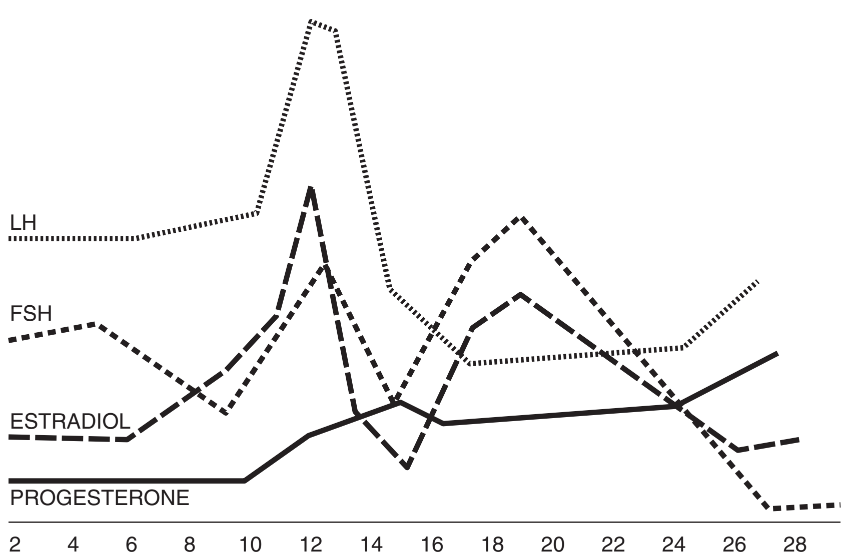


Figure 9–4. Menstrual cycle.

generation of the paramesonephric duct system. The medullary testes cords become the seminiferous tubules, which empty into the rete testes tubules, which in turn join the excretory mesonephric tubules (which become the efferent ductules) that come off the mesonephric or wolffian duct and eventually become the epididymis and the ductus deferens. The ductus deferens continues past the seminal vesicle and becomes the ejaculatory duct. The development of male external genitalia is caused by androgens secreted by the fetal testes. The genital tubercle elongates to become the phallus, pulling the urethral folds with it and eventually forming the penile urethra, which ends before the glans of the penis. The distal portion of the urethra is formed from the tip of the glans inward, eventually connecting with the penile urethra, in normal development. The scrotal swellings that contain the testes start in the inguinal region and then move caudally, each half joining in the midline to make the whole scrotum divided by the scrotal septum.

b. Function—In the testes, the seminiferous tubules are the site of spermatogenesis, and the surrounding Leydig cells produce testosterone. In order to achieve normal testicular function, the male pituitary secretes both FSH and LH. FSH and LH production is influenced by hypothalamic pulsatile secretion of GnRh, which begins at puberty. LH primarily stimulates production of testosterone by the Leydig cell. While FSH also increases testicular production of testosterone, it also, in concert with testosterone, stimulates sperm production by interaction with the Sertoli cells in the seminiferous tubules. Testosterone, produced by the Leydig cells, and inhibin, produced by the Sertoli cells, provide negative feedback to the pituitary and decrease LH and FSH production when levels are high enough. After spermatogenesis occurs in the seminiferous tubules, sperm maturation happens in the epididymis. Production of sperm takes around 75 days. About two-thirds of this time is spent in the seminiferous tubules and one-third in the epididymis before appearing in ejaculate. Semen is composed of sperm, along with secretions contributed by the prostate, vas deferens, and seminal vesicle. Analysis of semen is a key component of the evaluation of an infertile couple. Both the number and motility of sperm, as well as total amount and consistency of the ejaculate, are components of semen analysis. A normal sperm count is generally recognized as > 20 million sperm/mL, with more than 50% of sperm exhibiting forward progression. In addition, a normal volume is 2–5 mL.

5. Intercourse and Orgasm

Sexual response is a complex interplay of psychological, emotional, and physical factors. In normal sexual function, there are four physiologic phases recognized in both the male and female sexual response cycle:

1. **Excitement:** In women, during this phase vaginal lubrication takes place, and the labia majora and the clitoris enlarge. In the breast, nipple erection and breast swelling occur. The top of the vagina elevates and enlarges. In men, the penis becomes erect. In both men and women, heart and respiratory rate and blood pressure increase.
2. **Plateau:** During this phase, the physiologic changes that happened in the excitement phase intensify in both sexes. In women, the lower third of the vagina slightly narrows. In men, the testes enlarge by up to 50%. There may be a release of a small amount of fluid from the Cowper's and bulbourethral glands.

3. **Orgasm:** During female orgasm, rhythmic muscular contractions occur in the uterus and cervix and may extend into the vagina. In men, muscular contractions occur on the floor of the perineum. Semen travels from the seminal vesicles to the bulbous urethra, and the prostate simultaneously releases prostatic fluid into the bulbous urethra. These events are followed by ejaculation of semen from the penis.
4. **Resolution:** In women, both breast and genital tissues return to their preexcitement size. In men, the penis becomes flaccid. While men experience a variably timed refractory period during resolution where arousal cannot occur, women often do not experience a refractory period and may be able to have multiple orgasms.

While many men and women continue to be interested in sex as they age, aging does cause some changes in the sexual response in both men and women. In men, the refractory phase lengthens. In addition, multiple medications and chronic diseases can interfere with blood flow to the penis and cause difficulties with achieving and maintaining an erection. In postmenopausal women, vaginal lubrication decreases as estrogen levels fall and external genital and vaginal tissues atrophy. This can cause discomfort or even pain with intercourse.

6. Organ Structure and Function in Pregnancy

Virtually every organ system in a woman's body undergoes physiological changes with pregnancy.

a. Genital Tract—In general, the earliest obvious physiological sign of pregnancy is cessation of menses. At the same time, breast enlargement occurs. The vaginal mucosa becomes congested and goes from a pinkish to a purplish-blue color, referred to as **Chadwick's sign** since its description by J.R. Chadwick in 1886. In addition, the uterus begins to enlarge and soften. This softening is more prominent in the lower uterine segment and is known as **Heger's sign.** As pregnancy progresses, the muscle fibers that make up the uterine wall hypertrophy to allow growth of the uterus as the fetus grows. There is very little growth of new muscle fibers during pregnancy. In addition, there is a dramatic increase in fibrous and elastic tissue, especially in the external muscle layer of the uterus as pregnancy progresses. In order to support this growth, there is an increase in both blood vessels and lymphatic drainage. All of these changes allow the uterus to grow from an average nonpregnant weight of 70 g to 1,100 g at term. The uterine cavity accommodates a volume of approximately 10 cc in the nonpregnant state. At term, the average volume of the uterine cavity is 5 L but can accommodate as much as 20 L with such conditions as multiple pregnancies. Most of the growth in the uterus occurs in the top of the uterus, also known as the *fundus*, which enlarges in a rounded or domelike way over the tubal insertions or cornua. As the uterus grows, its muscle layer undergoes contractions that are irregular and usually painless. Since these contractions were described by J. Braxton Hicks in 1872, the phenomenon has been termed **Braxton Hicks contractions.** These contractions are infrequent in the earlier months of pregnancy and become more frequent in the last 2–4 weeks.

The lower portion of the uterus that opens into the vagina is the cervix. Its main components are collagen and elastic tissue as well as blood vessels. There are few smooth muscle fibers in the cervix. The cervix is lined with the endocervical glands, which grow both in number (hyperplasia) and size (hypertrophy) in pregnancy. These glands form a thick clot of mucus early in pregnancy that effectively blocks the intrauterine environment from the vagina. This clot or mucous plug is passed either before or during early labor and is often blood tinged, giving rise to the term *bloody show.* As the cervix prepares for labor at term, it softens and eventually dilates and effaces (thins) during labor. Dissociation of collagen is thought to be responsible for the remarkable ability of the cervix to dilate, allow passage of a baby into the vagina, and then resume its prelabor configuration.

The ovaries cease ovulation during pregnancy and change little in size. Usually, a single corpus luteum of pregnancy can be seen on the surface of the ovary during pregnancy. This corpus luteum, the remaining follicle after ovulation, produces progesterone support crucial to early pregnancy development. After 6–7 weeks of pregnancy (as dated from the LMP), the placenta takes over this function.

b. Cardiovascular and Hematologic Systems—In the left lateral recumbent position, cardiac output increases as both heart rate and stroke volume increase with pregnancy. These changes are markedly affected by maternal position as the pregnant uterus increases in size. In the supine position, both heart rate and stroke volume decrease because of compression of the gravid uterus on the vena cava. The diaphragm becomes elevated by the developing pregnancy, and this causes the heart to appear increased in size in radiographs. In 90% of pregnant women, a systolic flow murmur can be heard. All of these changes disappear soon after delivery. In addition, maternal position affects maternal blood pressure, with highest readings seen in the sitting position and lowest readings seen in the left lateral recumbent position.

► cram facts

Because of the second trimester dip in blood pressure, when women present for prenatal care in the second trimester, it is frequently difficult to differentiate between chronic hypertension and preeclampsia when they develop an elevation in blood pressure in the third trimester.

While intermediate readings are seen in the supine position in most women, some women become hypotensive in the supine position. This hypotension is caused by compression of the vena cava and therefore decrease in blood return to the heart from the lower half of the body. During normal pregnancy, blood pressure is lowest in the second trimester and rises modestly in the third trimester, usually to prepregnancy and first-trimester values in normal pregnancy. Blood volume increases by approximately 45% by the 28th week of pregnancy. This increased volume meets the needs of the enlarging uterus and fetus, helps to compensate for positional effects on venous return, and increases maternal reserves in anticipation of blood loss that normally occurs at delivery. While both plasma and red blood cell volume increase, plasma volume increases proportionally more, causing a normal physiologic fall in hemoglobin and hematocrit during late pregnancy.

► cram facts

Pregnancy-induced increase in red cell volume, along with maternal contribution of iron to the developing red cells in the fetus, is responsible for the increased iron requirement during pregnancy.Failure to meet this requirement from dietary or supplemental sources can result in profound maternal anemia.

During pregnancy, cardiovascular response to angiotensin II and the renin–angiotensin–aldosterone system is markedly lowered when compared to the nonpregnant state. Loss of this refractoriness to angiotensin II's pressor properties at the level of the blood vessel wall seems to play a key role in the development of pregnancy-induced hypertension and preeclampsia.

Several coagulation factors are increased during pregnancy. Fibrinogen levels increase by up to 50% over prepregnancy levels and are responsible, at least in part, for the elevation in erythrocyte sedimentation rate (ESR) seen in pregnancy. While clotting factors increase, the platelet count falls modestly in later pregnancy. In addition, maternal plasminogen (profibrinolysin) increases in pregnancy.

c. Respiratory System—Both respiratory rate (thought to be caused at least in part by increased progesterone) and tidal volume increase in pregnancy. In addition, because of increased red cell volume and cardiac output, the oxygen-carrying capacity of blood is increased. While functional residual capacity and residual volume in the lungs are decreased as the diaphragm is pushed up by the pregnant uterus, the sum total of changes in the respiratory tract enable increased oxygen delivery to meet increased demand in the pregnant woman (Table 9–5).

► cram facts

Because transit time through the gut is lengthened in pregnancy, aspiration is more common when general anesthesia is administered to pregnant women. Also, because of both the change in stomach position and decrease in esophageal sphincter tone seen in pregnancy, acid reflux or heartburn is common in the pregnant state. Because the intestines are displaced by the pregnant uterus, physical findings, such as the location of pain with appendicitis, can be altered in pregnancy.

d. Gastrointestinal System—Transit time through the gut is delayed in pregnancy. Progesterone as well as mechanical factors caused by the bulk of the pregnant uterus seem to play a role in this phenomenon. While most liver function tests are not affected in normal pregnancy, levels of alkaline phosphatase are uniformly quite high later in pregnancy because of placental alkaline phosphatase isoenzyme activitye.

e. Urinary Tract—Both glomerular filtration rate and renal flow increase in pregnancy. This causes a decrease in plasma creatinine and urea levels. There is increased loss of amino acids and water-soluble vitamins in the urine of pregnant women.

As the pregnant uterus rises out of the pelvis, it causes ureteral compression at the level of the pelvic brim. In addition, progesterone causes mild dilatation of the ureters. This relative stasis in the ureters is thought to explain the greater tendency toward the development of pyelonephritis in pregnancy.

f. Endocrine System—While the majority of the endocrine support of pregnancy is supplied by the placenta, there are some notable changes in the endocrine system during pregnancy. The pituitary gland increases in size, mostly secondary to the hyperplasia of lactotrophs, which produce prolactin. Prolactin levels markedly increase during pregnancy and decrease after delivery, even in women who choose to breast-feed. While the principal function of maternal prolactin secretion is thought to be stimulation of lactation, early in pregnancy increased prolactin levels are responsible for increase in glandular epithelial cells and alveolar cells in the breast. Prolactin also promotes alveolar cell secretion of breast milk components. Both fetal plasma and amniotic fluid have high prolactin levels. The function of prolactin at these sites has yet to be elucidated. Thyroid-binding globulin is increased in pregnancy because of elevated estrogen levels. hCG released by the placenta is stimulating to the thy-

9-5

PULMONARY FUNCTION IN PREGNANCY

Measure	Pregnant Compared to Nonpregnant
Respiratory rate	Increased
Tidal volume	Increased
Functional residual capacity	Decreased
Residual volume	Decreased
Oxygen-carrying capacity	Increased

roid. Total thyroxine (T_4) is increased, as is total triiodothyronine (T_3). Free T_4 levels remain normal. As hCG levels rise and plateau in pregnancy, TSH levels fall. The net effect is no alteration in maternal metabolic status when additional fetal metabolic activity is taken into account.

In normal pregnancy, fasting hypoglycemia, postprandial hyperglycemia and hyperinsulinemia are common. Increased insulin levels are at least in part caused by β-cell hypertrophy and hyperplasia and increased secretion. How pregnancy causes these pancreatic changes is not well understood, but estrogen, progesterone, and human placental lactogen are known to play a role. Prolonged hyperglycemia after a meal is caused by relative peripheral resistance to insulin seen in pregnancy. Glucagon production is decreased in postprandial pregnant women. These modifications act to ensure an increased and longer postprandial supply of glucose to the fetus. They also partially explain the increased tendency to develop gestational diabetes during pregnancy.

g. Placental Function—The placenta facilitates transfer of oxygen and other nutrients from the mother to the fetus and allows transfer of carbon dioxides and other wastes from the fetus to the maternal circulation. There is not a direct communication between maternal and fetal circulation. Nutrient and waste transfer occurs through the syncytiotrophoblasts that line the mature chorionic villi. Maternal blood is presented to these trophoblasts in the intervillous space on the maternal side of the placenta.

Villi are composed of an inner layer of cytotrophoblasts and an outer layer of syncytiotrophoblasts, which are over an inner connective tissue layer. The villi, which are in contact with the decidua basalis (the site of implantation of the pregnancy), go on to form the fetal component of the placenta. Some of these villi extend into the decidua and become anchoring villi, while most go on to end in the intervillous space and branch to form subdivisions that eventually become placental cotyledons. Each is supplied by both an artery and a vein. The placental cotyledon is the mature fetal side of the maternal–fetal communication system.

Fetal circulation to the placenta is through the two umbilical arteries, which carry deoxygenated blood to the placenta. At the placental end of the umbilical cord, the umbilical arteries branch beneath the amnion and eventually go to each placental cotyledon and further divide into capillary networks. Once blood is oxygenated through the chorion on the fetal side of the villous tree, it returns to the fetus via the venous collecting system in the cotyledons and then through the umbilical vein back to the fetus.

On the maternal side of placental circulation, maternal blood enters the intervillous space on the maternal side of the villi through arterial entrances and leaves through venous exits scattered over the uterine base of the placenta.

The amnion lines the fetal side of the uterine cavity and is fused with the chorion on the uterine surface not covered by the placenta. The amnion covers the placenta and here is in direct contact with the outer surface of the chorionic vessels. The amnion provides a membrane that contains the amniotic fluid and is also involved in the production of amniotic fluid. Placement of the growing fetus in a fluid environment allows cushioning against injury and allows fetal movement and growth. The amnion is also active in metabolism and produces vasoactive peptides, which are thought to modulate chori-

► cram facts

Amniocentesis is a procedure in which amniotic fluid is removed by placing a needle (under ultrasonic guidance) through the fetal membranes. When fluid is removed, fetal cells shed into the amniotic fluid can be cultured for chromosomal analysis to diagnose genetic abnormalities such as Down syndrome (trisomy 21) starting at about 16 weeks from the LMP. Also, later in pregnancy, it is possible to test amniotic fluid for fetal lung maturity.

onic vessel tone. In later pregnancy, fetal urination, breathing, movement, and swallowing modify both the amount and composition of amniotic fluid. Defects in both the fetal gastrointestinal and urinary tracts can be suspected based on amniotic fluid excess (polyhydramnios) or deficit (oligohydramnios).

h. Labor and Delivery—The exact mechanism that initiates labor and delivery in normal pregnancy remains unknown. In order for vaginal delivery of a baby to be achieved, several events must occur in both the uterus and cervix. Prior to labor and delivery, the uterus is relatively acontractile and the cervix remains closed. Prior to the beginning of active labor, uterine quiescence ceases, and the cervix softens and begins to dilate and efface, as well as move forward in the vagina. The fetal head, particularly in primiparous women, also begins to descend. All of these events are termed *cervical ripening* and constitute components of the Bishop Score (Table 9–6). The Bishop Score is an objective measurement that predicts the success of induction of labor with Pitocin. Prostaglandin sensitivity is felt to be at least partially responsible for cervical ripening and the initiation of labor. This theory forms the basis of the use of prostaglandin preparations applied locally to the cervix in attempts to initiate cervical ripening when induction of labor is desired for obstetric indications.

At a variable point in the ripening process, labor ensues. *Labor* is defined as the production of advanced cervical dilatation, effacement, and descent of the fetal presenting part by regular uterine contractions. The ultimate outcome of active labor is delivery of the fetus. Labor is divided into three stages. The first stage of labor may be ill defined but begins when regular contractions produce progressive dilatation and effacement of the cervix and ends when the cervix is completely dilated and effaced and allows passage of the fetal head through the cervix. In normal labor at term, at some time during or prior to the first stage of labor, spontaneous rupture of the membranes (amniotic sac) occurs.

The first stage of labor is further divided into latent and active phase based on the observation of consistent patterns of progression of cervical dilatation over time in normal labor. During the latent phase of labor, dilatation progresses more slowly. In general, the latent phase is thought to end when more rapid cervical dilatation is observed. This transition generally occurs at approximately 3 cm dilatation in a primiparous woman and at 4–5 cm in a multiparous woman. In the active phase of labor, cervical dilatation progresses at the lower limit of 1 cm/hr in a primiparous woman, with more rapid progression generally seen in multiparous women. It is important to emphasize that the rate of dilatation is more important than the absolute amount of dilatation in the diagnosis of latent- or active-phase labor since considerable variation can occur from pregnancy to

9-6

BISHOP SCORE

Score	Dilatation	Effacement	Consistency	Position	Station
0	Closed	0–30%	Firm	Posterior	High
1	1–2 cm	40–50%	Medium	Mid	–2
2	3–4 cm	60–70%	Soft	Anterior	–1–0
3	> 5 cm	> 80%	—	—	+1–+2

pregnancy. However, upper limits of time for both the completion of the latent phase and expected progression of cervical dilatation in active labor are important in the diagnosis and treatment of abnormalities of labor.

The active phase of labor is also divided into the acceleration and subsequent deceleration phase. As the cervix goes from 8 to 9 cm to complete (usually 10 cm) dilatation, a deceleration in the rate of dilatation is often observed (see Figure 9–5).

The second stage of labor is defined as the time from achievement of complete dilatation and effacement until delivery of the baby. During this time, a combination of uterine and voluntary maternal expulsive efforts cause the fetus to move down the vagina and be delivered. Normal delivery is accomplished from vertical lie with the fetus in the cephalic presentation in the occiput anterior position. At the beginning of the second stage, the fetal head is often slightly rotated to the left (LOA) or right (ROA). As the fetal head descends through the vagina, it flexes on the fetal chest and internally rotates into the occiput anterior (OA) position. As the fetal head reaches the perineum, it extends to accomplish delivery of the head. After delivery of the head, external rotation occurs and the fetal head generally returns to its LOA or ROA position. This facilitates delivery of the fetal shoulders in the anterior–posterior plane of the maternal pelvis, with the anterior fetal shoulder delivering first, followed quickly by delivery of the posterior shoulder and then the rest of the babyThe third stage of labor begins after delivery of the baby is completed. At this point, the cord is usually clamped and cut and the delivery of the placenta awaited. During this time, the placenta separates and is expelled from the uterus along with the fetal membranes. Immediately after delivery of the placenta and fetal membranes, the uterus contracts and decreases in size, an important event in the prevention of excessive maternal blood loss with delivery.

i. Structure and Function at the Cellular Level: Hypothalamic–Pituitary–Ovarian Axis—The regulation of ovulation and the normal menstrual cycle depend on a complex feedback system involving the hypothalamus, pituitary, and ovary. During the follicular phase, recruitment of follicles takes place, and the end result is the development of mature follicle destined to ovulate. While it is uncertain what triggers the recruitment of ovarian follicles for devel-

► cram facts

While the uterus is extremely sensitive to oxytocic agents (Pitocin) prior to delivery and these must be administered with care for augmentation and induction of labor, after delivery, uterine sensitivity decreases and increased amounts of oxytocic agents can be administered. However, rapid intravenous delivery of such agents after delivery can cause hypotension and antidiuresis, leading to water intoxication.

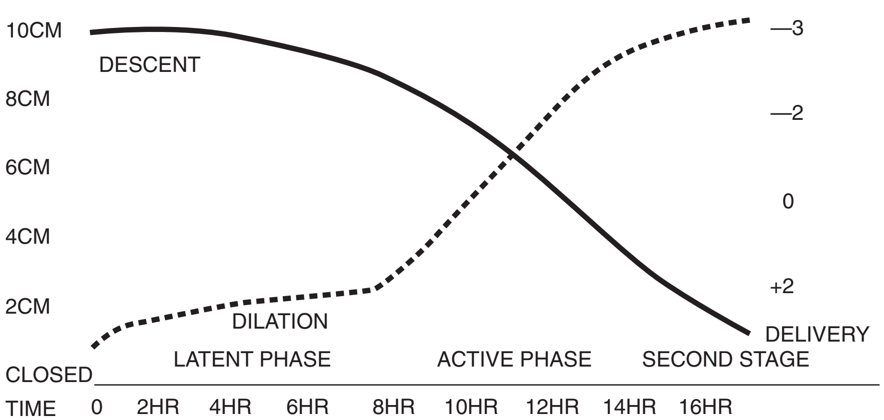


Figure 9–5. Normal labor curve.

► cram facts

Since most follicles die off by attrition, events that cause a hiatus in ovulation and follicular recruitment, such as use of birth control pills and repeated pregnancy, do not affect the age of menopause.

opment in any given cycle, it is known that the majority of ovarian follicles are destined to die off by attrition starting during fetal life after achieving maximal number at 16–20 weeks' gestation.

Follicular atresia continues throughout a woman's life and is not interrupted by anovulation or pregnancy. While several follicles will be recruited in a given cycle, usually only one of these follicles is destined to ovulate. In early follicular recruitment, granulosa cells proliferate. These events happen in response to increases in FSH. The theca layer organizes around the outside of the granulosa cells, which continue to proliferate. Granulosa cells in the early (preantral) follicle predominantly produce estrogen, with aromatization of androgens to estrogen stimulated by FSH as well. The follicle progresses to the antral stage as follicular fluid increases under the influence of FSH and estrogen. While both the theca and granulosa cells can produce progestins, androgens, and estrogens, granulosa cells predominantly produce estrogen under FSH stimulation of receptors on their surface, while theca cells have predominantly LH receptors, which produce androgens that can then be aromatized to estrogen under the influence of FSH in the granulosa cells. This LH-induced androgen and then subsequent added estrogen production is crucial in continued development of the follicle. Negative feedback of ovarian estrogen on FSH production by the pituitary serves to inhibit all but the development of the dominant ovarian follicle as the follicular phase progresses. This also produces a positive influence on LH secretion, which continues to rise during the later follicular phase. FSH also produces the appearance of LH receptors on the granulosa cells in the dominant follicle as the follicular phase progresses. Granulosa cells also secrete the peptides inhibin and follistatin under FSH stimulation. These peptides in turn directly suppress pituitary secretion of FSH.

In the preovulatory follicle, peak estradiol levels induce the LH surge, which initiates leutinization of the granulosa cells and conversion to predominant production of progesterone by these cells. Positive feedback of estrogen is facilitated by progesterone at this time, and this is thought to help induce the midcycle FSH peak. Prostaglandin synthesis is also stimulated in the follicle by the LH surge near the time of ovulation. Both progesterone and prostaglandins stimulate activity of proteolytic enzymes responsible for rupture of the follicle and release of the oocyte.

Even before ovulation occurs, granulosa cells begin to acquire leutin, which gives them the characteristic yellow appearance seen in the corpus luteum or follicle remaining after ovulation. Progesterone is predominantly produced by the granulosa cells and suppresses new follicular growth.

As the follicle matures, the oocyte resumes meiosis and approaches completion of its reduction division. Prior to this, from the second trimester of fetal life until just prior to ovulation, oocyte meiosis was arrested in the diplotene stage just prior to the first meiotic division. Prior to ovulation, the oocyte in the dominant follicle undergoes the first meiotic division and produces a secondary oocyte and polar body, each with 23 chromosomes. At the time of fertilization, the second meiotic division takes place, the second polar body is extruded, and the mature oocyte is produced, which then combines with the sperm.

The predominant follicular-phase ovarian production of estrogen causes proliferation of the endometrium. After ovulation, the endometrium under predominantly progesterone influence, becomes secretory, and the cells lining the endometrial glands evolve a slightly different appearance every day after ovulation, allowing postovulatory dating of the secretory endometrium. If pregnancy does not occur, both estrogen and progesterone levels fall, the corpus luteum regresses, and menstruation occurs. If fertilization and early pregnancy occurs, hCG maintains the corpus luteum function until placental production of steroid hormones is well established.

The entire menstrual cycle is dependent on the pulsatile secretion of GnRH from the hypothalamus. The amplitude and frequency of this secretion changes during the cycle, with smaller and more frequent pulses during the follicular phase as compared to the luteal phase.

j. Sex Steroids—All steroid hormones by definition are derived from the common chemical structure perhydrocyclopentanephrinephenanthrine, which is composed of three six-carbon rings and one five-carbon ring. The sex steroids are divided into three main groups, depending on the number of carbons in their structure. The 21-carbon molecules make up the pregnane derivatives that form the progestin corticoids. The 19-carbon molecules form the adrostane derivitaves that become the androgens. The 18-carbon molecules are the estrane derivatives that form estrogens.

Cholesterol is the basic building block from which all steroid hormones are synthesized. While all steroid-producing organs except the placenta can synthesize cholesterol from acetate, because of the large demand for production in the ovary, blood cholesterol is a major substrate for steroidogenesis in the ovary.

Steroidogenic pathways follow the same general steps regardless of the organ in which they are functioning. Because the ovary has different amounts of critical enzymes than the testes, different proportions of the female sex steroids (progesterones and estrogens) and androgens are formed in males and females. Because the ovary is lacking in the 21-hydroxylase and 11-β-hydroxylase enzyme activity present in the adrenal gland, it cannot produce gluco- and mineralocorticoids. When steroids are being produced, the number of carbons present in the cholesterol molecule are reduced but never increased. The following enzyme types achieve the reactions necessary:

- Desmolase—cleaves side chains.
- Dehydrogenase—change of hydroxyl to ketone group or vice versa.
- Hydroxylation—addition of OH group.
- Hydrogen removal—creation of a double bond.
- Saturation—addition of hydrogen to reduce double bonds.

> **cram facts**
>
> GnRH agonists can be used to suppress ovarian function since they suppress the pulsatile secretion of GnRH. Because of this ability to shut down normal ovarian function, GnRH agonists are used in the treatment of endometriosis and fibroids and are also used to facilitate control of ovulation timing for ovulation induction for assisted reproductive technologies such as in vitro fertilization (IVF).

> **cram facts**
>
> Antiviral therapy can be used to treat herpes in two ways:
>
> 1. Short courses of the antiviral agent acyclovir and its derivatives can shorten the duration and decrease the severity of a genital herpes outbreak. This treatment works best when initiated as early as possible in the course of the outbreak.
> 2. Individuals who have frequent genital herpes outbreaks can decrease the frequency of these outbreaks by taking continuous antiviral medication. However, no treatment to date eradicates the herpesvirus, no matter what the duration of treatment.

II. ABNORMAL PROCESSES

A. Infection

1. Sexually Transmitted Diseases

Sexually transmitted diseases (STDs) are among the oldest diseases recorded. There is an ever-expanding array of bacteria, viruses, and protozoa known to be transmitted sexually. When treating a patient for an STD, it is important to be nonjudgmental and thorough in discussion of sexual practices, need for partner(s) treatment, and techniques for prevention of STDs.

a. Herpes

- Viral infection with herpes simplex virus (HSV) type 1 usually oral infection, type 2 usually genital; both can infect both orally and genitally.
- Transmitted by direct contact between infected and susceptible surface. Presents as painful, vesicular lesion(s) occurring 3–7 days after contact; vesicle then becomes ulcer and may be accompanied by inguinal adenopathy. After first infection, virus becomes latent in nerve ganglia. Initial outbreak worst, can be accompanied by flulike symptoms and urinary retention. Initial outbreak lasts from 10 days to 6 weeks.
- About 50% of infected people experience recurrences at the site of primary infection with milder symptoms and shorter duration (3–6 days). Recurrence is often preceded by tingling or heavy sensation in the area. Recurrence can be triggered by stress, local trauma, or another systemic disease.
- Asymptomatic shedding can occur; viral shedding most likely during prodrome and with outbreak.
- Diagnosis confirmed by culture of suspicious lesion, most likely to be positive in first 48 hours after outbreak starts.
- When an active herpes infection is present in a pregnant woman at the time of delivery, systemic neonatal herpes infection can occur. Avoidance of direct contact between neonate and maternal lesions by cesarean section seems to prevent neonatal infection. Risk of neonatal infection at delivery is highest with maternal primary infection at the time of delivery. In addition, primary infection of the mother in the first trimester may cause intrauterine fetal infection with sequelae of spontaneous abortion, microcephaly, skin lesions, chorioretinitis, intrauterine growth retardation, and preterm labor.
- Herpetic lesions may facilitate infection with the human immunodeficiency virus (HIV).

b. Human Papillomavirus (Condyloma Acuminata or Genital Warts)

- DNA virus with more than 30 serotypes. Can infect externally (vulvar, perineal, perianal, penile, and scrotal surface) and internally (vagina, cervix, male urethra, male and female anus).
- Visible lesions most often caused by type 6 or 11. Types 16, 18, 31, 33, and 35 strongly associated with cervical, vaginal, and anal neoplasia as well as penile and vulvar cancers when seen externally. Progression to cancers more common in immunosuppressed patients.
- Lesions are termed *genital warts*—cauliflower-like in appearance and can resolve spontaneously or persist.
- Recurrences common, especially in smokers and immunosuppressed patients.
- Transmission not prevented by condom use.
- Pregnancy can cause proliferation of both internal and external warts, which regress postpartum.
- Treatment of local lesions can be accomplished by local destructive measures (freezing, laser, application of bi- or trichloroacetic acid or podophyllin) or by application of the topically applied immune modulator imiquimod. Many local lesions will resolve spontaneously with time. At the present time, there is no treatment that permanently eradicates the human papillomavirus from infected individuals.

- Can be detected in the cervix by hybrid DNA testing, currently available for use in conjunction with PAP smears in certain cases.

c. Syphilis

- Caused by spirochete *Treponema pallidum;* transmitted sexually by contact with mucocutaneous lesions, which can be present for up to the first year after infection. Also transmitted congenitally and by intravenous blood exposure.
- Primary syphilitic lesion is a *chancre*, painless ulceration appearing at site of infectious contact, appearing 10–90 days after exposure, which resolves spontaneously in 3–6 weeks. Chancre is contagious; darkfield examination of scrapings shows spirochetes.
- Secondary syphilis: 6 weeks to 6 months after initial infection, characterized by low-grade fever, generalized malaise, and lymphadenopathy accompanied by variably appearing rash that can involve palms of hands and soles of feet. Condyloma lata (gray plaques that commonly arise in moist areas) are contagious. At this time, highest concentration of spirochetes in blood. The central nervous system (CNS) is also involved in about 40% of people with secondary syphilis with symptoms including headache and meningismus. Secondary syphilis symptoms resolve without treatment.
- In the absence of treatment, after a variable length of latent syphilis, tertiary syphilis develops in about 33% of infected people. Although virtually any organ system can be affected, destruction of the CNS and the ascending aorta are most common. In addition, a necrotic lesion called a gumma can occur in any organ.
- The diagnosis of syphilis is usually made using serologic tests for syphilis. Two commonly utilized nontreponemal tests that rely on the presence of treponemal antibody are the VDRL (Venereal Disease Research Laboratory) and RPR (rapid plasma reagin). Because some other medical conditions can cause false-positive results (because of the detection of nontreponemal antibody), a positive VDRL or RPR is confirmed with a treponemal antigen test such as the fluorescent treponemal antibody absorption (FTA-ABS) or the *T. pallidum* particle agglutination (TP-PA). Nontreponemal titers are also used to follow treatment since the level of the titer correlates with disease activity. While nontreponemal tests often become negative after treatment, low levels of antibody may persist in adequately treated people for long periods of time. Treponemal tests remain positive in most people with a history of syphilis, but up to 25% of infected people will convert to negative, especially when treatment is instituted early in the course of the disease.
- Congenital syphilis occurs when a baby is born to a mother infected with *T. pallidum* and is most likely to occur when the mother has a primary or early secondary infection. Congenital transmission is thought to be less common when the mother has latent syphilis, with infection rates of 40% quoted for early latent and 14% for late latent. Symptoms of congenital syphilis include typical facies of congenital syphilis secondary to affected bone and mucocutaneous tissues (saddle nose) as well as rhinitis (snuffles). Babies can die from liver failure and, as with adult syphilis, any organ system can be affected. In untreated surviving babies, a latent period ensues and later sequelae include intersitial keratitis and eighth nerve deafness.
- Penicillin is the mainstay of treatment for syphilis. Amount and duration of treatment are determined by the stage of the disease at diagnosis.

► cram facts

Because of the severity of neonatal syphilis and the treatability of maternal syphilis, maternal screening for syphilis is done universally as part of prenatal care.

d. Gonorrhea

- Caused by gram-negative diplococci *Neisseria gonorrhoeae*.
- Initially causes urethritis in men and cervicitis in women. In women, can lead to pelvic inflammatory disease (PID). Up to 90% of women are initially asymptomatic; men almost always have symptoms soon after 3–5-day incubation period. Highly infectious, with risk of transmission from male to female after one exposure quoted as 80–90%.
- Sequelae include tubal damage and subsequent infertility with PID. In both sexes, if left untreated, disseminated gonococcal infection can occur, with accompanying pustular skin rash and asymmetric septic arthritis. Other complications can include less common perihepatitis (Fitz-Hugh–Curtis syndrome when accompanying PID) as well as endocarditis and meningitis.
- Infants can be infected when born to an infected mother. Neonatal infection is manifested as ophthalmia neonatorum and sepsis.
- Diagnosed by culture (needs to be done on special media [Thayer–Martin] in aerobic environment) or more recently by DNA-based testing using polymerase or ligase chain reactions (PCR and LCR) or DNA probe. In men, the diagnosis of urethritis is made based on observation of any one of the following: (a) a mucopurulent penile discharge, (b) Gram stain of urethral secretions showing > 5 WBC/HPF, or (c) positive leukocyte esterase test or > 10 WBC/HPF on microscopic examination of first morning urine. On Gram stain, if gram-negative diplococci are seen in the WBC in the smear, gonorrhea infection is diagnosed as the cause of the urethritis. When none of these tests are positive, direct testing by culture or DNA-based technology should be performed if the diagnosis is suspected on the basis of symptoms. Empiric treatment of known infected sexual partners is recommended regardless of symptoms. In women, mucopurulent discharge from the cervix is diagnostic of either gonorrhea or chlamydia (see below), and treatment is based on specific testing results as well as other accompanying symptoms or historical suspicion.
- While initially sensitive to penicillin, multiple penicillin-resistant strains of gonorrhea are common. Current treatment of choice is with the cephalosporin ceftriaxone, although other drugs such as ciprofloxacin are also effective. Duration of treatment depends on whether or not upper tract infection is suspected.

e. Chlamydia

- Caused by intracellular parasite *Chlamydia trachomatis*. Currently more common in the United States than *N. gonorrhoeae* infection, especially among sexually active adolescents and young adults.
- Causes cervicitis in women and urethritis in men, frequently asymptomatic in both sexes.
- Sequelae include PID (often with minimal symptoms) and subsequent tubal damage, increased risk of ectopic pregnancy and infertility in women, and epididymitis and Reiter's syndrome in men.
- Diagnosed by culture (requires cell culture) or more often by DNA-based LCR or PCR or DNA probe testing. See above for criteria for presumptive diagnosis if urethritis in men.
- Treatment of choice is either doxycycline or azithromycin. Duration of treatment depends on whether or not upper tract disease is suspected. Other agents are effective as well.

► **cram facts**

Because DNA-based testing for gonorrhea and chlamydia does not require the presence of live organisms to produce a positive result, test of cure after treatment is not done until at least 6 weeks post-treatment since this is how long it takes for dead organisms to be cleared.

f. Trichomoniasis

- Caused by the protozoan organism *Trichomonas vaginalis.*
- Causes a vaginitis in women with a foamy white to yellowish-green irritating discharge and urethritis in men; frequently, both sexes are asymptomatic (50% of infected women and 90% of infected men).
- Diagnosed by microscopic inspection of vaginal discharge, vaginal pH > 5.0 in infected women; causes cervical capillary inflammation and punctate hemorrhages resulting in "strawberry" cervical appearance. Can sometimes be seen on urinalysis in affected men.
- Associated with premature birth, low birth weight, and postpartum endometritis in infected pregnant women. It is uncertain whether *Trichomonas* is the causative factor in these women or whether it is a marker for other diseases that predispose to the above adverse pregnancy outcomes. Treatment of asymptomatic trichomoniasis in pregnant women has not been shown to lessen adverse outcomes.
- Partners of infected individuals should be presumptively treated.
- Treated with the antibiotic metronidazole. When treating patients with metronidazole, it is important to warn them against drinking alcohol while they are taking the drug since it can induce an Antabuse reaction.

h. Chancroid

- Caused by infection with *Haemophilus ducreyi* (gram-negative coccobacilli).
- Causes one or more painful genital ulcers that are negative for *T. pallidum* on darkfield exam and HSV on culture and have characteristic appearance of chancroid (lesion starts as a small papule and progresses to ulcerated lesion in 2–3 days) with accompanying regional lymphadenopathy. Regional adenopathy can develop into buboes, which will rupture if untreated and develop into an inguinal ulcer.
- Can culture, but media not widely available in the United States. Incubation time 1 day to many weeks, average 5–10 days.
- Though common worldwide, rare in the United States.
- Can be a cofactor for HIV transmission; also high incidence of coinfection with *T. pallidum* or HSV when chancroid present.
- Partners should be treated presumptively whether symptomatic or not.
- No known harmful effects in pregnancy.
- Treated by erythromycin or ceftriaxone; other agents may be effective.

i. Granuloma Inguinale (Donovanosis)

- Caused by *Calymmatobacterium granulomatis* (intracellular, gram-negative bacteria).
- Rare in United States, more common worldwide, especially in India, central Australia, southern Africa, and New Guinea.
- Presents as small painless papule that then becomes ulcerated and friable (though still painless) and exhibits exuberant granulomatous change. Between 8- and 80-day incubation. Accompanying inguinal groin swelling caused by subcutaneous spread of granuloma and not lymphadenopathy. Can have accompanying lymphedema and elephantitis of external genitalia.
- Occurs on both external and internal genitalia but can also occur extragenitally.
- Diagnosis made on clinical appearance; scrapings from lesions show dark-staining Donovan bodies.

- Treatment should be considered for exposed partners, though the value of treatment in asymptomatic contacts has not been established.
- Multiple treatment regimens recommended including doxycycline and trimethoprim–sulfamethoxazole.

j. Lymphogranuloma Venereum

- Caused by *Chlamydia trachomatis* serotypes L1, L2, L3. *C. trachomatis* cervicitis, urethritis, and PID are caused by serotypes D through K.
- Occurs rarely in the United States and mostly diagnosed in men.
- After a 4–21-day incubation period, occasionally a genital ulcer appears (and then spontaneously resolves) at the site of inoculation. About 1–4 weeks later, a tender, usually unilateral inguinal and/or femoral adenopathy develops that progresses to suppurative adenitis with the development of draining sinuses, which can continue for weeks to months. If untreated, disease progresses to a tertiary stage with further scarring and sinus and fistula development in vulva, perineum, vagina, and rectum.
- Serologic testing using a complement fixation titer for chlamyd- ial antibodies of > 1:64 is consistent with the diagnosis in suspect cases. Attempts can also be made to culture the organism from infected tissue.
- Treated with doxycycline.

k. Pediculosis Pubis (Pubic Lice)

- Caused by ectoparasite *Pediculosis pubis*.
- While usually transmitted by sexual contact, can be transmitted via fomites such as sheets, clothing, and towels. Incubation time can be up to 30 days. A 95% chance of transmission with one sexual contact makes pubic lice the most contagious STD known.
- Infestation causes intense pubic pruritus; lice, larvae, and nits can be seen with a magnifying glass.
- Removal of all nits with comb is an important adjunct to topical treatment.
- Exposed partners should be treated presumptively.
- Treated with topical application of permethrin or Lindane and other measures as outlined above.

l. Scabies

- Caused by the mite *Sarcoptes scabiei*, a parasite that burrows and then lives and reproduces under human skin.
- Infection in adults is usually sexually acquired but can occur in children from nonsexual contact as well as transmission by fomites.
- Main symptom is pruritus, which worsens at night. The area of contact with an infected person becomes infected.
- Diagnosis is suspected when classic linear burrows are seen under the skin, though erythema and papules can accompany burrows, as can excoriation marks. Diagnosis confirmed by microscopic examination of skin scrapings showing organisms or eggs.
- All contacts should be examined and treated, and linens and clothing should be cleaned in hot, soapy water or dry cleaned.
- Treated with topically applied permethrin, Lindane, or crotamiton and above measures.

m. Hepatitis A, B, and C

- All viral infections and all potentially sexually transmissible.
- **Hepatitis A** most commonly spread by fecal–oral route; household

and sexual contact (especially male homosexual contact) with infected person are most common forms of transmission.
  - Disease is self-limited and does not recur. Treatment is supportive.
  - Can be prevented by vaccination of high-risk individuals.
  - Diagnosis of acute infection made by serologic detection of hepatitis A IgM antibody with eventual development of IgG antibody.
- **Hepatitis B** transmitted by sexual contact as well as exposure to infected blood (highest concentrations of virus in infected blood with lower concentrations in body fluids such as semen and vaginal secretions).
  - Incubation period 6 weeks to 6 months from exposure to symptoms, though 50% of infected individuals are asymptomatic.
  - Treatment of symptomatic infected individuals is supportive.
  - Chronic infection and carrier status can occur in 2–6% of adults and is more common in infected infants (90%) and children under 5 (60%). Chronic infection carries a 15–25% risk of death from cirrhosis or hepatic cancer.
  - Infection can be prevented by administration of hepatitis B vaccine.
  - Chronic carrier status is diagnosed serologically by persistently positive hepatitis B surface antigen. Immunity (from either vaccination or prior infection) is characterized by positive hepatitis B surface antibody.
  - Babies born to mothers who are chronic carriers are very susceptible to infection. All pregnant women are routinely tested for carrier status since prompt postdelivery vaccination of babies greatly reduces perinatal transmission.
- **Hepatitis C** is the most common chronic bloodborne infection in the United States. Symptoms of acute infection are mild or absent.
  - Chronic infection develops in 75–85% of acutely infected people, and 60–70% have active liver disease.
  - Although percutaneous exposure to infected blood is by far the most common means of transmission, sexual exposure can result in infection.
  - Current treatment includes long-term therapy with interferon alone or in combination with ribavarin. Treatment is the subject of active research, and treatment recommendations are likely to change rapidly.
  - Hepatitis C is diagnosed serologically through detection of anti–hepatitis C or hepatitis C RNA.
  - There is currently no vaccine or immune globulin prophylaxis against hepatitis C.
  - Chronic hepatitis C can be treated with some success with interferon and other immune system modulators.

n. Human Immunodeficiency Virus

- Caused by a retrovirus, HIV infection is responsible for a spectrum of illness ranging from asymptomatic to full-blown acquired immune deficiency syndrome (AIDS). Current therapies can prolong the latent or asymptomatic period between infection and expression of AIDS. Infection is diagnosed by blood testing for antibody to the HIV-1 (most common in the United States) and HIV-2 viruses via a sensitive screening test such as the enzyme-linked immunosorbent assay (ELISA). Positive screening tests are confirmed by the

Western blot or immunofluorescent assay. Testing becomes positive in 95% of infected individuals within 3 month after exposure. Once the diagnosis has been made, in addition to prompt initiation of therapy, counseling on reduction of high-risk behavior should be undertaken. HIV transmission is accomplished through sexual contact with infected persons and subcutaneous exposure to infected blood. Perinatal transmission from infected mothers to infants can be reduced from 15–25% to < 2% through the use of antiretroviral agents, cesarean delivery, and avoidance of breast-feeding. All pregnant women should be offered HIV testing.

- HIV treatment is a continually evolving entity. Antiviral agents in combination can have a beneficial effect on the course of the disease.

o. Pelvic Inflammatory Disease (PID)

- Upper genital tract infection of the uterus, tubes, and ovaries (endometritis, salpingitis, oophoritis) with complications including development of tubo-ovarian abscess and pelvic peritonitis and even death from rupture of tubo-ovarian abscess or sepsis. Long-term complications include infertility and increased risk of ectopic pregnancy secondary to tubal damage.
- Caused by sexually transmitted cervicitis caused by gonorrhea and/or chlamydia, which injures endocervical surface epithelium, and polymicrobial ascending infection with initial organism as well as normal vaginal flora occurs. Typical onset of symptoms occurs after the menstrual period, which is felt to facilitate ascending infection. Bacteria can also be introduced via pelvic surgery or cervical instrumentation (abortion, dilation and curettage).
- Over 1 million cases diagnosed in the United States annually, with 16–25% of cases reported in adolescents.
- Since there is no definitive diagnostic test, diagnosis is made via combination of clinical criteria in sexually active women (Table 9–7). Definitive diagnosis can be made at laparoscopy, by evidence of endometritis on endometrial biopsy, or by evidence of tubo-ovarian abscess on ultrasound.
- Treated with combination antibiotics to cover gonorrhea and chlamydia as well as enteric anaerobes and gram-negative organisms.

p. Epididymitis

- Most commonly caused by gonorrhea or chlamydia in men under 35 as sequelae to urethritis. Can also be caused by *Escherichia coli* in homosexual men who are insertive partners in anal intercourse. In men over 35, more commonly nonsexually transmitted and caused by gram-negative organisms after urinary tract instrumentation. Diagnosis confirmed by culture of gonorrhea or chlamydia from urethral exudates or identification of > 5 WBC/HPF on urethral smear.

9-7

CLINICAL CRITERIA FOR THE DIAGNOSIS OF PID
Fever (can be low grade)
Uterine and adnexal tenderness on pelvic exam
Cervical motion tenderness
Mucopurulent cervical discharge (may not always be present)
Elevated white blood cell count

- Usually causes unilateral swelling and pain with palpable epididymal swelling and accompanying hydrocele.
- Treated by antibiotic regimens that cover gonorrhea and chlamydia along with bed rest and analgesics.
- Exposed sexual partners should be presumptively treated for gonorrhea or chlamydia or both, depending on culture results.

2. Mastitis

- Most commonly occurs in breast-feeding women.
- Can also occur after trauma to the breast or, more rarely, spontaneously.
- Usually caused by *Staphylococcus aureus*, treated with dicloxacillin.
- Abscess formation, requiring drainage, can occur.
- Lactating women who have mastitis should continue to breastfeed.

3. Vulvovaginitis

Characterized by an abnormal vaginal discharge often accompanied by vulvar and vaginal irritation and/or itching, vaginitis is seen when the normal vaginal ecosystem is disturbed either by infectious, environmental, or chemical agents (see Table 9–8). Vaginitis can be sign of STDs such as gonorrhea, chlamydia, and trichomoniasis (see above). In addition, chemical and allergic reactions as well as reaction to a foreign body in the vagina (such as a retained tampon) can cause vaginitis. Other than STDs, common infectious causes of vaginitis include the following.

a. Prepubertal Vulvovaginitis

- Most commonly caused by poor hygiene. This can include poor front-to-back wiping, overzealous cleansing with harsh soaps, the use of bubble bath, and wearing of tight, constrictive clothing.
- Treatment aimed at improving hygiene.
- If symptoms do not respond to treatment or sexual abuse is suspected, a more thorough exam to obtain cultures for gonorrhea, chlamydia, and other bacteria, as well as to rule out a vaginal foreign body, is indicated.

9-8

VAGINITIS

Causative Agent	Clinical Presentation	Diagnosis	Treatment
Candida (yeast)	Cottage cheese-like discharge and pruritus, commonly seen after use of broad-spectrum antibiotics Not sexually transmitted	Yeast buds and hyphae seen on wet mount of vaginal secretions, especially when mixed with KOH Vaginal pH normal (3.5–4.5)	Vaginal or oral antifungals
Bacterial vaginosis	Thin vaginal discharge with fishy odor, often exacerbated after intercourse, not thought to be sexually transmitted but higher pH of semen may facilitate overgrowth of bacteria causing BV	Bacteria-studded epithelial cells (clue cells) on wet mount of vaginal secretions Positive “whiff test” (fishy odor when vaginal secretions mixed with KOH) Vaginal pH elevated (> 4.5)	Oral or vaginal metronidazole Vaginal clindamycin
Atrophic vaginitis	Flattened and thinned vaginal mucosa with thin vaginal discharge, usually seen in postmenopausal or breast-feeding women	Absence of pathogens on wet mount, higher proportion of basal cells on wet mount of vaginal secretions	Vaginal estrogens
Trichomonas	Foamy white–pale green discharge, can be accompanied by vaginal discomfort	Motile, flagellated protozoa seen on wet mount of vaginal secretions	Metronidazole, oral Treat sexual partners

- Bacterial imbalance, best treated with antibiotics, is more frequently the cause of vulvovaginitis resistant to behavioral treatment in children. *Candida* infections are much less common in prepubertal girls.

3. Toxic Shock

- Caused by *S. aureus* endotoxin release when vaginal penetration prompted by foreign body, usually a tampon.
- Syndrome characterized by fever, hypotension, and diffuse rash, with desquamation of palms of hands and soles of feet. The vaginal mucous membranes are inflamed, and other organ systems (renal, respiratory, GI) are affected.
- Treated with antibiotic with activity against *S. aureus* and supportive care.

4. Autoimmune Hypogonadism

Premature ovarian failure can be associated with other autoimmune disorders. Therefore, when workup indicates ovarian failure as the cause for amenorrhea in a woman under 40 (see below), consider other autoimmune disease such as lupus, antibody-mediated thyroid disease, rheumatoid arthritis.

B. Traumatic and Mechanical Disorders

1. Female Urinary Incontinence

Incontinence is the involuntary loss of urine. This can be caused by abnormal transmission of increases in intra-abdominal pressure to the urethra (stress incontinence), by involuntary bladder contractions accompanied by the urge to void (urge incontinence), or by spontaneous overflow of an overdistended bladder (overflow incontinence). Frequently, incontinence has a mixed picture. This condition affects around 30% of women of reproductive age, and is increasingly common with advancing age.

a. Stress Incontinence

- Most commonly caused by loss of vaginal support of the bladder, the urethrovesical junction, and urethra, and therefore extra-abdominal placement of the urethra. Can result from vaginal trauma associated with childbirth but can be seen in nulliparous women, particularly with advancing age and decreased estrogen status. When abdominally located bladder pressure exceeds urethral pressure, urinary leakage occurs.
- Can be treated by surgical replacement of the urethrovesical junction to an intra-abdominal position in more severe cases.
- The drug phenylpropanolol amine causes α-adrenergic stimulation of the urethral smooth muscle and can be helpful in treatment. In addition, the antidepressant imipramine has both α-adrenergic and anticholinergic properties and can be helpful in treatment, especially when there is also a component of urge incontinence caused by detrusor instability (see below).
- Kegel exercises (voluntary contraction of the pubococcygeus muscle) can improve external urethral musculature tone and aid in treatment.

b. Urge Incontinence

- Most commonly caused by idiopathic detrusor instability or uncontrolled contractions of bladder detrusor muscle.
- Can also be caused by a variety of neurologic diseases such as Parkinson's disease and multiple sclerosis, as well as infection or bladder tumors.

- Treatment options for detrusor instability include behavior modification and biofeedback. Medical treatment includes anticholinergic and antispasmodic drugs such as oxybutynin.

c. Overflow Incontinence

- Occurs when bladder is filled beyond 300–400 mL.
- Can be associated with underlying neurological conditions that interfere with sensation of a full bladder and ability to voluntarily void.
- Can be treated by treating underlying condition if possible and by intermittent self-catheterization.

2. Testicular Torsion

Because the testicles are extra-abdominal organs, they are more prone to torsion than ovaries. This usually occurs in boys and younger men and presents with acute pain and unilateral testicular swelling. Prompt surgical treatment is necessary to avoid necrosis and loss of the testicle.

C. Neoplastic Disorders

1. Female Reproductive

a. Ovarian Neoplasm—While ovarian cancers are not the most common malignancy of the female genital tract, they are the most deadly. In the United States, about 27,000 new cases are diagnosed every year, and ovarian cancer is the cause of about 17,000 deaths. In general, 1.5% of women born in the United States develop ovarian cancer in their lifetime. Familial genetic predisposition to ovarian cancers, along with breast, endometrial, and/or colon cancers, is beginning to be understood. If a woman has one first-degree relative with ovarian cancer, her risk increases to 5%; with more than one first-degree relative, her risk rises to 7%. In women with more than one first-degree relative with ovarian cancer, there is a 3% chance that she has a hereditary ovarian cancer syndrome. Women who have a familial ovarian cancer syndrome have a 40% lifetime risk of developing ovarian cancer. These women may want to consider prophylactic oophorectomy once they have completed childbearing.

While a search for the cause of ovarian cancers has been frustrating to date, epidemiologic evidence would suggest a strong environmental influence. Ovarian cancers are more common in industrialized nations. In addition, long-term use (> 1 year) of oral contraceptives as well as childbearing seem to reduce the risk for ovarian cancer.

The early diagnosis of ovarian cancer is elusive. Frequently, the diagnosis is made after a long history of fairly vague gastrointestinal symptoms. There is to date no reliable early screening technique for asymptomatic women. Pelvic examination, as well as ultrasound in women with familial risk or women with symptoms, remains the mainstay of early diagnosis. Unfortunately, ultrasound carries a high false-positive rate. Invasive surgery and removal of the ovaries with its related morbidity and mortality is the method for distinguishing false- from true-positive adenexal ultrasound abnormalities.

To date, serum tumor markers such as CA 125 testing have not been shown to be helpful in the early diagnosis of ovarian cancer in the average-risk population of women.

While there is a confusing and wide variety of types of ovarian tumors, the epithelial variety is the most common, accounting for 85–90% of ovarian cancers seen in the United States. Ovarian tumors are classified based on the histogenesis of the normal ovary. As such, the broad categories of ovarian neoplasm are: epithelial, germ cell, gonadal stromal, nonspecific mesenchymal, and tumors metastatic to the ovary.

Ovarian cancer is staged surgically. The mainstay of treatment of ovarian cancer is removal of all existing tumor possible with chemotherapy follow-up. For FIGO (International Federation of Gynecology and Obstetrics) staging of ovarian cancers, see Table 9–9.

Epithelial Cell Tumors—There are six types of ovarian epithelial cell tumors: **serous, mucinous, endometrioid, clear cell, Brenner tumor**, and **carcinosarcomas and mixed mesodermal tumors.** These tumors are most commonly found at stage III, and the tumor type has very little influence on prognosis. When earlier-stage ovarian epithelial cell cancers are diagnosed, the histological grade is an important factor in prognosis.

Germ Cell Tumors—This category of ovarian neoplasms includes several different tumor types, all felt to derive from the gonadal germ cell. There is homology evident between the female and male germ cell tumors. They represent only 20% of all ovarian neoplasms. They occur more frequently in younger women and are among the success stories of chemotherapy on gynecologic malignancy treatment.

Dysgerminoma—Uncommon tumor accounting for 3–5% of ovarian malignancies and 1–2% of all ovarian neoplasms. Usually seen in adolescent and young adult women. Tumor is composed of undifferentiated germ cells with lymphocytic infiltration of the stroma, which can form granulomas. Can cause production of hCG secondary to containing syncytiotrophoblastic cells. This is the type of tumor that arises in the gonadal tissue of sexually abnormal females, such as those with gonadal dysgenesis or testicular feminization. In these cases, the dysgerminoma commonly develops in a preexisting gonadoblastoma.

9-9

OVARIAN CANCER STAGING

Stage	Description
I	Tumor limited to ovaries
Ia	Tumor limited to one ovary with no malignant ascites, no surface tumor present, and tumor capsule intact
Ib	Tumor limited to both ovaries, no malignant ascites, no tumor on ovarian surface, and capsule intact
Ic	As in Ia or Ib, but with ruptured capsule or ovarian surface tumor, malignant ascites, or positive peritoneal washings
II	Tumor involving one or both ovaries with pelvic extension
IIa	Metastatic disease or direct extension to uterus and/or tubes
IIb	Metastatic or direct extension to other pelvic tissues
IIc	As in IIa or IIb with ruptured capsule of malignant ascites or positive peritoneal washings
III	Disease involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal lymph nodes; also includes tumor implants on the liver capsule or serial surface of the bowel or omentum
IIIa	Gross tumor limited to the pelvis with microscopic abdominal peritoneal implants and negative lymph nodes
IIIb	Gross tumor limited to the pelvis with abdominal peritoneal nodes all < 2 cm diameter, negative lymph nodes
IIIc	Abdominal peritoneal implants > 2 cm and/or positive retroperitoneal or inguinal lymph nodes
IV	Distant metastases, parenchymal liver, or gastrointestinal mucosal mets. If pleural effusion present, must contain malignant cells to be stage IV

Dysgerminomas present with symptoms of rapid tumor growth such as abdominal enlargement and palpable abdominal mass. They are solid or lobulated fleshy tumors that are often quite large when removed. When discovered, the opposite ovary has a similar tumor 10–15% of the time.

Dysgerminomas show a predisposition to lymphatic spread and are sensitive to adjunctive therapy with both radiation and chemotherapy after primary surgical removal. Currently, chemotherapy is the more popular treatment modality since this allows more chance of preservation of fertility.

Often, there are more aggressive tumors present in dysgerminomas in sexually normal patients. These include endodermal sinus tumors and embryonal carcinoma.

Gonadoblastoma—This rare tumor is made up of both germ cells and gonadal stromal cells as seen in a Sertoli or granulosa cell tumor (see below). Chromosomal studies show abnormalities of the sex chromatin such as 45,X or mosaicism with 45,X/46,XY. Gonadoblastoma can present as primary amenorrhea, developmental abnormalities of the genitalia, and virilization.

This tumor can occur in both sexes; 80% occur in phenotypic women, and the rest are phenotypic men with a variety of gonadal abnormalities such as cryptorchidism and internal female secondary sex characteristics. When both the tumor and the contralateral gonad are removed, the prognosis is excellent.

Endodermal Sinus Tumor—This is the second most common malignant germ cell tumor and represents 22% of germ cell tumors. These tumors usually present clinically with abdominal pain and mass. They occur in younger patients, with the average age at diagnosis being 19. Endodermal sinus tumors cause elevation of serum **α-fetoprotein. (AFP).** The tumors grow rapidly and spread abdominally. Microscopically, tubules lined by a single layer of flattened cuboidal cells are seen and characteristic papillary structures surrounding a central blood vessel, known as **Schiller–Duval bodies,** are present. While this was a quickly progressive and fatal disease in the past, combination chemotherapy has significantly improved the prognosis.

Embryonal Carcinoma—This highly aggressive cancer represents 4% of malignant germ cell tumors. It has been confused with choriocarcinoma and endodermal tumors in the past. It is associated with hormonal abnormalities including precocious puberty, bleeding abnormalities, and hirsutism in about 50% of patients.

Large cells with papillary or glandlike features are seen on histology. Mitotic figures are abundant, and multinucleated giant cells resembling syncytial cells are present. The tumor is thought to arise from the primordial germ cell before embryonic and extraembryonic differentiation has taken place. AFP and hCG are elevated. A combination of surgical and multiagent chemotherapeutic treatments are used with much improved prognosis compared to surgery alone.

Choriocarcinoma—This rare tumor can arise in the ovary in one of three ways: primary gestational choriocarcinoma associated with an ovarian pregnancy; as a germ cell tumor mixed with other neoplastic germ cell elements (usually seen in prepubescent girls); or as a sequela to pregnancy and initially arising in other parts of the genital tract, mainly the uterus. The tumor secretes hCG. Modern combination chemotherapy has much improved the otherwise dismal prognosis in these patients.

Teratoma—Teratomas can be mature or immature, cystic or solid. They contain tissue of ectodermal, mesodermal, and endodermal origin. More than 90% of teratomas are mature cystic teratomas and are composed mainly of mature ectodermal tissue derivatives such as hair, skin, and teeth **(dermoid cysts).**

Immature teratomas are similarly composed of tissue from all three germ layers and contain immature structures. Immature teratomas always contain immature neural tissue, and the amount of this tissue determines the grade of the tumor. Prognosis is closely related to the grade of the tumor and the grade of any peritoneal implants found at the time of diagnosis. This is an uncommon tumor type, responsible for < 1% of all ovarian teratomas. It is most commonly found in the first 20 years of life and has very rarely been reported after menopause. Immature teratomas are never bilateral. In patients with advanced-grade tumors and implants, combination chemotherapy improves the prognosis.

Specialized Teratomas

- Struma ovarii is a specialized, rare teratoma composed of thyroid parenchymal tissue. About a third of patients with this tumor are clinically hyperthyroid. While these tumors may undergo malignant transformation, they are usually benign and cured by removal.
- Carcinoid tumors can be found in the ovary and are usually found in association with gastrointestinal or respiratory epithelium in a mature cystic teratoma. They also can be found in solid teratomas or mucinous tumors (see epithelial tumors above) or may occur alone in pure form. Ovarian carcinoid tumors are usually found in postmenopausal women. These tumors rarely metastasize and in contrast to carcinoid tumors of gastrointestinal origin, one-third of patients with ovarian carcinoid tumors have carcinoid syndrome without metastatic disease. Ovarian carcinoid tumors and coexisting carcinoid syndrome are completely treated by excision.

***Gonadal Stromal Tumors*—**These tumors are derived from **granulosa** and theca cells as well as **Sertoli** and **Leydig** cells and fibroblasts that originate in the gonadal stroma. They account for 5–10% of ovarian cancers and 5% of all ovarian tumors. They are also known as sex cord stromal tumors.

Granulosa and Theca Cell Tumors—These tumors occur in both reproductive and postmenopausal-aged women, and rarely (5% of the time) occur before puberty. While these tumors most commonly produce estrogen, they can less often produce androgens. The tumors are large and often are diagnosed when palpated on abdominal exam. Granulosa cell tumors can be cystic or solid and can be filled with serous, frequently bloody fluid. They are the most common estrogen-secreting tumors, and the estrogen they secrete can affect the endometrium, causing endometrial hyperplasia or even carcinoma. Breast tenderness can also result. On microscopic examination, **coffee bean–shaped cells** and **Call–Exner bodies** (also seen in developing follicles) are present. When granulosa cell tumors occur in children, they produce precocious puberty. These tumors are generally unilateral. When the tumor is confined to one ovary (as is most common at diagnosis) recurrence rates are only 5–10%. Chemotherapy improves survival in more advanced cases. Granulosa cell tumors are bilateral 2–5% of the time.

Thecomas are less common tumors and are always unilateral. These tumors are composed solely of benign theca cells.

Sertoli–Leydig cell tumors contain one or both of their name's cell types. These tumors are also called androblastomas or arrhenoblastomas since more primitive cells can recapitulate testicular development. There may or may not be endocrine manifestation of these tumors with accompanying virilization. They occur most commonly in younger women and account for < 0.5% of all ovarian neoplasms. They are usually unilateral (bilateral only in 5% of cases) and therefore unilateral salpingo-oophorectomy can be utilized for treatment of unilateral disease in younger women who desire preservation of fertility. Both granulosa cell and Sertoli–Leydig cell tumors are considered to have low malignant potential.

Gynandroblastoma—This designation is used when a mixed cell tumor with both granulosa and Leydig cell types is diagnosed. These tumors are very rare and can make estrogens and/or androgens. Like their individual cell-type tumors, they behave as tumors with low malignant potential.

***Nonspecific Mesenchyme-Derived Ovarian Tumors*—**Tumors of many varieties can arise from the supporting structures that the ovary has in common with most other organs. Examples of such tumors include fibromas, hemangiomas, lymphomas, and soft-tissue sarcomas. Of these, fibromas and lymphomas occur most commonly.

***Tumors Metastatic to the Ovary*—**Ten percent of ovarian tumors are actually metastatic disease from another primary site. While many primary cancers can metastasize to the ovary, breast, uterine, and gastrointestinal cancers are most commonly found. A **Krukenberg tumor** refers to a metastatic site in the ovary composed mostly of signet ring cells in metastases in the ovarian stroma. Krukenberg tumors commonly are metastatic disease from a primary gastric tumor. They grossly appear as solid or cystic tumors and can be confused with primary ovarian cancers (see Table 9–10).

b. Cervical Cancer—Reduction in rates of invasive cervical cancer is one of the success stories of modern-day cancer screening. This is because the cervix is accessible to inspection and testing and because the natural history of cervical cancer includes a lengthy preinvasive stage (7–10 years). There is good evidence that cervical cytologic screening programs (Pap tests) are successful in reducing the incidence, and therefore the death rate from, invasive cervical cancer. Current research indicates that there is a link between squamous cell cervical cancers and the human papillomavirus (HPV). Current technology allows the identification of common high- and low-risk types of HPV as an adjunct to cytologic screening with Pap smears. **Cervical intraepithelial neoplasia** (CIN) or **dysplasia** describes the cellular changes seen in cervical squamous cells, which are felt to be a precursor of cervical cancer.

Such changes are classified as mild, moderate, or severe (corresponding to CIN I, II, and III). More recently, The Bethesda System for Pap smear classifications group CIN I with HPV changes in the

9-10

OVARIAN TUMORS

Derivative Tissue Type	Tumors	Special Characteristics Clinical	Special Characteristics Pathology	Occurrence
Epithelial	Serous Mucinous Endometroid Clear cell Brenner Carcinosarcomas/mixed mesodermal	Usually found at stage 3	Tumor type not important in prognosis in early-stage disease	Most common tissue type in ovarian cancers, serous most common
Germ cell		More likely in younger women	Dysgerminoma can produce hCG	20% of ovarian neoplasms
	Dysgerminoma	Dysgerminoma commonly seen in patients with gonadal dysgenesis and testicular feminization		
	Gonadoblastoma	Can present as primary amenorrhea or virilization, also seen in patients with gonadal dysgenesis and testicular feminization	Has both germ and gonadal stromal cells	
	Endodermal sinus tumor	Rapidly growing, produces α-fetoprotein	Schiller-Duval bodies present	Second most common germ cell tumor type
	Embryonal carcinoma	Highly aggressive, can present as precocious puberty; hCG and AFP can be elevated		
	Choriocarcinoma	Rare, can arise de novo or after pregnancy Secretes hCG		
	Teratomadermoid	Benign dermoid common ovarian neoplasm seen in younger women	Teratomas have tissue from all three germ cell layers Dermoids contain ectodermal elements such as hair and teeth	90% of teratomas benign dermoids
	Immature	Immature teratoma is malignant	Immature teratoma contains immature neural tissue	
	Specialized teratoma Struma ovarii		Thyroid tissue tumor seen in ovary, usually benign	
	Ovarian carcinoid	Present with carcinoid symptoms, cured by removal of ovarian carcinoid tumor Usually seen postmenopausally	Often found within other teratomas, do not usually metastasize	
Gonadal/stromal	Granulosa cell tumors	Large tumors Present as precocious puberty or postmenopausal bleeding secondary to estrogen production, usually unilateral and do not recur Low malignant potential	See coffee bean–shaped nuclei or Call-Exner bodies	
	Theca cell tumors (thecomas)	Benign and unilateral		
	Sertoli-Leydig cell tumors (androblastomas and arrhenoblastomas	Usually unilateral and occur in younger women Can produce virilization Low malignant potential		
	Gynandroblastomas	Combination granulosa and Sertoli-Leydig cells Low malignant potential		
Nonspecific mesenchymal (arise in supporting tissue of ovary` common to other organs	Fibromas Hemangiomas Lymphomas Soft tissue sarcomas	Most common of this type are fibromas (benign) and lymphomas		
Metastatic to ovary	Common primaries: Breast Uterine GI tract—Krukenberg tumor	Metastatic from gastric cancer	Signet ring cell mets in ovarian stroma	10% of ovarian malignant tumors are metastatic from another primary

cytologic classification of **low-grade squamous intraepithelial lesions** (LGSIL) and group CIN II and III together as **high-grade squamous intraepithelial lesions** (HGSIL). Once CIN, with or without associated HPV change, has been found on Pap smear screening, Colposcopy and colposcopically directed biopsies of the cervix help direct further treatment. The likelihood that a lesion will progress to invasive cervical cancer seems to increase with the severity of the lesion. Risk factors for cervical cancer include early onset of sexual activity, history of multiple sexual partners, lower socioeconomic status, and smoking. In addition, women infected with HIV have a higher risk of developing invasive cervical cancer with a faster course from preinvasive to invasive disease.

While squamous cell cancers of the cervix account for 85–90% of cervical cancers, adenocarcinomas as well as tumors of mesenchymal origin (endocervical stromal sarcomas, carcinosarcomas, adenosarcomas, leiomyosarcomas, embryonal rhabdomyosarcomas) and other rare tumors such as melanomas, lymphomas, carcinoid, and metastatic disease can exist in the cervix. Adenocarcinomas of the cervix account for 10–15% of cervical cancers, with all others occurring very rarely.

Invasive cervical cancer spreads contiguously to the top of the vagina and the uterus and paracervical tissues. Disease can spread distantly by lymphatic spread and is found first in the pelvic and para-aortic lymph nodes. Advanced direct extension can also involve the rectal and bladder mucosa.

Cervical cancers are staged clinically on pelvic exam prior to surgery, in combination with preoperative cervical biopsy, radiographic studies of the urinary and gastrointestinal tract, as well as cystoscopy and colonoscopy (see Table 9–11).

Local excision or destruction with laser, cautery, or freezing is the treatment of choice for preinvasive lesions (CIN II–III). CIN I can be either observed or treated, depending on the patient's age

9-11

CERVICAL CANCER STAGING

Stage	Description
0	Carcinoma in situ (CIS)
I	Cancer confined to the cervix
Ia	No gross lesion, invasive cancer seen only microscopically, invasion limited to a maximum depth of 5 mm and no wider than 7 mm
Ia1	Stromal invasion no greater depth than 3 mm and no wider than 7 mm
Ia2	Stromal invasion 3–5 mm and no wider than 7 mm, vascular or lymphatic space involvement does not change the stage
Ib	Lesion either grossly visible or invasion greater depth than 5 mm, width greater than 7 mm on microscopic lesion, lesion limited to the cervix
Ib1	Clinical tumor no greater than 4 cm in size
Ib2	Clinical tumor more than 4 cm in size
II	Involvement of up to the upper two-thirds of the vagina or parametrial involvement that does not extend to the pelvic sidewalls
IIa	Evidence of vaginal but not parametrial involvement
IIb	Parametrial involvement not extending to the pelvic sidewall, with or without involvement of the upper two-thirds of the vagina
III	Extension to the pelvic sidewall or lower third of the vagina, hydronephrosis, or nonfunctioning kidney with no other etiology
IIIa	Involvement of the lower third of the vagina without parametrial extension to the pelvic sidewall
IIIb	Extension to the pelvic sidewall and/or hydronephrosis, nonfunctioning kidney
IV	Extension outside the reproductive tract
IVa	Involvement of rectal or bladder mucosa
IVb	Extension of disease outside the pelvis or distant metastases

and likelihood to adhere to recommended follow-up. Invasive cancers are treated with equal success by either surgery or radiation for stage I and IIa lesions. Surgical treatment includes radical hysterectomy with removal of parametrial tissues and the upper third of the vagina along with the uterus and tubes. Pelvic lymphadenectomy is also performed, and postoperative radiation is recommended for patients with positive lymph node spread.

Stage I cancers have a > 85% 5-year survival rate, while stage II disease has a 66% and stage III disease a 39% 5-year survival.

c. Vaginal Cancer—Squamous cell cancers are the most common cancers found in the vagina and almost always occur in the upper third of the vagina. As with cervical cancers, an early, preinvasive condition can be seen. While cervical lesions are usually unifocal, vaginal intraepithelial neoplastic lesions are often multifocal. Vaginal cancers are rare.

Both the spread (by direct extension and through pelvic lymph nodes) and symptoms (vaginal discharge, which is often bloody and exacerbated by intercourse) of vaginal cancers in the upper third of the vagina are similar to advanced cervical cancer.

Vaginal cancers are usually treated by radiation, while intraepithelial neoplasia is treated most commonly by local excision or laser ablation. Five-year survival for patients with stage I disease is 90%, with decreasing survival in advanced stages. Survival statistics are based on very small series of patients since this cancer is so rare (see Table 9–12).

The administration of diethylstilbestrol (DES) in the first and early second trimester of pregnancy was popular in the mid-1940s through the 1950s in an attempt to prevent miscarriage. Since that time, in utero exposure to DES has been shown to disrupt the usual transformation of müllerian-derived columnar epithelium to squamous epithelium in the upper vagina and cervical surface. This disruption leads to adenosis, where glandular cells persist either on the surface or beneath surface squamous epithelium in affected vaginal and ectocervical tissue. It is possible that the otherwise rare clear cell vaginal carcinomas observed in young DES-exposed women arise in this tissue.

d. Vulvar Neoplasia—Epithelial disorders of the vulva run the gamut from intraepithelial lesions to invasive cancers. While vulvar intraepithelial neoplasia (VIN) is usually seen in postmenopausal women in their 50s and 60s, it can be seen in both older and younger women. As with CIN, there is a strong association between infection with high-risk HPV types and VIN. These lesions are usually diagnosed with careful inspection of the vulva on routine pelvic

9-12

VAGINAL CANCER STAGING

Stage	Description
0	Carcinoma in situ
I	Limited to the vaginal wall
II	Involving subvaginal tissue but not extending to the vaginal sidewall
III	Extension to the vaginal sidewall
IV	Extension beyond the pelvis or to the rectal or bladder mucosa
IVa	Extension to adjacent organs and/or extension outside the pelvis
IVb	Distant metastases

exam or when the patient herself notices a lesion. The diagnosis is confirmed on vulvar biopsy. Treatment is surgical excision or laser vaporization.

Invasive vulvar cancer makes up 5% of all malignancies of the female genital tract. These tumors are almost always squamous cell in origin. Other tumor types, including melanoma, basal cell, and adenocarcinomas, are more rarely seen. While vulvar cancers are slow to spread beyond the vulva, when they do it is via the lymphatic drainage of the vulva. Invasive vulvar cancer is treated by radical vulvectomy plus inguinal and pelvic lymphadenectomy.

For staging of vulvar cancers, see Table 9–13.

e. Gestational Trophoblastic Disease—Gestational trophoblastic neoplasias (GTNs) once were most often fatal. However, with the addition of chemotherapy to the treatment, these are now among the most curable gynecologic cancers.

Hydatidiform Mole—When a complete molar pregnancy is present, no embryo develops and the uterus is filled with swollen chorionic villi with trophoblastic proliferation and absence of vasculature. All chromosomal material (with karyotypes of 46,XX usually seen in complete moles) is of paternal origin since moles are felt to arise from fertilization of an egg devoid of maternal chromosomal material. The less common partial mole has both placental and fetal tissue present with focal swelling and proliferation of villi. Partial moles usually have a triploid karyotype (69,XXX, XXY, or XYY) and the fetus usually dies in the first trimester.

When a complete mole is present, the patient may have a larger (50%) or smaller (30%) than expected uterine size based on dates. The hallmark of a complete mole is a markedly elevated **serum hCG**, and this marker is used to follow the success of treatment. **Theca lutein cysts**, which can become quite large, can develop on the ovaries, probably because of high hCG levels. When these are present, malignant sequelae to the mole (see below) are more likely. In addition, nausea and vomiting are frequently present. Moles can be responsible for the development of **preeclampsia** in the first trimester. Preeclampsia is not seen this early in normal pregnancies. **Hyperthyroidism** can also be present because high levels of hCG can cause acceleration of thyroid function.

9-13

VULVAR CANCER STAGING

Stage	TNM Class	Description
0	TIS	Carcinoma in situ
I	T1 N0 M0	Confined to the vulva or perineum, ≤ 2 cm in diameter Ia—stromal invasion < 1 mm Ib—stromal invasion > 1 mm
II	T2 N0 M0	Tumor confined to vulva and > 2 cm in size
III	T3 N0 M0 T3 N1 M0	Any size tumor with adjacent spread to lower urethra, vagina, and/or anus
	T1 N1 M0 T2 N1 M0	Unilateral node involvement
IVa	T1 N2 M0 T2 N2 M0 T3 N2 M0 T4 N (any) M0	Invasion of upper urethra, bladder, or rectal mucosa; pelvic bone and/or bilateral node involvement
IVb	T (any) N (any) M1	Any distant mets including pelvic lymph node involvement

Moles are currently usually diagnosed when a characteristic **snowstorm pattern** is seen in the uterus with absence of a fetus. Partial moles are inconsistently detected on ultrasound, and frequently the diagnosis of missed abortion is made preoperatively and partial mole discovered only on pathologic examination of products of conception. Women with partial moles are less likely to develop persistent or metastatic disease. While the incidence of hydatidiform mole is around 1/1,000 pregnancies, once a woman has had one mole she has a 1% chance of developing a mole in future pregnancies. Once a woman has had two moles, her risk for recurrence with a future pregnancy increases to 1 in 6.5. The likelihood of persistent or metastatic disease increases in repeated molar pregnancies as well.

Treatment for all moles is complete evacuation of the uterus, and hCG levels are followed until no hCG is detected for 6–12 months. In the absence of an intervening pregnancy, 20% of the time persistent disease is found, indicated by plateau or rising hCG titers. When this occurs, chemotherapy is the treatment of choice.

While a hydatidiform mole precedes malignant trophoblastic disease about half of the time it is detected, 25% of the time this diagnosis is preceded by a normal pregnancy and 25% of the time by an abortion or ectopic pregnancy. Common sites for metastases of GTN are lung, liver, and brain. See Table 9–14 for classification of GTN.

f. Uterine Cancer

Endometrial Cancer**—**The most common cancer to affect the uterus; endometrial cancer is the most common gynecologic malignancy, with 35,000 cases diagnosed in the United States every year, resulting in 6,000 deaths from the disease.

Endometrial **hyperplasia** describes an array of changes in the endometrium felt to be potential precursors to endometrial cancer. There are four patterns: **simple, complex, simple with atypia,** and **complex with atypia.** Atypical hyperplasia frequently coexists with endometrial cancer and is also far more likely to progress to endometrial cancer. While adenocarcinoma is the most common histologic subtype, adenoacanthoma, adenosquamous, clear cell, papillary, and secretory carcinomas are also seen. The papillary serous and clear cell varieties of endometrial cancer are recognized to be highly aggressive uterine cancers, even when diagnosed in the earliest stages. Otherwise, early-stage, low-grade dis-

9-14

GESTATIONAL TROPHOBLASTIC NEOPLASIA CLASSIFICATION

(1) Disease limited to uterus, nonmetastatic disease
(2) Disease outside of uterus, metastatic disease
- (a) Favorable prognostic factors:
  - (i) Last pregnancy within last 4 months
  - (ii) hCG prior to treatment < 40,000 mIU/mL
  - (iii) No liver or brain metastases
- (b) Poor prognostic factors:
  - (i) Last pregnancy > 4 months ago
  - (ii) Pretreatment hCG > 40,000 mIU/mL
  - (iii) Liver and/or brain metastatic disease
  - (iv) Prior chemotherapy treatment
  - (v) Disease occurring after a term pregnancy

ease has excellent posttreatment survival rates. For stage I grade 1 (well-differentiated) disease, 5-year survival is 94%.

Risk factors for endometrial adenocarcinoma include obesity, nulliparity, diabetes, and later menopause. Use of estrogens by themselves (without the addition of progesterone) has been repeatedly shown to increase risk of endometrial cancer and is largely avoided today. In addition, women who are taking tamoxifen for chemotherapy after the diagnosis of breast cancer (or more recently for prophylaxis in women at high risk of developing breast cancer) may have an increased risk of developing endometrial cancer. However, at least in appropriately treated women with the diagnosis of breast cancer (see section II.C.1.h), reduction in breast cancer recurrence seems to be greater than increased risk of endometrial cancer.

Use of oral contraceptives has been shown to decrease risk of endometrial cancer.

Endometrial cancer usually presents early in the course of the disease with abnormal uterine bleeding, especially after menopause. Prompt attention to this symptom with endometrial biopsy in this clinical setting leads to early diagnosis. Treatment is hysterectomy with removal of tubes and ovaries. Pelvic lymph node dissection and radiation are adjunctive treatments in more advanced disease; chemotherapy is usually reserved for very advanced cases or recurrent disease. See Table 9–15 for staging. In addition to staging, grade of differentiation (well [1], moderately [2] or poorly [3]) of adenocarcinoma is also an important factor in treatment and prognosis.

Nonendometrial Neoplasms of the Uterus

Leiomyoma—One of the more common gynecologic diagnoses. Leiomyomas (fibroids) are benign tumors of the myometrium and occur in up to 25% of women over 35. While most are asymptomatic, myomas can grow quite large and cause symptoms of pelvic heaviness and dysmennorrhea because of their size. Less frequently, they can cause hydronephrosis and subsequent renal damage secondary to physical pressure on the ureters. Myomas can be submucous, intramural, subserous, or pedunculated. Submucous fibroids are most commonly associated with heavy, frequent bleeding. Multiple fibroids frequently exist at multiple sites in the uterus. The tumors are estrogen dependent and frequently enlarge at a more rapid rate during pregnancy and tend to regress postmenopausally. Very rarely, they undergo

9-15

ENDOMETRIAL CANCER STAGING

Stage	Description
Ia	Tumor limited to the endometrium
Ib	Invasion of less than one-half of the myometrium
Ic	Invasion of more than one-half of the myometrium
IIa	Extension of cancer to cervix with endocervical glandular involvement only
IIb	Invasion of cervical stroma
IIIa	Tumor extends to uterine serosa and/or ovaries/tubes and/or positive cytology in peritoneal washings
IIIb	Metastatic disease in the vagina
IIIc	Disease involving pelvic or para-aortic lymph nodes
IVa	Involvement of bladder or bowel mucosa
IVb	Metastases distantly, includes metastatic disease in inguinal nodes and abdomen

malignant degeneration and become leiomyosarcomas (see below).

Uterine Sarcomas—While these are uncommon gynecologic tumors, they are very deadly. They account for about 4% of all uterine cancers. Uterine sarcomas can arise from the myometrium or from the endometrial stroma and glands. These tumors can contain tissue elements seen in the uterus (homologous) or can also contain tissue elements foreign to the uterus (heterologous).

These tumors usually appear in women in their 50s (leiomyosarcoma) or 60s (mixed mesodermal sarcomas and endometrial stromal sarcomas) and are characterized by a rapidly enlarging pelvic mass, often accompanied by vaginal bleeding. Leiomyosarcomas can rarely arise in myomas and are currently diagnosed histologically when > 10 mitoses/HPF are seen or when 5 mitoses with accompanying atypia/HPF are seen.

In order for a mixed müllerian tumor to be diagnosed, both carcinoma and sarcomatous elements must be found. In heterologous tumors, tissue not typically seen in the uterus such as bone, cartilage, or skeletal muscle (rhabdomyosarcoma seen in girls) must be seen. Early metastatic and hematogenous spread is common with mixed müllerian tumors and prognosis is poor.

Treatment is surgical for the uterine sarcomas, including total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), and pelvic lymphadenectomy. The value of postoperative radiation is controversial. Chemotherapy has been shown to improve outcome.

g. Fallopian Tube Carcinoma—Tubal cancer is rare and accounts for < 1% of gynecologic cancers. The average age at diagnosis is 50. Presenting symptoms include vaginal bleeding (50%); pain; and profuse, watery discharge. The diagnosis is frequently made postoperatively when surgery is done for recurrent postmenopausal bleeding without demonstrable uterine pathology or for a pelvic mass of unknown etiology. On microscopic examination, the carcinoma arises from the mucosal surface of inner tube. Cancer is present in both tubes about 10–25% of the time.

Treatment is surgical with TAH/BSO. Peritoneal cytology is obtained to aid in staging, and a partial omentectomy is indicated since the omentum is a common metastatic site. As with ovarian cancer, optimal debulking with removal of all disease that is evident seems to be the most important part of treatment. The role of chemotherapy is controversial. For staging of fallopian tube carcinoma, see Table 9–16.

h. Breast Neoplasia

Benign Breast Disease

- Symptoms of benign breast disease such as breast pain and swelling are very common and occur in more than 50% of women at some time in their lives. Benign conditions account for two-thirds of overall breast masses, including fibroadenomas, breast cysts, and papillomas. In the perimenopausal and postmenopausal age group, the likelihood that a breast mass is benign falls as the individual woman ages.
- Normal breast tissue contains predominantly adipose and fibrous tissue in the nonlactating state. When the fibrous elements cause irregularity or lumpiness in the breast on palpation, this is called fibrocystic change. Especially in the

9-16

FALLOPIAN TUBE CARCINOMA STAGING

Stage	Description
0	Limited to tubal mucosa (carcinoma in situ)
Ia	Limited to one tube, extension to submucosa or muscularis but not through serosa, ascites absent
Ib	As in Ia but growth limited to both tubes
Ic	Extension of tumor to tubal serosa, or ascites or peritoneal washing with malignant cells
IIa	Spread to uterus or ovaries
IIb	Spread to other pelvic tissues
IIc	As in IIa or b with ascites or peritoneal washings containing malignant cells
IIIa	Negative nodes with tumor limited to the pelvis, positive microscopic seeding of peritoneal surfaces of the pelvis
IIIb	As in IIIa but with peritoneal implants grossly visible but ≤ 2 cm in diameter
IIIc	Implants > 2 cm or positive nodes
IV	Distant metastases

premenstrual period, when these changes are the most prominent, pain and tenderness may be present. In addition, cysts can form in the breast, which are filled with clear to greenish fluid when drained.

- While there is no definitive treatment for fibrocystic breast changes, elimination of xanthenes (caffeine) and addition of vitamin E may be helpful.
- **Fibroadenomas** are the most commonly diagnosed breast masses in younger women. They are benign tumors and are often multiple and bilateral. They can be diagnosed either by needle biopsy or surgical excision.
- **Phylloides** tumors are rare breast lesions that contain both stromal and epithelial proliferation. They are slow growing and occur most commonly in premenopausal women. While most are benign, some do show histologic characteristics of malignancy.
- **Intraductal papillomas** usually present with a clear, unilateral, spontaneous, single-duct nipple discharge. It appears that these lesions rarely undergo malignant transformation.

Breast Cancer

- Risk factors for breast cancer include: nulliparity, first delivery after age 34, early menarche (before 12) or later menopause (after 50), higher socioeconomic status, obesity, Jewish ancestry, family or personal history of breast cancer, and high dietary fat intake. Certain inheritable mutations on the BRCA-1 and BRCA-2 genes have been shown to be associated with a greatly increased risk of breast cancer. Despite these risk factors, growing older and being a woman are the most important risk factors for the development of breast cancer.
- Early parity (before age 18), breast-feeding, early menopause or surgical castration, and observance of lower-fat diets and abstinence from alcohol all seem to confer some protection against breast cancer.
- Mammography and clinical and breast self-exam are usual first steps in the diagnosis, with breast biopsy as confirmation.
- Treatment involves either lumpectomy or mastectomy accompanied by axillary node dissection in most cases. Adjuvant radiation and chemotherapy are utilized with later-stage disease.
- **Ductal carcinoma in situ** (DCIS) is more frequently diagnosed as screening mammogram utilization has increased. Its natural

history and chance of progression to invasive breast cancer is incompletely understood, and therefore treatment modality is controversial. Both lumpectomy and mastectomy are treatment options. There is a 5%/year recurrence rate, with recurrences usually occurring at the original site. About half of these recurrences are DCIS and half are invasive cancers.

- **Lobular carcinoma in situ** (LCIS) is usually found incidentally on breast biopsy for benign disease. It is commonly multifocal and appears to be a precursor of invasive ductal carcinoma with a 1%/year recurrence rate. Treatment is controversial since it is debatable whether LCIS is a true cancer and recurrences tend to appear at different sites than the primary lesion.
- While radical mastectomy is the classical surgical treatment for breast cancer, recent studies have well established the safety of breast-conserving lumpectomy with ipsilateral lymph node dissection as surgical treatment for most women with stage 1 and 2 breast cancers (see Table 9–17). Sentinel lymph node biopsy, if negative, can preclude axillary node dissection in early-stage disease.
- Adjuvant radiation is commonly used when breast conserving procedures are utilized. Adjuvant chemotherapy is utilized when lymph nodes contain disease or when tumors are of a "high-risk" type. Long-term (5 years) treatment with tamoxifen is used in women with estrogen receptor–positive tumors.
- When invasive breast cancer is present, long-term survival (as well as treatment) is influenced by the presence and number of axillary lymph node metastases, the tumor's hormone receptor status (receptor-positive cancers have a better prognosis), the tumor size and grade, and the presence of vascular invasion as well as the location of the tumor in the breast.

2. Neoplasms of the Male Genital Tract

a. Testicular Cancer—Testicular tumors are the second most common cancer in men between the ages of 20 and 34. They are most commonly caused by germ cell neoplasms (95%) and less commonly by Leydig cell tumors.

- **Germ cell neoplasms** generally present with unilateral testicular enlargement. The most common type of germ cell neoplasm, a

9-17

BREAST CANCER STAGING

Stage	Description
0	Carcinoma in situ (LCIS or DCIS) or Paget's disease of the nipple without evidence of invasion
I	Tumor < 2 cm in greatest diameter without nodal or distant metastases
IIa	Tumor up to 2 cm in greatest diameter with evidence on ipsilateral axillary involvement of mobile node(s), or between 2- and 5-cm tumor size without nodal or distant metastases
IIb	Tumor of 2–5 cm with involvement of mobile ipsilateral axillary lymph node(s), or tumor > 5 cm without node involvement
IIIa	Tumor of any size with ipsilateral fixed axillary node involvement or tumor > 5 cm with ipsilateral mobile axillary node involvement
IIIb	Tumor of any size with extension to the chest wall and/or skin (peau d'orange) with any nodal status, any size tumor with metastases to ipsilateral internal mammary lymph node(s)
IV	Any size tumor with any nodal status with distant metastases

seminoma, is responsive to orchiectomy and radiation, with a 5-year survival of 100% for localized disease. When disseminated disease is present, survival drops to 20%.

- **Leydig cell tumors** are benign but can be associated with gynecomastia and precocious puberty in children.

b. Prostate Cancer—Prostate cancer is the second most common cancer in men. Early detection can be accomplished with digital rectal exam and palpation of the prostate and more recently by serum **prostate-specific antigen (PSA) testing.** In addition, early prostate cancers are found in surgical specimens from prostate surgeries done to relieve the symptoms of benign prostatic hypertrophy (see section II.J). More advanced disease can cause ureteral or urethral obstruction, and bone is a common site for distant metastases.

Treatment involves surgical removal of the prostate. Radiation, chemotherapy, and hormonal therapy are all utilized in treatment as well. Because prostatic cancer is a slowly progressive disease, watchful waiting is often the treatment of choice when early disease is diagnosed in older men whose life expectancy is < 10 years.

D. Disorders of Metabolic and Regulatory Processes

1. Female

a. Ovulatory Disorders

- Absence of ovulation usually produces an abnormal bleeding pattern in reproductive-aged women. This pattern can range from **oligomenorrhea** or **amenorrhea** to **menorrhagia** and **metrorrhagia.** Hirsutism also can accompany anovulation, although it can also be seen in ovulating women.
- Lack of or less frequent ovulation can cause infertility and may be a risk factor for later development of endometrial cancer because of long-term excess stimulation of the endometrium by estrogen.
- Central (pituitary and hypothalamic) causes of anovulation are hyperprolactinemia (often associated with a prolactin-secreting pituitary adenoma), other pituitary tumors, and factors that affect the pulsatile secretion of GnRH at the level of the hypothalamus such as stress, anorexia, and excessive exercise.
- Decrease in ovulation can also result from interference with the ovarian–pituitary feedback mechanism. In pregnancy, ovulation is suppressed because sex steroid levels do not fall and therefore subsequent elevation of FSH (which stimulates ovulation) does not occur.
- Thyroid disorders and liver disease can affect clearance of estrogen and allow continued elevation of estrogen levels and therefore suppression of FSH surge necessary to initiate ovulation.
- Obese women may not ovulate because of release of adipose-produced estrogen converted from androstenedione of adrenal origin.
- **Polycystic ovarian syndrome** (PCOS) describes a disorder of ovulation in which multiple small cysts are seen on the ovaries bilaterally in the setting of oligomenorrhea or amenorrhea. This is thought to be caused by repeated anovulation and subsequent chronic elevation of estrogens and androgens. Hence, acne and hirsutism are frequent components of this syndrome. Associated hyperinsulinemia secondary to insulin resistance is now well recognized. Women with chronic anovulation are at risk for future diabetes.

b. Endometriosis

- Classically, endometriosis causes secondary dysmenorrhea, which can then progress to continuous pelvic pain. Dyspareunia is also a common symptom.
- Endometriosis is caused by implantation of endometrial tissue in nonendometrial sites, most commonly the serosal surface of the uterus and tubes, the ovaries, and the pelvic peritoneum, particularly in the cul-de-sac and other dependent sites in the pelvis. Endometriosis can also be found on the peritoneal surface of the bowel as well as the rectal mucosa and bladder mucosa and in the rectovaginal septum. Pulmonary endometrial implants causing menstrual hemoptysis have also been described.
- Ectopic endometrial implants cause irritation and adhesion formation on the surrounding tissue and can form large collections called **endometriomas** on the ovary. Because the contents of these cystic masses resemble liquid chocolate, they are often referred to as **chocolate cysts.**
- Endometriosis is thought to contribute to infertility by causing tubal damage and possibly ovarian dysfunction.
- Severity of the disease on inspection of the pelvis does not always match the severity of symptoms.
- While several theories have been proposed for the pathogenesis of endometriosis, none have been proven. Theories include implantation of tissue following retrograde menstruation, decrease in cellular immunity allowing the implantation of endometrial tissue, and genetic predisposition.
- Current treatment involves surgical removal and/or hormonal treatment. Surgery can either be done in an attempt to remove or ablate existing implants or can involve removal of the uterus and or one or both ovaries (TAH/BSO considered to be definitive treatment). Hormonal treatment can involve either oral contraceptives to limit growth and attempted shedding of implants or GnRH agonists to limit pulsatile secretion of GnRh and therefore turn off the hypothalamic–pituitary–ovarian axis and turn off ovarian function and therefore stimulation of implants by eliminating pulsatile release of GnRH from the hypothalamus.

c. Precocious Puberty—Precocious puberty is defined as appearance of secondary sex characteristics and other signs of puberty (advanced bone age) before age 8 in girls and age 9 in boys. Further classified as central or peripheral. Can also see incomplete precocity.

Central Precocious Puberty

- Frequently idiopathic, chronologically early initiation of GnRh-stimulated gonadotropin secretion, which then stimulates ovarian sex steroid production.
- Can also be caused by CNS abnormality such as a tumor or inflammation.
- Follows normal progression of puberty: thelarche, pubarche, and menarche in girls, and testicular growth followed by growth of the penis and the appearance of pubic hair in boys.
- More common in females and more likely to have definable underlying CNS cause in males.
- **Congenital hypothalamic hamartoma** is the most common type of tumor to cause precocious puberty.

Peripheral (or GnRH-Independent) Precocious Puberty—Causes include abnormal production of gonadotropins or sex steroids in both boys and girls. These can arise from tumor production, enzyme deficiencies (congenital adrenal hyperplasia), and mutations of receptors (McCune–Albright syndrome and the autosomal dominant familial male precocious puberty). Hypothyroidism in children can also cause precocious puberty, possibly because high levels of thyroid-stimulating hormone (TSH) can attach to FSH receptors and promote ovarian sex steroid production.

Incomplete Precocity

- Isolated development of secondary sex characteristics—**thelarche, pubarche,** and **menarche.** May often be transient.
- Premature thelarche usually occurs before 2 years of age and is the result of isolated elevation of estrogen levels without gonadotropin elevation. In addition, bone maturation is not advanced, and the uterus and ovaries appear prepubertal on ultrasound. Regression is usually seen over time, and no specific treatment is necessary.
- Premature pubarche indicates the presence of pubic hair prior to age 8 in girls and age 9 in boys. It is attributed to early adrenal androgen secretion. Other diagnoses such as virilizing congenital adrenal hyperplasia and androgen-secreting tumors should be excluded
- Premature menarche can occur in infants as the result of withdrawal of maternal estrogen at birth. In older girls, vaginal infection, bleeding from vaginal trauma, as well as urinary tract bleeding can be confused with true premature menarche. In addition, rare tumors such as rhabdomyosarcoma and endodermal carcinoma, as well as clear cell vaginal carcinomas in DES-exposed girls, can be the cause of isolated vaginal bleeding. Isolated ovarian cysts with associated sex steroid production and subsequent menses do occur in the absence of other signs and symptoms of puberty.

d. Delayed Puberty—There are three broad categories of causes for delayed puberty: hypergonadotropic hypogonadism (lack of ovarian or testicular response), hypogonadotropic hypogonadism (failed hypothalamic or pituitary function), and constitutional delay or late activation of the hypothalamic–pituitary–gonadal axis.

***Hypergonadotropic Hypogonadism*—**Elevated FSH and LH, low or absent sex steroids.

- **Turner's syndrome** (45,X) is the most common cause of hypergonadotropic hypogonadism in girls. One of the consequences of a missing X chromosome seems to be an inability of the ovaries to respond to elevated levels of FSH and LH.
- Other abnormal karyotypes cause mixed gonadal dysgenesis. The most common karyotypes in these cases is 45,X/46,XY. Genitalia may be female, male, or ambiguous at birth depending on the amount of exposure to testosterone in utero. When Y chromosome is present in these cases, there is an increased chance of development of gonadal tumors, especially gonadoblastomas.
- Gonadal dysgenesis can occur with 46,XX and 46,XY karyotypes as well and lead to delayed puberty. With 46,XX dysgenesis, streak ovaries but otherwise normal internal genitalia are seen. With 46,XY gonadal dysgenesis, both internal and external genitalia can be ambiguous. Primitive gonads should be removed because of increased risk for development of go-

nadoblastoma and/or dysgerminoma. Both 46,XX and 46,XY gonadal dysgenesis may be caused by a mutation on the genetic locus for gonadal differentiation. **Perrault syndrome** describes 46,XX gonadal dysgenesis accompanied by sensorineural deafness.

- **Klinefelter's syndrome** is the most common cause of primary testicular failure in men. The patient's karyotype is 47,XXY, which results in small testes with azoospermia and euchnoidal skeletal proportions and elevation of FSH and LH secondary to inability of the testes to produce adequate levels of testosterone. Other chromosomal variations with additional X and/or Y chromosomes exist. In these cases, as the number of X chromosomes increases, intelligence decreases. Increased number of Y chromosomes is associated with aggressive and antisocial behavior.
- **Myotonic dystrophy**, a congenital condition characterized by progressive weakness and loss of muscle tone, is also associated with primary testicular failure.
- **Cryptorchidism**, or failure of the testes to descend, occurs in 3% of males at birth. By 1 year, most of these boys' testes have spontaneously descended. Ongoing cryptorchidism exposes the testes to higher intra-abdominal temperatures and can lead to defects in sperm but not testosterone production.
- **Testicular feminization** occurs when there is a congenital absence of testosterone receptors. Although cryptorchid abdominal testes are present, affected patients are genetically males but are phenotypically females with short vaginas because of inactivity of androgens during fetal growth. However, the uterus, cervix, and tubes are absent since the testes do secrete müllerian-inhibiting factor. Female secondary sex characteristics develop because of peripheral conversion of testosterone produced by the testes and adrenals to estrogen. There is absence of axillary and pubic hair since active testosterone receptors are not present. These patients are usually not aware of the abnormality until they reach puberty and have been raised as girls. Disclosure of the discrepancy between their karyotypic sex and phenotypic sex must be handled with caution and care.
- **Early gonadal trauma** (more common in boys than girls) can cause hypergonadotropic hypogonadism. Toxins, including chemotherapy, can be the cause, as can radiation. Mumps and gonococcal infections can also cause damage to the seminiferous tubules.
- **Autoimmune syndromes** can include autoimmune oophoritis which can lead to premature ovarian failure, even before puberty.

Hypogonadotropic Hypogonadism—Low FSH, LH, and sex steroids.

- Most commonly caused by idiopathic gonadotropin deficiency. This can have a sporadic as well as autosomal recessive, autosomal dominant, and X-linked inheritance pattern.
- In men who have hypogonadism, there is an X-linked genetic deletion called **Kallman's syndrome.**
- Other genetic mutations in genetic material involved in coding for FSH and/or LH have been described in patients with hypogonadotropic hypogonadism.
- **Congenital hypopituitarism** and structural abnormalities of the

hypothalamus can also cause hypogonadotropic hypogonadism. Associated hormonal deficiencies such as **diabetes insipidus** or **hyperprolactinemia** point to such central causes.
- Eating disorders can cause either amenorrhea or delayed puberty, as can chronic illnesses or intense exercise. All cause hypothalamic hypofunction.

Delayed Menarche

- When associated with otherwise normal development of secondary sex characteristics, delayed menarche can be caused by obstruction to menstrual flow or abnormalities of ovarian steroidogenesis.
- Anatomic causes include absence of the vagina with or without accompanying uterine agenesis (**Mayer–Rokitansky–Kuster–Hauser syndrome**). Imperforate hymens can also cause obstruction to outflow of menstrual blood.
- PCOS can also present with primary amenorrhea or delayed menarche with otherwise normal development. Hirsutism and acne are often accompanying signs of the androgen excess that is part of this heterogeneous disorder.
- In mild cases, **congenital adrenal hyperplasia** cannot manifest itself until puberty with premature adrenarche accompanying oligomenorrhea or amenorrhea. This is caused by either a **21-hydroxylase** (most common), **11β-hydroxylase**, or a **3β-hydroxysteroid dehydrogenase deficiency**, all of which lead to excess adrenal androgen production in affected girls with subsequent anovulation and virilization.

E. Infertility

- Infertility is defined as the inability of a couple to conceive after 1 year of trying to become pregnant. It is further defined as primary (never having become pregnant) or secondary (delay in current conception after prior conception).
- While infertility is estimated to affect around 13% of couples in the United States, it becomes much more common as women age past 35, reaching 85% by age 45.
- Causes of infertility include abnormalities in the male ejaculate (35%), pelvic anatomic factors including tubal factors that inhibit or impede sperm and egg meeting for fertilization (40%), disorders in ovulation (15%), and unexplained causes (10%).
- Tubal factor infertility can be seen when tubal scarring is caused by pelvic infection, endometriosis, or pelvic surgery.
- Anovulation can be treated by treating associated disorders such as hyperprolactinemia (with the drug bromocriptine, a dopamine agonist that inhibits prolactin secretion by the pituitary), thyroid dysfunction, or eating disorders. In cases of PCO, treat by ovulation induction. Ovulation induction agents include orally administered **clomiphene citrate**, which acts as an antiestrogen at the level of the pituitary and hypothalamus and therefore enhances frequency of FSH and LH pulsatile secretion and promotes ovulation, or injected **human menopausal gonadotropins (menotropins)** and **purified FSH (Metrodin).** GnRh agonists are often used in conjunction with metropin to turn off a woman's endogenous hormonal production and make the ovaries more responsive to medical attempts to induce ovulation. Clomiphene, menotropins, and Metrodin are all associated with ovarian hyperstimulation and increased chance of multiple births. These complications are much more common with metropin

► cram facts

Tubal factor infertility is a common sequela of pelvic inflammatory disease and endometriosis. In vitro fertilization bypasses the tubes by fertilization of retrieved eggs with sperm in vitro with reimplantation of embryos, after fertilization, directly into the uterus.

and Metrodin, and patients receiving these medication require close and specialized monitoring.

- **Semen analysis** allows for initial evaluation of male infertility. Sperm production can be affected by thyroid and adrenal disorders as well as systemic disease such as cystic fibrosis and myotonic dystrophy, in addition to previously discussed testicular and hypothalamic–pituitary disorders. When abnormalities are found, possible treatment options, in addition of treatment of the underlying condition of possible, include intrauterine insemination with washed sperm and intracytoplasmic sperm injection as part of assisted reproductive technology. In addition, donor sperm can be used for artificial insemination.
- **Varicoceles** are common abnormalities involving dilatation and increased tortuosity of the pampiniform plexus of veins in the spermatic cord. While not all men with varicoceles are infertile, this abnormality can cause increased temperature in the testicles and therefore interfere with normal sperm production. When an abnormality is found in the semen analysis in the male partner of a couple, consideration should be given to repair.

F. Recurrent Pregnancy Loss

- Defined as more three or more consecutive spontaneous abortions.
- Even with three or more spontaneous abortions, subsequent pregnancy success rate is 50%.
- To date, most (50–60%) spontaneous abortions are associated with an abnormal karyotype in the aborted fetus. These become more common with advancing maternal age. In addition, parents carrying uncommon balanced or robertsonian translocations can be phenotypically normal but have a very high risk of pregnancy loss.
- Uterine abnormalities such as **müllerian abnormalities** and those associated with in utero DES exposure and submucous fibroids have been associated with recurrent pregnancy loss secondary to distortion (fibroids) or malformation (DES exposure and müllerian abnormalities). Müllerian abnormalities refer to all different levels of incomplete fusion of the müllerian tubes in utero. They can range from the presence of two uterine horns and two cervices often accompanied by a separating vaginal septum in the upper third of the vagina (uterus didelphus) to a fused single uterus and cervix with the presence of a midline uterine septum, with all stages in between. When an incompletely formed uterine horn is present, often it cannot accommodate a growing pregnancy through viability. When a pregnancy implants in a uterine septum, it cannot receive the needed support from the endometrium. While these anomalies can be the cause of recurrent pregnancy loss, most women with müllerian anomalies have successful pregnancies. Therefore, surgical repair of these abnormalities is not necessarily indicated in the absence of prior pregnancy loss. Because of similar timing in development, urinary tract abnormalities frequently coexist with müllerian defects and should always be looked for when müllerian defects are diagnosed.
- A condition called **cervical insufficiency**, which leads to premature and often painless cervical dilatation in the second trimester, is a leading cause of pregnancy loss and can recur in future pregnancies. It can be treated by a combination of decreased maternal activity during pregnancy as well as cervical **cerclage.**
- Such chronic illnesses as diabetes and thyroid abnormalities are associated with recurrent pregnancy loss.
- Women with **antiphospholipid antibodies** have been identified as a

group at risk for increased venous and arterial clotting, which can result in early pregnancy loss.
- Cigarette smoking has been associated with higher rates of early pregnancy loss.
- When a patient experiences early pregnancy loss, recurrent or not, it is important to recognize that a similar grieving process takes place as when a more advanced pregnancy or child is lost. Helping patients acknowledge the gravity and importance of this loss while reassuring them that they (or their spouses) are not to blame is important in the care of women suffering from pregnancy loss at any gestational age.

G. Menopause

- Occurs at an average age of 52.
- Menstruation ceases because there are no more follicles pres-ent in the ovaries and therefore ovarian sex steroid production ceases.
- Accompanying symptoms include vaginal dryness and vasomotor symptoms, including hot flashes and night sweats.
- Bone loss, which begins around age 30, accelerates in the 5–7 years following menopause.
- While atrophy symptoms continue indefinitely after menopause, vasomotor symptoms are usually self-limited and last on average up to 5 years. Most women note some improvement by 2 years after their last menstrual period.
- Hormone replacement therapy can be helpful in the treatment of menopausal symptoms and preservation of bone but *may* increase risk of breast cancer and thromboembolic events including strokes and myocardial infarction.
- When a woman has a uterus, hormone replacement therapy (HRT) requires the replacement of both estrogen and progesterone in order to protect against endometrial cancer.
- When a woman has had a hysterectomy, only estrogen replacement (ERT) can be used.

H. Male Impotence

- In order for normal erectile function to occur, an intact nervous system, adequate arterial penile blood flow, and normal corpora cavernosa sinus system must be present. In addition, a normal hypothalamic–pituitary–testicular axis must be functioning so that testosterone can permit normal libido functioning. Defects in neurologic, vascular, and endocrine systems can affect erectile functioning. Impotence refers to inability of a man to either obtain or maintain an erection.
- Around 80% of impotence is associated with an underlying organic cause or side effect of medication. In general, impotence with an organic cause is gradual in onset with maintenance of normal libido. Diabetes is one of the most common organic illnesses associated with impotence. Many drugs, including antihypertensives, CNS depressants, antidepressants, and H_2 receptor antagonists have been linked to impotence. There are both medical (Viagra) and surgical (penile implants) options for selected men with impotence of organic cause.
- Twenty percent of impotence has an underlying psychological cause. When this is the case, onset is more acute and often impotence is sporadic and situationally related. The occurrence of nocturnal erections makes the diagnosis of psychogenic impotence more likely. This is best treated with psychological counseling or psychotherapy aimed at elucidating the underlying cause for the impotence.

I. Female Sexual Dysfunction

There are five distinct (though frequently overlapping) types of sexual dysfunction in women—dyspareunia, inhibited sexual desire, vaginismus, anorgasmia, and vulvodynia.

- **Dyspareunia** is defined as pain during intercourse. It can be caused by inadequate lubrication because of lack of sufficient foreplay or caused by vaginal atrophy in estrogen-deficient women. In addition, endometriosis is frequently associated with dyspareunia, as can be other conditions that cause scarring and adhesions in the pelvis. In addition, pelvic or vaginal infection can be responsible for dyspareunia. Women with a history of prior sexual abuse will also frequently complain of dyspareunia, as may depressed women.
- **Inhibited sexual desire** can be caused by chronic illness as well as many medications, especially those that depress the CNS. Decreased libido is also commonly noted in peri- and postmenopausal women; it is frequently more dramatic in onset in women who have undergone premenopausal surgical castration.
- **Vaginismus** can be caused by congenital abnormalities of the vagina, such as an imperforate or rigid hymen. It also can be caused by prior surgeries and subsequent vaginal scarring, psychological causes, or history of prior sexual abuse.
- **Anorgasmia** can be caused by premature ejaculation by a partner as well as guilt surrounding having sex. It is also a common side effect of certain antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs).
- **Vulvodynia** is a chronic condition with associated vulvar and introital pain, especially associated with pressure on the vaginal introitus. While infection, particularly with HPV, is often found, the cause for this disease frequently remains elusive.

J. Benign Prostatic Hypertrophy

Most men over the age of 55 experience enlargement of the prostate gland. Symptoms include urinary difficulties secondary to outflow obstruction of the bladder. Surgical resection of the prostate is a common treatment for this condition. Newer medical treatments include drugs that inhibit production of dihydrotestosterone (the active metabolite of testosterone at the cellular level) and therefore have some success in decreasing the size of the prostate. α_1-Adrenergic blocking agents are also used to relax the smooth muscle in the prostate and therefore relieve bladder outlet obstruction.

K. Gynecomastia

When the glandular tissue in the male breast proliferates and enlarges, this is called gynecomastia. It is a benign condition and occurs to some extent in up to 70% of prepubertal boys and up to one-third of men over 50.

- It is caused by an imbalance between estrogen (stimulates breast growth) and testosterone (inhibits breast growth).
- Increased production of estrogen by neoplasms, hypogonadism, liver disease, and hyperthyroidism are possible organic causes.
- Drugs including estrogens, antiandrogens, gonadotropics, alcohol, and cytotoxic agents have all been associated with gynecomastia.
- Gynecomastia should be differentiated from breast cancer (usually unilateral) and fatty enlargement of the breasts.

L. Pregnancy-Related Disorders

1. First-Trimester Pregnancy Loss

Approximately 20% of pregnancies end in first-trimester loss (see section II.F for causes). When a pregnancy is lost in the first trimester, the following terminology applies:

- **Threatened abortion** is defined as first-trimester bleeding without passage of products of conception and a closed cervix. This occurs in up to 25% of pregnancies and may or may not be followed by a spontaneous or missed abortion.
- **Inevitable abortion** is defined as first-trimester cervical dilatation with accompanying rupture of membranes. When this occurs early in pregnancy, the outlook for the pregnancy is dismal.
- **Incomplete abortion** refers to the situation when part of the products of conception is passed and part is retained in the uterus.
- **Missed abortion** is classically described as retention of dead products of conception and is currently diagnosed on ultrasound prompted by threatened abortion or uterine size less than dates.
- **Ectopic pregnancy** occurs in 1/100 pregnancies when an early pregnancy implants in an extrauterine site. The tube is the most common site for ectopic pregnancy implantation. Other sites include the ovary, cervix, broad ligament, and other pelvic peritoneal structures. Occasionally, a pregnancy that is implanted abdominally goes undetected and progresses to viability.
- Risk factors for ectopic pregnancy include: prior pelvic infection with tubal damage, prior ectopic pregnancy (recurrence rate 7–15% after first ectopic), endometriosis with coexisting tubal damage, pregnancy after tubal sterilization procedure (16–50%), and some assisted reproduction techniques such as gamete intrafallopian transfer (GIFT) and in vitro fertilization (IVF). While **heterotopic pregnancy** is exceedingly rare (1/30,000 pregnancies), IVF transfer of multiple embryos and ovulation induction has been shown to increase the likelihood of coexisting intrauterine and ectopic pregnancies.
- Death can result from ectopic pregnancies when rupture of the tube and subsequent intra-abdominal bleeding occurs. It is the second leading cause of maternal mortality in the United States.
- Pain, often accompanied by lighter vaginal bleeding after a missed menstrual period, is the usual presenting symptom with ectopic pregnancy.
- Ultrasound and rapid and reliable urine and serum pregnancy tests have made the early diagnosis of ectopic pregnancy much easier. For practical purposes, the diagnosis of ectopic pregnancy can be excluded if an intrauterine pregnancy is seen on ultrasound.
- The likelihood of ectopic pregnancy increases greatly when a serum hCG level is over 2,000 mIU/mL and no intrauterine pregnancy is seen on vaginal ultrasound done by a reliable examiner. When levels are under 2,000, serial hCG levels can be obtained. When an early pregnancy is healthy, the level of hCG doubles in 48–72 hours. In general, with both ectopic pregnancies and other early pregnancy mishaps, the level of hCG does not rise appropriately.
- Treatment of ectopic pregnancy is either surgical with or without preservation of the affected tube or, more recently, medical treatment with methotrexate, a chemotherapeutic agent also used in the treatment of recurrent disease in molar pregnancies.

2. Polyhydramnios

Polyhydramnios is excessive amniotic fluid. Normally, amniotic fluid volume peaks at around 1 liter at 36 weeks and decreases to lower volumes as term approaches. Polyhydramnios is arbitrarily defined as an amniotic fluid volume of > 2 liters.

- Congenital abnormalities that interfere with fetal swallowing can cause polyhydramnios. Such abnormalities include esophageal atresia.
- Open neural tube defects can be associated with polyhydramnios secondary to increased urination because of abnormal cerebrospinal stimulation or because of increased transudation of fluid from the exposed meninges.
- Maternal diabetes is commonly associated with polyhydramnios for unknown reasons.
- Conditions that cause an enlarged placenta, such as multifetal gestation and congenital syphilis, are also associated with polyhydramnios.
- The most common cause of polyhydramnios is idiopathic.

3. Intrauterine Infection

Certain maternal viral, bacterial, and protozoal infections can cause intrauterine infection and sequelae for the fetus.

a. Viral

- **Varicella** infection can be transmitted transplacentally from infected mother to fetus. In early pregnancy, such infections can be associated with fetal malformations in about 10% of cases of maternal infection. More problematic is maternal infection and fetal and newborn exposure at term. When newborns are exposed to varicella, they often have severe infections.
- Maternal **parvovirus** infection has been associated with increased fetal loss with accompanying hydrops and anemia, although most pregnant women who experience parvovirus infection have unaffected babies.
- Maternal **rubella** infection in early pregnancy has a high likelihood of fetal infection, which decreases as pregnancy progresses. Congenital rubella is a potent teratogen, with almost all babies infected in the first trimester showing congenital defects. Only 35% of babies infected between 13 and 16 weeks had associated anomalies, and defects are rare in babies infected after 16 weeks. Congenital rubella defects include deafness, heart disease, eye lesions, CNS defects, hematologic and pulmonary effects, as well as bone changes. Babies born with congenital rubella can also shed the virus for several months after birth and therefore may be infectious to other babies and nonimmune adults.
- **Cytomegalovirus** is the most common cause of fetal infection. It can cause fetal death or severe handicaps, including deafness, blindness, and mental retardation in survivors of congenital infection.

b. Bacterial Infections

- **Group B streptococcus** is a common inhabitant of the vagina and rectum. It can cause severe infection in exposed babies, but this happens to only about 10/1,000 babies born to colonized mothers. Neonatal infection is more common in babies born prematurely and after prolonged rupture of the membranes. Because colonization is so common (about 20% of women are colonized), various strategies are employed to treat colonized women in labor with the goal of preventing neonatal infection.

b. Protozoal Infections

- Primary maternal **toxoplasmosis** can have teratogenic fetal effects in 15% of pregnancies affected by infection in the first trimester. Effects of first-trimester infection include microcephaly, intracranial calcifications (which can be diagnosed on prenatal ultrasound), seizures, hydrocephalus, mental retardation, and blindness from chorioretinitis. Both maternal and fetal treatments have been proposed, but prevention of maternal infection is the best strategy. Since the disease is usually transmitted by the fecal–oral route from affected cats and through the ingestion of raw or undercooked meat, avoidance of changing cat litter and ingestion of raw or undercooked meat is advised for all pregnant women.

4. Bleeding During Pregnancy

- Placenta previa can be a cause of sudden, usually painless, and often profuse vaginal bleeding in the later second or third trimester. In this condition, the placenta partially or completely covers the cervix, and bleeding is caused by separation of the placenta from the area immediately around the cervical canal.
- Abruptio placenta occurs when the placenta separates partially or completely from the uterus before delivery. While the cause of abruption is usually unknown, it can occur after trauma to the pregnant abdomen and is seen more frequently when hypertensive disorders (see below) are present. Cocaine abuse and cigarette smoking during pregnancy have also been associated with increased incidence of abruption. Pain usually accompanies bleeding caused by abruption, and maternal and fetal alteration of vital signs are often out of proportion to the amount of bleeding seen since much bleeding can be concealed behind the placenta. Disseminated intravascular coagulopathy (DIC) can be a sequela of abruption.
- Rarely, the umbilical cord is inserted away from the body of the placenta (velamentous insertion) and the fetal blood vessels connecting the cord that course through the membranes rupture at the time of rupture of membranes. Termed *vasa previa*, this causes rapid loss of fetal blood with disastrous consequences for the fetus.

5. Hypertensive Disorders of Pregnancy

Hypertension is one of the more common underlying medical conditions that exists in women of reproductive age and is often exacerbated in pregnancy. In addition, pregnancy can induce hypertension. While terminology applied to the hypertensive disorders of pregnancy has been a frequent source of confusion, most authorities use the terminology developed by the American College of Obstetricians and Gynecologists. In this terminology, a distinction is made between pregnancy-induced hypertension without associated pathologic edema or proteinuria and preeclampsia, and pregnancy-aggravated hypertension with or without superimposed preeclampsia.

- The triad of hypertension, proteinuria, and pathologic edema defines preeclampsia. Preeclampsia is defined as severe by the frequency and intensity of associated hypertension and proteinuria. Presence of accompanying visual disturbances, thrombocytopenia, headache, oliguria, elevation of liver enzymes, pulmonary edema, and fetal growth restriction also make the diagnosis of severe preeclampsia.
- The cure for preeclampsia is delivery, which is indicated usually in cases of severe preeclampsia, even if the patient is remote from

term. Patients with mild preeclampsia are generally delivered at term or when severe preeclampsia develops.

- One of the most dramatic complications of preeclampsia is eclampsia, defined as convulsions precipitated by preeclampsia.
- Goals in management of pregnancies complicated by hypertension are the safest delivery of a fetus that survives intact and maintenance and restoration of maternal health. Bed rest, close monitoring of maternal vital signs and associated laboratory and other physiologic abnormalities, antihypertensive therapy for selected patients, antepartum fetal surveillance with ultrasound, and fetal heart rate testing help obstetricians make decisions about the safest timing and route for delivery.

6. Diabetes and Pregnancy

Diabetes can be a disease that exists prior to pregnancy (Type 1 or Type 2) or one that develops during pregnancy (gestational diabetes).

- Gestational diabetes usually resolves after the pregnancy is delivered. *Human placental lactogen*, which antagonizes the action of insulin, is felt to be the main factor that predisposes women to the development of diabetes during pregnancy. Insulin resistance increases as pregnancy progresses. When diagnosed, blood sugar abnormalities can usually be controlled by diet. Future pregnancies are frequently complicated by gestational diabetes, and these women are at higher risk for developing diabetes later in life.
- Gestational diabetes is associated with fewer pregnancy complications than preexisting diabetes.
- Preeclampsia happens more often to diabetic pregnant women, and diabetic women are more susceptible to infection.
- When blood sugar is poorly controlled around the time of conception and in the first trimester, there is an increased chance of major fetal anomalies.
- Fetal macrosomia is associated with pregnancies complicated by diabetes. This is felt to be caused when elevated levels of maternal glucose cross the placenta and induce increased insulin production by the fetus. Insulin has potent growth factor properties in the fetus. Fetal macrosomia can lead to delivery complications for both the mother and the fetus.
- Unexplained and sudden fetal death is more common in pregnancies complicated by diabetes.

7. Other Common Medical Problems Affecting Pregnancy

Some of the more common medical problems that women of reproductive age experience and their impact on and by pregnancy include:

- **Heart disease** complicates 1% of pregnancies. The increased cardiac output of pregnancy can predispose pregnant women with preexisting heart disease to cardiac failure in pregnancy. Women with pulmonary hypertension, coarctation of the aorta, and Marfan's syndrome are most likely to be adversely affected by the physiologic demands of pregnancy and delivery.
- **Asthma** is unpredictably affected by pregnancy, and one-third of the time asthma is unchanged, one-third improved, and one-third worsened. Hypoxia accompanying a severe asthma attack can have adverse fetal effects.

- **Chronic renal disease**, even with fairly normal renal function, is associated with increase in poor pregnancy outcome.
- Pregnancy can exacerbate crises in women with **sickle cell disease.**
- **Maternal hypothyroidism** can cause infertility. When hypothyroid women become pregnant and are not adequately treated, they may be at increased risk for preeclampsia, abruption, and low birth weight associated with medically indicated preterm delivery.
- **Maternal hyperthyroidism** has pregnancy complications similar to hypothyroidism when inadequately treated.
- **Postpartum thyroiditis** can occur in 5% of postpartum women without prior history of thyroid disease and can present with either hyper- or hypoactive thyroid function.
- Women with **lupus** have an increased risk of poor pregnancy outcome, including stillbirths and premature birth. Renal function can deteriorate and sometimes not recover in pregnant women with lupus. While pregnancy itself does not seem to affect severity of lupus, lupus flairs can be quite severe in the postpartum period.

8. Preterm Labor

Preterm labor is defined as labor with cervical change occurring before 36 weeks' gestation as defined by the last menstrual period. While innovations in neonatal care over the past several years have made survival of infants at lower and lower gestational ages a reality, obstetric efforts to reduce preterm birth have met with little success.

While the cause for preterm birth is unknown in the great majority of cases, several factors are associated with higher risk for preterm birth. These include:

- Spontaneous rupture of membranes (SROM) remote from term (also usually of unknown cause).
- Infection in the amniotic fluid, either after SROM or as a preexisting risk factor for both ROM and preterm labor.
- Fetal malformations.
- Maternal history of prior preterm delivery.
- Uterine anomalies.
- Fetal death.
- Serious maternal illness.
- Abruptio placenta.
- Induction of delivery secondary to hypertensive complications of pregnancy.

Bed rest, adequate hydration, and tocolytic agents form the mainstays of treatment of preterm labor. Tocolytic agents include magnesium sulfate, β-receptor agonists such as terbutaline and ritodrine, prostaglandin inhibitors such as indocin, and less commonly used calcium channel blockers. Detection of fetal fibronectin in the maternal cervix increases the likelihood of preterm delivery in patients with symptoms of preterm labor.

9. Postterm Pregnancy

Normal term gestation is defined as 38–42 completed weeks of pregnancy as dated by the first day of the last menstrual period in a woman with a 28-day menstrual cycle. Postterm pregnancy progresses beyond 42 weeks and occurs in up to 10% of pregnancies. When pregnancy is prolonged after 42 completed weeks, placental insufficiency and subsequent fetal injury and death become more likely. Therefore, obstetric surveillance is increased after 42 weeks and delivery is often induced.

10. Intrauterine Growth Retardation (IUGR)

Babies grow at a fairly uniform rate until the late second or early third trimester. After this, individual differences in fetal growth are seen, and a fetus is considered to be small for gestational age (SGA) when it weighs less than the 10th percentile for its gestational age. While a fetus may be small for gestational age because of constitutional factors, in general SGA babies are considered to have IUGR and be at increased risk for a variety of fetal and neonatal complications such as intrauterine death and postpartum hypoglycemia and hypothermia secondary to decreased glycogen stores. Intrauterine growth restriction can be either head sparing (asymmetrical) or symmetrical. Head-sparing IUGR usually carries a better prognosis once the baby is born since fetal malformations and infection are associated more commonly with symmetric IUGR.

Causes include:

- Maternal malnutrition.
- Fetal infections.
- Maternal renal disease.
- Multiple gestation.
- Placental abnormalities.
- Congenital malformations and chromosomal abnormalities.
- Teratogens and drugs.
- Maternal vascular disease, especially hypertension.

11. Postpartum Bleeding

Postpartum hemorrhage is defined as blood loss after delivery in excess of 500 cc.

- Abnormalities of placental implantation including placenta accreta (implantation of the placenta to the surface of the myometrium), increta (placenta invades myometrium), or percreta (placenta penetrates through the myometrium), as well as retained parts of a normally implanted placenta can cause postpartum hemorrhage. Removal of the placenta is the usual treatment for these conditions.
- Uterine infection, prolonged or rapid labor, delivery of a macrosomic infant or multiple gestation, and high parity are all associated with uterine atony, which can lead to postpartum hemorrhage. Treatments include oxytocic compounds (Pitocin), external uterine massage, and the use of prostaglandins, as well as uterine artery ligation and hysterectomy (in intractable cases only).
- Underlying coagulopathies such as von Willebrand's disease are often first diagnosed after a postpartum hemorrhage. Correction of the coagulopathy with blood transfusion usually helps to decrease bleeding.
- Vaginal, vulvar, and cervical lacerations caused by birth trauma can be responsible for postpartum hemorrhage. Repair of such lacerations is indicated to stop bleeding.

12. Postpartum Infection

- Infection, along with hemorrhage and preeclampsia, were the most common causes of maternal death in the past. Infection as a cause of maternal death is much less common since the advent of antibiotic treatment and aseptic technique. However, febrile morbidity is still very common in the postpartum period.

- Causes include urinary tract infection, breast engorgement, and uterine infection. Uterine infection is much more common after cesarean delivery than vaginal delivery. Offending organisms include group A, B and D strep, enterococcus, and gram-negative bacteria, as well as anaerobes and gonorrhea and chlamydia.

13. Postpartum Depression

Transient depressed mood or feeling is quite common in the postpartum period. Termed *postpartum blues*, this condition is usually transient and mild. However, some women experience severe depression in the postpartum period and require treatment. A woman with a prior history of depression is at higher risk for postpartum depression.

III. CONTRACEPTION AND FAMILY PLANNING

Modern contraception falls into one of three categories: hormonal methods, barrier methods, and intrauterine devices. In addition, natural family planning where intercourse is avoided around the time of ovulation can be an effective method for some motivated couples. There are many options available for couples who do not wish to become pregnant. When helping a couple choose a method of contraception, in addition to considering effectiveness, side effects, and contraindications for each method, it is important to be sensitive to religious and cultural beliefs which may make one method more appealing than another. In addition, it is important to be sure that it is realistic for the couple to be able to use the chosen method in an effective way.

A. Hormonal Contraception

Combination **oral contraceptives** (OCs) are a safe and effective way to prevent pregnancy for most women. They contain a combination of estrogen and progesterone. Because the pituitary gland is exposed to tonic levels of estrogen and progesterone, ovulation is suppressed. OCs also cause thickening of the cervical mucus, which inhibits sperm entry into the uterus and creates an endometrial environment that is not supportive of an early pregnancy.

Serious complications of OC use are uncommon but include an increase in thromboembolic events, specifically deep vein thrombosis and subsequent pulmonary embolism (much less common in lower-dose OCs), hypertension, exacerbation of migraine headaches, and induction of liver enzymes, causing more rapid metabolism of certain medications including seizure medications.

Less serious complications, while more common, are often transient and subside with continued pill use. These include weight gain, irritability, headache, and breakthrough bleeding.

Noncontraceptive advantages to OCs include a decreased amount of and more regular menses, less dysmenorrhea, decreased acne and hirsutism, as well as decreased risk for ovarian and uterine cancers with long-term (> 1 year) use.

Combination hormonal contraceptives have recently been developed for transdermal and intravaginal use. Other forms of hormonal contraception include the long-acting progestational agent **Depo-Provera**, which is administered by injection every 3 months. Return of fertility after Depo-Provera use can take up to 1 year. It is a highly effective method of contraception.

Combination or progesterone-only higher-dose pills are available for **emergency contraception**, which can be initiated in two doses with excellent effectiveness within 72 hours of unprotected intercourse.

Hormonal contraception, while effective in preventing pregnancy, does not prevent the transmission of sexually transmitted diseases.

B. Barrier Methods

Barrier methods include **condoms, cervical caps,** and **diaphragms.** They are all more effectively used in conjunction with vaginally applied spermicides. The cervical cap and diaphragm lose most of their effectiveness if spermicide is not used. Barrier methods are generally less effective than hormonal methods mostly because of greater potential for incorrect or neglected use. Condoms especially have an advantage in prevention of transmission of STDs.

C. Intrauterine Devices (IUDs)

Modern IUDs contain copper or progesterone and work by interfering with tubal transport of sperm and possibly by creating an intrauterine environment hostile to implantation. They are highly effective. Disadvantages include pain with insertion, possible perforation of the uterus and infection with insertion, possibly more severe PID secondary to a foreign body being in the uterus (infectious complications are much less common with modern IUDs), and possible increase in menstrual amount and cramps. They offer no protection against STDs.

IV. DOMESTIC VIOLENCE AND SEXUAL ABUSE

Between 8 and 12% of women in the United States report experiencing domestic violence every year. The violence is severe for 2–4% of all women. Given that this is such a common problem in our country, physicians are encouraged to ask every woman at every visit whether she is being hurt or abused at home. Even if a victim is unable to confide in her physician about her situation, she hopefully will hear that this is something her physician feels is important and she may feel more able to discuss her problems at another time.

When a woman confides a history of domestic violence, it is important to avoid such questions as “Why don’t you just leave?” and instead focus on making sure the woman knows that she does not deserve such treatment and that you are available to help her access the resources available in your community if and when she is ready to leave.

In general, perpetrators of domestic violence will not stop if untreated. They are frequently victims of childhood abuse or witnesses of domestic violence as children. This is an important point to make when discussing an abusive situation with a woman, especially if she has children in the home.

Research has shown that violence tends to occur in three phases that escalate over time. The cycle starts with name calling and verbal insults and possibly milder physical assault by the perpetrator. The victim tries to alter her behavior to calm the perpetrator, and this may succeed briefly, reinforcing the victim’s mistaken impression that she is the cause for the abusive behavior. In the next phase, the abuser “loses control” and the victim experiences more severe physical violence. After this, in the next phase, the abuser becomes apologetic and tries to “make it up” to the victim. Violence tends to escalate as the cycle repeats itself as does the abuser’s need to control the victim and the victim's belief that she is the cause for and deserving of the treatment she is receiving.

Domestic violence also seems to escalate (or even occur for the first time) during pregnancy.

The acronym **RADAR—R**emember to ask, **A**sk directly, **D**ocument findings, **A**ssess safety, and **R**eview options and refer—is commonly utilized to help physicians remember how to appropriately and helpfully ask each patient about domestic violence. Most communities have resources to aid victims in seeing a way out of their situation, and the physician is an important point of referral.

Abuse is perpetrated on girls by both family members and strangers as well as acquaintances and friends. Teenagers and women also very commonly experience sexual abuse. Survivors of sexual abuse, particularly childhood abuse, frequently have difficulties with pelvic exams and may present with chronic pelvic pain that is difficult to diagnose. Referral for treatment in recovering from the severe psychic trauma caused by this type of abuse can be quite helpful to some patients.

BIBLIOGRAPHY

Beckman CRB, Ling FW, Laube DW, et al. (eds.). *Obstetrics and Gynecology,* 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2002.

Callahan TL, Caughey AB, Heffner LJ (eds.). *Blueprints in Obstetrics and Gynecology,* 2nd ed. Malden, MA: Blackwell Science, 2004.

Cunningham FG (ed.) *Williams Obstetrics,* 22nd ed. New York: McGraw-Hill, 2005.

Hacker NF, Moore JG (eds.). *Essentials of Obstetrics and Gynecology,* 3rd ed. Philadelphia: W.B. Saunders, 1998.

Morgan M, Siddighi S (eds.). *Obstetrics and Gynecology,* 5th ed. (NMS series). Philadelphia: Lippincott Williams & Wilkins, 2004.

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The Respiratory System

10

I. NORMAL PROCESSES

A. Embryonic Development, Fetal Maturation, and Perinatal Changes

Lung derives from foregut at week 4. Endoderm forms into airway lining tissue. Mesoderm forms alveoli; cartilage and muscle. During the pseudoglandular period (5–17 weeks), the first four generations of bronchi form. During the canalicular period (15–25 weeks), respiratory bronchioles, terminal sacs, and vascular structures form. Terminal sacs proliferate and cells differentiate into type I (alveolar lining) and type II (surfactant producing) pneumocytes during the terminal sac period (24–29 weeks). Respiration is possible when the surfactant lecithin/sphingomyelin ratio is > 2 (week 26). Diaphragm develops from the septum transversum, pleuroperitoneal membranes, dorsal esophagus mesentery, and body wall muscles. Alveolar development ends about age 8.

► cram facts

An amniotic fluid lecithin/sphingomyelin ratio > 2.0 predicts normal respiration in a premature infant.

B. Organ Structure and Function

1. Upper Airways and Bronchi

Nasal turbinates filter, humidify, and regulate temperature of inspired air. Intrinsic laryngeal muscles close the epiglottis during swallowing; it is opened by the cricoarytenoid posterior muscle. The trachea has C-shaped anterior cartilage rings with a posterior membranous wall. The trachea divides at the carina into right and left mainstem bronchi; the first generations are cartilagenous; later bronchi are membranous. Terminal bronchioles are the last conducting airways. Transitional and respiratory bronchioles have alveolar components and terminate in alveolar ducts and sacs.

2. Pleura and Fluid Formation

Pleura is comprised of visceral pleura, covering the lung surface, and parietal pleura, covering the thoracic cage, diaphragm, and mediastinum. The pleural space has a few milliliters of lubricating fluid which comes from the parietal pleura and is taken up by visceral pleura and lymphatics. Pleural pressure is negative at rest due to opposing elastic recoil forces of the lung and chest wall.

► cram facts

While ventilation and perfusion are increased at lung bases, the V/Q ratio is highest at the lung apex.

3. Mechanics of Breathing

Resting lung volume occurs at functional residual capacity (FRC), where inward lung elastic recoil pressure is equal to outward chest wall recoil. Inspiration occurs when the diaphragm and external intercostals contract, creating more negative pleural pressure. Expiration is passive: inspiratory muscles relax, pleural pressure becomes less negative, and the lung elastic recoil contracts the lung back to FRC. Abdominal and internal intercostal muscles mediate forced expiration.

► cram facts

Obstruction is defined by a reduced $FEV_{1\%}$ (< 70%). Restriction is defined by a reduced total lung capacity.

Pulmonary Function Tests (PFTs)

Spirometry measures forced vital capacity (FVC), forced expired volume over one second (FEV_1), tidal volume (TV), inspiratory and expiratory reserve volumes (IRV and ERV), $FEV_{1\%}$ (ratio of $FEV_1/FVC \times 100$) and $FEF_{25-75\%}$ (average flow during the middle of an FVC effort) (Figure 10–1). Spirometry cannot measure total lung capacity (TLC), residual volume (RV), or FRC. FRC is measured by helium dilution or body box, RV and TLC are then calculated (Figure 10–2).

► cram facts

FRC, TLC, and RV cannot be measured by spirometry.

Lung capacities contain more than one volume. Total lung capacity (TLC) – lung volume at maximum inspiration = RV + ERV +

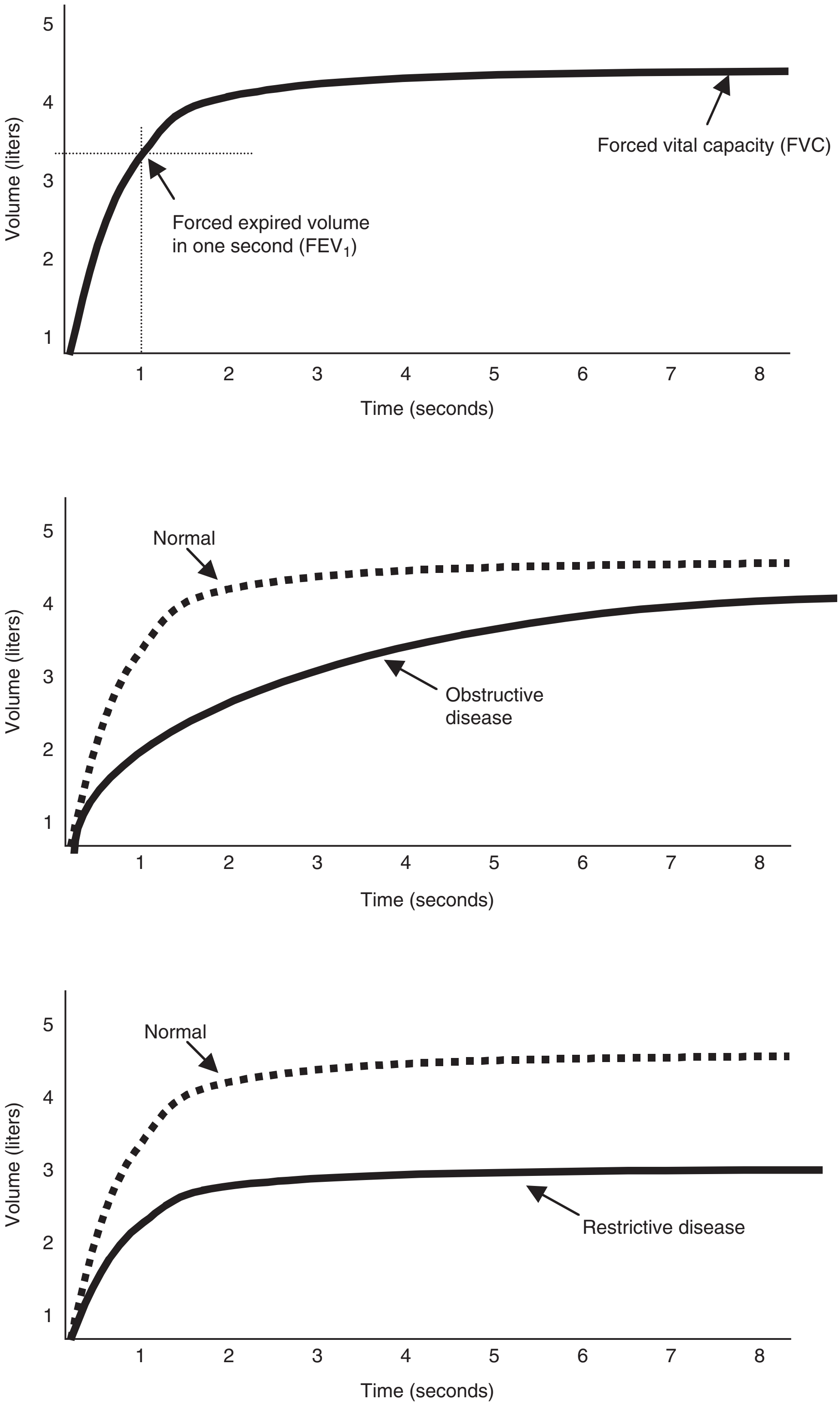

Figure 10–1. A. Spirometry: Volume time curve (normal). $FEV_{1\%} = FEV_1/FVC \times 100$. **B.** Obstructive lung disease: Decreased FEV_1, $FEV_{1\%}$. **C.** Restrictive disease: Decreased FEV_1, FVC, with increased $FEV_{1\%}$. Decreased TLC defines restriction (requires lung volume study).

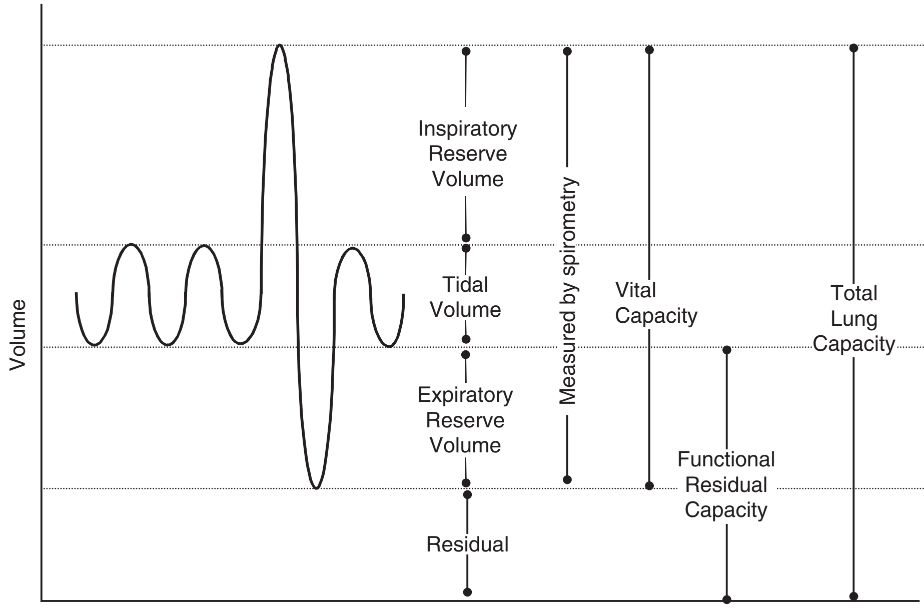

Figure 10–2. Lung volumes and capacities.

TV + IRV. Vital capacity is volume expired from TLC to RV = ERV + TV + IRV. FRC = RV + ERV.

Obstructive Disease—Defined as a reduced $FEV_{1\%}$ (< 70%). Characterized by low FEV_1, low or normal FVC, and normal TLC. A reduced $FEF_{25–75\%}$ suggests small-airway obstruction.

Restrictive Disease—Defined as *reduced TLC*. FEV_1 and FVC are low, $FEV_{1\%}$ is normal or high.

Combined Obstruction and Restriction—Reduced FEV_1, FVC, and $FEV_{1\%}$ and reduced TLC.

4. Ventilation and Regulation

Ventilation is stimulated by increased P_{CO_2} sensed by the medulla or the carotid and aortic body chemoreceptors or by decreased pH sensed in the medulla. Hypoxic drive is a lesser stimulus than P_{CO_2} unless hypoxia is severe. Anatomic dead space includes conducting airways that don't participate in gas exchange (measured by Fowler's method). Physiologic dead space includes alveoli that don't exchange gas (measured by Bohr's equation). The brain signals the diaphragm via the phrenic nerve (C3, C4, C5), and the external intercostals via spinal nerves.

5. Perfusion

Pulmonary arteries arise from the right ventricle and divide into arterioles, culminating in capillaries within alveolar walls. Normal pulmonary vessels have thin muscle layers, low pressure, and low resistance. Hypoxia causes local vasoconstriction to limit flow to diseased lung (in systemic circulation hypoxia causes vasodilation). Gravity increases ventilation (V) and blood flow (Q) at lung bases but the V/Q ratio is greatest at the apices (Figure 10–3). A V/Q ratio of 0 is shunt (perfusion with no ventilation); a V/Q ratio of infinity is physiologic dead space (ventilation without perfusion).

6. Pulmonary Defenses

Nasal turbinates block particles > 20 μm, while nasopharynx and larynx block particles > 10 μm. Particles 3–10 μm settle in the carina

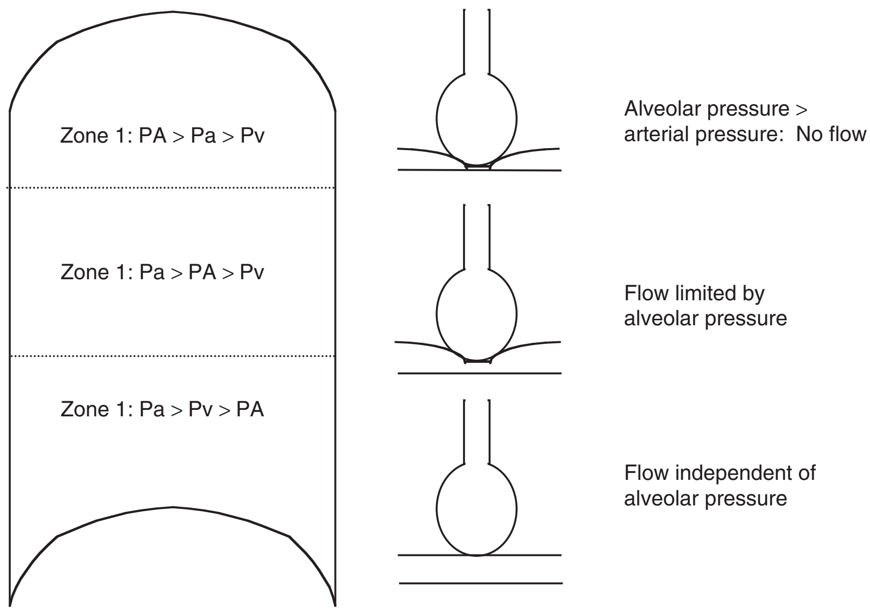

Figure 10–3. Lung zones. PA = alveolar pressure, Pa = pulmonary arteriolar pressure, Pv = pulmonary venous pressure.

and small airways and are removed by mucociliary transport. Particles < 2 μm settle in alveoli and are cleared by macrophages. Particles < 0.5 μm may remain suspended in air and are cleared by cough. Bronchospasm may prevent penetration of particles. Secretory IgA, complement, and surfactant are antibacterial.

C. Cell/Tissue Structure and Function

Gas exchange occurs in alveoli and respiratory bronchioles. Oxygen diffuses across epithelial type I pneumocytes, interstitium, and the endothelium of the capillary before binding to hemoglobin. Bohr-Haldane effect: Hemoglobin binds more oxygen and releases more CO_2 in the alveolus, where P_{CO_2} is low and P_{O_2} is high. Conversely, hemoglobin releases more oxygen and binds more CO_2 in peripheral tissue, where P_{CO_2} is high and P_{O_2} is low. Type II pneumocytes make surfactant, which lowers surface tension and keeps alveoli inflated. P_ACO_2 is effected directly by CO_2 production ($\dot{V}CO_2$) and inversely by alveolar ventilation (VA) – increasing VA decreases $PaCO_2$ and vice versa:

$$P_ACO_2 = \frac{k\,\dot{V}CO_2}{\dot{V}_A}$$

(k is a constant)

Alveolar P_AO_2 is determined by the pressure of inspired oxygen minus the amount of oxygen exchanged for carbon dioxide:

$$P_AO_2 = (PB - P_{H2O})\ FiO_2 - (PCO_2/R)$$

where PB is barometric pressure (sea level = 760 mm Hg), P_{H2O} is water vapor pressure (room air = 47 mm Hg), FiO_2 is the fraction of inspired oxygen (room air = 0.21), and R is the respiratory exchange ratio (usually 0.8). The alveolar–arterial (A-a) gradient is calculated by subtracting a measured arterial PaO_2 from the calculated alveolar P_AO_2. Normal A-a gradient is about 10 or less. (See section II.H.3.)

► cram facts

Mucoid *Pseudomonas* infection in a patient with obstructive lung disease should raise the suspicion for cystic fibrosis.

II. ABNORMAL PROCESSES

A. Genetic Disorders

1. Cystic Fibrosis

► Description and Symptoms

Cystic fibrosis is an autosomal recessive disease caused by a gene mutation located on the long arm of chromosome 7. The gene product is cystic fibrosis transmembrane conductance regulator (CFTR), a protein that transports chloride and other electrolytes across epithelial-cell membranes.

► Diagnosis

Sweat chloride test (chloride concentration > 80 mmol/L) with clinical findings or family history confirms the diagnosis. Genotype, semen analysis, and nasal potential–difference are helpful but neither establish nor rule out the diagnosis. Suggestive findings: Mucoid *Pseudomonas* lung infection, unexplained azoospermia, cystic bronchiectasis with hyperinflation on chest x-ray.

► Pathology

Early: Mucous obstruction of bronchioles and bronchi. *Late:* Bronchitis and bronchiolitis with edema and inflammation of the bronchial walls, submucosal gland hypertrophy, increased goblet cells, lung destruction from peribronchiolar/peribronchial fibrosis and cystic bronchiectasis.

► Treatment Steps

1. Prevent infection with postural drainage, chest physical therapy, inhaled β agonist, suppressive antibiotics (including inhaled tobramycin) and mucolytics (e.g., Dornase alfa [DNase]).
2. Treat infection when present (*Staphylococcus* and mucoid *Pseudomonas* most common).
3. Nutritional supplementation, pancreatic enzymes, and treatment of diabetes.

2. α_1-Antitrypsin Deficiency (α_1 Protease Inhibitor Deficiency)

► Description and Symptoms

α_1-Antitrypsin deficiency (A1ATD) occurs in about 1:2,000 births. Patients homozygous for the Z allele (Pi ZZ) for A1AT have plasma levels 10–15% of normal and are predisposed to develop emphysema if they smoke. Normals are Pi MM. Heterozygotes (Pi MZ) have partial deficiency but may be clinically unaffected. A1ATD is also the most common genetic liver disease; 10–20% of babies born with A1ATD may develop hepatitis and cirrhosis.

► Diagnosis

Low serum level of α_1-antitrypsin. Genetic phenotyping can detect carrier states.

► Pathology

Destruction of the alveolar walls and respiratory bronchioles result in panacinar emphysema.

► Treatment Steps

1. Smoking cessation.
2. Treat for chronic obstructive pulmonary disease (COPD).
3. α_1 protease inhibitor replacement if emphysema present.

B. Congenital Deformities

1. Pectus Excavatum (Funnel Chest)/Pectus Carinatum (Pigeon Breast)

► Description and Symptoms

Pectus excavatum: Inward depression of the sternum from the manubrium to the xiphoid process.
Pectus carinatum: Protrusion deformity of the sternum and anterior chest wall

► Diagnosis

Physical examination; PFTs usually normal, may show mild restriction; obstruction if chronic bronchitis present. Pectus excavatum is associated with Marfan's syndrome.

► Pathology

Thoracic kyphosis, functional heart murmurs, benign cardiac arrhythmias, and chronic bronchitis common. Pectus carinatum is associated with congenital atrial and ventricular septal defect.

► Treatment Steps

Surgical correction for cosmetic indication.

2. Kyphoscoliosis

► Description and Symptoms

Kyphosis—increased convexity of the thoracic spine; **scoliosis—**lateral deformity of the thoracic spine. Both may be asymptomatic.

> ► **cram facts**
>
> A scoliosis angle > 65° is associated with restrictive lung disease.

► Diagnosis

Physical examination, PFTs, chest x-ray.

► Pathology

Severe deformities (scoliosis angle > 65°) is associated with atelectasis with restrictive lung disease and compression of vessels, resulting in right ventricular hypertrophy and enlargement.

► Treatment Steps

Surgical correction if needed.

3. Tracheoesophageal Fistulas

► Description and Symptoms

Fistula between trachea and esophagus caused by incomplete separation of the lung bud from the esophagus during development, or acquired (trauma or tumor). Cough after swallowing, aspiration.

► Diagnosis

Suspected if neonate is unable to swallow secretions or when aspiration of feedings is seen. Fluoroscopic insertion of radiopaque catheter; computed tomography (CT) scan, but contrast may irritate lung.

► Pathology

May occur with or without concomitant esophageal atresia. In the most common form, upper segment of the esophagus ends in a blind pouch; lower segment originates from lower trachea.

► Treatment Steps

Surgical correction.

10-1

DEVELOPMENTAL ABNORMALITIES

Abnormality	Definition	Pathology	Diagnosis
Agenesis	Absence of a lobe, one or both lungs	Poorly developed bronchial tissue	Chest x-ray shows focal decreased lung volume. CT scan and/or angiogram confirms diagnosis
Aplasia/hypoplasia	Rudimentary bronchus ending in blind pouch or fully formed, small bronchus with no alveoli	Poorly developed bronchi ending in mesenchymal structure within the mediastinum	CT scan and/or pulmonary angiogram confirm the diagnosis
Bronchopulmonary sequestration	Nonfunctioning embryonic lung tissue supplied by anomalous systemic arterial flow	Cyst(s) within normal lung; supplied by aorta and drained by azygous or pulmonary veins	Chest x-ray (cyst); systemic arteriogram. Usually occurs in left lower lobe. May get infected

4. Developmental Abnormalities

See Table 10–1.

C. Infectious Disorders

1. Rhinitis

► Description and Symptoms

Inflammation of the nasal mucosa, characterized by symptoms of rhinorrhea and congestion.

► Diagnosis

History (febrile illness or allergic symptoms). Cultures are usually unhelpful. Allergy testing.

► Pathology

Infectious (most are viral), allergic, vasomotor (induced by cold air, spicy foods) or idiopathic.

► Treatment Steps

Most infections are viral and self-limited. Allergic rhinitis responds to antihistamines; topical steroids decrease inflammation, cromolyn prevents mast cell degranulation. Vasomotor rhinitis responds to vasoconstricting α-adrenergic decongestants (e.g., pseudoephedrine).

2. Pharyngitis

► Description and Symptoms

Sore throat; may involve tonsils, peritonsillar tissues, uvula, soft palate, and/or regional nodes.

► Diagnosis

History, physical. Throat culture to rule out *Streptococcus* and other bacteria.

► Pathology

Mucosal edema and erythema of upper airway. Viral infection much more common than bacterial. Exudates seen with Group A streptococcus, *Haemophilus influenzae*, and Epstein–Barr virus.

► Treatment Steps

Antibiotic if bacterial (ampicillin, trimethoprim–sulfamethoxazole, others). Viral are self-limited.

3. Epiglottitis

► Description and Symptoms

Epiglottis infection, usually by *H. influenzae,* causing fever, stridor, and upper airway obstruction.

► Diagnosis

Lateral neck x-ray; blood and throat culture. **Direct visualization and throat culture may precipitate airway closure and is contraindicated unless intubation/tracheostomy is available.**

► Pathology

Enlarged epiglottis, "beefy red," infection and inflammation of epiglottis and surrounding tissues.

► Treatment Steps

Antibiotic active against *Haemophilus* (e.g., β-lactamase–resistant penicillin or second-generation cephalosporin—inhibit cell wall synthesis; or choramphenicol—prevents protein transcription at 50s ribosome).

> **► cram facts**
>
> Appearance of a "beefy red" epiglottis in a child with sore throat suggests epiglottitis. Attempts to directly visualize or culture may precipitate acute airway obstruction.

4. Acute Bronchitis

► Description and Symptoms

Cough and sputum production associated with symptoms of upper respiratory tract infection (URI).

► Diagnosis

History, physical (scattered rhonchi, occasionally wheezes); sputum culture if bacteria suspected.

► Pathology

Infection of proximal bronchi. Usually viral in nonsmokers (rhinovirus, influenza, parainfluenza, respiratory syncytial virus [RSV], adenovirus); bacterial in smokers and patients with chronic obstructive pulmonary disease (COPD) (*H. influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*).

► Treatment Steps

Antibiotic active against usual organisms (e.g., doxycycline—binds to 30s ribosome; inhibits protein synthesis, β-lactamase–resistant penicillin or cephalosporin).

5. Bronchiolitis

► Description and Symptoms

Acute inflammatory disease of small airways, age < 2 years, presenting dyspnea and wheezing.

► Diagnosis

History (prodrome of URI, age < 2), physical (stridor, inspiratory rales, wheezing, tachypnea, hyperinflation), chest x-ray (hyperinflation); viral culture and serologies.

► Pathology

Inflammation of small, distant bronchioles; infection with RSV.

► Treatment Steps

Hydration, oxygenation, aerosol ribavirin if severe (guanosine analog, inhibits DNA polymerase).

6. Pleuritis

► Description and Symptoms

Inflammation of pleura leading to symptoms of pleuritic chest pain (sharp pain on inspiration), usually rapid onset, dyspnea, low-grade fever. Usually self-limited.

► Diagnosis

History and physical; chest x-ray; thoracentesis if fluid present.

► Pathology

Inflammation of pleura.

- *Pleurodynia:* Epidemic infection with coxsackie B or echovirus.
- *Pleuritis:* Pleural inflammation from infection, pulmonary infarction, collagen vascular disease, etc.

► Treatment Steps

Viral: self-limited. Steroids or immunosuppressive agents for collagen vascular disease.

7. Pneumonia

► Description and Symptoms

Infection of lung parenchyma. Lobar (involve one or more lobes), lobular ("patchy" involvement of lobules or segments and bronchi), or interstitial. Fever, dyspnea, cough usually productive. Also characterized by source: community acquired, health care associated, or immunocompromised (see Table 10–2).

► Diagnosis

Chest x-ray; Gram stain of sputum and blood culture. Serologic testing for viruses, *Rickettsia, Legionella, Mycoplasma. Pneumocystis:* Silver methanamine stains of bronchial fluid.

► Pathology

- **Lobar pneumonia:** *Early:* Spreading inflammmatory edema with polymorphonuclear neutrophils (PMNs) and organisms. *Red hepatization stage:* Alveolar inflammation with PMNs and organisms, alveoli filled with red blood cells (RBCs). Gray hepatization stage: Alveoli filled with fibrin, many PMNs and organisms, few RBCs (e.g., *Pneumococcus, Klebsiella*). Severe infection can lead to

10-2

PNEUMONIAS ASSOCIATED WITH IMMUNODEFICIENCY STATES

Immune Defect	Examples	Pneumonia
Humoral deficiency (B-cell dysfunction)	Common variable immunodeficiency, IgG or IgA deficiency, agammaglobulinemia, myeloma, glucocorticoids, radiation	Bacteria, especially encapsulated or gram-negative bacilli
Impaired phagocytosis (PMN dysfunction; complement deficiency)	Chronic granulomatous disease, acute myelogenous leukemia, Chediak–Higashi syndrome, Job's syndrome	Bacteria (*Staphylococcus aureus,* encapsulated organisms); fungi *(Aspergillus)*
Impaired cell-mediated immunity (T-cell dysfunction)	Acquired immune deficiency syndrome (AIDS), DiGeorge's syndrome, cytotoxic drugs, glucocorticoids, radiation, some common variable immunodeficiency	Fungi, *Pneumocystis carinii,* viral infection, *Mycobacterium avium* complex, *Nocardia*
Combined immunodeficiencies	Severe combined immunodeficiency (SCID) (reticular dygenesis, X-linked and recessive low T and B numbers, major histocompatibility complex [MHC] Class II deficiency, Nezelof's syndrome, Wiskott–Aldrich syndrome (bald lymphocytes, X-linked)	

parenchymal necrosis and pyogenic lung abscess (e.g., *Staphylococcus*).

- **Interstitial pneumonia:** Bronchial, bronchiolar, and alveolar epithelial inflammation, with lymphocytic infiltration (e.g., *Mycoplasma,* chlamydia, rickettsia, or viral [influenza, varicella, adenovirus, pertussis]); may be followed by PMN response if superinfection occurs. *Pneumocystis* is characterized by foamy eosinophilic alveolar infiltrate with the lymphocytic interstitial changes.

► Treatment Steps

1. Starting antibiotics early improves survival. Start by treating most likely organisms, then deescalate therapy based on culture results.
2. Community-acquired pneumonia: Need to treat for *Streptococcus pneumoniae, Haemophilus influenzae,* atypical organisms, especially *Legionella.*
3. Nosocomial (hospital acquired) or health care–associated pneumonia: Treat for *Pseudomonas* species and other gram-negative rods as well as methicillin-resistant *Staphylococcus aureus.*

8. Empyema

► Description and Symptoms

Infected pleural fluid, usually associated with pneumonia.

► Diagnosis

Thoracentesis. An effusion is likely to be complicated (hence more likely to loculate) if the pleural fluid shows one of the following: positive Gram stain, pH < 7.2, lactic dehydrogenase (LDH) > 1,000, or glucose < 40 mg/dL.

► Pathology

A parapneumonic effusion is any pleural effusion associated with pneumonia. Empyema has microoganisms in the pleural fluid. Untreated empyema can form fibropurulent exudates into which fibroblasts can grow, causing loculated effusions and a thick pleural peel.

► Treatment Steps

1. Drainage of empyema or a complicated parapneumonic effusion with a chest tube.
2. Antibiotics to treat organism.

9. Tuberculosis (TB)

► Description and Symptoms

Mycobacterium tuberculosis usually infects the lung, presents with fever, cough, night sweats, +/– hemoptysis. Other sites include brain, liver, spine (Pott's disease), adrenals, pleura, lymphatics.

► Diagnosis

- Chest x-ray: Reactivation: Upper lobe cavities. Primary infection: Lower lobe infiltrates. Miliary: Diffuse small round ("millet seed") opacities. A positive purified protein derivative (PPD) skin test denotes prior exposure (not necessarily active disease); a negative PPD doesn't rule out TB exposure. Sputum tests: Acid-fast (Ziehl–Neelsen) smear and culture; a direct fluorescent antibody or DNA probe is more rapid.

► cram facts

Criteria for exudative pleural effusion are: pleural fluid/serum protein ratio > 0.5, pleural fluid/serum LDH ratio > 0.6, or fluid LDH > 2/3 of the upper limit of normal serum level.

► cram facts

Primary tuberculosis infection occurs in lower lobes and is often asymptomatic. Reactivation occurs in upper lobes and is more likely to cavitate.

► cram facts

Never give a single anti-tuberculosis agent to a patient with active TB—it promotes resistance.

► Pathology

- **Primary infection:** Aspiration of *M. tuberculosis* into lower lobe leads to local granulomatous inflammatory response with histiocytes and Langhans' multinucleated giant cells, lymphoid cells, and fibrous tissue (Ghon focus). Regional lymph nodes involved with caseous and granulomatous lymphadenitis.
- **Secondary "reactivation" infection:** Upper lobe infection characterized by **caseation necrosis**, histiocytic (epithelioid) cell and giant Langhans' cell inflammation.
- **Miliary infection:** Disseminated hematogenously to any organ, more likely if immune suppressed.

► Treatment Steps

1. Active disease: Isoniazid (INH), rifampin, ethambutol, pyrazinamide +/– streptomycin. Using a single agent induces drug resistance. A 6-month regimen of 4 or 5 drugs for 2 months, then INH and rifampin for 4 months is recommended. Pyridoxine (B_6) prevents INH-induced neuropathy.
2. Latent disease: INH for 9 months. Always rule out active disease before giving INH as a single agent. Threshold to give INH for inactive (latent) disease is based on the size of the PPD skin test:
   - > 5 mm: For recent positive PPD, recent exposure, HIV, children < 5 years of age or abnormal CXR (upper lobe cavity).
   - > 10 mm: Immigrants from endemic area within 5 years, medical illnesses like diabetes, chronic renal insufficiency, organ transplants on immunosuppressive agents, or COPD requiring frequent corticosteroid treatment.
   - > 15 mm: For all other categories.

10. Fungal Infections

See Table 10–3 for fungal infections of the lung and Table 10–4 for pulmonary diseases caused by *Aspergillus fumigatus*.

10-3

FUNGAL INFECTIONS OF THE LUNG

Fungi	Morphology	Endemic Regions	Source	Clinical Type	Diagnosis
Histoplasma capsulatum	Biphasic fungus: mycelial and yeast phases	Ohio and Mississippi river basins, Mexico,Central America	Spores grow in excreta of bats and birds	a. Primary pulmonary b. Disseminated	Serology (not sensitive), urine for Histoplasma antigen
Blastomyces dermatitidis	Biphasic fungus	Missouri, Ohio, Tennessee, and Mississippi	Mycelial phase is infectious and found in soil and forest vegetation	Asymptomatic to severe disseminated pneumonia—nodules to multiple abscesses	Potassium hydroxide (KOH) stain of sputum or biopsy specimen of infected lung showing single bud on yeast
Coccidioides immitis	Biphasic fungus	Arid southwest United States, South/Central America	Infection from inhalation of spores	Subclinical, about one-third develop flulike syndrome or pneumonia; can cavitate	Culture, KOH prep of sputum, lung biopsy, complement fixation, skin test; highly infectious
Cryptococcus neoformans	Uniphasic: yeast	Worldwide	Pigeon droppings	Asymptomatic; may cause pneumonia, skin infection, meningitis	Antigen assay, KOH–India ink preparation shows thick capsule in CSF, skin test

10-4

SPECTRUM OF PULMONARY DISEASES CAUSED BY *ASPERGILLUS FUMIGATUS*

Clinical Manifestation	Pathology/Clinical Features	Diagnostic Tests	Treatment
Allergic bronchopulmonary aspergillosis (ABPA)	Immunologic response to *Aspergillus*; asthma, eosinophilia, pulmonary infiltrates, bronchiectasis	Total and *Aspergillus* specific IgE, serum precipitins, skin test	Corticosteroids Treatment of asthma
Mycetoma	Fibrin, cellular debris form mass within a cavity	Characteristic CXR withcrescent sign; serumprecipitins	Often no treatment; itraconazole of some benefit. Surgery if severe hemoptysis
Invasive *Aspergillus*	Necrotizing invasion of blood vessels with septate hyphae, hemorrhagic necrosis. Seen in patients with severe neutropenia	Clinical presentation: acute fever, dyspnea and chest pain in neutropenic patient. CT chest: ground glass “halo” around solid nodule or pulmonary infarction. Lung biopsy with culture	1. Amphotericin: Binds to ergosterol and opens pores in membrane 2. Voriconazole 3. Caspofungin

D. Immunologic Disorders

1. Asthma

► cram facts

Asthma is a disease of inflammation. Bronchospasm is secondary.

► Description and Symptoms

Airway inflammation with episodic reversible airway obstruction in response to provoking stimuli. Episodic dyspnea, wheezing, cough.

► Diagnosis

Pulmonary function tests (PFTs); response to bronchodilators, response to bronchoconstricting provocation agents (i.e., methacholine, cold air).

► Pathology

Inflammation with eosinophils, lymphocytes, and mast cells; epithelial cell desquamation; smooth muscle and mucous gland hypertrophy; mucus plugging; airway narrowing. Antigen binds to IgE, which stimulates mast cell release of preformed mediators, including histamine, and nonpreformed mediators, including leukotrienes via breakdown of arachidonic acid by the lipoxygenase pathway.

► Treatment Steps

Inhaled beta-agonists relax bronchial smooth muscle by stimulating cyclic AMP. β_2 agents are more pulmonary specific. Corticosteroids are anti-inflammatory. Leukotriene blockers (montelukast, zafirlukast) block inflammatory effects of leukotriene B4. Zileuton inhibits 5-lipoxygenase, prevents leukotriene formation. Cromolyn prevents mast cell degranulation and mediator release. Omalizumab, an anti-IGE monoclonal antibody, binds IgE.

2. Hypersensitivity Pneumonitis

► Description and Symptoms

Inhalation of organic dusts leading to fever, cough, dyspnea. Subacute and chronic forms have insidious onset of dyspnea. Antigens may be from microorganisms (“farmer’s lung”—thermophilic *Actinomyces,* moldy hay), animal protein (“bird fancier’s lung”), plants (“mushroom worker’s lung”).

► Diagnosis

Occupational and exposure history; chest x-ray (acute—interstitial and alveolar infiltrates; chronic—interstitial fibrosis), inhalation challenge; serum precipitins helpful but not diagnostic.

► Pathology

- Cell-mediated hypersensitivity (type IV) response to inhaled antigen.
- *Acute:* Alveolar and interstitial inflammation with lymphocytes, giant cells, plasma cells, and macrophages with foamy cytoplasm.
- *Chronic:* Noncaseating granulomas resembling sarcoidosis; interstitial fibrosis.

► Treatment Steps

1. Avoidance of precipitating antigen.
2. Corticosteroids turn off the hypersensitivity reaction.

3. Pulmonary Vasculitis

► Description and Symptoms

Diverse group of disorders characterized by inflammation of the vessel walls.

► Diagnosis

Open or thoracoscopic lung biopsy; antineutrophil cytoplasmic antibody (c-ANCA) is suggestive for Wegener's (but also positive in other vasculitides).

► Pathology

Inflammation extending through pulmonary blood vessels; fibrinoid necrosis, intimal proliferation, and perivascular necrosis. Thrombosis, vascular obstruction, and cor pulmonale may occur.

- **Leukocytoclastic vasculitis:** Neutrophils predominate. Associations: Infection, drugs, neoplasm.
- **Granulomatous vasculitis:** Lymphocytes predominate. Some specific disorders include:
    - **Wegener's granulomatosis:** Necrotizing granulomatous vasculitis (lung nodules, sinusitis and glomerulonephritis).
    - **Churg–Strauss syndrome:** Granulomatous and necrotizing vasculitis of lung, heart, skin, peripheral nerves associated with asthma and eosinophilia.
    - **Collagen vascular diseases:** may cause interstitial lung disease or pulmonary hypertension with pathology similar to primary pulmonary hypertension; pulmonary vasculitis is less common.

► Treatment Steps

Corticosteroids and other immunosuppressive drugs (e.g., azothioprine, cyclophosphamide).

E. Inflammatory Disorders

1. Chronic Obstructive Pulmonary Disease (COPD)

Any disease characterized by chronic airflow obstruction. Chronic bronchitis and emphysema are the most common and are usually caused by smoking. Coal dust, other occupational exposures may also cause COPD.

► **cram facts**

Chronic bronchitis is defined by symptoms of productive cough for 3 months in 2 successive years without other discernable cause.

a. Chronic Bronchitis

► Description and Symptoms

Defined by symptoms, not pathology: Chronic productive cough for 3 months in 2 successive years without other discernable cause. May be "simple" (symptoms without obstruction) or "obstructive."

► Diagnosis

History, PFTs (obstruction, near normal diffusion capacity for carbon monoxide [DLCO]), chest x-ray (peribronchial thickening); sputum Gram stain and culture during exacerbations.

► Pathology

Bronchi with hypertrophy and hyperplasia of submucosal glands, increased goblet cells. Reid index (the ratio of gland to bronchial wall thickness) is usually > 0.55.

b. Emphysema

► Description and Symptoms

Abnormal permanent enlargement of air spaces distal to terminal bronchioles with destruction of alveolar walls without fibrosis.

► Diagnosis

Chest x-ray (hyperinflated lungs, bullae), PFTs (obstruction with low DLCO).

► Pathology

- **Centrilobular emphysema—**focal areas of microbullae and air space enlargement emanating from respiratory bronchioles. Associated with smoking.
- **Panacinar emphysema—**dilation of all air spaces of the secondary lung lobule; seen in A1ATD.
- **Bullae—**areas of focal air space enlargement; may be isolated or part of extensive emphysema.

c. Bronchiectasis

► Description and Symptoms

Abnormal dilatation of bronchi; hemoptysis, recurrent infection, and profuse sputum production.

► Diagnosis

History (recurrent infection/hemoptysis/copious sputum production), high-resolution CT scan.

► Pathology

Dilation of proximal bronchi with PMN and monocyte bronchial wall inflammation, loss of normal ciliary anatomy and function. Cylindrical (uniform widening), saccular (saclike dilatations), or cystic.

► Treatment Steps: COPD

1. Inhaled β_2-agonists relax bronchial smooth muscle by stimulating cyclic AMP.
2. Inhaled anticholinergic agents (tiotropium or ipratropium bromide) relax smooth muscle and decrease sputum production by blocking effects of vagal tone.
3. Antibiotics for acute flare (especially for chronic bronchitis and bronchiectasis).
4. Chest physiotherapy/postural drainage for bronchiectasis—keeps airways clear of secretions.
5. Smoking cessation: Only treatment proven to slow COPD progression. Physician advice to discontinue is the most effective intervention; nicotine replacement and/or buproprion are helpful.

2. Adult Respiratory Distress Syndrome (Noncardiogenic Pulmonary Edema)

► Description and Symptoms

Acute onset of pulmonary edema due to change in permeability of alveolar capillary membrane. Associated with numerous causes including sepsis, trauma, massive aspiration, opiate drugs.

► Diagnosis

Chest x-ray (diffuse alveolar infiltrates), arterial blood gas (hypoxia), known risk factor, no cardiac cause of edema, normal or low pulmonary artery occlusion pressure.

► Pathology

Alveolar and interstitial edema, alveolar epithelial damage, hyaline membranes. Proliferative phase: Interstitial inflammation with PMNs, RBCs, fibrin, and debris. Fibrotic phase may follow.

► Treatment Steps

1. Mechanical ventilation.
2. Use of low tidal volume (5–8 mL/kg) limits trauma from ventilator; positive end expiratory pressure (PEEP) decreases oxygen requirement and limits oxygen toxicity.

F. Traumatic and Mechanical Disorders

1. Pneumothorax

► Description and Symptoms

Air in the pleural space. Chest pain, shortness of breath.

► Diagnosis

Physical exam (decreased breath sounds, tympany, tracheal shift away from pneumo); chest x-ray.

► Pathology

- **Spontaneous**: Rupture of subpleural emphysematous bleb, usually near lung apex. Secondary pneumothoraces may also occur in association with COPD, cavitary infection, carcinoma.
- **Traumatic**: Chest trauma or lung puncture allows air to enter pleural space via lung or chest wall.
- **Tension**: Flap acts as a one-way valve, allowing air to enter pleural space but not escape. Causes mediastinal shift, increased pleural pressure, decreased venous return, and shock.

► Treatment Steps

Chest tube into pleural space to water seal or suction relieves tension and allows lung to reinflate.

2. Aspiration and Aspiration Pneumonia

► Description and Symptoms

Aspiration of gastric or oropharyngeal contents or foreign body aspiration; associated with vomiting or depressed mental status. Cough, fever, shortness of breath.

► Pathology

- **Sterile aspiration:** Inhalation of low-pH stomach contents; intra-alveolar hemorrhage, edema, and PMN reaction with consolidation.

- **Bacterial aspiration:** Oropharyngeal mixed flora with anaerobes, microaerophilic and aerobic enteric bacteria; acute inflammation may progress to areas of necrosis and cavitation.
- **Foreign body aspiration:** May occlude bronchus, causing atelectasis (total obstruction) or hyperinflation ("ball–valve" allowing inspiration but not expiration).

► Diagnosis

History, chest x-ray, bronchoscopic evaluation for foreign body if history appropriate.

► Treatment Steps

1. **Bacterial aspiration:** Antibiotics that cover anaerobes (e.g., penicillin, clindamycin).
2. **Chemical aspiration:** No antibiotics; supportive treatment.

3. Flail Chest

► Description and Symptoms

Paradoxical motion of a portion of the chest wall after trauma.

► Pathology

Double fractures of three or more contiguous ribs or combined sternum and rib fractures. Segment of traumatized chest wall moves inward during inspiration.

► Diagnosis

Physical examination (paradoxical motion), chest x-ray (fractures).

4. Obstructive Sleep Apnea

► Description and Symptoms

Cessation of air flow during sleep due to upper airway obstruction. Symptoms of daytime somnolence, morning headache, loud snoring with periods of silence during airway occlusion.

► Diagnosis

Suspect in patients with obesity and daytime somnolence. Confirm with sleep study: Movement of abdomen and chest wall with no air flow at nose or mouth, usually in REM or stage IV sleep.

► Pathology

Loss of upper airway muscle tone during sleep leads to posterior shift of tongue and soft palate against the posterior pharyngeal wall, occluding the airway. May cause hypertension.

► Treatment Steps

Continuous positive airway pressure applied through nasal mask pushes the posterior tongue, uvula, and soft palate forward.

G. Neoplastic Disorders

1. Benign Pulmonary Neoplasms

► Description and Symptoms

Comprise < 5% of primary lung tumors; may present as a solitary nodule on x-ray, wheezing, or obstruction of a bronchus leading to pneumonia, bronchiectasis, or atelectasis.

► Diagnosis

Chest x-ray, CT scan, bronchoscopic or transthoracic needle biopsy.

► Pathology

1. **Bronchial (mucous gland) adenoma:** Papillary growth; cystic spaces lined by columnar cells.
2. **Papilloma:** Connective tissue stroma lined by epithelium; infiltrated with lymphocytes; viral or inflammatory etiology.
3. **Hamartoma:** May be endobronchial or parenchymal. Cartilage with epithelium-lined clefts.

► Treatment Steps

Remove surgically if obstructing bronchus or if etiology not clearly benign by CT scan or biopsy.

2. Malignant Pulmonary Tumors

a. Bronchogenic Carcinomas

► cram facts

Squamous and small cell tumors are centrally located; alveolar and adenocarcinomas are peripheral.

► cram facts

Lung cancer risk factors are multiplicative, not additive.

► Description and Symptoms

May be asymptomatic or present with cough, hemoptysis, weight loss, unexplained clubbing. Risk factors: Tobacco smoke, asbestos, radon gas, radiation. Risk factors are multiplicative, not additive.

► Diagnosis

Chest x-ray, CT scan, sputum cytology, bronchoscopic or needle aspiration biopsy. Staging may include bone scan, magnetic resonance imaging (MRI) of brain, CT of abdomen.

► Pathology

1. **Squamous cell:** Polypoid or sessile central mass obstructing bronchus. May cavitate. Malignant squamous cells connected by intercellular bridges, stratified layers in nests with keratotic debris. Highest correlation with smoking.
2. **Adenocarcinoma:** Usually peripheral. Neoplastic cuboidal or columnar cells forming glandular structures; enlarged nuclei with prominent nucleoli. Mucin in cytoplasm.
3. **Alveolar cell carcinoma:** Subtype of adenocarcinoma, originating in terminal bronchioles or alveoli. Well-differentiated columnar cells with basal nuclei lining alveolar spaces.
4. **Small cell carcinoma:** Central, often obstructing. May cavitate. Small malignant cells with little cytoplasm resemble lymphocytes. Rapidly progressive, tend to metastasize early. Associated with Eaton–Lambert syndrome (neuromuscular weakness).
5. **Large cell carcinoma:** Usually peripheral; large malignant cells with abundant cytoplasm without tendency to form glands or keratin ("undifferentiated"). Rapidly progressive.
6. **Metastatic cancer:** Usually peripheral, round lesions metastasizing from nonpulmonary cancer.

b. Bronchial Carcinoid Tumor

► Description and Symptoms

Rare, slow-growing central tumor. Rarely metastasizes if < 2 cm. Related to gastrointestinal (GI) carcinoids but serotonin production and carcinoid syndrome extremely uncommon in lung.

► Diagnosis

Chest x-ray, CT scan; bronchoscopic or transthoracic biopsy (but may bleed); surgical excision.

► Pathology

Polyp or infiltrative mass; small, uniformly staining clear cells; highly vascular.

► Treatment Steps: Malignant Tumors

1. Staging (usually by CT scan and/or biopsy).
2. Surgical excision if tumor is resectable.
3. Chemotherapy and radiation are palliative and can slow growth but aren't curative. Vinca alkaloids, paclitaxel (tubule dysfunction); cisplatin (X-links DNA); cyclophosphamide (alkylating agent).

H. Metabolic and Regulatory Disorders

1. Neonatal Respiratory Distress Syndrome

► Description and Symptoms

Impaired lung ventilation in (usually < 37 weeks' gestation) neonates caused by inadequate surfactant production; present in respiratory distress.

► Diagnosis

Respiratory distress in premature infant; chest x-ray (air bronchograms), blood gas (hypoxemia).

► Pathology

Pulmonary edema, alveoli lined with eosinophilic hyaline membrane; low lung compliance. May lead to bronchopulmonary dysplasia with inflammatory exudate followed by scarring, atelectasis, cystic alveolar destruction, and hypertrophic peribronchial and arteriolar smooth muscle.

► Treatment Steps

1. Mechanical ventilation with PEEP to decrease FiO_2 (high FiO_2 may cause retrolental fibroplasia in infant eyes and pulmonary fibrosis). Surfactant therapy improves lung compliance and inflation.
2. Prevention: Delay delivery until amniotic lecithin/sphingomyelin ratio > 2 and you detect amniotic phosphatidylglycerol. Increase surfactant by giving steroids to mother 24 hours before delivery.

2. Central Sleep Apnea

► Description and Symptoms

Cessation of breathing during sleep due to transient abolition of respiratory drive.

► Diagnosis

- History: Symptoms may be similar to obstructive apnea, but are often absent.
- Sleep study: Absence of air flow with no respiratory movement of abdomen or ribcage.

► Pathology

Defective response to high CO_2 levels due to defect in central drive or neuromuscular function.

► Treatment Steps

1. Stimulation of respiratory drive with protriptyline, modafinil, or progesterone.
2. Noninvasive mechanical ventilation using a nasal or full face mask.

3. Hypoxia

► Description and Symptoms

Decrease in oxygen tension (PO_2); shortness of breath.

► Diagnosis and Pathology

Five causes of hypoxia: Low FiO_2 (e.g., altitude), hypoventilation, shunt, ventilation/perfusion (V/Q) mismatch, and diffusion impairment. Hypoxia causes polycythemia, cyanosis, cor pulmonale, fatigue, confusion. Hypoventilation has elevated PCO_2, reduced PO_2, and normal A-a gradient. Cause may be impaired central drive (metabolic alkalosis, sedatives, CNS lesion, primary alveolar hypoventilation) or peripheral (neuromuscular disease, kyphoscoliosis, obesity). A-a gradient is increased in shunt, V/Q mismatch, and diffusion impairment. Hypoxia from a right-to-left shunt doesn't correct with oxygen. Diagnose atrial or ventricular septal defect by echocardiogram with "bubble" contrast). V/Q mismatch usually manifests as hypoxia with increased PCO_2 and elevated A-a gradient (COPD, pneumonia). Diffusion impairment diagnosed with DLCO measurement, may cause desaturation with exercise (emphysema, interstitial lung disease).

4. Hyperventilation Syndrome

► Description and Symptoms

Excessive alveolar ventilation resulting in arterial $PCO_2 < 37$.

► Diagnosis

Symptoms of dyspnea, perioral numbness; arterial blood gas.

► Pathology

Increased respiratory drive. Causes include: psychogenic, pain, hypoxia, drug induced (salicylates, methylxanthines, cocaine), metabolic acidosis, CNS infection, fever, pregnancy.

► Treatment Steps

Correct underlying cause. Increase PCO_2 by rebreathing into paper bag or rebreather mask.

I. Vascular and Circulatory Disorders

1. Pulmonary Emboli (PE)

► Description and Symptoms

Embolism from venous thrombus (95% from legs) to pulmonary circulation presenting with shortness of breath, acute chest pain, tachycardia, rarely hemoptysis.

► Diagnosis

Contrast helical CT, ventilation/perfusion scan (region of no perfusion with normal ventilation), pulmonary angiogram. Duplex leg ultrasound or elevated D-dimer levels suggestive.

► Pathology

Thrombus occluding pulmonary artery. Often, multiple emboli are present.

► Treatment Steps

1. Start anticoagulation when diagnosis is suspected with heparin (inhibits antithrombin III) or low-molecular-weight heparin (inhibits factor Xa and tissue factor inhibitor).

2. Thrombolytic agents (activate plasminogen) indicated for shock from PE.

Note: Other causes of emboli include schistosomiasis (obstruction by parasite or egg, vasculitis), air embolism (CNS damage), fat embolism (follows long-bone fractures; causes diffuse alveolar damage), amniotic fluid embolism (follows delivery, causes ARDS and disseminated intravascular coagulation), septic emboli, tumor emboli, and injected foreign body emboli (IV drug abusers).

2. Cor Pulmonale

► Description and Symptoms

Enlargement of the right ventricle due to increased right ventricular (RV) afterload caused by lung disease. Symptoms of underlying lung disease, edema.

► Diagnosis

Signs of right heart failure (peripheral edema, JVD, hepatomegaly) in setting of lung disease.

► Pathology

Hypertrophy and/or dilatation of the right ventricle. Pulmonary pathology of underlying disease.

► Treatment Steps

1. Treatment of underlying disease.
2. Diuretics help edema but may cause hypotension.

3. Primary Pulmonary Hypertension

► Description and Symptoms

Persistent elevation of pulmonary artery pressure without demonstrable cause. Unexplained dyspnea on exertion progresses to resting dyspnea.

► Diagnosis

Diagnosis of exclusion—vasculitis, PE, mitral stenosis, etc. should be ruled out. PFTs (isolated reduction in DLCO); pulmonary angiogram suggestive; lung biopsy for definitive diagnosis.

► Pathology

Vasoconstriction, medial hypertrophy, and intimal proliferation of arterioles, concentric intimal fibrosis (**"onion skinning"**), microaneurysms with endothelial proliferation (**plexiform lesions**).

► Treatment Steps

Calcium channel blockers and prostacycline may vasodilate pulmonary circulation (may not work in late disease); Bosantan: endothelin antagonist.

J. Idiopathic Disorders

1. Sarcoidosis

► Description and Symptoms

Multisystem disease; granulomatous inflammation of unknown etiology. Asymptomatic or dyspnea, ocular symptoms, or arthritis.

► Diagnosis

Chest x-ray stages: 0—normal; 1—hilar and/or mediastinal adenopathy; 2—diffuse interstitial disease; 3—adenopathy with interstitial

► cram facts

Presence of caseating granulomas should raise the suspicion of tuberculosis.

disease. Atypical x-rays also occur. PFTs (restriction, low DLCO), elevated angiotensin-converting enzyme, gallium scans helpful. Lung biopsy confirms diagnosis.

► Pathology

Noncaseating granulomas with whorls of fibroblasts, epithelioid and giant cells centrally, and peripheral mononuclear inflammatory cells.

► Treatment Steps

Often self-limited. Corticosteroids decrease the inflammatory response.

2. Idiopathic Pulmonary Fibrosis

► Description and Symptoms

Interstitial lung disease of unknown etiology causing progressive scarring and shortness of breath.

► Diagnosis

Chest x-ray, high-resolution CT scan, surgical lung biopsy, PFTs (restriction, low DLCO).

► Pathology

- **Desquamative interstitial pneumonia (DIP):** Alveoli filled with copious macrophages.
- **Usual interstitial pneumonia (UIP):** Interstitial lymphocytes, fibroblasts, and macrophages; collagen and fibrosis. Late stage: "Honeycomb lung"—fibrotic destruction of architecture, cysts.
- Respiratory bronchiolitis with interstitial lung disease (RBILD) is a mild form caused by smoking.

► Treatment Steps

No known cure. Corticosteroids often used. RBILD responds to smoking cessation.

3. Lymphocytic Interstitial Pneumonia (LIP)

► Description and Symptoms

Progressive interstitial infiltrates.

► Diagnosis

Chest x-ray (restriction, low DLCO), lung biopsy.

► Pathology

Sheets of lymphocytes infiltrating interstitium and alveoli. May transform into pulmonary lymphoma.

4. Alveolar Proteinosis

► Description and Symptoms

Rare interstitial disease caused by alveolar deposition of phospholipid material. Dyspnea, hypoxia.

► Diagnosis

Chest x-ray (alveolar consolidation); bronchoscopic lavage, lung biopsy. Serum LDH is often high.

► Pathology

Periodic acid–Schiff stain (PAS) positive amorphous lipid-rich granular material filling alveolar air spaces. No inflammatory cells present; increased type II pneumocytes, lamellar bodies on EM.

► Treatment Steps

Whole-lung lavage. High incidence of concomitant *Nocardia* infection.

4. Eosinophilic Granuloma

► Description and Symptoms

Nodular/reticulonodular disease. May present with spontaneous pneumothorax or pleuritic pain.

► Diagnosis

Lung biopsy. Chest x-ray, CT scan suggestive (cysts); PFTs (restriction, low DLCO).

► Pathology

Irregularly shaped peripheral nodules composed of histiocytes, macrophages, eosinophils, and lymphocytes. Hallmark: **Langerhans' cell** with intracytoplasmic X bodies. Form of histiocytosis X.

III. PSYCHOSOCIAL, CULTURAL, OCCUPATIONAL, AND ENVIRONMENTAL CONSIDERATIONS

Smoking cessation is key to preventing progression of COPD. Asking smoking history and advising smoking cessation are most effective means of stopping a patient from smoking. Nicotine replacement therapy (nicotine gum, sprays, and patches) are helpful adjuncts. Children are more likely to start smoking if their parents smoke. Smoking is more prevalent in urban areas. Passive smoking increases respiratory symptoms in children and may increase risk for airway obstruction.

Occupational factors can precipitate asthma. Allergic factors may sensitize patients who then will go on to nonspecific airway reactivity (western red cedar, isocyanates in spray paint, plastics, and glues), which may persist despite removal of offending antigen. Nonallergic irritants can cause allergic attacks to occur in patients with previously diagnosed asthma.

Reactive airway dysplasia syndrome (RADS) is caused by mucosal injury from a single overwhelming exposure to an inhaled toxin (e.g., chlorine, ammonia, sulfur gas, developer solutions) that causes persistent asthma symptoms in patients not previously asthmatic.

BIBLIOGRAPHY

Mason RJ, Broaddus C, Murray JF, Nadel JA (eds.). *Murray and Nadel's Textbook of Respiratory Medicine*, 4th ed. Philadelphia: Elsevier, 2005.

Niederman MS, Sarosi GA, Glassroth J. *Respiratory Infections*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.

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The Skin and Related Connective Tissue

11

I. NORMAL PROCESSES

A. Embryonic Development, Fetal Maturation, and Perinatal Changes

The epidermis originates from the ectoderm as a single undifferentiated layer. All layers of the mature epidermis are identified at 24 weeks. The dermis originates from mesenchymal cells that evolve into fibroblasts. Melanocytes originate from neural crest cells that migrate to the skin during fetal development.

Neonatal skin, compared with adult skin, is thinner and has less active hair follicles and sweat glands. Only premature infants suffer from increased skin permeability; however, all infants have a higher body surface-to-mass ratio in comparison to adults.

B. Organ Structure and Function

1. Skin Anatomy

The skin is the largest organ in the body, measuring approximately 2 square meters. It is divided into several layers: epidermis, dermis, and subcutaneous fat.

2. Skin Function

Most important is the epidermal barrier that prevents entry of outside substances and loss of endogenous water and proteins. Also, the skin is a very important part of the immune system and production of vitamin D via photochemistry. The dermis provides a strong vascularized supporting meshwork containing vessels, nerves, and adnexa. The subcutaneous fat is a thick protective layer that also provides insulation and stores energy.

► cram facts

Epidermal turnover is 30 days.

C. Cellular Components and Function

Epidermal keratinocytes form a protective, regenerating outer coat of cells. Melanocytes produce pigment for skin coloration and sun protection. Langerhans' cells catch foreign substances or organisms. Dermal fibroblasts produce the collagen and elastin meshwork. Cutaneous appendages such as hair follicles and sweat glands contain a number of specialized cells. Adipocytes form fat lobules in the subcutaneous fat.

D. Repair, Regeneration, and Changes Associated with Aging

Epidermal keratinocytes differentiate in the lowest layer and after 30 days slough off the uppermost layer. In this way, damaged cells (trauma, ultraviolet radiation, etc.) are replaced by new normal cells. Deep penetrating injuries that damage the dermal meshwork are replaced by a scar to maintain structural support.

The skin layers atrophy and develop mottled pigmentation and prominent telangiectases. This is pronounced in sun-damaged areas. Gradual loss of support and protection of the cutaneous blood vessels can cause large bruises (Bateman's purpura).

E. Skin Defense and Normal Flora

The skin barrier physically prevents organisms from entering the body. Langerhans' cells in the epidermis catch and deliver invading organisms to the regional lymph node, thereby triggering a T cell–mediated response. Keratinocytes produce and secrete a variety of immunomodulators. In addition, many types of leukocytes can be found in the skin during infection.

There are always small numbers of organisms present on the skin depending on location and environmental and individual factors. The most pathogenic skin organism is *Staphylococcus aureus,* which often colonizes the nares. *Staphylococcus epidermidis* often colonizes the skin.

II. ABNORMAL PROCESSES

A. Genetic Disorders

1. Atopic Dermatitis (Eczema)

► Description and Symptoms

Mild to severe itchy eruption that affects 10% of children, especially those with an atopic diathesis (seasonal allergies, asthma). Associated increased risk of skin infection. No cure available, though decreased severity with age.

► cram facts

Eczema is itchy.

► Diagnosis

Acute eczema consists of red plaques. Chronically inflamed skin has more prominent skin markings and scale. It is very unusual for eczema to affect the axilla or groin.

► Pathology

Spongiotic dermatitis.

► Treatment Steps

1. Daily moisturizer and PRN topical medications (steroids, tacrolimus, pimecro linius).
2. PRN oral antihistamines and antibiotics.

2. Keloid

► Description and Symptoms

Firm protuberant scar that extends beyond the boundary of the injury (see Figure 11–1). Keloids can be itchy or painful and often occur in certain locations (chest and shoulders) and racial groups (black, Asian, etc.).

► Diagnosis

Diagnosis is clinical and usually not difficult.

► Pathology

Altered wound healing and collagen synthesis.

► Treatment Steps

May be difficult as keloids tend to recur. Occlusive dressing, intralesional steroids, and pulsed-dye laser are treatment options.

3. Psoriasis

► Description and Symptoms

Scaly, red plaques that tend to affect the knees, elbows, scalp, and sacrum (see Figure 11–2). Most patients have a few small asymptomatic plaques; however, some have widespread lesions and/or pruritus. One percent incidence. Possible autosomal dominant inheritance with variable penetrance.

► cram facts

Typical psoriasis lesions are on the elbows and knees.

► Diagnosis

Clinical appearance, though may confirm with a biopsy.

Figure 11–1. Keloid.

► Pathology

An inflammatory reaction in the skin altered by environmental and genetic factors.

► Treatment Steps

Aggressiveness of therapy must be tailored to clinical situation. Many options available: Topical (steroids, calcipotriene, retinoids), ultraviolet light (A and B), and systemic (methotrexate, retinoids, cyclosporine, tumor necrosis factor-α inhibitors).

B. Congenital Disorders

1. Hemangioma

► cram facts

Hemangiomas resolve over the first decade of life.

► Description and Symptoms

Often presents as a red patch at birth which progresses through three phases: proliferative, plateau, and involution. Lesions may be small to large. Problematic if near vital organs or painful.

► Diagnosis

Clinical appearance.

► Pathology

Increased number of dermal vessels.

Figure 11–2. Psoriasis.

► Treatment Steps

1. Often no treatment needed as hemangiomas resolve spontaneously.
2. If problematic, consider steroids or laser treatment.

2. Neurofibromatosis Type I (NF1)

► Description and Symptoms

Autosomal dominant multisystem disorder with: multiple neurofibroma, café au lait macules, axillary freckling, Lisch nodules, optic gliomas, and sphenoid dysplasia. Fifty percent are inherited (autosomal dominant), 50% are spontaneous mutations.

► cram facts

Defective gene is NF1.

► Diagnosis

Two features of NF1 are needed for the diagnosis. Genetic testing for mutations in chromosome 17.

► Pathology

Mutation in chromosome 17.

► Treatment Steps

1. Genetic counseling and monitoring.
2. Painful or cosmetically disfiguring lesions may be surgically removed.
3. Laser treatment of café au lait lesions possible.

3. Port-Wine Stain

► Description and Symptoms

Cutaneous vascular malformation of capillaries present at birth. Initially red, the lesion may become purple with time. Unlike hemangiomas, port-wine stains persist unless treated. A variety of syndromes may be associated.

► Diagnosis

Clinical.

► Pathology

Dilated capillaries in the upper dermis.

► Treatment Steps

Multiple pulsed-dye laser treatments if cosmetically bothersome. Other medical problems (glaucoma, seizures) must be managed if part of a syndrome (Sturge–Weber syndrome).

4. Tuberous Sclerosis

► Description and Symptoms

AD multisystem disorder characterized by ash leaf (hypopigmented) macules, skin tumors (angiofibromas, Shagreen patch, periungual fibromas), and internal tumors (CNS, kidney, eye, and heart).

► Diagnosis

Requisite number of clinical criteria.

► Pathology

Mutation of chromosomes 9 and 16 causing decreased production of tumor suppressors (tuberin and hamartin).

► Treatment Steps

1. Genetic counseling and periodic monitoring for complications.
2. Laser treatment of skin lesions for cosmetic improvement.

C. Infectious Disorders

1. Bacterial Infections

a. Acne

► Description and Symptoms

Comedones and inflammatory papules common in teenagers and young adults. Mostly distributed on the face, chest, and back.

► Diagnosis

Clinical appearance.

► Pathology

Obstructed hair follicle leading to inflammation. Many underlying factors: *Propionibacterium acnes* infection, hormones, follicular cornification, sebum production.

► Treatment Steps

1. A plethora of agents available. Common topicals include benzoyl peroxide, antibiotics, and retinoids.
2. Systemic antibiotics (especially tetracycline derivatives) for more severe acne.
3. Isotretinoin (Accutane) is an excellent option for recalcitrant acne.

► cram facts

Isotretinoin is the strongest acne medication, but also has the most side effects.

b. Anthrax

► Description and Symptoms
Potentially fatal cutaneous, pulmonary, or gastrointestinal (GI) infection. Skin findings include a painless, rapidly evolving necrotic plaque on an exposed area such as the extremities or head/neck region.

► cram facts

Cutaneous anthrax is painless.

► Diagnosis
Clinical suspicion confirmed by Gram stain, culture, enzyme-linked immunosorbent assay (ELISA), or immunoblotting.

► Pathology
Infection by *Bacillus anthracis*, a toxin-producing, gram-positive bacillus that forms spores.

► Treatment Steps
Early administration of antibiotics (such as ciprofloxacin or doxycycline) and supportive care.

c. Cellulitis

► Description and Symptoms
Rapidly spreading erythema and edema often found in the extremities. Can be associated with pain and fever.

► Diagnosis
Clinical suspicion. Blood culture may be helpful.

► Pathology
Bacterial infection of the deep dermis and subcutaneous fat, usually by *Staphylococcus* or *Streptococcus*.

► Treatment Steps
Oral or IV antibiotics. Elevation of the affected extremity. Treatment of predisposing causes such as tinea pedis and other rashes.

d. Furuncle/Carbuncle

► Description and Symptoms
A red, tender nodule originating from a hair follicle (furuncle). A pustule or exudate is often seen. Multiple follicles may be involved (carbuncle) (see Figure 11–3).

► Diagnosis
Clinical suspicion. Bacterial culture of the exudates may be helpful.

► Pathology
Deep infection, usually by *Staphylococcus*, of a hair follicle.

► Treatment Steps
1. Incision and drainage.
2. Antibiotics.
3. Warm compresses.

e. Impetigo

► cram facts

Honey-colored crusts are typical of impetigo from *S. aureus*.

► Description and Symptoms
Red papules and plaques that form superficial vesicles leading to a characteristic "honey-colored" or "golden" crust. The lesions are often asymptomatic, but may be pruritic (see Figure 11–4).

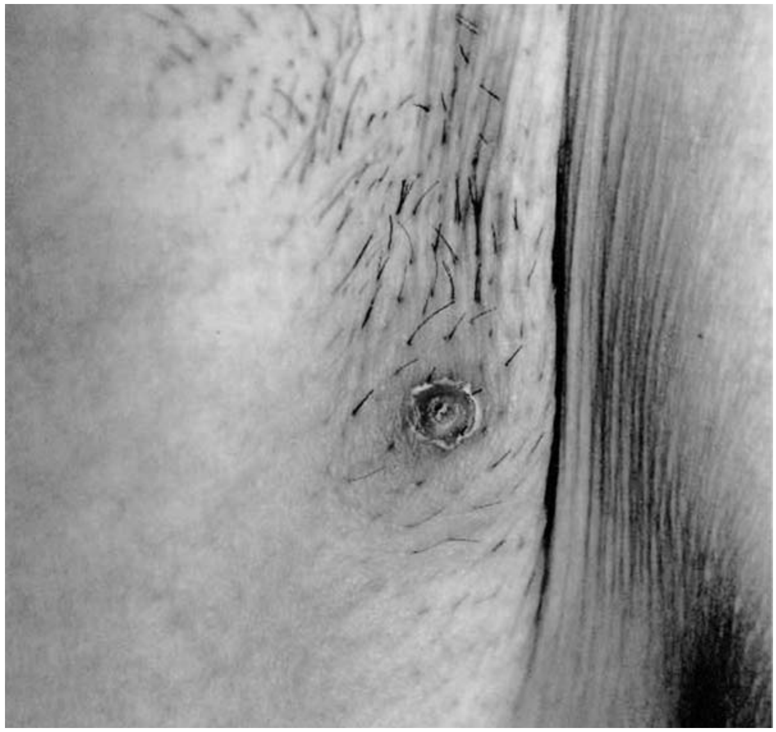

Figure 11–3. Furuncle.

► Diagnosis
Clinical suspicion. Bacterial culture can be helpful.

► Pathology
Superficial infection of the skin with *Streptococcus pyogenes*, occasionally *Staphylococcus aureus*. Often occurs after minor skin trauma.

Figure 11–4. Impetigo.

► Treatment Steps

Topical mupirocin or systemic antibiotics.

f. Necrotizing Fasciitis

► Description and Symptoms

An aggressive infection involving the fascia. Manifested by rapidly worsening skin discoloration and necrosis. High morbidity and mortality.

► Diagnosis

Clinical diagnosis.

► Pathology

Subcutaneous and fascial infection. Vessels and nerve damage found. Can be due to a variety of organisms (*Bacteroides, Enterobacteriaceae, Streptococcus, Vibrio*).

► Treatment Steps

1. Immediate debridement.
2. Supportive care.
3. Antibiotics.

2. Viral Infections

a. Herpes Simplex

► Description and Symptoms

Recurrent self-limited tender vesicular eruption most often found on the lips and genitalia. Prior to the recurrence, a tingling or burning sensation is usually felt.

► Diagnosis

Appropriate history and clinical appearance. Culture or polymerase chain reaction (PCR) may be used.

► Pathology

- *Herpes simplex virus 1*—mostly oral.
- *Herpes simplex virus 2*—mostly genital.

► Treatment Steps

Antivirals (famcyclovir, acyclovir, valacyclovir) taken at the first sign of recurrence may abort or shorten an episode.

b. Varicella-Zoster Virus

► Description and Symptoms

Initial airborne infection leads to the common childhood exanthem chickenpox (self-limited pruritic vesicular eruption). Recurrence in a dermatomal distribution is termed *zoster* (painful vesicular eruption) (see Figure 11–5).

► Diagnosis

Appropriate history and clinical appearance. Culture or PCR may be used.

► Pathology

Varicella-zoster virus infection.

► Treatment Steps

1. Isolation from unexposed or immunocompromised adults (including pregnancy).

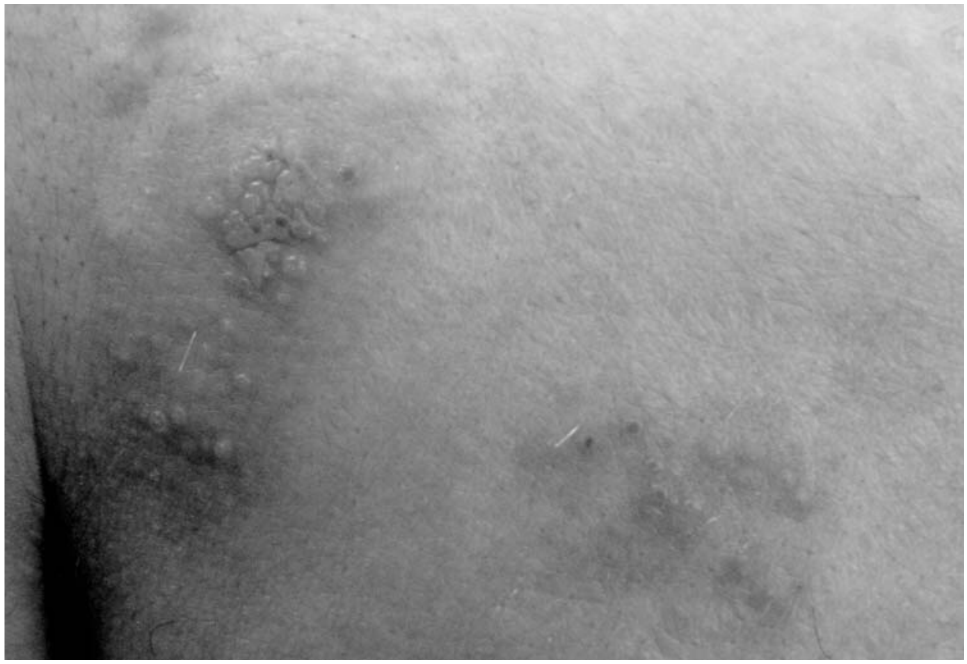

Figure 11–5. Varicella-zoster.

2. Antiviral and symptomatic therapy.
3. Encephalitis and pneumonia may be rare but dangerous complications.

d. Verruca

► Description and Symptoms

Warts can occur on any skin surface including the oral mucosa. In the genital region, they are termed *condyloma* and may be sexually transmitted. Usually asymptomatic, larger lesions may become tender with trauma or pressure.

► Diagnosis

Clinical. Biopsy can confirm.

► Pathology

Human papillomavirus (HPV) infection.

► Treatment Steps

1. Salicylic acid, liquid nitrogen, cantharidin, podophyllin, imiquimod, laser, and surgery all can be used to treat warts depending on location and patient preference.
2. Female partners of men with condyloma should have routine Pap smears (certain HPV types lead to cervical cancer).

3. Fungal Infections

a. Candidiasis

► Description and Symptoms

Often seen either as white cheesy plaques in the mucosa or red papules and pustules in the inguinal region.

► Diagnosis

Clinical. Skin scraping will demonstrate pseudohyphae.

► cram facts

Satellite papules and pustules are often seen in a lesion of candidiasis.

► Pathology
Infection with *Candida albicans* (usually).

► Treatment Steps
1. Nystatin cream or azole-based antifungal medications.
2. It is helpful to minimize precipitating factors (uncontrolled diabetes, antibiotic therapy, moist environment).

b. Tinea Versicolor

► Description and Symptoms
Scaly, thin plaques mostly on the trunk and proximal extremities. The lesions can be darker or lighter than the surrounding skin, hence "versicolor." Often asymptomatic.

► Diagnosis
Clinical. Skin scraping with KOH will demonstrate "spaghetti and meatball" appearance of short hyphae and spores.

► Pathology
Caused by *Malassezia furfur* (*P. ovale*).

► Treatment Steps
1. Topical antifungals in cream or shampoo form.
2. Oral azole-type antifungals very effective.

c. Tinea Corporis/Capitis/Cruris/Pedis

► Description and Symptoms
Red, scaly plaques that may be asymptomatic or itchy. Frequent cause of hair loss on the scalp. On the body, the lesions often have an annular (ring-shaped) appearance. On the feet, often seen between the toes and along the plantar portion of the foot (see Figure 11–6).

► cram facts

Tinea capitis is usually seen in young black children.

► Diagnosis
Clinical. Skin scraping with KOH will demonstrate hyphae.

► Pathology
Caused by a variety of dermatophyte fungi.

► Treatment Steps
Topical or systemic antifungal medications.

D. Inflammatory Disorders

1. Alopecia Areata

► Description and Symptoms
Patchy, nonscarring hair loss in normal looking skin. Most patients have small, localized patches. Some have widespread involvement. Can be associated with hypothyroidism.

► Diagnosis
Clinical appearance. Biopsy confirmatory.

► Pathology
Lymphocytic attack on the hair follicle ("swarm of bees" appearance on path) of unknown etiology.

► Treatment Steps
Topical or intralesional steroids are first-line treatments.

Figure 11–6. Tinea.

► cram facts

Eyelid rash is often found in dermatomyositis.

2. Dermatomyositis

► Description and Symptoms

Muscle weakness associated with typical skin findings: heliotrope rash (eyelids), Gottron's papules (hand), and poikiloderma (mottled sun damage—neck/chest/back).

► Diagnosis

Clinical criteria. Positive antinuclear antibody (ANA) and anti-Jo-1 antibody helpful.

► Pathology

Autoimmune disorder of unknown etiology.

► Treatment Steps

1. Sun protection.
2. Topical or systemic steroids.
3. Hydroxychloroquine, methotrexate.

3. Discoid Lupus Erythematosus (DLE)

► Description and Symptoms

Disc-shaped scarring plaques most commonly found on the head, upper chest/back, and arms. The lesions are slowly progressive, often with alopecia or pigmentary changes. Photosensitivity.

► Diagnosis
Lesions fairly characteristic. Confirmed with biopsy.

► Pathology
Five percent of patients with DLE have (or will have) systemic LE. Twenty-five percent of systemic LE patients have DLE lesions.

► Treatment Steps
1. Sun protection extremely important.
2. Topical or intralesional steroids.
3. Patients with extensive disfiguration may require treatment with hydroxychloroquine, isotretinoin, or thalidomide.

4. Lichen Planus (LP)

► Description and Symptoms
Chronic eruption that affects the mucous membranes, skin, and nails. The buccual mucosa often has a lacy white appearance. The skin has itchy, reddish-purple, flat-topped papules with an overlying fine, white, lacy scale (Wickham's striae) most commonly seen on the wrists, genitalia, and ankles (see Figure 11–7). The nails may be normal, but may be severely dystrophic.

► Diagnosis
Clinical suspicion confirmed by biopsy.

► Pathology
Unknown. Some drug eruptions can mimic rash. In addition, some studies indicate an association between LP and hepatitis C.

► Treatment Steps
1. Topical steroids and antihistamines.
2. Drug history and hepatitis screen may be helpful.

► cram facts

Lichen planus can be associated with hepatitis C viral infection.

5. Pityriasis Rosea

► Description and Symptoms
Transient eruption that tends to occur on the trunk of young adults. The first sign is usually a large red scaly plaque (herald patch), followed later by smaller oval, scaly plaques. The eruption lasts 3–8 weeks (see Figure 11–8).

Figure 11–7. Lichen planus.

Figure 11–8. Pityriasis rosea.

► Diagnosis
Clinical, however may be mimicked by syphilis (check rapid plasma reagin [RPR]).

► Pathology
Unknown etiology.

► Treatment Steps
No therapy needed. If symptomatic, topical steroids or UV light may be helpful.

6. Urticaria

► Description and Symptoms
Transient, nonscaly, red plaques (hives) each present < 24 hours. May be itchy. Divided into acute and chronic if present less or more than 6 weeks' duration. Rarely associated with angioedema, which can be fatal.

► Diagnosis
Clinical diagnosis.

► Pathology
Either idiopathic or triggered by exposure to a causative factor. Common causes include medications, food (shellfish, nuts, etc.), pressure, temperature, infection, and bee stings.

► Treatment Steps
1. Discover offending agent and avoid exposure.
2. Antihistamines are the mainstay of therapy.

E. Neoplastic Disorders

1. Actinic Keratosis

► Description and Symptoms
Thin, rough, scaly plaques that are more easily felt than seen. Mostly seen in a photodistribution in a setting of sun-damaged skin.

► Diagnosis
Clinical. Biopsy can confirm.

► Pathology

A very small percentage of these sun-induced lesions will degenerate into squamous cell carcinoma.

► Treatment Steps

1. Frequently treated during routine skin checks in sun-damaged patients.
2. Treatments include liquid nitrogen and topical products (5-fluorouracil and diclofenac).

2. Basal Cell Carcinoma

► Description and Symptoms

Pearly pink cancerous plaque with telangiectases on sun-damaged skin (see Figure 11–9). Prone to bleeding and ulceration. Almost zero risk of metastasis. Most common malignancy.

► cram facts

Basal cell carcinomas look shiny, hence the "pearly" look.

► Diagnosis

Clinical confirmed by biopsy.

► Pathology

Sun damage–induced skin cancer.

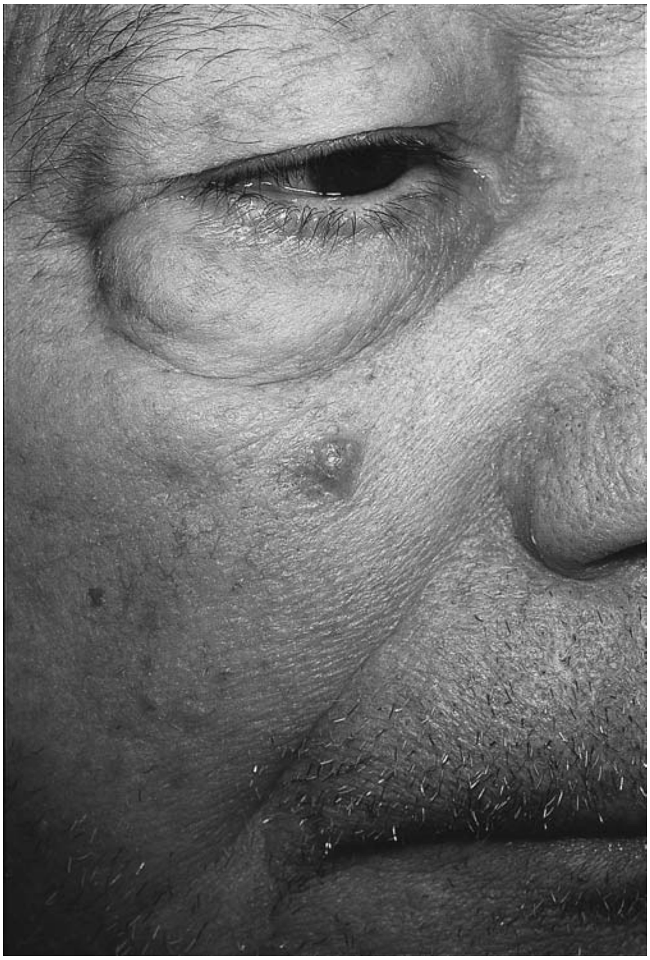

Figure 11–9. Basal cell carcinoma.

► Treatment Steps

1. Removal necessary via excisional surgery, Mohs' surgery, desiccation and curettage, topical medications (imiquimod, 5-fluorouracil).
2. Follow-up skin checks needed as patient at higher risk for other skin cancers.

3. Cutaneous T-Cell Lymphoma (Mycosis Fungoides)

► Description and Symptoms

Malignant patches progressing to plaques, tumors, and ulcers on the skin (see Figure 11–10). Usually very slow course and delayed diagnosis (6–8 years after onset). Sézary syndrome is more aggressive and manifested by diffuse erythema.

► Diagnosis

High index of clinical suspicion. Many biopsies often needed. Five- to 7-year delay from onset to diagnosis is typical.

► Pathology

Epidermal attack by malignant T-cell clones.

► Treatment Steps

Skin involvement often treated with PUVA, nitrogen mustard, and/or retinoids.

4. Melanoma

► Description and Symptoms

Dangerous skin cancer that often appears as an irregular changing mole. Warning signs: A (asymmetry), B (jagged border), C (multiple colors), and D (diameter > 6 mm) (see Figure 11–11).

► Diagnosis

Clinical confirmed by biopsy.

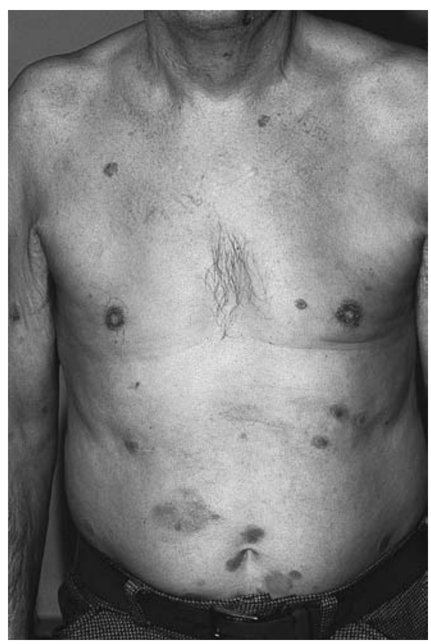

Figure 11–10. Mycosis fungoides.

Figure 11–11. Melanoma.

► Pathology

Risk factors include many unusual moles, positive family history, sunburns as a child.

► Treatment Steps

1. Sun protection starting early in life.
2. Self-monitoring of moles and periodic skin checks by a dermatologist.
3. Prognosis with surgical excision excellent if caught early.
4. Advanced (deep) melanoma that has metastasized responds poorly to treatment.

► cram facts

Melanoma prognosis is dependent on the depth of invasion.

5. Nevi (Moles)

► Description and Symptoms

Common skin-colored to brown macules and papules anywhere on the body. If present as an infant, they are called congenital nevi. Nevi with irregular pigmentation, jagged border, asymmetry, and/or large diameter are often biopsied to rule out melanoma.

► Diagnosis

Clinical. Confirmed by biopsy if needed.

► Pathology

Nests (groups) of melanocytes in the epidermis and/or upper dermis.

► Treatment Steps

1. Patients should be advised on sun protection and to report moles that change or develop atypical features.
2. Some are removed for cosmetic reasons.

6. Seborrheic Keratosis

► Description and Symptoms

Tan to brown scaly plaques that have a "stuck-on" appearance. Often occurs more with age.

► Diagnosis

Clinical. Biopsy can confirm.

► Pathology

Unknown etiology.

► Treatment Steps

If irritated or cosmetically bothersome, these can be removed with liquid nitrogen or curettage.

7. Squamous Cell Carcinoma

► Description and Symptoms

Crusted, keratotic, or ulcerated tumors (see Figure 11–12). Although most are low-grade malignancies, some areas carry a higher risk (lip, mucosa, ears, and midface) of metastasis.

► Diagnosis

Clinical confirmed by biopsy.

► Pathology

Tumors induced by either sun damage, arsenic exposure, or chronic wounds.

► Treatment Steps

Surgical excision, Mohs' surgery, or radiation therapy.

Figure 11–12. Squamous cell carcinoma.

F. Metabolic and Regulatory Disorders

1. Vitamin C Deficiency (Scurvy)

► Description and Symptoms

Skin findings include perifollicular petechiae, multiple ecchymoses, and "corkscrew hairs." In addition, there may be hematoma, edema, subperiosteal hemorrhage, anemia, and hemorrhagic gingivitis.

► Diagnosis

Clinical diagnosis, may be confirmed by serum ascorbic acid (vitamin C) levels.

► Pathology

Usually a result of inadequate diet in older alcoholics or psychiatric patients.

► Treatment Steps

Proper nutrition with vitamin C supplementation.

2. Marasmus/Kwashiorkor

► Description and Symptoms

Patients with marasmus tend to have dry, wrinkled, loose skin and appear thin and wasted. In kwashiorkor, patients may falsely appear well nourished due to an edematous abdomen. In addition, there are alternating color changes in the hair shaft and desquamating skin that resemble "flaky paint."

► Diagnosis

Clinical diagnosis.

► Pathology

Marasmus results from both protein and caloric deprivation. Kwashiorkor results from protein deprivation. There may be some overlap between the two.

► Treatment Steps

Adequate nutrition.

3. Niacin Deficiency (Pellagra)

► cram facts

Remember the 4 D's of pellagra: Diarrhea, Dementia, Dermatitis, Death.

► Description and Symptoms

Remember the 4 Ds: diarrhea, dementia, dermatitis, and eventually death. The skin tends to be photosensitive with redness, swelling and itching/pain after sun exposure. Later, there is often hyperpigmentation and scale. In addition, often angular cheilitis, dizziness, and later a variety of neurologic and GI symptoms.

► Diagnosis

Clinical suspicion. A skin biopsy may be helpful but nonspecific.

► Pathology

Niacin deficiency may be seen in patients on severely restricted diets and alcoholics. In addition, it may be seen in patients with carcinoid syndrome, Hartnup's disease, GI parasites, and psychiatric disorders.

► Treatment Steps

Fluid, electrolyte, and nutritional supplementation.

G. Vascular Disorders

1. Leukocytoclastic Vasculitis

► Description and Symptoms

Purpuric papules most often on the lower extremities usually lasting several weeks. Commonly associated with fever, arthralgias, and other systemic symptoms including renal involvement. May be idiopathic or associated with a variety of triggering factors (medications, infections, connective tissue disorders).

► Diagnosis

Clinical suspicion confirmed by biopsy.

► Pathology

Immune complex deposition in the cutaneous vessels leading to vascular destruction and extravasation of red blood cells (RBCs).

► Treatment Steps

1. If possible, treatment of the precipitating event or disorder.
2. A variety of medications can be helpful: nonsteroidal anti-inflammatory drugs (NSAIDs), dapsone, colchicine, or prednisone.

2. Stasis Dermatitis

► Description and Symptoms

Eczematous plaques on the bilateral lower legs/ankles accompanied by purple, hyperpigmented edematous skin. The skin may be itchy. Involved skin may easily ulcerate, heal slowly, and become superinfected.

► Diagnosis

Clinical history and appearance.

► Pathology

Poor venous return leading to chronic edema and stasis changes.

► Treatment Steps

1. It is important to minimize leg swelling by combining leg elevation, compression, and perhaps medication (diuretics if needed).
2. The eczematous plaques may be treated with moderate-potency topical steroids.
3. Ulcers need good wound care and careful antibiotic therapy when infected. Unfortunately, this tends to be a chronic problem without cure.

H. Skin Manifestations of Systemic Disease

1. Acanthosis Nigricans (AN)

► cram facts

Acanthosis nigricans looks like dirty skin that cannot be washed clean.

► Description and Symptoms

Velvety hyperpigmented plaques most often found on the neck, axillae, and antecubital fossa. Malignancy-associated AN may be pruritic.

► Diagnosis

Clinical appearance.

► Pathology

In children, AN is often familial, but may be associated with obesity/diabetes. Adults with sudden, extensive involvement may have an associated internal malignancy (most commonly a gastric adenocarcinoma).

► Treatment Steps

Treatment of the underlying disorder may be helpful.

2. Necrolytic Migratory Erythema

► Description and Symptoms

A "typical" patient with necrolytic migratory erythema has red, vesicular plaques with erosions and hyperpigmentation. Often associated is glossitis, stomatitis, weight loss, diabetes, and anemia. Most patients have an underlying pancreatic cancer that produces glucagons.

► Diagnosis

The physician must have a high incidence of suspicion, as this may be very hard to diagnose. Skin biopsy may show similar changes as can be seen with a variety of nutritional disorders.

► Pathology

Production of glucagons affects amino acid production.

► Treatment Steps

1. Find and treat underlying malignancy.
2. Somatostatin may be helpful to control the rash.

3. Porphyria Cutanea Tarda

► Description and Symptoms

Photodistributed blisters, crusts, and erosions that lead to scars and pigmentary changes (see Figure 11–13). May be associated with milia, hypertrichosis, and sclerodermoid changes.

► Diagnosis

Clinical suspicion confirmed by urine or serum porphyrins.

► Pathology

May be associated with viral hepatitis, hormonal therapies, hemodialysis, or alcohol intake. Etiology is a defect in the uroporphyrinogen decarboxylase enzyme used in the production of heme.

Figure 11–13. Porphyria cutanea tarda.

Figure 11–14. Pyoderma gangrenosum.

► Treatment Steps
1. Complete sun protection extremely important.
2. Treatment of underlying disorder.
3. Phlebotomy and low-dose antimalarials are treatment options.

4. Pyoderma Gangrenosum

► Description and Symptoms

Painful, rapidly expanding red, pustular papule that often develops into a large (10–20 cm), ulcerated plaque with undermined borders and a purple halo (see Figure 11–14). The ulcer may be deep enough to expose tendons and bone. Patients may have multiple lesions and the disease may flare without warning.

► Diagnosis

Diagnosis of exclusion. It is very important to rule out an infectious process with cultures and biopsy.

► Pathology

In 50% of patients there is an associated underlying systemic disease (most commonly inflammatory bowel disease or hematopoietic malignancy).

► Treatment Steps
1. Wound care is extremely important; however, debridement may worsen rather than improve the overall course.
2. Once the diagnosis is established, immunosuppressive therapy with steroids, cyclosporine, or dapsone is the treatment of choice.
3. Also, investigation and treatment of any underlying disorders may be helpful.

III. PRINCIPLES OF THERAPEUTICS

A. Drug Mechanisms and Effects

1. Glucocorticoids

A mainstay of dermatologic therapy for years, topical and systemic steroids exert many positive and negative effects. Topical steroids are categorized 1–7 (1 being the strongest). Steroids are excellent anti-inflammatory agents and can be used to treat a wide variety of inflammatory skin conditions from eczema to lupus. By eliminating the body's immune response, steroids can make infectious processes worse (often seen with tinea). In addition, topical steroid use may cause acne, atrophic skin, and striae. Systemic side effects from long-term excessive topical use or oral steroids may cause osteoporosis, hypertension, diabetes, obesity, muscle atrophy, avascular necrosis, and more.

2. Emollients

In many skin disorders, such as atopic dermatitis, it is very important to lubricate the skin. In general, ointments are better emollients than creams, which in turn are better than lotions. Equally important is the use of a gentle soap and short lukewarm showers or baths.

3. Sunscreen

Suncreen and sunblock forms a topical defense from UVA and UVB light, which over years may lead to wrinkles, pigmentary changes, and skin cancer. An SPF of 15 indicates the ability to stay out 15 times longer with protection than without to achieve the same level of sun damage from UVB. An ideal sunblock would sufficiently cover UVA and UVB, be waterproof, not cause acne, and spread easily.

4. Retinoids

Retinoids are often used for acne, psoriasis, and other skin disorders. Topical formulations are safe but may cause skin irritation. Systemic retinoids are more effective; however, they carry potential for serious side effects, including high triglycerides, teratogenicity, possible psychiatric alterations, and liver toxicity.

5. Antimicrobials

A variety of antibiotics, antifungals, and antiviral medication can be used to treat skin infections. There is an increasing problem with drug resistance, especially with antibiotics. An abnormal skin barrier becomes more susceptible to infection, one reason eczema flares may also improve with antibiotic therapy to treat superinfection.

6. Antineoplastic Agents

A variety of "antineoplastic" agents are used topically and systemically in dermatology. Topical 5-fluorouracil is commonly used for many actinic keratoses over large surface areas. Imiquimod cream may be used for a variety of skin growths including warts, basal cell cancer, squamous cell cancer, and others. Injectable bleomycin is an aggressive treatment for recalcitrant warts. Oral methotrexate is often used for patients with severe psoriasis.

7. Keratolytics

Dissolving thick or extensive excessive scale can be accomplished by several topical formulations. Urea, lactic acid, and salicylic acids are all products that can be applied topically to remove the scale and leave healthier skin.

B. Other Therapeutic Modalities

1. Ultraviolet Light

Light in the ultraviolet part of the spectrum can improve a variety of inflammatory and itchy skin disorders such as psoriasis and atopic dermatitis. Two forms generally used. UVB is less aggressive but less effective. PUVA (psoralen pill given prior to UVA treatment) is more effective but has more side effects (higher risk of skin cancer, burn, and photosensitivity).

2. Lasers

Concentrated monochromatic focused beams of light can selectively destroy targets in the skin. A variety are available with different wavelengths, energy levels, and pulse duration settings. Lasers allow for selective and targeted treatment of skin structures. Currently, laser hair and vessel removal are popular and widely available treatments.

3. Cryotherapy

The use of super cold agents such as liquid nitrogen to freeze and destroy skin lesions. Often application for as little as 5–10 seconds may be enough to permanently remove the target. Although well tolerated, a common side effect is a hypopigmented macule at the site of treatment.

4. Surgery

Excisional surgery is still the gold standard for removal of many skin lesions, especially skin cancer. Mohs' surgery is a specialized surgical technique using microscopic inspection of 100% of the surgical margin, thereby eliminating the need to take wide margins. Mohs' is often used for facial skin cancers due to the extremely high cure rate and sparing of normal tissue.

5. Electrodesiccation and Curettage

A curette is used to "scoop out" the soft, friable cancerous material (usually basal cell carcinoma), and the base of the lesion is treated with electrocautery. Cure rate in appropriate tumors approaches 95%.

6. Botox and Collagen

Both products are used extensively in cosmetic dermatology to temporarily improve facial appearance. Botox relaxes targeted facial muscles, thereby decreasing dynamic wrinkles (wrinkles caused by repeated squinting or frowning). Collagen acts as a filler, raising a depressed surface, in order to improve wrinkles and scars.

C. Adverse Drug Effects of Medications Used in Dermatology

1. Topical Medications

Common adverse effects include:

Acne medications (most)	Irritant contact dermatitis
Fragrant moisturizers	Allergic contact dermatitis
Keratolytics	Irritant contact dermatitis
Imiquimod	Irritant contact dermatitis
Tar products	Stains hair, skin, and clothes
Topical steroids	Skin atrophy and fragility (see Figure 11–15)
Topical antibiotics	Allergic contact dermatitis
Topical antifungals	Rarely cause adverse effect
Topical diphenhydramine	Allergic contact dermatitis
5-Fluourouracil	Extreme crusting and irritation

2. Systemic Medications

Common adverse effects include:

Acitretin	Xerosis and epistaxis
	Highly teratogenic
	Elevated triglycerides
Antibiotics	Exanthematous drug eruption
	Erythema multiforme and toxic epidermal necrolysis
	Candidiasis
	Hyperpigmentation (minocycline)
	Photosensitivity (doxycycline)

Figure 11–15. Steroid atrophy.

Anticonvulsants	Hypersensitivity syndrome
Antifungals	Drug interactions
	Elevated liver enzymes
Antihistamines	Drowsiness
	Dryness
Antimalarials	Retinopathy
	Elevated liver enzymes
	Hyperpigmentation
Aspirin	Purpura
	Hemorrhage
Azathioprine	Elevated liver enzymes
	Immunosuppression
Corticosteroids	Too many adverse effects for a full list
	Central obesity
	Diabetes and hypertension
	Psychosis anorexia and anxiety
	Osteoporosis and avascular necrosis
	Immunosuppression
Cyclosporine	Hypertension
	Slight risk of lymphoma
	Nephropathy
	Immunosuppression
	Hypertrichosis
Dapsone	Dose-related hemolysis
	Methemoglobinemia
	Neuropathy
Etanercept	Reactivation of tuberculosis
	Immunosuppresion
Interferon	Flulike symptoms
	Spastic diplegia in infants

Isotretinoin	Xerosis and epistaxis
	Highly teratogenic
	Elevated triglycerides
	Depression (controversial)
Methotrexate	Liver cirrhosis
	Blood testing inadequate
	Periodic liver biopsy
	Immunosuppression
	Anemia
Methoxsalen	Nausea
	Photosensitivity
Opiates	Pruritus
Thalidomide	Teratogenicity

D. Special Considerations Relating to Newborn and Elderly

1. Newborn

A premature infant has poorly developed skin, leading to excessive transepidermal water loss and a higher risk of infection. Using a petrolatum-based barrier ointment such as Aquaphor may help both. A full-term infant has normal skin but may be prone to systemic effects of topically applied medications (e.g., steroids) due to a low body surface area ratio. Most Caucasian infants are prone to cutis marmorata (mottled bluish-white skin) due to poor vascular control.

2. Elderly

Due to a combination of sun damage and medication use (steroids), patients who are older often may have paper-thin, fragile skin and must be treated with caution. In addition, many patients are on prophylactic aspirin and are prone to bleed during procedures. Often, elderly patients take many medications, leading to drug eruptions and interactions. Although an issue for many patients, the elderly often live on a fixed income (and without medication insurance) making cost-effective treatment necessary.

IV. PSYCHOSOCIAL, CULTURAL, OCCUPATIONAL, AND ENVIRONMENTAL CONSIDERATIONS

A. Influence of Emotional and Behavioral Factors on Disease Prevention, Progression, and Treatment

1. Compliance

Any medical regimen not used correctly (or at all in some circumstances) is nearly always doomed to failure. In many instances the patient is too busy, lazy, or unable to follow complicated directions. Poor compliance is sometimes attributed to a lack of communication between physician and patient due to language barriers, lack of time, or poor understanding of medical terminology. A patient who understands and agrees with the prescribed regimen of care is less likely to have adverse effects and more likely to improve.

2. Stress

Although hard to scientifically quantify, there is no doubt that stress plays a role in skin disease. There are multiple links between the central nervous system and cutaneous structures and vessels. Instant effects include "goosebumps" from contraction of the arrector pili to flushing when embarrassed. Temporary hair loss caused by telogen effluvium may occur after the stress of divorce, loss of a family member, or even labor and delivery. Harder to assess is the known propensity for skin disorders such as psoriasis, acne, and rosacea to flare in association with stress. Future advances in our understanding of the human nervous system may result in different and totally untapped therapies alone or in common with more routine measure.

3. Sun

Although essential for life on earth, the sun does produce intense ultraviolet radiation that gradually damages the skin. Fair-skinned patients are more susceptible to UV radiation than are dark-skinned patients. UV-induced skin damage is often not apparent acutely, unless there is a high enough exposure to cause a sunburn. In the long term, there is a clear association between skin cancer and sun exposure. In addition, UV radiation is responsible for the majority of visible age-related changes: wrinkles, lentigines, and skin atrophy. Sunblock is available, but should not replace commonsense measures (i.e., sitting in the shade, wearing protective clothes and hats, avoiding midday exposure).

B. Influence of Disease and Treatment on Person, Family, and Society

Although the skin is often overlooked in medicine, its health is vital to a patient's overall quality of life. Severe damage, as found in toxic epidermal necrolysis, may lead to death via loss of fluid, electrolytes, protein, and heat. Many rashes are extremely uncomfortable (pain or itch) and can lead to an inability to sleep or concentrate on other activities. Even when asymptomatic, skin disorders such as psoriasis or acne lead to disfigurement, which in turn may lead to low self-esteem and prejudice. In fact, many studies indicate that the outer appearance of a person has a huge impact on his or her success in a career and search for a mate. One only needs to look at the success of cosmetic dermatology, plastic surgery, and the billions spent on cosmetic products to appreciate the influence of appearance.

C. Occupational and Other Environmental Risk Factors for Disease of the Skin

In today's industrialized world, patients are exposed to thousands, if not millions, of potential allergens and irritants at work, home, and play. An excellent example of a person with an irritant contact dermatitis is a doctor who washes his hands frequently. Even though the doctor is not allergic to the soap, repeatedly scrubbing the hands may cause chronic irritation (redness, itchiness, and scale). An irritant dermatitis may be impossible to differentiate from an allergic reaction, and the two may be present concomitantly.

The most common allergic reactions occur to poison ivy, nickel, and fragrances. Certain professions lead to greater exposure and a higher risk of developing an allergy. For example, construction workers often become allergic to the chromate in cement. Regardless of etiology, the principles of therapy are the same: avoidance of triggers and symptomatic care with anti-inflammatory medications and skin care.

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