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To all our grandchildren—Austin, Bailey, Colby, Dylan, Gabriel, Phin, Rigney, Sofia, and those great-grandchildren yet to come—thank you for keeping us “young at heart.”

—Nannie and Poppie
Writing a new edition of a book always provides an opportunity to improve upon previous editions. This fourth edition of *Rapid Review Pathology* reflects these improvements thanks to many discussions I have had over the past 4 years with my colleagues in the basic sciences and my students, and comments from students in other medical schools. The most substantial changes in this new edition include a new chapter entitled “Diagnostic Testing,” more images, updated management of key diseases, more integration with the basic and clinical sciences, and more tables to summarize information, particularly in microbiology.

To users of the last edition of the book (*Rapid Review Pathology Revised Reprint, Third Edition*), a list of corrections and additions is available on your Student Consult page in the electronic version of *Rapid Review Pathology*, under the Extras tab. For instructions on how to activate your Student Consult version, see the PIN page on the inside front cover of your book and go to [www.studentconsult.com](http://www.studentconsult.com) to activate your PIN.

Edward F. Goljan, MD
The fourth edition of Rapid Review Pathology has been extensively revised to provide students with even more high-yield information and photographs than in previous editions. Many of the photographs are grouped together in collages to provide students with an opportunity to quickly review infectious diseases, dermatology, hematology, endocrinology, and many other key areas. In addition, the emphasis on margin notes and increased content in the summary tables provides the student with a “rapid review” of high-yield material for pathology examinations and USMLE and COMLEX Step 1 and 2 examinations.

As in previous editions, I especially want to thank Ivan Damjanov, MD, PhD, whose many excellent photographs have been utilized throughout the book. I highly recommend his recently published Elsevier book, Pathophysiology, as a companion text to the Rapid Review Pathology text for providing students with an even greater understanding of pathophysiologic processes in disease. I also thank Edward Klatt, MD, who graciously allowed the use of so many of his excellent images from Robbins and Cotran Atlas of Pathology, a resource that I also highly recommend as a source of high-quality images and supplementary learning.

Special thanks to Nicole DiCicco and Christine Abshire from Elsevier, who kept track of all the major changes in the third edition and helped facilitate the early publication of the book. Special thanks also to Karlis Sloka, DO, valued friend and teacher, whose understanding of disease processes helped me throughout the entire writing of the new edition. I want to thank Jim Merritt, Senior Content Strategist of Medical Education, who is the inspiration and primary energy behind the entire Rapid Review Series. Thanks Jim for a job well done! Finally, I would like to thank the myriad of medical students who have sent me e-mails with encouraging words on how the book has helped them not only perform well on boards, but also become better doctors. In particular, I would like to thank Gabriel Tonkin, who sent me referenced and updated material on numerous subjects that I used throughout the writing of the fourth edition.

Edward F. Goljan, MD
“Poppie”
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I. Purpose of Laboratory Tests
A. Screen for disease
1. General criteria for screening
   a. Effective therapy that is safe and inexpensive must be available.
   b. Disease must have a high enough prevalence to justify the expense.
   c. Disease should be detectable before symptoms surface in the patient.
   d. Test must not have many false positives (people misclassified as having disease).
   e. Test must have extremely high sensitivity.
2. Examples of screening tests
   a. Newborn screening for inborn errors of metabolism
      • Examples—phenylketonuria, galactosemia, congenital hypothyroidism, and maple syrup urine disease
   b. Adult screening tests
      (1) Mammography for breast cancer
      (2) Cervical Papanicolaou (Pap) smear for cervical cancer
      (3) Screen for human papillomavirus DNA
      (4) Colonoscopy to detect/remove precancerous polyps
      (5) Fecal occult blood testing to detect colon cancer
      (6) Prostate-specific antigen (PSA) to detect prostate cancer
         • Currently, there is debate over the usefulness of this test.
      (7) Bone densitometry scans to detect osteoporosis in women
      (8) Fasting lipid profiles to evaluate coronary artery risk
         • Includes total cholesterol, high-density–lipoprotein cholesterol, low-density lipoprotein, and total triglyceride
      (9) Fasting blood glucose or 2-hour oral glucose tolerance test to screen for diabetes mellitus
      c. Screening people with symptoms of a disease
         • Example—serum antinuclear antibody test to rule out autoimmune disease
B. Confirm disease; examples:
1. Anti-Smith and double-stranded DNA antibodies to confirm systemic lupus erythematosus
2. Chest x-ray to confirm pneumonia
3. Urine culture to confirm a urinary tract infection
4. Serum troponins I and T to confirm an acute myocardial infarction (AMI)
5. Tissue biopsy to confirm cancer
6. Fluorescent treponemal antibody absorption test to confirm syphilis
C. Monitor disease status; examples:
1. Hemoglobin (Hb) A\textsubscript{1c} to evaluate long-term glycemic control in diabetics
2. International normalized ratio (INR) to monitor warfarin therapy (anticoagulation)
3. Therapeutic drug monitoring to ensure drug levels are in the optimal range
4. Pulse oximeter to monitor oxygen saturation during anesthesia, asthmatic attacks
Test results in people with disease: TP and FN

- Test
  - True positive (TP)
  - False negative (FN)

- Test
  - False positive (FP)
  - True negative (TN)

1-1: People with disease either have true positive (TP) or false negative (FN) test results. People without disease either have true negative (TN) or false positive (FP) test results.

II. Operating Characteristics of Laboratory Tests

A. Terms for test results for people with a specific disease (Fig. 1-1)
   1. True positive (TP)
      - Definition—number of people with a specific disease who have a positive test result
   2. False negative (FN)
      - Definition—number of people with a specific disease who have a negative test result

B. Terms for test results for people without disease (see Fig. 1-1)
   1. True negative (TN)
      - Definition—number of people without disease who have a negative test result
   2. False positive (FP)
      - Definition—number of people without disease who have a positive test result

C. Sensitivity of a test
   1. Sensitivity of a test is obtained by performing the test on people that are known to have the specific disease for which the test is intended (e.g., systemic lupus erythematosus [SLE]).
   2. Definition—likelihood that a person with disease will have a positive test result
   3. Formula for calculating sensitivity is TP ÷ (TP + FN).
      - The FN rate determines the test’s sensitivity.
   4. Usefulness of a test with 100% sensitivity (no FNs)
      a. Normal test result excludes disease (must be a TN).
      b. Positive test result includes all people with disease.
         (1) Positive test result does not confirm disease.
         (2) Positive test result could be a TP or a FP.
      c. Tests with 100% sensitivity are primarily used to screen for disease.

D. Specificity of a test
   1. Specificity of a test is obtained by performing the test on people who do not have the specific disease for which the test is intended.
      - Control group should include people of various ages and both sexes, and those who have diseases that are closely related to the disease for which the test is intended.
   2. Definition—likelihood that a person without disease will have a negative test result
   3. Formula for calculating specificity is TN ÷ (TN + FP).
      - FP rate determines the test’s specificity.
   4. Usefulness of a test with 100% specificity (no FPs)
      a. Positive test result confirms disease (must be a TP).
      b. Negative test result does not exclude disease, because a test result could be a TN or a FN.

E. Comments on using tests with high sensitivity and specificity
   1. When a test with 100% sensitivity (or close to it) returns negative (normal) on a patient on one or more occasion, the disease can be excluded from the differential list.
      - For example, if the serum antinuclear antibody (ANA) test returns negative on more than one occasion, the diagnosis of SLE can be excluded.
   2. When a test with 100% sensitivity returns positive on a patient, a test with 100% specificity (or close to it) should be used to decide if the test result was a TP or a FP.
      a. For example if the serum ANA returns positive in a patient who is suspected of having SLE, the serum anti-Smith (Sm) and anti–double-stranded DNA test should be used because they both have extremely high specificity for diagnosing SLE.
      b. If either or both tests return positive, the patient has SLE.
      c. If both tests consistently return negative, the patient most likely does not have SLE but some other closely related disease.

III. Predictive Value of Positive and Negative Test Results

A. Predictive value of a negative test result (PV–)
   1. Definition—likelihood that a negative test result is a TN rather than a FN
   2. Formula for calculating PV– is TN ÷ (TN + FN).
      - PV– best reflects the true FN rate of a test.
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<td>High prevalence of disease</td>
<td>Decreases (FN &gt; TN)</td>
<td>Increases (TP &gt; FP)</td>
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1-2: Note that in a low prevalence situation (e.g., ambulatory population), the PV− increases, while the PV+ decreases. The reverse occurs in a high prevalence situation (e.g., cardiac clinic) in that the PV− decreases and the PV+ increases.

3. Tests with 100% sensitivity (no FNs) always have a PV− of 100%.
- Disease is excluded from the differential list.

B. Predictive value of a positive test result (PV+)
1. Definition—likelihood that a positive test result is a TP rather than a FP
- PV+ best reflects the true FP rate of a test.
2. Tests with 100% specificity (no FPs) always have a PV+ of 100%.
- Disease is confirmed.

C. Effect of prevalence on PV− and PV+
1. Definition—total number of people with disease in the population under study
- Population includes people with disease and people without disease.
2. To calculate prevalence, people with disease are in the numerator (TP + FN) and people with disease (TP + FN) and without disease (TN + FP) are in the denominator.
- (TP + FN) ÷ (TP + FN + TN + FP)
3. Low prevalence of disease (e.g., ambulatory population) (Figs. 1-2 and 1-3)
   a. PV− increases because more TNs are present than FNs.
   b. PV+ decreases because more FPs are present than TPs.
4. High prevalence of disease (e.g., cardiac clinic) (see Figs. 1-2 and 1-3)
   a. PV− decreases because more FNs are present than TNs.
   b. PV+ increases because more TPs are present than FPs.

IV. Creating Highly Sensitive and Specific Tests
A. Ideal test (Fig. 1-4A)
1. Ideal test has 100% sensitivity (PV− 100%) and 100% specificity (PV+ 100%).
2. Note in the schematic that there are no FNs or FPs, because there is no overlap between the normal and disease population.
3. Ideal test is nonexistent; however, there are some tests that have very high sensitivity and specificity that come close to being the ideal test (e.g., serum levels of troponins I and T in diagnosing an AMI).
4. Most normal ranges (reference intervals) do not distinguish the normal from the disease population (see Fig. 1-4B and C).
   - Note that there is an overlap between the normal and the disease population in parts B and C of Figure 1-4.
B. Establishing a test with 100% sensitivity and PV− (see Fig. 1-4B)
1. To establish a test with 100% sensitivity and PV−, set the cutoff point for the reference interval at the beginning of the disease curve (A).
   a. Note that this creates a test with 100% sensitivity and 100% PV−, because there are no FNs within the newly established reference interval (0 to A).
   b. Test can now be used to screen for disease.
2. Note that by increasing sensitivity there is always a corresponding decrease in the specificity and PV+ due to a greater number of FPs.
C. Establishing a test with 100% specificity and PV+ (see Fig. 1-4C)
1. To establish a test with 100% specificity/PV+, set the upper cutoff point for the reference interval at the end of the normal curve (B).
   a. Note that this creates a test with 100% specificity and 100% PV+, because there are no FPs outside the reference interval (0 to B).
   b. Test can now be used to confirm disease.
2. Note that by increasing specificity there is always a corresponding decrease in sensitivity and PV−, due to a greater number of FNs.

V. Variables Affecting Laboratory Test Results
A. Premature newborns
1. Variable hemoglobin (Hb) concentration depending on the gestational age
Anemia in prematurity:
loss of iron from mother; blood loss from venipuncture

2. Anemia in prematurity is due to:
   a. Iron deficiency, related to loss of the daily supply of iron from the mother’s iron stores
   b. Blood loss from excessive venipunctures in the premature newborn

B. Newborns
1. Newborns have higher normal ranges for Hb, Hct, and RBC counts than do infants and children.
2. HbF (2α/2γ globin chains) shifts the OBC to the left causing the release of EPO.
   • EPO causes an increase in Hb, Hct, and the RBC count.
3. Over the ensuing 8 to 12 weeks after birth, the Hb drops from 16.8 g/dL (range 14–20 g/dL) to 11 g/dL (this is called physiologic anemia).
Fetal RBCs containing HbF are destroyed by splenic macrophages. The unconjugated bilirubin derived from the initial destruction of fetal RBCs is responsible for physiologic jaundice of the newborn, which occurs ~3 days after birth.

4. HbF–containing cells are replaced by RBCs containing HbA (>97%), HbA₂ (2.0%), and HbF (1%).

5. Immunoglobulin (Ig) synthesis
   a. Synthesis of IgM begins shortly after birth.
   b. Newborns lack IgM isohemagglutinins (natural antibodies against blood groups) in their plasma.
      • For example, blood group A newborns lack anti-B IgM isohemagglutinin in their plasma.

Clinical correlation: Newborns with an increase in cord blood IgM may have an underlying congenital infection (e.g., cytomegalovirus, rubella). Their blood should be screened for antibodies against the common congenital infections.

6. IgG antibodies in newborns are of maternal origin.
   a. Newborns begin synthesizing IgG 2-3 months after birth.
   b. Adult levels of IgG are achieved by age 6 to 10 years.

Clinical correlation: A mother with a positive test for human immunodeficiency virus (e.g., IgG antibodies against the glycoprotein gp120) transplacentally transfers IgG antibodies to the fetus. This does not mean that the child is infected by the virus.
C. Children
1. When compared to an adult, children have higher serum alkaline phosphatase (ALP) levels.
   a. This is due to increased bone growth in children and release of ALP from osteoblasts.
   b. ALP removes the phosphate from pyrophosphate, which normally inhibits bone mineralization.
2. When compared to an adult, children have higher serum phosphorus levels.
   • For normal mineralization of bone to occur, phosphorus is required to drive calcium into bone; hence, the higher phosphorus levels in children.
3. When compared to an adult, children have a lower Hb concentration (11.5 g/dL; anemia <11.5 g/dL).
   a. This is most likely related to the increased serum phosphorus levels in children.
      • A proportionately greater amount of 2,3-bisphosphoglycerate (2,3-BPG) is synthesized because of the availability of phosphorus.
   b. Increasing 2,3-BPG synthesis causes a greater release of O2 to tissue (right shifts the O2 binding curve); hence, an 11.5 g/dL Hb concentration in a child delivers as much O2 to tissue as a 13.5 g/dL Hb concentration does in an adult.

D. Adults
1. When compared to men, women have slightly lower serum iron, ferritin, and Hb levels (12.5 g/dL; anemia <12.5 g/dL), which is attributed to:
   a. Monthly menstrual flow
   b. Lower testosterone levels than men
      • Testosterone stimulates erythropoiesis, which also contributes to the higher Hb level in men (13.5 g/dL; anemia <13.5 g/dL) than in women.
2. Advanced age
   a. Decrease in the glomerular filtration rate (GFR) and creatinine clearance (CCr)
      • Potentially harmful to the proximal kidney tubules if nephrotoxic drugs (e.g., aminoglycosides) are not dose-adjusted to the age and GFR of the patient.
   b. Increase in serum ALP
      (1) Increase in serum ALP is of bone origin and relates to degeneration of articular cartilage in the weight-bearing joints (osteoarthritis), a condition that invariably occurs in the elderly.
      (2) Reactive bone formation (called osteophytes) occurs at the margins of the joints, leading to the slight increase in serum ALP.
   c. When compared to young adult males, there is a slight decrease in the Hb concentration in elderly males.
      (1) Hb drops into the range of a normal adult woman (12.5 g/dL; anemia <12.5 g/dL) and should not be misinterpreted as anemia.
      (2) Decrease in Hb parallels the normal decrease in testosterone associated with aging.
   d. Often a loss of blood group isohemagglutinins (e.g., anti-B IgM in a group A individual) occurs because of a decrease in antibody synthesis.

Clinical correlation: Loss of isohemagglutinins explains why some elderly individuals transfused with the wrong type of blood do not develop a hemolytic transfusion reaction. For example, a blood group A individual inadvertently transfused with group B blood may not hemolysze the group B RBCs, because they do not have anti-B IgM antibodies. This is not to say that elderly people can safely be given any blood group for transfusion; they should receive blood group and Rh type specific blood.

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E. Pregnancy
1. Normal decrease in Hb concentration
   a. Due to an increase in plasma volume (PV) and RBC production (RBC mass) with a much greater increase in PV than in RBC mass
      • Dilutional effect decreases the Hb concentration (normal 11 g/dL; anemia <11 g/dL).
   b. Other effects of an increase in PV include:
      (1) Increased GFR and CCr
      (2) Increased renal clearance of blood urea nitrogen, creatinine, and uric acid with corresponding lower levels in serum
2. Increase in serum ALP (placental origin)
3. **Increase** in serum human placental lactogen (HPL)
   a. Normally synthesized by syncytiotrophoblasts lining the chorionic villi in the placenta
   b. Inhibits the sensitivity of peripheral tissue to insulin
      • Produces the normal **glucose intolerance** in pregnancy
   c. **Increases** β-oxidation of fatty acids
      • Excess acetyl CoA is produced, leading to increased liver synthesis of ketone bodies and the normal **ketonemia** in pregnancy.

4. Mild respiratory alkalosis
   a. Due to stimulation of the respiratory center by estrogen and progesterone
   b. Increased pulmonary clearance of CO₂ is responsible for the respiratory alkalosis and is not accompanied by an increase in respiratory rate.
   c. Decreased PCO₂ causes a corresponding increase in PO₂ in maternal blood, which increases the amount of oxygen that is available to the developing fetus.
      • Arterial PO₂ is usually >100 mm Hg in pregnancy.

5. **Increase** in the total serum thyroxine (T₄) and cortisol (refer to Chapter 23)
   a. Normal measurement of total serum T₄ and cortisol includes bound and free fractions.
   b. Estrogen increases liver synthesis of the binding proteins for T₄ (thyroid binding globulin) and cortisol (transcortin); however, the free hormone levels (metabolically active) are unaffected.
      • Because the free hormone levels are normal, the serum thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) are also normal.

F. **Hemolyzed blood specimen related to venipuncture**
   1. Potassium is the major intracellular cation; therefore a hemolyzed blood sample **falsey increases** serum potassium (FP).
   2. RBCs primarily use anaerobic glycolysis as a source of ATP; therefore lactate dehydrogenase (LDH), which normally converts pyruvate to lactate, is also **falsey increased** (FP).
CHAPTER 2  Cell Injury

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I. Tissue Hypoxia
A. Hypoxia

1. Definition—inadequate oxygenation of tissue
2. Factors contributing to the total amount of O₂ carried in blood
   a. Normally, O₂ diffuses down a gradient from the atmosphere to the alveoli, to plasma, and into the red blood cells (RBCs), where it attaches to heme groups (Table 2-1).
   (1) In the alveoli, O₂ increases the partial pressure of O₂ (Pdiff).
   (2) In the plasma of the pulmonary capillaries, O₂ increases the partial pressure of O₂ (Pao₂).
   (3) In the RBC, O₂ attaches to heme groups and increases the O₂ saturation (SaO₂).

b. Pao₂ and SaO₂ are reported in arterial blood gas analyses.
c. O₂ content is a measure of the total amount of O₂ carried in blood and includes the hemoglobin (Hb) concentration as well as the PaO₂ and SaO₂.
   • Decrease in O₂ content due to a decrease in Hb, PaO₂, or SaO₂ causes an increase in erythropoietin (EPO; refer to Chapter 12).

3. In hypoxia, there is decreased synthesis of adenosine triphosphate (ATP).
   a. ATP synthesis occurs in the inner mitochondrial membrane by the process of oxidative phosphorylation (see later).
   b. O₂ is an electron acceptor located at the end of the electron transport chain (ETC) in complex IV of the oxidative pathway.
   c. Lack of O₂ and/or a defect in oxidative phosphorylation culminates in a decrease in ATP synthesis.

Pulse oximetry (Fig. 2-1) is a noninvasive test for measuring SaO₂. It utilizes a probe that is usually clipped over a patient’s finger. A pulse oximeter emits light at specified wavelengths that identify oxyhemoglobin and deoxyhemoglobin, respectively. The wavelengths emitted by a pulse oximeter cannot identify dyshemoglobins such as methemoglobin (metHb) and carboxyhemoglobin (i.e., carbon monoxide bound to Hb [COHb]), which normally decrease the SaO₂ (see later). In the presence of these dyshemoglobins, the oximeter calculates a falsely high SaO₂. Unlike the standard oximeter, a co-oximeter emits multiple wavelengths and identifies metHb and COHb as well as oxyhemoglobin and deoxyhemoglobin. Hence, in the presence of these dyshemoglobins, the SaO₂ will be decreased. Pulse oximeters are very useful in following patients with respiratory failure, severe bronchial asthma, obstructive sleep apnea, and those under general anesthesia.

4. Clinical findings in hypoxia
   a. Cyanosis (bluish discoloration of skin and mucous membranes) (Fig. 2-2)
   b. Confusion
   c. Cognitive impairment
   d. Lethargy
### Table 2-1 Terminology Associated with Oxygen Transport and Hypoxia

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>CONTRIBUTING FACTORS</th>
<th>SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂ content</td>
<td>Total amount of O₂ carried in blood</td>
<td></td>
<td>Hb concentration in RBCs (most important factor)</td>
</tr>
<tr>
<td></td>
<td>O₂ content = (Hb g/dL × 1.34) × SaO₂ + PaO₂ × 0.003</td>
<td>Hb concentration</td>
<td>Hb is the most important carrier of O₂</td>
</tr>
<tr>
<td></td>
<td>PaO₂ content causes ↓EPO</td>
<td></td>
<td>Hb concentration determines the total amount of O₂ delivered to tissue</td>
</tr>
<tr>
<td></td>
<td>↓O₂ content causes ↑EPO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb concentration in RBCs (most important factor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PaO₂</td>
<td>Pressure keeping O₂ dissolved in the plasma of arterial blood (PaO₂ x 0.003)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SaO₂</td>
<td>Percentage of O₂ in inspired air</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average percentage of O₂ bound to Hb in the RBCs</td>
<td>Valence of heme iron in each of the four heme groups in RBCs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Same factors listed above for PaO₂</td>
<td>Fe²⁺ (reduced, ferrous) binds to O₂</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MetHb or COHb (DysHb)</td>
<td>Fe³⁺ (oxidized, ferric) does not bind to O₂</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OxyHb</td>
<td>OxyHb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DeoxyHb</td>
<td>DeoxyHb</td>
<td></td>
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<tr>
<td></td>
<td>MetHb or COHb (DysHb)</td>
<td>OxyHb</td>
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<td></td>
<td>DeoxyHb</td>
<td>DeoxyHb</td>
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<tr>
<td></td>
<td>OxyHb</td>
<td>DeoxyHb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal hand with cyanosis</td>
<td>Dyshemoglobin present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DeoxyHb</td>
<td>DeoxyHb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OxyHb</td>
<td>OxyHb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OxyHb = 94%</td>
<td>OxyHb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OxyHb + DeoxyHb = 94%</td>
<td>OxyHb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OxyHb + DeoxyHb + MetHb or COHb (DysHb)</td>
<td>OxyHb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OxyHb = 50%</td>
<td>OxyHb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OxyHb + DeoxyHb + MetHb or COHb (DysHb)</td>
<td>OxyHb</td>
<td></td>
</tr>
</tbody>
</table>

EPO, Erythropoietin; Fe²⁺, ferrous iron; Fe³⁺, ferric iron; Hb, hemoglobin; O₂, oxygen; PaO₂, partial pressure of alveolar O₂; PaO₂, partial pressure of arterial oxygen; SaO₂, arterial oxygen saturation.

**2-1:** Pulse oximetry is a noninvasive alternative for measuring SaO₂. It utilizes a probe that is usually clipped over a patient’s finger. The oximeter emits red and infrared light at specified wavelengths that identify oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb), respectively. The oximeter calculates the SaO₂ using the following equation: oxyHb/oxyHb + deoxyHb (A). The wavelengths emitted by a pulse oximeter cannot identify dyshemoglobins such as metHb and carboxyhemoglobin (i.e., carbon monoxide bound to Hb, [COHb]), which normally decrease the SaO₂. In the presence of these dyshemoglobins, the oximeter calculates a normal SaO₂, because metHb or COHb are not included in the calculation of SaO₂ in the equation in 1 (B). However, a co-oximeter, which emits multiple wavelengths, calculates the decrease in SaO₂, because it identifies metHb and COHb and includes them in the calculation of SaO₂: oxyHb/oxyHb + deoxyHb + MetHb or COHb (equation 2 in B). *(From Goljan E, Sloka K: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 78, Fig. 3-6.)*

**2-2:** Hand of a child with tetralogy of Fallot, a congenital heart disease associated with cyanosis. Note the blue-discoloration beneath the nails and the duskiness of the skin when compared to the hand of a normal adult. *(From Taylor S, Raffles A: Diagnosis in Color Pediatrics. London, Mosby-Wolfe, 1997, p 91, Fig. 3.6)*
B. Causes of tissue hypoxia

1. Ischemia
   a. Definition—decreased arterial blood flow to tissue or venous outflow of blood from tissue.
   b. Examples—coronary artery atherosclerosis, decreased cardiac output, and thrombosis of the superior mesenteric vein
   c. Consequences of ischemia
      (1) Atrophy (reduction in cell/tissue mass)
      (2) Infarction of tissue (localized area of tissue necrosis)
      (3) Organ dysfunction (inability to perform normal metabolic functions)

2. Hypoxemia
   a. Definition—decrease in PaO₂ measured in an arterial blood gas
   b. Normal PaO₂ depends on percent O₂ in inspired area, ventilation, perfusion, and diffusion of O₂ from the alveoli into the pulmonary capillaries (Fig. 2-3A).
   c. Causes of hypoxemia
      (1) Decreased inspired O₂ (PİO₂)
         - Examples—breathing at high altitude and breathing reduced %O₂ mist
      (2) Respiratory acidosis
         a. Respiratory acidosis is defined as retention of CO₂ in the lungs (refer to Chapter 5).
         b. Carbon dioxide (CO₂) retention in the alveoli always produces a corresponding decrease in Alveolar Po₂ (PAO₂) which, in turn, decreases both Pao₂ and Sao₂.

The sum of the partial pressures of O₂, CO₂, and nitrogen in alveoli of the lungs must equal 760 mm Hg at sea level. Assuming that the partial pressure of nitrogen is a constant, an increase in PACO₂ must be accompanied by a decrease in PAO₂ in order for the sum of the partial pressures to equal 760 mm Hg. The reverse is also true. If the PACO₂ is decreased (respiratory alkalosis), then PAO₂ must increase, which should increase Pao₂ and Sao₂ if ventilation, perfusion, and diffusion are normal in the lungs.

- ↑Alveolar PCO₂ = 
- ↓Alveolar PO₂ = ↓Pao₂ = ↓Sao₂

- Ventilation defect: lung perfused but not ventilated
- RDS: diffuse ventilation defect

- (c) A partial list of causes of respiratory acidosis includes depression of the medullary respiratory center (e.g., barbiturates), paralysis of the diaphragm (e.g., amyotrophic lateral sclerosis), and chronic bronchitis.

(3) Ventilation defect (see Fig. 2-3B)
   a. Definition—alveoli are perfused; however, there is impaired O₂ delivery to alveoli.
   b. Respiratory distress syndrome (RDS; refer to Chapter 17) is an example of a diffuse ventilation defect, where a lack of surfactant causes collapse of the distal airways (called atelectasis) in both lungs (note the arrows in Fig. 2-3).
• Diffuse ventilation defects produce intrapulmonary shunting of blood characterized by pulmonary capillary blood having the same Po2 and PCO2 as venous blood returning from tissue (i.e., a large fraction of pulmonary blood flow has not been arterialized).

(c) Inspired %O2 from 24% to 28% or greater does not significantly increase the Pao2 in diffuse ventilation defect involving both lungs (e.g., RDS).

• Smaller ventilation defects are compensated for in normally ventilated lung.

(4) Perfusion defect (see Fig. 2-3C)

(a) Definition—alveoli are ventilated but there is no perfusion of the alveoli
• Examples—pulmonary embolus (refer to Chapters 5 and 17) and fat embolism (refer to Chapter 5)

(b) Perfusion defects produce an increase in pathologic dead space.
• In pathologic dead space, the exchange of O2 and CO2 does not occur (normal dead space includes the mouth to the beginning of the respiratory bronchioles).

(c) Inspired %O2 from 24% to 28% or greater increases the Pao2 in perfusion defects, because they tend to be less extensive than ventilation defects.

• Other parts of ventilated and perfused lung have normal gas exchange; hence compensating for most perfusion defects (e.g., pulmonary embolus).

(5) Diffusion defect

(a) Definition—decreased diffusion of O2 through the alveolar-capillary interface into the pulmonary capillaries

(b) Examples—interstitial fibrosis, pulmonary edema

(6) Cyanotic congenital heart disease (e.g., tetralogy of Fallot; refer to Chapter 11)

• Shunting of venous blood into arterial blood causes a drop in the Pao2.

3. Hemoglobin (Hb)-related abnormalities

a. Anemia (refer to Chapter 12)

(1) Definition—decrease in Hb concentration

(2) Causes of anemia

(a) Decreased production of Hb (e.g., iron deficiency)

(b) Increased destruction of RBCs (e.g., hereditary spherocytosis)

(c) Decreased production of RBCs (e.g., aplastic anemia)

(d) Increased sequestration of RBCs (e.g., splenomegaly)

(3) Pao2 and Sao2 are normal.

• Total amount of O2 delivered to tissue is decreased (↓O2 content), which has no effect on normal O2 exchange in the lungs.

b. Methemoglobinemia (metHb)

(1) Definition—Hb with oxidized heme groups (Fe3+)

Methemoglobin is converted to the ferrous state (Fe2+) by the reduced nicotinamide adenine dinucleotide (NADH) reductase system located off of the glycolytic pathway in RBCs. Electrons from NADH are transferred to cytochrome b5 and then to metHb by cytochrome b5 reductase to produce ferrous Hb. Newborns are particularly at risk for developing methemoglobinemia after oxidant stresses (see later) owing to decreased levels of cytochrome b5 reductase until at least 4 months of age.

(2) Causes

(a) Oxidant stresses

• Examples—nitrite- and/or sulfur-containing drugs, nitrates (fertilizing agents), and sepsis

(b) Congenital deficiency of cytochrome b5 reductase

(3) Pathogenesis of hypoxia

(a) Fe3+ cannot bind O2; hence Pao2 is normal, but Sao2 is decreased.

• ↓Sao2 decreases O2 content, causing an increase in EPO.

(b) Ferric heme groups impair unloading of O2 by oxygenated ferrous heme in the RBCs (impairs cooperativity).

• MetHb shifts the O2-binding curve (OBC; see later) to the left.

MethHb reduction: NADH electrons → cytochrome b5 → cytochrome b5 reductase → heme Fe2+

MethHb: oxidant stresses (drugs, sepsis)

MethHb: heme Fe3+; normal Pao2, ↓Sao2

MethHb: shifts OBC to left; lactic acidosis

Ventilation defect: produces intrapulmonary shunting

Perfusion defect: lung ventilated but not perfused

Perfusion defect: ↑dead space

Diffusion defect: ↓O2 diffusion thru alveolar-capillary interface

Diffusion defect: interstitial fibrosis, pulmonary edema

Anemia: ↓Hb concentration; ↓O2 content

Anemia: ↓production Hb/RBCs; ↑destruction/sequestration RBCs

Anemia: normal Pao2/ Sao2; ↓O2 content

MetHb: heme Fe3+; cannot attach to O2
2-4: Arterial whole blood (left) versus arterial whole blood with increased concentration of methemoglobin (right). The arterial blood is bright red because of increased oxyhemoglobin level, whereas the arterial blood with increased methemoglobin has the characteristic chocolate-brown color due to increased deoxyhemoglobin (correlates with decreased arterial O\textsubscript{2} saturation). (From Kliegman R: Nelson Textbook of Pediatrics, 19th ed, Philadelphia, Elsevier Saunders, 2011, p 1673, Fig. 456.6; protocol based on personal communication with Dr. Ali Mansouri, December, 2002.)

(4) Clinical findings
   (a) Cyanosis at low levels (levels <20%)
   (b) Headache, anxiety, dyspnea, tachycardia (levels >20%)
   (c) Confusion, lethargy, lactic acidosis (levels >40%)
      - Lack of O\textsubscript{2} causes a shift to anaerobic glycolysis leading to lactic acidosis (see later)

Patients with methemoglobinemia have chocolate-colored blood (increased concentration of deoxyhemoglobin; Fig. 2-4) and cyanosis. Clinically evident cyanosis occurs at metHb levels >1.5 g/dL. Skin color does not return to normal after administration of O\textsubscript{2}. Treatment is intravenous methylene blue, which accelerates the enzymatic reduction of MetHb by NADPH-methemoglobin reductase located in the pentose phosphate shunt. This shunt is not normally operational in reducing metHb.

c. Carbon monoxide (CO) poisoning (also refer to Chapter 7)
   (1) Leading cause of death due to poisoning
   (2) Produced by incomplete combustion of carbon-containing compounds.
   (3) Causes include:
      - Automobile exhaust, smoke inhalation, wood stoves, indoor gasoline powered generators, and clogged vents for home heating units (e.g., methane gas)
(4) Pathogenesis of hypoxia
   (a) CO has a high affinity for heme groups and competes with O\textsubscript{2} for binding sites on Hb.
      - This decreases Sao\textsubscript{2} (if blood is measured with a co-oximeter) without affecting the Pao\textsubscript{2}.
   (b) CO inhibits cytochrome oxidase in the ETC (see later)
      - Cytochrome oxidase normally converts O\textsubscript{2} into water.
      - Inhibition of the enzyme prevents O\textsubscript{2} consumption, shuts down the ETC, and disrupts the diffusion gradient that is required for O\textsubscript{2} to diffuse from the blood into the tissue.
   (c) Similar to metHb, CO attached to heme groups impairs unloading of O\textsubscript{2} from oxygenated ferrous heme in RBCs into tissue (impairs cooperativity).
      - CO shifts the O\textsubscript{2}-binding curve (OBC; see later) to the left.
   (d) ↓Sao\textsubscript{2} decreases O\textsubscript{2} content causing an increase in EPO.
(5) Clinical findings
   (a) Cherry-red discoloration of the skin and blood.
   (b) Headache (first symptom at levels of 10%–20%)
   (c) Dyspnea, dizziness (levels of 20%–30%)
2-5: Oxygen-binding curve (OBC). Note that at the PO₂ in the tissue (ranges from 20–50 mm Hg) a left-shifted OBC still has an O₂ saturation (Sao₂) of 80% (only released 20% of its O₂ to tissue), a normal-shifted OBC has an Sao₂ of 50% (only released 50% of its O₂ to tissue), and a right-shifted curve has an Sao₂ of 20% (released 80% of its O₂ to tissue). 2,3-Bisphosphoglycerate (2,3-BPG) improves O₂ delivery to tissue by stabilizing the hemoglobin (Hb) in the taut form, which decreases O₂ affinity, hence facilitating the movement of O₂ from Hb into tissue by diffusion.

(d) Seizures, coma (levels of 50%–60%)
(e) Other findings—ataumatic rhabdomyolysis (myoglobin binds CO and prevents normal muscle function), delayed neurologic deficits (e.g., memory deficits, apathy)

(6) Laboratory findings
(a) ↑CO levels in blood if measured with a co-oximeter.
(b) Lactic acidosis (shift to anaerobic glycolysis; see later)
(c) ↓Sao₂ (if measured with a co-oximeter) and a normal PaO₂.

(7) Treatment
(a) Administer 100% O₂ therapy with nonrebreather mask or endotracheal tube.
(b) Hyperbaric oxygen therapy
d. Factors causing a left-shifted OBC (Fig. 2-5)
(1) Decreased 2,3-bisphosphoglycerate (2,3-BPG)
(a) 2,3-BPG is an intermediate of glycolysis in RBCs and is formed by conversion of 1,3-BPG to 2,3-BPG.
(b) Stabilizes the taut form of Hb, which ↓O₂ affinity and allows O₂ to move into tissue.
(2) Other factors include CO, alkalosis, methHb, fetal Hb, and hypothermia
(3) All factors that shift the OBC to the left increase affinity of Hb for O₂ with less release of O₂ to tissue.
• Example—at the capillary PO₂ concentration in tissue, a right-shifted OBC (↑2,3-BPG, acidosis, fever) has released most of its O₂ to tissue (80% to tissue), whereas a left-shifted OBC still has most of its O₂ attached to heme groups (only 20% to tissue; see Fig. 2-5).

At high altitude, the atmospheric pressure is decreased; however, the percentage of O₂ in the atmosphere remains the same (i.e., 21%). This produces hypoxemia, which stimulates peripheral chemoreceptors (e.g., carotid and aortic bodies) causing an increase in the respiratory rate (hyperventilation) leading to respiratory alkalosis. Respiratory alkalosis, in turn, increases intracellular pH, which activates phosphofructokinase, the rate-limiting enzyme in glycolysis. An increase in glycolysis leads to increased production of 1,3-BPG, which is converted to 2,3-BPG by a mutase reaction; this shifts the OBC to the right and increases the release of O₂ from RBCs into tissue.

C. Mitochondrial causes of ATP depletion
1. Enzyme inhibition of oxidative phosphorylation (Fig. 2-6)
**2-6:** Oxidative phosphorylation. The inner membrane of the mitochondria is the primary site for ATP synthesis. The BCL-2 gene proteins maintain mitochondrial membrane integrity, which prevents cytochrome c from leaving the mitochondria. See text for additional discussion. CN, Cyanide, CO, carbon monoxide. (Modified from Pelley J, Goljan E: Rapid Review Biochemistry, 3rd ed., Philadelphia, Mosby Elsevier, 2011, p 59, Fig. 5-8.)

The **oxidative part of the pathway** in the inner mitochondrial membrane transfers donated electrons from NADH and reduced flavin adenine dinucleotide (FADH₂) derived from the energy cycles to complex I and II, respectively, in the ETC. The electrons move through electron transport complexes to O₂, which is a strong electron acceptor located at the end of the chain on complex IV where it is converted to water. The transfer of electrons is coupled with the transport of protons (H⁺) across the inner mitochondrial membrane into the intermembranous space, which establishes both a proton and a pH gradient. The BCL-2 gene prevents cytochrome c in the ETC from leaving the mitochondria by maintaining the integrity of the mitochondrial membrane. Should cytochrome c enter the cytosol, caspases are activated, resulting in apoptosis of the cell (programmed cell death; see later). The **phosphorylation part of the pathway** involves the synthesis of ATP. A certain amount of heat is required to synthesize ATP. ATP synthesis occurs when the protons on the cytosolic side of the inner membrane enter small channels (proton pores) within the ATP synthase molecule (complex V) and reenter the mitochondrial matrix, where ATP is synthesized. The inner mitochondrial membrane is normally impermeable to protons except through the channel in the ATP synthase molecule. This relationship is critical to the maintenance of the proton gradient. If enzymatic reactions in electron transport are inhibited (e.g., cytochrome oxidase), the formation of protons and the proton gradient are disrupted as well, leading to a decrease in ATP synthesis.

- Enzyme inhibition at any level of oxidative phosphorylation decreases ATP synthesis and completely shuts down the ETC.
- CO and cyanide (CN) specifically inhibit cytochrome oxidase in complex IV of the ETC.
- CN poisoning (also refer to Chapter 7)
  1. Most frequently caused by combustion of synthetic products in house fires
     - Other causes include prolonged exposure to nitroprusside, ingestion of amygdalin in almonds, and suicidal consumption of CN compounds.
  2. Pathogenesis of hypoxia
     a. Cytochrome oxidase in complex IV of the ETC is inhibited, which prevents the consumption of O₂.
     b. Shutdown of the ETC prevents the diffusion of O₂ from blood to tissue, because there is a loss of the diffusion gradient (this also occurs in CO poisoning; see earlier).
TABLE 2-2 Comparison of Anemia, Carbon Monoxide Poisoning, Methemoglobinemia, and Cyanide Poisoning

<table>
<thead>
<tr>
<th></th>
<th>PaO₂</th>
<th>SaO₂</th>
<th>O₂-BINDING CURVE (OBC)</th>
<th>CYTOCHROME OXIDASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Carbon monoxide poisoning</td>
<td>Normal</td>
<td>Decreased</td>
<td>Left-shifted</td>
<td>Inhibited</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>Normal</td>
<td>Decreased</td>
<td>Left-shifted</td>
<td>Normal</td>
</tr>
<tr>
<td>Cyanide poisoning</td>
<td>Normal</td>
<td>Normal (O₂ not removed from blood)</td>
<td>Normal</td>
<td>Inhibited</td>
</tr>
</tbody>
</table>

- Oxygen extraction by the tissue decreases in parallel with the lower oxygen consumption in the ETC, with a resulting higher than normal venous oxygen content and Pvo₂ (partial pressure of O₂ in venous blood).
- In CN poisoning, the O₂ content of venous blood is essentially the same as the O₂ content of arterial blood.
  (c) CN poisoning most adversely affects the heart and central nervous system.
  (3) Clinical findings include:
    - Bitter almond smell of the breath, seizures, coma, arrhythmias, and cardiovascular collapse
  (4) Laboratory findings
    (a) Increased anion gap metabolic acidosis (refer the Chapter 5), due to increased serum lactate levels from anaerobic glycolysis
    - Inhibition of cytochrome oxidase in the ETC, causes a shift to anaerobic glycolysis for production of ATP
    (b) Increased venous O₂ content when compared to the arterial O₂ content (no extraction of O₂ in tissue)
  (5) Treatment is based on the high affinity of CN for ferric ions in metHb and for cobalt in hydroxycobalamin.
    (a) Former treatment involves infusion of sodium nitrite to produce cyanmetHb, followed by infusion of thiosulfate to produce thiocyanate, which is excreted.
    (b) Latter treatment involves infusion of hydroxycobalamin, which produces cyanocobalamin, which eventually produces vitamin B₁₂.
  (6) Table 2-2 compares anemia, CO poisoning, methemoglobinemia, and CN poisoning.

2. Uncoupling of oxidative phosphorylation
   a. Uncoupling proteins carry protons in the intermembranous space through the inner mitochondrial membrane into the mitochondrial matrix without damaging the membrane.
   (1) Since uncouplers bypass ATP synthase, ATP synthesis is decreased.
   (2) Examples of uncouplers include:
      (a) Thermogenin, a natural uncoupler in the brown fat of newborns
      (b) Dinitrophenol, which is used in synthesizing trinitrotoluene (TNT)
   b. If dinitrophenol is involved, the heat normally used to synthesize ATP is redirected into raising the core body temperature, leading to hyperthermia.
   c. If thermogenin is involved, the heat is used to stabilize body temperature and is not harmful to newborns.

Agents such as **alcohol** and **salicylates** are mitochondrial toxins. They damage the inner mitochondrial membrane, causing protons to move into the mitochondrial matrix. This may result in hyperthermia.

D. Tissues susceptible to hypoxia
   1. Watershed areas between terminal branches of major arterial blood supplies are susceptible to hypoxic injury.
      a. In watershed areas, the blood supply from the two vessels does not overlap.
      b. Examples include:
         (1) The area between the distribution of the anterior and middle cerebral arteries
           - Global hypoxia (e.g., shock) may result in a watershed infarction (see later) at the junction of these two overlapping blood supplies (Fig. 2-7A; refer to Chapter 26).
(2) The area between the distribution of the superior and inferior mesenteric arteries (i.e., splenic flexure, see Fig. 18-20C)
- Decreased blood supply to either of the previously mentioned vessels (e.g., thrombosis overlying an atherosclerotic plaque) produces a watershed infarction (called ischemic colitis; refer to Chapter 18) at the junction of these two overlapping blood supplies (splenic flexure in the left upper quadrant).

2. Subendocardial tissue
- Coronary vessels penetrate the epicardial surface; therefore the subendocardial tissue receives the least amount of O₂.

Factors decreasing coronary artery blood flow (e.g., coronary artery atherosclerosis) produce subendocardial ischemia, which is manifested by chest pain (i.e., angina) and ST-segment depression in an electrocardiogram (ECG). Increased thickness of the left ventricle (i.e., hypertrophy associated with aortic stenosis or essential hypertension) in the presence of increased myocardial demand for O₂ (e.g., exercise) also produces subendocardial ischemia.

3. Renal cortex and medulla
   a. The straight portion of the proximal tubule in the cortex is most susceptible to hypoxia.
      - Primary site for reclaiming bicarbonate and reabsorbing sodium (refer to Chapter 5)
   b. The thick ascending limb of the medulla is also susceptible to hypoxia (location of Na⁺/K⁺/2Cl⁻ symporter).
      - Primary site for regenerating free water, which is necessary for normal dilution and concentration of urine (refer to Chapter 5)

4. Neurons in the central nervous system
   a. Examples—Purkinje cells in cerebellum and neurons in the cerebral cortex
   b. Irreversible damage occurs ~5 minutes after global hypoxia (e.g., shock).
      - Most adversely affected cell in tissue hypoxia

5. Hepatocytes located around the central venule (see Fig. 2-7B)

In the portal triads (PT), hepatic artery tributaries carrying oxygenated blood and portal vein tributaries carrying unoxygenated blood empty their blood into the liver sinusoids (mixed oxygenated and unoxygenated blood), which drain blood into the central venules (V). The central venules become the hepatic vein, which empties into the inferior vena cava. Hepatocytes closest to the portal triads (zone I) receive the most oxygen and nutrients, whereas those furthest from the portal triads (zone III around the central venules) receive the least amount of oxygen and nutrients. Production of free radicals from drugs (e.g., acetaminophen, see later), tissue hypoxia (e.g., shock, CO poisoning), and alcohol-related fatty change of the liver (see later) initially damage zone III hepatocytes, which, owing to their relative lack of O₂, are more susceptible to injury. Depending on the severity of the injury, the other liver zones may also become involved.
E. Consequences of hypoxic cell injury

1. Reversible changes in the cells
   a. Decreased synthesis of ATP in the mitochondria causes the cells to shift to anaerobic glycolysis for ATP synthesis.
      (1) Low citrate levels and increased adenosine monophosphate (AMP) activate phosphofructokinase, the rate limiting enzyme of glycolysis.
      (2) Net gain of (2)ATP (see schematic; phosphoenolpyruvate [PEP]).

   (3) Pyruvate is converted to lactate, which decreases intracellular pH (lactic acidosis).
      (a) Lactic acid increases in the blood, producing an increased anion gap metabolic acidosis (refer to Chapter 5).
      (b) Intracellular lactic acid denatures structural and enzymic proteins.
      • Ultimately, this may result in coagulation necrosis in the cell (see later).
   b. Protein synthesis is decreased due to detachment of ribosomes from the rough endoplasmic reticulum (RER).

2. Irreversible changes in the cell
   a. Calcium (Ca$^{2+}$)-ATPase pump is impaired because of insufficient ATP
      • Normal function is to pump Ca$^{2+}$ out of the cytosol.
   b. Increased cytosolic Ca$^{2+}$ has five lethal effects
      (1) Cytosolic Ca$^{2+}$ activates enzymes.
         (a) Activation of phospholipase increases cell and organelle membrane permeability.
         (b) Activation of proteases damages the cytoskeleton.
         (c) Activation of endonucleases causes fading of nuclear chromatin (karyolysis).
         (d) Activation of ATPase leads to ↓ATP.
         (e) Cytosolic Ca$^{2+}$ directly activates caspases causing apoptosis of the cell.
      (2) Cytosolic Ca$^{2+}$ enters the mitochondria.
         (a) Mitochondrial membrane permeability is increased.
         • Cytochrome c in the ETC is released into the cytosol where it activates the caspases causing apoptosis (programmed cell death; see later).
         (b) Mitochondrial conductance channels (pores) are opened leading to loss of H$^{+}$ ions and membrane potential; therefore oxidative phosphorylation cannot occur, leading to a decrease in ATP synthesis.

II. Free Radical Cell Injury

A. Overview of free radicals (FRs)
   1. Definition—unstable chemical species that have a single unpaired electron in their outer orbital
   2. Attack a molecule and “steal” its electron, causing that molecule to become a FR and resulting in a chain of reactions that leads to cell death
   3. Primarily target nucleic acids and cell membranes
      a. In the nucleus, they produce DNA fragmentation and dissolution of chromatin.
      b. In the cell membrane and mitochondrial membranes, they produce fatty acid FRs that react with molecular O$_2$ to produce peroxy--fatty acid radicals (called lipid peroxidation).
      (1) FR damage to cell membranes causes increased permeability leading to increased cytosol Ca$^{2+}$ concentration (see earlier).
      (2) FR damage to mitochondrial membranes allows cytochrome c in the ETC to escape into the cytosol and activate caspases leading to apoptosis (see later).
   4. Damage cumulative as part of the normal aging process (refer to Chapter 6)
   5. Important in microbial killing by neutrophils and monocytes (see later and refer to Chapter 3)
   6. Important in the reperfusion injury associated with fibrinolytic therapy in an acute myocardial infarction (see later and refer to Chapter 11)
B. Production and types of free radicals

1. Reactive O₂ species (ROS)
   a. ROS include superoxide, hydrogen peroxide (H₂O₂), and hydroxyl radicals
      (1) H₂O₂ is technically not an FR but is classified as an ROS owing to its production of hydroxyl FRs by reacting with transition metals (Fe²⁺, Cu⁺) via the Fenton reaction (see later).
      (2) Hydroxyl FRs are the most destructive FRs.
   b. Administration of high concentrations of O₂ produces superoxide FRs.
   c. Ionizing radiation splits water into hydrogen and hydrogen FRs.
   d. NADPH oxidase reaction generates superoxide FRs in neutrophils and monocytes in phagolysosomes (discussed in Chapter 3)
   e. Xanthine oxidase acting upon xanthine (degradation product of ATP) produces superoxide FRs, which are important in reperfusion injury in a myocardial infarction (refer to Chapter 11).

2. Other examples of FRs
   a. Drugs—acetaminophen (see later)
   b. Chemicals—carbon tetrachloride (CCl₄; see later)
   c. Nitric oxide (NO)
      (1) FR gas produced by nitric oxide synthase in macrophages and endothelial cells
      (2) Reacts with superoxide FRs and forms a potent FR peroxynitrite that is bacteriocidal (refer to Chapter 3)
   d. Low-density lipoprotein (LDL)
      (1) Small dense subtypes of LDL enter the intima and are oxidized by FRs produced by macrophages, smooth muscle cells, and endothelial cells.
      (2) Oxidized LDL contributes to the formation of fatty streaks, which are progenitors of fibrous caps, the pathognomonic lesion of atherosclerosis (refer to Chapter 10).

C. Neutralization of free radicals

1. Superoxide dismutase (SOD)
   • Converts superoxide FRs into H₂O₂

2. Glutathione peroxidase (enhances glutathione [GSH])
   a. Enzyme in the pentose phosphate pathway
   b. Neutralizes H₂O₂, hydroxyl, and NAPQ1 (toxic intermediate of acetaminophen) FRs.

3. Catalase in peroxisomes degrades peroxide into water and O₂.

4. Vitamins C and E as antioxidants
   a. Antioxidants neutralize FRs by donating one of their own electrons.
      (1) Providing an electron stops the “electron stealing” of FRs.
      (2) Antioxidants remain stable and do not become a FR.
   b. Vitamin E (fat-soluble vitamin; refer to Chapter 8)
      (1) Prevents lipid peroxidation in cell membranes (see earlier).
      (2) Neutralizes oxidized LDL.
   c. Vitamin C (water-soluble vitamin; refer to Chapter 8)
      (1) Neutralizes FRs produced by pollutants and cigarette smoke
         • Smokers have decreased levels of vitamin C, because they are used up in neutralizing FRs derived from cigarette smoke.
      (2) Best neutralizer of hydroxyl FRs and regenerates vitamin E

D. Clinical examples of FR injury

1. Acetaminophen poisoning
   a. In normal doses, acetaminophen is glucuronylated or sulfated by the cytochrome P450 system in the smooth endoplasmic reticulum (SER) into a harmless metabolite that is excreted by the kidney.
   b. In toxic doses, acetaminophen causes diffuse chemical hepatitis due to its conversion by a cytochrome P450 isoenzyme into a toxic intermediate called NAPQ1 (drug FR).
      (1) Cytochrome P450 isoenzyme responsible for this conversion is called CYP2E1, which is part of the microsomal ethanol-oxidizing system (MEOS) located in the liver.
      (2) Liver cell necrosis initially occurs around the central venules (zone III).
      (3) Liver cell necrosis may occur at nontoxic levels in alcoholics.
         • Alcohol induces the synthesis of CYP2E1 isoenzyme, causing a higher percentage of acetaminophen to be converted to NAPQ1.
   c. N-Acetylcysteine is used to treat acetaminophen poisoning.
      (1) It is a precursor for the synthesis of glutathione.
      (2) Glutathione reduces levels of NAPQ1 and increases its excretion in the kidneys.
d. Acetaminophen in association with nonsteroidal antiinflammatory agents (NSAIDs) may cause renal papillary necrosis (refer to Chapter 20).

2. Carbon tetrachloride FRs
   a. CCl₄ is used as a solvent in the dry cleaning industry.
   b. Cytochrome P450 system in the SER converts CCl₄ into a FR.
   c. FRs produce liver cell necrosis with fatty change.

3. Ischemia/reperfusion injury in acute myocardial infarction (refer to Chapter 11 for complete discussion)
   - Superoxide FRs are involved in reperfusion injury, along with cytosolic Ca²⁺, and neutrophils.

4. Retinopathy of prematurity
   - Blindness due to destruction of retinal cells by superoxide FRs may occur in the treatment of RDS with high a concentration of O₂ >50%.

5. Iron overload disorders (hemochromatosis, hemosiderosis; refer to Chapter 19)
   a. Intracellular iron produces hydroxyl FRs, which damage the parenchymal cells.
      (1) Hydroxyl FRs are produced via the nonenzymatic Fenton reaction using hydrogen peroxide.
      (2) Fe²⁺ + H₂O₂ → Fe³⁺ + OH⁻ + OH⁻
   b. Consequences of FR injury include cirrhosis and exocrine/endocrine dysfunction of the pancreas.

6. Copper overload (Wilson disease; refer to Chapters 19 and 26)
   a. Wilson disease is characterized by inability to excrete copper into bile.
   b. Copper excess in hepatocytes increases the production of hydroxyl FRs.
      (1) Hydroxyl FRs are produced via the nonenzymatic Fenton reaction using hydrogen peroxide (similar to the reaction with iron shown earlier).
      (2) Consequences of FR injury include damage to hepatocytes leading to cirrhosis and damage to the lenticular nuclei in the brain.

III. Injury to Cellular Organelles (Fig. 2-8)
   A. Mitochondria
      - Salicylates and alcohol are mitochondrial toxins that produce megamitochondria with destruction of the cristae (Fig. 2-9).
   B. Smooth endoplasmic reticulum (SER)
      1. Induction (increased synthesis) of enzymes of the liver cytochrome P450 system
         a. Induction of the SER may be caused by:
            (1) Alcohol, barbiturates, and phenytoin
            (2) Alcohol increases the synthesis of CYP2E1 isoenzyme in the cytochrome P450 system.

---

2-8: Structure of the generalized cell. Cells have specialized structures depending on their origin and function. The components common to most human cells are shown in the schematic. (From Brown T. Rapid Review Physiology, 2nd ed, Philadelphia, Elsevier Mosby, 2012, p 1, Fig. 1-1.)

2-9: Hyperplasia of smooth endoplasmic reticulum (2) and damaged mitochondria (megamitochondria; 1) in alcoholic liver disease. Dark circular areas represent peroxisomes. (From MacSween R, Burt A, Portmann B, Ishak K, Scheuer P, Anthony P. Pathology of the Liver, 4th ed, London, Churchill Livingstone, 2002, p 288, Fig. 6-20.)
(a) This increases the metabolism of alcohol.
   - Alcohol is converted to acetaldehyde by alcohol dehydrogenase, and
     acetaldehyde to acetate by acetaldehyde dehydrogenase.
   (b) With alcohol excess, acetaldehyde conversion to acetate by acetaldehyde
     dehydrogenase is not fast enough; hence acetaldehyde level may increase and
     damage hepatocytes.
   (3) Phenobarbital increases the synthesis of CYP2B2 isoenzyme, which converts it into
     an inactive metabolite.
     - Alcohol inactivates the previously mentioned cytochrome system;
       hence, if both are consumed in large amounts, phenobarbital toxicity
       may occur.
   (4) Phenytoin increases the synthesis of CYP3A4, which accelerates its metabolism as
       well as other antiepileptic agents.
       b. Induction of enzyme synthesis in the cytochrome P450 system produces SER hyperplasia
       (see Fig. 2-9).
       - Increased drug detoxification causes lower than expected therapeutic drug levels.

2. Inhibition of enzymes of the cytochrome P450 system
   a. Inhibition of cytochrome enzymes may be caused by:
     (1) Proton receptor blockers (e.g., omeprazole)
     (2) Histamine H2-receptor blockers (e.g., cimetidine)
   b. Decreased drug detoxification leads to higher than expected therapeutic drug levels.
     • Example—cimetidine inhibits the metabolism of phenytoin leading to high serum
       levels.

C. Lysosomes
   1. Lysosomal enzyme formation and delivery to lysosomes
      a. Hydrolytic enzymes synthesized by the RER are transported to the Golgi apparatus for
         posttranslational modification.
      b. Enzyme modification involves attaching phosphate (via phosphotransferase) to mannose
         residues on hydrolytic enzymes to produce mannose 6-phosphate (P).
      c. Marked lysosomal enzymes attach to specific mannose 6-P receptors on the Golgi
         membrane.
      d. Vesicles containing the receptor-bound lysosomal enzymes (called endosomes) pinch off
         the Golgi and fuse with lysosomes in the cytosol.
         (1) Fusion of additional vesicles further increases the content of hydrolytic enzymes in
             lysosomes.
         (2) Some of the small vesicles that empty enzymes into the lysosomes return to the Golgi
             to bind more marked lysosomal enzymes, so the cycle repeats itself.
      e. Lysosomal functions include:
         (1) Fusion with primary phagocytic vacuoles in neutrophils, monocytes, and
             macrophages containing bacteria
             • These phagocytic vacuoles are now designated phagolysosomes.
         (2) Destruction of cell organelles (autophagy; see later)
         (3) Degradation of complex substrates (e.g., sphingolipids, glycosaminoglycans)
   2. Selected lysosomal disorders
      a. Inclusion (I)-cell disease

Inclusion (I)-cell disease is a rare inherited condition in which there is a defect in
posttranslational modification of lysosomal enzymes in the Golgi apparatus. Mannose residues on
newly synthesized lysosomal enzymes coming from the RER are not phosphorylated because of a
deficiency of phosphotransferase. Without mannose 6-phosphate to direct the enzymes to
lysosomes, vesicles that pinch off the Golgi empty the unmarked enzymes into the extracellular
space where they are degraded in the bloodstream. Undigested substrates (e.g., carbohydrates,
lipids, and proteins) accumulate as large inclusions in the cytosol. Symptoms include psychomotor
retardation and early death.

b. Deficiency of lysosomal enzymes involved in degradation of complex substrates
   characterize the lysosomal storage diseases (refer to Chapter 6).
   c. Chédiak-Higashi syndrome (CHS)
CHS is an autosomal recessive disease with a defect in a lysosomal transport protein that affects the synthesis and/or maintenance of storage of secretory granules in various cells (e.g., lysosomes in leukocytes, azurophilic granules in neutrophils, dense bodies in platelets). Granules in these cells tend to fuse together (fusion defect) to become megagranules (Fig. 2-10). In addition, there is a defect in microtubule function in neutrophils and monocytes that prevents the fusion of lysosomes with phagosomes to produce phagolysosomes. This produces a bactericidal defect. In particular, there is increased susceptibility to developing Staphylococcus aureus infections. Microtubular dysfunction also produces defects in chemotaxis (directed migration), which further exacerbates the susceptibility to infection.

D. Cytoskeleton

1. Normal functions
   a. Network of protein filaments in the cell
      - Maintain the shape of the cell and, in some cases, are involved in the motility of the cell
   b. Composed of microtubules, actin filaments, and intermediate filaments
      (1) Microtubules are polymers composed of the protein tubulin.
      (2) Actin thick and thin filaments are involved in the contractile process.
      (3) Intermediate filaments are important in the integration of cell organelles.

2. Defect in the synthesis of tubulin
   a. Tubulin is required for the synthesis of microtubules in the mitotic spindle.
   b. Synthesis occurs in the G2 phase of the cell cycle (refer to Chapter 3)
   c. Etoposide and bleomycin are chemotherapeutic agents that inhibit the synthesis of tubulin.

3. Mitotic spindle defects
   a. Synthesized in the M phase of the cell cycle
   b. Vinca alkaloids and colchicine bind to tubulin in microtubules, which interferes with the assembly of the mitotic spindle.
   c. Paclitaxel enhances tubulin polymerization which interferes with disassembly of the mitotic spindle.

4. Intermediate filament defects
   a. Ubiquitin, a stress protein, binds to damaged intermediate filaments.
      - Ubiquitin binding marks these damaged ("ubiquinated") filaments for degradation in proteasomes and lysosomes in the cytosol.
   b. Mallory bodies
      (1) Definition—ubiquinated cytokeratin intermediate filaments in hepatocytes in alcoholic liver disease (Fig. 2-11)
      (2) Appear as eosinophilic inclusion bodies in the cytosol of hepatocytes

CHS: giant lysosomal granules (fusion defect); defect in formation of phagolysosomes

Cytoskeleton: microtubules, actin filaments, intermediate filaments

G2 phase defects: etoposide, bleomycin

Mitotic spindle defects: vinca alkaloids, colchicine, paclitaxel

Ubiquitin: marker for damaged intermediate filaments
c. Lewy bodies
   (1) Definition—ubiquinated neurofilaments that are present in idiopathic Parkinson disease
   (2) Appear as eosinophilic cytoplasmic inclusions in degenerating substantia nigra neurons (refer to Chapter 26)

IV. Intracellular Accumulations

A. Types of accumulations (Table 2-3)

B. Fatty change in the liver
   1. Definition: cytosolic accumulation of triglycerides (TGs) in hepatocytes.
      • Liver-synthesized TGs are packaged in the very-low-density lipoprotein (VLDL) fraction (refer to Chapter 10).

<table>
<thead>
<tr>
<th>TABLE 2-3 Selected Intracellular Accumulations</th>
</tr>
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<tbody>
<tr>
<td><strong>SUBSTANCE</strong></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Bilirubin</td>
</tr>
<tr>
<td>Cholesterol</td>
</tr>
<tr>
<td>Glycogen</td>
</tr>
<tr>
<td>Hematin</td>
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<tr>
<td>Hemosiderin and ferritin</td>
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<tr>
<td>Melanin</td>
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<tr>
<td>Protein</td>
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<tr>
<td>Triglyceride</td>
</tr>
<tr>
<td>Exogenous Accumulations</td>
</tr>
<tr>
<td>Anthracotic pigment</td>
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<tr>
<td>Lead</td>
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</tbody>
</table>

ACTH, Adrenocorticotropic hormone; FR, free radical; GI, gastrointestinal.
2. Normal synthesis of TGs in the liver
   a. Synthesis of TGs occurs with conversion of dihydroxyacetone phosphate (DHAP), an intermediate of glycolysis, to glycerol 3-phosphate (G3-P).
   b. Addition of three fatty acids (FAs) to G3-P produces TGs.

   ![Diagram of DHAP to G3-P synthesis](image)

   c. Once TGs are synthesized, the VLDL lipoprotein fraction is produced.
      (1) Lipoproteins have hydrophilic (water-loving) groups of phospholipids, cholesterol, and proteins directed outward, so that they are soluble in the sodium-containing water, which comprises 90% of the plasma in blood.
      (2) Apoprotein B (apoB)-100 is the protein component of VLDL and also serves to enhance its secretion into the blood.

3. Fatty liver is most often caused by increased synthesis of TGs and less commonly by problems with the packaging of TGs into VLDL or its secretion into blood.
   a. Increased synthesis of TGs is caused by increased conversion of DHAP to G3-P, which occurs with kwashiorkor (refer to Chapter 8) and excessive alcohol consumption (refer to Chapter 19).
      (1) In kwashiorkor, there is increased intake of carbohydrates (CHO) and little to no intake of proteins.
         - Increased CHO intake increases the amount of DHAP produced during glycolysis, therefore providing more substrate for synthesizing TGs.
      (2) In alcohol excess, increased production of NADH from alcohol metabolism accelerates conversion of DHAP to G3-P (see previous reaction).

   ![Diagram of alcohol metabolism](image)

   (3) An additional factor enhancing TG synthesis in alcohol excess is increased availability of fatty acids (FAs) to combine with G3-P to form TGs.
      (a) Recall that acetyl CoA is used for synthesizing FAs and since acetyl CoA is the end product of alcohol metabolism, it is available to synthesize more FAs.
      (b) Alcohol increases the mobilization of FAs from TG stores in adipose tissue by activating hormone sensitive lipase, which hydrolyzes TG into FAs and glycerol.
      (c) β-Oxidation of FAs in the mitochondrial matrix is reduced, because NAD⁺, which is required for the oxidation process, is less available owing to its conversion to NADH in alcohol metabolism.

   b. Decreased packaging of TG into VLDL and secretion into the blood, resulting from decreased synthesis of apoB-100, causes fatty liver.
      (1) In kwashiorkor, because of decreased protein intake, apoB-100 synthesis is decreased.
      (2) TGs that are synthesized in the hepatocyte remain in the hepatocyte producing fatty change.

4. Morphology of fatty change in the liver
   a. Liver is normal size or enlarged and has a yellowish discoloration (Fig. 2-12A).
   b. Under the light microscope, hepatocytes have a clear space pushing the nucleus to the periphery (Fig. 2-12B).

C. Iron accumulation (see Table 2-3)

1. Ferritin (also refer to Chapter 12)
   a. Definition—soluble iron-binding protein that stores iron in macrophages
   b. Primarily synthesized and stored in macrophages (bone marrow most common site) and hepatocytes (second most common site)
   c. Small amounts of ferritin circulate in serum.
      (1) Serum levels directly correlate with bone marrow iron stores.
      (2) For example, a decrease in serum ferritin indicates iron deficiency

   ![Diagram of ferritin synthesis](image)
2. Hemosiderin
   a. Definition—insoluble product of ferritin degradation in lysosomes.
   b. Unlike ferritin, it does not circulate in serum.
   c. Appears as golden brown granules in hematoxylin-eosin stained tissue or as blue granules when stained with Prussian blue (see Fig. 19-7G).

D. Pathologic calcification
   1. Dystrophic calcification
      a. Definition—deposition of calcium phosphate in necrotic (damaged) tissue.
      b. Calcium deposition in tissue is unrelated to the serum calcium and phosphate levels, which are normal.
      c. Mechanism
         (1) Calcium enters the necrotic cells and binds to phosphate released from damaged membranes by phosphatase producing calcium phosphate.
         (2) Calcium phosphate is basophilic in the presence of hematoxylin-eosin stain (see Fig. 5-15).
      d. Examples include:
         (1) Calcification in chronic pancreatitis (Fig. 2-13)
         (2) Calcified atherosclerotic plaques
         (3) Periventricular calcification in congenital cytomegalovirus infection (see Fig. 26-14A)
   2. Metastatic calcification
      a. Definition—deposition of calcium phosphate in the interstitium of normal tissue
      b. Unlike dystrophic calcification, it is due to increased serum levels of calcium and/or phosphate.
(1) Common causes of hypercalcemia include primary hyperparathyroidism and malignancy-induced hypercalcemia.
(2) Common causes of hyperphosphatemia include chronic renal failure and primary hypoparathyroidism.
    - Excess phosphate drives calcium into normal tissue.
c. Examples of metastatic calcification include:
   (1) Calcification of renal tubular basement membranes in the collecting ducts (called nephrocalcinosis)
       - Produces nephrogenic diabetes insipidus and renal failure.
   (2) Calcification in the lungs, which can cause respiratory problems

V. Adaptation to Cell Injury: Growth Alterations
A. Atrophy
1. Definition—decrease in size and weight of a tissue or organ.
2. Causes
   a. Decreased hormone stimulation
      - Example—hypopituitarism causing atrophy of target organs, such as the thyroid and adrenal cortex
   b. Decreased innervation
      - Example—skeletal muscle atrophy following loss of lower motor neurons in amyotrophic lateral sclerosis
   c. Decreased blood flow
      - Example—cerebral atrophy due to atherosclerosis of the carotid artery (Fig. 2-14A)
   d. Decreased nutrients
      - Example—total calorie deprivation in marasmus (see Fig. 8-1)
   e. Increased luminal pressure
      (1) Example—atrophy of the renal cortex and medulla in hydronephrosis (see Fig. 20-8A)
         - ↑Luminal pressure of backed-up urine compresses vessels in the cortex and medulla leading to atrophy.
      (2) Example—thick pancreatic duct secretions in cystic fibrosis occlude the duct lumens, causing increased luminal back pressure and compression atrophy of the exocrine glands (see Fig. 2-14B)
         (a) Atrophy of exocrine glands causes malabsorption of proteins and fats (amylase from the salivary glands is enough to digest carbohydrates).
         (b) Eventually, all of the pancreas is damaged, including the islet cells, leading to type I diabetes mellitus.
3. Mechanisms
   a. Atrophy can be due to shrinkage of cells related to increased catabolism of cell organelles (e.g., mitochondria) and reduction in cytosol.
      (1) Organelles and cytosol form autophagic vacuoles.
         - Autophagy is a catabolic pathway that is used to degrade or recycle cellular components.
      (2) Autophagic vacuoles fuse with primary lysosomes (autophagolysosomes) for enzymatic degradation.
      (3) Undigested lipids derived from lipid peroxidation of cell membranes are stored as residual bodies (lipofuscin; see Fig. 2-14C).
         (a) Brown tissue discoloration may occur (called brown atrophy) from accumulation of lipofuscin in the primary lysosomes.
         (b) Brown atrophy is commonly seen in the elderly population and is considered a normal age-related finding.
   b. Atrophy can be due to loss of cells by apoptosis (programmed cell death, see later).
   c. Atrophy decreases protein synthesis and increases protein degradation.
      (1) Decreased protein synthesis usually occurs in catabolic conditions where there is wasting of muscle (e.g., wasting syndrome in cancer; refer to Chapter 9).
      (2) Increased protein degradation is handled by the ubiquitin-proteasome pathway (see earlier).
B. Hypertrophy
1. Definition—increase in cell size.
2. Hypertrophy in muscle tissue is caused by increased workload.
   a. Left ventricular hypertrophy occurs in response to an increase in afterload (resistance to overcome) or preload (volume to expel) (see Fig. 2-14D)
2-14: A, Atrophy of the brain. Note the narrow gyri and widened sulci. The meninges have been stripped from the right half of the brain. B, Pancreas in a patient with cystic fibrosis showing dilated ducts filled with thickened eosinophilic material. The duct epithelial cells are flattened and the ducts are surrounded with fibrous tissue. C, Liver showing hepatocytes with yellow-brown granules representing lipofuscin. D, Left ventricular hypertrophy, showing the thickened free left ventricular wall (right side) and the thickened interventricular septum. The right ventricle wall (left side) is of normal thickness. E, Benign prostatic hyperplasia. The prostatic glands show infolding into the glandular spaces. F, Barrett esophagus showing an extensive area of glandular (intestinal) metaplasia with numerous goblet cells. A small section of squamous epithelium remains on the right. G, Section of bronchus from a smoker showing focal squamous metaplasia (long arrow). Normal ciliated, pseudostratified columnar epithelium is present on the right (short arrow). H, Squamous dysplasia of the cervix, a precursor of squamous cell carcinoma. There is a lack of orientation of the squamous cells throughout the upper two thirds of the epithelium. Many of the nuclei are enlarged (arrows), are hyperchromatic, and have irregular nuclear margins. (A from Kumar V, Abbas A, Fausto N, Mitchell, R: Robbins Basic Pathology, 8th ed, Philadelphia, Saunders, 2007, p. 5, Fig. 1-4; B, E, and F from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, pp 169, 249, and 111; Figs. 9-6, 12-32, 6-26, respectively; C from Damjanov I, Linder J: Anderson’s Pathology, 10th ed, St. Louis, Mosby, 1996, p 371, Fig. 17-7; D and H from Kumar V, Fausto N, Abbas A: Robbins and Cotran’s Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, pp 561 and 1075, Fig. 12-3A; Fig. 22-19C, respectively; G from Corrin B: Pathology of the Lungs, London, Churchill Livingstone, 2000, p 460, Fig. 13.1.1.)
(1) In ventricular hypertrophy, the changes in wall stress produce changes in gene expression leading to the duplication of sarcomeres causing the muscles to be thicker or longer (refer to Chapter 11).

(2) In addition, there is an increase in cytosol, number of cytoplasmic organelles, and DNA content in each hypertrophied cell.

b. Skeletal muscle hypertrophy occurs in response to weight training.

3. Surgical removal of one kidney produces compensatory hypertrophy (some degree of hyperplasia) of the remaining kidney.

4. Cell enlargement occurs in cytomegalovirus (CMV) infections (see Fig. 17-5B)
   - Cytomegaly occurs because the virus increases the uptake of iron into the cytosol, which increases the growth of the cell.

C. Hyperplasia

1. Definition—increase in the number of normal cells.

2. Causes
   a. Increased hormone stimulation; examples include:
      (1) Endometrial gland hyperplasia, which is caused by an increase in estrogen (see Fig. 22-10D)
         - There is an increased risk for developing cancer.
      (2) Benign prostatic hyperplasia (BPH), which is caused by an increase in sensitivity to dihydrotestosterone (DHT) (see Fig. 2-14E)
         (a) Unlike endometrial gland hyperplasia, there is no increased risk for developing cancer.
         (b) BPH is frequently complicated by obstructive uropathy with thickening of the bladder wall by smooth muscle, which exhibits both hyperplasia and hypertrophy (see Fig. 21-4B).
   
   b. Chronic irritation; examples include:
      (1) Constant scratching of itchy skin, which can produce thickening (hyperplasia) of the epidermis
      (2) Bronchial mucous gland hyperplasia, which commonly occurs in smokers and asthmatics
      (3) Regenerative nodules in cirrhosis of the liver, which may occur in response to alcohol excess (see Fig. 19-7A, B, C)
   
   c. Chemical imbalance; examples include:
      (1) Hypocalcemia, which stimulates parathyroid gland hyperplasia (secondary hyperparathyroidism) to increase serum calcium levels back toward the normal range
      (2) Iodine deficiency, which produces thyroid enlargement (goiter; see Fig. 23-9A) as the gland works hard to increase thyroid hormone synthesis
         - Both hypertrophy and hyperplasia are operative in producing goiters.
   
   d. Stimulating antibodies
      - Hyperthyroidism in Graves disease is due to thyroid-stimulating antibodies (IgG) directed against thyroid hormone receptors, which cause the gland to synthesize excess thyroid hormone (see Fig. 23-8A).
   
   e. Viral infections
      (1) Skin infection by the human papillomavirus (HPV) produces epidermal hyperplasia or the common wart (see Fig. 25-2A).
      (2) Viral genes produce growth factors causing epidermal hyperplasia.

3. Mechanisms
   a. Hyperplasia depends on the regenerative capacity of different cell types (refer to Chapter 3).
   
   b. Labile cells (stem cells)
      (1) Stem cells are located in the bone marrow, crypts of Lieberkühn, and the basal cell layer of the epidermis.
      (2) Labile cells divide continuously.
      (3) Labile cells may undergo hyperplasia as an adaptation to cell injury.
   
   c. Stable cells (resting cells)
      (1) Examples of stable cells—hepatocytes, astrocytes, and smooth muscle cells
      (2) Stable cells divide infrequently, because they are normally in the G0 (resting) phase of the cell cycle.
      (3) Stable cells must be stimulated (e.g., growth factors, hormones, absence of tissue) to enter the cell cycle.
      (4) Depending on the cell type, stable cells may undergo hyperplasia and/or hypertrophy as an adaptation to cell injury.
Permanent cells: cannot divide; e.g., neurons, skeletal/cardiac muscle

Cancer risk in hyperplasia: endometrial hyperplasia, regenerative nodules in cirrhosis

Metaplasia: one adult cell type replaces another

Squamous to glandular epithelium: acid reflux distal esophagus (Barrett esophagus)

Glandular to other glandular epithelium: atrophic gastritis due to Helicobacter pylori

Glandular to squamous epithelium: bronchus in smoker; endocervix

Transitional to squamous epithelium: Schistosoma haematobium infection of urinary bladder

Mesenchymal metaplasia: bone developing in area of muscle trauma

Mechanism: reprogramming stem cells to utilize progeny cells with different gene expression

Stimuli for reprogramming: hormones (estrogen), vitamins (retinoic acid), chemicals (cigarette smoke)

Metaplasia and hyperplasia: risk for developing dysplasia; metaplasia > hyperplasia

d. Permanent cells (nonreplicating cells)
   (1) Examples of permanent cells—neurons and skeletal and cardiac muscle cells
   (2) Permanent cells are highly specialized cells that cannot replicate.
   (3) Of the permanent cells, only skeletal and cardiac muscle may undergo hypertrophy as an adaptation to injury.

4. Increased risk for progressing into cancer, in some types of hyperplasia; for example:
   a. Endometrial hyperplasia may progress into cancer (endometrial adenocarcinoma).
   b. Regenerative nodules in cirrhosis may progress into cancer (hepatocellular carcinoma).

D. Metaplasia

1. Definition—replacement of one fully differentiated cell type by another.
   a. Substituted cells are less sensitive to a particular stress.
   b. For example, mucus-secreting glandular epithelium is more likely to protect itself from acid injury than squamous epithelium.

2. Types of metaplasia
   a. Metaplasia from squamous to glandular epithelium
      (1) An example of this type of metaplasia occurs when there is acid reflux from the stomach into the distal esophagus.
      (2) The distal esophagus epithelium, which is normally squamous epithelium, is converted into epithelium showing an increase in goblet cells and mucus-secreting cells to protect itself from acid injury (see Fig. 2-14F; refer to Chapter 18).
      (3) This type of glandular metaplasia is called Barrett esophagus.
         (a) Note that the cell types involved in this metaplasia are normally present in the intestine (e.g., goblet cells); hence the term intestinal metaplasia (see Fig. 18-10B).
         (b) In a Barrett esophagus, there is an increased risk for developing cancer, in this case, a distal adenocarcinoma.
   b. Metaplasia from glandular to other types of glandular epithelium
      (1) This occurs in the pylorus and antrum epithelium in the stomach when there is an infection caused by Helicobacter pylori (refer to Chapter 18).
      (2) Inflammatory cytokines, which are released by the pathogen, produce a chronic gastritis that is characterized by an increase in the synthesis of goblet cells and Paneth cells; these cell types are normally present in intestinal epithelium (intestinal metaplasia).
      (3) In this type of chronic gastritis, there is an increased risk for developing a gastric cancer in the pylorus or antrum.
   c. Metaplasia from glandular to squamous epithelium
      (1) This occurs in the mainstem bronchus epithelium when pseudostratified columnar epithelium of the mainstem bronchus epithelium develops squamous metaplasia in response to irritants in cigarette smoke (see Fig. 2-14G).
         • There is an increased risk for developing squamous cancer of the mainstem bronchus.
      (2) Mucus-secreting endocervical cells encountering the acid pH of the vagina undergo squamous metaplasia.
   d. Metaplasia from transitional to squamous epithelium
      (1) This occurs in a Schistosoma haematobium infection in the urinary bladder, which causes transitional epithelium to undergo squamous metaplasia.
      (2) There is an increased risk for developing squamous cancer of the urinary bladder.
   e. Mesenchymal metaplasia involving connective tissue
      (1) Occurs when bone tissue develops in an area of muscle trauma (osseous metaplasia)
      (2) No risk for developing cancer

3. Mechanism
   a. Stem cells normally have an array of progeny cells that have different patterns of gene expression.
      • Under normal physiologic conditions, differentiation of these progeny cells is restricted.
   b. However, under stressful conditions, metaplasia may result from reprogramming stem cells to utilize progeny cells with a different pattern of gene expression; signals that may initiate this change include:
      (1) Hormones (e.g., estrogen)
      (2) Vitamins (e.g., retinoic acid)
      (3) Chemical irritants (e.g., cigarette smoke)
   c. Metaplasia is sometimes reversible if the irritant is removed.
E. Dysplasia
1. Definition—disordered cell growth
   - Potential precursor to cancer if the irritant is not removed
2. Risk factors for developing dysplasia
   a. Some types of hyperplasia (e.g., endometrial gland hyperplasia; see earlier)
   b. Some types of metaplasia (e.g., Barrett esophagus; see earlier)
   c. Infection
      - Example—HPV types 16 and 18 causing squamous dysplasia of the cervix
   d. Chemicals
      - Example—irritants in cigarette smoke, causing squamous metaplasia to progress to squamous dysplasia in the mainstem bronchus (see earlier)
   e. Ultraviolet (UV) light
      - Example—solar damage of the skin, causing squamous dysplasia
   f. Chronic irritation of skin
      - Example—skin in a third degree burn developing squamous dysplasia
3. Microscopic features of dysplasia (see Fig. 2-14H)
   a. Nuclear features of dysplasia
      (1) Increased mitotic activity, with normal mitotic spindles
      (2) Increased nuclear size and chromatin
   b. Disorderly proliferation of cells with loss of cell maturation as cells progress to the surface
4. Dysplasia may involve squamous, glandular, or transitional epithelium.
5. Dysplasia is sometimes reversible if the irritant is removed.

VI. Cell Death
- Cell death occurs when cells or tissues are unable to adapt to injury.

A. Necrosis
1. Definition—death of groups of cells, often accompanied by an inflammatory infiltrate
2. Coagulation necrosis
   a. Definition—preservation of the structural outline of dead cells
   b. Mechanism
      (1) Denaturation of enzymes and structural proteins
         - This may be due to intracellular accumulation of lactate (most common), ingestion of heavy metals (e.g., lead, mercury), or exposure of cells to ionizing radiation used in treating cancer.
      (2) Inactivation of intracellular enzymes (including those in the lysosomes) prevents dissolution (autolysis) of the cell.
         - Only neutrophils and macrophages coming in from normal tissue surrounding the area of coagulation necrosis can liquify and remove the dead tissue.
   c. Microscopic features (Fig. 2-15A)
      (1) Indistinct outlines of cells are present within dead tissue.
      (2) Nuclei are either absent or undergoing karyolysis (fading of nuclear chromatin).
   d. Infarction
      (1) Definition—gross manifestation of coagulation necrosis secondary to the sudden occlusion of a vessel.
         - An exception to this is a cerebral infarction, which is a gross manifestation of liquefactive necrosis (see later).
      (2) Usually wedge-shaped if dichotomously branching vessels (e.g., pulmonary artery) are occluded.
      (3) Pale (ischemic) types of infarctions
         - Increased density of tissue (e.g., heart, kidney, spleen) prevents RBCs released from damaged vessels from diffusing through the necrotic tissue; therefore the tissue has a pale appearance (see Fig. 2-15B).
      (4) Hemorrhagic (red) types of infarctions
         - Loose-textured tissue (e.g., lungs, small bowel, testicle) allows RBCs released from damaged vessels to diffuse through the necrotic tissue; therefore the tissue has a hemorrhagic appearance (see Fig. 2-15C).

Dry gangrene of the toes in individuals with diabetes mellitus is a form of infarction that results from ischemia. Coagulation necrosis is the primary type of necrosis that is present in the dead tissue (see Fig. 2-15D).
A. Acute myocardial infarction (MI) showing coagulation necrosis. This section of myocardial tissue is from a 3-day-old acute MI. The outlines of the myocardial fibers are intact; however, they lack nuclei and cross-striations. A neutrophilic infiltrate is present between some of the dead fibers. B. Acute MI showing a pale infarction of the posterior wall of the left ventricle (bottom left). C. Hemorrhagic infarction of lung. There is a roughly wedge-shaped area of hemorrhage extending to the pleural surface. The arrow shows an embolus in one of the pulmonary artery tributaries. D. Dry gangrene involves the first four toes. The dark black areas of gangrene are bordered by light-colored, parchment-like skin. E. Cerebral infarction with hemorrhage showing liquefactive necrosis of the cerebral cortex leaving a large cystic cavity. F. Wet gangrene of the leg. Note the pus (arrow) at the closing edges of the below-the-knee amputation site. G. Caseous granuloma showing a central area of acellular, necrotic material (asterisk) surrounded by activated macrophages (epithelioid cells), lymphocytes, and multiple multinucleated Langhans-type giant cells. H. Enzymatic fat necrosis in acute pancreatitis. Dark areas of hemorrhage are present in the head of the pancreas (left side), and focal areas of pale fat necrosis (arrow) are present in the peripancreatic fat. (A from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 375, Fig. 17-15; B from Damjanov I, Linder J: Anderson’s Pathology, 10th ed, St. Louis, Mosby, 1996, p 374, Fig. 17-13; C, E, G, and H from Kumar V, Fausto N, Abbas A: Robbins and Cotran’s Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, pp 138, 1365, 83, and 943, Figs. 4-19A, 28-16, 2-33, 19-5, respectively; D from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 18, Fig. 1-24; F from Grieg JD: Color Atlas of Surgical Diagnosis, London, Mosby-Wolfe, 1996, p 6, Fig. 2-2.)
e. Factors influencing whether an infarction will occur in tissue
   (1) Size of the vessel and the number of vessels occluded
      • Infarction is unlikely with sudden obstruction of more than one major branch
        of a pulmonary artery (e.g., saddle embolus), because sudden death usually
        occurs.
   (2) Infarction is likely if a thrombus overlies an atherosclerotic plaque in a coronary
      artery.
   (3) State of development of a collateral circulation
      • Infarction is less likely to occur if well-developed collateral circulation is present
        (e.g., arcade system of the superior and inferior mesenteric arteries).
   (4) Presence of a dual blood supply
      (a) Infarction is less likely to occur if dual blood supply is present (e.g., pulmonary
          and bronchial arteries in the lungs).
      (b) Renal and splenic arteries have end arteries with an inadequate network of
          anastomosing vessels beyond potential points of obstruction; hence infarction is
          more likely to occur in these tissues.
   (5) Sudden onset of ischemia in an organ with preexisting disease will more likely
      produce an infarction.
      • Example—a pulmonary embolus will more likely produce an infarction in a patient
        with preexisting chronic lung (decreased blood flow through pulmonary arteries)
        or heart disease (decreased flow through bronchial arteries) because of loss of the
        dual blood supply
   (6) Tissues with a high \( O_2 \) requirement (e.g., brain, heart) are more likely to infarct than
      other less sensitive tissues (e.g., skin, muscle, and cartilage).

3. Liquefactive necrosis
   a. Definition—necrotic degradation of tissue that softens and becomes liquified
   b. Mechanisms
      • It is caused by the release of lysosomal enzymes by necrotic cells and/or the release
        of hydrolytic enzymes by neutrophils entering the tissue.
   c. Examples
      (1) Central nervous system infarction
         • Autocatalytic effect of hydrolytic enzymes released by neuroglial cells produces a
           cystic space in the brain (see Fig. 2-15E).
      (2) Abscess in a bacterial infection
         • Hydrolytic enzymes released by neutrophils liquefy dead tissue producing a cavity
           filled with purulent material (see Fig. 3-8A).

Dry gangrene of the toes with a superimposed anaerobic infection (e.g., Clostridium perfringens)
leads to acute inflammation, in which liquefactive necrosis is the primary type of necrosis. This
condition is called wet gangrene (see Fig. 2-15F).

4. Caseous necrosis
   a. Definition—variant of coagulation necrosis
      • Acellular, cheese-like (caseous) material is present on gross examination
   b. Mechanism
      (1) Caseous material, most often present in granulomas (refer to Chapter 3), is produced
          by the release of lipid from the cell walls of Mycobacterium tuberculosis (also some
          atypical Mycobacteria) and systemic fungi (e.g., Histoplasma) after immune
          destruction by macrophages in the granulomas.
          • Excess lipid from these pathogens is responsible for the cheese-like appearance of
            the material.
      (2) Other diseases associated with granuloma formation do not exhibit caseation
          (noncaseating), because they lack excessive amounts of lipid.
          • Examples—Crohn disease, sarcoidosis, and foreign body giant cell granulomas
   c. Microscopic features
      (1) Caseous material is acellular and granular in appearance and is usually located in the
          center of a granuloma.
      (2) The caseous material is surrounded by activated macrophages, CD4 helper T cells,
          and multinucleated giant cells (see Fig. 2-15G; refer to Chapter 3).
5. Gummatous necrosis
   a. Definition—variant of coagulation necrosis associated with spirochetal diseases (e.g., tertiary syphilis)
   b. Mechanism
      • Gummatous necrosis is thought to be a hypersensitivity reaction directed against spirochetes.
   c. Locations for gummas
      (1) Skin and bone are the most common sites.
      (2) Other sites—liver (called hepatic lobatum), testicle, soft tissue
   d. Gross and microscopic appearance
      (1) Gummas are firm and rubbery, unlike a caseous granuloma.
      (2) Histologically, they do not have complete obliteration of cellular architecture unlike caseous necrosis.
         (a) Gummas are surrounded by a rim of fibroblasts, macrophages, lymphocytes, plasma cells, and occasional multinucleated giant cells.
         (b) Treponemes are rarely identified in the tissue.

6. Enzymatic fat necrosis
   a. Definition—necrosis peculiar to adipose tissue located around an acutely inflamed pancreas
   b. Mechanisms
      (1) Activation of pancreatic lipase and phospholipase (e.g., excess alcohol consumption)
         causes hydrolysis of triglycerides in fat cells with the release of fatty acids.
      (2) Calcium combines with the fatty acids to produce soap (saponification).
         • Dystrophic calcification commonly occurs in areas of saponification.
   c. Gross appearance
      • Chalky yellow-white deposits are primarily located in peripancreatic and omental adipose tissue (see Fig. 2-15H).
   d. Microscopic appearance
      • Pale outlines of fat cells are filled with basophilic staining calcified areas.

7. Traumatic fat necrosis
   a. Definition—necrosis that occurs in fatty tissue (e.g., female breast tissue, abdomen) as a result of blunt trauma or surgery
   b. Unlike pancreatic fat necrosis, it is not enzyme-mediated.

8. Fibrinoid necrosis
   a. Definition—necrosis that may occur in small muscular arteries, arterioles, venules, glomerular capillaries, valve leaflets, myocardium, and subcutaneous tissue
   b. Mechanism
      • Fibrinoid necrosis refers to the deposition of pink-staining proteinaceous material in damaged tissue.
   c. Examples—immune vasculitis (e.g., Henoch-Schönlein purpura), malignant hypertension, and rheumatic fever

B. Apoptosis
1. Definition—programmed, enzyme-mediated cell death
2. Normal and pathologic processes associated with apoptosis
   a. Normal destruction of cells during embryogenesis
      (1) Due to Sertoli cell synthesis of müllerian inhibitory substance (MIS), there is a loss of müllerian structures in a male fetus.
      (2) Other examples—normal removal of tissue between fingers and toes in the fetus, shaping of the inner ear, and cardiac morphogenesis
   b. Shrinkage of hormone-dependent tissue after withdrawal of the hormone
      (1) Sudden withdrawal of estrogen and progesterone in the menstrual cycle is the signal for apoptosis of endometrial gland cells leading to menses.
      (2) Removal of stimulating hormones (e.g., thyroid-stimulating hormone [TSH], adrenocorticotropic hormone [ACTH], follicle-stimulating hormone [FSH]) causes apoptosis-induced atrophy of the target tissue (e.g., thyroid, adrenal cortex, and ovarian follicles)
   c. Normal involution of the thymus with increasing age
   d. Death of tumor cells and virus infected cells by cytotoxic CD8 T cells
   e. Corticosteroid destruction of lymphocytes (B and T cells)
   f. Removal of acute inflammatory cells (e.g., neutrophils) from healing sites
   g. Damage to DNA by radiation, FRs, toxins
   h. Removal of misfolded proteins
### 2-16: Simplified schematic of apoptosis

Refer to the text for discussion. TNF, Tumor necrosis factor; TNFR, tumor necrosis factor receptor.

- **Examples**—amyloid, β-amyloid protein (Alzheimer disease), proteins in prion-related disease (Creutzfeldt-Jakob disease)
  - i. Defects in apoptosis can lead to development of cancer and autoimmune diseases.
  - j. Excessive apoptosis contributes to injury associated with several diseases—sepsis, acute myocardial infarction, ischemia, neurodegenerative diseases, and diabetes mellitus.

3. **Mechanisms** (Fig. 2-16)
   a. **Death receptor (extrinsic) pathway activation**
      1. Death receptors are cell surface receptors that transmit signals for apoptosis when they are bound by specific ligands (e.g., Fas, tumor necrosis factor [TNF]-α).
      2. TNF receptor 1 (TNFR1) is the best known death receptor and is activated by TNF-α.
      3. TNF-α is an important cytokine that is involved in systemic inflammation, autoimmune disease, and wasting (cachexia) in cancer.
      4. TNF-α is primarily produced by macrophages; however, it can also be produced by T cells, mast cells, endothelial cells, cardiac cells, and neurons, which explains its multiple disease associations.
      5. Activation of TNFR1 by TNF-α or other death receptors by their ligands (e.g., Fas) directly activates initiator caspases (caspase-8 and caspase-10) in the cytosol.
      6. Initiator caspases, in turn, activate effector caspases (proteases and endonucleases), which mediate the execution phase of apoptosis leading to death of a cell (see later).
         - a. Proteases destroy the cytoskeleton.
         - b. Endonucleases act on the nucleus of the cell causing pyknosis (nuclear condensation) and fragmentation.
   b. **Intrinsic (mitochondrial) pathway activation**
      1. Intrinsic (mitochondrial) pathway is the most important pathway for initiating apoptosis.
      2. Unlike the death receptor (extrinsic) pathway of apoptosis, the mitochondrial pathway involves the release of sensors that lead to leakage of mitochondrial proteins (cytochrome c) followed by activation of the caspases.
      3. In order to understand the previous cascade of events, an understanding of the BCL family of genes is important.
   c. **BCL gene family and the intrinsic pathway**
      1. **BCL gene family** contains genes that are antiapoptotic (BCL-2 gene) and genes that are proapoptotic (BAX and BAK genes).
      2. **BCL-2 gene** is located on chromosome 18, and its protein product resides in the inner mitochondrial membrane.
         - **BCL-2** proteins maintain mitochondrial membrane integrity and prevent the leakage of mitochondrial proteins that can trigger apoptosis (e.g., cytochrome c).

---

**Defects in apoptosis** →
- cancer, autoimmune disease

**Extrinsic pathway of apoptosis**
- requires TNF-α
- TNFR1 is a death receptor activated by TNF-α
- TNF-α: produced by macrophages (main source); endothelial and cardiac cells, and neurons
- TNFR1 binding with TNF-α activates initiator caspases 8 and 10
- Caspases: initiator caspases activate effector caspases (proteases, endonucleases)

**Intrinsic pathway of apoptosis**
- most important of the two pathways
- BCL gene family:
  - antiapoptotic genes (BCL-2 gene)
  - antiapoptotic genes (BAX, BAK genes)
- BCL-2 gene:
  - antiapoptosis gene; protein maintains mitochondrial membrane integrity to prevent leakage of cytochrome c
2-17: Apoptosis in acute viral hepatitis. There is swelling of the hepatocytes (dysfunctional Na⁺/K⁺-ATPase pump) and scattered inflammatory cells in areas of necrosis. The arrow shows a clear space, within which is a shrunken, eosinophilic staining apoptotic cell with a pyknotic nucleus. The open space at the top of the slide is a cross section of a central venule. (From MacSween R, Burt A, Portmann B, Ishak K, Scheuer P, Anthony P: Pathology of the Liver, 4th ed, London, Churchill Livingstone, 2002, p. 317, Fig. 7-4.)

<table>
<thead>
<tr>
<th>TABLE 2-4 Cell Necrosis Compared with Apoptosis</th>
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<tbody>
<tr>
<td>FEATURE</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>General</td>
</tr>
<tr>
<td>Size of cell</td>
</tr>
<tr>
<td>Enzymes involved</td>
</tr>
<tr>
<td>Genes involved</td>
</tr>
<tr>
<td>Role</td>
</tr>
</tbody>
</table>

(3) Damage to DNA, misfolded proteins, FR damage, viral infections, and other injurious events activate sensor genes in the BCL-2 gene family that release proteins that activate the proapoptotic genes (BAX and BAK).

(a) Activation of BAX and BAK genes produces protein products that form channels in the mitochondrial membrane that cause leakage of cytochrome c into the cytosol.

(b) Cytochrome c complexes with another protein leading to activation of an initiator caspase (caspase-9), which in turn activates effector caspases (proteases, endonucleases) that mediate the execution phase of apoptosis.

d. Execution phase of apoptosis

(1) Proteases destroy the cytoskeleton of the cell and endonucleases destroy the nucleus of the cell.

(2) Cytoplasmic buds begin to form on the cell membrane.

• Buds contain nuclear fragments, mitochondria, and other organelles.

(3) Cytoplasmic buds break off and form apoptotic bodies.

(4) Apoptotic bodies are phagocytosed by neighboring cells or macrophages.

4. Microscopic appearance

a. Cell detaches from neighboring cells

b. Apoptotic cells have deeply eosinophilic-staining cytoplasm with the hematoxylin-eosin stain (Fig. 2-17).

c. Nucleus is pyknotic, fragmented, or absent.

d. Inflammatory infiltrate is absent or minimal.

5. Table 2-4 compares cell necrosis with apoptosis.
**BOX 2-1 Clinical Enzymology**

**Enzymes** are protein catalysts of biological origin that increase the rate of chemical reactions without themselves being consumed or structurally altered. **Isoenzymes** (isoenzymes) are multiple forms of the same enzyme that differ in stereotypical, biochemical, and immunological properties (e.g., lactate dehydrogenase isoenzymes L1–L5; creatine kinase isoenzymes MM, MB, and BB). Measurement of individual isoenzymes is frequently more specific in identifying a disease than is total enzyme activity (e.g., CK-MB isoenzyme in identifying an acute myocardial infarction). **Isoforms** are subtypes of the individual isoenzymes (e.g., CK-MM isoforms).

Enzymes distribute in cell membranes (e.g., alkaline phosphatase), endoplasmic reticulum (e.g., \(\gamma\)-glutamyltransferase), lysosomes (e.g., muramidase), zymogen (e.g., amylase), cytoplasm (e.g., alanine aminotransferase, a transaminase), and mitochondria (e.g., aspartate aminotransferase, a transaminase).

Factors influencing the release of enzymes into body fluids include disruption or damage to the cell membrane (e.g., alanine aminotransferase, CK), increased synthesis owing to regeneration of injured cells (e.g., alkaline phosphatase), and enzyme induction in the smooth endoplasmic reticulum by drugs (e.g., alcohol and its effect on increasing \(\gamma\)-glutamyltransferase synthesis).

The amount of enzyme released into body fluids depends on the amount of tissue injury, the rate of diffusion out of the damaged cell, and the overall rate of catabolism or clearance of the enzyme. The following table lists important enzymes that are increased in tissue injury.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Diagnostic Use</th>
</tr>
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<tbody>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>Marker of diffuse liver cell necrosis (e.g., viral hepatitis)</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial enzyme preferentially increased in alcohol-induced liver disease</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>Marker of diffuse liver cell necrosis (e.g., viral hepatitis)</td>
</tr>
<tr>
<td></td>
<td>More specific for liver cell necrosis than AST</td>
</tr>
<tr>
<td>Creatine kinase MB (CK-MB)</td>
<td>Isoenzyme increased in acute myocardial infarction or myocarditis</td>
</tr>
<tr>
<td>Amylase and lipase</td>
<td>Marker enzymes for acute pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Lipase more specific than amylase for pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Amylase also increased in salivary gland inflammation (e.g., mumps)</td>
</tr>
</tbody>
</table>

**C. Pyroptosis**

1. **Definition**—proinflammatory programmed cell death that is different than apoptosis
   - Pyroptosis involves caspase-1, which differs from the caspases active in apoptosis (refer to **Chapter 4**).

2. Important role in the host defense system for fighting off microbial pathogens.
   - a. It occurs in monocytes, macrophages, and dendritic cells infected with certain types of microbial pathogens.
   - b. Microbial pathogens that may be killed by pyroptosis include *Salmonella typhimurium*, *Shigella flexneri*, *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Candida albicans*, adenovirus, and influenza virus.

3. Overwhelming activation of caspase-1 has also been implicated in the pathogenesis of several diseases that are **not** related to infectious stimuli, including:
   - Myocardial infarction (MI), neurodegenerative diseases, inflammatory bowel disease (IBD), cerebral ischemia, and endotoxic shock

**D. Enzyme markers of cell death (Box 2-1)**
I. Acute Inflammation (AI)

A. Definition of AI

1. Definition—transient and early response to injury
2. Characterized by the release of numerous chemical mediators
3. Leads to stereotypic small vessel and leukocyte responses
4. Not a synonym for infection

B. Cardinal signs of AI (Fig. 3-1)

1. Rubor (redness) and calor (heat)
   - Due to histamine-mediated vasodilation of arterioles
2. Tumor (swelling)
   a. Due to a histamine-mediated increase in venular permeability
   b. Synonymous with edema, which refers to increased fluid in the interstitial space
3. Dolor (pain)
   - Prostaglandin E\(_2\) (PGE\(_2\)) sensitizes specialized nerve endings to the effects of bradykinin and other pain mediators.
4. Functio laesa (loss of function)

C. Stimuli for AI

1. Infections (e.g., bacterial or viral)
2. Immune reactions (e.g., reaction to a bee sting)
3. Other stimuli include:
   - Tissue necrosis (e.g., acute myocardial infarction), trauma, radiation, burns, and foreign bodies (e.g., glass, splinter)

D. Sequential vascular events in AI

1. Vasocnstriction of arterioles
   - Due to a neurogenic reflex that lasts only a few seconds
2. Vasodilation of arterioles
   a. Histamine and other vasodilators (e.g., nitric oxide) relax vascular smooth muscle, causing increased blood flow.
      - Histamine is released from mast cells located in interstitial tissue around the small vessels (Fig. 3-2).
   b. Increased blood flow due to vasodilation of arterioles increases hydrostatic pressure (HP) in venule lumens.
3. Increased permeability of venules
   a. Histamine and other mediators contract endothelial cells in venules, producing endothelial gaps exposing bare basement membrane.
      - Tight junctions are simpler in venules than in arterioles.
   b. Transudate (fluid low in proteins and cells) moves through the intact venular basement membrane into interstitial tissue because of the increased HP.
4. Swelling of tissue (tumor, edema)
   - Net outflow of fluid from venules surpasses the capacity of lymphatics to remove fluid; hence, there is swelling of tissue.
5. Reduced blood flow
   - Reduced blood flow eventually occurs because of outflow of fluid into the interstitial tissue and increased uptake of fluid by lymphatics.
3-1: Signs of acute inflammation (AI). This neonate has the scalded child syndrome due to *Staphylococcus aureus*. Signs of AI that are present in the photograph include redness (rubor) and swelling (tumor). The infection is also associated with warm skin (calor) and pain (dolor). The yellow, raised areas are pustules filled with neutrophils. (From Bouloux, P: Self-Assessment Picture Tests Medicine, volume 3, London, Mosby-Wolfe, 1997, plate 75, Fig. 148.)

3-2: Electron micrograph of a tissue mast cell. The cytoplasmic granules contain histamine, eosinophil chemotactic factor, and other preformed inflammatory mediators. (Electron micrograph courtesy William Meek, Ph.D., Professor of Anatomy and Cell Biology, Oklahoma State University, Center for Health Sciences, Tulsa, Oklahoma.)

E. Sequential cellular events in AI (Fig. 3-3)

- Events described in the following section will emphasize neutrophil events in AI due to a bacterial infection (e.g., *Staphylococcus aureus*).

1. Neutrophils are the primary leukocytes in AI (Fig. 3-4).
   a. Peripheral blood neutrophils are subdivided into a circulating pool and a marginating pool (already adhering to endothelial cells).
   b. In the white population, ~50% are in the circulating pool and ~50% in the marginating pool; whereas in the black population, more neutrophils are in the marginating pool than the circulating pool.
      (1) Circulating pool is located in the central axial stream of blood flowing through small blood vessels.
      (2) In a complete blood cell count (CBC), the circulating pool is counted and evaluated in a peripheral blood smear.
   c. Neutrophil distribution in these pools can be altered by activating or inactivating neutrophil adhesion molecules (see later).

2. Margination of neutrophils
   a. In AI, RBCs aggregate into rouleaux ("stacks of coins") in the venules.
      - Caused by fibrinogen released from the liver
3-4: Acute inflammation. Histologic section of lung in bronchopneumonia showing sheets of neutrophils with multilobed nuclei. The pink staining material in between the neutrophils is an exudate, which is protein- and cell-rich fluid that is characteristic of AI. (From Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 182, Fig. 8-8.)

b. Rouleau mechanically forces neutrophils out of the central axial stream and pushes them to the periphery (called margination).
   - Caution: margination of neutrophils is not the same as the marginating pool of neutrophils.

3. Rolling of neutrophils
   a. Rolling occurs in venules and is due to expression of selectin adhesion molecules on neutrophils and venular endothelial cells.
   b. Selectins are carbohydrate-binding adhesion molecules.
   c. L-Selectin is located on leukocytes (e.g., neutrophils), whereas E-selectin and P-selectin are located on the surface of venular endothelial cells.
      1. P-selectin is produced in the Weibel-Palade bodies in venular endothelial cells.
      2. Weibel-Palade bodies are the "glue factory" of endothelial cells, because they synthesize P-selectin, an adhesion molecule for leukocytes, and von Willebrand factor, the adhesion molecule of the platelet (refer to Chapter 15).
   d. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) stimulate the expression of selectin ligands on the surface of neutrophils (L-selectin) and the expression of selectin molecules on the surface of venular endothelial cells (E-selectin, P-selectin; Fig. 3-5).
   e. Binding of circulating neutrophils to E-selectin and P-selectin on venular endothelial cells is weak and transient, causing them to "roll" (bind–detach, bind–detach) along the surface.

4. Firm adhesion in venules is due to neutrophil expression of β₂-integrins and venular endothelial cell expression of integrin adhesion molecules (ligands).
   a. Activation of neutrophil β₂-integrin (CD11a:CD18) adhesion molecules
      1. β₂-integrins are located on neutrophils and interact with corresponding ligands on venular endothelial cells (see later; see Fig. 3-5).
      2. β₂-Integrins on neutrophils are activated by C5a and leukotriene B₄ (LTB₄).
      3. Catecholamines and corticosteroids inhibit activation of these neutrophil adhesion molecules.
         a. Inhibition of neutrophil β₂-integrins, leads to an increase in the peripheral blood neutrophil count (called neutrophilic leukocytosis).
         b. This occurs because the normal marginating pool becomes part of the circulating pool, since they can no longer adhere to venular endothelium.
      4. Endotoxins enhance activation of neutrophil β₂-integrins.
         a. Enhanced activation of neutrophil β₂-integrins causes the total circulating neutrophil count to decrease (called neutropenia).
         b. This occurs because the normal circulating neutrophil pool becomes part of the marginating neutrophil pool.
   b. Activation of endothelial cell integrin adhesion molecules (ligands)
      1. IL-1 and TNF activate intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) on venular endothelial cells.
      2. Activated ICAM ligands bind to activated β₂-integrins on neutrophils causing them to firmly adhere to venular endothelium.
      3. Activated VCAM ligands firmly bind to activated β₂-integrins on eosinophils, monocytes, and lymphocytes.
3-5: The sequence of events in the migration of blood leukocytes to sites of infection. At sites of infection, macrophages and dendritic cells that have encountered microbes produce cytokines (e.g., tumor necrosis factor [TNF] and interleukin-1 [IL-1]) that activate the endothelial cells of nearby venules to produce selectins, ligands for integrins, and chemokines. Selectins mediate weak tethering and rolling of blood neutrophils on the endothelium; integrins mediate firm adhesion of neutrophils; and, chemokines activate the neutrophils and stimulate their migration through the endothelium to the site of infection. Blood monocytes and activated T lymphocytes use the same mechanisms to migrate to sites of infection. PECAM-1, Platelet-endothelial cell adhesion molecule-1.

(From Abbas A, Lichtman A: Basic Immunology Updated Edition: Function and Disorders of the Immune System, 3rd ed, Philadelphia, Saunders Elsevier, 2010, p 30, Fig. 2-7.)

c. Leukocyte adhesion deficiency (LAD) disorders
   (1) Autosomal recessive inheritance pattern
   (2) LAD type 1 is a deficiency of β2-integrin (CD11a:CD18).
      • CD stands for cluster of designation.
   (3) LAD type 2 is a deficiency of an endothelial cell selectin that normally binds neutrophils.
   (4) Clinical findings
      (a) First manifestation in either type is delayed separation of the umbilical cord (usually separates and sloughs by the end of the second postnatal week).
         • Neutrophil enzymes are important in cord separation; therefore in a histologic section of the surgically removed umbilical cord, no neutrophils would be seen adhering to venular endothelium or be seen in the interstitial tissue.
      (b) Additional clinical findings include severe gingivitis, poor wound healing, and peripheral blood neutrophilic leukocytosis (loss of the marginating pool).

5. Transmigration (diapedesis) of neutrophils
   a. Neutrophils moving along the venular endothelium dissolve the venular basement membrane (release type IV collagenase) exposed by previous histamine-mediated endothelial cell contraction and enter the interstitial tissue.
   b. Plasma-derived fluid rich in proteins and cells (i.e., exudate, pus) accumulates in the interstitial tissue.
   c. Functions of exudate
      (1) Dilutes bacterial toxins, if they are present
      (2) Provides opsonins (IgG, C3b) to assist in phagocytosis (see later)

6. Chemotaxis of neutrophils
   a. Neutrophils follow chemical gradients that lead to the infection site.
   b. Chemotactic mediators bind to neutrophil receptors.
      • Mediators include C5a, LTB4, bacterial products, and interleukin (IL)-8.
   c. Binding causes the release of calcium, which increases neutrophil motility.
7. Neutrophil phagocytosis (Fig. 3-6)
   a. Neutrophil phagocytosis is a multistep process, consisting of opsonization, ingestion, and killing.
   b. Neutrophil opsonization
      (1) Opsonins attach to bacteria (or foreign bodies).
         (a) Opsonins include IgG, the C3b fragment of complement, and other proteins (e.g., C-reactive protein).
         (b) Neutrophils have membrane receptors for IgG and C3b.
      (2) Opsonization enhances neutrophil recognition and attachment to bacteria (and foreign bodies).
      (3) Bruton agammaglobulinemia is an opsonization defect (refer to Chapter 4).
         • In Bruton agammaglobulinemia, pre–B cells cannot mature to B cells; therefore plasma cells, which are derived from B cells, cannot synthesize immunoglobulins (i.e., IgG).
   c. Neutrophil ingestion
      (1) Neutrophils engulf (phagocytose) and then trap bacteria in phagocytic vacuoles (phagosomes).
      (2) Primary lysosomes empty hydrolytic enzymes into phagocytic vacuoles producing phagolysosomes.
         • In Chédiak-Higashi syndrome (refer to Chapter 2), there is a defect in microtubule function, which prevents lysosomes from fusing with phagosomes to produce a phagolysosome.
   d. Neutrophil killing of bacteria/fungi by the $O_2$-dependent myeloperoxidase (MPO) system (see Fig. 3-6)
      (1) $O_2$-dependent MPO system only present in neutrophils and monocytes (not macrophages)
         • MPO is a neutrophil/monocyte lysosomal enzyme.
      (2) MPO system most potent microbialid system available to neutrophils and monocytes
      (3) Production of superoxide free radicals (FRs)
         • NADPH oxidase enzyme complex converts molecular $O_2$ to superoxide FRs, which releases energy called the respiratory, or oxidative, burst.
(4) Production of peroxide (H₂O₂)
   (a) Superoxide dismutase (SOD) converts O₂⁻ to H₂O₂.
   (b) Some peroxide is converted to hydroxyl FRs by iron via the Fenton reaction
       (refer to Chapter 2).
(5) Production of bleach (HOCl⁻)
   • MPO in the phagolysosome combines H₂O₂ with chloride (Cl⁻) to form
     hypochlorous FRs (HOCl⁻), which kill bacteria and some fungi.
(6) Chronic granulomatous disease (CGD) and MPO deficiency are examples of diseases
    that have a defect in the O₂-dependent MPO system.

**Chronic granulomatous disease (CGD)** is an X-linked recessive disorder (65% of cases) or
autosomal recessive disorder (30% of cases). The X-linked type is characterized by a mutation in
the CYBB gene that encodes for a component in the NADPH oxidase enzyme complex (PHOX
system) rendering the complex dysfunctional. The reduced production of O₂⁻ results in an absent
respiratory (oxidative) burst. Catalase-positive organisms that produce H₂O₂ (e.g., Staphylococcus
aureus, Nocardia asteroides, Serratia marcescens, Aspergillus species, and Candida species) are
ingested but not killed, because the catalase degrades the H₂O₂ produced by these pathogens.
Myeloperoxidase is present, but HOCl⁻ is not synthesized because of the absence of H₂O₂.
However, catalase-negative organisms (e.g., Streptococcus species) that produce H₂O₂ are ingested
and can be killed when myeloperoxidase combines H₂O₂ (derived from the bacteria) with Cl⁻ to
form HOCl⁻. Granulomatous inflammation occurs in tissue, because the neutrophils, which can
phagocytose bacteria but not kill most of them, are eventually replaced by cells associated with
chronic inflammation, mainly lymphocytes and macrophages. Macrophages fuse to form
multinucleated giant cells, which is a characteristic feature of granulomatous inflammation.
Patients with CGD have severe infections involving the lungs (pneumonia is the most common
infection), skin, visceral organs, and bones. The classic screening test for CGD is the nitroblue
tetrazolium (NBT) dye test. In this test, leukocytes in a test tube are incubated with the NBT dye,
which turns blue if superoxide FRs are present, indicating that the respiratory (oxidative) burst is
intact (considered to be a positive test). The NBT dye test is negative in the X-linked type of CGD
(NBT dye is not converted to a blue dye), because the NADPH oxidase enzyme complex is
dysfunctional. Because of its lack of sensitivity, the NBT dye test has essentially been replaced by a
more sensitive test involving oxidation of dihydrorhodamine to fluorescent rhodamine, which is
abnormal in both variants of CGD. Treatment of CGD involves prophylaxis and treatment of
infections and bone marrow transplantation.

**Myeloperoxidase (MPO) deficiency** differs from CGD in that both O₂⁻ and H₂O₂ are produced
(normal respiratory burst). However, the absence of MPO prevents synthesis of HOCl⁻.

(7) Deficiency of NADPH (e.g., glucose-6-phosphate dehydrogenase [G6PD] deficiency)
    produces a microbicidal defect.
   (a) NADPH is a cofactor for the NADPH oxidase complex; therefore absence of
       NADPH in G6PD deficiency, a hemolytic anemia (refer to Chapter 12), renders
       the enzyme nonfunctional.
   (b) Patients with G6PD deficiency are very susceptible to bacterial and certain
       fungal infections because the O₂-dependent MPO system is dysfunctional.
(8) **Table 3-1** compares CGD and MPO deficiency.

  e. Neutrophil killing of bacteria by O₂⁻-independent microbial systems
  (1) Oxygen-independent systems for killing bacteria refer to the release of lethal
      substances that are located in leukocyte granules.
  (2) Examples include:
       (a) Lactoferrin (present in neutrophil granules), which binds iron that is necessary
           for normal bacterial growth and reproduction
       (b) Major basic protein (MBP), an eosinophil product that is cytotoxic to
           helminths

**F. Chemical mediators in AI (Table 3-2)**
1. Chemical mediators derive from plasma, leukocytes, local tissue, and bacterial products.
   • Example—arachidonic acid mediators are released from membrane phospholipids in
     macrophages, endothelial cells, and platelets (Fig. 3-7)
2. Short half-lives (e.g., seconds to minutes)
3. May have local and systemic effects
   • Example—histamine may produce local signs of itching or systemic signs of anaphylaxis
### TABLE 3-1 Comparison of Chronic Granulomatous Disease and Myeloperoxidase Deficiency

<table>
<thead>
<tr>
<th></th>
<th>CHRONIC GRANULOMATOUS DISEASE</th>
<th>MYELOPEROXIDASE DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance pattern</td>
<td>X-linked recessive</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>NADPH oxidase</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Myeloperoxidase</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Respiratory burst</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Peroxide (H₂O₂)</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Bleach (HOCl)</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

### TABLE 3-2 Sources and Functions of Chemical Mediators

<table>
<thead>
<tr>
<th>MEDIATOR</th>
<th>SOURCE(S)</th>
<th>FUNCTION(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arachidonic Acid Metabolites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Macrophages, endothelial cells, platelets, PGH₂, major precursor of PGs and thromboxanes</td>
<td>PGE₂: vasodilation, pain, fever; PGI₂: vasodilation; inhibition of platelet aggregation</td>
</tr>
<tr>
<td>Thromboxane A₂</td>
<td>Platelets, converted from PGH₂ by thromboxane synthase</td>
<td>Vasoconstriction, platelet aggregation</td>
</tr>
<tr>
<td>Leukotrienes (LTs)</td>
<td>Leukocytes, converted from arachidonic acid by lipoxygenase-mediated hydroxylation</td>
<td>LTC₄, LTE₄: chemotaxis and activation of neutrophil adhesion molecules; LTC₄, LTD₄, LTE₄: vasoconstriction, increased venular permeability, bronchoconstriction; Zileuton inhibits 5-lipoxygenase: ↓synthesis LTE₄, LTD₄, LTE₄; Montelukast is a leukotriene receptor antagonist: ↓activity of LTC₄, LTD₄, LTE₄</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Product of kinin system activation by activated factor XII</td>
<td>Vasoconstriction, increased venular permeability, pain</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Leukocytes, endothelial cells</td>
<td>Activate neutrophils and stimulate their migration through the endothelium to the site of infection (chemotaxis; see Fig. 3-5)</td>
</tr>
<tr>
<td>Complement</td>
<td>Synthesized in liver (acute phase reactant)</td>
<td>C₃a, C₅a (anaphylatoxins): stimulate mast cell release of histamine; C₃b: opsonization; C₅a: activation of neutrophil adhesion molecules, chemotaxis; C₅–C₉ (membrane attack complex): cell lysis</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1, TNF</td>
<td>Macrophages (main source), monocytes, dendritic cells, endothelial cells</td>
<td>Initiate PGE₂ synthesis in the anterior hypothalamus, leading to production of fever; Activate endothelial cell adhesion molecules; TNF is a promoter of apoptosis (refer to Chapter 2)</td>
</tr>
<tr>
<td>IL-6</td>
<td></td>
<td>Primary cytokine responsible for increased liver synthesis of acute phase reactants (APRs), such as ferritin, coagulation factors (e.g., fibrinogen), and C-reactive protein</td>
</tr>
<tr>
<td>IL-8</td>
<td></td>
<td>Chemotaxis</td>
</tr>
<tr>
<td>Histamine</td>
<td>Mast cells (primary cell), platelets, enterochromaffin cells</td>
<td>Vasodilation, increased venular permeability</td>
</tr>
<tr>
<td>Nitric Oxide (NO)</td>
<td>Macrophages, endothelial cells, free radical gas released during conversion of arginine to citrulline by NO synthase</td>
<td>Vasodilation, bactericidal</td>
</tr>
</tbody>
</table>

*IL*, Interleukin; *PG*, prostaglandin; *TNF*, tumor necrosis factor.
Cell membrane phospholipids

<table>
<thead>
<tr>
<th>Linoleic acid (ω6)</th>
<th>Phospholipase A2 (Inhibited by corticosteroids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Lipoxygenase</td>
<td>Cyclooxygenase (Inhibited by aspirin/NSAIDs)</td>
</tr>
<tr>
<td></td>
<td>Receptors inhibited by montelukast</td>
</tr>
<tr>
<td>LTB4, LTC4, LTD4, LTE4</td>
<td>Thromboxane synthase (Platelet)</td>
</tr>
<tr>
<td></td>
<td>Prostacyclin synthase (Endothelial cell)</td>
</tr>
</tbody>
</table>

3-7: Simplified arachidonic acid metabolism. Arachidonic acid is released from membrane phospholipids by phospholipase A2. It is converted into prostaglandins (PGs) and thromboxane A2 (TXA2) in platelets from PGH2, the precursor prostaglandin, and into leukotrienes (LTs) by 5-lipoxygenase. Linoleic acid is an ω-6 essential fatty acid that is used to synthesize arachidonic acid. Phospholipase A2 is inhibited by corticosteroids; 5-lipoxygenase, by zileuton; receptors for LTC4, LTD4, LTE4, by montelukast; and cyclooxygenase (COX), by aspirin and NSAIDs. The COX-1 isofrom (not depicted) is constitutively expressed in various tissues, whereas the COX-2 isofrom (not depicted) is induced by various growth factors and proinflammatory cytokines. See text and Table 3-2 for further discussion. NSAIDs, nonsteroidal antiinflammatory drugs; PGII2, prostacyclin.

4. Mediators have diverse functions including:
   a. Vasodilation
      • Examples—histamine, nitric oxide, PGII2
   b. Vasoconstriction
      • Example—thromboxane A2 (TXA2)
   c. Increasing venular permeability
      • Examples—histamine, bradykinin, LTC4, LTD4, LTE4, C3a, and C5a (anaphylatoxins)
   d. Producing pain
      • Examples—PGE2, bradykinin
   e. Producing fever
      • Examples—PGE2, IL-1, TNF
   f. Chemotaxis
      • Examples—C5a, LTB4, IL-8
   g. Liver synthesis of acute phase reactants (APRs; e.g., fibrinogen, ferritin, complement, hepcidin, C-reactive protein)
      • IL-6 stimulates APR synthesis.

G. Types of AI
   1. Location, cause, and duration of inflammation determine the morphology of an inflammatory reaction.
   2. Purulent (suppurative) inflammation
      a. Definition—localized proliferation of pus-forming organisms, such as S. aureus (e.g., skin abscess; Fig. 3-8A).
      b. S. aureus contains coagulase, which cleaves fibrinogen into fibrin and traps bacteria and neutrophils, and therefore keeps the lesion localized.
   3. Fibrinous inflammation
      a. Definition—inflammation due to increased vessel permeability, with deposition of a fibrin-rich exudate on the surface of the tissue (see Fig. 3-8B).
      b. Commonly occurs on the serosal lining of the pericardium, peritoneum, or pleura.
         (1) Friction rub may be heard over the precordium in fibrinous pericarditis associated with a myocardial infarction or rheumatic fever (refer to Chapter 11).
         (2) Friction rub may be heard over the precordium or lungs in fibrinous pleuritis secondary to a pulmonary infarction or pneumonia (refer to Chapter 17).
         (3) Small bowel obstruction from serosal adhesions between other loops of bowel may occur from peritoneal irritation related to previous abdominal surgery (refer to Chapter 18).
   4. Serous inflammation
      a. Definition—inflammation with a thin, watery exudate that has an insufficient amount of fibrinogen to produce fibrin.
      b. Examples—blister in second degree burns, viral pleuritis

S. aureus: most common cause of a skin abscess

Fibrinous inflammation: exudate covering serosal surfaces (heart, lungs, peritoneum)

Serous inflammation: thin watery exudate; blister, viral pleuritis
I. Infection: most common cause of chronic inflammation

A. Definition of CI

• Prolonged inflammation (weeks to years) that most often results from persistence of an injury-causing agent

B. Causes of CI

1. Infection is the most common cause of CI.
   • Examples—tuberculosis (TB), leprosy, hepatitis C
2. Autoimmune disease
- Examples—rheumatoid arthritis, systemic lupus erythematosus
3. Inflammatory reaction to sterile agents
- Examples—silica, uric acid, silicone in breast implants

C. Morphology of CI
1. Cell types that define CI
   a. Monocytes and macrophages (key cells); lymphocytes, plasma cells, and eosinophils
      (Fig. 3-9).
   b. Transforming growth factor (TGF)-β is chemotactic for macrophages, lymphocytes, and fibroblasts.
2. Destruction of parenchyma
   - With loss of parenchyma, there is loss of functional tissue, with repair by fibrosis.
3. Formation of granulation tissue
   a. Definition—highly vascular tissue composed of blood vessels and activated fibroblasts
      (Fig. 3-10).
      - Blood vessels derive from preexisting blood vessels and de novo from endothelial cell
        precursors recruited from the bone marrow (i.e., angiogenesis).
        - Important growth factors in angiogenesis—vascular endothelial cell growth factor,
          fibroblast growth factor, epidermal growth factor, platelet derived growth factor,
          TGF-β
      - Vascularization is essential for normal wound healing.
      - Granulation tissue is precursor of scar tissue.
   b. Fibronectin is required for granulation tissue formation.
      - Cell adhesion glycoprotein located in the extracellular matrix (ECM)
        - It binds to collagen, fibrin, and cell surface receptors (e.g., integrins).
      - Chemotactic factor that attracts fibroblasts (synthesize collagen) and endothelial cells
        (form new blood vessels, angiogenesis)
4. Comparison table of AI and CI (Table 3-3)
5. Granulomatous inflammation
   a. Definition—specialized type of chronic inflammation
   b. Causes
      (1) Infections
         - Examples—TB and systemic fungal infection (e.g., histoplasmosis)
      (2) Noninfectious causes
         - Examples—sarcoidosis and Crohn disease
         - Sarcoidosis and Crohn disease have noncaseating granulomas (i.e., hard
           granulomas).
TABLE 3-3 Comparison of Acute and Chronic Inflammation

<table>
<thead>
<tr>
<th></th>
<th>ACUTE INFLAMMATION</th>
<th>CHRONIC INFLAMMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Microbial pathogens, trauma, burns</td>
<td>Persistent AI, foreign bodies (e.g., silicone, glass), autoimmune disease, certain types of infection (e.g., TB, leprosy)</td>
</tr>
<tr>
<td><strong>Primary cells involved</strong></td>
<td>Neutrophils</td>
<td>Monocytes/macrophages (key cells), B and T lymphocytes, plasma cells, fibroblasts</td>
</tr>
<tr>
<td><strong>Primary mediators</strong></td>
<td>Histamine (key mediator), prostaglandins, leukotrienes</td>
<td>Cytokines (e.g., IL-1), growth factors</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td>Present</td>
<td>Less prominent</td>
</tr>
<tr>
<td><strong>Scar tissue</strong></td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Few days</td>
<td>Weeks, months, years</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Complete resolution, progression to chronic inflammation, abscess formation</td>
<td>Scar tissue formation, disability, amyloidosis (refer to Chapter 4)</td>
</tr>
<tr>
<td><strong>Main immunoglobulin</strong></td>
<td>IgM</td>
<td>IgG</td>
</tr>
<tr>
<td><strong>SPE effect</strong></td>
<td>Mild hypoalbuminemia</td>
<td>Polyclonal gammopathy; greater degree of hypoalbuminemia</td>
</tr>
<tr>
<td><strong>Peripheral blood leukocyte response</strong></td>
<td>Neutrophilic leukocytosis</td>
<td>Monocytosis</td>
</tr>
</tbody>
</table>

AI, Acute inflammation; SPE, serum protein electrophoresis; TB, tuberculosis.

c. Morphology of a granuloma
   (1) Definition—pale, white nodule with or without central caseation
   (2) Usually well-circumscribed in tissue (see Fig. 2-15G)
   (3) Cell types in an infectious granuloma (e.g., tuberculosis)
      (a) Epithelioid cells (activated macrophages) and mononuclear cells consisting of
          CD4 helper T cells, specifically, T helpers cells of the Th1 type (memory T cells)
      (b) Multinucleated giant cells formed by fusion of epithelioid cells
         • Multinucleated giant cell nuclei are usually located at the periphery of the
           granuloma.
      (4) TNF-α is important in the formation and maintenance of TB and systemic fungal
          granulomas.
         (a) TNF-α and interferon-γ recruit cells for granuloma formation.
         (b) TNF-α inhibitors cause the breakdown of granulomas, which may result in
             dissemination of disease (e.g., disseminated TB).
      (5) Specifics concerning the sequence of events in the formation of a granuloma are fully
          discussed in Chapter 4 under type IV hypersensitivity reactions.

III. Tissue Repair

A. Factors involved in tissue repair
   1. Parenchymal cell regeneration
   2. Repair by connective tissue (fibrosis)

B. Parenchymal cell regeneration
   1. Cell regeneration depends on the ability of cells to replicate (refer to Chapter 2).
      a. Labile cells (e.g., stem cells in epidermis) and stable cells (e.g., fibroblasts) can replicate.
      b. Permanent cells cannot replicate.
         • Cardiac and striated muscle are replaced by scar tissue (fibrosis).
   2. Cell regeneration depends on factors that stimulate parenchymal cell division and migration.
      • Stimulatory factors include loss of tissue and production of growth factors (Table 3-4).
   3. Cell cycle (Fig. 3-11)
      a. Phases
         (1) G0 phase
         • Resting phase of stable parenchymal cells
         (2) G1 phase
            (a) Synthesis of RNA, protein, organelles, and cyclin D
            (b) Most variable phase in the cell cycle
         (3) S (synthesis) phase
            • Synthesis of DNA, RNA, and protein.
Table 3-4 Factors Involved in Tissue Repair

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>FUNCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular endothelial cell growth factor (VEGF)</td>
<td>Stimulates angiogenesis (embryonic angiogenesis, particularly in the heart), repair of tissue, cancer angiogenesis (stimulates from preexisting vessels)</td>
</tr>
<tr>
<td></td>
<td>Stimulation factors: TNF released by macrophages, hypoxia via hypoxia-inducible factor released by cells</td>
</tr>
<tr>
<td>Fibroblast growth factor (FGF)</td>
<td>Chemotactic for fibroblasts; stimulates keratinocyte migration, angiogenesis, wound contraction</td>
</tr>
<tr>
<td>Epidermal growth factor (EGF)</td>
<td>Chemotactic for neutrophils, macrophages, fibroblasts, endothelial cells (angiogenesis), smooth muscle cells (angiogenesis)</td>
</tr>
<tr>
<td>Platelet-derived growth factor (PDGF)</td>
<td>Chemotactic for macrophages, lymphocytes, fibroblasts, smooth muscle cells (angiogenesis)</td>
</tr>
<tr>
<td>Transforming growth factor-β (TGF-β)</td>
<td>Chemotactic for macrophages, lymphocytes, fibroblasts, smooth muscle cells (angiogenesis)</td>
</tr>
<tr>
<td>Interleukins (IL), Cytokines</td>
<td></td>
</tr>
<tr>
<td>IL-1</td>
<td>Stimulates synthesis of metalloproteinases (i.e., enzymes containing trace metals)</td>
</tr>
<tr>
<td></td>
<td>Stimulates synthesis and release of acute phase reactants from the liver</td>
</tr>
<tr>
<td>Tumor necrosis factor (TNF)</td>
<td>Activates macrophages; stimulates release of acute phase reactants</td>
</tr>
</tbody>
</table>

Table 3-4: Factors Involved in Tissue Repair

3-11: Cell cycle. The G1 to S phase is the most critical phase of the cell cycle and is controlled by the p53 and RB1 suppressor genes. Refer to a more detailed discussion in the text. (Modified from Burns E, Cave D: Rapid Review: Histology and Cell Biology, Philadelphia, Mosby, 2004, p 36, Fig. 3-5.)

(4) G2 phase
   • Synthesis of tubulin, which is required to produce microtubules in the mitotic spindle

(5) M (mitotic) phase
   • Two daughter cells are produced.

b. Regulation of the G1 checkpoint (G1 to S phase)
   (1) It is the most critical phase of the cell cycle.
      • Mutations in genes that enter the S phase are copied, hence the risk for cancer.
   (2) Control proteins include cyclin-dependent kinase 4 (Cdk4) and cyclin D
      (a) Growth factors activate nuclear transcribing proto-oncogenes (refer to Chapter 9) to produce cyclin D and Cdk4.
      (b) Cyclin D binds to Cdk4, forming a complex causing the cell to enter S phase.
   (3) Role of the RB1 (retinoblastoma) suppressor gene in the cell cycle
      (a) RB1 protein product arrests the cell in the G1 phase.
      (b) Cdk4 phosphorylates the RB1 protein, causing the cell to enter S phase.
         • If the RB1 protein is not phosphorylated, the cell remains in G1 phase.
4. Restoration to normal
   a. Requires preservation of the basement membrane
   b. Requires a relatively intact ECM (e.g., collagen, adhesive proteins)
      • Laminin, the key adhesion protein in the basement membrane, interacts with type IV collagen, cell surface receptors, and components in the ECM.

C. Repair by connective tissue (fibrosis)

1. Repair by connective tissue occurs when injury is severe or persistent.
   • Tissue in a third-degree burn cannot be restored to normal, owing to loss of skin, basement membrane, and connective tissue infrastructure.

2. Steps in connective tissue repair
   a. Requires neutrophil transmigration (refer to previous discussion) to liquefy injured tissue and then macrophage transmigration to remove the debris
   b. Requires formation of granulation tissue, the precursor of scar tissue (see earlier discussion)
      • Granulation tissue accumulates in the ECM and eventually produces dense fibrotic tissue (scar).
   c. Requires the initial production of type III collagen.

Collagen is the major fibrous component of connective tissue. Tropocollagen, the structural unit of collagen, is a triple helix of α-chains. Tropocollagen undergoes extensive posttranslational modification. Hydroxylation reactions in the rough endoplasmic reticulum convert proline to hydroxyproline and lysine to hydroxylysine. Ascorbic acid is required in these hydroxylation reactions. Hydroxyproline residues produce bonds that stabilize the triple helix in the tropocollagen molecule.

Hydroxylysine residues are oxidized to form an aldehyde residue that produces covalent cross-links at staggered intervals between adjacent tropocollagen molecules. Lysyl oxidase is a metalloproteinase enzyme containing copper that mediates the cross-linking of tropocollagen molecules. Cross-linking increases the overall tensile strength of collagen (also elastic tissue). Type I collagen in skin, bone, and tendons has the greatest tensile strength, whereas type III collagen, the initial collagen in wound repair, has poor tensile strength (fewer cross-links than type I collagen). Cross-linking of collagen and elastic tissue increases with age. This leads to decreased elasticity of skin, joints, and blood vessels, the latter resulting in vessel instability and rupture with minor trauma (e.g., senile purpura; refer to Chapter 15). Decreased cross-linking (e.g., vitamin C deficiency) reduces the tensile strength of collagen. In vitamin C deficiency, the structurally weakened collagen is responsible for a bleeding diathesis (e.g., bleeding into skin and joints) and poor wound healing (refer to Chapter 7). Ehlers-Danlos syndrome (EDS) consists of a group of mendelian disorders characterized by defects of type I and type III collagen synthesis and structure. Clinical findings include hypermobile joints, aortic dissection (most common cause of death), mitral valve prolapse, bleeding into the skin (ecchymoses), rupture of the bowel, and poor wound healing (Fig. 3-12).

d. Dense scar tissue produced from granulation tissue contains type III collagen that must be remodeled.
   (1) Remodeling increases the tensile strength of scar tissue.
   (2) Metalloproteinases (collagenases containing zinc) replace type III collagen with type I collagen, which increases the tensile strength of the wound to ~70% to 80% of the original after ~3 months.
      • Scar tissue after 3 months is primarily composed of acellular connective tissue that is devoid of inflammatory cells and adnexal structures and is surfaced by an intact epidermis.
3. Primary, secondary, and tertiary intention wound healing (Box 3-1, Fig. 3-13)
   a. Healing by primary intention
      (1) Definition—approximation of the wound edges by simple suturing, skin graft replacement, or flap closure
      (2) Reserved for the healing of clean surgical wounds
   b. Healing by secondary (spontaneous) intention
      (1) Definition—wound remains open and will close by reepithelialization, which results in contraction of the wound
      (2) Reserved for highly contaminated wounds

**BOX 3-1 Wound Healing by Primary, Secondary, Tertiary Intention**

**Primary Intention**
Day 1: Fibrin clot (hematoma) develops. Neutrophils infiltrate the wound margins (PDGF chemotactic to neutrophils). There is increased mitotic activity of basal cells of squamous epithelium in the apposing wound margins (FGF, EGF involved in keratinocyte migration).
Day 2: Squamous cells from apposing basal cell layers migrate under the fibrin clot and seal off the wound after 48 hours. Macrophages emigrate into the wound (PDGF, TGF-β chemotactic to macrophages).
Day 3: Granulation tissue begins to form (FGF, EGF, PDGF, TGF-β all involved in angiogenesis). Initial deposition of type III collagen by fibroblasts begins but does not bridge the incision site (FGF, PDGF, TGF-β chemotactic to fibroblasts). Macrophages replace neutrophils.
Days 4–6: Granulation tissue formation peaks, and collagen bridges the incision site.
Week 2: Collagen compresses blood vessels in fibrous tissue, resulting in reduced blood flow. Tensile strength is ~10%.
Month 1: Collagenase remodeling of the wound occurs (breaks peptide bonds), with degradation of type III collagen and replacement by type I collagen. Tensile strength increases, reaching ~80% within 3 months. Scar tissue is devoid of adnexal structures (e.g., hair, sweat glands) and inflammatory cells.

**Secondary Intention**
Typically, these wounds heal differently from primary intention:
- More intense inflammatory reaction than primary healing
- Increased amount of granulation tissue formation than in primary healing
- Wound contraction caused by increased numbers of myofibroblasts

**Tertiary Intention**
Contaminated wound is initially treated with débridement and antibiotics
Wound is surgically closed (suture, skin graft replacement, flap)

EGF, Epidermal growth factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor.
3° intention: contaminated wound debrided and treated with antibiotics before surgically closing the wound.

Infections: MCC of impaired wound healing

S. aureus: MC pathogen causing wound infection

MRSA: resistant to β-lactam antibiotics

Greatest risk factors for wound infection: disruption of skin and malnutrition

MRSA carriers: 20%–40% people carry MRSA in anterior nares

MRSA: majority CA-MRSA produce Panton-Valentine leukocidin (accelerates apoptosis neutrophils); possible progression to necrotizing fasciitis

Diabetes mellitus: ↓ blood flow, ↑ tissue glucose levels

Nutritional deficiencies: malnutrition, insufficient vitamin C and copper/zinc

Glucocorticoids: prevent scar formation

Keloids: raised scars extending beyond borders of original wound

Hypertrophic scar: raised scar remaining in confines of original wound

Normal scar: haphazard collagen bundles

Keloid/hypertrophic scar: collagen bundles in same plane as epidermis

Severe injury liver: regenerative nodules and fibrosis; danger of cirrhosis

c. Healing by tertiary intention (delayed primary closure)
   (1) Definition—contaminated wound that is initially treated with repeated débridement and topical or systemic antibiotics for several days to control infection
   (2) Once the wound is considered ready for closure, surgical intervention (i.e., suturing, skin graft replacement, flap) is performed.

D. Factors that impair healing
   1. Persistent infection
      a. Most common cause of impaired wound healing
      b. S. aureus is the most common pathogen.
      c. Nosocomial and community-acquired methicillin-resistant S. aureus (MRSA) wound infections are increasing.
         (1) MRSA strains are resistant to β-lactam antibiotics (e.g., penicillin, cephalosporin).
         (2) Disruption of skin and malnutrition are the greatest risk factors for wound infections.
      (3) Key to preventing wound infections is proper hand washing.
         • Approximately 20% to 40% of people are carriers of MRSA in their anterior nares.
      (4) Majority of community-acquired MRSA (CA-MRSA) infections produce the Panton-Valentine leukocidin.
         (a) Accelerates apoptosis of neutrophils; hence not many neutrophils are present in the wounds to phagocytose and destroy the bacteria
         (b) Causes the infection to progress to necrotizing fasciitis
      (5) Trimethoprim-sulfamethoxazole-DS (primary) or IV vancomycin (alternative) are frequently used in treating these infections.
   2. Diabetes mellitus
      • Increases susceptibility to infection by decreasing blood flow to tissue and increasing tissue levels of glucose.
   3. Nutritional deficiencies
      a. Decreased protein (e.g., malnutrition)
      b. Vitamin C deficiency (see earlier discussion)
      c. Trace metal deficiency
         (1) Copper deficiency leads to decreased cross-linking in collagen (also in elastic tissue).
         (2) Zinc deficiency leads to defects in removal of type III collagen in wound remodeling.
            • Type III collagen has decreased tensile strength, which impairs wound healing.
   4. Glucocorticoids
      a. Interfere with collagen formation and decrease tensile strength
      b. Useful clinically in preventing excessive scar formation
         (1) Dexamethasone is used along with antibiotics to prevent scar formation in bacterial meningitis.
         (2) Plastic surgeons inject high potency steroids into wounds to prevent excessive scar tissue formation.
   5. Keloids and hypertrophic scars
      a. Keloids are raised scars that grow beyond the borders of the original wound (Fig. 3-14).
         (1) Develop in 15% to 20% of African-Americans, Asians, and Hispanics; suggests a genetic predisposition
         (2) Often refractory to medical and surgical intervention
      b. Hypertrophic scars are raised scars that remain within the confines of the original wound.
         • Frequently regress spontaneously
      c. Normal scars have collagen bundles that are randomly arrayed (not all in the same direction), whereas keloids and hypertrophic scars have stretched collagen bundles arranged in the same plane as the epidermis.

E. Repair in other tissues
   1. Liver
      a. Mild injury (e.g., hepatitis A)
         • Regeneration of hepatocytes with restoration to normal is possible if the cytoarchitecture is intact.
      b. Severe or persistent injury (e.g., hepatitis C)
         (1) Regenerative nodules develop that show twinning of liver cell plates (two cells thick); a double line of hepatocytes is present, and nuclei seem to run in parallel (Fig. 3-15).
Inflammation and Repair

3-14: Keloid formation. Note the raised, thickened scar over the dorsum of the hand. Unlike a hypertrophic scar, keloids grow beyond the borders of the original wound and are refractive to medical and surgical therapy. (From Lookingbill D, Marks J: Principles of Dermatology, 3rd ed, Philadelphia, Saunders, 2000, p 115, Fig. 8-5A.)

3-15: Regenerative nodule in liver injury. Note the twinning of cell plates. The plates are thicker than normal, owing to division of hepatocytes. A double row of nuclei along each hepatocyte plate is evident. Portal triads are not present in regenerative nodules. (From MacSween R, Burt A, Portmann B, Ishak K, Scheuer P, Anthony P: Pathology of the Liver, 4th ed, London, Churchill Livingstone, 2002, p 590, Fig. 13.6.)

(2) Portal triads are not present in regenerative nodules.
(3) Increased fibrosis occurs around the regenerative nodules, which leads to cirrhosis of the liver if the injurious agent is not removed (refer to Chapter 19).

2. Lung
   a. Type II pneumocytes are the key repair cells of the lung.
   b. Replace damaged type I and type II pneumocytes and synthesize surfactant.

3. Brain
   a. Astrocytes proliferate in response to an injury (e.g., brain infarction).
      • Proliferation of astrocytes is called gliosis.
   b. Microglial cells (macrophages) are scavenger cells that remove debris (e.g., myelin).

4. Peripheral nerve transection
   a. Without innervation, muscle atrophies in ~15 days.
   b. After nerve transection, there is distal degeneration of the axon and myelin sheath and proximal axonal degeneration up to the next node of Ranvier.
      (1) Macrophages and Schwann cells phagocytose axonal/myelin debris.
      (2) Nerve cell body undergoes central chromatolysis.
         (a) Nerve cell body swells.
         (b) Nissl bodies (composed of rough endoplasmic reticulum and free ribosomes) disappear centrally, and the nucleus moves to the periphery.
   (3) Schwann cells proliferate in the distal stump.
   (4) Axonal sprouts develop in the proximal stump and extend distally using the Schwann cells for guidance.
   (5) Regenerated axon grows 2 to 3 mm/day.
   (6) Axon becomes remyelinated.
   (7) Muscle is eventually reinnervated.

5. Heart
   a. Cardiac muscle is permanent tissue.
   b. Damaged muscle is replaced by noncontractile scar tissue.

6. Skeletal muscle postexercise
   a. After exercise, there is damage to the sarcomeres in skeletal muscle.
      • A sarcomere is the basic unit of a muscle and gives skeletal muscle its striated appearance.
   b. Satellite cells are stem cells that repair and form new myofibers in sarcomeres that have been damaged by mechanical strain.

IV. Laboratory Findings Associated with Inflammation

A. Leukocyte alterations
   1. Acute inflammation (e.g., bacterial infection)
      a. Absolute neutrophilic leukocytosis (Fig. 3-16)

   Lung injury: type II pneumocyte is repair cell
   Brain injury: proliferation of astrocytes (gliosis) and microglial cells
   Wallerian degeneration: distal degeneration of the axon
   Peripheral nerve transection: Schwann cell is key in reinnervation
   Cardiac muscle damage: permanent tissue; repair by fibrosis
   Skeletal muscle postexercise: myofiber repair by satellite cells (muscle stem cells)
   Neutrophilic leukocytosis: cytokine release of postmitotic neutrophils from the bone marrow
(1) Various cytokines (e.g., IL-1) release the postmitotic pool of neutrophils (metamyelocytes, band neutrophils, segmented neutrophils) from the bone marrow causing an absolute (increased number) neutrophil leukocytosis.

(2) Presence of increased numbers of band neutrophils (usually >10%) and occasional metamyelocytes is called a left-shifted smear.

b. Toxic granulation
(1) Definition—presence of dark blue to purple primary granules in metamyelocytes, bands, and segmented neutrophils
   - Primary granules contain MPO and other chemicals and begin forming in the promyelocyte stage of neutrophil development.
(2) Due to an abnormality in the maturation of the primary granules
(3) Commonly occurs in severe inflammatory conditions (infectious and noninfectious).

c. Döhle bodies (Fig. 3-17)
(1) Definition—round to oval pale grayish-blue inclusions that are found in the periphery of the cytoplasm of neutrophils
   - Electron microscopy shows that they consist of stacks of rough endoplasmic reticulum.
(2) Commonly seen in conjunction with toxic granulation.

d. Increase in serum IgM
(1) In AI, serum IgM peaks in 7 to 10 days.
(2) Isotype switching (μ heavy chain replaced by γ heavy chain) in plasma cells converts IgM to IgG in 12 to 14 days.

2. Chronic inflammation (e.g., tuberculosis, rheumatoid arthritis)
   a. Absolute monocytes is the primary leukocyte finding in CI.
   b. Increased serum IgG is the key finding in CI.

3. Table 3-5 summarizes cells involved in inflammation (Fig. 3-18A to D).

4. Peripheral blood finding associated with corticosteroid therapy
   a. Absolute neutrophilic leukocytosis
   (1) Corticosteroids inhibit activation of neutrophil adhesion molecules (see previous discussion).
      - Marginating pool becomes part of the circulating pool.
   (2) They increase bone marrow release of neutrophils from the postmitotic pool (see Table 3-5).
TABLE 3-5 Summary of Leukocytes

<table>
<thead>
<tr>
<th>CELL</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
</table>
| Neutrophil (see Fig. 3-16) | Key cell in acute inflammation.  
Receptors for IgG and C3b: important in phagocytosis of opsonized bacteria.  
Bone marrow neutrophil pools  
Mitotic pool: myeloblasts, promyelocytes, myelocytes  
Postmitotic pool: metamyelocytes, band neutrophils (stabs), segmented neutrophils |

Peripheral blood neutrophil pools  
Marginating pool: adherent to the endothelium; account for ~50% of peripheral blood pool (greater percentage in black population)  
Circulating pool: measured in complete blood cell count (CBC); account for ~50% of peripheral blood pool (less percentage in black population)  
Causes neutrophilic leukocytosis  
Infections (e.g., acute appendicitis)  
Sterile inflammation with necrosis (e.g., acute myocardial infarction)  
Drugs inhibiting neutrophil adhesion molecules: corticosteroids, catecholamines |

Monocytes and macrophages (see Figs. 3-18A and 13-2D) | Key cells in chronic inflammation  
Receptors for IgG and C3b  
Monocytes become macrophages: fixed (e.g., macrophages in red pulp of spleen), wandering (e.g., alveolar macrophages)  
Functions: phagocytosis, process antigen, enhance host immunologic response (secrete cytokines like IL-1, TNF)  
Causes of monocytosis: chronic inflammation, autoimmune disease, malignancy |

B cells and T cells (see Figs. 3-18B and 13-2C) | Peripheral blood lymphocyte count: T cells 60%–70%, B cells 10%–20% of the total  
B cell function: become plasma cells when antigenically stimulated  
T cell functions: cellular immunity (type IV HSR), cytokines regulate B cells, defense against intracellular pathogens (e.g., tuberculosis)  
Causes of B/T lymphocytosis: chronic inflammation, autoimmunity, malignancy |

Plasma cells (see Figs. 3-9 and 3-18C) | Antibody producing cells derived from B cells  
Morphology: well-developed rough endoplasmic reticulum (site of protein synthesis). Bright blue cytoplasmic staining with Wright-Giemsa. Nucleus eccentrically located and has perinuclear clearing. |

Mast cells and basophils (see Fig. 3-2) | Release mediators in acute inflammation and allergic reactions (type I HSR)  
Receptors for IgE  
Early release reaction: release of preformed mediators (i.e., histamine, chemotactic factors, proteases)  
Late phase reaction: new synthesis and release of PGs and LTs, which enhance and prolong the acute inflammatory process. |

Eosinophils (see Figs. 3-18D and 13-2A) | Receptors for IgE  
Red granules contain crystalline material. Become Charcot-Leyden crystals in the sputum of asthmatics.  
Preformed chemical mediators in granules  
Major basic protein (MBP) kills invasive helminths.  
Histaminase neutralizes histamine.  
Arylsulfatase neutralizes leukotrienes.  
Functions  
Modulate type I HSR by neutralizing histamine and leukotrienes  
Destruction of invasive helminths: IgE receptors interact with IgE coating the surface of invasive helminths → antibody dependent cytotoxicity reaction (type II HSR) causes the release of MBP → kills helminths  
Causes of eosinophilia  
Type I HSR reactions: allergic rhinitis, bronchial asthma.  
Invasive helminthic infections excluding pinworms and adult worms in ascariasis, which are not invasive  
Dientamoeba fragilis: only protozoa that produces eosinophilia |

b. Decrease the number of B and T cells (T cells > B cells), eosinophils, and monocytes in the peripheral blood.  
• Corticosteroids are a signal for apoptosis of these cells.  

B. Erythrocyte sedimentation rate (ESR)  
1. Definition—rate (mm/hour) of settling of RBCs in a vertical tube  
2. Plasma factors and RBC factors that promote RBC rouleau formation (stack of coins appearance) increase the ESR (Fig. 3-19).
3-18: A, Macrophage. Note the phagocytic debris in the cytosol. B, Lymphocyte. Note the large nucleus and scant cytoplasm. C, Plasma cell. Note the extensive rough endoplasmic reticulum and dark globules of immunoglobulin in the cytosol. D, Eosinophil. Note the crystalline material in the cytosol that become Charcot-Leyden crystals in sputum of asthmatics. (A thru D courtesy William Meek, Ph.D., Professor and Vice Chairman of Anatomy and Cell Biology, Oklahoma State University, Center for Health Sciences, Tulsa, Oklahoma.)

3-19: Rouleaux formation. The arrows show red blood cells stacked like coins. This is due to an increase in fibrinogen and/or immunoglobulins. (From Goldman L, Ausiello D: Cecil’s Medicine, 23rd ed, Philadelphia, Saunders Elsevier, 2008, p 1175, Fig. 161-19.)

RBC rouleau (stack of coins appearance): ↑ESR; ↑fibrinogen/immunoglobulins

CRP: marker of necrosis and disease activity

a. Caused by an increase in fibrinogen (AI/CI) and/or immunoglobulins (e.g., multiple myeloma).
b. Abnormally shaped RBCs (e.g., sickle cells) do not produce rouleaux.

C. C-reactive protein (CRP)
   1. Acute-phase reactant
   2. Clinical usefulness
      a. Very sensitive indicator of necrosis associated with AI
         • Increase in inflammatory (disrupted) atherosclerotic plaques (useful tool in cardiology) and bacterial infections
      b. Excellent monitor of disease activity (e.g., rheumatoid arthritis).

D. Serum protein electrophoresis in inflammation
Proteins in serum are separated into individual fractions by serum protein electrophoresis (SPE; Fig. 3-20). Charged proteins placed in a buffered electrolyte solution will migrate toward one or the other electrode when a current is run through the solution. Proteins with the most negative charges (e.g., albumin) migrate to the positive pole, or anode, and those with the most positive charges (e.g., γ-globulins) remain at the negatively charged pole, or cathode. Beginning at the anode, proteins separate into five major peaks on cellulose acetate—albumin, followed by α₁-, α₂-, β-, and γ-globulins. The γ-globulins in decreasing order of concentration are IgG, IgA, and IgM (IgD and IgE are in very low concentration).

1. Acute inflammation (Fig. 3-21A)
   a. Slight decrease in serum albumin
      (1) Decrease in albumin is a catabolic effect of inflammation
      (2) Amino acids designated for the synthesis of albumin are used by the liver to synthesize APRs (e.g., fibrinogen, hepcidin).
   b. Normal γ-globulin peak
      • Serum IgM level is increased in AI; however, it does not reach a high enough concentration to alter the configuration of the γ-globulin peak.
2. Chronic inflammation (see Fig. 3-21B)
   a. There is a greater decrease in serum albumin associated with CI than with AI, owing to a prolonged synthesis of APRs.
   b. Increase in γ-globulins is due to the marked increase in synthesis of IgG in CI.
      • Diffuse increase in the γ-globulin peak in CI is due to many clones of benign plasma cells producing IgG, hence the term polyclonal gammopathy.
I. Cells of the Immune System

A. Innate (natural) immunity

1. Definition—nonadaptive immune response to microbial pathogens as well as nonmicrobial antigens that have been released during cell death or injury

2. Types of effector cells in innate immunity (Table 4-1)
   a. Phagocytic cells (e.g., neutrophils, macrophages, monocytes)
   b. Natural killer (NK) cells (large granular lymphocytes) and dendritic cells
   c. Microglial cells (macrophage of the central nervous system)
   d. Kupffer cells (macrophage of the liver)
   e. Eosinophils, mast cells
   f. Mucosal/endothelial cells

3. Toll-like receptors (TLRs) in innate immunity
   a. Definition—proteins expressed on activated effector cells (listed earlier)
   b. TLRs recognize nonself antigens (molecules) commonly shared by pathogens.
      • Examples of pathogen-associated molecular patterns (PAMPs) include endotoxin in gram-negative bacteria and peptidoglycan in gram-positive bacteria.
   c. PAMPs are not present on normal host effector cells.
   d. Interaction of TLRs on effector cells with PAMPs
      (1) Interaction initiates intracellular transmission of activating signals to nuclear transcription factors (NF), one of the most important being NFκB.
         • NFκB is the “master switch” to the nucleus for induction of inflammation.
      (2) Genes are encoded for mediator production.
      (3) Mediators are released into the serum or spinal fluid.
   d. Examples of innate immunity mediators (also refer to Chapter 3) include:
      (a) Nitric oxide (NO)
      (b) Cytokines (e.g., tumor necrosis factor, interleukin-1 [IL-1])
      (c) Adhesion molecules for neutrophils and monocytes (e.g., selectin)
      (d) Reactive oxygen species (ROS, e.g., peroxide)
      (e) Antimicrobial peptides (e.g., defensins)
      (f) Chemokines (activate neutrophil and monocyte chemotaxis)
      (g) Complement proteins and complement regulatory proteins (e.g., decay accelerating factor)
   e. TLRs also react with nonself antigens (molecules) released from damaged tissue, which are called DAMPs (damage-associated molecular patterns) or cell death–associated molecules.
      (1) Many DAMPs are derived from the plasma membrane, nucleus, endoplasmic reticulum, mitochondria, and cytosol.
         • Examples of DAMPs include heat shock protein, which is expressed in response to stresses such as heat, hypoxia, and toxic compounds; chromatin-associated HMGB1 (high-mobility group box 1), which is a major mediator of endotoxic shock; and purine metabolites (ATP, adenosine, uric acid).
### Table 4-1 Types of Effector Cells

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>DERIVATION</th>
<th>LOCATION</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural killer cells</td>
<td>Bone marrow stem cells</td>
<td>Peripheral blood (large granular lymphocytes; 10%-15%)</td>
<td>Recognize class I MHC proteins: they have Fc receptors for IgG; when activated, they release IFN-γ. Activate macrophage destruction of microbes via release of IFN-γ. Kill virus-infected and neoplastic cells via attachment to altered class I proteins or binding to IgG-coated target cells (ADCC; type II HSR).</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Conversion of monocytes into macrophages in connective tissue</td>
<td>Connective tissue; organs (e.g., alveoli, lymph node sinuses, spleen and liver, bone marrow)</td>
<td>Involved in phagocytosis and cytokine production. Act as APCs to T cells. Kill intracellular microbes (Mycobacteria, systemic fungi) after activation by IFN-γ released by activated CD4 T helper cells.</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>Bone marrow stem cells</td>
<td>Skin (Langerhans cells), sinuses of lymph nodes</td>
<td>Act as APCs to T cells in the paracortex of lymph nodes and B cell in the germinal follicles. Produce interferons and antiviral cytokines that inhibit infection and reproduction.</td>
</tr>
</tbody>
</table>

ADCC, Antibody-dependent cell-mediated cytotoxicity; APC, antigen-presenting cell; HSR, hypersensitivity reaction; IFN, interferon; IL, interleukin.

(2) DAMPs are recognized by TLRs, which causes the release of proinflammatory cytokines and chemokines.

4. Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)
   a. Definition—cytosolic receptors expressed predominantly in dendritic cells, monocytes, and macrophages that are important in recognizing PAMPs and DAMPs
      • NLRs function in concert with TLRs.
   b. Pathogens that activate NLRs include:
      • *Salmonella typhimurium, Shigella flexneri, Pseudomonas aeruginosa, Legionella pneumophila, Candida albicans*, and certain viruses (e.g., hepatitis C, adenovirus, influenza virus)
   c. DAMPs that activate NLRs are listed earlier.
   d. When NLRs are activated, they form multiprotein inflammasome complexes that facilitate activation of caspase-1 (refer to Chapter 2, discussion of pyroptosis), which in turn increases secretion of IL-1β and IL-18.
   e. When secreted in appropriate amounts, IL-1β and IL-18 have a beneficial role in inflammation by attracting immune cells to the site of infection.
   f. Overwhelming overproduction of IL-1β and IL-18 has been implicated in the pathogenesis of several diseases, including:
      1. Autoimmune disease (e.g., rheumatoid arthritis, multiple sclerosis), Crohn disease, gout, Alzheimer disease, metabolic syndrome, and atherosclerosis
      2. Antagonists of the IL-1β receptor (e.g., anakinra, a recombinant homolog of the human IL-1 receptor) have been used in treating some of the diseases just mentioned with excellent results.

5. Examples of noncellular innate immunity responses to infections
   a. Sequestration of iron in the liver and macrophages by hepcidin (refer to Chapter 12)
      1. Iron is essential for bacterial growth and reproduction.
      2. IL-6 increases synthesis and release of hepcidin by the liver.
      3. Hepcidin decreases iron reabsorption in the duodenum and also prevents iron release from macrophages in the bone marrow and other sites.

Hepcidin: keeps iron away from bacteria
b. Synthesis and release of acute phase reactants (APRs; refer to Chapter 3) by the liver
   (1) IL-6 is the most important cytokine causing liver synthesis and release of APRs.
   (2) Some APRs inhibit or destroy microbial pathogens; for example:
      (a) C-reactive protein (CRP) enhances opsonization.
      (b) Complement component C3b enhances opsonization.
      (c) Complement component C5a is chemotactic to neutrophils and mast cells.
      (d) Ferritin is a soluble iron-binding protein within macrophages (keeps iron away from bacteria).

c. Protective bacteria in the colon
   (1) Limit the dominance of pathogenic microbes (e.g., Clostridium difficile, Clostridium botulinum)
   (2) Compete for nutrients, which limits nutrients to nourish pathogenic microbes
   (3) Compete for receptors for binding to host cells
   (4) Activate host defenses

d. Human β-defensins
   (1) Definition—antimicrobial peptides produced by mucosal epithelial cells
   (2) Constitutive (continually transcribed) or inducible by tumor necrosis factor (TNF)-α
   (3) Functions include:
      (a) Attraction of neutrophils
      (b) Resistance to colonization of microbes to mucosal surfaces

e. Epithelial barriers
   • Skin and mucous membranes

f. Physiologic barriers
   (1) Fever inhibits viral and bacterial reproduction.
   (2) Interferon-γ (IFN-γ) activates macrophages, which cause the death of macrophage-processed Mycobacteria and systemic fungi.
   (3) IFN-α and IFN-β inhibit the growth of viruses.
   (4) Acid gastric pH inhibits bacterial growth.

g. Chemical barriers (refer to Chapter 3)
   • Chemotactic factors (e.g., C5a, leukotriene B₄), opsonization (e.g., C3b, IgG, C-reactive protein), O₂-dependent myeloperoxidase system

5. Examples of human diseases associated with mutations or dysfunction of TLRs include:
   a. Invasive meningococcal disease, recurrent invasive Streptococcus pneumoniae disease
   b. Gram-negative bacterial sepsis, Staphylococcus aureus sepsis
   c. Susceptibility to Salmonella infection
   d. Dissemination of Mycobacterium tuberculosis, lepromatous leprosy
   e. Recurrent otitis media, malaria, Legionella pneumophila infections, necrotizing enterocolitis in premature infants

B. Adaptive (acquired) immunity
1. Rather than recognizing PAMPs, as in innate immunity, antigens produced by microbial pathogens are recognized by B and T lymphocytes, which eliminate the microbial agents.
   2. B lymphocytes produce antibodies (i.e., humoral immune response).
      a. Antibodies are primarily directed against extracellular microbial pathogens.
      b. Naïve mature B cells begin to produce both immunoglobulin M (IgM) and IgD at birth.
         (1) Antigen-stimulated B cells may differentiate into IgM antibody-secreting cells, or via class (isotype) switching, they may produce IgG (begins at 3 months of age), IgE, or IgA.
         (2) Isotype switching to other Ig classes involves changes in the heavy chain locus in the constant region of the gene.
         (3) Isotype switching is induced by a combination of CD40 ligand-mediated signals and cytokines (e.g., IFN-γ for IgG, IL-4 for IgE, and transforming growth factor in mucosal tissues for IgA), which are modulated by CD4 helper T cells.
      c. Table 4-2 summarizes key information concerning B cells.

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The thin outer epidermis of skin and the thick dermis prevent invasion by microbial organisms. Sebum contains lactic acid and fatty acids, both of which reduce the pH of skin and inhibit bacterial growth.
3. T cells are primarily involved in cell-mediated immunity (CMI).
   a. Subdivided into CD4 helper and CD8 cytotoxic T cells
   b. Activated T cells eliminate microbial pathogens that reside within cells.
   c. Functions are summarized in Table 4-2.
4. Fig. 4-1 depicts humoral and cell-mediated immunity.

II. Major Histocompatibility Complex

A. Overview of the major histocompatibility complex (MHC)
1. Definition—located on the short arm of chromosome 6 and known collectively as the human leukocyte antigen (HLA) system
2. Coding for membrane-associated glycoproteins
   • Located on all nucleated cells and platelets with the exception of mature RBCs
3. Code for membrane-associated glycoproteins
4. HLA genes and their subtypes transmitted to children from their parents

B. Class I molecules
1. Encoded on three closely linked loci that are designated HLA-A, HLA-B, and HLA-C.
   a. Genes are codominantly expressed, meaning that genes encoding these molecules from both parental chromosomes are expressed (i.e., HLA-A molecules from both the mother and the father are produced; Fig. 4-2).
      1. In a family, the chance of a sibling having a 0-, 1-, or 2-haplootype HLA match with another sibling is 25%, 50%, and 25%, respectively.
      2. Parents are a 1-haplootype match.
   b. Gene products from these loci are present on all nucleated cells and platelets except mature RBCs.

CD4 and CD8 T lymphocytes: cell-mediated immunity
CMI: destroys intracellular microbial pathogens
MHC: HLA system; chromosome 6
MHC: located on all nucleated cells/platelets except RBCs
HLA genes: transmitted from parents to child
Class I molecules: HLA-A, HLA-B, and HLA-C loci
HLA-A, HLA-B, and HLA-C loci: molecules codominantly expressed
4-1: Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that primarily target extracellular microbes. In cell-mediated immunity, T lymphocytes either activate macrophages to destroy phagocytosed microbes or kill infected cells. (From Abbas A, Lichtman A: Basic Immunology: Function and Disorders of the Immune System, 3rd ed, Philadelphia, Saunders Elsevier, 2011, p 5, Fig. 1-4.)

4-2: Chance of a sibling with haplotype $A_2B_2C_2D_2/A_4B_4C_4D_4$ having a 0-, 1-, or 2-haplotype match in a family in which the father is haplotype $A_3B_3C_3D_3/A_4B_4C_4D_4$ and the mother is haplotype $A_1B_1C_1D_1/A_2B_2C_2D_2$. Note that there is a 25% chance for a 2-haplotype match ($A_2B_2C_2D_2/A_4B_4C_4D_4$), a 25% chance for a 0-haplotype match ($A_1B_1C_1D_1/A_3B_3C_3D_3$), and a 50% chance of a 1-haplotype match ($A_2B_2C_2D_2/A_3B_3C_3D_3$) or ($A_1B_1C_1D_1/A_4B_4C_4D_4$). Using a parent as a transplant donor is considered a 1-haplotype match. An identical 2-haplotype match is rarely achieved owing to crossing over between the individual loci during meiosis when homologous chromosomes align with each other. (From Goljan EF: Star Series: Pathology, Philadelphia, Saunders, 1998, p 63, Fig. 4-2.)
Table 4-3  HLA Associations with Disease

<table>
<thead>
<tr>
<th>HLA ANTIGEN</th>
<th>DISEASE ASSOCIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A3</td>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>Ankylosing spondylitis, Reiter syndrome, postinfectious arthritis</td>
</tr>
<tr>
<td>HLA-BW47</td>
<td>21-Hydroxylase deficiency (also lack HLA-B8)</td>
</tr>
<tr>
<td>HLA-DR2</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>HLA-DR3</td>
<td>Graves disease, systemic lupus erythematosus</td>
</tr>
<tr>
<td>HLA-DR5</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>HLA-DR3/DR4</td>
<td>Type I diabetes mellitus</td>
</tr>
<tr>
<td>HLA-DR4</td>
<td>Hashimoto thyroiditis</td>
</tr>
<tr>
<td>HLA-DQ2</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>HLA-DQ81</td>
<td>Guillain-Barré syndrome</td>
</tr>
</tbody>
</table>

2. Class I molecules are recognized by CD8 T cells and NK cells.
   a. Altered class I antigens (e.g., virus-infected cell, neoplastic cell) lead to destruction of the cell.
   b. Rule of 8: CD8 T cells recognize class I molecules (8 × 1 = 8)

C. Class II molecules
1. Class II molecules are encoded in the HLA-D region, which is subdivided into HLA-DP, HLA-DQ, and HLA-DR subregions.
2. Class II molecules are present on antigen-presenting cells (APCs).
   • APCs include B cells, macrophages, and dendritic cells.
3. Class II molecules are recognized by CD4 T cells.
   • Rule of 8: CD4 T cells recognize class II molecules (4 × 2 = 8)

D. HLA associations with disease (Table 4-3)

E. Applications of HLA testing
1. Transplantation workup (see later)
   • Close matches of HLA Class I (A, B) typing and HLA Class II (DR) typing on the patient and each potential donor increase the chance of graft survival.
2. Determining disease risk
   • Example—individuals positive for HLA-B27 have an increased risk for developing ankylosing spondylitis (90-fold relative risk).

F. Developing antibodies against HLA antigens
1. Pregnancy
   • Caused by fetal-maternal bleeds during the pregnancy or delivery (refer to Chapter 16).
2. Blood transfusion
   • From the presence of HLA antigens on platelets and leukocytes that are in the transfused blood
3. Previous transplantation
   • Antibodies develop against organ HLA antigens that are foreign to the recipient.

III. Hypersensitivity Reactions (HSRs)
A. Type I (immediate) hypersensitivity (Table 4-4)
1. Definition—IgE antibody–mediated activation of mast cells or basophils (effector cells) followed by an acute inflammatory reaction
2. IgE antibody production (sensitization; Fig. 4-3)
   a. Allergens (e.g., pollen, drugs) are first processed by APCs (macrophages or dendritic cells).
   b. APCs then release IL-4, which induces naïve CD4 T cells to become CD4 T_{h}2 cells that produce IL-4 and IL-5.
      (1) IL-4 causes plasma cells to switch from IgM to IgE synthesis.
      (2) IL-5 stimulates the production and activation of eosinophils.
3. Mast cell activation (reexposure)
   a. Allergen-specific IgE antibodies are bound to mast cells.
   b. Allergens cross-link IgE antibodies specific for the allergen on mast cell membranes.
   c. IgE triggering causes an early phase reaction that is characterized by mast cell release of preformed mediators.
### Table 4-4 Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>REACTION</th>
<th>PATHOGENESIS</th>
<th>EXAMPLES</th>
</tr>
</thead>
</table>
| Type I IgE-dependent activation of mast cells/basophils | Atopic hypersensitivity: usually strong familial predisposition; occurs in 40% of people in United States; exposure to allergens (usually environmental—dust [mite], food [peanuts, shellfish], animal dander, insect envenomations [bees, wasps, hornets]; transferable by serum Drug hypersensitivity: e.g., penicillin; usually a metabolic intermediate rather than the intact drug causes the reaction Transfusion reaction in IgA immunodeficiency: some cases are associated with IgE antibodies directed against IgA from previous exposure to IgA in blood products; antigen-specific IgE antibodies are located on mast cells and presence of IgA causes mast cell release of histamine; most cases of anaphylaxis have an unknown mechanism Clinical findings: rhinitis and conjunctivitis (stuffy nose and itchy eyes; usually seasonal); asthma (wheezing); dermatitis (eczema; refer to Chapter 25, Fig. 25-9B); hives (urticaria; refer to Chapter 25; Fig. 25-9P); vomiting and diarrhea (various foods); systemic anaphylaxis (shock, widespread edema, hives, wheezing [bronchospasm], inspiratory stridor; refer to Chapter 17) if laryngeal edema is present; most likely to be associated with bee envenomation, penicillin, and peanuts | **Reactions** Type I IgE-dependent reaction Pathogenesis: Rapid Review Pathology Atopic hypersensitivity: usually strong familial predisposition; occurs in 40% of people in United States; exposure to allergens (usually environmental—dust [mite], food [peanuts, shellfish], animal dander, insect envenomations [bees, wasps, hornets]; transferable by serum Drug hypersensitivity: e.g., penicillin; usually a metabolic intermediate rather than the intact drug causes the reaction Transfusion reaction in IgA immunodeficiency: some cases are associated with IgE antibodies directed against IgA from previous exposure to IgA in blood products; antigen-specific IgE antibodies are located on mast cells and presence of IgA causes mast cell release of histamine; most cases of anaphylaxis have an unknown mechanism Clinical findings: rhinitis and conjunctivitis (stuffy nose and itchy eyes; usually seasonal); asthma (wheezing); dermatitis (eczema; refer to Chapter 25, Fig. 25-9B); hives (urticaria; refer to Chapter 25; Fig. 25-9P); vomiting and diarrhea (various foods); systemic anaphylaxis (shock, widespread edema, hives, wheezing [bronchospasm], inspiratory stridor; refer to Chapter 17) if laryngeal edema is present; most likely to be associated with bee envenomation, penicillin, and peanuts **Type II Antibody-dependent reactions** Complement-dependent antibody reactions Cell lysis (IgM mediated): Example: anti-I cold antibodies (IgM) in immune hemolytic anemia due to Mycoplasma pneumoniae (refer to Chapter 12) Example: transfusion of group A blood (contains anti-B-IgM antibodies) into a group B individual (refer to Chapter 16) Cell lysis (IgG mediated): IgG attaches to the basement membrane/matrix → activates the complement system → C5a is produced (chemotactic factor) → recruitment of neutrophils/monocytes recruited to the activation site → enzymes, reactive oxygen species released → tissue is damaged (see Fig. 4-5) Example: Goodpasture syndrome with IgG antibodies directed against pulmonary and glomerular capillary basement membranes (refer to Chapter 20) Example: when IgG antibodies are directed against the proton pump in parietal cells (refer to Chapter 12) Example: acute rheumatic fever, in which IgG antibodies similar to those present in the M protein of certain strains of Group A Streptococcus pyogenes are directed against antigens in the human heart, skin, brain, subcutaneous tissue, and joints (refer to Chapter 11) Phagocytosis (see Fig. 4-6A): Example: IgG (IgG 1) immune hemolytic anemia, in which RBCs coated by IgG and/or C3b are phagocytosed and destroyed by splenic macrophages (refer to Chapter 12) Example: ABO hemolytic disease of the newborn, in which a Group O mother has anti-A,B-IgG antibodies that cross the placenta and attach to fetal blood group A or B red blood cells that are phagocytosed by splenic macrophages (have receptors for IgG) and destroyed (refer to Chapter 16) Example: penicillin attaches to RBCs → IgG antibodies are made against penicillin → splenic macrophages phagocytose the RBCs Example: idiopathic thrombocytopenic purpura, in which platelets have IgG antibodies directed against their GpIIb IIIa fibrinogen receptors and are removed by splenic macrophages Complement-independent antibody reactions Antibody (IgG)-dependent cell-mediated cytotoxicity: Example: natural killer cell destruction of antibody-coated neoplastic and virus-infected cells Antibody (IgE)-dependent cell-mediated cytotoxicity: Example: helminth in tissue is coated by IgE antibodies → eosinophil IgE receptors attach to the IgE → eosinophils release major basic protein, which kills the helminth Antibodies directed against cell surface receptors: Example: in Graves disease (see Fig. 4-6B schematic on left), IgG antibodies directed against thyroid hormone receptors stimulate the gland to synthesize excessive amounts of thyroid hormone (refer to Chapter 23) Example: in myasthenia gravis (see Fig. 4-6B schematic on right), IgG autoantibodies directed against acetylcholine receptors impair the function of the receptor (refer to Chapter 24) Type III Deposition of antigen-antibody complexes Systemic lupus erythematosus (DNA–anti-DNA immunocomplexes; discussed later in the chapter) Arthus reaction: farmer’s lung, involving thermophilic actinomyces in moldy hay Serum sickness: systemic immunocomplex disease due to injection of a foreign serum (e.g., horse antihyermocytoglobulin), chronic exposure to an antigen (e.g., hepatitis B surface antigen leading to polyarteritis nodosa [refer to Chapter 10], drugs [e.g., penicillin]; typical clinical findings include fever, rash (urticaria, maculopapular), arthralgia, painful lymphadenopathy, splenomegaly, and eosinophilia a few days or weeks after exposure to the previously listed antigens Poststreptococcal glomerulonephritis, type IV diffuse proliferative glomerulonephritis in SLE, IgA glomerulonephropathy, membranous glomerulonephropathy (refer to Chapter 20); polyarteritis nodosa (refer to Chapter 10); subacute bacterial endocarditis (refer to Chapter 11) Type IV Antibody-independent T cell–mediated reactions Coiled helper T granulomas associated with systemic fungal (e.g., Histoplasma, Coccidioides) and mycobacterial infections (Mycobacterium tuberculosis, MAI, Mycobacterium leprae); tuberculin reaction; chronic asthma (eosinophil-mediated); multiple sclerosis; rheumatoid arthritis; type IV DM; allergic contact dermatitis (e.g., poison ivy/oak/sumac [see Fig. 25-9D]), chemicals (e.g., nickel, formaldehyde), topical antibiotics (e.g., neomycin, sulfonamides), rubber gloves; graft rejection CBG-mediated cytotoxicity: destruction of virus-infected, neoplastic, or donor graft cells

*DM, Diabetes mellitus; Gp, glycoprotein; MAI, Mycobacterium avium-intracellulare; MS, multiple sclerosis; RBC, red blood cell; SLE, systemic lupus erythematosus.*
The sequence of events in type I (immediate) hypersensitivity reactions. Type I hypersensitivity reactions are initiated by the introduction of an allergen, which stimulates CD4 T\(_{h2}\) reactions and immunoglobulin E (IgE) production. IgE binds to Fc receptors on mast cells, and subsequent exposure to the allergen leads to cross-linking of subjacent IgE antibodies, causing activation of the mast cells and the release of preformed mediators (e.g., histamine) that produce an inflammatory reaction. Not shown in the schematic is the late phase reaction, in which the mast cells synthesize and release prostaglandins, leukotrienes, and platelet-activating factor, which prolong the inflammatory response. (From Abbas A, Lichtman A: Basic Immunology: Function and Disorders of the Immune System, 3rd ed, Philadelphia, Saunders Elsevier, 2011, p 208, Fig. 11-2.)

(1) Preformed chemicals include histamine, eosinophil chemotactic factor, and serotonin.
   (a) Histamine increases smooth muscle contraction, produces vasodilation, and increases capillary permeability.
   (b) Eosinophils release histaminase to neutralize histamine and arylsulfatase to neutralize histamine and leukotrienes.
   (c) Serotonin produces vasodilation, increases capillary permeability, and constricts smooth muscle.
(2) Early phase chemicals produce tissue swelling and constriction of bronchi and terminal bronchioles.

   d. Late phase reaction
   (1) Mast cells synthesize (de novo) and release prostaglandins (PGs), leukotrienes (LTs), and platelet-activating factor (PAF).
   (2) These inflammatory mediators prolong the acute inflammatory reaction initiated by the early phase chemical mediators.
      (a) LTs increase vascular permeability, cause bronchospasm (contract smooth muscle cells), and recruit neutrophils, eosinophils, and monocytes.
      (b) PGD\(_2\) increases mucus production and bronchospasm.
      (c) PAF has similar functions as leukotrienes and prostaglandins and also causes platelet aggregation.
4. Tests used to evaluate type I hypersensitivity
   a. Scratch (prick) test (best overall sensitivity)
      • Positive response is a histamine-mediated wheal and flare reaction after introduction
        of an allergen into the skin (Fig. 4-4).
   b. Radioallergosorbent test (RAST)
      • Detects IgE antibodies in serum that were made against specific allergens.

5. Clinical examples of type I hypersensitivity reactions (see Table 4-4)

**4-4:** Scratch (prick) test showing a classic wheal and flare reaction against antigens in flour and wheat. The patient was a baker. (From Fitzpatrick JE, Morelli JG: Dermatology Secrets Plus, 4th ed, Philadelphia, Elsevier Mosby, 2011, p 65, Fig. 9.2.)

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**Desensitization therapy** in atopic individuals involves repeated injections of increasingly greater amounts of allergen, resulting in production of IgG antibodies that attach to allergens and prevent them from binding to mast cells.

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**B. Type II (cytotoxic) hypersensitivity**

1. Definition—an antibody is directed against antigens on the cell membrane or in the extracellular matrix

2. Complement-dependent reactions
   a. Cell lysis (IgM-mediated)
      (1) Antibody (IgM) directed against antigen on the cell membrane activates the complement system, leading to lysis of the cell by the membrane attack complex (MAC; C5-C9).
      (2) Clinical examples are discussed in Table 4-4.
   b. Cell lysis (IgG-mediated) (Fig. 4-5)
      (1) IgG attaches to the basement membrane/matrix → activates complement system → C5a is produced (chemotactic factor) → neutrophils/monocytes recruited to activation site → enzymes and reactive oxygen species are released → tissue is damaged
      (2) Clinical examples discussed in Table 4-4
   c. Phagocytosis (Fig. 4-6A)
      (1) Fixed macrophages (e.g., in spleen or liver) phagocytose hematopoietic cells (e.g., RBCs) coated by IgG antibodies and/or complement (C3b).
      (2) Clinical examples are discussed in Table 4-4.

3. Complement-independent reactions
   a. Antibody (IgG)-dependent cell-mediated cytotoxicity (ADCC)
      (1) Cells are coated by IgG → leukocytes (neutrophils, monocyte, NK cells) bind to IgG → activated cells release inflammatory mediators and cause cell lysis
      (2) Clinical examples discussed in Table 4-4.
4-5: **Type II hypersensitivity** with complement-mediated antibody destruction of antigens in tissue. Antibodies (other than immunoglobulin E [IgE]) may cause tissue injury and disease by binding directly to their target antigens on cells and extracellular matrix. An example of this mechanism occurs in Goodpasture syndrome, in which IgG antibodies are directed against antigens in collagen within the basement membrane of pulmonary and glomerular capillaries. (Modified from Abbas A, Lichtman A: Basic Immunology: Function and Disorders of the Immune System, 3rd ed, Philadelphia, Saunders Elsevier, 2011, p 214, Fig. 11-7.)

4-6: **Type II hypersensitivity reactions.** Antibodies may cause disease by opsonizing cells (e.g., RBCs) for phagocytosis (A). In addition, they may produce disease by interfering with normal cellular functions, such as hormone receptor signaling (B). In Graves disease, stimulatory IgG antibodies against the TSH receptor cause increased function. In myasthenia gravis, blocking antibodies prevent acetylcholine binding to acetylcholine receptors. TSH, Thyroid-stimulating hormone. (Modified from Abbas A, Lichtman A: Basic Immunology: Function and Disorders of the Immune System, 3rd ed, Philadelphia, Saunders Elsevier, 2011, p 215, Fig. 11-8.)
4-7: **Type III hypersensitivity.** Immunocomplexes in the lumen of the blood vessel attach to the vessel wall. They locally activate the complement system, leading to recruitment of inflammatory cells (e.g., neutrophils) that damage the tissue. The result is small vessel vasculitis. *(Modified from Abbas A, Lichtman A: Basic Immunology: Function and Disorders of the Immune System, 3rd ed, Philadelphia, Saunders Elsevier, 2011, p 214, Fig. 11-7.)*

**Immune complex–mediated tissue injury**

- **Mechanism of antibody deposition**
  - Circulating immune complexes
  - Blood vessel
  - Site of deposition of immune complexes
  - Complement- and Fc receptor–mediated recruitment and activation of inflammatory cells
  - Neutrophils
  - Vasculitis

- **Effector mechanisms of tissue injury**

b. Antibody (IgE)-dependent cell-mediated cytotoxicity
  - Clinical example discussed in **Table 4-4.**

c. Antibody directed against cell surface receptors (see **Fig. 4-6B**)
  1. IgG autoantibodies directed against cell surface receptors impair function of the receptor or stimulate function.
  2. Clinical examples discussed in **Table 4-4.**

4. Some tests that are used to evaluate type II hypersensitivity disease
   a. Direct Coombs test detects IgG and/or C3b or C3d (degradation product of C3b) attached to RBCs (see **Fig. 12-27A**).
   b. The indirect Coombs test detects antibodies in serum against antigens on the surface of RBCs (e.g., anti-D; see **Fig. 12-27B**).

C. **Type III (immunocomplex) hypersensitivity**

1. Definition—circulating antigen-antibody complexes (e.g., DNA [antigen]-anti-DNA [antibody]) produce acute inflammation with damage to tissue at the site of their deposition

2. Formation of immunocomplexes (ICs) and mechanism of tissue damage (**Fig. 4-7**)
   a. First exposure to antigen leads to the synthesis of antibodies.
   b. Second exposure leads to formation of antigen-antibody complexes that circulate in the blood; they are usually deposited in vessel walls and, less commonly, in extravascular sites (e.g., joints, basement membrane of skin).
     - In normal circumstances, ICs are cleared from the blood by the reticuloendothelial system, but occasionally they persist and deposit in tissues.
   c. When ICs deposit in tissue, they activate the complement system and produce C5a, which attracts neutrophils that ultimately damage the tissue.

3. Arthus reaction
   a. Definition—formation of immunocomplexes at a localized site
   b. Example—exposure of an antigen into the skin in a previously sensitized animal that has circulating antibodies against that antigen leads to localized immunocomplex formation in vessel walls at the site of the injection; subsequently, neutrophil infiltration and fibrinoid necrosis are induced, resulting in vessel thrombosis and ischemic ulceration
   c. Example—farmer's lung is a hypersensitivity pneumonitis due to exposure to thermophilic actinomycetes growing in moldy hay
     - Antibodies are formed and upon reexposure to moldy hay, ICs are produced that produce acute inflammation in the lungs (hypersensitivity pneumonitis; refer to **Chapter 17**).

4. Clinical examples are listed in **Table 4-4.**

5. Immunofluorescent staining of tissue biopsies identifies IC deposition (e.g., ICs in glomeruli in certain types of glomerulonephritis; refer to **Chapter 20**).
D. Type IV hypersensitivity

1. Definition—antibody-independent, T cell–mediated type of immunity (i.e., CMI)
   a. Initiated by antigen activated T cells of the CD4 and/or CD8 subtype.
   b. Inflammatory response is sometimes “delayed” (hours or days; delayed-type hypersensitivity [DTH]).

2. Functions of CMI
   a. Controls infections caused by viruses, fungi, helminths, mycobacteria, and intracellular bacterial pathogens
   b. Important in certain types of graft rejection
   c. Involved in tumor surveillance

3. Types of CMI reactions
   a. DTH is a type of CMI that primarily involves CD4 T cells (killing Mycobacterium tuberculosis will be used as an example) (Fig. 4-8A).
      (1) First phase of DTH involves processing of antigen (tubercle bacilli in this case) by APCs (alveolar macrophages in this case).
      (2) After processing the tubercle bacilli, alveolar macrophages interact with class II antigen sites on naïve CD4 T cells located in lymph nodes, causing them to secrete IL-2, which stimulates proliferation of the CD4 T cells.
      (3) Alveolar macrophages secrete IL-12 causing the naïve CD4 T cells to differentiate into CD4 T_{H1} subset cells, or memory cells.
      (4) CD4 T_{H1} cells produce interferon (IFN)-γ, which further amplifies the conversion of naïve cells to memory T cells.
      (5) Some of these memory cells remain in lymph nodes, whereas others enter the circulation where they remain in the memory pool for long periods.
      (6) If the CD4 T_{H1} cells are reexposed to the tubercle bacilli at a later date via interaction with macrophages, they release IFN-γ which activates the macrophages, thus enhancing their ability to phagocytose and kill the bacteria.
         (a) Activated alveolar macrophages change their appearance and are called epithelioid cells, because they resemble epithelial cells when stained with hematoxylin–eosin.
         (b) With the help of TNF, the epithelioid cells aggregate and are surrounded by a collagen of CD4 T cells producing a granuloma.
            • Activated alveolar macrophages frequently fuse to form multinucleated giant cells (see Fig. 2-15G).
         (c) Because cell walls of tubercle bacilli (also systemic fungi) have a high lipid content, the central portion of the granulomas are composed of granular material representing caseous necrosis (refer to Chapter 2).

4-8: Type IV hypersensitivity (HSR). Type IV HSR responses are mediated by T cells through three different pathways. In the first pathway (A), CD4 T_{H1} subset cells recognize soluble antigens and release interferon-γ (IFN-γ) to activate effector cells, in this case macrophages (Mφ), and cause tissue injury. In the second pathway (B), eosinophils pre-dominate in T_{H2}-mediated responses. CD4 T_{H2} cells produce cytokines to recruit and activate eosinophils, leading to their degranulation and tissue injury. In the third pathway (C), damage is caused directly by CD8 T cells, which interact with altered class I antigens on neoplastic, virus-infected, or donor graft cells. The activated CD8 T cells release chemicals that lyse the cells. IL, Interleukin. (Modified from Goldman L, Schafer AI: Cecil's Medicine, 24th ed, Philadelphia, Saunders Elsevier, 2012, p 230, Fig. 46-4.)
erythema, edema, dermatitis: pruritus, lymphocytes circulating effector T cytokine release from
Elicitation phase: TH1 subset memory cells
Induction phase: CD4 T
CD4 T
PPD reaction dependent on CMI competency
CMI diminished in elderly/people with AIDS
CD4 T
subsets: cytokines recruit neutrophils/monocytes
DTH chronic asthma: macrophages, CD4 T
subsets, eosinophils
Allergic contact dermatitis: poison ivy, topical drugs, rubber, chemicals
Induction phase: CD4 T
Elicitation phase: cytokine release from circulating effector T lymphocytes
Allergic contact dermatitis: pruritus, erythema, edema, vesicles
CD8 T cell cytotoxicity: T cells interact with altered class I antigen sites
CD8 T cell cytotoxicity: lysis of neoplastic, virus-infected, donor graft cells
Patch test: confirm allergic contact dermatitis

7. Tuberculin skin reaction is another example of DTH involving CD4 T cells
   a. Purified protein derivative (PPD) containing antigen of the tubercle bacillus is injected intradermally.
   b. Langerhans cells in skin (dendritic cell in the skin) phagocytose and process the PPD.
   c. Langerhans cells, via their class II antigen sites, react with CD4 T
      memory cells causing activation of both cells and the release of cytokines that
      produce the inflammatory reaction, which reaches its peak in 24 to 72 hours.
   d. Extent of the inflammatory reaction depends on the competency of CMI in the
      patient.
      - For example, in elderly patients, CMI is diminished; hence the degree of
        erythematous swelling of skin is less than in a young person.
      - Another example is a person with AIDS, in which CMI is markedly
        diminished due to loss of CD4 T cells.

b. In DTH, if the APCs release IL-1, IL-6, and IL-23 along with transforming growth factor
   (TGF)-β, naïve CD4 T cells differentiate into Th17 subset cells.
   1. Activation of this subset causes the release of cytokines that recruit neutrophils and
      monocytes to the inflammatory site.
   2. This is important as a host defense against extracellular bacterial pathogens
      (neutrophils) and fungi (neutrophils and monocytes) as well as in immune-mediated
      chronic inflammatory reactions that are often involved in autoimmune disease
      (monocytes).

   c. DTH involving macrophages, CD4 T
      subset cells, and eosinophils in chronic asthma
         (see Fig. 4-8B)
         1. Macrophages process antigen, and via their class II antigen sites they interact with
            CD4 T
            subset cells, causing the release of eotaxin, IL-4, and IL-5.
         2. IL-5 and eotaxin recruit and activate eosinophils (effector cells), which release MBP,
            cationic protein, and LTs.
         3. Inflammatory reaction results in epithelial cell damage in the lungs,
            bronchoconstriction, and the potential for chronic, irreversible airway disease (refer
            to Chapter 17).

d. DTH in allergic contact dermatitis
   1. Allergic contact dermatitis occurs after sensitization to plant materials (e.g., poison
      ivy, poison oak, poison sumac; refer to Chapter 25), topically applied drugs (e.g.,
      neomycin, benzocaine, sulfonamides), rubber gloves, or chemicals (e.g., nickel,
      formaldehyde).
   2. Pathophysiology of contact dermatitis involves induction (i.e., sensitization) and
      elicitation phases.
      a. In the induction phase, small molecules (usually <500 daltons) of the allergen
         enter the skin and bind to carrier proteins located on Langerhans cells in the
         suprabasilar area of skin.
      b. Langerhans cells take up and process the antigen.
      c. Processed antigen is presented to CD4 T cells, which differentiate in regional
         lymph nodes into CD4 T
         subset memory cells, whereas others become effector CD8 T memory lymphocytes that enter into the circulation.
      d. In the elicitation phase, reexposure to the antigen leads to penetration of the
         skin, uptake and processing by Langerhans cells, and presentation of processed
         antigen to the circulating effector CD8 T memory lymphocytes.
      e. Activation of these lymphocytes causes the release of cytokines that mediate the
         characteristic inflammatory response of allergic contact dermatitis, usually
         within hours of reexposure.
      f. Key clinical findings include pruritus, erythema, edema, and the formation of
         vesicles containing clear fluid.

e. CD8 T cell–mediated cytotoxicity
   1. CD8 cytotoxic T cells interact with altered class I antigens on neoplastic, virus-
      infected, or donor graft cells, which causes cell lysis (see Fig. 4-8C).
   2. Activated cytotoxic CD8 T cells lyse the cells by releasing preformed perforins and
      granzymes that are normally stored in granules in the cells.

4. Tests used to evaluate type IV hypersensitivity disorders
   a. Patch test to confirm allergic contact dermatitis
      - Example—a suspected allergen (e.g., nickel) is placed on an adhesive patch and is
        applied to the skin to see if a skin reaction occurs.
TABLE 4-5 Some Types of Transplants

<table>
<thead>
<tr>
<th>TYPE OF TRANSPLANT</th>
<th>COMMENTS</th>
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</table>
| Cornea            | Best allograft survival rate  
Risk of transmission of Creutzfeldt-Jakob disease |
| Kidney            | Better survival with kidney from living donor than from cadaver |
| Bone marrow       | Graft contains pluripotential cells that repopulate host stem cells  
Host assumes donor ABO group  
Danger of graft-versus-host reaction and cytomegalovirus infection |

b. Tests used to evaluate whether CMI is intact include:
1. Quantitative count of T cells
2. Various mitogenic assays (functional test of T lymphocytes)
3. Erythematous skin reaction to Candida

C. Lack of a response to mitogenic assays and/or lack of a skin response to Candida is called anergy.

5. Additional clinical examples are listed in Table 4-4.

IV. Transplantation Immunology

A. Factors that enhance graft viability
1. ABO blood group compatibility between recipients and donors.
   • Most important requirement.

   • People must have previous exposure to blood products to develop anti-HLA cytotoxic antibodies.

3. Close matches of HLA-A, HLA-B, HLA-C (minor importance), and HLA-DR loci between recipients and donors.

4. Chance of a sibling in a family having another sibling with a 0-, 1-, or 2-haplotype match is illustrated in Figure 4-2.

B. Types of grafts
1. Autograft (i.e., self to self)
   a. Autografts have the best survival rate.
   b. Example—skin graft from one part of the body to another part

2. Syngeneic graft (isograft)
   • Syngeneic grafts are grafts between identical twins.

3. Allograft
   a. Allografts are grafts between genetically different individuals of the same species.
   b. Examples of allografts (Table 4-5)

4. Xenograft
   a. Graft between two different species
   b. Example—transplant of a pig's heart valve into a human

C. Types of rejection
1. Transplantation rejection involves a humoral and/or cell-mediated host response against MHC antigens in the donor graft.

2. Hyperacute rejection (Fig. 4-9A)
   a. Definition—irreversible reaction that occurs within minutes or hours after transplantation
   b. Pathogenesis of hyperacute rejection
      (1) Type II HSR involving immunoglobulin and complement that targets the endothelium of small vessels (e.g., arterioles, capillaries), which causes a neutrophilic infiltrate with fibrinoid necrosis and vessel thrombosis, leading to infarction
      • Since the reaction is irreversible, the organ must be removed.
      (2) Causes of hyperacute rejections include:
         (a) ABO incompatibility (e.g., blood group A person inadvertently receives a kidney from a blood group B person)
         (b) Reaction between preformed anti-HLA antibodies in the recipient directed against similar donor HLA antigens located in the vascular endothelium
      (3) These reactions are uncommon because of pretransplantation screening (see later).

3. Acute rejection
   a. Most common transplant rejection.
   b. Definition—reversible reaction that occurs usually within days or weeks after a transplantation

Anergy: no response to mitogenic assays and/or skin response to Candida

ABO blood group compatibility: most important requirement for successful transplantation

Graft viability: absence preformed anti-HLA antibodies; close matches for HLA-A, HLA-B, HLA–C-DR loci

Autograft: self to self; best survival rate

Syngeneic graft: graft between identical twins

Allograft: graft between genetically different individuals of same species

Xenograft: graft between two different species

Hyperacute rejection: irreversible, type II

Hyperacute rejection: small vessel vasculitis; neutrophils, fibrinoid necrosis, thrombosis

Causes: ABO mismatch, anti-HLA antibodies

Acute rejection: most common (MC) rejection; reversible; type II/IV
4-9: Mechanisms of graft rejection. A, In hyperacute rejection, preformed antibodies (e.g., ABO, HLA) react with alloantigens on the vascular endothelium of the graft, activate complement, and trigger rapid intravascular thrombosis and necrosis of the vessel wall. B, In acute rejection, CD8+ T lymphocytes reactive with alloantigens (foreign antigen) on graft endothelial cells and parenchymal cells cause damage to these cell types. Inflammation of the endothelium is called endotheliitis. Alloreactive antibodies also may contribute to vascular injury. C, In chronic rejection, there is vessel atherosclerosis and cytokine-induced proliferation of smooth muscle cells, leading to luminal occlusion. Not shown in the figure is cytokine stimulation of fibroblasts leading to interstitial fibrosis. This type of rejection is most likely a chronic delayed-type hypersensitivity (DTH) reaction to alloantigens in the vessel wall. APC, Antigen processing cell. (From Abbas A, Lichtman A: Basic Immunology: Function and Disorders of the Immune System, 3rd ed, Philadelphia, Saunders Elsevier, 2011, p 201, Fig. 10-9.)

Key cell in donor graft: dendritic cells with classes I and II MHC molecules

Acute rejection type IV: endotheliitis, interstitial tissue inflammation

Key cells in recipient in type IV: CD4 T cell (DTH), CD8 T cell (cytotoxicity)

(1) Combination of a type IV and type II hypersensitivity reaction

(2) Dendritic cells in the donor organ (e.g., kidney) have high levels of both class I and class II MHC molecules.

(a) Recipient CD4 T cells react against the class II MHC molecules on the donor dendritic cells and differentiate into subset T11 memory cells and, in some cases, T117 effector cells.

- Cytokines (e.g., IFN-γ) from activated memory CD4 T cells activate macrophages, which attack both vessels (endotheliitis) and parenchymal cells, leading to extensive tissue damage (type IV DTH).

(b) Recipient CD8 T cells react against class I MHC molecules on the donor dendritic cells and also attack class I MHC molecules (Fig. 4-9B) in parenchymal cells and endothelial cells (type IV cell-mediated cytotoxicity HSR).

- Alloreactive antibodies also contribute to vascular damage (type II HSR).

(c) Histologic sections of the donor organ reveal large numbers of mononuclear cells (CD4 and CD8 T cells, macrophages) in the interstitium.
(3) The antibody-mediated type II HSR part of acute rejection is caused by the recipient having preexisting alloreactive antibodies (e.g., anti-HLA antibodies) against donor HLA antigens.

- Alloreactive antibodies are antibodies from one individual that will recognize antigens on cells or tissues of another, genetically nonidentical individual.
  (a) These antibodies activate complement, leading to small vessel damage (endothelitis; shown in Fig. 4-9B).
  (b) Small vessel damage is characterized by a necrotizing vasculitis with neutrophils, fibrinoid necrosis, and vessel thrombosis.
  (c) Presence of complement component C4d (degradation product of C4 activation) in the inflammatory tissue indicates that the complement system has been activated and is an important marker that there is a humoral component in the rejection.

(4) If the vasculitis is less acute or the graft is rejected months or years later, the vessels are more likely to show intimal thickening with proliferation of smooth muscle cells reminiscent of atherosclerosis.

c. Acute rejection is potentially reversible with immunosuppressive therapy (e.g., cyclosporine).

- Immunosuppressive therapy is associated with an increased risk of cervical squamous cell cancer, malignant lymphoma, and squamous cell carcinoma of the skin (most common cancer).

4. Chronic rejection (see Fig. 4-9C)

a. Definition—irreversible reaction that occurs over months to years, usually in patients that have survived acute rejection due to immunosuppression therapy

b. Pathogenesis of chronic rejection

- Most likely due to a chronic delayed hypersensitivity reaction involving CD4 T cells

c. Main pathologic findings related to release of cytokines by CD4 T cells include:

  (1) Atherosclerosis of vascular endothelium related to proliferation of intimal smooth muscle cells (refer to Chapter 10)
  (2) Smooth muscle proliferation leading to obliteration of vascular lumens
  (3) Proliferation of fibroblasts leading to intimal fibrosis with atrophy of epithelial tissue (not shown in Fig. 4-9C; e.g., renal tubular cell atrophy, glomerular sclerosis)

(4) Interstitial infiltrate of plasma cells and eosinophils

5. Infections associated with transplantation

a. Cytomegalovirus (CMV) is the most common infection in transplant recipients.

- CD8 T cells are important in controlling latent CMV infections (prevent them from recurring).

b. In solid organ transplantation, Candida is the most common infection, followed by Aspergillus.

c. In bone marrow transplantation, Aspergillus is the most common infection followed by Candida.

6. Transplantation tests

a. Identify class I and II proteins on recipient and donor lymphocytes.

  (1) React donor and recipient lymphocytes against a battery of anti-HLA antibodies.

  - This testing is very important in kidney and bone marrow transplants.

  (2) In some solid organ transplants, HLA matching is not performed (e.g., heart, lung, liver transplants).

b. Test for compatibility of the recipient and donor class II antigens

  (1) Recipient and donor lymphocytes mixed together in culture

  (2) Compatible if the lymphocytes do not undergo mitosis

  (3) Incompatible if lymphocytes undergo mitosis

c. Lymphocyte cross-match

  (1) Screen for the presence of anti-HLA antibodies in the recipient.

  (2) Recipient serum is reacted against donor lymphocytes.

  (3) Lysis of donor lymphocytes indicates that the recipient has anti-HLA antibodies against certain HLA antigens on donor lymphocytes.

  (4) Absence of lysis of donor lymphocytes indicates that the recipient does not have anti-HLA antibodies against HLA antigens on donor lymphocytes.

  (5) This testing is important in preventing hyperacute rejections.
4-10: Acute graft versus host reaction (GVH). In GVH, donor T cells attack host MHC antigens located in the skin, bile duct epithelium, and mucosa of the gastrointestinal tract. (Modified from Actor JK: Elsevier’s Integrated Immunology and Microbiology, Philadelphia, Mosby, 2007, p 68, Fig. 8-4.)

D. Graft-versus-host (GVH) reaction
1. Definition—immunocompetent T cells in the donor graft recognize recipient antigens as foreign and react against them
2. Key prerequisites for GVH
   a. Donor graft must contain immunocompetent T cells
   b. Recipient must be immunocompromised.
   c. Recipient must have MHC antigens that are foreign to donor T lymphocytes.
3. Causes of GVH
   a. GVH is a potential complication in bone marrow transplants (85% of cases), liver transplants, and blood transfusion given to patients with a T cell immunodeficiency (e.g., DiGeorge syndrome) or normal newborns.
   b. Removing T cells from bone marrow transplants markedly reduces the incidence of GVH.
4. Acute GVH (Fig. 4-10)
   a. Donor CD8 cytotoxic T cells recognize host tissue as foreign, proliferate in the host tissue, and produce severe organ damage.
      - Type IV cytotoxic T cell HSR
   b. Clinical findings include:
      1. Bile duct necrosis leading to jaundice
      2. Gastrointestinal mucosa ulceration leading to bloody diarrhea
      3. Generalized skin rash, sometimes leading to desquamation
      4. Hepatosplenomegaly
   c. Treatment
      1. Anti-thymocyte globulin or monoclonal antibodies before grafting
      2. Cyclosporine reduces the severity of the reaction.

E. Types of grafts (see Table 4-5)

V. Autoimmune Disease
A. Definition
1. Definition—loss of self-tolerance, resulting in immune reactions that are directed against host tissue (self-antigens)
2. Self-antigens include class I and II MHC antigens, nuclear, and cytoplasmic antigens.
B. Mechanisms
1. Strong association with certain HLA types (e.g., class I and class II genes; see earlier).
   a. In general, class I–related diseases (e.g., ankylosing spondylitis [HLA-B27]) are more common in men than women.
   b. In general, class II–related diseases (e.g., rheumatoid arthritis [HLA-DR4]) are more common in women than men.
   c. Having an HLA type associated with an autoimmune disease does not guarantee that the person will develop that disease.
   d. Various environmental triggers are required to initiate the autoimmune disease in genetically susceptible individuals.
2. Infection as an environmental trigger for autoimmune disease
   a. Mechanisms include:
      (1) Upregulation of co-stimulators on APCs (contain class I and class II HLA antigens) leading to the formation of self-reactive CD4 T cells and CD8 cytotoxic T cells that damage tissue.
         • Self-reactive lymphocytes means that they release IL-2, causing clonal proliferation of the CD4 and CD8 T cells.
      (2) Sharing of antigens between host and pathogen (molecular mimicry)
         • Example—in rheumatic fever, certain strains of Streptococcus pyogenes producing pharyngitis have antigens in their M proteins that are similar to antigens in the human heart, joints, and other tissues
   (3) Polyclonal activation of B lymphocytes
      (a) This results in the formation of autoantibodies against host tissue.
      (b) Polyclonal activators include Epstein-Barr virus (EBV), HIV, and CMV.
   b. Viruses implicated in producing autoimmune disease include:
      (1) Coxsackievirus—myocarditis (B3), type I diabetes mellitus (B4)
      (2) Measles virus—allergic encephalitis
      (3) CMV—systemic sclerosis
      (4) EBV—hepatitis B, systemic lupus erythematosus (SLE), rheumatoid arthritis
      (5) human herpesvirus (HHV)-6, influenza A virus—multiple sclerosis
   c. Bacteria implicated in producing autoimmune disease include:
      (1) S. pyogenes—rheumatic fever
      (2) Chlamydia trachomatis—Reiter syndrome
      (3) Enteric Klebsiella pneumoniae, Shigella species—ankylosing spondylitis
      (4) Mycoplasma pneumoniae, Campylobacter jejuni—Guillain-Barré syndrome

3. Drugs as an environmental trigger for autoimmune disease
   a. Procainamide and hydralazine
      (1) These drugs bind to histones, causing them to become immunogenic.
   b. Methyldopa
      (1) Methyldopa alters Rh antigens on the surface of RBCs.
      (2) IgG autoantibodies develop against histones, producing a lupus-like syndrome.

4. Hormones as a trigger for autoimmune disease
   a. Approximately 90% of all autoimmune diseases occur in women.
   b. It is possible that estrogen triggers B cells to produce antibodies against DNA.

5. Release of sequestered antigens (antigens that are not normally exposed to the immune system) as a trigger for autoimmune disease
   a. Tissues with sequestered antigens include testicles (sperm), lens, uveal tract, and the central nervous system (CNS).
      • Damage to these tissues may result in autoimmune disease (e.g., azoospermia, endophthalmitis, encephalitis).
   b. Intracellular antigens like DNA and histones are not normally exposed to the immune system.
      (1) In SLE, genetic, immunologic, and environmental factors damage cells leading to the formation of autoantibodies against double-stranded DNA (dsDNA).
      (2) Second exposure to the release of DNA produces immunocomplexes (type III HSR), leading to various manifestations of the disease (e.g., diffuse proliferative glomerulonephritis; see following discussion).

6. Ultraviolet (UV) light as a trigger for autoimmune disease
   a. UV radiation is important in producing the characteristic malar rash that is present in SLE.
   b. UV radiation induces apoptosis of keratinocytes, releasing sequestered intracellular nuclear antigens.
   c. This leads to formation of autoantibodies that combine with the nuclear antigens to form immunocomplexes (ICs).
   d. Immunocomplexes produce a vasculitis, which is responsible for the erythematous rash in SLE.

7. Non-MHC genes associated with autoimmune disease
   a. Definition—group of genes that interfere with normal immune regulation and self-tolerance
b. PTPN-22 gene encodes for a functionally defective protein tyrosine phosphatase that cannot control tyrosine kinase activity, which is important in normal lymphocyte responses.
   • Most frequently implicated in producing autoimmune diseases (e.g., type 1 diabetes mellitus, rheumatoid arthritis).

c. NOD-2 gene has been implicated in Crohn disease.
   • Allows intestinal bacteria to enter the bowel and produce chronic inflammation

d. Interferon regulatory factor 5 (IRF5) increases interferon activity.

e. STAT4 is a signaling molecule that is important in lymphocyte activation.

C. Classification of autoimmune disorders
1. Organ-specific disorders; examples include:
   a. Addison disease
      • Immune destruction of the adrenal cortex (refer to Chapter 23)
   b. Pernicious anemia
      • Immune destruction of parietal cells in the stomach (refer to Chapter 18)
   c. Hashimoto thyroiditis
      • Immune destruction of the thyroid (refer to Chapter 23)

2. Systemic disorders; examples include:
   a. SLE
   b. Rheumatoid arthritis (refer to Chapter 24)
   c. Systemic sclerosis

D. Laboratory evaluation of autoimmune disease
1. Serum antinuclear antibody (ANA) test
   a. Serum ANA is the most useful screening test for autoimmune disease.
   b. ANAs are directed against various nuclear antigens.
      (1) DNA
         • Antibodies against dsDNA are present in patients with SLE who have renal disease.
      (2) Histones
         • Anti-histone antibodies are present in drug-induced lupus.
      (3) Acidic proteins
         a. Anti-Smith (Sm) antibodies are present in SLE.
         b. Anti-ribonucleoprotein (RNP) antibodies are present in systemic sclerosis (most common) and SLE.
      (4) Nucleolar antigens
         • Anti-nucleolar antibodies are present in systemic sclerosis.
   c. Serum ANA is a fluorescent antibody test.
      (1) Patterns of immunofluorescence are useful in making specific diagnoses.
         a. Patterns include speckled, homogeneous, nucleolar, and rim.
         b. For example, a rim pattern correlates with anti-dsDNA antibodies and the presence of renal disease in SLE.
      (2) Serum ANA provides a titer of the antibody that can be followed at various time intervals to indicate disease activity.

2. Specific antibody tests document organ-specific autoimmune diseases.
   • Example—antibodies directed against the proton pump in parietal cells are diagnostic of pernicious anemia

3. Table 4-6 summarizes autoantibodies that are involved in various autoimmune diseases.

E. SLE
1. Definition—chronic, multisystem, autoimmune disease that primarily involves skin, joints, serosal membranes, blood cells, nervous system, and kidneys
2. Epidemiology
   a. Primarily affects women of childbearing age
   b. More common in blacks, Asians, and Hispanics than in whites
3. Etiology and pathogenesis
   a. Genetic factors
      (1) Certain HLA associations are more common in people with SLE than in the general population (e.g., HLA-A1, HLA-DR3).
      (2) Inherited deficiencies of certain complement components increase the risk for developing SLE (e.g., C2 deficiency).
b. Environmental triggers are important in exacerbating SLE or triggering its initial onset; examples include:
   (1) Infectious agents (EBV)
   (2) Ultraviolet light (see earlier)
   (3) Estrogen (see earlier)
   (4) Medications (e.g., procainamide, hydralazine)

Mechanism of injury
   (1) ICs (e.g., DNA–anti-DNA; type III HSR) are most important in producing inflammation in the skin, glomeruli/tubules, joints, and small vessels.
   (2) Autoantibodies are important in the pathogenesis of various cytopenias involving RBCs, neutrophils, lymphocytes, and platelets.
      • All of these cytopenias are type II HSRs.

4. Clinical findings
   a. Constitutional symptoms
      • Fatigue (most common), fever, arthralgia, and weight loss
   b. Hematologic findings
      • Autoimmune hemolytic anemia, thrombocytopenia, leukopenia (neutropenia and lymphopenia)
   c. Lymphatic findings
      • Generalized painful lymphadenopathy and splenomegaly

<p>| Table 4-6: Autoantibodies in Autoimmune Disease |</p>
<table>
<thead>
<tr>
<th><strong>AUTOANTIBODIES</strong></th>
<th><strong>DISEASE</strong></th>
<th><strong>TEST SENSITIVITY (%)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-acetylcholine receptor</td>
<td>Myasthenia gravis</td>
<td>&gt;85</td>
</tr>
<tr>
<td>Anti–basement membrane</td>
<td>Goodpasture syndrome</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Anticentromere</td>
<td>CREST syndrome</td>
<td>40</td>
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<tr>
<td></td>
<td>Diffuse systemic sclerosis</td>
<td>&lt;2</td>
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<tr>
<td>Antiendomysial IgA</td>
<td>Celiac disease</td>
<td>95</td>
</tr>
<tr>
<td>Antigliadin IgA</td>
<td>Celiac disease</td>
<td>80</td>
</tr>
<tr>
<td>Antihistone</td>
<td>Drug-induced lupus</td>
<td>90–95</td>
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<tr>
<td>Anti-insulin</td>
<td>Systemic lupus erythematosus Type 1 diabetes</td>
<td>50–70</td>
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<tr>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Anti–islet cell</td>
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<td>75–80</td>
</tr>
<tr>
<td>Anti–intrinsic factor</td>
<td>Pernicious anemia</td>
<td>60</td>
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<tr>
<td>Anti–parietal cell</td>
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<td>Antimicrosomal</td>
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<td>Anti-Smith (Sm)</td>
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<td>Anti–SS-A (Ro)</td>
<td>Sjögren syndrome Systemic lupus erythematosus</td>
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<td>30–50</td>
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<tr>
<td>Anti–SS-B (La)</td>
<td>Sjögren syndrome</td>
<td>60–90</td>
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<td>Antithyroglobulin</td>
<td>Systemic lupus erythematosus Hashimoto thyroiditis</td>
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<td>Anti–tissue transglutaminase IgA</td>
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<td>Anti–DNA topoisomerase</td>
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</tr>
<tr>
<td>Antimitochondrial</td>
<td>CREST syndrome Primary biliary cirrhosis</td>
<td>10–20</td>
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<td>90–100</td>
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<td>Antimyeloperoxidase</td>
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<td>80 (p-ANCA)</td>
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<td>Antinuclear</td>
<td>Systemic lupus erythematosus Systemic sclerosis Dermatomyositis</td>
<td>&lt;100</td>
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<td>Polymyositis MCTD</td>
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<td>Primary biliary cirrhosis</td>
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<td>Wegener granulomatosis</td>
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<td></td>
<td>&gt;90 (c-ANCA)</td>
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<td>Anti–ribonucleoprotein</td>
<td>MCTD</td>
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<tr>
<td>Anti–TSH receptor</td>
<td>Graves disease</td>
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c-ANCA, Cytoplasmic antineutrophil cytoplasmic antibody; CREST, calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia; MCTD, mixed connective tissue disease; p-ANCA, perinuclear antineutrophilic cytoplasmic antibody; TSH, thyroid-stimulating hormone.
Musculoskeletal findings

1. Arthralgia (joint pain) is one of the most common initial complaints.
   - Morning stiffness in the hands is particularly common.
2. Arthritis
   a. Most common sites are the proximal interphalangeal and metacarpophalangeal joints in both hands and the wrists.
   b. It is usually symmetric, nonerosive, and nondeforming, unlike rheumatoid arthritis, which is deforming.

Skin findings

1. A butterfly-shaped malar rash over the cheeks and bridge of the nose with sparing of the nasolabial folds is very characteristic (Fig. 4-11A).
2. UV light exposure either initiates or exacerbates the rash.
3. Immunofluorescence (IF) studies show IC deposition along the basement membrane in both involved and uninvolved areas of skin.

Renal findings

1. The kidney is the most common visceral organ involved in SLE.
2. Diffuse proliferative glomerulonephritis is the most common and severe glomerular disease.
   - It presents with a nephritic syndrome (hematuria, RBC casts in the urine, hypertension; refer to Chapter 20).
3. Chronic renal failure is a common cause of death.

Cardiovascular findings

1. Fibrinous pericarditis (serositis) with or without effusion is the most common cardiac finding (refer to Chapter 11).
2. Libman-Sacks endocarditis (refer to Chapter 11)
   - Sterile vegetations over the mitral valve surface produce valve deformity and mitral valve regurgitation.

Respiratory findings

1. Pleuritic chest pain with or without an effusion is the most common respiratory finding.
   - Inflammation of the pleural membrane (serositis) is a key finding in SLE.
2. Interstitial fibrosis may occur, leading to restrictive lung disease (refer to Chapter 17).

CNS findings

1. Headache (most common), psychosis, seizures, strokes
2. Vessel thrombosis causing strokes is most often associated with the antiphospholipid (APL) syndrome (refer to Chapter 15).

Pregnancy-related findings

1. Complete heart block in newborns may occur.
   - Caused by IgG anti–Sjögren syndrome (SS)-A (Ro) antibodies crossing the placenta and attacking the newborn’s cardiac conduction system
2. Recurrent spontaneous abortions commonly occur.
   - Complication of thrombosis from APL antibodies (refer to Chapter 15)

Drug-induced lupus erythematosus

a. Drugs most often involved are procainamide (most common) and hydralazine.

b. Clinical findings
   - Serositis (lungs, pericardium), arthralgia, fever

c. Features that distinguish drug-induced lupus from SLE include:
   1. Antihistone antibodies
   2. No antibodies against native DNA
   3. No decrease in serum complement levels
   4. A low incidence of renal and CNS involvement
   5. Disappearance of symptoms and laboratory test results when the drug is discontinued

Laboratory testing

a. Serum ANA
   1. Best screening test for SLE (sensitivity ~100%)
      - False negative test results are uncommon (refer to Chapter 1).
   2. Specificity of serum ANA is 80%.
      - False positive test results are due to other autoimmune diseases (e.g., systemic sclerosis)
4-11: A, Malar rash in systemic lupus erythematosus showing the butterfly-wing distribution. B, Raynaud phenomenon: Raynaud phenomenon in systemic sclerosis is due to a digital vasculitis. The usual color changes are white (this patient) to blue to red. It is one of the first signs of systemic sclerosis. C, Systemic sclerosis. The skin is erythematos and tightly bound. The fingertips are tapered (called sclerodactyly) and have digital infarcts (arrows) due to fibrosis of the digital vessels. D, Systemic sclerosis. Note the thinned lips and characteristic radial furrowing around the mouth, giving a pursed-lip appearance. This is due to increased deposition of collagen in the subcutaneous tissue. There are also dilatations of small vessels (telangiectasia) on the face. E, Dermatomyositis. Note the characteristic purple papules overlying the knuckles and proximal and distal interphalangeal joints (Gottron patches). F, Dermatomyositis. Note the characteristic swelling and red-mauve discoloration below the eyes. (A from Marx J: Rosen’s Emergency Medicine Concepts and Clinical Practice, 7th ed, Philadelphia, Mosby Elsevier, 2010, p 1498, Fig. 116.1, taken from Habif TP: Clinical Dermatology, 4th ed. New York, Mosby, 2004, pp 592–606; B from Savin JA, Hunter JAA, Hepburn NC: Diagnosis in Color: Skin Signs in Clinical Medicine. London, Mosby-Wolfe, 1997, p 205, Fig. 8.43; C, D, and F courtesy R.A. Marsden, MD, St. George’s Hospital, London; E from Firestein G, Budd RC, Harris ED, Jr: Kelley’s Textbook of Rheumatology, 8th ed, Philadelphia, Saunders, 2008, Fig. 47-9.)
b. Anti-dsDNA antibodies and anti-Sm antibodies
   (1) Both of these tests are used to confirm the diagnosis of SLE.
      (a) Both have a very high specificity (i.e., very few false positive results).
      (b) Both have very low sensitivity (i.e., increased false negative results).
   (2) Specificity for anti-dsDNA is 99% and 100% for anti-Sm.
c. Anti-Ro (SS-A) and anti-La (SS-B) antibodies have low sensitivity and specificity.
d. APL antibodies (refer to Chapter 15)
e. Lupus erythematosus (LE) cell
   (1) Definition—neutrophil containing phagocytosed altered DNA
   (2) No longer available for the diagnosis of SLE
f. Serum complement
   • Usually decreased because of activation of the complement system by ICs.
g. Immunofluorescence (IF) testing
   (1) Identify ICs in a band-like distribution along the dermal-epidermal junction of involved and uninvolved skin (called band test).
   (2) IF studies of kidney biopsies are used to identify different types of glomerulonephritis.

7. Prognosis
   a. Improved survival in SLE is due to advances in diagnosis and treatment.
      • 90% 5-year and 80% 10-year survival rate
   b. Most common causes of death are infection due to immunosuppression, and chronic renal failure (CRF).

F. Systemic sclerosis (scleroderma)

1. Definition—multisystem disease characterized by vascular dysfunction, excessive production of collagen that primarily targets the skin (scleroderma) and visceral organs, and immune dysfunction.
   • Two major forms—limited systemic sclerosis (called CREST syndrome) and diffuse systemic sclerosis
2. Epidemiology
   a. Female dominant disorder that usually presents in the third and fourth decades of life
   b. Increased incidence in the black female population
3. Etiology and pathogenesis
   a. Increase in CD4 T\(_\text{cyt}\) cells reacting against an unknown antigen
      • T cells release cytokines that activate inflammatory cells and fibroblasts.
   b. Increase in autoantibody production, particularly against DNA topoisomerase I (old term anti–ScI-70) and centromeres
   c. Endothelial dysfunction is the earliest manifestation of the disease.
      (1) Vascular injury, particularly involving the digital vessels, is most likely related to cytokines released by CD4 T\(_\text{cyt}\) cells and other unknown factors.
      (2) In digital vessels, there is a decrease in vasodilators (nitric oxide, PGI\(_2\)) and an increase in vasoconstrictors (endothelin).
      (3) Damaged endothelial cells release platelet-derived growth factor (PDGF) and TGF-\(\beta\); this attracts fibroblasts and causes perivascular fibrosis, with narrowing of vessel lumens leading to ischemic injury (see later).
   d. Progressive fibrosis in skin and visceral organs is increased.
      • Primarily due to an increase in PDGF and TGF-\(\beta\)
4. Clinical findings
   a. Raynaud phenomenon in digital vessels
      (1) Sequential color changes (white to blue to red) are caused by digital vessel vasculitis/thrombosis and perivascular fibrosis (see Fig. 4-11B, C; also refer to Chapter 10).
         • Most common initial complaint in systemic sclerosis and eventually occurs in all cases
      (2) Fingers are tapered and claw-like (called sclerodactyly) and often have digital infarcts (see Fig. 4-11C).
   b. Cutaneous findings
      (1) Skin is the most common overall target organ.
      (2) Cutaneous changes begin with edema manifested as swollen fingers and hands.
      (3) Edema is followed by the development of firm, thickened skin (due to subcutaneous fibrosis), beginning in the fingers and extending proximally to involve the upper arms, shoulders, trunk, neck, and face.
(4) Extensive dystrophic calcification is present in the subcutaneous tissue.
(5) Skin in the face has a tightened appearance and radial furrowing occurs around the lips, giving the mouth a mouse-like appearance (see Fig. 4-11D).

c. Gastrointestinal tract findings
(1) Gastrointestinal tract is involved in almost all cases.
(2) Esophageus findings
   (a) Dysphagia (difficulty in swallowing) occurs with both solids and liquids.
   (b) Peristalsis is absent in the lower two thirds of the esophagus, because of extensive collagen deposition in the lamina propria and submucosa.
   (c) Esophageal mucosa is thin and often has areas of ulceration.
   (d) Esophageal strictures are common.
   (e) Dysfunction of the lower esophageal sphincter leads to reflux of gastric acid and glandular metaplasia (Barrett esophagus; refer to Chapter 2).
(2) Stomach findings
   • Collagen deposition in the wall of the stomach produces dysmotility and postprandial bloating.
(3) Small intestine findings
   (a) Loss of villi produces malabsorption of carbohydrates, fats, and protein.
   (b) Small bowel dysmotility produces cramps and bloating.
   (c) Diverticula (usually wide-mouthed) develop.
(4) Large intestine findings
   • Colonic hypomotility produces constipation.

d. Respiratory findings
(1) Dyspnea and nonproductive cough are early findings of lung involvement.
(2) Pulmonary hypertension (PH) may occur due to endothelial cell dysfunction similar to what was previously discussed in the digital vessels.
   • This produces right ventricular hypertrophy and right-sided heart failure (called cor pulmonale; refer to Chapter 17).
(3) Interstitial fibrosis produces restrictive lung disease, hypoxemia, and respiratory failure (most common cause of death).

e. Renal findings
(1) Renal problems occur in the majority of cases.
(2) Vasculitis involving afferent and efferent arterioles is characterized by fibrinoid necrosis and smooth muscle cell proliferation (called "onion skinning" or hyperplastic arteriolosclerosis; see Fig. 20-7B).
   (a) Vasculitis causes thrombosis and infarction in the kidneys.
   (b) Malignant hypertension may occur (sudden increase in systolic and diastolic blood pressure, renal failure, and cerebral edema).

5. Clinical findings in limited systemic sclerosis (CREST syndrome)
   a. C—calcification
   b. R—Raynaud phenomenon
   c. E—Esophageal dysmotility
   d. S—sclerodactyly (i.e., tapered, claw-like fingers)
   e. T—telangiectasias (i.e., multiple punctate blood vessel dilations)

6. Laboratory findings
   a. Serum ANA positive in 70% to 90% of cases in both diffuse and limited systemic sclerosis.
   b. Anti-DNA topoisomerase antibody is positive in 30% to 70% of cases of diffuse systemic sclerosis and 10% to 20% of cases in limited systemic sclerosis (CREST syndrome).
   c. Centromere antibodies are present in 40% of persons with limited systemic sclerosis.

7. Treatment
   a. d-Penicillamine—slows skin fibrosis
   b. Cyclophosphamide—useful if interstitial fibrosis is present

G. Noninfectious inflammatory myopathies
1. Definition—group of immune-mediated disorders with symmetrical muscle involvement and involvement of other organ systems.
   • Disorders include polymyositis (PM), dermatomyositis (DM)
2. Polymyositis (PM)
   a. Epidemiology
      (1) Female dominant disease with an increased incidence in the black population.
      (2) Primarily occurs in persons aged 40 to 60 years.
PM: female dominant; Tblacks; T risk malignancies (lung, bladder, lymphoma)

PM: CD8 T cells/CD4 T_{h}1, viruses (HIV, HTLV-1), environmental triggers → autoantibodies

PM muscle involvement: upper/lower extremity, trunk, shoulders/hips, neck extensors

PM: oropharyngeal/ upper esophagus dysphagia solids/liquids

PM: interstitial fibrosis

PM: ↑ serum CK/ aldolase; < ANA; ↑ anti–Jo-1

PM: EMG (myopathic dysfunction); biopsy (lymphocytic/macrophage infiltrate, atrophy not prominent)

PM: corticosteroids first-line treatment

DM: CD4 T cells target skeletal muscle capillaries; antibody/complement involvement

DM: Gottron patches over knuckles/PIP joints; heliotrope eyes

DM: muscle atrophy; lymphocytic infiltrate

MCTD: signs/symptoms – SLE, systemic sclerosis, PM

MCTD: female dominant, renal disease uncommon

(3) Increased risk of malignant neoplasms (15%-20% of cases), particularly lung and bladder cancer, and non-Hodgkin malignant lymphomas.

b. Etiology and pathogenesis
(1) Cytotoxic CD8 T cells (predominant cell) and CD4 T_{h}1 subset cells that activate macrophages damage unidentified antigens in myocyte fibers in skeletal muscle.
   (a) Triggers for the T cell response may be associated with viruses including human retroviruses (HIV, human T-cell lymphotropic virus 1 [HTLV-1]) and coxsackievirus B.
   (b) The viruses just mentioned damage skeletal muscle, leading to altered class I and II MHC antigens.
(2) Autoantibodies are directed against transfer RNA synthetases and other nuclear and cytoplasmic antigens in skeletal muscle.

c. Clinical findings
(1) Constitutional signs
   • Fever, morning stiffness, fatigue, and weight loss
(2) Symmetrical, proximal muscle weakness (with or without pain) in both the upper and lower extremities, trunk, shoulders, and hips
(3) Dysphagia for solids and liquids in oropharynx and upper esophagus
   • These areas contain skeletal muscle rather than smooth muscle.
(4) Respiratory difficulties are related to interstitial lung disease

d. Laboratory findings
(1) Serum creatine kinase (CK) and aldolase are markedly increased.
(2) Antibody findings
   (a) Serum ANA increased in 30% to 60% of cases.
   (b) Anti–transfer RNA synthetase (Jo-1) antibodies increased in 25% of cases.
(3) Electromyography shows myopathic dysfunction.
(4) Muscle biopsies show necrotic and regenerating muscle and a lymphocytic and macrophage infiltrate.
   • Muscleatrophy is not a prominent feature.

e. Treatment and prognosis
(1) Corticosteroids are the first-line treatment.
(2) Majority respond well to therapy (80% 5-year survival).

3. Dermatomyositis (DM)
a. Epidemiology of DM is similar to PM, including the increased risk for malignancies.
b. Etiology and pathogenesis
(1) Activated CD4 T cells primarily target the capillaries in skeletal muscle.
(2) Antibodies and complement are involved in the capillary damage.
(3) Foci of myofiber injury accompanies microvascular changes.
c. Clinical findings
(1) Muscle complaints are similar to those in PM.
(2) Cutaneous findings are key.
   (a) Reddish-purple papules called Gottron patches are noted over the knuckles and proximal interphalangeal (PIP) joints in both hands (see Fig. 4-11E)
   (b) Purple-red eyelid discoloration occurs (called heliotrope eyelids or "raccoon eyes"; see Fig. 4-11F).
d. Laboratory findings
(1) Similar to those described for PM
(2) Muscle biopsies show an inflammatory reaction (primarily lymphocytic).
   (a) Unlike PM, atrophy of muscle fibers is a prominent feature.
   (b) Damage to the capillaries in the muscle leads to ischemia and atrophy of the muscle fibers.
e. Treatment
   • Corticosteroid therapy is the first-line treatment.

H. Mixed connective tissue disease (MCTD)
1. Definition—signs and symptoms similar to SLE, systemic sclerosis, and PM.
2. Epidemiology
   a. Female dominant disease
   b. Occurs in persons aged 15 to 25 years
   c. Renal disease uncommon
3. Etiology and pathogenesis
   a. Activation of T cells and B cells, the latter producing antibodies against U1-RNP (ribonucleoprotein)
b. Vascular endothelial proliferation and an infiltrate of B and T cells occurs in involved tissues.

4. Clinical findings
   a. Vascular findings
      • Raynaud phenomenon (>95% of cases) and sclerodactyly (50% of cases), similar to systemic sclerosis
   b. Musculoskeletal findings
      • Arthralgia and arthritis involving the hands (>95% of cases)
   c. Gastrointestinal findings
      • Esophageal dysmotility similar to systemic sclerosis (65% of cases)
   d. Respiratory findings
      (1) Pulmonary hypertension, pleuritis
      (2) High association with antiphospholipid antibodies if pulmonary hypertension is present
   e. Cardiovascular findings
      • Pericarditis (40% of cases)
   f. CNS findings
      • Trigeminal neuralgia is common.

5. Laboratory findings
   a. Positive serum ANA (95% to 99% of cases)
   b. Anti-ribonucleoprotein antibodies (U1-RNP; ~100% of cases)
   c. Other antibodies frequently found in MCTD include antiphospholipid antibodies, rheumatoid factor, anti–dsDNA (similar to SLE), and anti–DNA topoisomerase (similar to systemic sclerosis).

VI. Immunodeficiency Disorders

A. Definition
   • Definition—either primary (usually genetically determined) or secondary disorders that involve defects in B cells, T cells, complement, or phagocytic cells

B. Risk factors
   1. Prematurity
   2. Autoimmune diseases (e.g., SLE)
   3. Lymphoproliferative disorders (e.g., malignant lymphoma)
   4. Infections (e.g., HIV)
   5. Immunosuppressive drugs (e.g., corticosteroids)

C. Summary of primary immunodeficiency disorders (Table 4-7)

D. Acquired immunodeficiency syndrome (AIDS)
   1. Epidemiology
      a. Most common cause of death to infection worldwide
      b. Internationally, sub-Saharan Africa has the greatest number of people with AIDS.
      c. Virus characteristics
         (1) HIV is a retrovirus that causes AIDS (Fig. 4-12).
            • A key feature of retroviruses is the enzyme reverse transcriptase, which converts viral RNA into proviral dsDNA.
         (2) HIV-1 most common cause of AIDS in United States; HIV-2 more restricted (most prevalent in Western Africa).
         (3) Virus cannot penetrate intact skin or mucosa.
            • Ulceration of skin or mucosa must be present for the virus to enter CD4 T cells or dendritic cells in tissue.
         (4) HIV contains three retroviral genes.
            (a) The gag gene directs synthesis for inner structural proteins (e.g., p24 core antigen).
            (b) The env gene directs synthesis for the viral envelop with outer structural proteins that give cell-type specificity (e.g., glycoprotein [gp]120 binds the virus to the host CD4 T cell).
            (c) The pol gene directs synthesis for reverse transcriptase, integrase, and protease.
      d. Modes of transmission
         (1) Sexual transmission (~80% of cases)
            (a) Man-to-man transmission by anal intercourse most common cause in United States (~50% of cases).
            (b) Heterosexual transmission (30% of cases)
               • Most common cause of AIDS in developing countries
<table>
<thead>
<tr>
<th>TABLE 4-7 Congenital Immunodeficiency Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISEASE</strong></td>
</tr>
<tr>
<td>-----------</td>
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<tr>
<td><strong>B-Cell Disorders</strong></td>
</tr>
<tr>
<td>Bruton agammaglobulinemia</td>
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<tr>
<td>IgA deficiency</td>
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<tr>
<td>Common variable immunodeficiency (CVID)</td>
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<tr>
<td><strong>T-Cell Disorder</strong></td>
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<tr>
<td>DiGeorge syndrome (thymic hypoplasia)</td>
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<tr>
<td><strong>Combined B- and T-Cell Disorders</strong></td>
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<tr>
<td>Hyper-IgM syndrome</td>
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<tr>
<td>Severe combined immunodeficiency (SCID)</td>
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</table>
**TABLE 4-7 Congenital Immunodeficiency Disorders—cont’d**

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DEFECT(S)</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>XR disorder: mutation in a gene that encodes for a protein that is involved in the assembly of actin filaments in the cytoskeleton of all hematopoietic cells; defect in actin causes problems in cell migration, signal transduction, and other cell functions. The structure of the human immune deficiency virus (HIV)-1 virion. See text for discussion.</td>
<td>Symptom triad: atopic eczema, thrombocytopenia, SP infections Increased risk for malignancy (lymphoma and leukemia) Infections due to encapsulated organisms (Streptococcus pneumoniae), Pneumocystis jiroveci, viral infections Defective CMI ↓IgM, normal IgG, TlgA and IgE Bone marrow transplantation is essential for survival</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>AR disorder Mutation in a gene that encodes for DNA repair enzymes Thymic hypoplasia</td>
<td>Cerebellar ataxia, telangiectasia (dilated vessels) in the eyes and skin ↑Risk for malignancy (lymphoma and/or leukemia; adenocarcinoma e.g., stomach, breast) ↑Serum α-fetoprotein (AFP) and carcinoembryonic antigen (CEA) Defective CMI: ↓total lymphocyte count; defective T cell function Deficient antibody production to viral or bacterial antigens ↓IgA 50-80%; ↓IgE; normal to TlgM; ↓IgG2/↓IgG4, normal to ↓total IgG; ↓T cell function</td>
</tr>
</tbody>
</table>

AlHA, Autoimmune hemolytic anemia; AR, autosomal recessive; CMl, cell-mediated immunity; GI, gastrointestinal; GVH, graft-versus-host; Ig, immunoglobulin; ITP, idiopathic thrombocytopenic purpura; MA, pernicious anemia; SLE, systemic lupus erythematosus; SP, sinopulmonary; XR, sex-linked recessive.

4-12: The structure of the human immune deficiency virus (HIV)-1 virion. See text for discussion. From Kumar V, Fausto N, Abbas A, Aster J: Robbins and Cotran Pathologic Basis of Disease, 8th ed, Philadelphia, Saunders Elsevier, 2010, p 237, Fig. 6.43.

(c) Prior or current sexually transmitted diseases (STDs) increases the risk for HIV infection:
- Gonorrhea/chlamydia (threefold risk), syphilis (sevenfold risk), herpes genitalis (25-fold risk).

(2) Intravenous drug abuse (IVDA; ~20% of cases)
- Rate of HIV infection is markedly increasing in female sex partners of male IV drug abusers.

(3) Other modes of transmission
   (a) Vertical transmission
       - Transplacental route, blood contamination during delivery, breast-feeding
       - Most pediatric cases of AIDS are due to transmission of the virus from mother to child.
   (b) Accidental needlestick
       - Most common mode of infection in health-care workers
       - 0.3% seroconversion risk

STDs ↑Risk for HIV
IVDA: 2nd MCC AIDS
Pediatric AIDS: MC due to vertical transmission
Accidental needlestick: MCC HIV in health-care workers
Blood products: blood bank screens for HIV with p24 antigen assay

Body fluids with HIV: blood, semen/vaginal secretions, breast milk

Cells infected by HIV: CD4 T cells, macrophages, dendritic cells, astrocytes

HIV cytotoxic to CD4 T cells

Macrophages/dendritic cells: reservoirs for HIV

HIV enters interrupted mucosal surfaces genital tract/anus

Follicular dendritic cells: major reservoir for HIV during latency

HIV binding: gp120, chemokine co-receptors

(c) Blood products
- Risk is estimated to be 1 in more than 2 million units of blood transfused.
- Reduced risk is due to blood banks screening blood with the p24 antigen assay.

e. Body fluids containing HIV
- Blood, semen, vaginal secretions, breast milk

2. Pathogenesis
a. Major cells infected by HIV-1 are CD4 T cells, macrophages, dendritic cells, and astrocytes
   (1) HIV is cytotoxic to CD4 T cells; hence the number of these cells decreases as disease progresses.
   (2) Macrophages contain large numbers of viral particles in cytoplasmic vacuoles; however, unlike CD4 T cells, they are resistant to the cytopathic effects of the virus.
   - Important reservoirs of the virus.
   (3) Similar to macrophages, dendritic cells also contain large numbers of the virus and are important reservoirs of the virus.

b. Primary infection due to HIV occurs via entry of the virus through interrupted mucosal surfaces in the genital tract/anus where it infects CD4 T cells and dendritic cells in the underlying tissue.
   (1) These cells, which are filled with viral particles, drain into lymph nodes and spleen where the virus is held in check by the patient’s immune system.
   (2) Follicular dendritic cells in the germinal centers of the lymph nodes are the major reservoirs of the virus during the early latent stages of the disease before the virus is released into the blood and produces the acute retroviral syndrome (see later).

c. Life cycle of HIV-1 (Fig. 4-13)
   (1) Gp120 in the viral envelope binds to CD4 and various chemokine co-receptors.
   (2) The viral membrane fuses with the host cell membrane and gains entry into the cytoplasm.
   - Gp41 helps with fusion of the virus to the host cell membrane.

4-13: The life cycle of human immunodeficiency virus type 1 (HIV-1). The sequential steps in HIV reproduction are shown, from initial infection of a host cell to release of a new virus particle (virion). For the sake of clarity, the production and release of only one new virion are shown. An infected cell actually produces many virions, each capable of infecting nearby cells, which spreads the infection. (From Abbas A, Lichtman A: Basic Immunology: Function and Disorders of the Immune System, 3rd ed, Philadelphia, Saunders Elsevier, 2011, p 233, Fig. 12-8.)
(3) Viral protease uncoats the virus, which results in release of viral RNA.
(4) Reverse transcriptase converts viral RNA into dsDNA.
(5) Integrate inserts the viral DNA into the host cell’s DNA and becomes a provirus.
   • Provirus may be latent for months or years (latent infection).
(6) Activation of the host cell by an extrinsic stimulus (e.g., microbial infection), leads to upregulation of transcription factors (e.g., NK-kB), which stimulates transcription of genes encoding for cytokines (e.g., IL-2 and its receptor).
(7) These cytokines also stimulate gene transcription of the HIV genome causing the release of viral RNA into the cytoplasm.
(8) Synthesis of HIV proteins produces an HIV core structure containing the RNA.
(9) The HIV core structures migrate to the cell membrane, acquire a lipid bilayer, and form buds containing infectious viral particles that detach from the membrane.
(10) The mature, infectious viral particles are now able to infect other cells.

3. Laboratory tests are summarized in Table 4-8.

4. Natural history of HIV infection (Fig. 4-14)
   a. Acute phase
      (1) Approximately 3 to 6 weeks after infection individuals experience fever, malaise, and generalized painful lymphadenopathy, which usually subsides within a few days.
      (2) Greatest risk for contracting HIV is the first few weeks of infection (range is 1 in 5 to 1 in 250 chance per coital act).
   b. Asymptomatic carrier phase
      (1) This is an asymptomatic period that lasts 2 to 10 years after contracting the infection.
      (2) The CD4 T-cell count is >500 cells/mm³.
      (3) Viral replication occurs in follicular dendritic cells in the germinal follicles of lymph nodes and in macrophages.
         • Cytotoxic T cells control but do not clear HIV reservoirs.
   c. Early symptomatic phase
      (1) CD4 T-cell count is 200 to 500 cells/mm³.
      (2) Generalized painful lymphadenopathy
      (3) Non–AIDS-defining infections occur, including hairy leukoplakia (glossitis caused by EBV [see Fig. 18-2B]) and oral candidiasis (see Fig. 18-2)
      (4) Fever, weight loss, diarrhea

### Table 4-8 Laboratory Tests Used in HIV and AIDS

<table>
<thead>
<tr>
<th>TEST</th>
<th>USE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>Screening test</td>
<td>Detects anti-gp120 antibodies</td>
</tr>
<tr>
<td></td>
<td>Newer 4th generation screening tests</td>
<td>Sensitivity –100%, Positive within 3–5 weeks; all in 3 months Detect antibodies for HIV-1, HIV-2, and p24 antigen (see later)</td>
</tr>
<tr>
<td>Western blot and nucleic acid assays</td>
<td>Confirmatory tests</td>
<td>Western blot is used if ELISA is positive or indeterminate. Positive test: presence of p24 antigen and gp41 antibodies, and either gp120 or gp160 antibodies. Test misses a significant number of people with HIV who have indeterminate test results HIV-1 RNA in vitro nucleic acid assays now replacing the Western blot as a confirmatory test Specificity –100%.</td>
</tr>
<tr>
<td>p24 antigen</td>
<td>Indicator of active viral replication</td>
<td>Positive before seroconversion and when AIDS is diagnosed (two distinct peaks) Test is used by blood banks to screen for HIV; has markedly decreased the chance for contracting HIV by blood transfusion</td>
</tr>
<tr>
<td>CD4 T-cell count</td>
<td>Monitoring immune status</td>
<td>Useful in determining when to initiate HIV treatment and when to administer prophylaxis against opportunistic infections</td>
</tr>
<tr>
<td>HIV viral load</td>
<td>Detection of actively dividing virus</td>
<td>Most sensitive test for diagnosis of acute HIV before seroconversion Recommended at least one time per year</td>
</tr>
</tbody>
</table>

AIDS, Acquired immunodeficiency syndrome; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus.
d. Organ systems affected by AIDS (Table 4-9)

1. Criteria
   - HIV-positive with CD4 T-cell count ≤200 cells/mm³ and/or an AIDS-defining condition
2. Most common AIDS-defining infections
   - *Pneumocystis jiroveci* pneumonia (Fig. 4-15A), systemic candidiasis
3. AIDS-defining malignancies
   - Kaposi sarcoma (see Fig. 4-15B), Burkitt lymphoma (EBV), primary CNS lymphoma (EBV), cervical carcinoma

**Table 4-9 Organ Systems Affected by AIDS**

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>CONDITION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>Increased risk for atherosclerotic coronary artery disease</td>
<td>Major cause of death in AIDS patients</td>
</tr>
<tr>
<td>Central nervous system (CNS)</td>
<td>AIDS dementia complex (see Fig. 26-14C)</td>
<td>Caused by HIV</td>
</tr>
<tr>
<td></td>
<td>Primary CNS lymphoma</td>
<td>Multinucleated microglial cells reservoir of virus</td>
</tr>
<tr>
<td></td>
<td>Cryptococcosis (see Fig. 26-16A)</td>
<td>Caused by CMV</td>
</tr>
<tr>
<td></td>
<td>Toxoplasmosis (see Fig. 26-16D, E)</td>
<td>Caused by EBV</td>
</tr>
<tr>
<td></td>
<td>CMV retinitis (see Fig. 26-26M)</td>
<td>Most common extranodal site for lymphoma</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Esophagitis</td>
<td>Caused by Candida, herpesvirus, CMV</td>
</tr>
<tr>
<td></td>
<td>Colitis (see Fig. 18-16C)</td>
<td>Caused by Cryptosporidium, Microsporidium, Isospora, CMV</td>
</tr>
<tr>
<td></td>
<td>Perianal</td>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Biliary tract infection</td>
<td>Caused by CMV</td>
</tr>
<tr>
<td>Renal</td>
<td>Focal segmental glomerulosclerosis</td>
<td>Causes hypertension and nephrotic syndrome (most common cause of nephrotic syndrome)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pneumonia (see Fig. 4-15A)</td>
<td>Caused by <em>Pneumocystis jiroveci</em> and <em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>Skin</td>
<td>Kaposi sarcoma (see Fig. 4-15B)</td>
<td>Caused by HHV-8</td>
</tr>
<tr>
<td></td>
<td>Bacillary angiomatosis (see Fig. 10-13A)</td>
<td>Caused by Bartonella henselae</td>
</tr>
<tr>
<td></td>
<td>Shingles (see Fig. 25-1J)</td>
<td>Herpes zoster</td>
</tr>
</tbody>
</table>

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HHV-8, human herpesvirus type 8.

**AIDS:** CD4 T-cell count ≤200 cells/mm³ and/or AIDS-defining lesion

**AIDS-defining malignancies:** Kaposi sarcoma, Burkitt lymphoma 1° CNS lymphoma, cervical carcinoma
(4) Causes of death
   • Disseminated infections (CMV, Mycobacterium avium-intracellulare [MAI] complex)
e. Immunologic abnormalities
   (1) Lymphopenia, due to a low CD4 T-cell count
   (2) Cutaneous anergy, due to a defect in CMI from decreased CD4 T cells
   (3) Hypergammaglobulinemia, due to polyclonal B cell stimulation by EBV and CMV
   (4) CD4:CD8 ratio <1 (normally the ratio is >2, but lysis CD4 T cells cause low ratio)
   (5) NK cell cytotoxicity function is decreased.
f. CD4 count and risk for certain diseases
   (1) 700 to 1500: normal
   (2) 200 to 500: oral thrush, herpes zoster (shingles), hairy leukoplakia
   (3) 100 to 200: *P. jiroveci* pneumonia, AIDS dementia
   (4) Below 100: toxoplasmosis, cryptococcosis, cryptosporidiosis
   (5) Below 50: CMV retinitis, MAI complex, progressive multifocal leukoencephalopathy, primary CNS lymphoma (due to EBV)

5. Pregnant women with AIDS
   • Treatment with a reverse transcriptase inhibitor reduces transmission to newborns to <8%.

6. Treatment
   a. The earlier the treatment, the better the survival.
   b. Highly active antiretroviral therapy (HAART) therapy is the principal method for preventing immune deterioration.
      • Most clinicians are beginning this therapy when the CD4 T-cell count is 350 to 500 cells/mm$^3$.
c. Classes of drugs that are used
   (1) Nucleoside reverse transcriptase inhibitors
   (2) Protease inhibitors
   (3) Nonnucleoside reverse transcriptase inhibitors
   (4) Fusion inhibitors
   (5) Co-receptor antagonists (entry inhibitors)
   (6) HIV integrase strand transfer inhibitors
d. **Fig. 4-16** shows the sites of actions for some of the drugs in the previous list.

**D. Complement system disorders**
1. Overview of the complement system
   a. Complement is synthesized in the liver.
b. Part of innate immune defense and is one of the acute phase reactants released in inflammation (refer to Chapter 3)

c. Circulates as an inactive protein
   (1) Complement is activated by IgM, IgG-antigen complexes, and endotoxin.
   (2) Only complement cleavage products are functional.

d. Functions of complement cleavage products
   (1) C3a, C5a (anaphylatoxins)
      • Stimulate mast cell release of histamine.
   (2) C3b
      • Opsonization
   (3) C5a
      (a) Activation of neutrophil adhesion molecules
      (b) Neutrophil chemotaxis
   (4) C5b-C9 (membrane attack complex [MAC])
      • Cell lysis

2. Complement pathways (Fig. 4-17)
   a. Classical pathway
      (1) Activated by ICs that contain antibodies bound to an antigen
      (2) Contains complement components C1, C4, and C2
      (3) Requires antibody to activate the pathway
      (4) C1 esterase inhibitor
         (a) Inactivates the protease activity of C1
            • C1 normally cleaves C2 and C4 to produce the C4b2a complex (C3 convertase).
         (b) Deficient in hereditary angioedema (discussed later)

   b. Alternative pathway
      (1) Activated by lipopolysaccharides (endotoxin from gram-negative bacteria), viruses, and fungi
      (2) Contains complement components factor B, properdin, and factor D
      (3) Does not require antibodies for its activation

   c. Lectin pathway
      (1) Very important for the destruction of microbial pathogens (bacteria, fungi, viruses, and protozoa)
      (2) Mannose-binding protein is structurally similar to the C1 complex.
         • Protein complexes with mannose-associated serine protease.
      (3) Protein attaches to mannose and other carbohydrate molecules on the wall of gram-negative pathogens (e.g., Salmonella, Neisseria, Listeria), fungi (e.g., Candida, Cryptococcus), viruses (e.g., HIV, respiratory syncytial virus, influenza A), and protozoa (e.g., Leishmania).
      (4) Does not require antibodies for its activation

   d. Membrane attack complex (C5b-C9)
      • Final common pathway for the classical, alternative, and lectin pathways
4-17: Complement cascade. Activation of complement through the classical pathway (via immune complexes; e.g., systemic lupus erythematosus), the alternative pathway (via endotoxins [lipopolysaccharides]), or the lectin pathway (via pathogens with mannose on the cell wall; e.g., Salmonella, Candida) promote activation of C3 and C5, leading to formation of the membrane attack complex (C5b-C9). Decay accelerating factor (DAF) degrades C3 convertase and C5 convertase in both the classical and alternative pathways. The functions of C3a, C3b, C5a, and C5b-9 are described in the text. (Modified from Actor JK: Elsevier’s Integrated Immunology and Microbiology, 2nd ed, Philadelphia, Mosby, 2011, Fig. 6-6.)

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary angioedema (see Fig. 4-18)</td>
<td>Autosomal dominant (AD) disorder with deficiency of C1 esterase inhibitor. Continued C1 activation decreases C2 and C4 and increases their cleavage products, which have anaphylatoxic activity. Normal C3. Swelling of face, oropharynx, digits.</td>
</tr>
<tr>
<td>C2 deficiency</td>
<td>Most common complement deficiency. Association with septicemia (usually Streptococcus pneumoniae) and SLE.</td>
</tr>
<tr>
<td>C6-C9 deficiency</td>
<td>Increased susceptibility to disseminated Neisseria gonorrhoeae or Neisseria meningitidis infections.</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria (PNH)</td>
<td>Acquired stem cell disease with a mutation in the PIG (phosphatidyl inositol glycan) complementation group A gene in a myeloid stem cell clone that results in a defect in the anchoring of inhibitors of complement (CD55 [decay accelerating factor] and CD59) on the surface of RBCs, neutrophils, and platelets; inhibitors normally degrade C3 and C5 convertase on hematopoietic cell membranes. Complement-mediated intravascular lysis of red blood cells (hemoglobinuria), platelets, and neutrophils leads to pancytopenia. Diagnosis made with flow cytometry to detect the clones.</td>
</tr>
</tbody>
</table>

e. Decay accelerating factor (DAF)
   1. DAF is present on cell membranes of hematopoietic cells and other cells in the body.
   2. It enhances the degradation of C3 convertase and C5 convertase in the classical and alternative pathways.
   3. Deficient in paroxysmal nocturnal hemoglobinuria (PNH) (Table 4-10; refer also to Chapter 12).

3. Epidemiology and clinical findings
   a. Complement deficiencies are uncommon.
   b. Deficiencies in complement predispose to infection via the following mechanisms:
      1. Ineffective opsonization, due to a lack of C3b
      2. Defects in cell lysis, due to a lack of MAC components
   c. Deficiencies associated with opsonization defects usually present with recurrent pyogenic infections due to encapsulated bacteria (e.g., Streptococcus pneumoniae).
      - Infections are more likely to occur at an early age (few months to a few years of age).
   d. Deficiencies in early classical pathway components (i.e., C1, C4, C2) do not have recurrent infections but are more often predisposed to developing autoimmune disease, particularly SLE.
Deficiencies in the formation of MAC have a high risk for developing recurrent infection with *Neisseria gonorrhoeae* or *Neisseria meningitidis*.

- Children and neonates are more likely to have severe pyogenic infections and sepsis.

Summary of complement disorders (see Table 4-10; Fig. 4-18)

4. Testing of the complement system
   a. Total hemolytic complement assay (CH50)
      - Tests the functional ability of both complement systems
   b. Test results indicating activation of the classical system
      1. Decreased C4, C3
      2. Normal factor B
   c. Test results indicating activation of the alternative system
      1. Decreased factor B, C3
      2. Normal C4
   d. Test results indicating activation of both systems
      - Decreased C4, factor B, C3

VII. Amyloidosis

A. Amyloid characteristics

1. Definition—fibrillar protein that is deposited in interstitial tissue, resulting in organ dysfunction by pressure atrophy of adjacent cells

2. Composed of linear, nonbranching filaments (electron microscopy) in a β-pleated sheet (x-ray diffraction pattern) (Fig. 4-19A)

3. Eosinophilic staining with hematoxylin-eosin (H&E) stain (see Fig. 4-19B)

4. Congo red stain of tissue turns amyloid red, and polarizing microscopy shows an apple green (similar to a Granny Smith apple) birefringence (Fig. 4-19C).
   - Polarization appearance is due to the β-pleated sheet conformation

5. Derived from three major precursor proteins:
   a. Immunoglobulin light chains, with λ light chains more frequently involved than κ light chains
      - Light chains in urine are called Bence Jones proteins.
   b. Serum amyloid A (SAA) protein, which is an acute phase reactant synthesized and released by the liver in inflammation
   c. Amyloid precursor protein (APP); gene located on chromosome 21
6. Other important precursor proteins include:
   a. Transthyretin, which is a normal carrier protein for thyroxine and retinoic acid (vitamin A)
   b. \( \beta_2 \)-Microglobulin, which is the light chain component of the MHC (see earlier)
   c. Prion proteins, which normally maintain neuronal membranes

**B. Pathogenesis**

1. Majority of types of amyloidosis have misfolded proteins, which self-associate and accumulate in the interstitial tissue
   - Misfolded proteins are normally removed by proteasomes, but in some types of amyloidosis, this system of removal is dysfunctional.
2. In amyloidosis due to serum amyloid A protein, enzyme defects in monocytes may be responsible for the accumulation of AA protein (amyloid derived from serum amyloid A protein) in the interstitial tissue.

**C. Classification (Table 4-11)**

**D. Clinical presentation**

1. Common presenting signs include fatigue, dyspnea, edema, paresthesias, and weight loss.
2. Kidney involvement
   a. Most common overall organ involved
   b. Glomeruli, interstitial tissue, arteries, and arterioles are all involved.
   c. Proteinuria in the nephrotic range leads to generalized pitting edema and cavity effusions (refer to Chapter 20).

---

**Table 4-11** Common Types of Amyloidosis and Associated Clinical Findings

<table>
<thead>
<tr>
<th>TYPE OF AMYLOIDOSIS</th>
<th>DISEASE ASSOCIATIONS</th>
<th>FIBRIL PROTEIN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic Amyloidosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocytic dyscrasias (primary</td>
<td>Plasma cell disorders (e.g., multiple myeloma, other monoclonal plasma cell dyscrasias [10% of all monoclonal gammopathies])</td>
<td>AL (designation for amyloid derived from immunoglobulin light chains, particularly ( \lambda ) light chains)</td>
</tr>
<tr>
<td>Reactive systemic amyloidosis</td>
<td>Chronic inflammation: rheumatoid arthritis (MC), ankylosing spondylitis, inflammatory bowel disease (Crohn disease, ulcerative colitis), tuberculosis, leprosy, osteomyelitis, renal cell carcinoma, Hodkin lymphoma, heroin abusers (“skin popping”)</td>
<td>AA (designation for amyloid derived from serum amyloid A protein)</td>
</tr>
<tr>
<td>Hemodialysis-associated amyloidosis</td>
<td>Chronic renal failure</td>
<td>( A\beta_{\text{m}} ) (designation for amyloid derived from ( \beta_2 )-microglobulin)</td>
</tr>
<tr>
<td><strong>Hereditary Amyloidosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>Autosomal recessive Increased production of IL-1 Fever, inflammation of serosal membranes (pleura, peritoneum, synovium)</td>
<td>AA (designation for amyloid derived from serum amyloid protein)</td>
</tr>
<tr>
<td>Familial amyloidotic neuropathies</td>
<td>Autosomal dominant Peripheral and autonomic nerve disorders</td>
<td>ATTR (designation for amyloid derived from transthyretin)</td>
</tr>
<tr>
<td>Systemic senile amyloidosis</td>
<td>Amyloidosis of elderly patients (70+ years old) Predominantly involves the heart (restrictive cardiomyopathy, conduction defects)</td>
<td></td>
</tr>
<tr>
<td><strong>Localized Amyloidosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senile cerebral</td>
<td>Alzheimer disease (refer to Chapter 26)</td>
<td>( A\beta ) (designation for amyloid derived from amyloid precursor protein, which is coded for by chromosome 21)</td>
</tr>
<tr>
<td><strong>Endocrine Amyloid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medullary carcinoma of thyroid</td>
<td>Sporadic and familial (MEN IIA, IIB)</td>
<td>A Cal (designation for amyloid derived from calcitonin)</td>
</tr>
<tr>
<td>Islets of Langerhans</td>
<td>Type II diabetes mellitus</td>
<td>AIAPP (designation for amyloid derived from islet amyloid polypeptide)</td>
</tr>
</tbody>
</table>

MC, Most common; MEN, multiple endocrine neoplasia.
3. Pulmonary involvement
   - Lung findings include fatigue and dyspnea.
4. Gastrointestinal involvement
   a. Diarrhea is of the malabsorptive type with loss of carbohydrates, proteins, and fat.
   b. MacroGLOSSIA (enlarged tongue) leads to problems with speech and swallowing.
5. Cardiac involvement
   a. Restrictive cardiopathy is present because of infiltration of amyloid between myocardial fibers (refer to Chapter 11).
       (1) Ejection fraction is frequently preserved.
       (2) Produces a diastolic dysfunction type of left-sided heart failure (LHF; refer to Chapter 11)
   b. Conduction defects are very common.
6. Nervous system involvement
   - Dementia (Alzheimer disease), peripheral neuropathies (paresthesias, muscle weakness), and disabling autonomic neuropathies may occur.
7. Liver involvement
   a. Hepatomegaly is a common finding in systemic amyloidosis.
   b. Pressure atrophy of hepatocytes; however, functional impairment is uncommon
8. Spleen involvement
   a. Common in the systemic type of amyloidosis
   b. If white pulp (splenic lymphoid follicles) is involved, the splenic surface looks like it is impregnated with grains of sand (called a sago spleen).
   c. If red pulp is involved, the splenic surface has a waxy appearance (called a lardaceous spleen).
9. In hemodialysis-associated amyloidosis, musculoskeletal involvement is common.
   - Clinical findings include carpal tunnel syndrome, destructive arthropathy, bone cysts, and fractures.
10. Hemostasis abnormalities
    a. Factor X deficiency may occur in the AL type (designation for amyloid derived from light chains) of systemic amyloidosis.
       - Factor X binds to amyloid fibrils.
    b. Skin hemorrhages are common around the orbit and in areas where the skin is pinched (called pinch purpura).
       - Vascular instability is due to amyloid infiltration of small blood vessels.

E. Techniques used to diagnose amyloidosis
1. Serum and urine immunoelectrophoresis is useful in detecting monoclonal spikes in serum and light chains (Bence Jones protein) in urine (refer to Chapter 14).
   - Bone marrow aspiration and/or biopsy is useful to detect malignant plasma cell infiltrates (refer to Chapter 14).
2. Tissue biopsy is useful to detect amyloid.
   a. Tissues commonly biopsied include the omental fat pad, rectum, and gingiva.
   b. If these tissues do not reveal amyloidosis, then organ biopsy may be necessary (e.g., liver biopsy).
3. Two-dimensional Doppler echocardiography is useful in diagnosing ventricular filling problems (diastolic dysfunction) in cardiac involvement.
4. Nuclear imaging
   a. Nuclear imaging with technetium-labeled aprotinin may detect cardiac amyloidosis.
   b. Serum amyloid P component (SAP) scintigraphy has high sensitivity for detecting amyloid in multiple organ sites.
   - SAP has a high affinity for amyloid.

F. Treatment
1. In amyloidosis due to plasma cell dyscrasias (e.g., multiple myeloma), treatment of the dyscrasia is useful in controlling the amyloidosis.
2. Other treatment modalities:
   a. Anti–tumor necrosis factor drugs in amyloidosis involving the kidneys
   b. Autologous bone marrow transplants in those patients with preserved organ function
   c. Hemodialysis or renal transplantation in those patients with renal failure

G. Prognosis
1. Poor prognosis in systemic amyloidosis; better prognosis with localized disease
2. Better control of diseases that produce inflammation-associated types of amyloidosis has reduced the incidence of these types of systemic amyloidosis.
I. Water and Electrolyte Disorders

A. Body fluid compartments

1. Total body water (TBW) is ~60% of the body weight in kilograms.
   a. TBW distribution (Fig. 5-1)
      (1) Intracellular fluid (ICF) compartment
          • ICF equals ~40% of body weight in kilograms.
      (2) Extracellular fluid (ECF) compartment
          • ECF equals ~20% of body weight in kilograms.
      (3) ECF is subdivided into interstitial and vascular compartments.
          • Vascular compartment—heart, aorta, pulmonary artery, muscular arteries, arteries, capillaries, venules, and veins
      b. Sodium (Na⁺) is the major ECF cation.
         • Chloride (Cl⁻) is the major ECF anion.
      c. Potassium (K⁺) is the major ICF cation.
         • Phosphate (PO₄³⁻) is the major ICF anion.

2. Plasma osmolality (POsm)
   a. Definition—number of solutes in plasma (i.e., tonicity of ECF)
      (1) Isotonic state = normal POsm
      (2) Hypotonic state = decreased POsm
      (3) Hypertonic state = increased POsm
   b. POsm = 2 (serum Na⁺) + serum glucose/18 + serum blood urea nitrogen (BUN)/2.8 = 275–295 mOsm/kg
      • Most of the normal POsm correlates with the serum Na⁺ concentration.
   c. Urea diffuses freely between ECF and ICF compartments.
      (1) Nephrologists frequently use the term effective osmolality (EOsm).
         • Urea is excluded, because it does not affect the osmotic gradient.
      (2) EOsm = 2 (serum Na⁺) + serum glucose/18

3. Na⁺ and glucose are limited to the ECF compartment (impermeant solutes).
   a. Changes in their concentration produce an osmotic gradient (see later).
      (1) Water shifts between the ECF and ICF compartments by osmosis.
         (a) Osmosis is the tendency for water to pass through a cell membrane into a solution in which the solute concentration is higher, thus equalizing the concentrations of solutes on both sides of the membrane.
         (b) If there is an osmotic gradient between the ECF and ICF compartments, water moves from a low to a high solute concentration.
      (2) Water shifts do not occur with alterations in urea concentration.
         • Urea is a permeant solute and diffuses between the ECF and ICF without altering the osmotic gradient.
   b. Hyponatremia (decreased POsm) establishes an osmotic gradient causing water to shift from the ECF compartment (low solute concentration) into the ICF compartment (high solute concentration) (Fig. 5-2A).
      • ICF compartment expands.
5-1: Body fluid compartments. The intracellular fluid (ICF) compartment is the largest compartment followed by the extracellular fluid compartment (ECF). The ECF compartment is subdivided into the interstitial fluid compartment and the vascular compartment, which includes the heart, arteries, arterioles, capillaries, venules, and veins.

5-2: Osmotic shifts in hyponatremia (A) and hypernatremia or hyperglycemia (B). In hyponatremia (A), water moves from the compartment with lowest solute concentration (ECF compartment) to the compartment with highest solute concentration (ICF compartment) by the law of osmosis; hence there is expansion of the intracellular fluid (ICF) compartment. In hypernatremia or hyperglycemia (B), water moves from the ICF compartment into the ECF compartment by osmosis; hence the ICF compartment contracts. ECF: Extracellular fluid; ICF: intracellular fluid.

c. Hypernatremia and hyperglycemia (increased POs) cause water to shift from the ICF compartment (low solute concentration) into the ECF compartment (high solute concentration) (see Fig. 5-2B).
   • ICF compartment contracts.

B. Isotonic, hypotonic, and hypertonic disorders
1. Serum Na⁺ concentration (mEq/L) approximates the ratio of total body Na⁺ (TBNa⁺) to total body water (TBW).
   a. Serum Na⁺ ~ TBNa⁺/TBW
      • TBNa⁺ is the sum total of all ECF Na⁺ (vascular compartment + interstitial compartment); unlike serum Na⁺, which is the Na⁺ concentration in mEq/L of serum/plasma in the vascular compartment (i.e., 136–145 mEq/L).
   b. Clinical findings that correlate with TBNa⁺ status
      (1) Decreased TBNa⁺ produces signs of volume depletion.
         (a) Some authors use the term "dehydration" instead of volume depletion.
            • Dehydration refers to a loss of pure water, not water and Na⁺.
         (b) Mucous membranes are dry (Fig. 5-3A) and there is decreased skin turgor (i.e., skin tenting when the skin is pinched; see Fig. 5-3B and C)
         (c) Blood pressure (BP) decreases (hypotension) and pulse increases (tachycardia) when sitting/standing up from a supine position (i.e., positive tilt test).
      (2) Increased TBNa⁺ produces body cavity effusions (e.g., ascites) and dependent pitting edema (see Fig. 5-3D).
         (a) Dependent pitting edema is due to an excess of Na⁺-containing fluid in the interstitial space (>2–3 L)
            • Because of the low protein content in edema fluid, fluid obeys the law of gravity and moves to dependent portions of the body (e.g., ankles, if standing; sacral area, if supine).
         (b) Alteration in Starling forces must be present to produce pitting edema and body effusions (see later).

Fluid movement across a capillary/venule wall into the interstitial space is driven by Starling forces (not osmosis). The net direction of fluid movement depends on which Starling force is dominant. An increase in plasma hydrostatic pressure (HP) and/or a decrease in plasma oncotic pressure (OP; i.e., decrease in serum albumin) causes fluid to diffuse out of capillaries/venules into the interstitial space, resulting in dependent pitting edema and body cavity effusions. Starling forces are more fully discussed later in the chapter.
Increase in TBNa\(^+\) increases plasma hydrostatic pressure

- Increase in hydrostatic pressure is due to an increase in plasma volume.

Increase in TBNa\(^+\) increases body weight.

- Increase in TBNa\(^+\) is the most common cause of weight gain in a hospitalized person.

Normal TBNa\(^+\) is associated with normal skin turgor and hydration.

2. Isotonic fluid disorders (Table 5-1)

a. Isotonic loss of fluid

1. Definition—net isotonic loss of Na\(^+\) and H\(_2\)O (↓TBNa\(^+\)/↓TBW)

2. POsm and serum Na\(^+\) are normal (hypovolemic normonatremia).

- Arrows represent the magnitude of change in TBNa\(^+\) and TBW.

3. No osmotic gradient or fluid shift exists between compartments.

- ECF volume contracts; ICF volume remains unchanged.

4. Signs of volume depletion are present.

5. Example—adult diarrhea (secretory type; refer to Chapter 18)

6. Treatment (Rx)

- Parenteral infusion of normal saline or its equivalent

\(^\uparrow\) Patient weight in hospital: ↑TBNa\(^+\)

Isotonic loss or gain: serum Na\(^+\) normal

Gain in fluid: ECF always expands

Loss in fluid: ECF always contracts

Isotonic loss: ↓TBNa\(^+\)/↓TBW; secretory diarrhea

Rx isotonic loss: normal saline
**b. Isotonic gain of fluid**

1. Definition—net isotonic gain of Na\(^+\) and H\(_2\)O (↑TBNa\(^+\)/↑TBW)
2. POsm and serum Na\(^+\) are normal (hypervolemic normonatremia).
3. No osmotic gradient or fluid shift exists between compartments.
   - ECF volume expands; ICF volume remains unchanged.

**TABLE 5-1 Isotonic and Hypotonic Disorders**

<table>
<thead>
<tr>
<th>COMPARTMENT ALTERATION</th>
<th>POsm/Na(^+)</th>
<th>ECF VOLUME</th>
<th>ICF VOLUME</th>
<th>CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ECF and ICF volume</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal hydration</td>
</tr>
</tbody>
</table>
| Isotonic net loss Na\(^+\) + H\(_2\)O | Normal ↓TBNa\(^+\)/↓TBW | Contracted | Normal | Hypovolemic normonatremia
  - Adult diarrhea (secretory type; e.g., cholera) |
| Isotonic net gain Na\(^+\) + H\(_2\)O | Normal ↑TBNa\(^+\)/↑TBW | Expanded | Normal | Hypervolemic normonatremia
  - Infusion of excessive isotonic saline |
| Net loss Na\(^+\) in excess of H\(_2\)O | Decreased ↓↓TBNa\(^+\)/↓↓TBW | Contracted | Expanded | Hypovolemic hyponatremia
  - Loop diuretics
  - Addison disease
  - 21-Hydroxylase deficiency |
| Net gain in water (no sodium) | Decreased TBNa\(^+\)/↑↑TBW | Expanded | Expanded | Euvolemic hyponatremia
  - SIADH
  - Compulsive water drinker |
| Net gain in H\(_2\)O in excess of Na\(^+\) | Decreased ↑TBNa\(^+\)/↑TBW | Expanded | Expanded | Hypervolemic hyponatremia
  - RHF
  - Cirrhosis
  - Nephrotic syndrome |

*ECF, Extracellular fluid; ICF, intracellular fluid; POsm, plasma osmolality; RHF, right-sided heart failure; SIADH, syndrome of inappropriate antidiuretic hormone; TB, total body; TBW, total body water.*

**Normal (isotonic) saline (0.9%)** approximates plasma tonicity (POsm). It is infused in patients to maintain the blood pressure when there is a significant loss of sodium-containing fluid (e.g., blood loss, diarrhea, sweat). As expected, some of the normal saline enters the interstitial compartment and some remains in the vascular compartment, the latter being responsible for raising the blood pressure. Other solutions that are used include lactated Ringer and 5% albumin. The latter remains in the vascular compartment, so less is required to maintain the blood pressure.
(4) Pitting edema and body cavity effusions may be present.
   - Elderly people or people with renal dysfunction are likely to have pitting edema/effusions.
(5) Example—excessive infusion of isotonic saline
(6) Treatment
   (a) Restrict sodium and water intake
   (b) Loop diuretics remove excess sodium and water
3. Hypotonic fluid disorders (see Table 5-1)
   a. Hyponatremia ($\downarrow$POsm) is always present.
      (1) Osmotic gradient is present.
      (2) Water shifts into the ICF compartment (expands).
   b. Hypertonic loss of Na$^+$
      (1) Definition—net loss of Na$^+$ in excess of water ($\downarrow\downarrow$TBNa$^+$/\downarrow$TBW)
      (2) POsm and serum Na$^+$ are decreased (hypovolemic hyponatremia).
      (3) ECF volume contracts; ICF volume expands.
      (4) Signs of volume depletion are present.
      (5) Examples include:
         - Loop diuretics/thiazides (excessive), Addison disease (loss of mineralocorticoids), 21-hydroxylase deficiency (loss of mineralocorticoids).
      (6) Treatment
         - Infuse normal saline or equivalent
   c. Gain of pure water
      (1) Definition—net gain in water (TBNa$^+$/↑↑TBW)
      (2) Decrease in POsm and serum Na$^+$ (euvolemic hyponatremia)
      (3) Expansion of both ECF and ICF compartments
      (4) Normal skin turgor, because TBNa$^+$ is normal
      (5) Examples include:
         - Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), compulsive water drinking
      (6) Treatment
         - Restrict water
   d. Hypotonic gain of Na$^+$
      (1) Definition—net gain in H$_2$O in excess of Na$^+$ (↑TBNa$^+$/↑↑TBW)
      (2) Decrease in POsm and serum Na$^+$ (hypovolemic hyponatremia)
      (3) Expansion of both compartments
      (4) This type of fluid gain produces pitting edema and body effusions associated with Starling force alterations; examples include:
         (a) Right-sided heart failure (RHF) with an increase in venous hydrostatic pressure
         (b) Cirrhosis and nephrotic syndrome with a decrease in plasma oncotic pressure (the former from decreased synthesis of albumin and the latter from increased loss of albumin in the urine)
In an alcoholic, rapid intravenous fluid correction of hyponatremia with saline may result in central pontine myelinolysis (see Fig. 26-18), an irreversible demyelinating disorder. However, as a general rule, all intravenous replacement of sodium-containing fluids should be given slowly over the first 24 hours regardless of the cause of the underlying serum sodium imbalance.

In the previously discussed pitting edema states, the cardiac output is decreased, because fluid is trapped in the interstitial space and body cavities. A decrease in cardiac output causes the release of catecholamines, activation of the renin-angiotensin-aldosterone system, stimulation of antidiuretic hormone (ADH) release, and increased renal retention of Na$^+$. The kidney reabsorbs a slightly hypotonic, Na$^+$-containing fluid ($\uparrow\uparrow$TBNa$^+$/↑↑TBW). Because these pitting edema states have alterations in Starling forces (increased hydrostatic pressure and/or decreased oncotic pressure), the Na$^+$-containing fluid reabsorbed by the kidneys is redirected into the interstitial space once it reaches the capillaries and venules. This further exacerbates the pitting edema and body cavity effusions. Unfortunately, the cardiac output will continue to be decreased until the cause of the decreased cardiac output is corrected.

<table>
<thead>
<tr>
<th>Isotonic gain</th>
<th>↑TBNa$^+$/↑↑TBW; ↑↑isotonic saline infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx isotonic gain</td>
<td>restrict water; loop diuretics</td>
</tr>
<tr>
<td>Hypotonic disorders</td>
<td>hyponatremia always present; ICF expansion</td>
</tr>
<tr>
<td>Hypertonic loss</td>
<td>↓↓TBNa$^+$/↓TBW</td>
</tr>
<tr>
<td>Hypertonic loss</td>
<td>loop diuretics/thiazides (excessive), Addison, ↓21-hydroxylase</td>
</tr>
<tr>
<td>Rx hypotonic loss</td>
<td>infuse normal saline or equivalent</td>
</tr>
<tr>
<td>Central pontine myelinolysis</td>
<td>rapid correction hyponatremia with saline in alcoholic</td>
</tr>
<tr>
<td>Hypotonic gain water</td>
<td>TBNa$^+$/↑↑TBW; SIADH, compulsive water drinking</td>
</tr>
<tr>
<td>Rx hypotonic gain water</td>
<td>restrict water</td>
</tr>
<tr>
<td>Hypotonic gain water + Na$^+$/↑↑TBW</td>
<td></td>
</tr>
<tr>
<td>Pitting edema states</td>
<td>RHF, cirrhosis, nephrotic syndrome; ↓cardiac output</td>
</tr>
</tbody>
</table>
Rx pitting edema states: restrict water/sodium; diuretics

Hypertonic disorder:
hypernatremia/ hyperglycemia; ICF contraction

Hypertonic conditions:
ICF always contracted

Hypotonic loss Na\(^+\) + water: ↓TBNa\(^+\)/↓↓TBW

Hypotonic loss Na\(^+\) + water: osmotic diuresis/ diarrhea, sweating, vomiting

Table 5-2 Hypertonic Disorders

<table>
<thead>
<tr>
<th>COMPARTMENT ALTERATION</th>
<th>POsm/Na(^+)</th>
<th>ECF VOLUME</th>
<th>ICF VOLUME</th>
<th>CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net loss of H(_2)O in excess of Na(^+)</td>
<td>Increased ↓TBNa(^+)/↓↓TBW</td>
<td>Contracted</td>
<td>Contracted</td>
<td>Hypovolemic hypernatremia</td>
</tr>
<tr>
<td>Hypotonic loss of Na(^+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net loss of only water</td>
<td>Increased TBNa(^+)/↓↓TBW</td>
<td>Contracted (mild)</td>
<td>Contracted</td>
<td>Euvolemic hypernatremia</td>
</tr>
<tr>
<td>Loss of water</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net gain Na(^+) in excess of H(_2)O</td>
<td>Increased ↑↑TBNa(^+)/↑TBW</td>
<td>Expanded</td>
<td>Contracted</td>
<td>Hypervolemic hypernatremia</td>
</tr>
<tr>
<td>Hypertonic gain of Na(^+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>↑Glucose ↓Na(^+) (dilutional effect from H(_2)O coming out of the ICF compartment)</td>
<td>Contracted</td>
<td>Contracted</td>
<td>Diabetic ketoacidosis</td>
</tr>
</tbody>
</table>

ECF, Extracellular fluid; ICF, intracellular fluid; POsm, plasma osmolality; TB, total body; TBW, total body water.

(4) Hypertonic fluid disorders (Table 5-2)

a. An increase in POsm is most often due to hypernatremia or hyperglycemia.
   (1) An osmotic gradient is present.
   (2) Water shifts from the ICF compartment (contracts) to the ECF compartment (expands).

b. Hypotonic loss of Na\(^+\)
   (1) Definition—net loss of H\(_2\)O in excess of Na\(^+\) (↓TBNa\(^+\)/↓↓TBW)
   (2) Both POsm and serum Na\(^+\) are increased (hypovolemic hypernatremia).
   (3) Both compartments contract.
   (4) Signs of volume depletion are present.
   (5) Examples include:
      • Sweating, osmotic diuresis (e.g., glucosuria, mannitol), diarrhea (osmotic type— laxatives; refer to Chapter 18), and vomiting
   (6) Treatment
      • Isotonic saline if hypotension is present and then switch to oral replacement or more hypotonic Na\(^+\)-containing intravenous fluids.

c. Loss of pure water
   (1) Loss of water (TBNa\(^+\)/↓↓TBW)
   (2) Both POsm and serum Na\(^+\) are increased (euvolemic hypernatremia).
(3) Both compartments are contracted.
   - ECF contraction is mild, because there is no loss of Na+
(4) Skin turgor is normal, because TBNa+ is normal.
(5) Examples include:
   - Diabetes insipidus (loss of ADH or refractoriness to ADH), insensible water loss (e.g., fever, where water evaporates from the warm skin surface)
(6) Treatment
   - Water replacement
d. Hypertonic gain of Na+
   (1) Definition—net gain in Na+ in excess of H2O (↑↑TBNa+/↑TBW)
   (2) Both P0sm and serum Na+ are increased (hypervolemic hypernatremia).
   (3) ECF compartment expands; ICF compartment contracts.
   (4) Pitting edema and body cavity effusions may be present.
   (5) Examples include:
      - Infusion of NaHCO3 or Na+-containing antibiotics, excessive ingestion of NaCl

e. Hypertonic state due to hyperglycemia
   (1) Primarily occurs in diabetic ketoacidosis (DKA) and hyperosmolar nonketotic coma (HNKC), which occurs in type 2 diabetes mellitus (refer to Chapter 23).
   (2) Both compartments contract.
      a. With excessive amounts of water moving out of the ICF compartment into the ECF compartment (more so than with hypernatremia), there is a dilutional effect on the serum Na+, causing hyponatremia.
      b. P0sm is increased because of hyperglycemia, whereas serum sodium is decreased because of dilutional hyponatremia.
      c. Water does not remain in the ECF, because glucose in urine acts as an osmotic diuretic, causing a major loss of both water and Na+
   (3) Signs of volume depletion are present.
      - Glucosuria produces a hypotonic loss of water and Na+ (osmotic diuresis), causing signs of volume depletion.
   (4) Treatment of DKA and HNKC is discussed in Chapter 23.

C. Volume control (Box 5-1)

**BOX 5-1 Volume Control**

Protection of the intravascular volume is paramount to normal survival. Maintenance of the extracellular fluid (ECF) volume involves the integration of factors that (1) control thirst (e.g., increased P0sm and angiotensin II [ATII]); (2) activate the renin-angiotensin-aldosterone (RAA) system (e.g., reduced renal blood flow, sympathetic nervous system stimulation); (3) stimulate the baroreceptors in the arterial circulation (e.g., decreased effective arterial blood volume); (4) increase free water reabsorption to concentrate the urine (e.g., antidiuretic hormone); and (5) increase renal reabsorption of Na+ and water.

**Effective Arterial Blood Volume**

Effective arterial blood volume (EABV) is a conceptual term that refers to the portion of the ECF that is in the vascular space. In most instances, it correlates directly with the ECF volume and TBNa+ status of the individual (i.e., ↓EABV // ↓ECF//↑TBNa+ or ↑EABV // ↑ECF/↑TBNa+). However, in edema states, where there is an alteration in Starling forces (e.g., right-sided heart failure), the redistribution of fluid (a transudate) from the intravascular compartment into the interstitial fluid compartment increases the total ECF volume at the expense of reducing the venous return of blood to the right side of the heart, reducing cardiac output and reducing EABV (↓EABV // ↑ECF/↑TBNa+). Hence an increase in total ECF volume does not always correlate with an increase in the EABV.

**Baroreceptors and the Renin-Angiotensin-Aldosterone System**

Control of the EABV is monitored by the pressure impacting upon the high pressure arterial baroreceptors located in the aortic arch and carotid sinus, and the flow of blood to the renal arteries. When the baroreceptors are activated by a decreased EABV, signals are sent to the medulla to increase sympathetic tone, leading to release of catecholamines. The release of catecholamines causes vasoconstriction of peripheral resistance arterioles (increases diastolic blood pressure), vasoconstriction (increases venous return to the heart), an increase in heart rate (chronotropic effect), and an increase in cardiac contractility (inotropic effect). Signals are also sent to the supraoptic and paraventricular nuclei in the hypothalamus to synthesize and release antidiuretic hormone (ADH; vasopressin) from nerve endings located in the posterior pituitary. ADH enhances the reabsorption of free water (H2O; water without electrolytes) from the collecting tubules.
**BOX 5-1 Volume Control—cont’d**

in the kidneys and is a potent vasoconstrictor of the peripheral resistance vessels. Finally, the RAA system is activated owing to reduced blood flow to the juxtaglomerular (JG) apparatus located in the afferent arterioles and by direct sympathetic stimulation of the JG apparatus with subsequent release of the enzyme renin. Renin initiates the following reaction sequence: it cleaves renin substrate (angiotensinogen) into **angiotensin I** (ATI), which is converted by pulmonary **angiotensin-converting enzyme** (ACE) into **angiotensin II** (ATII). ATII has four functions:

1. Vasoconstriction of peripheral resistance arterioles
2. Stimulation of aldosterone synthesis and release from the zona glomerulosa (aldosterone increases reabsorption in exchange for potassium ions [K+] and hydrogen ions [H+])
3. Direct stimulation of the thirst center in the brain
4. Enhances activity of the Na+/H+ antiporter in the proximal renal tubule

All of these events are an attempt to increase the EABV before medical intervention.

In contradistinction, when there is an increase in EABV, there are many counterregulatory mechanisms that act to eliminate the excess fluid before medical intervention. An increase in EABV is associated with a corresponding increase in cardiac output. This stretches the arterial baroreceptors, which triggers cessation of sympathetic outflow from the medulla. This, in turn, leads to inhibition of ADH synthesis and release, vasodilation of peripheral resistance arterioles, decreased cardiac contraction, inhibition of the RAA system, and decreased renal retention of Na+ and water. Other counterregulatory factors include **atrial natriuretic peptide** (ANP), prostaglandin E2, and **brain natriuretic peptide** (BNP). ANP is released from the left and right atria in response to atrial distention (e.g., left- and/or right-sided heart failure). ANP has multiple functions, including (1) suppression of ADH release, (2) inhibition of the effect of ATII on stimulating thirst and aldosterone secretion, (3) vasodilation of the peripheral resistance vessels, (4) direct inhibition of Na+ reabsorption in the kidneys (diuretic effect), and (5) suppression of renin release. Prostaglandin E2 (1) inhibits ADH, (2) blocks Na+ reabsorption in the kidneys, and (3) is a potent intrarenal vasodilator that offsets the vasoconstrictive effects of ATII and the catecholamines. BNP increases in the blood when the right and/or left ventricles experience volume overload (e.g., left- and/or right-sided heart failure).

**Renal Mechanisms in Volume Regulation**

The response of the kidney to volume alterations is closely integrated with many of the events previously described. The reabsorption of solutes from the proximal tubules is dependent on the **filtration fraction** (FF) in the glomerulus in concert with Starling forces that operate in the peritubular capillaries. The FF is the fraction of the renal plasma flow (RPF) that is filtered across the glomerular capillaries into the tubular lumen. It is calculated by dividing the **glomerular filtration rate** (GFR) by the RPF (FF = GFR / RPF). Normally, the FF is ~20%, with the remaining 80% of the RPF entering the efferent arterioles, which divide to form the intricate peritubular capillary microcirculation. Because prostaglandin E2, a vasodilator, controls the afferent arteriolar blood flow into the glomerulus, and ATII, a vasoconstrictor, monitors the efferent arteriolar blood flow leaving the glomerulus, the FF is significantly affected by alterations in their caliber. Starling forces in the peritubular capillaries determine how much of the fluid from the proximal tubule is reabsorbed back into the ECF compartment. A low peritubular capillary hydrostatic pressure (Pc) coupled with a high oncotic pressure (Po) is responsible for enhancing the reabsorption of solutes from the tubular lumen into the tubular cell out into the lateral intercellular space, and into the peritubular capillary.

This occurs when the EABV is decreased (e.g., ECF volume depletion, or hypovolemia). A high Pc, coupled with a low Pc results in the loss of solutes in the urine in conditions when the EABV is increased (e.g., ECF volume overload, or hypervolemia). When hypovolemia is present in the ECF, the EABV is reduced and the FF is increased (TFF = ΔGFR / ΔRPF), hence increasing the filtered load of Na+ and other solutes. The Pc is decreased and the Po is increased, resulting in the reabsorption of the filtered Na+ plus other solutes into the ECF compartment (e.g., urea) in osmotic proportions. The previous mechanism is so effective that a random urine Na+ (UNa+) measurement is usually <20 mEq/L and is often 0 when hypovolemia is extreme. In the presence of an increased EABV (B), or hypervolemia, the FF is decreased (ΔFF = TFF / GFR), the filtered load of Na+ and other solutes is decreased, the Pc is increased, and the Po is decreased, hence favoring loss of the filtered Na+ plus other solutes (e.g., urea, uric acid) in the urine (random UNa+ >20 mEq/L).

**DECREASED EFFECTIVE ARTERIAL BLOOD VOLUME**

**INCREASED EFFECTIVE ARTERIAL BLOOD VOLUME**
D. Overview of functions of the major nephron segments

1. Proximal renal tubule
   a. Primary site for Na\(^+\) reabsorption
      (1) Na\(^+\) reabsorption is increased when cardiac output is decreased.
         - (a) ↓EABV → ↑FF → P\(_{O}\) > P\(_{H}\) (refer to Box 5-1)
         - (b) Examples—congestive heart failure, cirrhosis, hypovolemia
      (2) Na\(^+\) reabsorption is decreased when cardiac output is increased.
         - (a) ↑EABV → ↓FF → P\(_{H}\) > P\(_{O}\) (refer to Box 5-1)
         - (b) Examples—mineralocorticoid excess, isotonic gain in fluid
   b. Primary site for reclamation of bicarbonate (HCO\(_3^-\); Fig. 5-4)
      (1) Definition—mechanism for reclaiming (retrieving) filtered HCO\(_3^-\) back into the blood
         • Not the same as regenerating (synthesizing) HCO\(_3^-\) (see later).
      (2) Hydrogen ions (H\(^+\)) in tubular cells are exchanged for Na\(^+\) in the urine (Na\(^+\)/H\(^+\) antiporter or exchanger).
      (3) H\(^+\) combines with filtered HCO\(_3^-\) to form H\(_2\)CO\(_3\) in the brush border of the proximal tubules.
      (4) Carbonic anhydrase (c.a.) dissolves H\(_2\)CO\(_3\) to H\(_2\)O and CO\(_2\).
         • CO\(_2\) and H\(_2\)O are reabsorbed into proximal renal tubular cells.
      (5) H\(_2\)CO\(_3\) is reformed in proximal renal tubular cells.
         • H\(_2\)CO\(_3\) dissociates into H\(^+\) and HCO\(_3^-\).
      (6) HCO\(_3^-\) is reabsorbed into the blood.
   c. Clinical effect of lowering the renal threshold for reclaiming HCO\(_3^-\)
      (1) Normal renal threshold for reclaiming HCO\(_3^-\) is 24 mEq/L, which means that it can only reclaim (retrieve) up to that threshold, and any excess HCO\(_3^-\) is lost in the urine.
         • A key point to remember is that the serum HCO\(_3^-\) concentration is equal to the renal threshold for reclaiming HCO\(_3^-\).
      (2) If the renal threshold is lowered from the normal of 24 mEq/L to 15 mEq/L (example), then the proximal tubule can only reclaim 15 mEq/L causing the serum HCO\(_3^-\) to drop to 15 mEq/L (metabolic acidosis), and the urine pH to become >5.5 from loss of HCO\(_3^-\) in the urine.
         • Urine loss of HCO\(_3^-\) continues to occur until the serum HCO\(_3^-\) matches the renal threshold; then urine pH returns to normal.

Carbonic anhydrase inhibitors (e.g., acetazolamide) lower the renal threshold for reclaiming HCO\(_3^-\). HCO\(_3^-\) combines with Na\(^+\) to form NaHCO\(_3\), which is excreted, hence acting as a proximal tubule diuretic. Loss of HCO\(_3^-\) produces metabolic acidosis (see later).
5-5: Na\(^{+}\)-K\(^{+}\)-2Cl\(^{-}\) symporter in the medullary segment of the thick ascending limb. This is the primary symporter for generating free water (fH\(_2\)O) and is also important in non-PTH reabsorption of calcium (Ca\(^{2+}\)). See the text for a full discussion. ATP; Adenosine triphosphate; o, obligated; PTH, parathyroid hormone. (From Goljan EF, Sloka KI: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 34, Fig. 2-6.)

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d. Clinical effect of raising the renal threshold for reclaiming HCO\(_3\)^-

1. Volume depletion due to excess vomiting is an example of raising the renal threshold for reclaiming (retrieving) HCO\(_3\)^-.
2. Raising the threshold means that proportionately more of the filtered HCO\(_3\)^- is reclaimed, which means that metabolic alkalosis (\(\uparrow\)HCO\(_3\)) is going to be maintained in the patient.
   - Raising the renal threshold for reclamation of HCO\(_3\)^- is the most important factor in maintaining the high serum HCO\(_3\)^- that occurs in metabolic alkalosis due to vomiting (see later).

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In heavy metal poisoning with lead or mercury, the proximal tubule cells undergo coagulation necrosis, which produces a nephrotoxic acute tubular necrosis (refer to Chapter 20). All of the normal proximal renal tubule functions are destroyed, resulting in a loss of sodium (hyponatremia), glucose (hypoglycemia), uric acid (hypouricemia), phosphorus (hypophosphatemia), amino acids, bicarbonate (type II proximal renal tubular acidosis), and urea in the urine. This is called Fanconi syndrome.

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2. Thick ascending limb (TAL; medullary segment)

a. Primary function is to generate free water (fH\(_2\)O, water that is **not** attached to any Na\(^{+}\), K\(^{+}\), or Cl\(^{-}\))
   - A secondary function is to reabsorb calcium (Ca\(^{2+}\)).

b. Generation of fH\(_2\)O primarily occurs in the active Na\(^{+}\)-K\(^{+}\)-2Cl\(^{-}\) symporter
   - (Fig. 5-5).

c. Water that is proximal to the Na\(^{+}\)-K\(^{+}\)-2Cl\(^{-}\) symporter is all obligated (o) water, which refers to water that is bound to Na\(^{+}\) (oNa\(^{+}\)), K\(^{+}\) (oK\(^{+}\)), and Cl\(^{-}\) (oCl\(^{-}\)).
   1. Obligated water must accompany every Na\(^{+}\), K\(^{+}\), or Cl\(^{-}\) excreted in urine.
   2. Obligated water **cannot** be reabsorbed by ADH, only fH\(_2\)O.

d. Symporter separates the H\(_2\)O attached to Na\(^{+}\), K\(^{+}\), and Cl\(^{-}\), and it becomes fH\(_2\)O.
   1. fH\(_2\)O is entirely free of electrolytes.
   2. Reabsorption of fH\(_2\)O in collecting tubules by ADH concentrates the urine.
   3. Loss of fH\(_2\)O in collecting tubules in the absence of ADH dilutes urine.

e. Na\(^{+}\)/K\(^{+}\)-ATPase pump moves reabsorbed Na\(^{+}\) into the interstitium.
   1. Reabsorbed Cl\(^{-}\) and K\(^{+}\) diffuse through channels into the interstitium (not the blood-stream).
   2. These electrolytes in the interstitium are important in maintaining the extremely high osmolality in the interstitium of the renal medulla.

f. Symporter reabsorbs Ca\(^{2+}\) **without** the assistance of parathyroid hormone (PTH).

g. Loop diuretics block the Cl\(^{-}\) binding site in the Na\(^{+}\)-K\(^{+}\)-2Cl\(^{-}\) symporter.
5-6: Na⁺-Cl⁻ symporter in the early distal tubule. This symporter generates free water and also is the primary site for PTH-dependent reabsorption of calcium (Ca²⁺) using the Na⁺ channel. See the text for the full discussion. ATP, Adenosine triphosphate. (From Goljan EF, Sloka Kl: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 35, Fig. 2-7.)

**Loop diuretics** (e.g., furosemide) are the mainstay for the treatment of congestive heart failure and hypercalciemia. They decrease TBNa⁺ and TBW (see earlier) and also decrease reabsorption of Ca²⁺ by the Na⁺-K⁺-2Cl⁻ symporter. The drug attaches to the Cl⁻ binding site of the symporter, which not only inhibits reabsorption of Na⁺, K⁺, and Cl⁻ but also impairs the generation of H₂O. Electrolytes are lost in the urine as obligated water. Because the normal dilution process is impaired (because less H₂O is generated), patients must be warned against consuming excess water. Loop diuretics also produce a hypertonic loss of Na⁺ in the urine (see earlier), which, along with impaired dilution, may produce hyponatremia. Additional electrolyte abnormalities include hypokalemia and metabolic alkalosis (see later).

1. **Na⁺-Cl⁻ symporter in the early distal tubule**
   a. Primarily reabsorbs Na⁺, Cl⁻, and Ca²⁺.
   b. Na⁺ and Ca²⁺ share the same site for reabsorption (Fig. 5-6).
   c. Thiazides inhibit the Cl⁻ site in the Na⁺-Cl⁻ symporter.

2. **Thiazides**, in addition to being diuretics, are the mainstay for the treatment of hypertension in both the black and the elderly populations. In both groups, renal retention of Na⁺ is the primary cause of the hypertension (refer to Chapter 10). Thiazides are also used in the treatment of hypercalciuria in people who develop Ca²⁺ renal stones (refer to Chapter 21). The drug attaches to the Cl⁻ site and inhibits Na⁺ and Cl⁻ reabsorption. This leaves the Na⁺ channel open for Ca²⁺ reabsorption. Hyponatremia may occur because of hypertonic loss of sodium (see previous discussion) in the urine. Additional electrolyte abnormalities include hypokalemia and metabolic alkalosis (see later), particularly if thiazides are taken in excess. Hypercalciemia may also be a complication; however, this is uncommon and is more likely to occur if the patient has primary hyperparathyroidism with an increase in PTH.

3. **Amiloride** and **triamterene** are diuretics with a K⁺-sparing effect. They bind to the luminal membrane Na⁺ channels, hence inhibiting Na⁺ reabsorption and K⁺ excretion.
5-7: Na\(^+\)-K\(^+\) epithelial channels (A) and Na\(^+\)-H\(^+\) epithelial channels (B) in the late distal and collecting duct. The Na\(^+\)-K\(^+\) epithelial channel (A) reabsorbs Na\(^+\) in exchange for K\(^+\). This is the primary channel for the excretion of K\(^+\). If K\(^+\) is depleted (B), then Na\(^+\) exchanges with H\(^+\) ions. For every H\(^+\) ion excreted in the urine, there is a corresponding gain of a (HCO\(_3\)\(^−\)) bicarbonate into the blood. See the text for a full discussion. ATP, Adenosine triphosphate. (From Goljan EF, Sloka KI: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 36, Fig. 2-8.)

5-8: H\(^+\)/K\(^+\)-ATPase pump in the collecting tubule. This is the primary pump for the excretion of excess H\(^+\) ions, and it also reabsorbs K\(^+\). It is an aldosterone-enhanced pump. Note that H\(^+\) in the urine is excreted as titratable acid (NaH\(_2\)PO\(_4\)) or NH\(_4\)Cl. See the text for a full discussion. ATP, Adenosine triphosphate. (From Goljan EF, Sloka KI: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 37, Fig. 2-9.)

e. Clinical effect of increased distal delivery of Na\(^+\) from loop/thiazide diuretics acting proximal to these epithelial channels
   (1) Since more Na\(^+\) is delivered to these channels than usual, there is an increase in Na\(^+\) reabsorption and K\(^+\) loss in the urine.
   (2) This produces hypokalemia, particularly if K\(^+\) supplements are not taken by the patient.
   (3) Furthermore, when hypokalemia occurs, Na\(^+\) exchanges with H\(^+\) ions, producing metabolic alkalosis (see previous discussion).

5. Aldosterone-enhanced H\(^+\)/K\(^+\)-ATPase pump (Fig. 5-8)
   a. Located in the collecting tubules
   b. Primary pump for excretion of excess H\(^+\) ions that must be eliminated daily
      (1) H\(^+\) ions are excreted into the tubule lumen in exchange for K\(^+\).
      (2) H\(^+\) combines with HPO\(_4\)\(^−\) to produce NaH\(_2\)PO\(_4\) (titratable acidity).
      (3) H\(^+\) also combines with NH\(_3\) and Cl\(^−\) to produce NH\(_4\)Cl.
         • NH\(_4\)Cl is the most effective way of removing excess H\(^+\) ions.
      (4) Both titratable acid and NH\(_4\)Cl acidify the urine.
   c. HCO\(_3\)\(^−\) is synthesized de novo and is reabsorbed into the blood.
      • This is an important pump for regenerating (synthesizing) HCO\(_3\)\(^−\).
Spironolactone is a diuretic with a K⁺-sparing effect. It inhibits aldosterone, which results in a loss of Na⁺ in the urine (see Fig. 5-7, A) and retention of K⁺ in the blood (K⁺-sparer; see Fig. 5-7A). Hyperkalemia may occur in some cases. H⁺ is retained, causing metabolic acidosis (see Fig. 5-7B and Fig. 5-8).

An angiotensin-converting enzyme (ACE) inhibitor is important in the treatment of congestive heart failure. Inhibition of the enzyme causes a decrease in angiotensin II (ATII) and aldosterone. ATII is normally a vasoconstrictor of peripheral resistance arterioles, which increases afterload (resistance the heart must contract against). Aldosterone normally reabsorbs sodium and increases preload (volume in the left ventricle). Therefore an ACE inhibitor decreases both afterload and preload. The inhibition of aldosterone is short-lived and is frequently counterbalanced by the use of spironolactone or other K⁺-sparing agents.

6. Electrolyte changes in Addison disease (also see Chapter 23)
   a. Most often due to autoimmune destruction of the adrenal cortex
   b. Pathogenesis of electrolyte abnormalities
      • Both aldosterone and other mineralocorticoids are deficient.
   c. Clinical and laboratory findings
      (1) Hyponatremia and hyperkalemia
         (a) The aldosterone-enhanced Na⁺ and K⁺ epithelial channels in the late distal tubule and collecting ducts are impaired (see Fig. 5-7A).
         (b) A hypertonic loss of Na⁺ in urine causes hyponatremia, and decreased excretion of K⁺ produces hyperkalemia.
         (c) Hypertonic loss of Na⁺ produces signs of volume depletion.
      (2) Retention of H⁺ ions, produces metabolic acidosis.
         (a) The aldosterone-enhanced H⁺/K⁺-ATPase pump in the collecting ducts is impaired (see Fig. 5-8).
         (b) This causes retention of H⁺ ions (acidosis) and interferes with regeneration of HCO₃⁻, causing a decrease in serum HCO₃⁻, which, by definition, is metabolic acidosis.
         (c) Loss of K⁺ does not significantly affect the serum K⁺ level; therefore hyperkalemia prevails in Addison disease.

7. Primary aldosteronism (also refer to Chapter 23)
   a. Epidemiology
      (1) Most frequently caused by excessive secretion of aldosterone from a benign adenoma (30%-50%) arising in the zona glomerulosa of the adrenal cortex.
      (2) Other causes—bilateral zona glomerulosa hyperplasia, adrenal carcinoma producing aldosterone
   b. Pathogenesis of electrolyte abnormalities
      • There is increased activity of the aldosterone-enhanced Na⁺-K⁺ epithelial channels in late distal/collecting ducts and H⁺/K⁺-ATPase pumps in the collecting ducts.
   c. Laboratory findings
      (1) Increased activity of aldosterone-enhanced Na⁺-K⁺ epithelial channels
         (a) Increased Na⁺ reabsorption causes mild hyponatremia (sometimes high normal serum Na⁺), and increased K⁺ excretion causes hypokalemia (see Fig. 5-7A).
            - Hypokalemia produces severe muscle weakness and polyuria (see later, section I.F.3.).
         (b) Increased Na⁺ reabsorption causes hypernatremia and increased loss of H⁺ in urine, which is counterbalanced by a gain in HCO₃⁻ causing metabolic alkalosis (see Fig. 5-7B).
      (2) Enhanced activity of the aldosterone-enhanced H⁺/K⁺-ATPase pump (see Fig. 5-8)
         (a) Increased excretion of H⁺ causes metabolic alkalosis, and increased regeneration of HCO₃⁻ causes metabolic alkalosis.
         (b) The amount of K⁺ reabsorbed by this pump does not override the amount of K⁺ excreted by the Na⁺-K⁺ epithelial channels; hence hypokalemia prevails as the primary K⁺ abnormality in primary aldosteronism.
   d. Clinical findings related to an increase in plasma volume (PV) from excess Na⁺ in the ECF compartment
      (1) ↑PV → ↑stroke volume (SV) → ↑systolic blood pressure (SBP; refer to Chapter 10)
(2) Excess Na\(^+\) in the ECF compartment enters smooth muscle cells of the peripheral resistance arterioles (refer to Chapter 10).
  - Excess Na\(^+\) opens up Ca\(^{2+}\) channels in the smooth muscle, causing vasoconstriction and an increase in diastolic blood pressure (DBP).

(3) ↑PV → ↑renal blood flow → inhibits renin-angiotensin-aldosterone (RAA) system → ↓plasma renin activity (PRA)

(4) ↑PV → ↑glomerular filtration rate → ↑peritubular capillary hydrostatic pressure (P\(_t\)) → ↓proximal tubule reabsorption of Na\(^+\) (refer to Box 5-1)

(a) Excessive loss of Na\(^+\) in the urine prevents pitting edema in primary aldosteronism and other mineralocorticoid excess states.
  - In addition, excess PV increases atrial dilation, causing the release of atrial natriuretic peptide (ANP), and ventricular dilation, causing the release of brain natriuretic peptide (BNP). Both peptides elicit sodium diuresis and play a major role in preventing pitting edema as well.

(b) Though Na\(^+\)-containing fluid is increased in interstitial tissue, there is not enough to produce pitting edema.

(c) In mineralocorticoid excess states, this paradox of not developing pitting edema is called the “escape phenomenon.”

e. Treatment
  - Surgery, if it is due to a benign adenoma

E. Clinical conditions associated with dilution and concentration of urine

1. Overview of normal of urine

a. Urine osmolality (UOsm) in the late distal tubule/collection ducts is ~150 mOsm/kg.
  - Most of the water is fH\(_2\)O and only a small amount is oH\(_2\)O accompanying solute that has not been reabsorbed.

b. Decreased POsm inhibits the release of ADH from the posterior pituitary.
  - Absence of ADH results in loss of fH\(_2\)O in urine, which defines dilution.

c. Diabetes insipidus (also refer to Chapter 23)

(1) Epidemiology
  - In central diabetes insipidus (CDI), there is an absence of ADH.
    - Common causes include CNS trauma and tumors.
  - In nephrogenic diabetes insipidus (NDI), the collecting tubules are refractory to ADH.
    - Common causes of NDI include drugs (e.g., demeclocycline, lithium) and hypokalemia (see later, section I.F.3.).

(2) Pathogenesis of electrolyte abnormalities
  - Urine is always being diluted and never concentrated.
  - As expected, UOsm is less than POsm.

(3) Clinical and laboratory findings
  - Increase in POsm increases thirst (polydipsia).
  - Inability to reabsorb fH\(_2\)O causes polyuria.
  - Hypernatremia is due to loss of pure water (TBNa\(^+\)/↓↓TBW).
  - POsm is >295 mOsm/kg; UOsm <500 mOsm/kg.
  - Water deprivation studies distinguish CDI from NDI

Water deprivation studies distinguish CDI from NDI. After water deprivation, UOsm is decreased in both CDI and NDI (<300 mOsm/kg). After injection of desmopressin acetate (ADH), POsm is >800 mOsm/kg in CDI (indicating concentration), whereas in NDI, it is still <300 mOsm/kg, because the collecting tubules are refractory to ADH.

(4) Treatment
  - CDI is treated with desmopressin acetate.
    - Volume depletion decreases polyuria, because of increased reabsorption of Na\(^+\) and water from the proximal renal tubules.

2. Overview of normal concentration of urine

a. Increase in POsm stimulates ADH synthesis and release into the blood.

b. ADH reabsorbs fH\(_2\)O out of the collecting ducts and concentrates urine.

(1) fH\(_2\)O is reabsorbed and brings the increased POsm into the normal range.

(2) As expected, UOsm is greater than POsm.
c. In chronic renal failure (CRF), both concentration and dilution are lost.
d. Syndrome of inappropriate ADH
   (1) Epidemiology
      (a) SIADH accounts for ~50% of hyponatremia in hospitalized patients.
      (b) Ectopic production of ADH is the most common cause of SIADH.
         • Small cell carcinoma of the lung is the most common neoplasm ectopically
           producing ADH.
      (c) Drugs that enhance ADH effect also produce SIADH and include:
         • Chlorpropamide, cyclophosphamide, vincristine, vinblastine, amitriptyline,
           haloperidol, phenothiazines, and narcotics
      (d) Other causes—hypothyroidism/hypocortisolism (thyroxine/cortisol normally
           inhibit ADH)
   (2) Pathophysiology of electrolyte abnormalities
      (a) Urine is always being concentrated, never diluted, because ADH is always
          present.
         • As expected, UOsm is greater than POsm.
      (b) A hypotonic gain of water is producing a dilutional hyponatremia
          (TBNa+/↑↑TBW) and an increase PV.
         • Serum Na+ <120 mEq/L is diagnostic of SIADH
      (c) An increase in PV increases the peritubular capillary hydrostatic pressure (P\text{H}).
         • Because P\text{H} is greater than P\text{o}, there is decreased proximal tubular cell
           reabsorption of Na+ (refer to Box 5-1).
         • Random urine Na+ >40 mEq/L is characteristic of SIADH.
   (3) Clinical findings
      • Mental status abnormalities, seizures, and coma commonly occur, because of
        cerebral edema (H\text{2}O movement into ICF compartment).
   (4) Treatment
      • Mild SIADH is treated by restricting water.

**Demeclocycline** is often used when a patient has a small cell carcinoma of the lung. The drug
inhibits the effect of ADH on the collecting tubules (acquired NDI), causing loss of H\text{2}O in
the urine. It is unnecessary to restrict water while the patient is taking the drug.

**F. Potassium (K\text{+})** disorders

1. Functions of potassium include:
   a. Regulation of neuromuscular excitability and muscle contraction
   b. Regulation of insulin secretion
      (1) Hypokalemia inhibits insulin secretion.
      (2) Hyperkalemia stimulates insulin secretion.

2. Control of potassium
   a. Aldosterone
      (1) Aldosterone increases K\text{+} excretion in Na+-K\text{+} epithelial channels (see Fig. 5-7A).
      (2) Aldosterone increases K\text{+} reabsorption of K\text{+} in H\text{+}/K\text{+}-ATPase pump (see Fig. 5-8).
   b. Arterial pH
      (1) Alkalosis causes H\text{+} to move out of cells and K\text{+} into cells (Fig. 5-9A).
         • Potential for developing hypokalemia

   **5-9:** Potassium (K\text{+}) shifts related to alkalosis (A) and acidosis (B). Note that in alkalosis, when the H\text{+} ions are
decreased, H\text{+} ions are available in cells for exchange with K\text{+} to balance the charges. This may result in hypokalemia.
Similarly, in acidosis, when H\text{+} ions are increased, cells can buffer the H\text{+} ions in exchange for K\text{+}. This may
result in hyperkalemia. See the text for a full discussion of other factors that affect potassium levels.

**Rx SIADH: restrict water**

**Demeclocycline: inhibits ADH; produces NDI**

**CRF: loss of concentration and dilution**

**SIADH: common cause of hyponatremia in hospitalized patient**

**SIADH: MCC small cell carcinoma of lung**

**SIADH: always concentrating never diluting**

**SIADH: UOsm greater than POsm**

**SIADH: serum Na+ <120 mEq/L; TBNa+/↑↑TBW**

**UOsm and random UNa+ increased in SIADH**

**Hypokalemia inhibits insulin secretion**

**Hyperkalemia stimulates insulin secretion**

**Aldosterone has primary control of K\text{+}**

**Alkalosis causes K\text{+} to move into cells; potential for hypokalemia**
Acidosis causes $K^+$ to move out of cells; potential for hyperkalemia

Insulin, $\beta_2$-agonists enhance Na$^+$/K$^+$-ATPase pump: $K^+$ moves into cell; hypokalemia

Digitalis, $\beta$-blockers, succinylcholine inhibit Na$^+$/K$^+$-ATPase pump: $K^+$ moves out of cell; hyperkalemia

Loop/thiazide diuretics: MCC hypokalemia

Hypokalemia: muscle weakness; ECG shows U wave

Hypokalemia: polyuria; NDI due to vacuolar nephropathy

Hypokalemia: rhabdomyolysis

Hyperkalemia: ECG shows peaked T waves; heart can stop in diastole

(2) Acidosis causes H$^+$ to move into cells (for buffering) and $K^+$ out of cells (see Fig. 5-9B).
  - Potential for developing hyperkalemia

(3) Insulin and $\beta_2$-agonists (e.g., albuterol) enhance Na$^+/K^+$-ATPase pump → $K^+$ shift into cells → potential for hypokalemia.

(4) Digitalis, $\beta$-blockers, and succinylcholine inhibit Na$^+/K^+$-ATPase pump → $K^+$ shift out of cells → potential for hyperkalemia.

3. Hypokalemia (serum $K^+$ <3.5 mEq/L)
   a. Causes (Table 5-3)
   b. Clinical and laboratory findings
      (1) Muscle weakness and fatigue are the most common complaints.
      - Muscle weakness is due to changes in intracellular/extracellular $K^+$ membrane potential.
      (2) Electrocardiogram (ECG) shows U waves (Fig. 5-10).
      (3) Polyuria
      - In severe hypokalemia, collecting tubule cells become distended with fluid (vacuolar nephropathy), rendering them refractory to ADH (i.e., NDI).
      (4) Rhabdomyolysis
      - Hypokalemia inhibits insulin → ↓ muscle glycogenesis → rhabdomyolysis (rupture of muscle) due to lack of ATP
   c. Treatment
      (1) Oral/parenteral replacement of potassium
      (2) ACE inhibitors (inhibit aldosterone, which reduces renal $K^+$ losses)
      (3) Potassium-sparing diuretics, angiotensin II receptor blockers

4. Hyperkalemia (serum $K^+$ >5 mEq/L)
   a. Causes (Table 5-4)
   b. Clinical findings
      (1) Ventricular arrhythmias
      - Severe hyperkalemia (e.g., 7–8 mEq/L) causes the heart to stop in diastole.

TABLE 5-3 Causes of Hypokalemia

<table>
<thead>
<tr>
<th>PATHOGENESIS</th>
<th>CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased intake</td>
<td>Occurs in elderly patients and those with eating disorders</td>
</tr>
<tr>
<td>Transcellular shift (intracellular)</td>
<td>Alkalosis (intracellular shift of $K^+$): vomiting, loop/thiazide diuretics, hyperventilation (respiratory alkalosis)</td>
</tr>
<tr>
<td>Drugs enhancing the Na$^+/K^+$-ATPase pump: insulin, $\beta_2$-agonists (e.g., albuterol)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal loss</td>
<td>Diarrhea (~30 mEq/L in stool)</td>
</tr>
<tr>
<td>Laxatives</td>
<td>Vomiting (~5 mEq/L in gastric juice)</td>
</tr>
<tr>
<td>Renal loss</td>
<td>Loop and thiazide diuretics (most common cause): excessive exchange of Na$^+$ for $K^+$ in late distal and collecting tubules</td>
</tr>
<tr>
<td>Osmotic diuresis: glucosuria</td>
<td></td>
</tr>
<tr>
<td>Mineralocorticoid excess: primary aldosteronism, 11-hydroxylase deficiency, Cushing syndrome, glycyrrhizic acid (licorice, chewing tobacco), secondary aldosteronism (cirrhosis, congestive heart failure, nephrotic syndrome; decreased cardiac output decreases blood flow and activates renin-angiotensin-aldosterone system)</td>
<td></td>
</tr>
</tbody>
</table>

5-10: Electrocardiogram showing hypokalemia. A positive wave after the T wave is called a U wave (arrow). U waves are a sign of hypokalemia. (From Goldman L, Schafer AI: Cecil's Medicine, 24th ed, Philadelphia, Saunders Elsevier, 2012, p 737, Fig. 119-2A.)
(2) ECG shows peaked T waves (Fig. 5-11).
- Due to accelerated repolarization of cardiac muscle
- Muscle weakness and depressed/absent deep tendon reflexes
- Hyperkalemia partially depolarizes the cell membrane, which interferes with membrane excitability.

c. Treatment
(1) Low-potassium diet
(2) β-Adrenergic agonists (shifts K⁺ into cells)
(3) Calcium gluconate (cardioprotective by stabilizing cardiac cell membranes against depolarization)
(4) Intravenous insulin with glucose (shifts K⁺ into cells), loop diuretics (lose K⁺ in urine), cation exchange resins (exchange Na⁺ for K⁺ in colon)

II. Acid-Base Disorders

**Compensation** refers to respiratory and renal mechanisms that bring the arterial pH close to but not into the normal pH range (7.35–7.45). In primary respiratory acidosis and alkalosis, compensation is metabolic alkalosis and metabolic acidosis, respectively. In primary metabolic acidosis and alkalosis, compensation is respiratory alkalosis and respiratory acidosis, respectively. When the expected compensation remains in the normal range, an uncompensated disorder is present. If compensation moves outside the normal range but does not bring pH into the normal range, a partially compensated disorder is present. When compensation brings the pH into the normal range, full compensation is present, which rarely occurs with the exception of chronic respiratory alkalosis, particularly at high altitude. The pH defines the primary acid-base disorder. For example, if there is a metabolic acidosis (↓HCO₃⁻), a respiratory alkalosis (↓Paco₂), and an acid pH (↓pH), the primary disorder is metabolic acidosis, and respiratory alkalosis is compensation.

**Table 5-4 Causes of Hyperkalemia**

<table>
<thead>
<tr>
<th>PATHOGENESIS</th>
<th>CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue breakdown</td>
<td>Pseudohyperkalemia (e.g., hemolysis of RBCs due to traumatic venipuncture, thrombocytosis, leukocytosis)</td>
</tr>
<tr>
<td></td>
<td>Rhabdomyolysis (rupture of muscle)</td>
</tr>
<tr>
<td>Increased intake</td>
<td>Increased intake of salt substitute</td>
</tr>
<tr>
<td></td>
<td>Infusion of old blood</td>
</tr>
<tr>
<td></td>
<td>K⁺-containing antibiotics</td>
</tr>
<tr>
<td>Transcellular shift (extracellular)</td>
<td>Acidosis</td>
</tr>
<tr>
<td></td>
<td>Drugs inhibiting the Na⁺/K⁺-ATPase pump: β-blocker (e.g., propranolol), digitalis toxicity, succinylcholine</td>
</tr>
<tr>
<td>Decreased renal excretion</td>
<td>Renal disease: renal failure (most common cause), interstitial nephritis (legionnaires disease, lead poisoning, sickle cell nephropathy, analgesic nephropathy, obstructive uropathy)</td>
</tr>
<tr>
<td></td>
<td>Mineralocorticoid deficiency: Addison disease, 21-hydroxylase deficiency, hyporeninemic hypoaldosteronism (destruction of juxtaglomerular apparatus, type IV RTA)</td>
</tr>
<tr>
<td></td>
<td>Drugs: spironolactone (inhibits aldosterone), triamterene, amiloride (inhibit Na⁺ channels)</td>
</tr>
</tbody>
</table>

RTA, Renal tubular acidosis.

**5-11: Electrocardiogram (lead V₃) showing hyperkalemia. Arrows show peaked T waves, which are a sign of hyperkalemia.** (From Goldman L, Schafer AI: Cecil's Medicine, 24th ed, Philadelphia, Saunders Elsevier, 2012, p 738, Fig. 119-3A.)
### Table 5-5 Causes of Respiratory Acidosis and Alkalosis

<table>
<thead>
<tr>
<th>ANATOMIC SITE</th>
<th>RESPIRATORY ACIDOSIS</th>
<th>RESPIRATORY ALKALOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS respiratory center</td>
<td>Depression of center: trauma, barbiturates, narcotics, brainstem disease</td>
<td>Overstimulation: anxiety, high altitude, normal pregnancy (estrogen/progesterone effect), salicylate poisoning, endotoxic (septic) shock, cirrhosis</td>
</tr>
<tr>
<td>Upper airway</td>
<td>Obstruction: acute epiglottitis (<em>Haemophilus influenzae</em>), croup (parainfluenza virus), obstructive sleep apnea, obesity</td>
<td></td>
</tr>
<tr>
<td>Chest wall disorders</td>
<td>Severe kyphoscoliosis, flail chest, ankylosing spondylitis</td>
<td>Rib fracture: hyperventilation from pain</td>
</tr>
<tr>
<td>Muscles respiration</td>
<td>Muscle weakness: ALS, phrenic nerve injury, Guillain-Barré syndrome, polymyelitis, myasthenia gravis, hypokalemia, hypophosphatemia (↓ATP), botulism, muscular dystrophy</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>Obstructive disease: chronic bronchitis, cystic fibrosis</td>
<td>Restrictive disease: sarcoidosis, asbestosis</td>
</tr>
<tr>
<td></td>
<td>Other: pulmonary edema (severe), ARDS, RDS, severe bronchial asthma</td>
<td>Others: pulmonary embolus, pulmonary edema (early), mild bronchial asthma (early phases before they get tired), early phase of ARDS, chronic illness in a hospital (chronic respiratory alkalosis; very common), pneumothorax (tension and spontaneous), mechanical ventilation</td>
</tr>
</tbody>
</table>

*ALS, Amyotrophic lateral sclerosis; ARDS, acute respiratory distress syndrome; ATP, adenosine triphosphate; RDS, respiratory distress syndrome.*

**Formulas** are available that calculate the expected compensation for an arterial blood gas disorder. Calculation for the expected compensation of a blood gas disorder helps in identifying whether there is more than one primary acid-base disorder in a patient (called a mixed disorder; see later). The formulas are located in the appendix.

**A. Primary alterations in arterial Pco₂ (Paco₂ = 33–45 mm Hg)**

1. Respiratory acidosis
   a. Causes (Table 5-5)
   b. Pathogenesis
      1. Respiratory acidosis is due to alveolar hypoventilation with retention of CO₂.
      2. Paco₂ >45 mm Hg
         - ↓pH ~ ↑HCO₃⁻/↑↑Pco₂
      3. Metabolic alkalosis is compensation.
         a. Serum HCO₃⁻ ≤30 mEq/L defines an acute respiratory acidosis.
         b. Serum HCO₃⁻ >30 mEq/L (indicates renal compensation) defines a chronic respiratory acidosis.
   c. Clinical and laboratory findings
      1. Somnolence
      2. Cerebral edema (vasodilation of cerebral vessels)
      3. Cyanosis skin/mucous membranes (refer to Chapter 2)
      4. Hypoxemia (↓Pao₂; refer to Chapter 2)
   d. Treatment
      1. Treat the underlying condition
      2. Cautious use of O₂ (danger of taking away the stimulus for breathing)
      3. Ventilatory support

2. Respiratory alkalosis
   a. Causes (see Table 5-5)
   b. Pathogenesis
      1. Respiratory alkalosis is characterized by alveolar hyperventilation with elimination of CO₂.
      2. Paco₂ <33 mm Hg
         - ↑pH ~ ↓HCO₃⁻/↓↓Pco₂
      3. Metabolic acidosis is compensation.
         a. Serum HCO₃⁻ ≥18 mEq/L defines acute respiratory alkalosis.
         b. Serum HCO₃⁻ <18 mEq/L, but >12 mEq/L (indicates renal compensation) defines chronic respiratory alkalosis.
Normal Plasma Acidosis (no gap) Acidosis (gap)

Normal Plasma

- Sodium (Na⁺)
- Chloride (Cl⁻)
- Bicarbonate (HCO₃⁻)
- Albumin

Acidosis (no gap)

- Sodium (Na⁺)
- Chloride (Cl⁻)
- Bicarbonate (HCO₃⁻)
- Albumin

Acidosis (gap)

- Sodium (Na⁺)
- Chloride (Cl⁻)
- Bicarbonate (HCO₃⁻)
- Albumin

5-12: Comparison of increased anion gap (AG) metabolic acidosis and normal anion gap metabolic acidosis. Note that unmeasured anions (UA) are increased in the increased AG type of metabolic acidosis and are normal in the normal AG metabolic acidosis. Also note that the chloride (Cl⁻) is increased in normal AG metabolic acidosis and normal in increased AG metabolic acidosis. (From Kliegman R: Nelson Textbook of Pediatrics, 19th ed, Philadelphia, Elsevier Saunders, 2011, p 234, Fig. 52.4.)

### c. Clinical findings

1. Light-headedness and confusion
2. Signs of tetany (also refer to Chapter 23)
   a. Thumb adduction into the palm (carpopedal spasm; see Fig. 23-13A)
   b. Perioral twitching when the facial nerve is tapped (Chvostek sign)
   c. Perioral numbness and tingling

### B. Primary alterations in HCO₃⁻ (22–28 mEq/L)

1. Metabolic acidosis
   a. Pathogenesis
      1. Serum HCO₃⁻ <22 mEq/L
         - ↓pH ~ ↓HCO₃⁻/↓Pco₂
      2. Respiratory alkalosis is compensation.
      3. Addition of an acid to the ECF compartment produces an increased anion gap (AG) type of metabolic acidosis (see later).
      4. Loss of HCO₃⁻ or inability to synthesize or reclaim HCO₃⁻ produces a normal AG type of metabolic acidosis (see later).
         - Loss of HCO₃⁻ is counterbalanced by a gain in Cl⁻ anions.
      5. Figure 5-12 contrasts the two types of metabolic acidosis.
   b. Increased AG type of metabolic acidosis
      1. Causes of an increased AG metabolic acidosis (Table 5-6)
      2. Formula for calculating AG and pathogenesis of increased AG metabolic acidosis
         a. AG = serum Na⁺ − (serum Cl⁻ + serum HCO₃⁻) = 12 mEq/L +/− 2, in which 12 mEq/L represents anions not accounted for in the formula (e.g., phosphate, albumin, sulfate) but are normally present in serum.
         b. If the AG is >12 mEq/L ± 2, there are additional anions present that should not be there (e.g., lactate, salicylate, acetocacteate anions).
      3. Excess H⁺ ions of the acid (e.g., lactic acid) are buffered by HCO₃⁻, which decreases the serum HCO₃⁻ (H⁺ + HCO₃⁻ → H₂CO₃ → H₂O + CO₂).
      4. Loss of HCO₃⁻ (negative anions) from buffering H⁺ ions is counterbalanced by anions of the acid (e.g., lactate anions).
         - Example—for every HCO₃⁻ ion lost, there is a corresponding lactate anion to replace it.
      5. Example of an anion gap calculation—serum Na⁺ 130 mEq/L (135–147), serum Cl⁻ 88 mEq/L (95–105), serum HCO₃⁻ 10 mEq/L (22–28)
         - AG = 130 − (88 + 10) = 32 mEq/L (12 mEq/L ± 2).

### Alkalosis

Alkalosis increases the number of negative charges on albumin (more COO⁻ groups on acidic amino acids). Therefore calcium is displaced from the ionized calcium fraction and is bound to albumin, causing a decrease in ionized calcium levels and signs of tetany (see Fig. 23-13A).

### Tetany

Tetany: commonly occurs in acute respiratory alkalosis

### Alkalosis

↑COO⁻ groups in acidic amino acids on albumin

### Metabolic acidosis

- Serum HCO₃⁻ <22 mEq/L
- ↓pH ~ ↓HCO₃⁻/↓Pco₂

### Respiratory alkalosis

- Compensation for metabolic acidosis

- ↑AG: additional anions are present that should not be there
- Metabolic acidosis: ↓HCO₃⁻ due to buffering of excess H⁺ from an acid
- ↑AG metabolic acidosis: anions of acid replace buffered HCO₃⁻
- Lactic acidosis: most common ↑AG metabolic acidosis
### TABLE 5-6 Causes of Increased Anion Gap Metabolic Acidosis

<table>
<thead>
<tr>
<th>CAUSES</th>
<th>PATHOGENESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis</td>
<td>Product of pyruvic acid metabolism</td>
</tr>
<tr>
<td></td>
<td>Most common type of TAG metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td>Any cause of tissue hypoxia with concomitant anaerobic glycolysis: e.g., shock, CN poisoning, CO poisoning, severe hypoxemia (Pao₂ &lt;35 mm Hg), severe CHF, severe anemia (Hb &lt;8 g/dL), uncoupling of oxidative phosphorylation (e.g., dinitrophenol), respiratory failure; diabetic ketoacidosis and hyperosmolar nonketotic coma (both produce shock from loss of Na⁺ fluid by osmotic diuresis)</td>
</tr>
<tr>
<td></td>
<td>Alcoholism: pyruvate is converted to lactate from the excess of NADH in alcohol metabolism.</td>
</tr>
<tr>
<td></td>
<td>Liver disease: the liver normally converts lactate to pyruvate, and pyruvate is used to synthesize glucose by gluconeogenesis (Cori cycle). Liver disease (e.g., hepatitis, cirrhosis) causes lactate to accumulate in the blood.</td>
</tr>
<tr>
<td></td>
<td>Renal failure Drugs/chemicals: phenformin, salicylates, methanol and ethylene glycol metabolites</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>Diabetic ketoacidosis (type 1 diabetes mellitus): accumulation of AcAc and β-OHB. Alcoholism: acetyl CoA in alcohol metabolism is converted to ketoacids. Increase in NADH causes AcAc to convert to β-OHB, which is not detected with standard tests for ketone bodies.</td>
</tr>
<tr>
<td></td>
<td>Starvation, normal pregnancy, ketogenic diet</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Retention of acids: e.g., sulfuric acid, phosphoric acid, uric acid</td>
</tr>
<tr>
<td>Salicylate poisoning</td>
<td>Salicylic acid is an acid. It is also a mitochondrial toxin that uncouples oxidative phosphorylation, leading to tissue hypoxia and lactic acidosis. In some cases, excess salicylate overstimulates the CNS respiratory center, producing a primary respiratory alkalosis.</td>
</tr>
<tr>
<td>Ethylene glycol poisoning</td>
<td>Ethylene glycol is in antifreeze. It is converted to glycolic and oxalic acid by alcohol dehydrogenase. Oxalate anions combine with calcium to produce calcium oxalate crystals that obstruct the renal tubules, causing renal failure. It increases the osmolar gap. IV infusion of ethanol decreases the metabolism of ethylene glycol, because alcohol dehydrogenase is preferentially metabolizing alcohol. Unmetabolized ethylene glycol is removed by hemodialysis. Another treatment is the use of fomepizole (4-methylpyrazole), which inhibits alcohol dehydrogenase. Osmolal gap &gt;10 mOsm/kg.</td>
</tr>
<tr>
<td>Methyl alcohol poisoning</td>
<td>Methyl alcohol is present in windshield washer fluid, Sterno, and solvents for paints. It is converted into formic acid by alcohol dehydrogenase. Formic acid damages the optic nerve, causing optic neuritis and the potential for permanent blindness. IV infusion of ethanol decreases the metabolism of methyl alcohol, because alcohol dehydrogenase is preferentially metabolizing alcohol. Another treatment is the use of fomepizole (4-methylpyrazole), which inhibits alcohol dehydrogenase. Osmolal gap &gt;10 mOsm/kg.</td>
</tr>
</tbody>
</table>

**AcAc, Acetoacetate; AG, anion gap; β-OHB, β-hydroxybutyrate; CHF, congestive heart failure; CN, cyanide; CO, carbon monoxide; Hb, hemoglobin; IV, intravenous; NADH, reduced form of nicotinamide adenine dinucleotide.**

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**Calculation of the osmolal gap** is useful in evaluating causes of an increased AG metabolic acidosis. The plasma osmolality (POsm) is calculated as follows: POsm = 2 (serum Na⁺) + serum glucose/18 + serum blood urea nitrogen/2.8 + serum ethanol (mg/dL)/4.6 (if the patient is drinking ethanol) and is then subtracted from the measured POsm. A difference of <10 mOsm/kg is normal. A difference of >10 mOsm/kg is highly suspicious for methanol or ethylene glycol poisoning.

---

c. Normal AG metabolic acidosis
   1. Causes (Table 5-7)
   2. Acidosis is due to a loss of H⁺ ions or an inability to synthesize (regenerate) or reclaim (retrieve) HCO₃⁻ in the kidneys.
   3. Cl⁻ anions increase to counterbalance the reduction in HCO₃⁻ anions (also called hyperchloremic normal AG metabolic acidosis).
   4. Example—serum Na⁺ 136 mEq/L, serum Cl⁻ 110 mEq/L, serum HCO₃⁻ 14 mEq/L
      a. AG = 136 – (110 + 14) = 12 mEq/L
      b. Drop of 10 mEq/L of HCO₃⁻ from normal (24 – 14 = 10) is counterbalanced by a gain of 10 mEq/L of Cl⁻ ions (100 + 10 = 110).

d. Clinical findings in both types of metabolic acidosis
   1. Hyperventilation (Kussmaul breathing)
   2. Warm shock
      a. Acidosis vasodilates peripheral resistance arterioles.

---

**Osmol gap:** useful in diagnosing methanol or ethylene glycol poisoning

**Normal AG metabolic acidosis:** Cl⁻ anions replace HCO₃⁻
### Causes of Normal Anion Gap Metabolic Acidosis

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>PATHOGENESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>In children, diarrhea is the most common cause of normal anion gap metabolic acidosis. There is a loss of HCO₃⁻ in diarrheal stool. The source of HCO₃⁻ is from the pancreas, which alkalizes the gastric meal so the pancreatic and small bowel enzymes are functional.</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>The drug binds HCO₃⁻ as well as bile salts, vitamins, and some drugs.</td>
</tr>
<tr>
<td>Drainage of bile or pancreatic secretions</td>
<td>Bile and pancreatic secretions contain large amounts of HCO₃⁻.</td>
</tr>
<tr>
<td>Type I distal renal tubular acidosis</td>
<td>There is inability to regenerate HCO₃⁻ because of a dysfunctional H⁺/K⁺-ATPase pump in the collecting tubules (refer to Fig. 5-8). Excess H⁺ ions in the blood combine with Cl⁻ anions producing a normal anion gap metabolic acidosis. Hypokalemia is severe. Inability to secrete H⁺ ions decreases titratable acidity and the production of NH₄Cl causing the urine pH to be &gt;5.5. Ammonia (NH₃), which normally diffuses into the urine from the medullary interstitium around the collecting ducts, cannot be excreted as NH₄Cl because H⁺ ions are not being excreted into the urine by the dysfunctional H⁺/K⁺-ATPase pump. In addition, the lack of H⁺ ions decreases the excretion of titratable acid (NaH₂PO₄). Causes: amphothericin B, lithium, analgesics, light chains in multiple myeloma, autoimmune disease (e.g., SLE, RA, SS), sickle cell trait/disease Rx: oral administration of HCO₃⁻.</td>
</tr>
<tr>
<td>Type II proximal renal tubular acidosis</td>
<td>The renal threshold for reclaiming HCO₃⁻ is lowered from a normal of ~24 mEq/L to ~18 mEq/L (refer to Fig. 5-4). Urine pH is initially &gt;5.5 (alkaline), because of a loss of the filtered HCO₃⁻ in the urine. However, when the serum HCO₃⁻ eventually equals the renal threshold for reclaiming HCO₃⁻ (~18 mEq/L), the proximal tubules can reclaim the filtered HCO₃⁻, causing the urine pH to drop to &lt;5.5 (acid). Therefore early in the pathogenesis of proximal RTA the urine is alkaline, but later in the disease, the urine is acidic. Hypokalemia may occur due to K⁺ binding to HCO₃⁻. Causes: carbonic anhydrase inhibitors (most common cause), primary hyperparathyroidism (PTH, proximal tubule HCO₃⁻ reclamation), proximal tubule nephrotoxic drugs (e.g., aminoglycosides, valproic acid, streptozotocin), proximal tubule nephrotoxic chemicals (e.g., lead, mercury), Wilson disease Rx: thiazides to produce volume depletion, which increases the renal threshold for reclaiming HCO₃⁻.</td>
</tr>
<tr>
<td>Type IV renal tubular acidosis</td>
<td>This is the most common RTA in adults. It is also the only renal tubular acidosis with hyperkalemia. Type IV RTA is due to aldosterone deficiency from destruction of the JG apparatus in the afferent arterioles. Two prominent causes of this destruction are hyaline arteriolosclerosis of the afferent arterioles in DM (refer to Chapter 10) and acute or chronic tubulointerstitial inflammation (e.g., legionnaires disease). Destruction of the JG apparatus produces a hyporeninemic hypoaldosteronism. Since aldosterone controls the Na⁺-K⁺ epithelial channels, loss of aldosterone leads to loss of Na⁺ in the urine and retention of K⁺ in the blood, the latter producing hyperkalemia. Furthermore, aldosterone controls the H⁺/K⁺-ATPase pump in the collecting tubule; therefore there is less excretion of H⁺ into the urine in type IV RTA. The role of hyperkalemia is critical to understand the pathophysiology of type IV RTA, because it inhibits the synthesis of ammonia in the proximal tubules. Normally, glutamic dehydrogenase converts α-ketoglutarate to glutamine and NH₃. In the cell, NH₃ is converted to NH₄⁺, which is excreted into the urine in exchange for Na⁺. Some of the NH₄⁺ remains in the urine to eventually become NH₄Cl, while the remainder is reabsorbed in the thick ascending limb and deposited in the medullary interstitial fluid around the collecting ducts. NH₃ in this latter site eventually diffuses into the urine and combines with H⁺ that is excreted by the H⁺/K⁺-ATPase pump. With this as background, in type IV RTA, it is important to understand that hyperkalemia inhibits ammonia formation in the proximal tubule by altering the intracellular pH. K⁺ enters the renal cells in exchange for H⁺, which leaves the cell, causing an intracellular alkalosis. Intracellular alkalosis inhibits NH₃ synthesis from glutamine. Hence, type IV RTA is not only a problem with hypoaldosteronism and its effect on inhibiting the Na⁺-K⁺ epithelial channels and inhibiting the H⁺/K⁺-ATPase pump, but it is also a problem in ammoniagenesis in the proximal tubule and excretion of NH₄Cl in the urine. In spite of this, the urine pH is usually acidic (pH &lt;5.5).</td>
</tr>
</tbody>
</table>

DM, Diabetes mellitus; JG, juxtaglomerular; PTH, parathyroid hormone; RA, rheumatoid arthritis; RTA, renal tubular acidosis; Rx, treatment; SLE, systemic lupus erythematosus; SS, Sjögren syndrome.
Metabolic alkalosis:

- lose H⁺ or gain HCO₃⁻
- there is a gain in HCO₃⁻ because of enhanced function of the aldosterone-enhanced Na⁺-H⁺ epithelial channels in the late distal and collecting ducts leading to increased synthesis of HCO₃⁻ and metabolic alkalosis (see Fig. 5-7B). Infusion of normal saline does not correct the metabolic alkalosis (chloride-resistant).

Causes:
- primary aldosteronism
- 11-hydroxylase deficiency
- Cushing syndrome

Clinical findings:
- hyperventilation, warm shock, osteoporosis

Table 5-8 Causes of Metabolic Alkalosis

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>PATHOGENESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>There is a loss of hydrochloric acid in vomiting that results in volume depletion. For every H⁺ ion lost in the vomitus, there is a corresponding HCO₃⁻ in the blood that produces metabolic alkalosis. Because of volume depletion, the renal threshold for reclaiming HCO₃⁻ is increased. This occurs because in volume depletion, there is increased exchange of H⁺ ions for Na⁺ in the Na⁺H⁺ antipporter (see Fig. 5-4). The increase in H⁺ ions in the urine allows for more of the filtered HCO₃⁻ to be converted into H₂O and CO₂ in the brush border, which enters the proximal tubule and is converted HCO₃⁻, which, in turn, enters the blood. This increase in reclaiming of filtered HCO₃⁻ is what maintains the metabolic alkalosis in vomiting. However, if volume depletion is corrected (e.g., infusion of normal saline), the renal threshold for reclaiming HCO₃⁻ goes back to normal, and the excess HCO₃⁻ is lost in the urine. This defines a chloride-responsive type of metabolic alkalosis (i.e., infusion of saline corrects the metabolic alkalosis).</td>
</tr>
<tr>
<td>Mineralocorticoid excess</td>
<td>There is a gain in HCO₃⁻ because of enhanced function of the aldosterone-enhanced Na⁺-H⁺ epithelial channels in the late distal and collecting ducts leading to increased synthesis of HCO₃⁻ and metabolic alkalosis (see Fig. 5-7B). Infusion of normal saline does not correct the metabolic alkalosis (chloride-resistant). Causes: primary aldosteronism, 11-hydroxylase deficiency, Cushing syndrome</td>
</tr>
<tr>
<td>Loop and thiazide diuretics</td>
<td>Block in Na⁺ reabsorption in the Na⁺-K⁺-2Cl⁻ symporter by loop diuretics and the Na⁺-Cl⁻ symporter by thiazides leads to augmented late distal and collecting tubule reabsorption of Na⁺ and excretion of H⁺ (Na⁺-H⁺ epithelial channels), leading to increased synthesis of HCO₃⁻ (see Fig. 5-7B). Volume depletion also increases the proximal tubule reclamation of HCO₃⁻, which maintains the metabolic alkalosis (chloride-responsive metabolic alkalosis).</td>
</tr>
<tr>
<td>Other causes</td>
<td>Nasogastric suction</td>
</tr>
</tbody>
</table>

(3) Osteoporosis
- Bone buffers excess H⁺ ions causing loss of both organic and mineralized bone.

e. Treatment
(1) Alkalining agents (e.g., sodium bicarbonate, type I distal renal tubule acidosis)
(2) Insulin for type 1 diabetes mellitus

2. Metabolic alkalosis
a. Pathogenesis
(1) Due to a loss of H⁺ ions or gain in HCO₃⁻.
(2) Serum HCO₃⁻ >28 mEq/L
  - ↑pH ~ ↑↑HCO₃⁻/↑PCO₂
(3) Respiratory acidosis is compensation.

b. Types and causes of metabolic alkalosis (Table 5-8)
(1) Chloride responsive
  (a) Causes of metabolic alkalosis that fall under this category include vomiting and loop/thiazide diuretics.
  (b) Characteristic findings include:
    - Volume depletion
    - Decreased serum Cl⁻
    - Correction by infusion of normal saline (origin of the term Cl⁻ responsive)
(2) Chloride resistant
  (a) Causes of metabolic alkalosis that fall under this category are due to mineralocorticoid excess (e.g., primary aldosteronism).
  (b) Characteristic findings include:
    - Volume excess
    - Increased serum Cl⁻
    - No correction by infusion of normal saline (origin of the term Cl⁻ resistant)

c. Clinical findings
- Increased risk for ventricular arrhythmias is due to left shift in oxygen-binding curve by alkalosis causing hypoxia (refer to Chapter 2).

d. Treatment
(1) Acidifying agents for severe metabolic alkalosis
(2) Spironolactone (aldosterone inhibitor for mineralocorticoid excess)
(3) ACE inhibitors (useful in treating mineralocorticoid excess by blocking aldosterone synthesis)
TABLE 5-9 Selected Electrolyte Profiles

<table>
<thead>
<tr>
<th>SERUM Na⁺ (mEq/L)</th>
<th>SERUM K⁺ (mEq/L)</th>
<th>SERUM Cl⁻ (mEq/L)</th>
<th>SERUM HCO₃⁻ (mEq/L)</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>136–145</td>
<td>3.5–5.0</td>
<td>95–105</td>
<td>22–28</td>
<td>Normal ranges</td>
</tr>
<tr>
<td>118</td>
<td>3.0</td>
<td>84</td>
<td>22</td>
<td>SIADH: dilutional effect of excess water on all electrolytes</td>
</tr>
<tr>
<td>128</td>
<td>5.9</td>
<td>96</td>
<td>40</td>
<td>Addison disease: lack of aldosterone causes loss of Na⁺ (hyponatremia), retention of K⁺ (hyperkalemia), and decreased synthesis of HCO₃⁻ (normal AG metabolic acidosis—calculated AG is 12 mEq/L; see Fig. 5-7A and B)</td>
</tr>
<tr>
<td>130</td>
<td>2.9</td>
<td>80</td>
<td>36</td>
<td>Vomiting: loss of Na⁺ and K⁺ in vomitus (hyponatremia, hypokalemia); volume depletion causes increased reclamation of HCO₃⁻ in proximal tubule (metabolic alkalosis; see Fig. 5-4) Loop and thiazide diuretics: hypertonic loss of Na⁺ in urine (hyponatremia); augmented exchange of Na⁺ for K⁺ in Na⁺-K⁺ epithelial channel (hypokalemia) and increased loss of H⁺ and regeneration of HCO₃⁻ (metabolic alkalosis, see Fig. 5-7A and B)</td>
</tr>
<tr>
<td>146</td>
<td>2.8</td>
<td>110</td>
<td>33</td>
<td>Mineralocorticoid excess: primary aldosteronism; augmented exchange of Na⁺ for K⁺ (mild hypernatremia, severe hypokalemia), and increased synthesis of HCO₃⁻ (metabolic alkalosis, see Fig. 5-7A and B)</td>
</tr>
<tr>
<td>138</td>
<td>4.0</td>
<td>90</td>
<td>10</td>
<td>Increased anion gap metabolic acidosis (e.g., lactic acidosis). The calculated anion gap is 38 mEq/L</td>
</tr>
<tr>
<td>140</td>
<td>2.2</td>
<td>114</td>
<td>14</td>
<td>Normal anion gap metabolic acidosis (e.g., diarrhea). The calculated anion gap is 12 mEq/L</td>
</tr>
</tbody>
</table>

SIADH, Syndrome of inappropriate antidiuretic hormone.

C. Mixed acid-base disorders
1. Blend of two or more primary acid-base disorders occurring at the same time.
2. Clues suggesting a mixed disorder (also see appendix)
   a. Presence of a normal pH due to a combination of a primary acidosis and a primary alkalosis; for example:
      (1) Salicylate intoxication, particularly in adults
         (a) Salicylic acid produces a primary metabolic acidosis.
         (b) Salicylates can overstimulate the respiratory center, causing primary respiratory alkalosis.
         (c) If there is no respiratory center overstimulation, the pH is acidic, indicating a simple primary metabolic acidosis with compensatory respiratory alkalosis.
      (2) Patient with chronic bronchitis who is taking a loop diuretic
         (a) Chronic bronchitis produces a primary respiratory acidosis.
         (b) Loop diuretics produce a primary metabolic alkalosis.
   b. Presence of an extreme acidemia due to a primary metabolic acidosis plus a primary respiratory acidosis; for example:
      • Cardiorespiratory arrest with primary respiratory acidosis (no ventilation) and primary metabolic acidosis (lactic acidosis from hypoxia)
   c. Presence of an extreme alkalemia due to a primary metabolic alkalosis plus a primary respiratory alkalosis; for example:
      • Severe vomiting (metabolic alkalosis) + hyperventilation (respiratory alkalosis)
D. Selected electrolyte profiles (Table 5-9)
E. Selected arterial blood gas profiles (Table 5-10)

III. Edema
A. Definition
• Increased fluid in the interstitial space of the ECF compartment
B. Types
1. Transudate (also refer to Chapter 3)
   a. Protein-poor (<3 g/dL) and cell-poor fluid

Mixed acid-base disorder: two or more primary acid-base disorders
Salicylate intoxication: mixture 1° metabolic acidosis and 1° respiratory acidosis; normal pH
Chronic bronchitis + loop diuretic = 1° chronic respiratory acidosis + 1° metabolic alkalosis and normal pH
Cardiorespiratory arrest = 1° respiratory acidosis + 1° metabolic acidosis = extreme acidemia
Clues for mixed disorder: normal pH; extreme acidemia or alkalemia
Edema: excess fluid in interstitial space
Transudate: protein-poor and cell-poor fluid
TABLE 5-10 Selected Arterial Blood Gas Profiles

<table>
<thead>
<tr>
<th>pH</th>
<th>PaCO₂ (mm Hg)</th>
<th>HCO₃⁻ (mEq/L)</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.35–7.45</td>
<td>33–45</td>
<td>22–28</td>
<td>Normal ranges</td>
</tr>
</tbody>
</table>
| 7.00  | 52            | 13            | Mixed disorder (extreme acidemia): primary metabolic acidosis (HCO₃⁻ <22 mEq/L), primary respiratory acidosis (PaCO₂ >45 mm Hg)  
Example: cardiorespiratory arrest |
| 7.20  | 74            | 28            | Acute respiratory acidosis, uncompensated (PaCO₂ >45 mm Hg, HCO₃⁻ <30 mEq/L)  
Example: CNS respiratory center depression (e.g., barbiturate poisoning) |
| 7.33  | 60            | 31            | Chronic respiratory acidosis with partially compensated metabolic alkalosis (PaCO₂ >45 mm Hg, HCO₃⁻ >30 mEq/L)  
Examples: chronic bronchitis, cystic fibrosis |
| 7.28  | 28            | 12            | Metabolic acidosis with partially compensated respiratory alkalosis (HCO₃⁻ <22 mEq/L, PaCO₂ <33 mm Hg)  
Examples: disorders associated with increased and normal anion gap metabolic acidosis |
| 7.42  | 22            | 14            | Mixed disorder (normal pH): primary metabolic acidosis (HCO₃⁻ <22 mEq/L), primary respiratory alkalosis (PaCO₂ <33 mm Hg)  
Examples: salicylate poisoning, septic shock |
| 7.50  | 47            | 35            | Metabolic alkalosis with partially compensated respiratory acidosis (HCO₃⁻ >28 mEq/L, PaCO₂ >45 mm Hg)  
Causes: loop/thiazide diuretics, vomiting, mineralocorticoid excess |
| 7.56  | 24            | 21            | Acute respiratory alkalosis with partially compensated metabolic acidosis (PaCO₂ <33 mm Hg, HCO₃⁻ <22 mEq/L)  
Causes: anxiety, pulmonary embolus, normal pregnancy |

b. Clinically associated with dependent pitting edema (see Fig. 5-3D) and body cavity effusions (see Fig. 19-7E)  
- The lack of significant amounts of protein and complete absence of cells allows a transudate to obey the law of gravity and to settle in dependent areas of the body (e.g., ankles when standing, sacral area when supine). |
c. Always associated with an alteration in Starling forces (see later) |

2. Exudate (refer to Chapter 3)  
a. Protein-rich (>3 g/dL) and cell-rich (e.g., neutrophils) fluid. |
b. Produces swelling of tissue but no pitting edema, because of increased viscosity due to increased protein and cells. |

3. Lymphedema (see Fig. 10-12B)  
a. Protein-rich fluid  
b. Increased viscosity prevents pitting edema. |

4. Myxedema  
a. Primarily due to an increase in hyaluronic acid (a glycosaminoglycan; see Fig. 23-8C)  
b. Increased viscosity prevents pitting edema. |

C. Pathophysiology  
1. Transudates are associated with an alteration in Starling forces.  
a. Two Starling forces present in the vascular system (capillaries/venules) are hydrostatic pressure (HP) and oncotic pressure (OP; Fig. 5-13).  
(1) HP favors movement of fluid (transudate) out of capillaries/venules.  
(2) OP equates with the serum albumin level and opposes filtration of fluid out of capillaries/venules.  
(3) In normal circumstances, plasma OP is greater than HP. |
b. Clinical examples of increased HP include:  
(1) Pulmonary edema in left-sided heart failure (see Fig. 11-2A)  
(2) Peripheral pitting edema in right-sided heart failure (RHF; see Fig. 5-3D)  
(3) Portal hypertension (PH) in cirrhosis producing ascites (see Fig. 19-7E) |
c. Clinical examples of decreased OP (hypoalbuminemia) producing peripheral pitting edema and ascites include:  
(1) Malnutrition with decreased protein intake (see Fig. 8-1, left)  
(2) Cirrhosis with decreased synthesis of albumin (see Fig. 19-7E)  
(3) Nephrotic syndrome with increased loss of protein in urine (>3.5 g/24 hours)  
(4) Malabsorption with decreased absorption of protein
5-13: Starling forces in a capillary. Hydrostatic pressure (HP) pushes fluid out of capillaries/venules, while oncotic pressure (OP) keeps fluid in vessels. On the left of the schematic, HP is greater than OP, so fluid is leaving the vessel and entering the interstitial space (net transudation). In the middle, both pressures are equal, so there is no fluid movement into the interstitial space. On the right of the schematic, OP is greater than HP, hence there is net reabsorption of fluid. (From Brown T: Rapid Review Physiology, 2nd ed, Philadelphia, Elsevier Mosby, 2012, p 133, Fig. 4.44.)

d. Clinical example where both HP and OP are involved
   • Ascites in cirrhosis—↑hydrostatic pressure (portal vein hypertension), ↓oncotic pressure (hypoalbuminemia)
e. Renal retention of sodium and water
   (1) This increases HP (increases plasma volume) and decreases OP (dilutional effect on albumin).
      • Periorbital edema is a common finding due to the loose interstitial tissue in that area.
   (2) Examples—acute and chronic renal failure, glomerulonephritis
2. Increased vascular permeability in venules (refer to Chapter 3)
   a. It produces the exudate associated with acute inflammation.
   b. Examples—tissue swelling following a bee sting, cellulitis
3. Lymphatic obstruction
   a. It produces lymphedema.
   b. Examples include:
      (1) Lymphedema following modified radical mastectomy and radiation (see Fig. 10-12B)
      (2) Lymphedema in filariasis, due to Wuchereria bancroftii (see Fig. 10-12C)
      (3) Scrotal and vulvar lymphedema, due to lymphogranuloma venereum (see Fig. 22-1C)
      (4) Breast lymphedema (inflammatory carcinoma), due to blockage of subcutaneous lymphatics by malignant cells (see Fig. 22-20F)
4. Increased synthesis of extracellular matrix components (e.g., glycosaminoglycans)
   a. T cell cytokines stimulate fibroblasts to synthesize hyaluronic acid.
   b. Examples—pretibial myxedema and exophthalmos in Graves disease (see Fig. 23-8B and C); periorbital puffiness in Hashimoto thyroiditis (see Fig. 23-7B)

IV. Thrombosis
   A. Definition
      • Intravascular mass attached to the vessel wall that is composed of varying proportions of coagulation factors, RBCs, and platelets

   B. Pathogenesis (also refer to Chapter 10 and Chapter 15)
      1. Endothelial cell injury
         a. Turbulent blood flow at arterial bifurcations
         b. Homocysteine, oxidized low-density lipoprotein, cigarette smoke, cytokines
      2. Stasis of blood flow
         a. Sluggish blood flow due to prolonged bed rest or sitting (e.g., long airplane flight, immobilization in bed)
         b. Left atrial dilatation due to mitral stenosis
      3. Hypercoagulability (refer to Chapter 15)
         a. Activation of the coagulation system
            • Example—disseminated intravascular coagulation
         b. Hereditary or acquired factor deficiencies
            • Examples—hereditary antithrombin III deficiency, oral contraceptives

- Ascites in cirrhosis: ↑HP (portal vein hypertension), ↓OP (hypoalbuminemia)
- Renal retention sodium and water: ↑Hydrostatic pressure; renal failure, glomerulonephritis
- ↑Vascular permeability: acute inflammation
- Lymphedema: lymphatic obstruction
- Lymphedema: modified radical mastectomy and radiation; inflammatory carcinoma breast; filariasis
c. Antiphospholipid syndrome
- Due to lupus anticoagulant and/or anticardiolipin antibodies

d. Thrombocytosis
- Malignancy, essential thrombocytosis

C. Types of thrombus
1. Venous thrombus
   a. Pathogenesis
   - Stasis of blood flow (most common), hypercoagulable state, in a low velocity vehicle
   
   b. Sites
   - (1) Deep veins in the lower extremities (most common site)
     - (a) Deep veins in the thigh (e.g., popliteal vein, femoral vein)
       - Thrombi extend (propagate) into the pelvic veins.
     - (b) Deep veins below the knee (most common overall site; e.g., anterior, posterior, peroneal veins; calf venous sinuses)
       - Thrombi may extend into the popliteal and femoral veins.
   
   - (2) Other sites include:
     - Axillary vein, superior vena cava, hepatic vein, and dural sinuses

c. Composition
- (1) Adherent, occlusive, dark red fibrin clot (sometimes called red thrombi)
- (2) Thrombi contain entrapped RBCs (primary component), white blood cells, and platelets (Fig. 5-14A, B, C shows the sequence of venous clot formation).

d. Clinical findings
- (1) Extremity vessel thrombosis produces pain, swelling, skin discoloration.
- (2) Lower extremity venous thrombi commonly embolize to the pulmonary arteries (sudden death, pulmonary infarction).
- (3) Hepatic vein thrombosis produces painful hepatomegaly (refer to Chapter 19).

5-14: Schematic of formation of a venous clot in the lower extremity. A, There is disruption of the endothelium with platelet adhesion and early formation of fibrin strands from activation of the coagulation system. B. The fibrin from activation of the coagulation system is forming a meshwork that anchors the clot to the wall of the vessel and traps red blood cells (predominant component), white blood cells, and platelets. C, The clot is fully formed and consists of layers of fibrin with entrapped blood cells. 

Insert, Fibrin clot appearance with a scanning electron microscope. Fibrin strands are trapping predominantly red blood cells and a few platelets (small white structures). (From Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 129; Fig. 6-6; Insert from Damjanov I, Linder J: Anderson’s Pathology, 10th ed, St. Louis, Mosby, 1996, p 479, Fig. 22.4C.)
2. Arterial thrombus
   a. Pathogenesis
   (1) Most commonly due to endothelial cell injury related to turbulent blood flow at bifurcations or over atherosclerotic plaques in high velocity vessels (see Chapter 10).
   (2) In some cases, they are mixed thrombi composed of platelets held together by fibrin and RBCs held together by fibrin.
   (3) Hypercoagulability and stasis of blood flow are uncommon causes of an arterial thrombus.

   b. Sites
   (1) Most arterial thrombi develop in high velocity vessels (e.g., elastic and muscular arteries).
      (a) Most of these thrombi overlie disrupted atherosclerotic plaques.
         • In descending order of frequency these sites include coronary (Fig. 5-15), cerebral, and femoral arteries.
      (b) Thrombus composition in muscular arteries and aortic branches
         • Adherent, usually occlusive (in muscular arteries), gray-white fibrin clots primarily composed of platelets (refer to Chapter 15).
         • Inhibitors of platelet aggregation prevent their formation (e.g., aspirin, clopidogrel).
      (c) Clinical findings include:
         • Infarction (e.g., myocardial infarction, small bowel infarction, renal infarction)
         • Stroke (e.g., thrombosis of the middle cerebral artery or branch of the carotid artery)
   (2) Thrombus composition in the heart chambers and aorta
      (a) These are laminated thrombi with alternating pale and red areas (lines of Zahn; see Fig. 10-7).
         • Mixed type of thrombus
         • Pale areas composed of platelets held together by fibrin
         • Red areas composed of RBCs and other blood cells held together by fibrin

(4) Dural sinus thrombosis produces intracerebral hemorrhage.
(5) Superior vena caval thrombosis produces jugular vein distention and stroke (refer to Chapter 10).

   e. Treatment (refer to Chapter 15)
   (1) Anticoagulants like heparin and warfarin prevent the formation of venous thrombi.
      • They do not dissolve venous thrombi but do prevent further formation or propagation of the thrombus.
   (2) Fibrinolytic system (plasmin) breaks down the thrombus to restore blood flow.
(b) Examples of thrombi that develop in heart chambers include:
   • A thrombus adherent to the left ventricle wall in an acute myocardial infarction (called a mural thrombus)
   • A thrombus adherent to the left atrial wall in mitral stenosis
(c) Thrombi in the aorta usually develop in aneurysms (outpouching of the vessel; refer to Chapter 10).
   • Example—abdominal aortic aneurysm (see Fig. 10-7)
(d) Aspirin (or other platelet aggregation inhibitors) alone with anticoagulant therapy (e.g., heparin and warfarin) prevent the formation of mixed thrombi.
(e) Embolization to distant sites is the most common clinical complication with these types of thrombi.

3. Postmortem clot
   a. Fibrin clot of plasma (resembles chicken fat) forms without entrapped cells.
   b. It is not attached to the vessel wall.

V. Embolism
A. Definition
   • Detached mass (e.g., clot, fat, gas) that is carried through the blood to a distant site.

B. Pulmonary thromboembolism (PE; refer to Chapter 17)
1. Site of origin
   a. Most emboli originate from the deep veins of the lower extremities (e.g., femoral vein) and pelvis.
   b. Others originate from the pelvic veins or the vena cava.
2. Clinical findings
   a. Sudden death
      (1) This is usually a saddle embolus that occludes the major pulmonary artery branches on both sides (see Fig. 17-8A)
      (2) Cause of death is acute right heart strain (acute cor pulmonale).
   b. Pulmonary infarction
      (1) Small thromboemboli occlude medium-sized or small pulmonary arteries, which in some cases produce a hemorrhagic infarction (see Fig. 2-15C).
      (2) Less than 10% of thromboemboli to the lungs produce infarction.
         • This is due to the dual blood supply of the lungs, mainly the pulmonary arteries and the bronchial arteries (refer to Chapter 17)
      (3) Clinical findings include:
         (a) A sudden onset dyspnea (difficulty breathing) and tachypnea (rapid breathing), with or without pleuritic chest pain
         (b) Hemoptysis (coughing up blood)

C. Paradoxical embolism
   • Most frequently due to venous emboli passing through an atrial septal defect (ASD) or a ventricular septal defect (VSD) into the systemic circulation.

D. Systemic embolism
1. Definition
   • Emboli traveling in the arterial system.
2. Causes
   a. Most emboli originate from the left side of the heart (80% of cases); examples include:
      (1) Mural thrombus in the left ventricle
      (2) Thrombus in the left atrium in mitral stenosis
         • Atrial fibrillation predisposes to atrial clot formation and embolization.
      (3) Atrial myxoma (see Fig. 11-25), sterile/infected vegetations from the aortic and/or mitral valve (see Fig. 11-20A)
   b. Systemic emboli not originating in the left heart include:
      (1) Mixed thrombus in an abdominal aortic aneurysm (see Fig. 10-7)
      (2) Ulcerated atherosclerotic plaques (e.g., middle cerebral artery plaque)
3. Target sites include:
   a. Lower extremities (most common site; 75% of cases; Fig. 5-16)
   b. Brain (via the middle cerebral artery), small bowel (via the superior mesenteric artery)
   c. Spleen, kidneys, upper extremities
4. Complications include:
   a. Pale infarctions in the digits, spleen, and kidneys
   b. Hemorrhagic infarctions in the brain and small bowel (refer to Chapter 2)
E. Fat embolism

1. Epidemiology
   a. Clinical diagnosis in most cases
   b. Most often due to traumatic fracture of long bones (e.g., femur) or pelvis
   c. Less common causes include:
      • Trauma to fat-laden tissues (liposuction), fatty liver, and decompression sickness

2. Pathogenesis
   a. At the fracture site, microglobules of marrow fat with or without hematopoietic tissue enter ruptured marrow sinusoids and venules.
      (1) Microglobules initially deposit in pulmonary capillaries.
      (2) Microglobules enter arteriovenous shunts in the lungs, from which they embolize to distant sites (e.g., brain, spleen, kidneys).
   b. Microglobules obstruct the microvasculature particularly in the lungs and brain (Fig. 5-17) where they produce ischemia and inflammation.
      • Fatty acids derived from breakdown of fat damage vessel endothelium, causing platelet/leukocyte adherence to areas of injury and to fat globules themselves.

3. Clinical findings
   a. Symptoms and signs begin 24 to 72 hours after trauma.
      • Patients are symptomatic in less than 10% of cases.
   b. Delirium and coma are common neurologic findings.
   c. Pulmonary findings include dyspnea and tachypnea.
      • Fat microglobules blocking pulmonary capillaries cause hypoxemia ( perfusion defect).
   d. Petechiae commonly develop over the chest and upper extremities.
      • Petechiae are due to thrombocytopenia from platelet adhesion to microglobules and to damaged endothelial tissue (platelet thrombi).
   e. Mortality rate, though low, is more likely to occur in elderly patients or those with underlying medical problems.

4. Laboratory findings
   a. Hypoxemia (\( \downarrow \text{Pa}_2 \)) occurs with an increase in the Alveolar-arterial (A-a) gradient ( perfusion defect).
   b. Fat globules may be present in urine, pulmonary capillary blood, and bronchoalveolar lavage material.
   c. Thrombocytopenia

5. Treatment
   • Supportive, including oxygen and mechanical ventilation
F. **Amniotic fluid (AF) embolism**

1. **Epidemiology**
   a. Occurs during labor or immediately postpartum.
   b. Maternal mortality approaches 80%.

2. **Pathogenesis**
   a. Tears in placental membranes and/or rupture of uterine veins
   b. AF enters the maternal circulation.
      • Precipitates cardiorespiratory collapse (possibly an anaphylactic reaction to fetal antigens) and disseminated intravascular coagulation (DIC; procoagulants are present in AF).

3. **Clinical findings**
   a. Abrupt onset of dyspnea, cyanosis, hypotension, and bleeding.
      (1) Dyspnea is due to pulmonary edema and/or acute respiratory distress syndrome (ARDS).
      (2) Bleeding is due to DIC.
      (3) Over 50% of patients die within an hour of the previously mentioned symptoms and signs.
   b. Diagnosis is confirmed at autopsy.
      • Fetal squamous cells, lanugo hair, fat from vernix caseosa are present in maternal pulmonary vessels.
   c. Women who survive have permanent neurologic impairment (85% of cases).

4. **Laboratory findings**
   a. Hyoxemia, respiratory acidosis
   b. Prothrombin time (PT) is usually prolonged (due to DIC).

5. **Treatment**
   • Supportive, including oxygen and mechanical ventilation

G. **Decompression sickness (DCS)**

1. **Epidemiology**
   a. Form of gas embolism
   b. Most common cause is scuba and deep sea diving.

2. **Pathogenesis**
   a. Atmospheric pressure increases with depth.
   b. Nitrogen gas is forced out of alveoli and dissolves in blood and tissues.
   c. Rapid ascent causes nitrogen to come out of solution to form gas bubbles in tissue/vessel lumens.

3. **Clinical findings**
   a. Severe pain develops in joints, skeletal muscles, and bones (“the bends”).
   b. Gas bubbles block pulmonary vessels causing edema, hemorrhage, and atelectasis (collapse of airways).
   c. Vertebal back pain and symptoms occur that mimic spinal cord trauma (e.g., loss of anal sphincter tone).
   d. Other complications
      (1) Pneumothorax (refer to Chapter 17)
         • Complication associated with a sudden rise to the surface
         • Rupture of preexisting subpleural or intrapleural bleb due to changes in pressure
         • Collapsed lung and sudden onset of dyspnea and pleuritic chest pain
      (2) Pulmonary thromboembolism (PE)
         • Increased venous pressure at increased depth produces stasis and thrombus formation in the lower extremities.
         • Pulmonary thromboembolism occurs causing dyspnea and pleuritic chest pain.
   e. Chronic changes (called caisson disease)
      (1) Caused by persistence of gas emboli in bone
      (2) Produces aseptic necrosis (bone infarctions) in the femur, tibia, and humerus

4. **Treatment for acute DCS**
   a. Recompression in a high-pressure chamber forces nitrogen gas back into solution.
   b. This is followed by slow decompression.

VI. **Shock**

A. **Definition**

- Reduced perfusion of tissue, which results in impaired oxygenation of tissue.
B. Types

1. Hypovolemic shock
   a. Shock is due to excessive loss of sodium-containing fluid (e.g., blood, sweat), causing hypotension and multiorgan failure.
   b. Massive blood loss is the most common cause.
      (1) Loss of >20% of blood volume (~1000 mL) results in shock.
      (2) Common causes of external blood loss include penetrating trauma and gastrointestinal bleeding.
      (3) Common causes of internal blood loss are trauma to a solid organ (e.g., spleen, liver) and a ruptured abdominal aortic aneurysm.
      (4) There is no initial drop in hemoglobin (Hb) and hematocrit (Hct) concentration, but there is an equal loss of RBCs and plasma.
         a. Plasma is replaced first with fluid from the interstitial space.
         b. Infusion of 0.9% normal saline immediately uncovers the RBC deficit.
         c. An increase in peripheral blood reticulocytes (indicators of effective marrow erythropoiesis) begins in 5 to 7 days (refer to Chapter 12).

c. Pathophysiology
   (1) Decreased cardiac output (CO)
      • Due to a decreased volume of blood
   (2) Decreased left ventricular end-diastolic pressure (LVEDP).
      • Loss of blood volume in left ventricle lowers the LVEDP
   (3) Increased peripheral vascular resistance (PVR)
      • Due to vasoconstriction of arterioles from catecholamines, ADH, and angiotensin II, which are released in response to the decreased CO
   (4) Decreased mixed venous oxygen content (MVO₂)
      a. MVO₂ is the best indicator of tissue hypoxia.
      b. It is measured in the right side of the heart with a Swan-Ganz catheter.
      c. MVO₂ indicates the degree of extraction of O₂ from blood delivered to tissue.
      d. In hypovolemic shock, decreased blood flow through the microcirculation leads to increased extraction of O₂ from the blood and a decreased MVO₂.

d. Clinical findings
   (1) Exam reveals cold, clammy skin due to vasoconstriction of skin vessels
   (2) Hypotension is present along with a rapid, weak pulse (compensatory response to decreased CO).
   (3) Urine output is decreased because of decreased renal blood flow and glomerular filtration rate.

e. Laboratory findings
   • Increased anion gap type of metabolic acidosis due to lactic acidosis from anaerobic glycolysis (see previous discussion).

f. Treatment
   • Fluid replacement (e.g., normal saline, blood transfusions for bleeding)

2. Cardiogenic shock
   a. Most commonly caused by an acute myocardial infarction (AMI).
      • Other causes include myocarditis, acute valvular dysfunction (e.g., infective endocarditis), and cardiomyopathy.

b. Pathophysiology
   (1) Decreased CO.
      • Due to decreased force of contraction in the infarcted left ventricle (LV)
   (2) Increased LVEDP
      • Because CO is decreased, blood accumulates in the LV, causing an increase in pressure and volume.
   (3) Increased PVR
      • Same mechanism as in hypovolemic shock
   (4) Decreased MVO₂
      • Same mechanism as in hypovolemic shock

c. Clinical findings (refer to Chapter 11)
   • Chest pain is followed by signs similar to those seen in hypovolemic shock.

d. Laboratory findings
   • Increased creatine kinase MB fraction, increased troponin I and T (gold standard)

e. Treatment of cardiogenic shock (refer to Chapter 11)
3. Septic shock
   a. Epidemiology
      (1) Microbes invade the bloodstream (septicemia).
      (2) Most common sites for infection leading to sepsis in descending order are the lungs, blood, abdomen, urinary tract, and skin.
      (3) Most common cause of death in intensive care units
      (4) Mortality rate is 20% to 30%.
   b. Microbial pathogens
      (1) Gram-positive organisms—65% of cases; coagulase-negative *Staphylococci* and *Staphylococcus aureus* most common
      (2) Gram-negative organisms—25% of cases; *Escherichia coli* most common
      (3) Systemic fungi—9% of cases; *Candida* species most common
   c. Pathogenesis
      (1) Lipoteichoic acid in gram-positive pathogens causes the release of tumor necrosis factor (TNF) and interleukin (IL)-1 (refer to Chapter 3).
      (2) Endotoxins (lipopolysaccharide) are released by gram-negative bacteria.
         a. They activate macrophages, causing release of IL-1 and TNF.
            • IL-1 produces fever
            • TNF damages endothelial cells causing them to release vasodilators like nitric oxide (NO) and prostaglandin (PG)\(_2\).
         b. Endotoxins activate the alternative complement pathway.
            • Anaphylatoxins (C3a and C5a) are produced, which stimulate mast cell release of histamine (vasodilator).
         c. Endotoxins damage tissue, causing the release of tissue thromboplastin.
         d. Endotoxins activate neutrophil adhesion molecules causing the circulating pool to become of the marginating pool (produces neutropenia; refer the Chapter 3).
   d. Pathophysiology
      (1) Initial increase in CO
         • Due to rapid blood flow through dilated PVR arterioles (NO and PG\(_2\) are vasodilators), causing increased venous return of blood to the right heart (analogous to opening up flood gates in a dam)
      (2) Decreased LVEDP
      (3) Decreased PVR
      (4) Increased MVO\(_2\)
         • Tissues are unable to extract O\(_2\), because of the increased blood flow through the microcirculation related to dilated PVR arterioles.
   e. Clinical and laboratory findings in early septic shock
      (1) Warm skin, due to vasodilation of the skin vessels
      (2) Hypotension, due to vasodilation of arterioles and increased vascular permeability (damage to endothelial cells)
      (3) Strong peripheral pulses, due to the increased CO
      (4) Activation of the coagulation system leading to DIC (refer to Chapter 15)
      (5) Increased risk for developing acute respiratory distress syndrome (refer to Chapter 17)
      (6) Hematologic findings include:
         • Anemia (bleeding), thrombocytopenia (trapped and consumed in thrombi), and neutropenia (margination of neutrophils from adhesion molecule activation)
   f. Treatment
      (1) Broad antibiotic coverage
      (2) Adjunctive support with intravenous fluids, inotropic drugs (e.g., dopamine), electrolyte management

4. Summary of pathophysiologic findings in shock (Table 5-11)

C. Complications
1. Ischemic acute tubular necrosis (refer to Chapter 20)
   • Coagulation necrosis of the proximal tubule cells and the tubular cells in the thick ascending limb produce renal tubular cell casts that occlude tubular lumens producing oliguria and renal failure.
2. Multiple organ dysfunction syndrome (MODS)
   a. Most common cause of death in septic shock
   b. Associated with widespread endothelial cell and parenchymal cell injury
   c. Multifactorial pathophysiology
      (1) Tissue hypoxia with a lack of ATP becomes widespread.
      (2) Endotoxins and various cytokines have direct cytotoxic effect.
      (3) Damage to tissue serves as a stimulus for apoptosis (refer to Chapter 2).
      (4) DIC produces fibrin thrombi in the microvasculature of most organs, leading to tissue damage.
      (5) Myocardial depressants (e.g., endotoxins, TNF) produce myocardial dysfunction.

<table>
<thead>
<tr>
<th>TYPE OF SHOCK</th>
<th>CO</th>
<th>PVR</th>
<th>LVEDP</th>
<th>MVO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiogenic (septic)</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Endotoxic (septic)</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

CO, Cardiac output; LVEDP, left ventricular end-diastolic pressure; MVO₂, mixed venous oxygen content; PVR, peripheral vascular resistance.

MODS: MCC of death in shock

Table 5-11 Summary of Pathophysiologic Findings in Hypovolemic, Cardiogenic, and Septic Shock
I. Mutations
A. Definition
1. Permanent change in the nucleotide sequence or arrangement of DNA
2. Mutations involving germ cells (e.g., ovum) can be transmitted to offspring.
3. Mutations involving somatic cells are not transmitted to offspring.

B. Point mutations
1. Definition—produce a change in a single nucleotide base within a gene
2. Silent mutation (Fig. 6-1A)
   • Definition—altered DNA codes for the same amino acid without changing the phenotypic effect.
3. Missense mutation (see Fig. 6-1B)
   a. Definition—altered DNA codes for a different amino acid, which changes the phenotypic effect
   b. Account for 50% of disease-causing mutations

4. Nonsense mutation (see Fig. 6-1C)
   a. Definition—altered DNA codes for a stop codon that causes premature termination of protein synthesis
   b. Account for 10% of disease-producing mutations

In both sickle cell trait and sickle cell disease, a missense mutation occurs when adenine replaces thymidine, causing valine to replace glutamic acid in the sixth position of the β-globin chain. As a result, RBCs spontaneously sickle in the peripheral blood if the amount of sickle hemoglobin is greater than 60%.

In β-thalassemia major, a nonsense mutation produces a stop codon that causes premature termination of DNA transcription of the β-globin chain. Consequently, there is no synthesis of hemoglobin A (αβ). There is a corresponding increase in hemoglobin A2 (αδ) and hemoglobin F (αγ) in β-thalassemia major.

C. Frameshift mutation
1. Definition—insertion or deletion of one or more nucleotide bases shifts the reading frame of the DNA strand
2. If the number of bases that is added or deleted is not a multiple of three, a frameshift results in premature termination of protein synthesis downstream from the mutation.
   a. Accounts for 25% of disease-causing mutations
   b. Example—in Tay-Sachs disease, a four-base insertion results in an altered DNA code leading to decreased synthesis of hexosaminidase (stop codon; Fig. 6-2).
6-1: Point mutations: silent mutation (A), missense mutation (B), nonsense mutation (C). In a silent mutation (A), the altered DNA codes for the same amino acid and thus does not change the phenotypic effect. In a missense mutation (B), the altered DNA codes for a different amino acid, which changes the phenotypic effect. In a nonsense mutation (C), the altered DNA codes for a stop codon that causes premature termination of protein synthesis. (From Pelley JW, Goljan E: Rapid Review Biochemistry, 2nd ed, Philadelphia, Mosby Elsevier, 2007, p 190, Fig. 10-11.)

![Diagram of RNA editing](image)

6-2: Frameshift mutation in Tay-Sachs disease. In a frameshift mutation, insertion or deletion of one or more nucleotides shifts the reading frame of the DNA strand. In Tay-Sachs disease, a four-base insertion (TATC) alters the reading frame for the synthesis of hexosaminidase, leading to formation of a stop codon that reduces the synthesis of the enzyme.

3. If the number of base pairs that is either deleted or inserted is a multiple of three, it is not a frameshift mutation.
   a. In this type of mutation, the translated protein has either gained or lost amino acids.
   b. Example—in cystic fibrosis (CF), a three-nucleotide deletion that normally codes for phenylalanine produces a protein (i.e., cystic fibrosis transmembrane regulator [CFTR]) that is missing phenylalanine (refer to Chapter 17).
   c. The defective CFTR is degraded in Golgi apparatus.

D. **Trinucleotide repeat disorders**
   1. Trinucleotide repeat disorders (TRDs) are examples of DNA replication errors.
      - Uncommon cause of a disease-causing mutation.
   2. Definition—there is amplification of a sequence of three nucleotides, which prevents normal expression of the gene
      a. Most trinucleotide repeats contain guanine (G) and/or cytosine (C).
      b. Examples of trinucleotide repeat disorders and their triplet repeats include:
         1. Fragile X syndrome (FXS): CGG repeat
         2. Myotonic dystrophy: CTG repeat
         3. Friedrich ataxia: GAA repeat
         4. Huntington disease (HD): CAG repeat
   3. Tendency for expanding (amplifying) trinucleotide repeats is highly dependent on the sex of the parent transmitting the disease.
      - For example, expansion of trinucleotide repeats in FXS primarily occurs in oogenesis, whereas in HD, it occurs in spermatogenesis.
   4. Number of trinucleotide repeats determines severity of the disease.
      - For example, in FXS, unaffected individuals have 5 to 54 CGG repeats; those with premutations have 55 to 200 CGG repeats (normal to mild disease); whereas those with full mutations have >200 repeats (more severe disease).
5. Amplification that occurs in noncoding areas of the gene (intron) produce a loss-of-function type of mutation manifested as a decrease in protein synthesis.
   a. Examples of diseases that fit under this category include FXS, myotonic dystrophy, and Friedreich ataxia.
   - Because protein synthesis is decreased in the previously mentioned disorders, multiple organ systems are adversely affected.
   b. Another characteristic is the progression from premutations to full mutations in germ cells in future generations, due to increased amplification of triplet repeats in gametogenesis.
      (1) Disease activity that increases in severity with each generation is called anticipation.
      (2) Example of anticipation—FXS, a sex-linked disease
         (a) Carrier males with a premutation are phenotypically normal or mildly affected (mild mental retardation).
         (b) Because it is an X-linked recessive disease, all his female children are carriers with a premutation (phenotypically normal or mild mental retardation), but all the male children are normal.
         (c) When a carrier female with a premutation has children, 50% of the males will have a full mutation, because in oogenesis, there is amplification of the CGG repeats and a premutation is converted into a full mutation (>200 repeats).
         (d) Furthermore, 50% of her daughters have the potential for full mutations and will be symptomatic (more severe mental retardation than a premutation).
         (e) When the affected daughters have children, even more triplet repeats are produced during oogenesis; hence the affected males and females in this generation have more severe disease than those in the previous generation.

6. Amplifications that occur in the coding region of the gene (exon) all have CAG triplet repeats that code for glutamine residues.
   a. In this group, the expansion of CAG repeats that encode for glutamine residues produces neurodegenerative types of disorders (polyglutamine disorders); examples include:
      - HD and various subtypes of spinocerebellar ataxia
   b. Proteins that are produced with an excess of glutamine residues are misfolded and produce aggregates that:
      (1) Suppress transcription of other genes
      (2) Interfere with mitochondrial (mt) function
      (3) Trigger apoptosis of neurons
   c. Aggregates also produce intranuclear inclusions, which are a key feature of the previously mentioned neurodegenerative diseases.

II. Mendelian Disorders
   A. Overview of mendelian disorders
      1. Definition—single-gene mutations that produce large effects
      2. Majority are familial (80%–85% of cases), however, the remainder are new mutations.
      3. Patterns of single-gene mutations chiefly depend on whether a dominant or recessive phenotype is present in a chromosome pair:
         a. Dominant phenotype is expressed when only one chromosome of a pair carries the mutant allele.
         b. Recessive phenotype is expressed only when both chromosomes of a pair carry mutant alleles.
      4. Chromosomal location of the gene locus of the mutation may be on an autosome (chromosomes 1 to 22) or on a sex chromosome (chromosomes X and Y).
         - The vast majority of sex chromosome disorders are X-linked.
      5. Four basic single-gene mutation disorders:
         a. Autosomal recessive (AR; most common type)
         b. Autosomal dominant (AD)
         c. X-linked recessive (XR)
         d. X-linked dominant (XD)
B. Autosomal recessive (AR) disorders

1. Inheritance pattern characteristics (Fig. 6-3)
   a. Individuals must be homozygous (aa) for the mutant recessive gene (a) to express the disorder.
   b. Homozygotes (aa) are symptomatic early in life.
   c. Heterozygous individuals (Aa) are usually asymptomatic carriers.
      - Dominant gene (A) overrides the mutant recessive gene (a).
   d. Both parents must be heterozygous (Aa) to transmit the disorder to their children.
      - Example—Aa × Aa → AA, Aa, Aa, aa (25% without disorder [AA]; 50% asymptomatic carriers [Aa]; 25% with disorder [aa])
   e. New mutations are uncommon.
   f. Complete penetrance is common (i.e., homozygotes will express the disease).

2. AR protein defects are listed in Table 6-1.

3. Selected inborn errors of metabolism are discussed in Table 6-2 and shown in Figures 6-4 through 6-8.
   a. Most metabolic disorders are due to an enzyme deficiency.
   b. Substrate and intermediates proximal to the enzyme block increase.
   c. Intermediates and the end-product distal to the enzyme block decrease.
   d. Lysosomal storage diseases (LSD; Table 6-3; Figs. 6-9 and 6-10)
      - Enzyme deficiencies lead to accumulation of undigested substrates (e.g., glycosaminoglycans [GAGs], sphingolipids, glycogen) in lysosomes.

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### Table 6-1 Protein Defects Associated with Selected Mendelian Disorders

<table>
<thead>
<tr>
<th>PROTEIN TYPE</th>
<th>SPECIFIC PROTEIN</th>
<th>DISORDER</th>
<th>INHERITANCE PATTERN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme</td>
<td>C1 esterase inhibitor deficiency</td>
<td>Hereditary angioedema</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Structural</td>
<td>Sickle hemoglobin</td>
<td>Sickle cell disease</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Transport</td>
<td>Cystic fibrosis transmembrane regulator</td>
<td>Cystic fibrosis</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Receptor</td>
<td>Low-density lipoprotein receptor</td>
<td>Familial Hypercholesterolemia</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Growth regulating</td>
<td>Neurofibromin</td>
<td>Neurofibromatosis</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Hemostasis</td>
<td>Factor VIII</td>
<td>Hemophilia A</td>
<td>X-linked recessive</td>
</tr>
</tbody>
</table>

---

Cystic fibrosis (CF) is an AR disorder with a carrier rate of 1/25. To calculate the prevalence of CF in the population, the number of couples at risk of having a child with CF (1/25 × 1/25, or 1/625) is multiplied by the chance of having a child with CF (1/4). Prevalence of CF = 1/625 × 1/4, or 1/2500. Note how it is possible to calculate the carrier rate if given the prevalence of the disease by dividing 1/2500 by 4 to get the number of couples at risk, and then taking the square root of 1/625 to get the carrier rate of 1/25.
<table>
<thead>
<tr>
<th>ERROR</th>
<th>DEFICIENT ENZYME</th>
<th>ACCUMULATED SUBSTRATE(S)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaptonuria (see Figs. 6-4, 6-5)</td>
<td>Homogentisate oxidase</td>
<td>Homogentisate (black pigment); binds to collagen (connective tissue, tendons, cartilage)</td>
<td>Black urine (undergoes oxidation when exposed to light); black pigmentation nose, ears, cheeks; black cartilage in joint and intervertebral disc producing degenerative arthritis</td>
</tr>
<tr>
<td>Galactosemia (see Fig. 6-6)</td>
<td>GALT</td>
<td>Galactose 1-phosphate (toxic to liver, CNS) Galactitol (alcohol sugar, increase produces osmotic damage in lens)</td>
<td>Mental retardation, cirrhosis, fasting hypoglycemia (decrease in gluconeogenic substrates distal to block), cataracts (osmotic damage) Avoid dairy products (galactose derives from lactose)</td>
</tr>
<tr>
<td>Hereditary fructose intolerance (see Fig. 6-7)</td>
<td>Aldolase B</td>
<td>Fructose 1-phosphate (toxic substrate)</td>
<td>Cirrhosis, hypoglycemia (decrease in gluconeogenic substrates), hypophosphatemia (used up in phosphorylating fructose) Avoid fructose (e.g., honey) and sucrose (glucose + fructose)</td>
</tr>
<tr>
<td>Homocystinuria (see Fig. 6-8)</td>
<td>Cystathionine synthase</td>
<td>Homocysteine and methionine</td>
<td>Mental retardation, vessel thrombosis (homocysteine); lens dislocation, arachnodactyly (similar to Marfan syndrome; called genetic heterogeneity)</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>Branched chain α-ketoacid dehydrogenase</td>
<td>Leucine, valine, isoleucine, and their ketoacids</td>
<td>Mental retardation, seizures, feeding problems, sweet-smelling urine</td>
</tr>
<tr>
<td>Phenylketonuria (see Fig. 6-4)</td>
<td>Phenylalanine hydroxylase</td>
<td>Phenylalanine Neurotoxic by-products</td>
<td>Mental retardation, microcephaly, mousy odor (phenylalanine converted into phenylacids), ↓pigmentation (melanin derives from tyrosine) Must be exposed to phenyllanine (milk) before phenylalanine is increased) Restrict phenylalanine; avoid sweeteners containing phenylalanine (e.g., NutraSweet) Add tyrosine to diet Pregnant women with PKU must be on a phenylalanine-free diet or newborns will be mentally retarded at birth</td>
</tr>
<tr>
<td>“Malignant” phenylketonuria (see Fig. 6-4)</td>
<td>Dihydropterin reductase</td>
<td>Phenylalanine Neurotoxic by-products</td>
<td>Similar to PKU Inability to metabolize tryptophan or tyrosine, which both require BH₄. This ↓synthesis of neurotransmitters (serotonin and dopamine, respectively). Neurologic problems occur despite adequate dietary therapy. Restrict phenylalanine in diet. Administer L-dopa and 5-hydroxytryptophan to replace neurotransmitters. Administer BH₄.</td>
</tr>
<tr>
<td>McArdle disease</td>
<td>Muscle phosphorylase</td>
<td>Glycogen</td>
<td>Glycogenesis with muscle fatigue and a propensity for rhabdomyolysis with myoglobinuria There is no lactic acid increase with exercise due to lack of glucose in muscle and a corresponding lack in anaerobic glycolysis (lactic acid is the end-product).</td>
</tr>
<tr>
<td>Pompe disease</td>
<td>α-1,4-Glucosidase (lysosomal enzyme)</td>
<td>Glycogen</td>
<td>Glycogenesis, cardiomegaly with early death from heart failure (restrictive cardiomyopathy)</td>
</tr>
<tr>
<td>Von Gierke disease</td>
<td>Glucose-6-phosphatase (gluconeogenic enzyme)</td>
<td>Glucose 6-phosphate</td>
<td>Glycogenesis, enlarged liver and kidneys (both contain gluconeogenic enzymes), fasting hypoglycemia (no response to glucagon or other gluconeogenesis stimulators)</td>
</tr>
</tbody>
</table>

*Site of enzyme activity.

AcAc, Acetoacetate; AcCoA, acetyl CoA; DHAP, dihydroxyacetone phosphate; GALT, galactose-1-phosphate uridyltransferase; G-3P, glyceraldehyde 3-phosphate; PKU, phenylketonuria.
Genetic and Developmental Disorders

6-4: Phenylketonuria and alkaptonuria biochemical pathways. In phenylketonuria, there is a deficiency of phenylalanine hydroxylase (interrupted ellipse) with a buildup of products proximal to the enzyme block (e.g., phenylalanine, phenylpyruvate, phenyllactate) and a decrease in substrates distal to the block (e.g., tyrosine, which is a precursor of melanin). In alkaptonuria, there is a deficiency of homogentisate (homogentisic acid) oxidase (solid ellipse) with proximal accumulation of homogentisic acid, which turns black in urine upon oxidation. It also deposits in cartilage (e.g., intervertebral disks and joints), producing degenerative arthritis. (From Pelley JW, Goljan E: Rapid Review Biochemistry, 2nd ed, Philadelphia, Mosby Elsevier, 2007, p 139, Fig. 8-4.)

6-5: Alkaptonuria. The urine on the left is unexposed to light. The urine on the right turns black when exposed to light because of an increase in homogentisic acid. (From Taylor S, Raffles A: Diagnosis in Color Pediatrics, London, Mosby-Wolfe, 1997, p 217, Fig. 8.20.)

6-6: Galactosemia. There is an increase in galactose and galactitol (alcohol sugar) proximal to the block and a decrease in glucose 1-phosphate distal to the block (hypoglycemia in fasting state). GALT, Galactose-1-phosphate uridyltransferase; P, phosphate; UDP, uridine diphosphate. (From Pelley JW, Goljan E: Rapid Review Biochemistry, 2nd ed, Philadelphia, Mosby Elsevier, 2007, p 104, Fig. 6-10.)
6-7: Hereditary fructose intolerance. Hereditary fructose intolerance is caused by a deficiency of aldolase B. This causes an increase in fructose 1-phosphate (toxic substance) and fructose (proximal) and a decrease DHAP and glyceraldehyde 3-phosphate, a three-carbon intermediate in glycolysis and gluconeogenesis. In hereditary fructose intolerance, hypoglycemia occurs in the fasting state. DHAP, Dihydroxyacetone phosphate; P, phosphate. (From Pelley JW, Goljan EF: Rapid Review Biochemistry, 2nd ed, Philadelphia, Mosby Elsevier, 2007, p 104, Fig. 6-11.)

6-8: Homocystinuria. In this inborn error of metabolism, cystathionine synthase is deficient, causing an increase in homocysteine and methionine. Homocysteine produces vessel thrombosis. CH₃, Methyl group. (From Pelley JW, Goljan EF: Rapid Review Biochemistry, 2nd ed, Philadelphia, Mosby Elsevier, 2007, p 143, Fig. 8-5.)

Table 6-3 Selected Lysosomal Storage Disorders

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>DEFICIENT ENZYME</th>
<th>ACCUMULATED SUBSTRATE</th>
<th>CLINICAL FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher disease (adult type) (see Fig. 14-15A)</td>
<td>Glucocerebrosidase</td>
<td>Glucocerebroside</td>
<td>Most common lysosomal storage disease Seen in Eastern European (Ashkenazic) Jews (1/14 carrier rate) In type I disease, there is hepatosplenomegaly; fibrillar-appearing macrophages in liver, spleen, and bone marrow. Pancytopenia from marrow involvement and hypersplenism from enlarged spleen. There is no CNS involvement. Replacement therapy with recombinant enzyme is effective.</td>
</tr>
<tr>
<td>Hurler syndrome (see Fig. 6-10)</td>
<td>α-1-Iduronidase</td>
<td>Dermatan and heparan sulfate (mucopolysaccharides or glycosaminoglycans) accumulate in mononuclear phagocytic cells, lymphocytes, endothelial cells, intimal smooth muscle cells, and fibroblasts</td>
<td>Normal at birth but develop severe mental retardation and hepatosplenomegaly by 6-24 months. Coarse facial features, short neck, corneal clouding, coronary artery disease, vacuoles in circulating lymphocytes. XR form (Hunter syndrome) is milder</td>
</tr>
<tr>
<td>Niemann-Pick disease (see Fig. 14-15B)</td>
<td>Sphingomyelinase</td>
<td>Sphingomyelin</td>
<td>Seen in Eastern European (Ashkenazic) Jews (1/90 carrier rate) Signs and symptoms begin at birth. Type A very severe and involves CNS (psychomotor dysfunction; short life-span). Type B does not have CNS involvement and survive into adulthood. Phagocytic cells involved in liver (hepatomegaly), spleen (massive splenomegaly), lymph nodes, and bone marrow. Phagocytes have a foamy appearance (zebra bodies on EM). Cherry red macula present in 30%-50% of cases.</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Hexosaminidase</td>
<td>GM₁ ganglioside</td>
<td>Seen in Eastern European (Ashkenazic) Jews (1/30 carrier rate) Normal at birth but manifest signs and symptoms by 6 months of age Motor (muscle weakness) and mental deterioration, whorled configurations in neurons, cherry-red macula (pale ganglion cells with excess gangliosides accentuate the normal red color of the macular choroid)</td>
</tr>
</tbody>
</table>

CNS, Central nervous system; EM, electron microscopy; XR, sex-linked recessive.
Genetic and Developmental Disorders

4. Other AR disorders include:
   - Hemochromatosis, 21-hydroxylase deficiency, Wilson disease, and thalassemia

C. Autosomal dominant (AD) disorders
   1. Inheritance pattern characteristics (Fig. 6-11).
      a. One dominant mutant gene (A) is required to express the disorder
         (1) Heterozygotes (Aa) express the disorder.
         (2) Most homozygotes (AA) are spontaneously aborted in most cases.
            • This means that most of the living individuals with AD disorders are heterozygotes (Aa) at birth.
         (3) Example—Aa × aa → Aa, Aa, aa, aa (50% have the disorder [Aa]; 50% do not have the disorder [aa])
New mutations: paternally inherited

Delayed manifestations: symptoms/signs occur later in life

Complete penetrance: all individuals with mutation express disease

Incomplete penetrance: phenotypically normal; transmit disease to children

Variable expressivity: express disease but severity varies

b. Some disorders arise by new mutations.
   - Most new mutations occur in germ cells of elderly males (paternally inherited).

c. Delayed manifestations of disease
   (1) Symptoms and signs may not occur early in life.
   (2) Examples—in adult polycystic kidney disease, cysts are not present at birth; in familial polyposis, polyps are not present at birth

d. Penetrance
   (1) Complete penetrance (see Fig. 6-11A)
      - All individuals with the mutant gene express the disorder (e.g., familial polyposis).
   (2) Incomplete penetrance (see Fig. 6-11B)
      (a) Individuals with the mutant gene are phenotypically normal.
      (b) However, they can transmit the disorder to their offspring (e.g., Marfan syndrome).

e. Variable expressivity
   (1) All individuals with the mutant gene express the disorder but at different levels of severity.
   (2) Example—in neurofibromatosis, some patients may have a few café au lait spots (coffee-colored flat lesions) or numerous neurofibromas (pedunculated, pigmented lesions; see Fig. 26-5A)

f. A male-to-male transmission essentially confirms an autosomal dominant inheritance.

2. AD protein defects (see Table 6-1)
   - Enzyme deficiencies are relatively uncommon in AD disorders.

3. Other AD disorders include:
   - HD, osteogenesis imperfecta, achondroplasia, tuberous sclerosis, hereditary spherocytosis, von Willebrand disease, myotonic dystrophy, and familial hypercholesterolemia

D. X-linked recessive (XR) disorders

1. Inheritance pattern characteristics of XR disorders
   a. Males must have the mutant recessive gene on the X chromosome to express the disorder.
      (1) Y chromosome disorders are more likely to involve defects in spermatogenesis.
      (2) X chromosome in a male is active, whereas in females, random inactivation of one of their two X chromosomes leaves ~50% of their X chromosomes active while the other X chromosome is an inactive Barr body located on the cell's nuclear membrane.

b. Affected males (XY) transmit the mutant gene to all of their daughters (Fig. 6-12).
   (1) Males are hemizygous for the X-linked mutant gene.
      - The Y chromosome is not homologous to the X chromosome; hence the term hemizygous.
   (2) Example—XY × XX → XX, XX, XY, XY
   (3) Daughters (XX) are usually asymptomatic carriers.
      - Heterozygous females (XX) usually are asymptomatic because of the paired normal allele, unlike affected males (XY), who do not have a paired homologous allele.

6-12: Pedigree of an X-linked recessive disorder. The affected male transmits the mutant gene on the X chromosome to both of his daughters and none of his sons. Both daughters are asymptomatic heterozygous carriers of the mutant gene. The daughter with four children has transmitted the mutant gene to 50% of her sons.
c. Asymptomatic female carriers (X mutant gene) transmit the disorder to 50% of their male offspring and 50% of their female offspring, who are asymptomatic carriers.
   - Example—XX × XY → XX, XX, XY, XY

d. In rare cases, female carriers are symptomatic.
   (1) Occurs if maternally derived X chromosomes without the mutant gene are preferentially inactivated.
      - Therefore only paternally derived X chromosomes with the mutant gene remain.
   (2) Offspring of a symptomatic male and asymptomatic female carrier can have a symptomatic female child (XX).
      - Example—XX × XY → XX, XX, XY, XY
      - However, because of random inactivation of one of the X chromosomes, the disease is usually not as severe as in a male.

2. XR protein defects (see Table 6-1)
   - Enzymes are the most common type of proteins affected in XR disorders.

3. Fragile X syndrome (FXS)
   a. Epidemiology
      (1) FXS is an X-linked recessive trinucleotide repeat disorder (CGG; discussed earlier).
      (2) Carrier rate for affected males is 1/1550 (some authors say 1/2500–4000) and 1/8000 for affected females.
      (3) Most common mendelian disorder causing mental retardation.
   b. Pathogenesis
      (1) Genetic defect is at the distal end of the long arm of the X chromosome (band Xq27.3).
         - At this site, CGG amplification produces a constriction that gives the appearance of a fragile portion of the X chromosome, hence the term fragile X (Fig. 6-13A).
         - The familial mental retardation-1 (FMR1) gene is located at this site.
         - Loss of function of this gene, which is most abundantly expressed in the brain and testis, is responsible for mental retardation in FXS as well as other findings listed later.
      (2) Males with a premutation (60–200 repeats) are usually asymptomatic or mildly affected and can transmit the premutation to their daughters.
(3) Males with the full mutation (>200 CGG repeats, see earlier discussion) have manifestations of FXS.
   - Mothers of nearly all males with FXS have premutation (60–200 repeats) or FXS (>200 repeats).
(4) Females with a premutation (60–200 repeats) are usually asymptomatic, or they have a mild degree of mental retardation and/or premature ovarian failure (25% of cases).
   - However, during oogenesis, the number of CGG multiples is amplified and exceeds 200 CGG repeats; hence a male child will have the full mutation and develop FXS, whereas the female child will have a 50% chance of having FXS (see later for explanation).
(5) Half of the females with the full mutation on a single X chromosome are asymptomatic, because of random inactivation of more than half of the affected X chromosomes.
   - The other 50% of females have FXS, although the degree of mental retardation is much less than in males with FXS.

c. Clinical findings
   (1) Affected males have mental retardation with an IQ range of 20 to 70.
   (2) Females with FXS and less affected males have IQs that approach 80.
   (3) Facial changes (see Fig. 6-13B)
      - Long face, large mandible, everted ears, high-arched palate
   (4) Macro-orchidism (enlarged testes) at puberty is almost universal.
      - Normal testicular volume at puberty is 17 mL, whereas in individuals with FXS, the volume is >25 mL.
   (5) Other findings include mitral valve prolapse, pectus excavatum, scoliosis, and hyperextensible joints.

d. Diagnosis
   (1) DNA analysis (polymerase chain reaction) to identify trinucleotide repeats is the best test.
   (2) Fragile X chromosome study (false negative rate of 20%)

4. Lesch-Nyhan syndrome
   a. Deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT).
      - HGPRT is normally involved in salvaging the purines hypoxanthine and guanine.
   b. Clinical findings
      - Mental retardation, hyperuricemia, and self-mutilation

5. Other XR disorders include:
   - Androgen insensitivity syndrome, chronic granulomatous disease, Bruton agammaglobulinemia, and glucose-6-phosphate dehydrogenase deficiency

E. X-linked dominant (XD) disorders
1. Inheritance pattern characteristics
   a. Same as XR except the dominant mutant gene causes disease in males and females (Fig. 6-14)
   b. Distinguished from AD disorders by the fact that there is no male-to-male transmission
      - This is impossible in X-linked inheritance, because males transmit the Y chromosome to their sons.

6-14: Pedigree of an X-linked dominant disorder. In these rare disorders, female carriers and males with the mutant dominant gene express the disorder. The distribution is similar to that of X-linked recessive disorders, except that carrier females are symptomatic. It is distinguished from an autosomal dominant disorder because there is no male-to-male transmission, as noted in the pedigree.
2. Vitamin D–resistant rickets
   a. Defect in renal and gastrointestinal reabsorption of phosphate (hypophosphatemia)
   b. Defective bone mineralization (i.e., osteomalacia), because phosphate is required to drive calcium into bone.

III. Chromosomal Disorders

A. General considerations
1. Most human cells are diploid (46 chromosomes).
   a. Autosomes: 22 pairs
   b. Sex chromosomes (XX in females and XY in males): 1 pair
2. Gametes, the products of meiosis, are haploid (23 chromosomes).
3. Lyon hypothesis
   a. In females, one of the two X chromosomes (X paternal, X maternal) is randomly inactivated (Fig. 6-15).
      • Inactivation occurs on day 16 of embryonic development.
   b. Inactivated X chromosome is called a Barr body.
      • Attached to the nuclear membrane of cells and can be counted in squamous cells obtained by scraping the buccal mucosa
   c. Normal females have one Barr body per cell, and normal males have none.
   d. Inactivation accounts for parental derivation of the X chromosomes in females.
      • ~50% of X chromosomes are paternal and ~50% are maternal.

B. Chromosomal alterations
1. Definition—numeric or structural abnormalities of autosomes or sex chromosomes
2. Nondisjunction (Fig. 6-16)
   a. Definition—unequal separation of chromosomes in meiosis
   b. Results in 22 or 24 chromosomes in the egg or sperm
   c. Examples—Turner syndrome (22 + 23 = 45 chromosomes); Down syndrome (24 + 23 = 47 chromosomes; trisomy)
3. Mosaicism
   a. Definition—nondisjunction of chromosomes during mitosis in the early embryonic period
   b. Two chromosomally different cell lines are derived from a single fertilized egg
   c. Mosaicism most often involves sex chromosomes (e.g., Turner syndrome).

**Barr body**: inactivated X chromosome

Number of Barr bodies = number of X chromosomes – 1

**Nondisjunction**: unequal separation of chromosomes in meiosis

**Mosaicism**: nondisjunction in mitosis; most often involves sex chromosomes

**6-15**: Random X chromosome inactivation early in female development. Shortly after conception of a female embryo, both the paternal and maternal X chromosomes (pat and mat, respectively) are active. Within the first week of embryogenesis, one or the other X chromosome is chosen at random to become the future inactive X chromosome, through a series of events involving the X inactivation center in Xq13.2 (black box in the schematic). That X becomes the inactive X (Xi indicated by the blue shading) in that cell and its progeny, and it forms the Barr body in interphase nuclei. (From Nussbaum R, McInnes R, Willard H. Thompson & Thompson Genetics in Medicine, 7th ed, Philadelphia, Saunders Elsevier, 2007, p 102, Fig. 6-13.)
4. Translocation
   a. Definition—transfer of chromosome parts between nonhomologous chromosomes
   b. Balanced translocation
      • Definition—translocated fragment is functional
   c. Robertsonian translocation
      • Definition—balanced translocation between two acrocentric chromosomes (centromere is near the end of the chromosome; e.g., chromosomes 14 and 21)

In one type of Down syndrome, the mother of an affected child has 45 (not 46) chromosomes because of a Robertsonian translocation between the long arms of chromosomes 21 and 14. This produces one long chromosome (14;21) and one very short chromosome. The short chromosome is lost in subsequent divisions. The mother also has one chromosome 14 and one chromosome 21. The father has the normal 46 chromosomes. The affected child has 46 chromosomes with three functional 21 chromosomes. This includes chromosome (14;21) and chromosome 21 from the mother and chromosome 14 and chromosome 21 from the father (Fig. 6-17).
5. Deletion
   a. Definition—loss of a portion of a chromosome
   b. Cri du chat syndrome
      (1) Loss of the short arm of chromosome 5
      (2) Clinical findings
         • Mental retardation, cat-like cry, and ventricular septal defect (VSD)

C. Disorders involving autosomes
1. Down syndrome
   a. Epidemiology
      (1) Causes
         (a) Nondisjunction (95% of cases, trisomy 21; Fig. 6-18)
         (b) Robertsonian translocation (4% of cases; 46 chromosomes; see Fig. 6-17)
         (c) Mosaicism (1% of cases)
      (2) Risk factors
         (a) Increased maternal age is the major risk factor.
            • Meiotic nondisjunction of chromosome 21 occurs in oogenesis, usually in meiosis I.
            • It occurs in 1 in 25 live births in women over 45 years of age.
            • Approximately 75% of concepti with trisomy 21 die in embryonic or fetal life.
         (b) A female with Down syndrome has a 50% risk of having children with Down syndrome.
      (3) Median age at death is 47 years
   b. Clinical findings
      (1) Mental retardation
         (a) Down syndrome is the most common chromosomal abnormality associated with mental retardation.
         (b) Patients may have mild retardation (IQ 50–75; usually mosaics) or severe retardation (IQ 20–35).
      (2) General appearance
         (a) Muscle hypotonia is present at birth.
            • Down syndrome is the most common cause of the “floppy baby” syndrome.
         (b) Upslanting of palpebral fissures, epicanthic folds, flat facial profile, and macroglossia with protuberant tongue (Fig. 6-19A)
         (c) Simian crease (see Fig. 6-19B)
      (3) Congenital heart defects
         (a) Heart defects are present in 40% to 50% of patients.
         (b) Heart defects are the major factor affecting survival in early childhood.
         (c) Endocardial cushion defects (43%), VSD (32%), atrial septal defect (10%), tetralogy of Fallot (6%), and isolated patent ductus arteriosus (4%)
6-19: Down syndrome. A. The face shows a mongoloid slant of the palpebral fissures (separation between the upper and lower lids), prominent upward slanting of the epicanthal folds (skin folds of the upper eyelids; arrow), a flat nasal root (portion between the eyes) and small nose, low-set ears, and a small mouth with a large tongue (macroglossia). Not shown is the short stature of the child. B. The hand shows a single palmar (simian) crease (arrow). (From Taylor S, Raffles A: Diagnosis in Color Pediatrics, London, Mosby-Wolfe, 1997, p 6-7, respectively; Figs 1.11, 1.13, respectively.)

(4) Gastrointestinal tract abnormalities
   (a) Tracheoesophageal fistula
       • Proximal esophagus ends blindly; distal esophagus arises from trachea
         (see Fig. 18-7)
   (b) Duodenal atresia
       • Atresia (see later) of the small bowel distal to where the common bile
         duct empties into the duodenum; vomiting of bile stained fluid at birth
         (see Fig. 18-18C)
   (c) Hirschsprung disease
       • Aganglionic segment in large bowel; problem with stooling at birth
         (see Fig. 18-18E and F)

(5) Hematologic abnormalities
   (a) Increased risk for developing leukemia
   (b) Acute lymphoblastic leukemia and acute megakaryocytic leukemia are the most
       common types of leukemia (refer to Chapter 13).
   (c) Leukemia is usually preceded by transient myeloproliferative diseases.

(6) Central nervous system (CNS) abnormalities
   (a) Most patients develop the neuropathologic signs of Alzheimer disease by 35 to
       40 years of age.
   (b) Chromosome 21 codes for amyloid precursor protein, which is the progenitor
       for Aβ protein. When phosphorylated, this protein induces apoptosis of
       neurons (refer to Chapter 26).
   (c) Alzheimer disease is the major factor affecting survival in older individuals.

(7) Immune abnormalities
   • Increased risk for developing hypothyroidism, lung infections, and diabetes
     mellitus

(8) Fertility abnormalities
   (a) Males are usually unable to father children.
   (b) Females have decreased fertility and an increased incidence of miscarriages.

(9) Other abnormalities in Down syndrome
   • Umbilical hernia, gap between 1st and 2nd toe, and atlantoaxial instability
     (danger of spinal cord compression)

C. Diagnosis
   (1) Maternal screening with the triple test
       (a) Decreased serum α-fetoprotein (AFP)
       (b) Decreased urine unconjugated estriol (uE3)
       (c) Increased serum human chorionic gonadotropin (hCG)
(d) The triple test has a sensitivity of ~70% and must be followed by invasive
diagnostic tests.
(2) Invasive diagnostic testing (sensitivity ~100%)
   (a) Amniocentesis with chorionic villous sampling
   (b) Percutaneous umbilical blood sampling
   (c) Cytogenetic and DNA studies used to confirm the diagnosis

2. Trisomy 18: Edwards syndrome
   a. Second most common trisomy syndrome (incidence 1/8000 births)
   b. Clinical findings
      (1) Mental retardation
      (2) Clenched fist with overlapping fingers (Fig. 6-20A)
      (3) Rocker-bottom feet (see Fig. 6-20B)
      (4) VSD
      (5) Early death

3. Patau syndrome
   a. Trisomy 13 has an incidence of 1/15,000 births.
   b. Clinical findings
      (1) Mental retardation
      (2) Cleft lip and palate
      (3) Polydactyly, VSD, cystic kidneys
      (4) Early death

D. Disorders involving sex chromosomes

1. Turner syndrome
   a. Epidemiology
      (1) Most common sex chromosome abnormality in females (1/3000 female
          births)
      (2) As many as 15% of spontaneous abortions are due to Turner syndrome.
      (3) Normal intelligence
      (4) Karyotype abnormalities
         (a) 45,X karyotype (most conceptuses are nonviable)
            • The majority are due to a paternal nondisjunction.
         (b) Structural abnormalities (e.g., isochromosomes, deletion)
         (c) Mosaicism (most common cause of Turner syndrome; see later)
            • 45,X/46,XX karyotype (most common type)
            • 45,X/46,XY (risk for developing gonadoblastoma of the ovary; refer to
              Chapter 22)
            • Using sensitive DNA techniques, mosaicism accounts for up to 75%
              of all cases of Turner syndrome, because most 45,XO conceptuses are
              nonviable.
   b. Clinical and laboratory findings
      (1) General abnormalities on physical exam
         (a) Short stature is a cardinal finding in Turner syndrome (>95% of cases).
            • Growth hormone and insulin-like growth factor-1 are normal.
            • Short stature is due to deletion of a second SHOX gene located on the X
              chromosome.
6-21: A, Aborted Turner syndrome fetus with a 45,X karyotype showing lymphedema of the hands, feet, and neck. Most 45,X karyotypes are aborted. B, Turner syndrome is characterized by a webbed neck. Other findings included include short stature, primary amenorrhea, and delayed secondary sex characteristics (e.g., underdeveloped breasts).

(A from Damjanov I, Linder J: Anderson's Pathology, 10th ed, St. Louis, Mosby, 1996, p 338, Fig. 16.21; B from Bouloux P-M: Self-Assessment Picture Tests: Medicine, Vol. 1. London, Mosby-Wolfe, 1996, p 45, Fig. 90.)

- The SHOX gene is critical for regulation of growth and, unlike most genes, remains active on both X chromosomes; hence a deletion of one of the two SHOX genes causes the short stature.

(b) Carrying angle of the arms is increased (cubitus valgus).
(c) Short fourth metacarpal or metatarsal bone produces the knuckle (index finger)-knuckle-dimple (short 4th metacarpal/metatarsal bone)-knuckle sign.
(d) Shield chest with widely spaced nipples and underdeveloped breasts is present.
(e) Pubic hair development is normal.

(2) Lymphedema may occur in the hands, feet, and neck in infancy (Fig. 6-21A).
- The webbed neck in Turner syndrome is caused by dilated lymphatic channels (cystic hygroma) and persists into adult life (see Fig. 6-21B).

(3) Cardiovascular abnormalities
(a) Congenital heart disease occurs in 20% to 50% of cases.
(b) A hypoplastic left heart is the major cause of mortality in early infancy.
(c) Preductal coarctation commonly occurs and often presents with left-sided heart failure.
(d) Bicuspid aortic valves are another common cardiac abnormality.

(4) Genitourinary abnormalities
(a) Both ovaries are replaced by fibrous stroma (called streak gonads).
- Increased risk for developing ovarian dysgerminoma
(b) Ovaries are devoid of oocytes by 2 years of age.
- Some women with mosaicism are fertile.
(c) Primary amenorrhea occurs with delayed sexual maturation.
- Turner syndrome is the most common genetic cause of primary amenorrhea.
- Estradiol and progesterone are decreased.
- Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are increased.
(d) Incidence of horseshoe kidneys is increased.

(5) Hypothyroidism, due to Hashimoto thyroiditis, occurs in 10% to 30% of cases.
(6) No Barr bodies form in the XO types.
2. Klinefelter syndrome
   a. Epidemiology
      (1) Most common genetic cause of male hypogonadism and occurs in 1/500 to 1/1000 live male births
   (2) Causes
      (a) Nondisjunction is the most common cause of the syndrome (90% of cases) and produces 47 chromosomes with an XXY karyotype.
         • Maternal and paternal nondisjunction in meiosis I occurs in roughly equal proportions.
         • One Barr body forms through random inactivation of one of the two X chromosomes.
      (b) Mosaicism is the remaining cause of the syndrome, with the most common karyotype being 46,XY/47,XXY.
   (3) Testicular abnormalities and female secondary sex characteristics do not develop until puberty.
   b. Pathophysiology
      (1) Testicular volume at puberty is decreased (<17 mL) and is due to atrophy.
         (a) Histologic exam reveals fibrosis of seminiferous tubules with absence of spermatogenesis (azospermia; infertility) and loss of Sertoli cells.
         (b) Loss of Sertoli cells leads to a decrease in inhibin and a corresponding increase in FSH (loss of negative feedback with inhibin).
         • Leydig cells are prominent (mainly because of atrophy of other portions of the testis).
         • Increased synthesis of aromatase very likely converts a little of the testosterone that is synthesized by the Leydig cells into estradiol; however, this does not fully explain why patients with Klinefelter syndrome have hypogonadism and feminization.
      (2) Primary reason for hypogonadism and feminization is that testosterone does not have a normal interaction with androgen receptors.
         (a) X chromosome carries genes that encode for androgen receptors, testis function, brain development, and growth.
         (b) Testosterone mediates its function through the androgen receptor.
         (c) Gene on the X chromosome that is responsible for androgen receptor synthesis contains CAG trinucleotide repeats.
         (d) Functional response of testosterone is dependent on the number of CAG repeats in the androgen receptor.
            • Testosterone interacts better with androgen receptors that have the smallest number of CAG repeats.
            • In Klinefelter syndrome, the X chromosome with the shortest CAG repeats is preferentially inactivated, leaving behind androgen receptors that have the longest CAG repeats.
            • Testosterone does not interact with androgen receptors with the longest CAG repeats, which, along with increased conversion into estradiol by aromatase, causes hypogonadism and leaves estradiol unopposed by any androgen effects causing feminization.
   c. Clinical and laboratory findings
      (1) Signs of male hypogonadism
         (a) Characteristic feature in late puberty is persistent gynecomastia (breast development in a male; Fig. 6-22A).
         (b) Facial, body, and pubic hair are diminished
         (c) Hair distribution in the pubic region resembles that of a female (lack of extension of hair from the mons pubis to the umbilicus; see Fig. 6-22A).
         (d) Penis is small (microgenitalis) because of decreased fetal production of testosterone in utero.
         (e) Testicular volume is decreased from testicular atrophy.
      (2) Body habitus
         • Eunuchoid body habitus with disproportionately long legs (see Fig. 6-22A).
      (3) Intelligence
         (a) Mean IQ is lower than normal.
         (b) Minor developmental and learning disabilities are present in most cases.
         (c) In variants that have more than two X chromosomes, the IQ is lower.
(4) Cardiovascular abnormalities
   - Mitral valve prolapse (MVP; sometimes severe) is present in 50% of adults.
(5) Endocrine abnormalities
   - Increased incidence of type 2 diabetes mellitus and metabolic syndrome (insulin resistance; refer to Chapter 23).
(6) Laboratory findings include:
   (a) Decreased serum testosterone and increase serum LH
   (b) Increased serum FSH and estradio1
   (c) Decreased serum inhibin
   (d) Azooospermia (no sperm)
(7) Increased risk for developing:
   - Autoimmune disease (systemic lupus erythematosus [SLE]), rheumatoid arthritis, Sjögren syndrome, breast cancer, and osteoporosis

3. XYY syndrome (see Fig. 6-22B)
   a. Paternal nondisjunction
   b. Occurs in 1/2000 live births
   c. Associated with aggressive (sometimes criminal) behavior
   d. Normal gonadal function

IV. Other Patterns of Inheritance
A. Multifactorial (complex) inheritance
   1. Definition—inheritance is due to complex interactions between a number of genetic and environmental factors
   2. Incidence of ~50/1000 live births
   3. Examples
      a. Open neural tube defects
         • Associated with decreased maternal folic acid levels
      b. Type 2 diabetes mellitus
         • Associated with obesity, which down-regulates insulin receptor synthesis
      c. Other examples include gout, cleft lip/palate, congenital heart defects, pyloric stenosis, and coronary artery disease

B. Mitochondrial DNA disorders
   1. Function of mitochondrial DNA (mtDNA)
      • Codes for enzymes that are involved in mitochondrial oxidative phosphorylation reactions
2. Inheritance pattern
   a. Affected females transmit the mutant gene to all their children (Fig. 6-23).
      • Ova contain mitochondria with the mutant gene.
   b. Affected males do not transmit the mutant gene to any of their children.
      • Sperm lose their mitochondria during fertilization.

3. Examples—Leber hereditary optic neuropathy, myoclonic epilepsy

C. Genomic imprinting
   1. Inheritance pattern
      a. Inheritance depends on whether the mutant gene is of maternal or paternal origin.
      b. Examples of genomic imprinting include Prader-Willi (PW) syndrome and Angelman syndrome.

2. Pathogenesis (Fig. 6-24)
   a. Normal changes in the maternal chromosome 15 occur during gametogenesis.
      1. The expression of PW genes (series of genes) is imprinted.
         • Imprinted means that gene has been inactivated by methylation.
**6-25: A**, Prader-Willi syndrome. Note the marked obesity in this child and small penis. Parental informed consent, as approved by the Baylor College of Medicine Institutional Review Board, was obtained to publish the photographs. **B**, Angelman syndrome. Note the happy face and wide-based gait; hence, the term “happy puppet” for this syndrome. *(A, from Sahoo T, del Gaudio D, German JR, et al: Prader-Willi phenotype caused by paternal deficiency for the H19-65 C/D box small nucleolar RNA cluster, Nat Genet 40:719–721, 2008; B, from Taylor S, Raffles A: Diagnosis in Color Pediatrics, London, Mosby-Wolfe, 1997, p 200, Fig. 7.32.)*

(2) The Angelman gene (UBE3A) is active.
- Active means that the gene has *not* been methylated.

b. Normal changes in the paternal chromosome 15 occur during gametogenesis.
   (1) PW genes are active.
   (2) Angelman gene expression is imprinted.

c. Microdeletion of the entire gene site on paternal chromosome 15 causes PW syndrome.
   (1) There is complete loss of expression of the PW genes.
   (2) On the maternal chromosome, the PW genes are imprinted and the Angelman gene is active.

d. Microdeletion of the entire gene site on maternal chromosome 15 causes Angelman syndrome.
   (1) There is complete loss of Angelman gene expression.
   (2) On the paternal chromosome, the Angelman gene is imprinted and the PW genes are active.

3. Clinical findings in PW syndrome *(Fig. 6-25A)*
   a. Neonatal hypotonia and genital hypoplasia are present at birth.
   b. Other findings include short stature (due to growth hormone deficiency) and hyperphagia (insatiable appetite) leading to obesity.
   - The satiety defect is due to increased levels of gherlin, a polypeptide hormone produced by the stomach and arcuate nucleus in the hypothalamus that increases food intake.

4. Clinical findings in Angelman syndrome *(see Fig. 6-25B)*
   a. Mental retardation
   b. Jerky, wide-based gait with hand flapping (resembles a marionette)
   c. Outbursts of inappropriate laughter (“happy puppet” syndrome).

**V. Disorders of Sex Differentiation**

**A. Normal sex differentiation**

1. Y chromosome
   a. Compared to other chromosomes, it is relatively gene poor (contains ~50 genes).
   b. SRY gene is the sex-determining gene on the Y chromosome.
   c. Presence of a single Y gene determines the male sex.

2. Presence of the Y chromosome *(Fig. 6-26A)*
   a. SRY gene encodes a testis-determining factor that causes the undifferentiated gonad to develop into a testis.
b. Müllerian inhibitory substance (MIS), synthesized in the Sertoli cells of the testes, causes the paramesonephric ducts to undergo apoptosis.

c. Function of fetal testosterone
   • Testosterone develops the mesonephric duct structures, which include the epididymis, seminal vesicles, and vas (ductus) deferens.

d. 5α-Reductase, in peripheral tissue, converts testosterone to dihydrotestosterone (DHT).

e. Functions of fetal DHT
   (1) In the male embryo, the genitalia is phenotypically female before DHT is produced.
   (2) What phenotypically appears to be labia fuses to become the scrotum.
   (3) What phenotypically appears to be a clitoris becomes elongated into a penis.
   (4) Fetal DHT also develops the prostate gland.

3. Absence of the Y chromosome (see Fig. 6-26B)
   a. Absence of the Y chromosome causes gonadal tissue to differentiate into an ovary beginning as early as the 8th week of gestation and continuing for several weeks.
   b. Fallopian tubes, uterus, and upper vagina develop from the paramesonephric ducts (müllerian ducts), while mesonephric duct structures undergo apoptosis.
   c. Contact of the uterovaginal primordium (sinus tubercle) with the urogenital sinus induces the formation of sinovaginal bulbs that fuse to form a vaginal plate, which canalizes to form the lumen of the vagina.

B. True hermaphrodite
   1. Definition—the fetus has a testis on one side and an ovary on the other side or a fusion of ovarian and testicular tissue (ovotestes)
   2. Karyotype is 46,XX in 50% of cases, whereas the remaining are mosaics with a 46,XX/46,XY karyotype.

C. Pseudohermaphrodite
   1. Definition—the phenotype (external appearance) and genotype (true genetic sex) do not match
Male pseudohermaphrodite: genotype XY; phenotype ambiguous or completely female

AIS MCC male pseudohermaphroditism

Female pseudohermaphrodite: genotypically female; phenotypically ambiguous or virilized

Adrenogenital syndrome: MCC female pseudohermaphroditism

XR disorder; male pseudohermaphroditism

Loss-of-function mutation in androgen receptor gene on X chromosome

Prenatal undervirilization of external genitalia; loss of pubertal male changes

Testicles in inguinal canal at birth or abdominal cavity

Absence of fallopian tubes, uterus, cervix, upper vagina; MIS is functional

Absence of epididymis, seminal vesicles, vas deferens, prostate; no fetal testosterone effect

2. Male pseudohermaphroditism
   a. Definition—patients are genotypically males (XY with testes), and phenotypically, the external genitalia are ambiguous (male and female looking) or completely female.
   b. Examples of male pseudohermaphroditism include androgen insensitivity syndrome (AIS, see later) and deficiency of 5α-reductase.

3. Female pseudohermaphroditism
   a. Definition—patients are genotypically female (XX with ovaries), but phenotypically have ambiguous genitalia or are virilized
   b. Gonads are normal ovaries and the internal genitalia are normal.
   c. Most common cause is adrenogenital syndrome due to 21- or 11-hydroxylase deficiency (refer to Chapter 23).

D. Androgen insensitivity syndrome (AIS; testicular feminization) (Fig. 6-27)

1. Epidemiology
   a. XR disorder
   b. Most common cause of male pseudohermaphroditism

2. Pathogenesis
   a. Loss-of-function mutation in the androgen receptor gene on the long arm of the X chromosome (Xq11-13)
      • Loss of receptor function means that even though male hormone synthesis is normal, the effects of the hormone in tissue do not occur, resulting in prenatal undervirilization of external genitalia and loss of pubertal changes one would expect in a male (e.g., voice changes, male distribution of hair, acne).
   b. Complete loss of the androgen receptor or alterations in substrate binding affinity to the receptor

3. Clinical and laboratory findings
   a. At birth, testicles are present in the inguinal canal or the abdominal cavity.
   b. Paramesonephric duct structures are absent (fallopian tubes, uterus, cervix, upper vagina), because MIS is present and initiates apoptosis of those structures in-utero.
   c. Male accessory structures (epididymis, seminal vesicles, vas deferens, prostate gland) are absent.
      • In AIS, there is no testosterone effect on development of the mesonephric duct structures, because the androgen receptors are absent or nonfunctional.

6-27: Androgen insensitivity syndrome. The patient is genotypically male, but phenotypically female. The vagina ends as a blind pouch. (From Bouloux, P: Self-Assessment Picture Tests Medicine, volume 3, London, Mosby-Wolfe, 1997, p 24, Fig. 48.)
d. External genitalia remain female in appearance.
   (1) There is no DHT effect on the external genitalia.
   (2) Vagina ends as a blind pouch.
      • Lower two-thirds of the vagina is not of paramesonephric duct origin (see previous discussion).
e. If not identified in the newborn period, patients present with primary amenorrhea in their teenage years.
f. Gynecomastia is usually present as a postpubertal finding.
g. If the testes are not surgically removed, there is an increased risk for developing a gonadoblastoma (refer to Chapter 22).
h. Laboratory test findings
   (1) Karyotype is essential in order to differentiate an undermasculinized male from a virilized female.
   (2) Normal male serum levels of testosterone/DHT
   (3) Slight increase in serum luteinizing hormone (LH)
   (4) Slight increase in serum estradiol
      (a) Since estrogen activity is unopposed and estrogen receptors are present, the patient has female phenotypic findings.
      (b) Term “unopposed” means that testosterone function is neutralized by the absence or nonfunctionality of the androgen receptors.
   (5) Mutation analysis of the androgen receptor gene detects up to 95% of the mutations.

4. Majority reared as female

VI. Congenital Anomalies
A. Epidemiology
1. Definition—defect is recognized only at birth (“born with”).
   • Genetic means that the disorder is one that is determined by genes.
2. Occur in 3% to 5% of all newborns
3. Most common cause of death in children <1 year of age
4. Major causes
   a. Genetic
      • Examples—chromosome abnormalities (most common; 10%–15% of cases), single-gene mutations (2%–10% of cases)
   b. Maternal (6%–8% of cases)
      (1) Maternal diabetes mellitus
         (a) Increased risk of neural tube defects and congenital heart disease
         (b) Maternal hyperglycemia causes fetal macrosomia, because hyperinsulinemia in the fetus increases muscle mass and stores of fat in the adipose (refer to Chapter 23).
      (2) Maternal SLE
         • Newborn may develop congenital heart block if the mother has anti-Ro antibodies that cross the placenta (refer to Chapter 24)
      (3) Maternal hypothyroidism (refer to Chapter 23)
         (a) Newborn may develop cretinism with severe mental retardation.
         (b) Thyroid hormone is necessary for normal development of the brain.
c. Drugs and chemicals (1% of cases; Table 6-4; Fig. 6-28A)
d. Congenital infections (2%–3% of cases; Table 6-5; see Fig. 6-28B)
   (1) Newborn with a congenital infection has an increase in cord blood IgM
      • IgM normally is not synthesized in the fetus unless there is a congenital infection.
   (2) Vertical transmission; routes of transmission:
      (a) Transplacental (most common route)
      (b) Birth canal
      (c) Breast-feeding
e. Ionizing radiation (1% of cases)
   • Produces malformations (see later) in the embryonic period (see later) causing microcephaly, skull defects, blindness, and open neural tube defects (e.g., spina bifida)
f. Multifactorial causes (20%–25% of cases)
   • Multifactorial (complex) inheritance disorders (e.g., open neural tube defects [see Fig. 26-4A, B, D, and E], congenital heart disease, cleft lip/palate [see Fig. 18-1])
5. Types of errors in morphogenesis
   a. Malformations
      (1) Definition—disturbances in the morphogenesis (development) of an organ
      (2) Mainly occur during embryogenesis (first 9 weeks of pregnancy; Fig. 6-29)
         (a) Most occur between the third and ninth weeks of embryogenesis.
         (b) Most susceptible period is during the fourth and fifth weeks, when organs are
             being formed from the germ cell layers (ectoderm, endoderm, mesoderm).
   b. Deformations
      (1) Definition—caused by extrinsic factors that physically impinge on fetal
          development in utero

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**TABLE 6-4 Teratogens Associated with Congenital Defects**

<table>
<thead>
<tr>
<th>TERATOGEN</th>
<th>DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (see Fig. 6-28A)</td>
<td>Mental retardation (leading cause in the Western Hemisphere), microcephaly, congenital heart defects (VSD, ASD), attention deficit, diagnostic facial features (thinning of the upper lip, epicanthal folds, flat nasal bridge, short nose, hirsute forehead, short palpebral fissures) Mechanism: acetaldehyde, a breakdown product of alcohol metabolism, disrupts cellular differentiation and growth (disrupts retinoic acid and hedgehog signaling pathways), disrupts DNA and protein synthesis, and inhibits cell migration.</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Microcephaly, low birth weight, renal agenesis, intestinal atresia, congenital heart disease, urinary tract abnormalities (urethral obstruction, hydronephrosis, hypospadias urethra opens on undersurface of penis). Mechanism: disruption of normal growth and development as a result of vascular insufficiency.</td>
</tr>
<tr>
<td>DES</td>
<td>Vaginal and/or cervical clear cell carcinoma (develops from remnants of paramesonephric ducts; see Fig. 22-3B) paramesonephric duct defects (uterine abnormalities, cervical incompetence) Mechanism: inhibits normal differentiation of paramesonephric structures</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Nail and distal phalanx hypoplasia, cleft lip and/or palate, neuroblastoma, bleeding (vitamin K deficiency)</td>
</tr>
<tr>
<td>Retinoic acid</td>
<td>Hearing defects, missing ear lobes, visual impairment, facial dysmorphism, mental retardation, CNS defects, cardiovascular defects Mechanism: disrupts Hox gene function (important in determining the different structures that develop in the anterior-posterior axis)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Amelia (absent limbs), phocomelia (seal-like limbs), deafness</td>
</tr>
<tr>
<td>Tobacco</td>
<td>IUGR, low birth weight, prone to sudden infant death syndrome</td>
</tr>
<tr>
<td>Valproate</td>
<td>Neural tube defects (valproate is a folate antagonist), autism</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Nasal hypoplasia, agenesis corpus callosum, fetal bleeding, and death</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Craniofacial and limb abnormalities</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Teeth and bone maldevelopment</td>
</tr>
<tr>
<td>Lithium</td>
<td>Tricuspid valve abnormalities</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Ototoxicity</td>
</tr>
</tbody>
</table>

ASD, Atrial septal defect; DES, diethylstilbestrol; IUGR, intrauterine growth retardation; VSD, ventricular septal defect.

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**6-28:** A, Fetal alcohol syndrome. Note the wide-spread eyes (hypertelorism), inner epicanthal folds, short nose, hirsute forehead, and thin upper lip. B, Congenital cytomegalovirus infection. Note the enlarged renal tubular cells with basophilic (usually eosinophilic) nuclear inclusions. (A from Zitelli B: Atlas of Pediatric Physical Diagnosis, 3rd ed, London, Mosby, 1997; B from Damjanov I, Linder J: Anderson’s Pathology, 10th ed, St. Louis, Mosby, 1996, p 349, Fig. 16.28A.)
c. Disruption
(1) Definition—type of deformation that results from destruction of irreplaceable normal fetal tissue
(2) Deformation may be due to vascular insufficiency (e.g., thrombosis of vessels in the placenta), trauma, or teratogens.
(3) Amniotic bands are an example of a disruption.
  • Due to rupture of the amnion with formation of fibrous bands that encircle parts of the fetus leading to partial amputation of a limb or constriction rings around digits

d. Agenesis
(1) Definition—complete absence of an organ due to absence of the anlage (primordial tissue)
(2) Example—renal agenesis

e. Aplasia
(1) Definition—the anlage (primordial tissue) is present but it never develops into the organ
(2) Example—lung aplasia with tissue containing rudimentary ducts and connective tissue

f. Hypoplasia
(1) Definition—primordial tissue develops incompletely, but the tissue is histologically normal
(2) Example—microcephaly (small brain), hypoplastic left heart

Oligohydramnios (decreased amniotic fluid) from decreased production of fetal urine (e.g., renal agenesis, cystic disease of the kidneys) restricts fetal movement in the uterine cavity. As a result, newborns have flat facial features (Potter facies), compression of the skull vault, dysplastic/displaced ears, underdevelopment of the chest wall, and club feet (talipes equinovarus; Fig. 6-30A and B).

(2) Occur between the ninth week and term after fetal organs have developed
(3) Most often due to restricted movement in the uterine cavity (called uterine restraint); examples include:
  (a) Maternal factors such as a malformed uterus or large leiomyomas (smooth muscle tumors) in the uterine wall that bulge into the uterine cavity
  (b) Placental factors such as oligohydramnios (see later) or twin pregnancies
Sensitive or critical periods in embryonic development. Congenital anomalies that occur in the embryonic period of development (first 9 weeks of pregnancy) produce malformations. Anomalies after that period produce deformations. (From Seidel H, Ball J, Dains, J, Benedict G: Mosby's Guide to Physical Examination, 6th ed, St. Louis, Mosby Elsevier, 2006, p 111, Fig. 5.5.)

- Atresia
  1. Definition— incomplete formation of a lumen
  2. Example— duodenal atresia (see Fig. 18-18, C)

B. Pathogenesis
1. Timing of the teratogenic insult
   a. Malformations occur during the embryonic period (from 3 to 9 weeks).
   b. Deformations occur during the fetal period (ninth week to term).
2. Alterations during key steps in morphogenesis
   a. Mutations may occur in genes normally involved in morphogenesis.
      - Example— mutations of the Hox genes alter development of craniofacial structures
   b. Alterations in cell proliferation, migration, and apoptosis

Pregnant women should not be treated for acne with retinoic acid. Retinoic acid disrupts the function of the Hox genes, which are important in producing proteins that are involved in the patterning of craniofacial structures, vertebrae, and limbs. Dysfunction of these genes results in craniofacial, central nervous system, and cardiovascular defects.

VII. Perinatal and Infant Disorders
A. Stillbirth
1. Definition— birth of a dead child
2. Most frequently caused by an abruptio placentae
   - In placental abruption, there is premature separation of the placenta because of a retroplacental blood clot (Fig. 22-14E)
3. Other causes include:
   - Maternal diabetes mellitus, infection, and Rh hemolytic disease of newborn

B. Spontaneous abortion (miscarriage)
1. Definition— termination of a pregnancy before 20 weeks gestation
2. Most common complication in early pregnancy
   a. Overall spontaneous abortion rate is 15%-20%.
   b. Majority occur in the first trimester.
3. Most often caused by a fetal karyotypic abnormality, which is trisomy 16 in ~50% of cases.
4. Predisposing factors
   a. Advanced maternal age
   b. Infections (e.g., Streptococcus agalactiae, Listeria monocytogenes)
   c. Tobacco, alcohol use

C. Sudden infant death syndrome (SIDS)
1. Epidemiology
   a. Definition— sudden and unexpected death of an apparently healthy infant under 1 year of age, which remains unexplained after a thorough case investigation and autopsy
   b. In the United States, it is the most common cause of death of an infant between age 1 month and 1 year.

- Atresia: incomplete formation of lumen
- Congenital anomalies: timing of teratogenic insult important
- Retinoic acid: disrupts Hox gene function; craniofacial, CNS, cardiovascular defects
- Hox genes: involved in patterning of craniofacial structures, vertebrae, limbs
- Stillbirth: birth of a dead child
- Abruptio placentae MCC stillbirth
- Spontaneous abortion: termination of pregnancy before 20 weeks
- MC complication early pregnancy
- Spontaneous abortion: most commonly caused by trisomy 16
- SIDS: sudden, unexpected death of healthy infant <1 year old
- In U.S, MCC infant death between 1 month and 1 year of age
Majority of deaths before age 6 months

Multifactorial; maternal/infant risk factors

Petechiae MC finding at autopsy; sign of tissue hypoxia

Brainstem (hypoplasia, arcuate nucleus; astroglisis); cerebellum (astroglisis)

SGA: group with highest mortality rate

LGA: most often due to maternal DM

Prematurity: gestation age <37 weeks; <2500 g

Prematurity MCC neonatal death/morbidity

Premature rupture of membranes MCC prematurity

Chorioamnionitis: inflammation of placental membranes

Funisitis: inflammation of umbilical cord

Complications: RDS, necrotizing enterocolitis, intraventricular hemorrhage

c. Most deaths occur between 2 and 4 months of age.
   • ~90% occur in infants <6 months of age.
d. Death usually occurs during sleep.

2. Pathogenesis
   a. No single cause of SIDS (multifactorial condition)
   b. Maternal risk factors include:
      • Smoking, young age, frequent childbirths, and inadequate prenatal care
   c. Infant risk factors include
      • Prematurity, prior sibling with SIDS, prior history of a mild respiratory infection, sleeping prone or on the side (should be supine), neural developmental delay, and a brainstem defect increasing the risk for not being able to be aroused from slow wave sleep

3. Autopsy findings
   a. Petechiae on the visceral and parietal pleura, epicardium, and thymus is the most common finding (~80% of cases).
   b. Nonspecific signs of tissue hypoxia are present (e.g., extramedullary hematopoiesis).
   c. Thickened pulmonary arteries are present with pulmonary vascular engorgement and edema.
   d. Brainstem shows microscopic changes from hypoxia (e.g., hypoplasia of the arcuate nucleus).
   e. Astroglisis (hypertrophy and hyperplasia of astrocytes) is present in the cerebellum and brainstem.

D. Prematurity and intrauterine growth retardation (IUGR)

1. Newborn classification based on weight and gestational age
   a. Appropriate for gestational age (AGA)
   b. Small for gestational age (SGA)
      • Highest mortality rate
   c. Large for gestational age (LGA)
      • Most often associated with maternal diabetes mellitus

2. Prematurity
   a. Definition—gestational age <37 weeks
      • Newborns usually weigh <2500 g.
   b. Most common cause of neonatal death and morbidity
   c. Risk factors
      (1) Premature rupture of the membranes (most common cause)
      (2) Intrauterine infection
         (a) Inflammation of the placental membranes (called chorioamnionitis)
         (b) Inflammation of the umbilical cord (called funisitis)
         (c) Pathogens that have been implicated include S. agalactiae, Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis, Trichomonas vaginalis, Neisseria gonorrhoeae, and Chlamydia trachomatis.
      (3) Placental abnormalities (e.g., placenta previa, abruptio placenta; refer to Chapter 22)
      (4) Twin pregnancies (refer to Chapter 22)
      (5) Maternal factors, including poor nutrition, low socioeconomic status, and smoking
d. Complications
   (1) Respiratory distress syndrome (RDS, decreased surfactant; refer to Chapter 17)
   (2) Necrotizing enterocolitis (intestinal ischemia; refer to Chapter 17)
   (3) Intraventricular hemorrhage (Fig. 6-31)

6-31: Intraventricular hemorrhage in an infant with prematurity. (From Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 120, Fig. 5-29.)
3. Intrauterine growth retardation (IUGR)
   a. Definition—<10% of predicted fetal weight for gestational age
   b. Usually occurs in SGA infants
   c. Maternal causes
      (1) Most common cause of IUGR in SGA infants
      (2) Examples include preeclampsia (refer to Chapter 22), poor nutrition, drug
          addiction, alcoholism, and smoking.
   d. Fetal causes include chromosomal disorders, congenital malformations, and congenital
      infections.
      • Symmetrical growth retardation of all organ systems
   e. Placental causes include abruptio placentae, placental infarction due to vessel
      thrombosis, and a single umbilical artery.
      (1) Asymmetric growth retardation
      (2) Example—the brain is spared relative to visceral organs such as the liver
   f. About 85% of IUGR infants have oligohydramnios.
      (1) Blood flow from peripheral organs (kidneys) is diverted to the brain.
      (2) Renal perfusion and urinary flow rates are reduced in IUGR infants.
   g. Ultrasonography is a common initial step in the workup of IUGR.

E. Neonatal period
1. Definition—first 4 weeks of life
2. Majority of deaths in childhood occur during this period
3. Common causes of death include RDS and congenital anomalies.

VIII. Diagnosis of Genetic and Developmental Disorders

A. Invasive testing
1. Amniocentesis
   a. Amniocentesis is used to identify prenatal genetic defects.
   b. Increased risk of complications if performed early in the pregnancy (e.g., 10th to
      14th weeks)
   c. Amniotic fluid (AF), which is primarily composed of fetal urine, contains fetal cells that
      can be cultured for fetal tests.
   d. α-Fetoprotein (AFP) is commonly measured in AF.
      (1) It is a fetal glycoprotein produced mainly in the liver, secreted into the circulation,
          and excreted by the kidneys.
      (2) It enters the maternal bloodstream via the placenta, amniotic membranes, and
          maternal-fetal circulation, which explains why AFP is measured in AF and
          maternal serum.
   2. Chorionic villus sampling
      a. This test is performed transcervically or transabdominally between the 10th and 12th
         weeks of pregnancy
      b. Results of possible fetal abnormalities are available earlier in the pregnancy than with
         amniocentesis.

B. Noninvasive testing
1. Ultrasonography (US)
   a. Ultrasonography is important in the assessment of fetal age, fetal sex, multiple
      pregnancies, fetal viability, and for detection of possible fetal morphologic
      abnormalities.
   b. Examples of fetal abnormalities that are detected include open neural tube defects (e.g.,
      anencephaly, meningomyelocele), cystic hygroma (Turner syndrome), chromosomal
      aneuploidy syndromes (e.g., trisomy syndromes, Turner syndrome), and certain types
      of single-gene disorders (e.g., osteogenesis imperfecta).
   2. Maternal triple marker screening
      a. AFP
         (1) It is increased in open neural tube defects and decreased in Down syndrome.
         (2) In open neural tube defects, it is causally related to folic acid deficiency
             before conception.
      b. Serum human chorionic gonadotropin (hCG)
         (1) Levels of hCG vary with gestational age.
         (2) In Down syndrome, serum hCG is increased.
      c. Urine for unconjugated estriol
         (1) Estriol is an excellent marker of fetal, placental, and maternal dysfunction (refer to
             chapter 22).
         (2) In Down syndrome, there is a decrease in urine unconjugated estradiol.

IUGR: maternal factors most often responsible
Fetal causes IUGR: symmetrical growth retardation
Placental causes IUGR: asymmetric growth retardation; brain spared
IUGR: majority have oligohydramnios
Neonatal period: first 4 weeks of life
Neonatal period: common causes of death are RDS/ congenital anomalies
Identifies prenatal genetic defects
AF is primarily fetal urine; contains fetal cells
AFP measured in AF and maternal serum
Chorionic villus sampling detects fetal abnormalities earlier than amniocentesis
US: assessment fetal age/sex/viability, multiple pregnancies, fetal morphologic abnormalities
Open neural tube defect: folic acid deficiency before conception; ↑AFP
Down syndrome: ↓AFP
Down syndrome: ↑serum hCG
Down syndrome: ↓urine unconjugated estradiol
C. Genetic analysis

1. Chromosome karyotyping
   - Karyotyping identifies numeric and structural abnormalities.

2. DNA molecular assays (e.g., polymerase chain reaction, fluorescence in situ hybridization [FISH])
   - Highly sensitive and specific tests that are useful in diagnosing a spectrum of mutations

IX. Aging

A. Theories of aging

1. Stochastic (random error) theories
   a. Somatic mutation theory
      - Proposes that genetic damage from ionizing radiation produces mutations in DNA leading to failure in critical bodily functions
   b. DNA repair theory
      - States that the inability to repair DNA damage is responsible for age-related and dependent detrimental effects
   c. Cross-linking theory
      (1) This theory suggests that increased cross-linking of proteins in the extracellular matrix (e.g., collagen, elastin, crystallin) impairs the diffusion of essential nutrients to tissue.
      (2) Nonenzymatic glycosylation (a type of cross-linking involving glucose attachment to proteins) is also thought to impair diffusion of essential nutrients to tissue.
         - Example—glycosylation of collagen and the eye lens protein crystallin is associated with cataracts in elderly people

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**Table 6-6 Age-Dependent Changes**

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory</td>
<td>Presbycusis: sensorineural hearing loss, particularly at high frequency</td>
</tr>
<tr>
<td></td>
<td>Otosclerosis: fusion of ear ossicles producing conductive hearing loss</td>
</tr>
<tr>
<td>Body composition</td>
<td>Total body fat increases while total body water and lean body mass decrease: water-soluble medications (e.g., cimetidine, digoxin, ethanol) have decreased volume of distribution causing higher levels in the plasma. Fat-soluble drugs (e.g., chlordiazepoxide) have a larger volume of distribution causing a decreased plasma concentration; excretion from the body is at a slower rate, which increases half-life and extends pharmacologic effects.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Blunted maximal cardiovascular responses to exercise</td>
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<tr>
<td>Central nervous</td>
<td>Cerebral atrophy with mild forgetfulness</td>
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<td></td>
<td>Impaired sleep patterns such as insomnia, early wakening</td>
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<tr>
<td></td>
<td>Decreased dopaminergic synthesis: parkinsonian-like gait</td>
</tr>
<tr>
<td></td>
<td>Decrease in cerebral blood flow and increase in blood-brain barrier permeability: increases sensitivity to medications that affect CNS</td>
</tr>
<tr>
<td>Female reproductive</td>
<td>Breast and vulvar atrophy</td>
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<tr>
<td></td>
<td>Decreased estrogen and progesterone: ↑FSH and LH, respectively</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Decreased gastric acidity: predisposes to <em>Helicobacter pylori</em> infection</td>
</tr>
<tr>
<td></td>
<td>Decreased colonic motility: constipation predisposing to diverticulosis</td>
</tr>
<tr>
<td>General</td>
<td>Increased body fat: decreased number insulin receptors (glucose intolerance)</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Liver mass decreases 25%–35% with increasing age: liver blood flow decreases 35%–45%; hence, medications have a longer duration of effect</td>
</tr>
<tr>
<td>Immune</td>
<td>Decreased skin response to antigens (called anergy)</td>
</tr>
<tr>
<td>Male reproductive</td>
<td>Prostate hyperplasia: predisposes to urinary retention</td>
</tr>
<tr>
<td></td>
<td>Prostate cancer: most common cancer in men</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Osteoarthritis in weight-bearing joints: wearing down of articular cartilage in the femoral head</td>
</tr>
<tr>
<td>Renal</td>
<td>Kidney loses 20%-25% of renal mass as people age from 30 to 80 years</td>
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<tr>
<td></td>
<td>Decreased GFR (↓10% per decade from the age of 30 years): increased risk of drug toxicity from slow clearance of drugs</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Mild obstructive pattern in pulmonary function tests: e.g., ↑TLC, ↓vital capacity</td>
</tr>
<tr>
<td></td>
<td>Mild hypoxemia and increased A-a gradient</td>
</tr>
<tr>
<td>Skin</td>
<td>Decreased skin elasticity due to increased crossbridge formation between collagen fibers Senile purpura over the dorsum of the hands (see Fig. 15-7) and lower legs</td>
</tr>
<tr>
<td>Visual</td>
<td>Cataracts: visual impairment, increased risk for falls</td>
</tr>
<tr>
<td></td>
<td>Presbyopia: inability to focus on near objects</td>
</tr>
</tbody>
</table>

A-a, Alveolar-arterial; FSH, follicle-stimulating hormone; GFR, glomerular filtration rate; LH, luteinizing hormone; TLC, total lung capacity.
### Table 6-7 Age-Related Changes

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Atherosclerosis: increased risk for coronary artery disease, heart failure, peripheral vascular disease, strokes</td>
</tr>
<tr>
<td></td>
<td>Aortic stenosis: most common valvular abnormality in the elderly</td>
</tr>
<tr>
<td></td>
<td>Systolic hypertension: due to loss of aortic elasticity</td>
</tr>
<tr>
<td></td>
<td>Giant cell arteritis: large vessel vasculitis involving aortic arch vessels</td>
</tr>
<tr>
<td>Central nervous</td>
<td>Alzheimer disease: most common cause of dementia in people &gt;65 years</td>
</tr>
<tr>
<td></td>
<td>Parkinson disease</td>
</tr>
<tr>
<td></td>
<td>Subdural hematomas: due to falls</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Female reproductive</td>
<td>Increased incidence of cancers of the breast, endometrium, ovary</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Increased incidence of colorectal cancer</td>
</tr>
<tr>
<td>Immune</td>
<td>MGUS: most common cause of monoclonal gammopathy</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Osteoporosis: vertebral column in females and femoral head in males</td>
</tr>
<tr>
<td></td>
<td>Polymyalgia rheumatica: muscle and joint pain associated with an increased erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>Renal/urogenital tract</td>
<td>Renovascular hypertension secondary to atherosclerosis</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pneumonia: usually <em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Primary lung cancer: particularly in smokers</td>
</tr>
<tr>
<td>Skin</td>
<td>UVB-induced cancers: e.g., basal cell carcinoma (most common)</td>
</tr>
<tr>
<td></td>
<td>Actinic (solar) keratosis: precursor for squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Pressure sores: pressure on capillaries is the most important risk factor</td>
</tr>
<tr>
<td>Visual</td>
<td>Macular degeneration: most common cause of blindness in the elderly</td>
</tr>
</tbody>
</table>

MGUS, Monoclonal gammopathy of undetermined significance; UVB, ultraviolet light B.

d. Free radical (FR) theory (refer to Chapter 2)

1. This theory suggests that most aging changes are due to FR damage of cell membranes and nuclear proteins

   - High levels of FR metabolizing enzymes (e.g., superoxide dismutase) have been found in longer-lived species.

2. Programmed cell death theory

   a. Proposes that the process of aging is part of a genetically programmed continuum of development and maturation

   b. Supported by the similarity of attained age in identical versus nonidentical twins, increased longevity in certain families, and the presence of genetic defects in people with premature aging (e.g., Down syndrome; progeria)

### B. Age-dependent changes

- Definition—changes that are inevitable with age (Table 6-6)

### C. Age-related changes

- Definition—changes that have a greater incidence with age but are not inevitable with age (Table 6-7)
I. Chemical Injury
A. Tobacco use
   1. Epidemiology
      a. Leading cause of premature death in developed countries
      b. Most preventable cause of death worldwide
      c. Rate of cigarette smoking is increasing in females and decreasing in males
      d. Chemical components of tobacco
         (1) Nicotine
            a. Rapidly absorbed
            b. Addictive chemical in tobacco smoke
            c. Cotinine is the most important metabolite of nicotine.
               • Cotinine screening test for blood or urine is used to detect whether a person is a smoker.
            d. Nicotine patch is an effective treatment for ulcerative colitis.
         (2) Important noxious chemicals in cigarette smoke
            a. Polycyclic hydrocarbons are carcinogens that damage DNA.
            b. Tar is a resinous compound that contains most of the carcinogenic agents in cigarette smoke.
               • Tacky, brown material left behind in a cigarette filter and gives the teeth and fingers holding the cigarette a brownish-yellow film.
            c. Phenol is carcinogenic and irritates mucosa.
            d. Nitrosamine is a carcinogen that damages DNA.
            e. Nitrogen oxides damage cilia and irritate mucosa.
               • Also a major component of smog
            f. Carbon monoxide attaches to heme groups (decreases arterial oxygen saturation), shifts the oxygen-binding curve to the left, and inhibits cytochrome oxidase in the electron transport chain (refer to Chapter 2).
            g. Formaldehyde damages cilia and irritates mucosa.

   e. Smokeless tobacco (e.g., chewing tobacco)
      (1) Can cause nicotine addiction
      (2) Increases risk for developing squamous cell cancer of the buccal mucosa and gums
   f. Passive (secondhand) smoke inhalation
      (1) Secondhand smoke has its most serious impact on children.
         • It increases the risk for developing respiratory and middle ear infections, and it exacerbates asthma.
      (2) Increased risk for lung cancer and coronary artery disease (CAD).

2. Systemic effects associated with tobacco use (Table 7-1)
3. Beneficial effects of smoking cessation
   a. Live longer, regardless of age, than those who continue to smoke
      • If cessation is before age 50 years, reduction in risk of dying in the next 15 years is cut in half compared with those who continue to smoke.
   b. Lower risk for developing cardiovascular disease
      • Risk approaches that of a nonsmoker after 15 years.
Table 7-1  Systemic Effects Associated with Tobacco Use

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Acute myocardial infarction: increases atherosclerosis in coronary arteries</td>
</tr>
<tr>
<td></td>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular disease: increases atherosclerosis of the femoral and popliteal arteries</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>Central nervous</td>
<td>Strokes: intracerebral bleeding, subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Increased risk for oropharyngeal cancer: squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Increased risk for upper and midesophageal cancer: squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Increased risk for stomach cancer: adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux disease: decreases tone of lower esophageal sphincter</td>
</tr>
<tr>
<td></td>
<td>Increased risk for peptic ulcers and delayed healing of peptic ulcers</td>
</tr>
<tr>
<td></td>
<td>Increased risk for pancreatic cancer: adenocarcinoma</td>
</tr>
<tr>
<td>General</td>
<td>Low birth weight in newborns, intrauterine growth retardation</td>
</tr>
<tr>
<td></td>
<td>Neutrophilic leukocytosis: decreased activation of neutrophil adhesion molecules</td>
</tr>
<tr>
<td></td>
<td>Decreased concentration of ascorbic acid (used up in neutralizing hydroxyl free radicals) and β-carotenes</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Increased risk for cervical cancer: squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>? Decreased free testosterone in males (↑SHBG; ↑binding of free testosterone)</td>
</tr>
<tr>
<td></td>
<td>Decreased estrogen in females (early menopause)</td>
</tr>
<tr>
<td></td>
<td>Increased risk for kidney cancer: renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Increased risk for urinary bladder cancer: transitional cell carcinoma</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>Increased risk for acute myeloblastic leukemia</td>
</tr>
<tr>
<td>Integument</td>
<td>Increased facial wrinkling</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Osteoporosis: due to decreased estrogen in females and decreased free testosterone in males</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Increased risk for laryngeal cancer: squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Chronic obstructive pulmonary disease: chronic bronchitis, emphysema</td>
</tr>
<tr>
<td></td>
<td>Increased risk for lung cancer: squamous cell carcinoma, small cell carcinoma, some types of adenocarcinoma</td>
</tr>
<tr>
<td>Special senses</td>
<td>Decreased sense of smell and taste</td>
</tr>
<tr>
<td></td>
<td>Blindness: macular degeneration</td>
</tr>
<tr>
<td></td>
<td>Cataracts</td>
</tr>
</tbody>
</table>

SHBG, Sex hormone–binding globulin.

c. Lower risk for developing lung cancer
   • Risk approaches that of a nonsmoker after 15 years.
d. Lower risk for developing a stroke
   • Risk approaches that of a nonsmoker after 5 to 15 years.e. Other benefits include:
   (1) Reduced risk for cancers of the mouth, larynx, esophagus, pancreas, kidney, and urinary bladder
   (2) Improved pulmonary function regardless of severity of the disease
   (3) Reduced risk for pneumonia, influenza, and bronchitis

B. Alcohol abuse
1. Epidemiology
   a. Most common recreational drug taken in the United States
   b. Third leading cause of preventable death in the United States
c. Risk factors for alcohol-related disease
   (1) Amount and duration of alcohol intake
   (2) Female sex or Asian descent (see later)
d. Legal blood alcohol limit for driving is 80 mg/dL (0.08%)  
2. Alcohol reabsorption and metabolism
   a. Alcohol is reabsorbed in the stomach and small intestine (most absorption) via diffusion.
   b. Metabolism mainly occurs in the liver and some in the stomach
   (1) Gastric metabolism is decreased in women, because of decreased levels of alcohol dehydrogenase, which normally converts alcohol into acetaldehyde.
      (a) Unmetabolized alcohol diffuses into the blood, causing higher levels of alcohol than in individuals with normal amounts of alcohol dehydrogenase.
         • Furthermore, women have a lower total body fluid volume than men of the same weight (more fat, less muscle); therefore the same amount of alcohol intake leads to a higher serum concentration of alcohol in women than in men.
      (b) The previous point explains why there is enhanced vulnerability of women to acute and chronic complications of alcohol.

Live longer; ↓risk for heart disease, lung cancer, stroke
Alcohol MC recreational drug
Stomach/liver metabolize alcohol; stomach/small bowel reabsorb alcohol
Women at risk for acute/chronic alcohol complications; ↓alcohol dehydrogenase
7-1: Alcohol metabolism. Note that alcohol metabolism causes an increase in NADH, which leads to increased synthesis of triglyceride, lactic acid, and \( \beta \)-OHB. An increase in lactate and \( \beta \)-OHB produces an increased anion gap metabolic acidosis. By forcing pyruvate to become lactate, there is less pyruvate as substrate for gluconeogenesis, which produces a fasting hypoglycemia. DHA\textsubscript{P}, Dihydroxyacetone phosphate; NAD\textsuperscript{+}, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; \( \beta \)-OHB, \( \beta \)-hydroxybutyric acid; TG, triglyceride. (From Pelley JW, Goljan EF: Rapid Review Biochemistry, 2nd ed. Philadelphia, Mosby, 2007, p 172, Fig. 9-6.)

(2) Three enzyme systems in the liver are involved for the biotransformation of alcohol to acetaldehyde.
   a. Cytosol of the liver—alcohol dehydrogenase (the rate-limiting enzyme of alcohol metabolism) is the key enzyme
   b. Microsomal ethanol-oxidizing system (MEOS)—CYP2E1 isoenzyme is the key enzyme (refer to Chapter 2)
   c. Peroxisomes—catalase is the key enzyme

(3) Conversion of acetaldehyde by acetaldehyde dehydrogenase to acetic acid occurs in the mitochondria.
   - Acetic acid (acetate) is then converted into acetyl coenzyme A (CoA) by acetylcoenzyme A synthetase.

c. Important products of alcohol metabolism (Fig. 7-1; also refer to Chapter 2)
   (1) Increase in reduced nicotinamide adenine dinucleotide (NADH) causes conversion of:
      a. Pyruvate to lactate, leading to lactic acidosis
      b. Acetoacetate to \( \beta \)-hydroxybutyrate (\( \beta \)-OHB), producing \( \beta \)-OHB ketoacidosis
      c. Dihydroxyacetone phosphate to glycerol 3-phosphate, which increases liver synthesis of triglyceride (TG; refer to Chapter 2).
   (2) Acetyl coenzyme A (acetyl CoA) is used to synthesize fatty acids for triglyceride synthesis and is also used to synthesize ketoacids.

3. Systemic effects (Table 7-2)

4. Laboratory findings (also refer to Chapter 19)
   a. Increased risk for developing fasting hypoglycemia
      - Excess NADH in alcohol metabolism causes pyruvate (substrate for gluconeogenesis) to be converted to lactate.
   b. Increased risk for developing an increased anion gap metabolic acidosis (refer to Chapter 5) due to:
      (1) Lactic acidosis (as just mentioned, when pyruvate is converted to lactate)
      (2) \( \beta \)-OHB ketoacidosis
         a. Excess acetyl CoA is converted to \( \beta \)-OHB acid in the liver.
         b. \( \beta \)-OHB acid is not detected with a urine dipstick or by the blood test for ketone bodies.
   c. Other findings
      (1) Hyperuricemia (potential for developing gout)
         - Lactic acid/\( \beta \)-OHB acid excretion into urine increases uric acid reabsorption in the proximal tubules \( \rightarrow \) hyperuricemia
(2) Hypertriglyceridemia
- Due to increased production of glycerol 3-phosphate, the key substrate for triglyceride synthesis in the liver (refer to Chapter 2)

(3) Serum aspartate aminotransferase (AST) is greater than serum alanine aminotransferase (ALT) in liver disease (90% sensitivity, 75% specificity)
- Alcohol is a mitochondrial toxin that causes release of AST, which is located in the mitochondria (refer to Chapter 2).

(4) Increased serum γ-glutamyltransferase (GGT; 75% sensitivity, 90% specificity)
- Alcohol induces smooth endoplasmic reticulum (SER) hyperplasia, causing increased synthesis of GGT, which is an SER enzyme (refer to Chapter 2).

C. Other drugs of abuse
1. Sedatives, stimulants, and hallucinogens are summarized in Table 7-3.
2. CNS effects of long-term drug abuse
   a. Damage to neurotransmitter receptor sites
   b. Risk for cerebral atrophy (e.g., alcohol abuse)
3. Complications of intravenous drug use (IVDU)
   a. Hepatitis C recently surpassed hepatitis B as the most common hepatitis due to IVDU.
   b. Human immunodeficiency virus infection
   c. Infective endocarditis (tricuspid/aortic valves)
      • Most often caused by *Staphylococcus aureus*
   d. Tetanus
      • Complication of “skin popping” using a dirty needle

D. Adverse effects of therapeutic drug use (Table 7-4)

1. Acetaminophen overdose (refer to Chapter 2 for fuller discussion)
   a. Converted to free radicals in the liver
   b. May damage the liver (e.g., mild to fulminant hepatitis)
   c. May damage the kidneys (e.g., renal papillary necrosis).
2. Aspirin (acetyl salicylic acid) overdose
   a. General symptoms
      • Tinnitus, vertigo, change in mental status (confusion, seizures), tachypnea
   b. Acid-base disorders
      (1) Respiratory alkalosis may occur initially (within 12–24 hours; refer to Chapter 5).
          (a) Alkalosis is due to direct stimulation of the respiratory center.
          (b) Respiratory acidosis may occur as a late finding.
      (2) After respiratory alkalosis, there is a shift to an increased anion gap metabolic acidosis, particularly in children.
      (3) Mixed primary respiratory alkalosis and metabolic acidosis is more likely to occur in adults than children (refer to Chapter 5).
   c. Hyperthermia with aspirin overdose (refer to Chapter 2)
      (1) Salicylates damage the inner mitochondrial membrane.
      (2) Oxidative energy is released as heat, *not* as adenosine triphosphate.
   d. Other potential complications include hemorrhagic gastritis and fulminant hepatitis.

### Table 7-4 Adverse Reactions Associated with Therapeutic Drug Use

<table>
<thead>
<tr>
<th>REACTION</th>
<th>DRUG(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Dyscrasias</td>
<td>Aplastic anemia, Chloramphenicol, alkylating agents</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>Penicillin, methyldopa, quinidine</td>
</tr>
<tr>
<td>Macrocytic anemia</td>
<td>Methotrexate (most common), phenytoin, oral contraceptives, 5-fluorouracil</td>
</tr>
<tr>
<td>Platelet dysfunction</td>
<td>Aspirin, other NSAIDs</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Heparin (most common cause in hospital), quinidine</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Dilated cardiomyopathy, Doxorubicin, daunorubicin</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>Tinnitus, vertigo, Salicylates</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Angioedema, ACE inhibitors (↑ bradykinin)</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Photosensitive rash</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Hemorrhagic gastritis, Iron, salicylates</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Cholestasis, Oral contraceptives, estrogen, anabolic steroids</td>
</tr>
<tr>
<td>Fatty change</td>
<td>Amiodarone, tetracycline, methotrexate</td>
</tr>
<tr>
<td>Hepatic adenoma</td>
<td>Oral contraceptives, anabolic steroids</td>
</tr>
<tr>
<td>Liver necrosis</td>
<td>Acetaminophen (most common), isoniazid, salicylates, halothane, iron</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Asthma, Aspirin, other NSAIDs</td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>Bleomycin, busulfan, nitrofurantoin, methotrexate</td>
</tr>
<tr>
<td>Systemic</td>
<td>Drug-induced lupus, Procainamide, hydralazine</td>
</tr>
</tbody>
</table>

**ACE**, Angiotensin-converting enzyme; **NSAID**, nonsteroidal antiinflammatory drug.
3. Disorders associated with exogenous estrogen without progestin (unopposed estrogen)
   a. Risk for cancer (adenocarcinoma) of the endometrium and breast
   b. Risk for venous thromboembolism (refer to Chapters 5 and 10)
      (1) Decreases the synthesis of antithrombin III (ATIII)
          • ATIII normally neutralizes activated coagulation factors.
      (2) Increases the synthesis of factors I (fibrinogen), V, and VIII
      (3) Venous thromboembolism in the lower extremity may result in a pulmonary infarction.
   c. Risk for intrahepatic cholestasis with jaundice
   d. Risk for myocardial infarction and stroke
4. Disorders associated with oral contraceptives (OCPs; estrogen + progestin)
   a. Risk for adenocarcinoma of the breast and cervical squamous cell carcinoma (SCC)
   b. Risk for venous thromboembolism
      • Similar pathogenesis as discussed for estrogen without progestin
   c. Risk for folic acid deficiency (macrocytic anemia)
      • OCPs decrease jejunal reabsorption of folic acid.
   d. Risk for hypertension
      (1) Due to increased synthesis of angiotensinogen, which is converted into angiotensin II (ATII), a vasoconstrictor
      (2) Most common cause of hypertension in young women
   e. Risk for hepatic adenoma
      • Benign tumor with increased risk for rupturing and producing intraperitoneal hemorrhage
   f. Risk for intrahepatic cholestasis with jaundice
   g. Risk for cholesterol gallstones
      • Estrogen increases cholesterol excretion in the bile.
E. Injuries caused by environmental chemicals (Table 7-5)
F. Injuries caused by arthropods and reptiles (Table 7-6; Fig. 7-2)
II. Physical Injury
A. Mechanical injury
1. Types of skin wounds
   a. Contusion (bruise)
      • Definition—due to blunt force injury to blood vessels with subsequent escape of blood into tissue
   b. Abrasion
      • Definition—superficial excoriation of the epidermis
   c. Laceration
      (1) Definition—jagged tear of skin with intact bridging blood vessels, nerves, and connective tissue
      (2) Usually caused by the force of a blunt object (e.g., baseball bat)
   d. Incision
      (1) Definition—skin wound produced by a sharp object (e.g., knife, razor)
      (2) Sharp margins and severed bridging blood vessels
2. Gunshot wounds
   a. Contact wounds
      (1) Contact wounds are stellate-shaped.
      (2) Contain soot and gunpowder (called fouling)
   b. Intermediate-range wounds
      • Powder tattooing (stippling) of the skin around the entrance site (Fig. 7-3)
   c. Long-range wounds
      • Do not have powder tattooing
   d. Exit wounds
      • Typically larger and more irregularly shaped than entrance wounds
3. Motor vehicle accidents (MVAs)
   a. Most common cause of death in people ages 1 to 44 years
   b. Account for 26% of all injury-related deaths
   c. Frequently alcohol-related (~20% of cases)
4. Shaken baby syndrome
   a. More than 50% of deaths in child abuse are due to shaken baby syndrome.
   b. Majority are infants, who are <1 year old
   c. Characteristic signs

- Unopposed estrogen: adenocarcinoma endometrium/breast
- Risk venous thromboembolism: intrahepatic cholestasis
- Risk myocardial infarction/stroke
- OCP: risk breast adenocarcinoma, cervical SCC
- Risk folic acid deficiency (macrocytic anemia)
- OCP MCC death hypertension in young women → Tangiotensinogen → ↑ ATII
- Risk hepatic adenoma causing intraperitoneal hemorrhage
- Risk of intrahepatic cholestasis/cholesterol gallstones
- Bee/wasp/hornet sting: MCC death due to a venomous bite
- Contusion: blunt force injury to blood vessels with blood leaking into tissue
- Abrasion: superficial excoriation of epidermis
- Laceration: jagged tear with intact bridging vessels/nerves/connective tissue
- Incision: wound with sharp margins; severed blood vessels
- Contact wound: stellate-shaped; fouling (soot + gunpowder)
- Intermediate-range wound: powder tattooing
- Long-range wound: no powder tattooing
- Exit wounds: larger than entrance wound
- MVAs MCC death ages 1 to 44 years
- Shaken baby syndrome: >50% deaths from child abuse
<table>
<thead>
<tr>
<th>CHEMICAL</th>
<th>SOURCE</th>
<th>TOXIC EFFECTS/TREATMENT</th>
</tr>
</thead>
</table>
| Air pollution chemicals       | Smog                         | Sulfur dioxide: produces burning sensation in nose and throat, dyspnea, asthma attacks in susceptible individuals  
Carbon monoxide (see later)  
Ozone: produced by interaction of O₂ with UV light to produce O₃. Ozone layer 10-30 miles above earth’s surface is beneficial (absorbs dangerous solar emission). Ground level ozone is produced by interaction of nitrogen oxides, organic compounds, and UV light. The chemicals just mentioned are present in industrial emissions and motor vehicle exhaust. This type of ozone produces FRs that damage respiratory epithelial cells, inflame the upper respiratory tract, and exacerbate asthma.  
Nitrogen dioxide: damages cilia and irritates airway mucosa  
Particulate matter (soot): particles <10 µm enter alveoli and are phagocytosed by macrophages, causing the release of inflammatory mediators. Lead: can accumulate over time and cause damage (see later)                                                                 |
| Arsenic                       | Pesticides, contaminated ground water, vineyard workers | Inhibits enzymes that require lipoic acid as a cofactor (e.g., pyruvate dehydrogenase), causing increased conversion of pyruvate to lactate  
Severe headaches, abdominal pain, diarrhea, delirium, convulsions, transverse bands in nails (Mees lines), death  
Squamous cell carcinoma of skin, liver angiosarcoma, lung cancer  
Treatment: chelating agents: succimer (2,3-dimercaptosuccinic acid) or dimercaprol (BAL)                                                                                                                                   |
| Asbestos (refer to Chapter 17) | Insulation, roofing material, shipyard worker | Primary lung cancer, mesothelioma                                                                                                                                                                                                                                                                                                                   |
| Benzene                       | Solvent, chemical industry workers | Acute leukemia, aplastic anemia                                                                                                                                                                                                                                                                                                                     |
| Carbon monoxide (CO) (refer to Chapter 2) | Automobile exhaust, house fires, generators | Headache (first sign), cherry-red skin, coma  
↓O₂ saturation, normal PaO₂; lactic acidosis (due to hypoxia)  
Treatment: O₂ via tight fitting mask or endotracheal tube (100% O₂); hyperbaric oxygen chamber                                                                                                                                                             |
| Cyanide (CN) (refer to Chapter 2) | House fires | Odor of bitter almonds; coma, seizures, heart dysfunction, metabolic acidosis (serum lactate >10 mmol/L), due to inhibition of cytochrome oxidase in ETC and subsequent shift to anaerobic glycolysis as only ATP source  
Treatment: amyl nitrite (produces metHb which combines with CN to form cyanmetHb) followed by thiosulfate (CN converted to thiocyanate) or infusion of hydroxocobalamin, which produces cyanocobalamin (precursor of vitamin B₁₂; this is the treatment of choice if CN and CO poisoning are concurrent as in a house fire) |
| Ethylene glycol (refer to Chapter 5) | Antifreeze  
End product: oxalic acid | Increased anion gap metabolic acidosis  
Acute renal failure  
Treatment: IV infusion of ethanol or fomepizole (4-methylpyrazole), which inhibits alcohol dehydrogenase                                                                                                                                 |
| Isopropyl alcohol             | Rubbing alcohol  
End product: acetone | Fruity odor to breath (acetone); can progress into deep coma  
Does not produce increased anion gap like ethanol, methanol, and ethylene glycol, but does increase the osmolal gap (refer to Chapter 5)  
Treatment: hemodialysis                                                                                                                                                                                                                              |
| Lead (refer to Chapter 12)    | Lead-based paint, batteries, metal casting | Microcytic anemia with coarse basophilic stippling, nephrotoxicity in proximal tubule  
Treatment: chelating agents: succimer, dimercaprol (BAL), EDTA                                                                                                                                                                                                                 |
| Mercury                      | Fish most important source | Diarrhea, constricted visual fields, nephrotoxicity in proximal tubule, tachycardia, hyperhidrosis (increased sweating), peripheral neuropathy, hypertension  
Treatment: chelating agents: succimer, penicillamine, or dimercaprol (BAL)                                                                                                                                                                                                 |
| Methanol (refer to Chapter 5) | Windshield washer fluid  
End product: formic acid | Increased anion gap metabolic acidosis  
Blindness due to optic atrophy  
Treatment: IV infusion of ethanol or fomepizole (4-methylpyrazole), which inhibits alcohol dehydrogenase                                                                                                                                 |
| Organophosphates              | Pesticides | Salivation, lacrimation, urinary/fecal incontinence, diaphoresis, blurred vision, hypotension, bradycardia, muscle fasciculations  
Decreased serum and RBC cholinesterase levels  
Treatment: atropine; pralidoxime has also been used                                                                                                                                                                                                 |
| Polyvinyl chloride           | Plastics industry | Liver angiosarcoma                                                                                                                                                                                                                                                                                                                                 |

ATP, Adenosine triphosphate; BAL, British anti-lewisite; EDTA, ethylenediaminetetraacetic acid; ETC, electron transport chain; FRs, free radicals; RBC, red blood cell; UV, ultraviolet.
DIC, Disseminated intravascular coagulation.

Table 7-6 Injuries Caused by Arthropods and Reptiles

<table>
<thead>
<tr>
<th>AGENT</th>
<th>VENOM</th>
<th>TOXIC EFFECTS/TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coral snake (elapid)</td>
<td>Neurotoxin: binds to presynaptic nerve terminals and acetylcholine</td>
<td>Snake has “red on yellow” bands (red and yellow kill a fellow); “red on black” is a harmless scarlet king snake (red and black friend of jack). Toxic effects: paralysis (diplopia, respiratory muscles), fixed and contracted pupils; death by respiratory failure. Treatment: elapid antivenin</td>
</tr>
<tr>
<td>Rattlesnake, copperhead, water moccasin (crotalids) (see Fig. 7-2A)</td>
<td>Venom cytohemoneurotoxic</td>
<td>Toxic effects: local edema/pain with progressive development of ecchymoses and bleeding into tissue, shock, DIC. Treatment: avoid tourniquets and suction/incision kits; place constriction bands above bite to reduce venous/lymphatic flow but still maintain pulse; sheep antivenin (equine serum discontinued) with monospecific antibodies</td>
</tr>
<tr>
<td>Latrodectus spp. (black widow spiders) (see Fig. 7-2B)</td>
<td>Latrotoxin (acts through Ca&lt;sup&gt;2+&lt;/sup&gt;-mediated channels to cause release of acetylcholine and norepinephrine from nerve terminals)</td>
<td>Painful bite followed by increasing local pain; small erythematous macule develops within an hour, which then becomes a “target” lesion with a pale center surrounded by erythema; severe muscle cramps/spasms develop in trunk, thighs, and abdomen, the latter simulating an acute abdomen; hypertension may occur. Treatment: supportive; Latrodectus antivenin is available</td>
</tr>
<tr>
<td>Loxosceles (brown recluse spider) (see Fig. 7-2C)</td>
<td>Necrotoxins</td>
<td>Initially painless bite; painful reddish blister forms in several hours, with extensive skin necrosis occurs over next 3–4 days, with eschar formation by the end of the first week; may become infected; surgical débridement may be necessary. Treatment: supportive measures; antibiotics if necessary</td>
</tr>
<tr>
<td>Scorpion (see Fig. 7-2D)</td>
<td>Neurotoxin</td>
<td>Poisonous species in southwestern U.S. deserts (Centruroides spp.) Toxic effects: initially has painful sting followed by numbness, hypertension, ascending motor paralysis leading to death. May cause acute pancreatitis. Treatment: supportive; antivenin (goat serum) only with severe toxicity</td>
</tr>
<tr>
<td>Bees, wasps, hornets</td>
<td>Histamine and other components</td>
<td>As a group, they are the most common cause of death due to a venomous bite in the United States. Reactions range from localized erythema and swelling to an anaphylactic reaction (dyspnea, wheezing, inspiratory stridor [laryngeal swelling], shock, death). Treatment: epinephrine 0.3–0.5 mL of 1:1000 concentration intramuscularly in adults; long-term management: insect sting kit with premeasured epinephrine; skin desensitization</td>
</tr>
<tr>
<td>Fire ants</td>
<td>Insoluble alkaloid</td>
<td>Swarm when provoked and attack in great numbers; painful bites with papules becoming sterile pustules in several hours; necrosis, scarring, secondary infection can occur; death may occur in some cases. Treatment: local wound care; desensitization is available</td>
</tr>
</tbody>
</table>

(1) Retinal hemorrhages
- May be the only sign of the shaken baby syndrome and should be confirmed by an ophthalmologist
(2) Multiple fractures of long bones
(3) Subdural hematomas

B. Thermal injury
1. Burns
   a. Epidemiology
      (1) Causes of burns in descending order include fire/flame, scalds, contact with hot objects, electricity, and chemicals.
      (2) Most common sites for burns in descending order include upper extremities, lower extremities, and head and neck
   b. Pathophysiology
      (1) Common denominator in all burns is protein denaturation.
      (2) Burn injury is divided into three concentric zones.
         (a) Center of the burn
            - Irreversible injury with coagulation necrosis (refer to Chapter 2)
         (b) Zone of ischemia around the center
            - Reduction in the dermal microcirculation, which puts this area at risk for irreversible damage

Key finding: retinal hemorrhages
MCC burns is fire
MC site for burn is upper extremities
Common denominator in burns is protein denaturation
Center of burn has irreversible coagulation necrosis
Zone of ischemia has reduction in dermal microcirculation

7-3: Intermediate-range gunshot wound showing powder tattooing (tippling). (From Damjanov I, Linder J: Anderson’s Pathology, 10th ed, St. Louis, Mosby, 1996, p 90, Fig. 5.12B.)

Zone of hyperemia due to immediate and transient increase in perfusion

Depth of burn determines potential for skin regeneration

Sources for skin regeneration: basal layer of cells at margins; dermal skin appendages

1st degree burn: limited to epidermis

(c) Zone of hyperemia around the area of ischemia
   • Characterized by redness of the skin due to an immediate and transient increase in perfusion

(3) Ability of the skin to regenerate depends on the depth of the burn.

(4) Regeneration of the damaged epidermis derives from two primary sources.
   (a) In small burns, proliferation of basal layer of cells from the uninjured adjacent epidermis can reepithelialize the burn.
   (b) In large burns, the major source of regenerative epithelial cells comes from the dermal skin appendages (hair follicles and sebaceous glands).

c. Classification of burns (Table 7-7)
   (1) First-degree burns
      (a) Definition—limited to the epidermis (e.g., sunburn)
      (b) Heal in a few days without scarring
**Table 7-7: Burn Classification**

<table>
<thead>
<tr>
<th>TYPE OF BURN</th>
<th>APPEARANCE</th>
<th>SURFACE</th>
<th>SENSATION</th>
<th>HEALING TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree</td>
<td>Red</td>
<td>Dry</td>
<td>Painful</td>
<td>Few days</td>
</tr>
<tr>
<td>Second degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>Red, clear blisters; blanches with pressure</td>
<td>Moist</td>
<td>Painful</td>
<td>2–3 weeks</td>
</tr>
<tr>
<td>Deep</td>
<td>White with some red areas, hemorrhagic blisters, less blanching with pressure</td>
<td>Less moist than superficial</td>
<td>Painful</td>
<td>Weeks; danger of progressing to third-degree burn</td>
</tr>
<tr>
<td>Third degree</td>
<td>White, brown</td>
<td>Dry, leathery</td>
<td>Painless in area of burn</td>
<td>Requires excision and graft</td>
</tr>
<tr>
<td>Fourth degree</td>
<td>Brown, charred, visibly thrombosed vessels</td>
<td>Dry</td>
<td>Painless in area of burn</td>
<td>Requires excision and graft</td>
</tr>
</tbody>
</table>


(2) Second-degree burns are subdivided into superficial and deep.
   (a) Superficial second degree burns extend into the superficial, papillary dermis (partial-thickness burn; Fig. 7-4).
   (b) Deep second degree burns extend into the deep, reticular dermis (partial thickness burn).

(3) Third-degree burns
   (a) Definition—extend through both the epidermis and dermis (full thickness burn; Fig. 7-5)
   (b) Destruction of adnexa and nerves (painless)
   (c) Scarring is inevitable.
      • Keloids commonly occur (refer to Chapter 3).
      • Potential for developing SCC in scar (refer to Chapter 9).

(4) Fourth-degree burns
   • Definition—extend through the skin and subcutaneous fat into the underlying muscle and bone

**7-4: Superficial second-degree burn:** Note the redness of the skin and clear vesicles. (From Marx J: Rosen’s Emergency Medicine, 7th ed, Philadelphia, Mosby Elsevier, 2010, p 760, Fig. 60-1.)

**7-5: Third-degree burn:** Note the central area of coagulation necrosis and the surrounding area of erythema. (From Marx J: Rosen’s Emergency Medicine, 7th ed, Philadelphia, Mosby Elsevier, 2010, p 760, Fig. 60-3.)

2nd degree superficial: extends into papillary dermis; partial-thickness burn

2nd degree deep: extends into reticular dermis; partial-thickness burn

3rd degree burn: extends through epidermis/dermis; full-thickness

SCC risk in keloids

4th degree burn: extends thru skin, subcutaneous fat, muscle/bone
Complications of severe burns

1. Hypovolemic shock may occur due to loss of plasma from the burn surface (refer to Chapter 5).
   - Loss of protein from the plasma loss may result in generalized pitting edema.
2. Infection of the wound site and sepsis may occur.
   - Sepsis due to *Pseudomonas aeruginosa* is the most common cause of infection in burn patients.
   - Other pathogens include methicillin-resistant *S. aureus* and *Candida* species.
3. Curling ulcers may occur in the proximal duodenum (refer to Chapter 18).
4. Hypermetabolic syndrome may occur if >40% of the body surface is burned.
   - Due to excess heat loss from the damaged skin surface, leading to an increase in the resting (basal) metabolic rate (BMR).
5. Smoke inhalation may result in carbon monoxide (CO) poisoning and cyanide (CN) poisoning (refer to Chapter 2).

### 2. Minor heat syndromes

#### a. Heat edema

1. Definition—mild swelling of the feet, ankles, and hands
2. Due to cutaneous vasodilation with gravitational pooling of blood in extremities
3. Commonly occurs in nonacclimatized elderly people, who encounter climactic stresses when visiting tropical and semitropical areas
4. May also occur in healthy travelers moving from a cold to a hot environment
5. Heat edema is self-limited and requires no treatment.

#### b. Heat cramps (Table 7-8)

1. Definition—painful, involuntary spasmodic contractions of muscle that occur after exercise
   - Muscle cramps begin to occur when the person has stopped exercising and is relaxing.
   - Pain usually starts in the calves but may progress to other muscle groups.
   - Cramps are due to deficiency of sodium, chloride, and fluids in muscle fibers.
     - Serum electrolytes frequently show hyponatremia and hypochloremia.
2. Rapidly relieved by ingesting commercially available electrolyte solution drinks

#### c. Heat exhaustion (see Table 7-8)

1. Definition—significant volume depletion (salt and water depletion) under conditions of heat stress
2. Clinical findings
   - Malaise, orthostatic hypotension (from volume depletion), dizziness, headache, nausea, and vomiting are common findings.
   - Core temperature is variable and ranges from normal to <40° C (104° F).
   - Profuse sweating may occur
   - Mental status examination is normal
3. Laboratory studies
   - Hemoconcentration (e.g., ↑hemoglobin/hematocrit) occurs because of a decrease in plasma volume.
   - Serum Na⁺ is variable depending upon previous intake of fluid.
     - Hypernatremia (no intake), normonatremia, or hyponatremia (patient drank too much water without electrolytes)
4. Treatment
   - Oral fluid intake should be increased with both water and salt replacement.
   - If intravenous fluids are required, normal saline is recommended until the patient is hemodynamically stable.
   - Heat exhaustion may progress to heatstroke if it is not treated promptly.
3. Major heat syndrome: classic heatstroke (CHS; see Table 7-8)
   a. Predisposing factors
      (1) CHS usually occurs in periods of sustained, high ambient temperatures and humidity
during the summer months.
      (2) Victims are often elderly and poor and live in underventilated apartments/homes
that have no air-conditioning.
      (3) Infants and children are also at risk.
      (4) Majority of victims have chronic disorders (e.g., psychiatric disorders, alcoholism)
that require medication (e.g., diuretics, neuroleptics).
   b. Clinical presentation is similar to heat exhaustion, except for the following:
      (1) Core body temperature is >40°C (104°F).
      (2) Skin is hot and dry (anhidrosis).
      (3) Mental status exam is abnormal (e.g., do not know time, date).
      (4) CNS dysfunction is present (e.g., coma, seizures, delirium).
   c. Laboratory findings
      (1) Mild respiratory alkalosis
      (2) Mild increase in serum creatine kinase (CK)
4. Major heat syndrome: exertional heatstroke (EHS)
   a. Predisposing factors
      (1) Usually occurs in athletes and military recruits, whose cooling mechanisms are
overridden by endogenous heat production from heavy exercising
      (2) Victims are young and healthy as opposed to those with CHS, who are usually
elderly with predisposing factors and medications.
   b. Clinical presentation is much more severe in EHS than in CHS.
      (1) Core body temperature is >40°C (104°F).
      (2) Profuse sweating is present in 50% of cases.
      (3) CNS dysfunction is present (e.g., coma, seizures, delirium, convulsions [75% of
cases]).
   c. Laboratory findings
      (1) Marked lactic acidosis is present.
      (2) Marked increase in serum CK may occur, with myoglobinuria secondary to
rhabdomyolysis (rupture of muscle).
      (3) Acute renal failure (ARF) with oliguria may occur, causing an increase in blood urea
nitrogen and creatinine (refer to Chapter 20).
      (4) Coagulation abnormalities are common, the worst of which is disseminated
intravascular coagulation (DIC; refer to Chapter 15).
      (5) Hepatic damage is common, causing an increase in serum transaminases.
      (6) Hypocalcemia occurs because of calcium binding to damaged muscle.
   d. Treatment
      (1) Rapid cooling to <40°C (104°F)
      (2) Intravenous fluids (normal saline, lactated Ringer)
5. Frostbite
   a. Epidemiology of frostbite and related cold injuries
      (1) Most common freezing injury to tissue
      (2) Trench foot and immersion foot are nonfreezing injuries related to exposure to
wet cold.
      (3) Chilblain (pernio) is a nonfreezing injury due to exposure to dry cold.
   b. Pathogenesis of frostbite
      (1) Frostbite occurs when tissue is exposed to temperatures less than 0°C
      (2) Direct damage to tissue is caused by ice crystallization in cells.
      (3) Stasis of blood flow, due to vasodilation, leads to thrombosis and ischemia of tissue.
   c. Clinical findings
      (1) In the prefreeze phase, anesthesia develops.
         (a) Endothelial leakage of plasma
         (b) Constriction of the microvasculature
         (c) Increased viscosity of the plasma
      (2) In the freeze-thaw phase, there is ice crystallization in the extracellular tissue,
causeing water to exit the cell. The results are intracellular volume depletion and
cell death.
      (3) Immediately after thawing, there is microvascular collapse, sludging, stasis, and
cessation of blood flow in the capillaries, venules, and arterioles.
         • Tissues are deprived of nutrients and oxygen, and necrosis occurs.

CHS: high ambient temperature; poor, elderly without air-conditioning
CHS: chronic disorders (psychiatric, alcoholism) requiring medication
Core body temp >40°C (104°F); skin hot/dry; mental status abnormal; CNS dysfunction
Mild respiratory alkalosis; mild ↑ serum CK
EHS: athletes/military recruits; endogenous heat production overrides cooling mechanisms
EHS: Core body temp >40°C (104°F); profuse sweating; severe CNS dysfunction
Lactic acidosis, rhabdomyolysis, ARF, DIC, liver damage, hypocalcemia
Frostbite MC freezing injury to tissue
Frostbite: tissue exposed to temperature <0°C
Frostbite: ice crystallization; stasis of blood flow
Prefreeze: endothelial plasma leakage; vasoconstriction; ↑ plasma viscosity
Freeze-thaw phase: extracellular ice crystallization; intracellular volume depletion → death
Postthaw: microvascular collapse → necrosis
(4) Frozen tissue is yellow, waxy, mottled, or violaceous-white in color; it is numb and edematous (Fig. 7-6).

(5) Favorable signs after thawing are normal sensation, warm skin, and normal skin color.

(6) Clear to hemorrhagic blisters may occur.

c. Treatment

(1) Rapid, complete thawing by immersion of the injured part in 40° C to 41° C circulating water

(2) Pain medications are required for the intense pain that commonly occurs when blood flow to the tissue is reestablished.

(3) Tissue should be handled gently and injured parts elevated to minimize edema formation.

(4) Never use dry heat or allow tissue to refreeze.

(5) Rubbing or friction massage should be avoided.

C. Electrical injury

1. Epidemiology

a. Most injuries occur in children or in adults at work.

b. Fifth leading cause of fatal occupational injuries

c. Electricity terms

(1) Current—measure of the amount of energy that flows through an object; expressed in amperes

• Main determinant of tissue injury

(2) Alternating current (AC)—electrical source with changing direction of current flow

(3) Direct current (DC)—unchanging direction of current flow

(4) Frequency—number of transitions from positive to negative per second in AC

(5) Resistance—tendency of a material to resist the flow of electrical current

(6) Voltage—measure of the difference in electrical potential between two points; is determined by the electrical source

(7) Ohm's law

(a) Current (I) = Voltage (V)/Resistance (R)

(b) An equivalent expression of the law, V = I × R

(8) In the United States, household wiring has 120 volts of AC.

(9) Voltage in high tension transmission lines exceeds 100,000 volts, whereas voltage in distribution lines is 7000 to 8000 volts. This voltage is further stepped down before delivery to homes.

2. Pathophysiology

a. Current is the main determinant of damage to tissue.

(1) According to Ohm's law (I = V/R), increasing R or decreasing V decreases current (I) though tissue.

(2) Decreasing R or increasing V increases current (I) through tissue.
b. AC exposure at the same voltage is three time more dangerous than DC.
   (1) AC induces tetanic (continuous) muscle contractions; therefore it is more difficult for the victim to separate themselves from the source.
   (2) DC produces a single muscle spasm, often throwing the victim from the source.
c. Wet skin decreases R, which increases I.
d. Dry skin increases R, which decreases I.
e. Tissue damage increases with increased voltage and duration of exposure.
   - High voltage injuries (>1000 volts) are more dangerous than low voltage injuries (<1000 volts).
f. Current moving from the left arm to the right leg
   - Most dangerous route, because it affects the heart and may cause cardiorespiratory arrest
3. Lightning injury
a. Lightening accounts for 100 to 200 deaths/year.
b. Case fatality rate is 25% to 35%, with ~70% of victims having permanent damage (e.g., chronic pain syndromes, sympathetic nervous system injury, neurocognitive injury).
c. Current surge can affect all major organ systems.
d. Overall most common cause of death from lightening is cardiorespiratory arrest.
D. Drowning
1. Epidemiology
a. Fourth most common cause of accidental death in the United States
b. In children 1 to 4 and 10 to 14 years old, it is the second most common cause of accidental death in the United States.
c. Risk factors
   (1) Acute ethanol intoxication is a contributing factor to drowning among adults and teenagers in 30% to 50% of cases.
   (2) Other factors include seizures, trauma, child abuse/neglect, suicide, and cardiovascular disease.
2. Terminology and pathophysiology
a. Definition—death by suffocation from immersion in liquid
b. Near drowning—survival following asphyxia secondary to submersion
c. Wet drowning—aspiration of water occurred during the event
   (1) Approximately 80% to 90% of drownings are classified as wet drowning.
   (2) Initial laryngospasm on contact with water is followed by relaxation and aspiration of water.
   (3) Amount of water that is aspirated is variable and may result in pulmonary edema, loss of surfactant with atelectasis, and risk for pulmonary infections.
d. Immersion syndrome—sudden death after submersion in very cold water, most likely due to a vagally mediated asystolic cardiac arrest
e. Dry drowning—asphyxia caused by intense laryngospasm without aspiration
f. A diving reflex occurs in water that is colder than 20°C (70°F); characteristics include:
   (1) Bradycardia
   (2) Peripheral vasoconstriction
      - Shunts blood to more vital areas
   (3) Blood shifting
      - Shift of blood to the thoracic cavity to prevent lung collapse
   (4) A longer survival without O₂ in both conscious and unconscious people
g. Cause of death
   (1) Most often relates to asphyxia caused by laryngospasm and closure of the glottis, leading to hypoxemia and combined respiratory and metabolic acidosis
   (2) Tonicity of the water (fresh water versus salt water) does not appear to play a significant role as a cause of death in drowning, because not all drowning victims have water in their lungs.
E. High altitude injury
1. Overview of changes in high altitude (refer to Chapter 2)
a. O₂ concentration is 21%; however, the barometric pressure is decreased
b. Hypoxemia stimulates the peripheral chemoreceptors, which increases the respiratory rate and causes respiratory alkalosis.
   - Decrease in alveolar PaCO₂ causes a corresponding increase in alveolar Po₂, which slightly increases the arterial Po₂.
c. Respiratory alkalosis increases glycolysis by activating phosphofructokinase (PFK), the rate-limiting reaction of glycolysis.
   • Results in an increased synthesis of 2,3-bisphosphoglycerate (2,3-BPG), which shifts the O₂-binding curve (OBC) to the right, caused increased delivery of oxygen to tissue

2. Acute mountain sickness (AMS)
   a. Usually occurs at elevations >8000 feet (>2440 m)
      (1) At this altitude, the arterial saturation of O₂ (Sao₂) is <90%.
      (2) Moderate altitude is between 8000 and 10,000 feet (2438–3048 m).
      (3) High altitude is between 10,000 and 18,000 feet (3048–5486 m).
      (4) Extreme altitude is >18,000 feet (>5486 m).
   b. Risk factors
      (1) Rate of ascent
      (2) Extreme altitude
      (3) Previous symptoms of AMS
      (4) Duration of stay at high altitude
   c. Clinical findings
      (1) Headache (most common)
      (2) Fatigue, dizziness, anorexia, nausea, insomnia
   d. Treatment
      (1) Mild cases are usually self-limiting.
      (2) Moderate cases benefit from rest, supplement oxygen, and aspirin/acetaminophen for headache.
      (3) If severe, immediate descent is indicated.

3. High altitude pulmonary edema (HAPE)
   a. More common above 14,500 feet (4420 m)
   b. Noncardiogenic pulmonary edema with increased protein (exudate)
   c. Immediate descent is required.
   d. Treatment is with O₂ and nifedipine.

4. Acute cerebral edema, or high altitude cerebral edema (HACE).
   a. More common above 12,000 feet (3658 m)
   b. Clinical findings include ataxia, stupor, coma
   c. Treatment includes immediate descent, O₂, and dexamethasone.

III. Radiation Injury
A. Ionizing radiation injury
   1. Examples of ionizing radiation include x-rays and γ-rays.
   2. Pathophysiology
      a. Injury correlates with the type of radiation, cumulative dose, and amount of surface area exposed.
      b. Direct or indirect DNA injury occurs via formation of hydroxyl free radicals (refer to Chapter 2).
   3. Tissue susceptibility
      a. Most radiosensitive tissues (highest mitotic activity) include:
         (1) Lymphoid tissue (most sensitive)
         (2) Bone marrow
         (3) Mucosa of the gastrointestinal tract and germinal tissue
      b. Least radiosensitive tissues include:
         (1) Bone (least sensitive)
         (2) Brain, muscle, and skin
   4. Radiation effects in different tissues
      a. Hematopoietic system
         (1) Lymphopenia (first change)
         (2) Thrombocytopenia
         (3) Bone marrow hypoplasia
      b. Vascular system
         (1) Thrombosis (early), fibrosis (late)
         (2) Ischemic damage
      c. Integumentary system
         (1) Acute effects are erythema, edema, and blistering.
         (2) Chronic effect is radiodermatitis
            • Potential for SCC
d. Gastrointestinal system
   (1) Acute effect is diarrhea.
   (2) Chronic effect is the development of adhesions with a potential for bowel obstruction (refer to Chapter 18).

5. Cancers caused by radiation
   a. Acute leukemia (most common; refer to Chapter 13)
   b. Papillary carcinoma of the thyroid (refer to Chapter 23)
   c. Osteogenic sarcoma (refer to Chapter 24)

B. Nonionizing radiation injury
1. Ultraviolet light B (UVB) is most damaging to the skin.
   a. Pathogenesis of injury with UVB light (refer to Chapter 9)
      (1) Pyrimidine (thymine) dimers distort the DNA helix (see Fig. 9-11).
      (2) p53 suppressor gene is inactivated.
      (3) RAS proto-oncogene is activated.
   b. General effects of UVB light injury
      (1) Sunburn
      (2) Actinic (solar) keratosis (see Fig. 25-8A)
         • Precursor of SCC (2%–5% of cases)
      (3) Corneal burns from skiing
   c. Cancers associated with UVB light injury
      (1) Basal cell carcinoma (BCC; most common) (see Fig. 25-8B, C)
      (2) SCC (see Fig. 25-8D)
      (3) Malignant melanoma (see Fig. 25-6H)

2. Laser radiation may cause third-degree burns.
I. Nutrient and Energy Requirements in Humans

A. Recommended dietary allowance (RDA)
   1. Definition—optimal dietary intake of nutrients that under ordinary conditions will keep the general population in good health
   2. Varies with sex, age, body weight, diet, and physiologic status

B. Daily energy expenditure (DEE)
   1. Factors influencing the DEE
      a. Basal metabolic rate (BMR)
      b. Thermic effect of food
      c. Physical activity
   2. Basal metabolic rate
      a. Definition—rate at which the body uses energy to support all the involuntary activities that are necessary to sustain life
         (1) Examples—circulation, respiration, temperature maintenance, hormone secretion, nerve activity, new tissue synthesis, and maintenance of ion pumps
         (2) Thyroid hormones control BMR.
      b. BMR accounts for ~60% of the DEE.
         • For example, a person who needs 2000 calories a day may spend as many as 1000 to 1600 calories to support basal metabolism.
      c. Key factors affecting BMR
         (1) Body mass—the greater the amount of lean body tissue, the higher the BMR
            • Lean body tissue is more metabolically active than fat, so the way to increase BMR to the maximal rate is to make endurance and strength-building activities a daily habit.
         (2) Gender—men's lean body mass greater than women's
         (3) Hypothyroidism—BMR is lower (hypometabolic)
         (4) Hyperthyroidism—BMR is higher (hypermetabolic)
   3. Thermic effect of foods
      a. Definition—energy expended in response to having eaten a meal (sometimes called diet-induced thermogenesis)
      b. Uses about 5% to 10% of a meal's energy value
   4. Degree of physical activity

II. Dietary Fuels

A. Carbohydrates
   1. Glucose
      a. Stored primarily as glycogen in liver and muscle
         (1) Muscle uses glycogen to support its own energy needs.
         (2) Liver uses glycogen to supply glucose to other tissues during the fasting state.
      b. Mature red blood cells (RBCs) use only glucose for energy.
         • Lack mitochondria and use anaerobic glycolysis for generating adenosine triphosphate (ATP)
      c. Complete oxidation of glucose produces 4 kcal/g.
2. Enzymatic digestion of carbohydrates (CHOs)
   a. Digestion begins in the mouth.
      (1) Amylase from the salivary glands breaks down polysaccharides (e.g., starch) into disaccharides (lactose, maltose, sucrose).
      (2) In Sjögren syndrome, the salivary glands are destroyed and amylase is not available to digest polysaccharides.
   b. Pancreatic amylase
      • In chronic pancreatitis, CHO are not malabsorbed because predigestion by salivary amylase occurs in the mouth.
   c. Brush border intestinal enzymes (disaccharidases)
      (1) Lactase hydrolyzes lactose to give galactose and glucose, maltase hydrolyzes maltose to produce two glucose molecules, and sucrase hydrolyzes sucrose to form fructose and glucose.
      (2) Disaccharidases produce glucose, galactose, and fructose.
         (a) In certain types of diarrhea (e.g., Rotavirus), the brush border is temporarily destroyed and disaccharidases cannot hydrolyze disaccharides.
         (b) People with lactase deficiency cannot hydrolyze lactose in dairy products.

B. Proteins
1. Amino acids (AAs) are substrates for gluconeogenesis.
   a. Transaminases remove amine groups to form a corresponding α-ketoacid.
   b. Examples—alanine aminotransferase (ALT) removes the amine group from alanine to form pyruvate, whereas aspartate aminotransferase (AST) removes an amine group from aspartate to produce oxaloacetate (OAA).

2. Digestion of protein
   a. Digestion begins in the stomach (pepsin and acid)
      (1) Hydrochloric acid (HCl) cleaves pepsinogen into pepsin.
         (a) HCl is synthesized by parietal cells.
         (b) If acid is absent (e.g., chronic atrophic gastritis), protein cannot be digested.
      (2) Pepsin cleaves proteins into smaller polypeptides.
   b. Pancreatic proteases (e.g., trypsin) and peptidases secreted by intestinal epithelial cells hydrolyze polypeptides to release amino acids.
      • In chronic pancreatitis, pancreatic proteases are deficient and polypeptides cannot be hydrolyzed to AAs.
   c. AAs are reabsorbed by villi in the small intestine.
      • In celiac disease, there is autoimmune destruction of the villi; therefore reabsorption of AAs is compromised.

3. Complete oxidation of protein produces 4 kcal/g.

C. Fats
1. Triglycerides (TG)
   a. Major dietary lipid
   b. Long-chain free fatty acids (FAs) are the major source of energy for all cells except RBCs and brain tissue.
   c. Plants contain unsaturated and saturated fats.
      (1) Monounsaturated fats are present in olive oil and canola oil.
      (2) Polyunsaturated fats are present in soybean oil and corn oil.
      (3) Saturated fats are present in coconut oil and palm oil.
   d. Animal fats contain unsaturated and saturated fats.
      (1) Animal fats from adipose contain saturated fats.
      (2) Animal fats from muscle and organ tissues contain polyunsaturated and monounsaturated fats.

2. Essential fatty acids
   a. Dietary fats also contain polyunsaturated essential fatty acids.
   b. Functions of linolenic acid (ω-3) and linoleic acid (ω-6)
      (1) Important in the synthesis of eicosanoids (refer to arachidonic acid metabolism in Chapter 3)
         • Eicosanoids are important in muscle contraction/relaxation, blood vessel constriction/relaxation, blood clot formation, blood lipid regulation, and immune response to injury and infection, including fever, inflammation, and pain.
      (2) Important as structural and functional components in cell membranes
      (3) Contribute lipids to the brain and nerves
      (4) Important in normal growth and vision

- Amylase breaks down polysaccharides to disaccharides (lactose, maltose, sucrose)
- Disaccharides: lactose, maltose, sucrose
- Lactase converts lactose to galactose + glucose
- Maltase converts maltose to two glucose molecules
- Sucrase converts sucrose to fructose + glucose
- Disaccharidases: produce glucose, galactose, fructose
- AAs: substrates for gluconeogenesis
- Transaminases remove amine groups from AAs to produce an α-ketoacid
- AST converts alanine to oxaloacetate and releases pyruvate; ALT converts aspartate to oxaloacetate
- Protein digestion begins in stomach
- HCl cleaves pepsinogen into pepsin
- Pepsin cleaves proteins into polypeptides
- Pancreatic proteases hydrolyze polypeptides to release AAs
- AAs require functioning villi for reabsorption
- TG major dietary lipid
- FAs major energy source for all tissues except RBCs and brain
- Monounsaturated fats: olive oil, canola oil
- Polyunsaturated fats: soybean oil and corn oil
- Saturated fats: coconut oil, palm oil
- Animal fats from adipose are saturated
- Animal fats from muscle/organ are polyunsaturated and monounsaturated
- Essential FAs: linolenic (ω-3), linoleic (ω-6)
Linoleic acid (ω-6) is required for arachidonic acid synthesis. 

Essential FAs: scaly dermatitis, hair loss, poor wound healing.

Fat digestion begins in small intestine.

Pancreatic lipase hydrolyzes TGs to MGs and FAs.

Bile salts form micelles containing MGs, FAs, fat-soluble vitamins, CH esters.

Malabsorption of fats produces fat soluble–vitamin deficiencies.

Fat digestion: pancreatic enzymes → bile salts/ acids → intestinal cells (chylomicrons)

Intestinal cells package resynthesized TG into chylomicrons.

ApoB48 required for formation/secetration chylomicrons.

Chylomicrons contain diet-derived TGs.

Complete oxidation FAs produces 9 kcal/g.

Malnutrition correlates best with BMI.

BMI = weight in kg/height in m².

PEM is defined as a BMI <16 kg/m².

Body fat stores: skinfold thickness, density, conductivity, DEXA.

Somatic protein stores in skeletal muscle evaluated with mid-arm circumference.

Visceral protein stores evaluated with serum albumin/transferrin.

Kwashiorkor: CHO intake > protein intake; total calories normal.

Visceral protein; serum albumin/ transferrin.

(5) Assist in gene regulation and genetic activities affecting metabolism
(6) Help maintain the outer structures of the skin, which protects against water loss
(7) Support immune functions

Clinical findings associated with deficiency of essential fatty acids.

1. Scaly dermatitis and hair loss
2. Poor wound healing

3. Digestion of dietary triglyceride
   a. Digestion occurs in the small intestine.
      1. Dietary TGs are hydrolyzed by pancreatic lipase.
         a. Hydrolysis products are monoglycerides (MGs) and FAs.
         b. In chronic pancreatitis, pancreatic lipase is deficient and fats are undigested, which produces a fatty stool (steatorrhea).
      2. Bile salts/acid produce micelles to enhance reabsorption of fats by villi in the small intestine.
         a. Micelles contain MGs, FAs, fat-soluble vitamins, and cholesterol (CH) esters.
            • Note that all the fat-soluble vitamins (vitamins A, D, E, and K) are packaged in micelles along with the products of fat digestion; hence any disease producing malabsorption of fats also produces deficiencies of all the fat-soluble vitamins.
         b. In bile salt deficiency, micelles are not formed, which produces a fatty stool.
      3. Once reabsorbed, intestinal cells resynthesize TGs and package them into chylomicrons, which enter lymphatics and then the blood.
            • Absence of apoB48 in abetalipoproteinemia compromises both the formation and secretion of chylomicrons into the blood.
         b. Loss of the villus surface in celiac disease results in fatty stools and deficiencies of fat-soluble vitamins.

   b. Complete oxidation of fat produces 9 kcal/g.

III. Protein-Energy Malnutrition

A. Overview of protein-energy malnutrition (PEM)
   1. PEM is best determined by using the body mass index (BMI), which correlates extremely well with body fatness.
   2. BMI = weight in kilograms/height in meters squared
      a. Normal range for BMI is 18.5 to 24.9 kg/m².
      b. PEM is defined as a BMI <16 kg/m².
   3. Evaluation of body fat stores is also evaluated by:
      a. Measuring thickness of skinfolds in various parts of the body with standardized calipers
      b. Density measurements (e.g., underwater weighing)
      c. Measurement of conductivity of tissue using bioelectrical impedance
      d. Dual energy x-ray absorptiometry (DEXA), which measures total body fatness, fat distribution, and bone density
   4. Somatic protein stores in skeletal muscle are evaluated by measuring the circumference of the mid-arm.
   5. Visceral protein stores in organs (most is in the liver) are evaluated by measuring serum albumin and transferrin levels.

B. Kwashiorkor
   1. Pathogenesis
      a. Intake of CHO is greater than the intake of protein.
         • Total caloric intake is normal; however, it primarily consists of CHO.
      b. Visceral protein is predominantly decreased, whereas somatic protein is relatively unchanged.
         1. Somatic protein is relatively unchanged, because CHO are protein sparing.
            a. Breakdown of liver glycogen into glucose provides the main source of energy.
            b. Proteins in muscle do not need to be degraded into AAs and converted into glucose by gluconeogenesis.
         2. Visceral protein is decreased because the liver is unable to synthesize proteins (e.g., albumin and other proteins).
            a. This is related to oxidative (free radical) damage to cellular protein synthesis brought on by infections (e.g., parasitic, fungal, bacterial) superimposed on malnutrition.
(b) This pathophysiology explains why antioxidants, antibiotics, and normal protein diets are imperative in the treatment of the disease.

2. Clinical findings (Fig. 8-1, left)
   a. Pitting edema and ascites
      • Caused by hypoalbuminemia leading to a loss of plasma oncotic pressure (refer to Chapter 5)
   b. Massive hepatomegaly (refer to Chapter 2)
      (1) Caused by a fatty liver
      (2) Pathogenesis of the fatty liver is due to:
          (a) Decreased synthesis of apolipoproteins.
              • ApoB-100 is required for assembly and secretion of very-low-density lipoproteins (VLDLs) in the liver.
          (b) Increased synthesis of VLDL from glycerol 3-phosphate, a three-carbon intermediate substrate of glycolysis.
   c. Diarrhea
      (1) Due to mucosal atrophy in the small intestine with loss of the villi and concurrent loss of the brush border disaccharidases
      (2) In addition, problems with cellular immunity predispose patients to parasitic infections in the bowel.
      (3) Loss of disaccharidases like lactase causes problems in using milk-based products as a food supplement.
   d. Anemia
      (1) RBC precursors in bone are decreased, leading to anemia.
      (2) Multiple vitamin deficiencies are usually present, leading to anemia.
          (a) Folic acid and vitamin B₁₂ are commonly deficient and produce a macrocytic anemia (refer to Chapter 12).
          (b) Iron deficiency, due to decreased intake of iron and loss of blood from parasitic infections in the small intestine, produces a microcytic anemia (refer to Chapter 12).
   e. Cutaneous changes
      (1) Alternating zones of hyperpigmentation and hypopigmentation in areas of desquamation give the skin a “flaky paint” appearance (see Fig. 8-1).
      (2) Hair changes also occur with loss of color, leading to alternating bands of dark hair and light hair (“flag sign”; see Fig. 8-1).
   f. Increased risk for infections
      • Cell-mediated immunity (CMI; T cells) is compromised, predisposing patients to parasitic infections.

---

Excess CHO intake spares protein breakdown as energy source

Pitting edema/ascites characteristic of kwashiorkor; ↓plasma oncotic pressure

Fatty liver due to ↓apoB synthesis and ↑VLDL synthesis

Diarrhea: loss of villi/disaccharidases; parasitic infections

Anemia multifactorial: RBC hypoplasia; iron/folic acid/vitamin B₁₂ deficiencies

Flaky paint dermatitis; flag sign in hair

Defective CMI: parasitic infections
g. Growth retardation
   • Due to the lack of essential nutrients in the diet
h. Psychological disturbances
   • Patients are usually apathetic, listless, and anorexic, which contributes to the poor prognosis in kwashiorkor.

C. Marasmus
1. Pathogenesis
   a. Total calorie deprivation with a dietary deficiency of both protein and CHOs
   b. Decrease in somatic protein (muscle protein)
2. Clinical findings (see Fig. 8-1, right)
   a. Extreme muscle wasting (“broomstick extremities”)
      (1) Due to the breakdown of muscle protein for energy
      • AAs from muscle breakdown are used as substrates for gluconeogenesis.
      (2) Loss of subcutaneous fat
      • Due to a decrease in leptin stores in the adipose, which stimulates the hypothalamic-pituitary axis to release cortisol, a lipolytic agent
   b. Growth retardation, anemia, defects in cellular immunity similar to kwashiorkor
3. Table 8-1 compares findings in kwashiorkor and marasmus.

D. Secondary PEM
1. Epidemiology
   a. Secondary PEM is common in the elderly (living alone or in hospitals or nursing homes), chronic alcoholics, the homeless population, and bedridden patients.
   b. Present in 30% to 50% of elderly individuals in hospitals or nursing homes
      (1) Elderly patients commonly consume less than two thirds of the RDA.
      (2) Accumulated illnesses, medications, and social circumstances deplete body caloric reserves for the stress of acute illness or surgery.
      (3) Factors responsible for reduced intake include:
         (a) Diminished senses of taste and smell, thus rendering food less palatable
         (b) Suppressed appetite or absorption of nutrients in the gastrointestinal tract from accumulated illnesses and medications
         (c) Social factors such as reduced income, social isolation, and depression
         (d) Advanced age
2. Clinical findings
   a. Depletion in subcutaneous fat and skeletal muscle similar to marasmus
   b. Ankle or sacral edema similar to kwashiorkor

<table>
<thead>
<tr>
<th>CLINICAL FINDINGS</th>
<th>KWASHIORKOR</th>
<th>MARASMUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total caloric intake</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Protein intake</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Carbohydrate intake</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Pitting edema and ascites</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Muscle wasting</td>
<td>Not present</td>
<td>Present</td>
</tr>
<tr>
<td>Loss subcutaneous fat</td>
<td>Not present</td>
<td>Present</td>
</tr>
<tr>
<td>Somatic protein loss</td>
<td>Not present</td>
<td>Present</td>
</tr>
<tr>
<td>Visceral protein loss</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Decreased serum albumin/transferrin</td>
<td>Present</td>
<td>Slightly present</td>
</tr>
<tr>
<td>Anemia</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Mucosal atrophy small bowel villi</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Defect in cellular immunity</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Multiple vitamin deficiencies</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>“Flaky paint” dermatitis</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>“Flag sign” in hair</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Apathy, listlessness, poor appetite</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

2° PEM is most common in the elderly population

Marasmus: total calorie deprivation; ↓ protein/CHOs

Loss subcutaneous fat

Poor prognosis due to apathy, listlessness, and lack of appetite

Extreme muscle wasting is common in marasmus
c. Increased risk for infection, impaired wound healing from nutrient deficiencies, and increased risk for death after surgery, particularly hip replacement.

IV. Eating Disorders and Obesity

A. Anorexia nervosa

1. Epidemiology and pathogenesis
   a. Definition—self-induced starvation leading to secondary PEM (Fig. 8-2)
      • Intense fear of gaining weight or becoming fat even while underweight
   b. View themselves as fat even when emaciated
   c. Etiology unknown, but is probably multifactorial (sociocultural, psychological, familial, genetic factors, possibly altered serotonin metabolism).
   d. Carries highest death rate of all the psychiatric disorders
   e. Laxative abuse is common and often results in a laxative bowel and hypokalemia, the latter precipitating cardiac arrhythmias and possible death.
   f. Most commonly occurs in teenage girls and young women
      • Female/male ratio is 9:1.
   g. History of sexual abuse is present in 50% of cases.

2. Clinical findings
   a. Secondary amenorrhea (refer to Chapter 22)
      (1) Decreased secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus
         • Caused by an excessive loss of body fat and weight
      (2) Serum gonadotropins (i.e., follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) are decreased, leading to decreased levels of estradiol.
   b. Osteoporosis
      (1) Caused by hypoestrinism (refer to Chapter 24)
      (2) Estrogen normally enhances osteoblastic activity and inhibits osteoclastic activity.
         • Lack of estrogen leads to decreased osteoblastic activity and increased osteoclastic activity.
   c. Cutaneous findings
      (1) More lanugo hair (fine, downy hair) is present on the face.
      (2) Skin is dry and may also be yellow because of increased carotene levels.
         • Due to decreased metabolism of carotenes in the diet caused by euthyroid sick syndrome (refer to Chapter 23)
Dry skin, brittle nails,
sparse scalp hair; yellow skin (carotene)

Euthyroid sick syndrome: bradycardia, hypotension, cold intolerance, skin/nail changes

Peripheral edema; Trisk cardiac arrhythmias, sudden death

Serum GnRH, estradiol, FSH, LH

Growth hormone, cortisol (stress hormones)

MCC death is ventricular arrhythmia due to hypokalemia

Bulimia nervosa: bingeing with self-induced vomiting

Female dominant; more common than anorexia nervosa

Eroded enamel, parotid/salivary gland swelling; hematemesis (tear/rupture distal esophagus)

Vomiting: hyponatremia/hypokalemia; metabolic alkalosis

Laxative abuse: hyponatremia/hypokalemia; metabolic acidosis; hypomagnesemia, hypocalcemia

MCC death is ventricular arrhythmia due to hypokalemia

Obesity = BMI

Prevalence increases with age, declines after sixth decade

Independent risk factor for ischemic heart disease

Major preventable cause of death/disability in United States

(3) Nails are brittle and scalp hair is sparse.
(4) Axillary and pubic hair is preserved.

d. Euthyroid sick syndrome (refer to Chapter 23)
   • Decreased thyroid hormone is associated with bradycardia, hypotension, cold intolerance, and the changes in the skin, nails, and hair just listed.

e. Mild peripheral edema

f. Increased risk for cardiac arrhythmias and sudden death

3. Laboratory findings
a. Decreased serum GnRH, estradiol, FSH, and LH
   • Absence of the cyclic surge in LH (no stimulus for ovulation)

b. Increased serum growth hormone and cortisol (stress hormones)

4. Treatment
   • Selective serotonin reuptake inhibitors

5. Most common cause of death is a ventricular arrhythmia usually related to hypokalemia from laxative abuse.

B. Bulimia nervosa

1. Epidemiology and pathogenesis
   a. Definition—binge eating with self-induced vomiting

b. More common than anorexia nervosa

c. Predominantly seen in teenage girls and young women
   • Female/male ratio is 10:1

d. Etiology is unknown, but is probably multifactorial (socio-cultural, psychological, and familial).

e. More common in Western societies where there is a strong cultural pressure to be slender

f. Commonly associated with anorexia nervosa

2. Clinical findings
   a. Complications of vomiting
      (1) Eroded enamel due to acid injury
      (2) Hypokalemia and metabolic alkalosis
      (3) Parotid and salivary gland swelling
      (4) Hematemesis from tears/rupture of the distal esophagus (refer to Chapter 18)

b. No emaciation or amenorrhea is present unless the patient also has anorexia nervosa

3. Laboratory findings
   a. Electrolyte abnormalities from vomiting—hyponatremia, hypokalemia, metabolic alkalosis (increased serum bicarbonate) (refer to Chapter 5)
   b. Diarrhea from laxative abuse—hyponatremia, hypokalemia, hypomagnesemia (magnesium is required for synthesis and release of parathyroid hormone), hypocalcemia, normal anion gap metabolic acidosis (refer to Chapter 5)

4. Treatment
   • Selective serotonin reuptake inhibitors

5. Most common cause of death is a ventricular arrhythmia, usually related to hypokalemia from laxative abuse and vomiting.

C. Obesity

1. Epidemiology
   a. Overweight is defined as a BMI of 25 to 29.9 kg/m².
      (1) Obesity is a BMI >30 kg/m².
      (2) Morbid obesity is a BMI ≥40 kg/m².
   
b. Obesity is a worldwide epidemic.

c. Prevalence increases with advancing age and levels off after the sixth decade, when weight begins to decline.

d. Independent risk factor for ischemic heart disease

e. Obesity in adolescence is significantly associated with increased risk of severe obesity in adulthood.

f. Obesity is a major preventable cause of death and disability in the United States.

g. Evidence suggests that weight loss can reverse or arrest the harmful effects of obesity.

h. Risk factors for increased morbidity/mortality are associated with the type of fat distribution.
   (1) Excess fat in the waist and flanks is a more important risk factor than excess fat in the thighs and buttocks.
(2) Excess visceral fat in the abdominal cavity has greater significance than excess subcutaneous fat.
   • Magnetic resonance imaging is used to access the amount of visceral fat.

2. Pathogenesis
   a. Energy balance dysfunction (EBD)
      (1) Energy balance involves complex neuron circuits in the arcuate nucleus and the paraventricular nuclei of the hypothalamus that control food intake and energy expenditure.
      (2) Involves signals from the adipose (leptin) and stomach (ghrelin) that impact on the arcuate nucleus and paraventricular nuclei (PVN) to control food intake and energy expenditure.

3. Leptin, a hormone secreted by the adipose tissue, stimulates the anorexigenic neurons (suppresses appetite) in the PVN and inhibits the orexigenic neurons (normally stimulate appetite) in the lateral hypothalamus.
   • Leptin also increases energy expenditure by stimulating the sympathetic nervous system (increases BMR) and the release of cortisol (breaks down fat stores) and thyroxine (increases BMR).

4. Ghrelin, a gut hormone secreted from the stomach, stimulates the orexigenic neurons in the hypothalamus (stimulates appetite) and inhibits the anorexigenic neurons (normally suppresses appetite).
   • Ghrelin also decreases energy expenditure by inhibiting the anorexigenic center, which normally activates the sympathetic nervous system and increases the release of cortisol and thyroxine.

5. Decrease/dysfunction of leptin produces EBD by leaving ghrelin activity unopposed (↑appetite, ↓energy expenditure).

b. Genetic factors account for 5% to 10% of obesity.
   • Example—metabolic syndrome (obesity, hypertension, diabetes)

c. Acquired causes—chronic ingestion of excess calories, hypothalamic lesions

d. Insulin
   (1) Insulin normally inhibits lipolysis or the breakdown of triglyceride in the adipose to fatty acids.
   (2) In type 2 diabetes mellitus (DM), there is an increase in insulin due to less insulin receptors and post-receptor defects (refer to Chapter 23).
   • Because of hyperinsulinemia, there is increased TG storage in the adipose.

3. Clinical findings (Table 8-2)

4. Treatment
   a. Weight reduction by caloric restriction

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**Table 8-2 Clinical Findings Associated with Obesity**

<table>
<thead>
<tr>
<th>CLINICAL FINDING</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Increased incidence of estrogen-related cancers (e.g., endometrial, breast) because of increased aromatase stores in adipose and conversion of androgens to estrogens</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>Increased incidence of cholecystitis and cholesterol stones; bile is supersaturated with cholesterol</td>
</tr>
</tbody>
</table>
| Diabetes mellitus, type 2 | Increased adipose downregulates insulin receptor synthesis  
Hyperinsulinemia increases adipose stores  
Weight reduction upregulates insulin receptor synthesis |
| Hepatomegaly     | Fatty change accompanied by liver cell injury and repair by fibrosis |
| Hypertension     | Hyperinsulinemia increases sodium retention, leading to increase in plasma volume  
Left ventricular hypertrophy and stroke complicate hypertension |
| Hypertriglyceridemia | Hypertriglyceridemia decreases serum high-density lipoprotein levels, increasing risk of coronary artery disease |
| Increased low-density lipoprotein levels | Hypercholesterolemia predisposes to coronary artery disease |
| Obstructive sleep apnea | Weight of adipose tissue compresses upper airways, causing respiratory acidosis and hypoxemia  
Potential for developing cor pulmonale (pulmonary hypertension and right ventricular hypertrophy) |
| Osteoarthritis   | Degenerative arthritis in weight-bearing joints (e.g., femoral heads) |
8-3: Classification and functions of the vitamins. Water-soluble vitamins are usually cofactors in key biochemical reactions, whereas fat-soluble vitamins are involved in growth and development of tissue (vitamin A), neutralization of free radicals (vitamin E), bone mineralization and maintenance of serum calcium (vitamin D), and hemostasis (vitamin K). (From Pelley J, Goljan E: Rapid Review Biochemistry, 3rd ed, Philadelphia, Mosby Elsevier, 2011, p 40, Fig. 4.2.)

b. Gastrointestinal lipase inhibitors
   - Orlistat blocks digestion and absorption of ingested dietary fat.

c. Sympathomimetic medications
   - Example—phentermine increases norepinephrine in the neuronal cleft, resulting in appetite suppression

d. Bariatric surgeries
   1. Restrictive surgeries that limit the amount the stomach can hold and also slow the rate of emptying
   2. Restrictive malabsorptive bypass procedures combine the element of gastric restriction and selective malabsorption (e.g., Roux-en-Y gastric bypass).

V. Fat-Soluble Vitamins
A. Overview of fat- and water-soluble vitamins
1. Figure 8-3 summarizes the primary functions of the fat-soluble and water-soluble vitamins.
2. Reabsorption of fat-soluble vitamins depends on normal fat reabsorption in the small bowel.
   a. Recall from the previous discussion of fat digestion (II.C.3.), that MGs, FAs, fat soluble vitamins (A, D, E, K), and cholesterol esters are packaged in micelles, which are then reabsorbed by the villi.
   b. Therefore factors that interfere with fat reabsorption (e.g., chronic pancreatitis, bile salt deficiency, loss of villi) also lead to deficiencies of fat-soluble vitamins.
3. Vitamin toxicities are more common with fat-soluble vitamins than water-soluble vitamins, the latter excesses being lost in the urine.
4. All the water-soluble vitamins are cofactors for enzyme reactions, with the exception of folic acid.
5. In addition to food intake, microflora in the large intestine can synthesize and reabsorb bacterially synthesized water-soluble vitamins (e.g., thiamine, folic acid, biotin, riboflavin).
6. In general, it is better to obtain fat-soluble vitamins in natural foods that contain those vitamins rather than by taking manufactured vitamin pills.

B. Vitamin A
1. Retinol
   a. Retinol (Fig. 8-4)
      1. Dietary β-carotenes and retinol esters are sources of retinol.
      2. After reabsorption in the small intestine, β-carotenes are converted into retinol.
         a. Increased β-carotenes in the diet cause the skin to turn yellow (hypercarotenemia).
Nutritional Disorders

8-4: Vitamin A absorption and transport. Ingested retinol esters and β-carotenes are converted to retinol, the key absorption and transport form of vitamin A. In the small intestine, retinol is converted to retinol esters, the key storage form of vitamin A. When needed, retinol is released from the liver into the bloodstream, where it complexes with retinol-binding protein (RBP). Within cells, retinol is irreversibly oxidized to retinoic acid, which binds to nuclear receptors and activates gene transcription. (From Pelley J, Goljan E: Rapid Review Biochemistry, 3rd ed, Philadelphia, Mosby Elsevier, 2011, p 45, Fig. 4-4.)

- Sclera remains white, whereas in jaundice the sclera is yellow, which can be used to distinguish the two conditions.
- Vitamin toxicity does not occur with an increase in serum carotene.
- Retinol is taken up by apoE receptors in the liver and stored in Ito cells as retinyl esters, the storage form of vitamin A.
- When retinyl esters are mobilized, retinol is bound to retinol-binding protein (RBP) and transported to tissue where there are receptors for RBP.
- In tissue, RBP is released and enters the blood, whereas retinol is oxidized to retinoic acid.
- Retinoic acid is important in the differentiation of epithelial tissue and in growth and reproduction.

2. Retinal
   - Product of the oxidation of retinol
   - Oxidation product is used to synthesize rhodopsin in the rods, the most light-sensitive pigment in the eye (important in reduced light).

3. Sources
   - Preformed vitamin A is present in liver, egg yolk, butter, and milk.
   - β-Carotenes are present in dark-green and yellow vegetables.
   - Reabsorption of vitamin A occurs in the small intestine along with triglyceride breakdown products of pancreatic lipase (MGs and FAs), which are packaged in micelles formed by bile salts and acids.

4. Functions
   - Normal vision in reduced light (night vision)
   - Potentiates the differentiation of mucus-secreting epithelium
   - Stimulates the immune system
   - Stimulates growth and reproduction

5. Causes of vitamin A deficiency
   - Diet lacking sufficient yellow and green vegetables
   - Fat malabsorption (e.g., celiac disease; see II.C.3.)

6. Causes of vitamin A toxicity
   - Consumption of the liver of polar bears, whales, sharks, and tuna
     - Toxicity is a common finding in Eskimos, who hunt and eat polar bear and whale livers.
   - Using megadoses of vitamin A
   - Treatment of acne with isotretinoin

7. Clinical findings in vitamin A deficiency and toxicity (Table 8-3)

8. Clinical uses
   - Treatment of acne (e.g., isotretinoin)
### Table 8-3 Fat-Soluble Vitamins: Clinical Findings in Deficiency and Toxicity

<table>
<thead>
<tr>
<th>VITAMIN</th>
<th>SIGNS OF DEFICIENCY</th>
<th>SIGNS OF TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin A</strong></td>
<td>Impaired night vision is an early finding. Blindness may occur due to squamous metaplasia of the corneal epithelium, which is normally nonkeratinizing squamous epithelium (produces keratomalacia). Conjunctival epithelium (normally pseudostratified columnar epithelium with goblet cells) also undergoes squamous metaplasia, producing localized keratin debris (called Bitot spot) or more extensive areas of keratinization (called xerophthalmia). Vitamin A deficiency is a major cause of blindness worldwide (see Fig. 8-6A). Follicular hyperkeratosis may occur from loss of sebaceous gland function related to plugging of the ducts by excess keratin (see Fig. 8-6B). Vitamin A deficiency is a major cause of worldwide growth retardation in children. Other findings in vitamin A deficiency include pneumonia (squamous metaplasia of the ciliated columnar epithelium of the bronchi) and renal calculi.</td>
<td>Signs of hypervitaminosis A include papilledema with blurred vision; seizures (due to an increase in intracranial pressure); hepatitis; bone pain (due to periosteal proliferation); and bone resorption and fractures (retinoic acid stimulates osteoclast production and activation).</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td>Signs of vitamin D deficiency in both adults and children include pathologic fractures, due to an excess of unmineralized osteoid; tibial bowing, due to soft bones (see Fig. 8-6C); continuous muscle contraction (tetany), due to low serum ionized calcium levels (refer to Chapter 23). Signs of vitamin D deficiency (rickets) exclusively seen in children include craniotabes (soft skull bones with delayed suture and fontanel closing); rachitic rosary (defective mineralization and overgrowth of unmineralized epiphyseal cartilage in the costochondral junctions); frontal bone thickening and bossing of the forehead; short stature (often 3rd percentile); pectus carinatum (“pigeon breast,” anterior protrusion of the sternum). Adults who develop vitamin D deficiency do not have craniotabes or rachitic rosaries, because the bone or cartilage in these areas has already been mineralized. Bone remodeling is defective, because newly formed osteoid is excessive and left unmineralized, causing the bone to be soft, hence the term osteomalacia (soft bone).</td>
<td>Signs of hypervitaminosis D include hypercalcemia with metastatic calcification of soft tissue, renal calculi, and bone pain.</td>
</tr>
<tr>
<td><strong>Vitamin E</strong></td>
<td>Hemolytic anemia may result from free radical damage to the lipid in the RBC membrane. Peripheral neuropathy and degeneration of the posterior column (poor joint sensation) and spinocerebellar tracts (ataxia) may result from free radical damage. In the neonate, vitamin E deficiency presents with hemolytic anemia, peripheral edema, and thrombocytosis.</td>
<td>Excessive intake of vitamin E has a synergistic effect with warfarin anticoagulation. It causes over-anticoagulation manifested by bleeding and a markedly prolonged prothrombin time and calculated INR. Giving vitamin K reverses the over-anticoagulation.</td>
</tr>
<tr>
<td><strong>Vitamin K</strong></td>
<td>Newborns with vitamin K deficiency develop hemorrhagic disease of the newborn (CNS bleeding, ecchymoses) due to deficiency of the vitamin K dependent coagulation factors (II, VII, IX, and X). Adults with vitamin K deficiency develop gastrointestinal bleeding and ecchymoses (bleeding) in the skin. The prothrombin time and partial thromboplastin time are both prolonged (refer to Chapter 15).</td>
<td>If a pregnant woman is taking excessive amounts of vitamin K, the newborn child may develop a hemolytic anemia, jaundice, and kernicterus (refer to Chapter 16).</td>
</tr>
</tbody>
</table>

INR, International normalized ratio.

**Clinical Rx:** acne, APL, measles, hairy leukoplakia, retinitis pigmentosa

- **Ergocalciferol (plants)** → cholecalciferol (vitamin D₃)
- **Photoconversion**
  - 7-dehydrocholesterol → cholecalciferol; 90% endogenously derived vitamin D

b. Treatment of acute promyelocytic leukemia (APL; refer to Chapter 13)
   - Causes leukemic cells to differentiate into neutrophils, which subsequently undergo apoptosis and die

c. Treatment of measles
   1. Vitamin A deficiency is almost universally present in malnourished children in underdeveloped countries.
   2. When these children develop measles, post-measles blindness is a common complication of the infection because of underlying vitamin A deficiency.
   3. Treatment with vitamin A decreases the risk for developing blindness by increasing corneal stromal repair.

d. Treatment of hairy leukoplakia due to Epstein-Barr virus (used topically)
e. Treatment of retinitis pigmentosa

### C. Vitamin D

1. **Sources**
   - Fish oil, egg yolk, liver, grains, fortified milk contribute 10% of required vitamin D.

2. **Metabolism** (Fig. 8-5; refer to Chapter 23)
   - Preformed vitamin D in plants called ergocalciferol is converted to cholecalciferol (vitamin D₃).
   - Endogenous synthesis of vitamin D in the skin occurs by photoconversion of 7-dehydrocholesterol via sunlight into cholecalciferol (vitamin D₃).
   - Accounts for ~90% of endogenously derived vitamin D.
   - Cholecalciferol (vitamin D₃) is an over-the-counter vitamin supplement and is frequently measured to determine a person’s vitamin D status.
8-5: Vitamin D metabolism. Most vitamin D comes from photoconversion of 7-dehydrocholesterol to cholecalciferol (vitamin D₃).

c. Reabsorption of vitamin D occurs in the small intestine in association with fat reabsorption (see vitamin A discussion).
d. Liver hydroxylation of vitamin D to 25-hydroxyvitamin D (25-[OH]-D; calcidiol) occurs in the cytochrome P-450 system.
   • 25-Hydroxylases are CYP27A1 and other cytochrome P isoenzymes.
e. Kidney hydroxylation by 1-α-hydroxylase produces 1,25-(OH)₂-D (active form of vitamin D; calcitriol) in the proximal tubule.
   (1) Parathyroid hormone (PTH) synthesizes 1-α-hydroxylase in the proximal tubules.
   (2) In sarcoidosis, macrophages in granulomas synthesize 1-α-hydroxylase and synthetize vitamin D, producing hypervitaminosis D (refer to Chapter 17).
f. Calcitriol attaches to nuclear receptors in target tissues (e.g., osteoblasts).
g. Feedback control of calcitriol synthesis is calcium-mediated.
   (1) Hypocalcemia stimulates the release of PTH.
      • PTH increases the synthesis of 1-α-hydroxylase (1-α-OHase), which increases the synthesis of calcitriol.
   (2) Hypercalcemia inhibits the release of PTH.
      • Decreased PTH decreases the synthesis of 1-α-hydroxylase, which decreases the synthesis of calcitriol.

3. Functions of calcitriol
   a. Functions as a hormone
   b. Important in the maintenance of serum calcium and phosphorus
      • It increases calcium and phosphorus reabsorption from the small bowel and kidneys.
c. Required for mineralization of epiphyseal cartilage and osteoid matrix in bone formation
   (1) Vitamin D receptors are located on osteoblasts and mature chondrocytes.
   (2) Attachment to the receptor stimulates the release of alkaline phosphatase.
      • It dephosphorylates pyrophosphate, which normally inhibits bone mineralization.
   (3) Vitamin D also stimulates osteoblasts to synthesize osteocalcin, a calcium-binding protein that is involved in the deposition of calcium in bone.
d. Stimulates conversion of macrophage stem cells into osteoclasts in the bone marrow.
e. Stimulates the maturation of cells, including those in the immune system.

4. Causes of vitamin D deficiency
   a. Renal failure is the most common cause of vitamin D deficiency.
      • Decrease in 1-α-hydroxylation
   b. Inadequate exposure to sunlight
      • Inadequate exposure to sunlight (e.g., clothes, black skin, sunscreen) decreases photoconversion of 7-dehydrocholesterol to cholecalciferol.
c. Fat malabsorption (see II.C.3.)
d. Chronic liver disease
   • Decreased synthesis of 25-(OH)-D in the CYP-450 system
   • Induction of the liver cytochrome P-450 enzyme system (e.g., alcohol)
      • Increased metabolism of 25-(OH)-D into an inactive metabolite
f. Infants with exclusive breast-feeding without vitamin D supplementation
   • Human breast milk has low levels of vitamin D.
5. Causes of vitamin D toxicity
   a. Megadoses of vitamin D may cause toxicity.
   b. Increased synthesis of vitamin D in granulomas in sarcoidosis (refer to Chapter 17).

6. Clinical findings in vitamin D deficiency and toxicity (see Table 8-3; Fig. 8-6)

D. Vitamin E
1. Sources
   - Nuts (almonds, seeds), green leafy vegetables, olives, vegetable oil, and wheat germ
2. Functions
   a. Antioxidant that protects cell membranes from lipid peroxidation by free radicals
   b. Prevents the oxidation of low-density lipoprotein to a free radical form (oxidized low-density lipoprotein [LDL]), which is more atherogenic
   c. Protects cell membranes in the lungs from free radical damage by superoxide when high concentrations of O\textsubscript{2} are used (e.g., treatment of respiratory distress syndrome in neonates).
3. Causes of vitamin E deficiency
   a. Fat malabsorption in children with cystic fibrosis (CF; see earlier section, II.C.3.)
      - Chronic pancreatitis is universal in cystic fibrosis; therefore pancreatic lipase is deficient and unable to hydrolyze dietary fat into monoglycerides and fatty acids.
   b. Abetalipoproteinemia, due to chylomicrons accumulating in villi and preventing micelle reabsorption into the small intestine (refer to Chapter 10)
4. Megadoses of vitamin E may be toxic
5. Clinical findings in vitamin E deficiency and toxicity (see Table 8-3)

E. Vitamin K
1. Sources
   - Colon bacteria synthesize vitamin K (most common source); dark green vegetables are major dietary sources.
2. Endogenously synthesized vitamin K is activated by the liver microsomal enzyme epoxide reductase.
   - Anticoagulant effect of coumarin derivatives results from the inhibition of epoxide reductase.
3. Function (also refer to Chapter 15)
VI. Water-Soluble

γ-Carboxylates glutamate residues in vitamin K–dependent procoagulants and anticoagulants (proteins C and S, which degrade factors V and VIII)

1. Procoagulants include factors II (prothrombin), VII, IX, and X.
2. Procoagulants that are synthesized by the liver are nonfunctional.

b. γ-Carboxylation allows vitamin K–dependent procoagulants to actively bind to calcium in fibrin clot formation.
   - Calcium is important in the normal coagulation pathway, because it binds to the vitamin K–dependent coagulation factors that are involved in the formation of a fibrin clot.

4. Causes of vitamin K deficiency
   a. Use of broad-spectrum antibiotics
      (1) Antibiotics destroy bacteria in the colon that synthesize vitamin K.
      (2) Antibiotics are the most common cause of vitamin K deficiency in a hospitalized patient.
   b. Newborns
      (1) Bacterial colonization of the bowel does not occur until they are 5 to 6 days old.
      (2) Newborns must receive an intramuscular injection of vitamin K at birth, because they are essentially anticoagulated from days 3 to 5. In this period, vitamin K–dependent factors are nonfunctional because they are not γ-carboxylated.
      - Vitamin K injection prevents hemorrhagic disease of the newborn (refer to Chapter 15).
      - Breast milk is deficient in vitamin K.
   c. Coumarin derivatives/cirrhosis
      (1) Both of these decrease epoxide reductase activation of vitamin K.
      (2) Rat poison is warfarin; hence children/adults who inadvertently or purposely ingest rat poisoning will develop life-threatening bleeding that can only be reversed by infusion of fresh frozen plasma.

Warfarin is an anticoagulant that inhibits epoxide reductase, which prevents any further γ-carboxylation of the vitamin K–dependent coagulation factors. However, full anticoagulation does not immediately occur, because previously γ-carboxylated factors are still present. Prothrombin has the longest half-life; therefore full anticoagulation requires at least 3 to 4 days before all functional prothrombin has disappeared. This explains why patients are initially placed on both heparin and warfarin, because heparin provides immediate anticoagulation in the patient by enhancing ATIII activity.

d. Fat malabsorption (see II.C.3.)
   - Because vitamin K is normally reabsorbed with fat in micelles, fat malabsorption (e.g., celiac disease) cause decreased intestinal reabsorption of the vitamin.

5. Toxicity caused by excessive intake of vitamin K is uncommon.
6. Clinical findings in vitamin K deficiency and toxicity (see Table 8-3)

VI. Water-Soluble Vitamins

A. Thiamine (vitamin B₁)

1. Sources
   a. Liver, eggs, whole grain cereal, rice, and wheat
   b. Removal of the outer layer of grain in the refining process (white rice, white bread) significantly lowers thiamine content.

2. Functions
   a. Cofactor in biochemical reactions that produce ATP
      - Example—conversion of pyruvate to acetyl CoA by pyruvate dehydrogenase produces 2 NADH, which produces a total of 6 ATP in oxidative phosphorylation (Fig. 8-7)
   b. Cofactor in transketolase reactions in the pentose phosphate pathway
      - Transketolase is involved in two-carbon transfer reactions that provide fructose 6-phosphate and glyceraldehyde 3-phosphate intermediates for glycolysis in the fed state and gluconeogenesis in the fasting state.
      - Thiamine levels are evaluated by measuring RBC transketolase activity.

3. Causes of thiamine deficiency
   a. Chronic alcoholism (in the United States) is the most common cause.
   b. Diet of unenriched rice is the most common cause of deficiency in developing countries.

4. Clinical findings in thiamine deficiency are summarized in Table 8-4.
8-7: Overview of ATP yield from complete oxidation of glucose. Substrate-level phosphorylation generates 2 ATP per glucose molecule in the cytosol; however, the bulk of the energy output is derived from electron flow through the electron transport chain (ETC) and coupled oxidative phosphorylation. Electrons from cytosolic NADH move into mitochondria by the malate-aspartate shuttle to produce 38 ATP, or by the glycerol phosphate shuttle, which results in a slightly lower ATP yield (i.e., 36 ATP). Note that thiamine is a cofactor for pyruvate dehydrogenase conversion to acetyl CoA, which is used to synthesize citrate for the citric acid cycle (acetyl CoA + oxaloacetic acid $\rightarrow$ citrate), which is the main source of ATP. Therefore a deficiency of thiamine plays a key role in the overall synthesis of ATP. (From Pelley J, Goljan E: Rapid Review Biochemistry, 3rd ed, Philadelphia, Mosby Elsevier, 2011, p 66, Fig. 6-2.)

**TABLE 8-4 Water-Soluble Vitamins: Clinical Findings in Deficiency**

<table>
<thead>
<tr>
<th>VITAMIN</th>
<th>SIGNS OF DEFICIENCY</th>
</tr>
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</table>
| Thiamine (vitamin B₁) | Dry beriberi: peripheral neuropathy (demyelination)  
Wernicke syndrome: ataxia, confusion, nystagmus, ophthalmoplegia; hemorrhages present in the mamillary bodies (refer to Chapter 26, see Fig. 26-21B)  
Korsakoff syndrome: antegrade and retrograde amnesia; demyelination in the limbic system (refer to Chapter 26)  
Wet beriberi: dilated cardiomyopathy with biventricular heart failure and dependent pitting edema; cardiac muscle lacks ATP; intravenous thiamine reverses cardiomyopathy in some cases (refer to Chapter 11) |
| Riboflavin (vitamin B₂) | Corneal neovascularization, glossitis (magenta tongue), cheilosis (cracked lips), angular stomatitis (fissuring at the angles of the mouth) |
| Niacin (vitamin B₃) | Pellagra: diarrhea, dermatitis (hyperpigmentation in sun-exposed areas; see Fig. 8-9A), dementia (3 Ds of pellagra) |
| Pyridoxine (vitamin B₆) | Sideroblastic anemia (microcytic anemia with ringed sideroblasts (see Fig. 12-13), convulsions, peripheral neuropathy |
| Cobalamin (vitamin B₁₂) | Megaloblastic anemia with hypersegmented neutrophils (see Fig. 12-18D), pancytopenia, neurologic disease (posterior column and lateral corticospinal tract demyelination [see Fig. 12-18A], peripheral neuropathy, dementia), glossitis (refer to Chapter 12)  
Vitamin B₁₂ deficiency in infants exclusively seen in breast-fed infants of vitamin B₁₂–deficient mothers |
| Folic acid | Megaloblastic anemia with hypersegmented neutrophils, pancytopenia, and glossitis; neurologic abnormalities not present (refer to Chapter 12)  
Open neural tube defects: several gene defects affecting enzymes and proteins involved in transport and metabolism of folic acid implicated in pathogenesis of open neural tube defects (see Fig. 26-4A, B, D, and E; refer to Chapter 26) |
| Biotin | Dermatitis, alopecia, lactic acidosis possible  
Biotin is cofactor in pyruvate carboxylase reaction where pyruvate converted to oxaloacetate; with biotin deficiency, conversion to oxaloacetate blocked; pyruvate level increases and is converted by pyruvate dehydrogenase to lactic acid |
| Ascorbic acid (vitamin C) | In vitamin C deficiency (scurvy), collagen weakened from insufficient cross-bridge formation between tropocollagen molecules; resulting decrease in collagen tensile strength in capillary and venule walls causes them to rupture, producing skin hemorrhages, periocular hemorrhages (ring of hemorrhage around hair follicles; see Fig. 8-9B), hemarthrosis (bleeding into joints), and bleeding gums with loose teeth (see Fig. 8-9C)  
Additional findings in scurvy include anemia (combined iron and folic acid deficiency), glossitis, poor wound healing, bone fragility and joint pains, calcium oxalate stones in the urine, and corkscrew hairs (see Fig. 8-9D) |
B. Riboflavin (vitamin B₂)

1. Sources
   - Liver, dairy products, nuts, green leafy vegetables, and soybeans.
2. Active forms include flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN).
   a. FAD is a cofactor associated with succinate dehydrogenase conversion of succinate to fumarate in the citric acid cycle (CAC).
   b. FMN is in complex I and FAD in complex II of the electron transport chain (ETC).
      • Both accept two electrons in these locations to produce their reduced forms, FMNH₂ and FADH₂, respectively.
3. Deficiency of riboflavin is uncommon but is most often caused by severe malnourishment.
4. Clinical findings in riboflavin deficiency are summarized in Table 8-4.

C. Niacin (vitamin B₃, nicotinic acid; Fig. 8-9A)

1. Sources
   - Most animal products, fruits and vegetables, and seeds
2. Functions
   a. Active forms of niacin include:
      (1) Oxidized nicotinamide adenine dinucleotide (NAD⁺)
      (2) Oxidized nicotinamide adenine dinucleotide phosphate (NADP⁺)
   b. NAD⁺ and NADP⁺ are cofactors in oxidation-reduction reactions.
      (1) In general, NAD⁺ oxidation-reduction reactions are catabolic (e.g., glycolysis).
      (2) In general, NADP⁺ oxidation-reduction reactions are anabolic (e.g., fatty acid and cholesterol synthesis).
3. Causes of deficiency (pellagra)
   a. Corn-based diets are the major cause of niacin deficiency, because corn is deficient in tryptophan and niacin.
   b. Deficiency of tryptophan
      (1) Tryptophan is used to synthesize niacin.
      (2) Causes of tryptophan deficiency
         (a) Corn-based diet
         (b) Hartnup disease
             • Inborn error of metabolism with inability to reabsorb tryptophan in the small bowel and kidneys
         (c) Carcinoid syndrome
             • Tryptophan is used up in the synthesis of serotonin (refer to Chapter 18).
4. Clinical findings in niacin deficiency are summarized in Table 8-4.
5. Excessive intake of niacin (nicotinic acid)
   a. Leads to flushing caused by vasodilation
      • Adverse effect of nicotinic acid, a lipid-lowering drug that decreases serum triglyceride and cholesterol and increases high-density lipoproteins
   b. Intrahepatic cholestasis leading to jaundice (less likely with slow-release preparations)

D. Pyridoxine (vitamin B₆)

1. Sources
   - Meats, fish, seeds, wheat germ, and whole-grain flour
2. Functions
   - Required for transamination (Fig. 8-8), heme synthesis (see Fig. 12-8), and neurotransmitter synthesis.
3. Causes of pyridoxine deficiency
   a. Isoniazid (used in treating tuberculosis)
      • Drug inactivates the vitamin
   b. Drinking goat milk
      • Is deficient in vitamin B₆
   c. Chronic alcoholism
      • Vitamin is degraded in the liver
4. Clinical findings in pyridoxine deficiency are summarized in Table 8-4.

E. Vitamin B₁₂ (cobalamin) (refer to Chapter 12)

F. Folic acid (refer to Chapter 12)

G. Biotin

1. Present in most foods
2. Function
   a. Cofactor in carboxylase reactions
8-8: Transamination. In transamination reactions, amino acids can be synthesized from α-ketoacids, or ketoacids can be synthesized from amino acids. Pyridoxine is the cofactor for aminotransferase for these reaction. Note that if the amine group (H$_2$N$^-$; square) is removed from alanine by alanine aminotransferase (ALT) pyruvate is formed and is used as a substrate for gluconeogenesis. Similarly, if the amine group (H$_2$N$^-$; square) is removed from aspartate by aspartate aminotransferase (AST), oxaloacetate is formed and is used as a substrate for gluconeogenesis. (Modified from Pelley J, Goljan E: Rapid Review Biochemistry, 3rd ed, Philadelphia, Mosby Elsevier, 2011, p 99, Fig. 8-1.)

b. Examples include:
(1) Conversion of pyruvate to oxaloacetate (OAA) by pyruvate carboxylase in gluconeogenesis.
(2) Conversion of propionyl CoA to methylmalonyl CoA by propionyl CoA carboxylase in odd-chain fatty acid metabolism, the end product of which is succinyl CoA.
3. Causes of biotin deficiency
a. Eating raw eggs (avidin in eggs binds biotin)
   • One would have to consistently consume over 20 raw eggs a day to become biotin deficient.
b. Taking antibiotics (destroys colonic microflora that synthesize the vitamin)
4. Clinical findings in biotin deficiency are summarized in Table 8-4.

H. Ascorbic acid (vitamin C; see Fig. 8-9B, C, D)
1. Sources
   • Fruits, vegetables, liver, fish, and milk
2. Functions
   a. Important in collagen synthesis
      (1) Vitamin C hydroxylates lysine and proline residues in the rough endoplasmic reticulum (RER) of fibroblasts.
      (2) Lysyl oxidase, a copper-containing enzyme, oxidizes the lysine side chain to reactive aldehydes that spontaneously form cross-links between tropocollagen molecules.
      (3) Cross-linking of collagen molecules is responsible for the tensile strength of collagen.
         (a) The abnormal tropocollagen molecules with defective cross-linking are poorly secreted from the fibroblast and are also subject to enzymatic degradation; hence the amount of structurally abnormal collagen that is synthesized is decreased.
         (b) Since osteoid in bone is composed of collagen, there is inadequate synthesis of structurally weak osteoid in vitamin C deficiency.
            • Causes bone fragility and joint pain
         (c) In addition, the structurally abnormal collagen in small blood vessels (venules, capillaries) results in a bleeding diathesis (e.g., bleeding gums, bleeding into the skin, hemarthrosis) and results in poor wound healing.
   b. Antioxidant activity
      (1) Vitamin C regenerates vitamin E (also an antioxidant; see V.C.2.).
      (2) Vitamin C neutralizes hydroxyl free radicals (FRs; refer to Chapter 2).
   c. Reduces nonheme iron (oxidized; Fe³⁺) in plants to heme iron (reduced; Fe²⁺), which is now suitable for reabsorption in the duodenum
      • In vitamin C deficiency, there is decreased reabsorption if heme iron in the duodenum, which could lead to iron deficiency anemia (microcytic anemia; refer to Chapter 12).
   d. Keeps tetrahydrofolate (FH₄) in folic acid metabolism in its reduced form (see Fig. 12-16)
      (1) FH₄ in its reduced form is important in single-carbon transfer reactions (e.g., DNA synthesis, synthesis of methionine).
      (2) Vitamin C deficiency is a cause of folic acid deficiency (macrocytic anemia).
   e. Cofactor for conversion of dopamine to norepinephrine in catecholamine synthesis (see Fig. 23-20A)
3. Causes of vitamin C deficiency
   a. Diets lacking fruits and vegetables
   b. Cigarette smoking
      • Vitamin C is used up in neutralizing free radicals in cigarette smoke.
4. Clinical findings in vitamin C deficiency are summarized in Table 8-4.

VII. Trace Elements
A. Definition of trace elements
   • Definition—micronutrients that are required in the normal diet
B. Zinc
   1. Functions
      a. Cofactor for metalloenzymes (e.g., collagenase in wound remodeling; refer to Chapter 3)
      b. Important in growth and spermatogenesis in children.
Table 8-5 Trace Metals: Clinical Findings in Deficiency

<table>
<thead>
<tr>
<th>TRACE METAL</th>
<th>EFFECTS OF DEFICIENCY</th>
</tr>
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<tbody>
<tr>
<td>Chromium</td>
<td>Metabolic: impaired glucose tolerance, peripheral neuropathy</td>
</tr>
<tr>
<td>Copper</td>
<td>Blood: microcytic anemia (cofactor in ferroxidase)</td>
</tr>
<tr>
<td></td>
<td>Vessels: aortic dissection (weak elastic tissue)</td>
</tr>
<tr>
<td></td>
<td>Metabolic: poor wound healing (cofactor in lysyl oxidase)</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Teeth: dental caries</td>
</tr>
<tr>
<td>Iodide</td>
<td>Thyroid: thyroid enlargement (goiter; see Fig. 23-9A), hypothyroidism</td>
</tr>
<tr>
<td>Selenium</td>
<td>Muscle: muscle pain and weakness, dilated cardiomyopathy</td>
</tr>
<tr>
<td>Zinc</td>
<td>Metabolic: poor wound healing (cofactor in collagenase)</td>
</tr>
</tbody>
</table>

2. Causes of zinc deficiency
   a. Alcoholism, diabetes mellitus, chronic diarrhea
   b. Acrodermatitis enteropathica
      (1) Autosomal recessive disease
      (2) Clinical findings include:
         • Dermatitis, growth retardation, decreased spermatogenesis, and poor wound healing
   3. Clinical findings in zinc deficiency (Table 8-5)

C. Copper
1. Functions
   • Cofactor for ferroxidase (binds iron to transferrin), lysyl oxidase (cross-linking of collagen and elastic tissue), and tyrosinase (melanin synthesis)
2. Causes of copper deficiency
   • Most often due to total parenteral nutrition (TPN)
3. Clinical findings in copper deficiency (see Table 8-5)
4. Copper excess is seen in Wilson disease (refer to Chapter 19 for full discussion)
   a. Autosomal recessive disease
   b. Defect in eliminating copper into bile
   c. Defect in incorporating copper into ceruloplasmin, the binding protein for copper.
   d. Clinical findings include:
      (1) Chronic liver disease (hepatitis, cirrhosis)
      (2) Kayser-Fleischer ring in the cornea (see Fig. 19-7I)
      (3) Basal ganglia degeneration producing chorea, parkinsonism, and dementia (see Fig. 26-21A)
   e. Laboratory findings include:
      (1) Decreased total serum copper, because ceruloplasmin is decreased
      (2) Increased serum free (unbound to ceruloplasmin) copper
      (3) Increased urine copper

D. Iodine
1. Function
   • Used to synthesize thyroid hormone (refer to Chapter 23)
2. Causes of iodine deficiency
   • Most often due to inadequate intake of iodized table salt
3. Clinical findings (see Table 8-4)

E. Chromium
1. Functions
   a. Component of glucose tolerance factor, which maintains a normal serum glucose
   b. Cofactor for insulin that facilitates the binding of glucose to adipose and muscle glucose transport units (GLUTs)
   c. Useful supplement in patients with diabetes mellitus
2. Causes of chromium deficiency
   • Deficiency is most often due to TPN.
3. Clinical findings in chromium deficiency (see Table 8-5)

F. Selenium
1. Functions
   • Component of glutathione peroxidase, which produces reduced glutathione, an antioxidant that converts hydrogen peroxide to water
2. Causes of selenium deficiency
   • Deficiency is most often due to TPN.
3. Clinical findings in selenium deficiency (see Table 8-5)

G. Fluoride
1. Function
   a. Component of calcium hydroxyapatite in bone and teeth
   b. Prevents the formation of dental caries
2. Causes of fluoride deficiency
   • Inadequate intake of fluoridated water
3. Clinical findings in fluoride deficiency (see Table 8-5)
4. Clinical findings of fluoride excess
   a. Chalky deposits on the teeth
   b. Calcification of ligaments
   c. Increased risk for bone fractures

VIII. Mineral and Electrolyte Deficiency and Excess (Table 8-6)
IX. Dietary Fiber
A. Types of dietary fiber
1. Insoluble fiber
   a. Nonfermentable
      • Examples—wheat bran, wheat germ, fruits and vegetables
   b. Absorbs water, which increases the bulk of stool
   c. Softens the stool and causes more frequent elimination
2. Soluble fiber
   a. Fermentable
      • Examples—oat bran, psyllium seeds, fruits
   b. Softens stool
   c. Increases fecal bacterial mass
B. Benefits of increased dietary fiber
1. Binds potential carcinogens and excretes them in stool
   a. Lithocholic acid
      (1) Lithocholic acid is the only bile acid that is not reabsorbed in the terminal ileum.
         • Insoluble fiber would eliminate the lithocholic acid that would have contact with
           the bowel mucosa.
      (2) Lithocholic acid may have a causative role in producing colorectal cancer.

<table>
<thead>
<tr>
<th>TABLE 8-6 Mineral and Electrolyte Deficiency and Excess</th>
</tr>
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<tbody>
<tr>
<td>Calcium</td>
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<tr>
<td>Phosphorus</td>
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<tr>
<td>Sodium</td>
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<td>Potassium</td>
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<tr>
<td>Magnesium</td>
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</table>

*PTH, Parathyroid hormone.*
b. Estrogen
   (1) Some estrogen in the stool is reabsorbed back into the blood.
       • Insoluble fiber would eliminate the estrogen that would normally be
         reabsorbed.
   (2) Increased estrogen increases the risk for endometrial and breast cancer.
2. Decreases the risk for developing diverticulosis by preventing constipation
3. Decreases the risk for developing heart disease
   • Soluble fiber increases the loss of cholesterol in stool.

X. Special Diets
A. Sodium-restricted diets
   1. Reduces blood pressure (refer to Chapter 10)
   2. Nonpharmacologic treatment for:
      a. Essential hypertension (refer to Chapter 10)
      b. Congestive heart failure (refer to Chapter 11)
      c. Chronic renal disease (refer to Chapter 20)
      d. Cirrhosis (refer to Chapter 19)
B. Protein-restricted diets
   1. Reduce the formation of urea and ammonia (refer to Chapter 19)
   2. Used in the treatment of:
      a. Chronic renal failure (refer to Chapter 20)
         (1) Kidney is the primary site for the removal of urea produced by the urea cycle in the
             liver.
         (2) In chronic renal disease, the urea cannot be excreted and its accumulation in the
             blood produces toxic changes in multiple organ systems.
      b. Cirrhosis of the liver (refer to Chapter 19)
         (1) In cirrhosis, the urea cycle is impaired; hence the normal conversion of ammonia
             to urea in the urea cycle cannot occur, leading to an increase in serum ammonia
             and a decrease in serum blood urea nitrogen.
         (2) Increased serum ammonia produces hepatic encephalopathy (drowsiness, mental
             status abnormalities, coma).
I. Nomenclature

A. Benign tumors

1. Definition—unregulated proliferation of cells that does not invade or spread to other sites
2. Suffix "-oma" generally indicates a benign tumor.
   - Exceptions to the rule are seminomas (testicular cancer), lymphoma (malignancy of lymph nodes), glioma (malignancy of glial cells in the brain), mesothelioma (malignancy of pleural serosa), and neuroblastoma (malignancy of neuroblasts).
3. Derivation of benign tumors of epithelial origin
   a. Arise from ectoderm (e.g., squamous and transitional epithelium) or endoderm (e.g., glandular epithelium)
   b. Example—tubular adenomas (adenomatous polyps) arise from glands in the colon (Fig. 9-1A)
4. Benign tumors of connective tissue origin
   a. Arise from mesoderm
   b. Example—lipomas derive from adipose tissue (see Fig. 9-1B)
5. Unusual tumors that are usually benign
   a. Mixed tumors
      (1) Definition—neoplastic cells with two different morphologic patterns, but they derive from the same germ cell layer
      - Not the same as a teratoma (see later)
      (2) Example—pleomorphic adenoma of parotid gland
   b. Teratomas
      (1) Definition—derive from more than one germ cell layer
      - Tissue derived from ectoderm, endoderm, and mesoderm (see Fig. 9-1C)
      (2) Sites—ovaries (most common site), testes, anterior mediastinum, and pineal gland
      - Midline location (pineal gland, anterior mediastinum) or close to the midline (ovaries and testes)

B. Malignant tumors (cancer)

1. Definition—unregulated proliferation of cells that invade and are able to spread to other sites
2. Carcinomas
   a. Derive from epithelial tissue—squamous, glandular, transitional epithelium
   b. Sites for squamous cell carcinoma (SCC; see Fig. 9-1D and E)
      - Oropharynx, larynx, upper/middle esophagus, lung, cervix, skin
   c. Sites for adenocarcinoma (glandular epithelium; see Fig. 9-1F and G)
      - Lung, distal esophagus to rectum, pancreas, liver, breast, endometrium, ovaries, kidneys, prostate
   d. Sites for transitional cell carcinoma (TCC)
      - Urinary bladder, ureter, renal pelvis
3. Sarcomas
   a. Derive from connective tissue; therefore they are all of mesodermal origin
   b. Approximately 40% of sarcomas are located in lower extremities
   c. Example—osteogenic (bone) sarcoma (see Fig. 9-1H)
A, Tubular adenoma (adenomatous polyp) of the colon. Note the fibrovascular stalk (arrow) lined by normal colonic mucosa and a branching head surfaced by dysplastic (blue-staining) epithelial glands. The epithelium is glandular; therefore it derives from the endoderm. B, Lipoma showing a well-circumscribed yellow tumor. Adipose tissue is connective tissue; therefore it derives from the mesoderm. C, Cystic teratoma of the ovary, showing the cystic nature of the tumor. Hair is present, and a tooth is visible (arrow). Teratomas can arise from ectoderm (this photograph), endoderm, and mesoderm. D, Schematic shows keratin pearls (concentric layers of eosin-staining keratin similar to the layers of a pearl). E, Squamous cell carcinoma. The many well-differentiated foci of eosinophilic-staining neoplastic cells produce keratin in layers (keratin pearls). Note how squamous epithelium takes up the red eosin stain. F, Schematic shows glands lined by neoplastic glandular cells with hyperchromatic and irregular nuclei, and a gland lumen with material in the lumen. G, Adeno-carcinoma. Irregular glands infiltrate the stroma. The nuclei lining the gland lumens are cuboidal and contain nuclei with hyperchromatic nuclear chromatin. Glandular cells appear to pile up on each other. Many of the gland lumens contain secretory material (arrow). H, Osteogenic sarcoma of the distal femur. The light-colored mass of tumor in the metaphysis abuts the epiphyseal plate (arrow) and has spread laterally out through the cortex and into the surrounding tissue. (A from Kumar V, Fausto N, Abbas A: Robbins and Cotran’s Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 860, Fig. 17-57A; B, C, D, and F from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, pp 77, 79, 78, 78, Figs. 4-7, 4-11, 4-10A, 4-10B, respectively; E from Klatt F: Robbins and Cotran’s Atlas of Pathology, Philadelphia, Saunders, 2006, p 302, Fig. 13-35; G and H from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, pp 139, 369, Figs. 7-59, 17-35B, respectively.)
C. Tumor-like conditions
1. Hamartoma
   a. Definition—nonneoplastic overgrowth of disorganized tissue indigenous to a particular site
   b. Examples—bronchial hamartoma (contains cartilage), Peutz-Jeghers polyp (contains glandular tissue)
2. Choristoma (heterotopic rest)
   a. Definition—mass of nonneoplastic normal tissue in a foreign location
   b. Examples—pancreatic tissue in stomach wall; brain tissue in nasal cavity

II. Properties of Benign and Malignant Tumors
A. Components of benign and malignant tumors
1. Parenchyma
   • Definition—neoplastic component that determines biological behavior
2. Stroma
   a. Definition—nonneoplastic supportive tissue
   b. Most infiltrating carcinomas induce production of a dense, fibrous stroma (called desmoplasia).

B. Differentiation in benign and malignant tumors
1. Benign tumors
   • Definition—usually well differentiated (resemble parent tissue)
2. Malignant tumors
   a. Well-differentiated or low grade cancer
      (1) Cancer cells resemble parent tissue
      (2) Examples—parenchyma shows keratin pearls (characteristic of squamous tissue; see Fig. 9-1D and E) or glandular lumens with secretions (characteristic of normal gland lumens with secretions; see Fig. 9-1F and G)
   b. Poorly differentiated, high grade, or anaplastic
      • No differentiating features (e.g., no glands, no keratin staining material)
   c. Intermediate grade
      • Features are between a low- and high-grade cancer (e.g., occasional gland-like structures are seen, or areas that look like keratin are present, whereas the rest of the tumor has no differentiation)

C. Cell organelles in malignant versus normal cells
1. Organelles in the cytoplasm when compared to a normal cell (Fig. 9-2)
   a. Fewer mitochondria
   b. Less prominent rough endoplasmic reticulum (RER)
   c. Loss of cell-to-cell adhesion molecules (cadherins)
      • Cadherins are a group of calcium-dependent transmembrane proteins that play an important role in cell-to-cell adhesion.
2. Nuclear features when compared to a normal cell
   a. Nucleus is larger, has irregular borders, and has more chromatin (hyperchromatic)
   b. Nucleolus is larger and has irregular borders
   c. Mitoses have normal and atypical mitotic spindles (Fig. 9-3).

D. Biochemical changes in malignant cells
1. Rely on anaerobic glycolysis for energy
   • Greater accumulation of lactic acid than a normal cell would make in a hypoxic situation
2. Increased uptake of glucose analog
   a. Special test has been developed in which cancer cells take up a glucose analog with positron emission tomography (PET)
   b. PET scan is widely used in the diagnosis, staging, and monitoring of therapy of various kinds of cancer.
3. Do not process glucose as well as normal cells, and store glucose in the form of glycogen within the cytosol
4. Some cancers derive energy from β-oxidation of fatty acids rather than anaerobic glycolysis (e.g., prostate cancer).

E. Growth rate in benign and malignant tumors
1. Benign tumors usually have a slow growth rate.
2. Malignant tumors have a variable growth rate.
   a. Growth rate correlates with degree of differentiation of the malignant tumor.
   b. Example—anaplastic (high-grade) cancers have an increased growth rate, whereas low-grade cancers have a slow growth rate.
9-2: Schematic showing normal organelles in a normal cell on the left (A) and a malignant cell (B) on the right. Note that when compared to a normal cell, a malignant cell has fewer mitochondria, less prominence of the rough endoplasmic reticulum with an increase in free ribosomes, loss of cell adhesion molecules between cells (cadherins and occludens), and a larger nucleus with irregular borders, excess chromatin, and a larger, irregular nucleolus. Tumor antigens are sometimes expressed on the surface of malignant cells (CEA). CEA, Carcinoembryonic antigen. (Modified from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 80, Fig. 4-12.)

9-3: Leiomyosarcoma with an atypical mitotic spindle in the center of the slide. (From Rosai J: Rosai and Ackerman’s Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 1609, Fig. 19.182.)

Clinically detectable:
30 population doublings to produce 10^9 cells (1 g tissue)

Tumors with ↑growth rate treated with cell cycle–specific chemotherapy

Methotrexate inhibits S phase; vincristine inhibits M phase

Most benign/malignant tumors arise from single precursor cell (monoclonal)

3. Clinically detectable tumor mass must have 30 population doublings to produce 10^9 cells, which equals 1 g of tissue.
4. Malignant cells with an increased growth rate (e.g., acute leukemia) are treated with cell cycle–specific chemotherapy agents.
   a. Methotrexate inhibits the S phase of the cell cycle (duplication of DNA), whereas vincristine inhibits the mitotic (M) phase of the cell cycle.
   b. When malignant cells are killed, other malignant cells quickly enter the cycle, and the cycle repeats itself so that the size of the tumor begins to shrink (this is called debulking of the tumor).

F. Monoclonality in benign and malignant tumors
1. Nonneoplastic proliferations derive from multiple cells (polyclonal).
2. Benign and most malignant tumors derive from a single precursor cell.
The monoclonal origin of neoplasms has been shown by studying glucose-6-phosphate dehydrogenase (G6PD) isoenzymes A and B in selected neoplasms (e.g., leiomyoma of the uterus). All the neoplastic smooth muscle cells in uterine leiomyomas have either the A or the B G6PD isoenzyme. Nonneoplastic smooth muscle proliferations in the uterus (e.g., pregnant uterus) have some cells with the A isoenzyme and others with the B isoenzyme, indicating their polyclonal origin.

G. Telomerase activity in benign and malignant tumors
1. Telomere complexes
   a. Definition—repetitive sequences of nontranscribed DNA located at the ends of chromosomes
   b. Prevent end-to-end fusion of chromosomes during normal mitosis and, along with other factors, are important in determining the longevity of a cell
   c. Shorten with each round of replication and eventually, when only a few nucleotide bases remain, the genome becomes unstable, which produces a signal for apoptosis
2. Benign tumors have normal telomerase activity.
3. Malignant cells have upregulation of telomerase activity, which prevents the naturally programmed shortening of telomere complexes with cell replication; hence the cell no longer undergoes apoptosis.

H. Upregulation of decay accelerating factor (DAF) by malignant cells
1. DAF normally degrades C3 convertase and C5 convertase in the classical and alternative complement pathways (see Fig. 4-17).
2. Upregulation of DAF ensures that degradation of the convertases just mentioned prevents formation of the membrane attack complex (MAC; C5b-9); therefore cancer cells cannot be killed by the MAC.

I. Local invasion and metastasis
1. Benign tumors
   a. Do not invade
      • Exception is a dermatofibroma, which invades tissue but does not metastasize (refer to Chapter 25)
   b. Usually enclosed by a fibrous tissue capsule
      • Exception is a uterine leiomyoma, which does not have a fibrous tissue capsule
2. Malignant tumors
   a. Invade tissue
      • Second most important criterion for malignancy
   b. Some tissues resist invasion.
      • Examples—mature cartilage, elastic tissue of arteries
   c. All malignant tumors require O₂ and nutrients to survive and do so by stimulating angiogenesis within the tumor and its metastatic sites (Fig. 9-4).
      (1) Angiogenesis, or new blood vessel formation, occurs by forming capillary sprouts from preexisting capillaries (parent capillaries) and/or by stimulating the synthesis of endothelial precursor cells (EPCs) from the bone marrow that migrate to the tumor site.

   9-4: The schematic shows tumor-induced angiogenesis, which refers to the sprouting of new capillaries from preexisting vessels. For a tumor to survive it must have an adequate blood supply to provide oxygen and nutrients or it will die. Refer to the text for a full discussion. (Modified from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 76, Fig. 4-6.)
(2) Vascular endothelial growth factor (VEGF) and other growth factors produced by the tumor (refer to Chapter 3) directly act on endothelial cells in the parent capillaries to develop new capillary sprouts.
   • Tumor necrosis factor (TNF) released by macrophages is important in stimulating tumor cells to produce these angiogenesis factors.
(3) Chemotactic factors produced by the tumor cells and inflammatory cells (particularly macrophages) assist in attracting endothelial cells from the parent capillaries to form the new capillary sprouts.
(4) Enzymes (e.g., proteases) regulate the balance between angiogenesis and the many factors that can inhibit angiogenesis (e.g., angiotatin, endostatin).
   • They also degrade basement membranes in parent vessels to allow endothelial cells to migrate and form new capillary sprouts.
(5) EPCs from the bone marrow are also used in new vessel formation.
(6) Monoclonal antibodies have been developed to inhibit tumor angiogenesis.
   (a) For example, bevacizumab is a recombinant humanized antibody that inhibits the binding of VEGF to endothelial cells in new capillary sprouts.
   (b) They are indicated for the treatment of metastatic colon cancer and non–small cell carcinoma of the lung.

d. Sequence of hematogenous (capillary) invasion by malignant tumors is illustrated in Figure 9-5.
(1) The same sequence of invasion also applies to invasion of a lymphatic vessel or a venule.

9-5: Sequential steps involved in the hematogenous spread of cancer from a primary to a distant site. Initially there is clonal proliferation of a subset of primary tumor cells that have the capacity to metastasize. In order to invade from the primary site, the cancer cells must lose their cell-to-cell adhesion molecules, obtain the capacity to move through tissue, adhere to and degrade the basement membrane, pass through the extracellular matrix, and penetrate the vascular wall of a capillary (intravasation). In the bloodstream, the cancer cells encounter host defense cells (e.g., cytotoxic T cells, killer cells) and some are destroyed (type IV hypersensitivity reaction; refer to Chapter 4). Those that survive form tumor cell emboli that attach to the capillary endothelium of a distant organ (e.g., lung) and repeat the process of invasion of the capillary wall into the tissue of the distal organ, where it sets up a metastatic focus of tumor that will grow and continue to spread. (From Kumar V, Fausto N, Abbas A, Aster J: Robbins and Cotran Pathologic Basis of Disease, 8th ed, Philadelphia, Saunders Elsevier, 2010, p 298, Fig. 7-36.)
(2) The schematic shows the primary tumor resting on top of the basement membrane of a capillary.
   • Note the importance of angiogenesis in maintaining the viability of the primary tumor as well as the metastatic foci.
(3) Within the primary tumor, there is clonal proliferation of cells that develops the capacity to invade and metastasize.
   • All other primary tumor cells cannot invade and metastasize.
(4) First key step in invasion is for malignant cells to lose their cell-to-cell adhesion molecules (cadherins; see II.C.1.).
(5) Second key step is for cell receptors to attach to laminin (a glycoprotein) in the basement membrane and to release metalloproteinases (e.g., collagenases, stromelysins, gelatinases) to degrade the basement membrane and other enzymes to degrade the interstitial connective tissue.
   • Tissue inhibitors of metalloproteinases neutralize these tumor-produced enzymes and limit the degree of invasion.
(6) Third key step is for cell receptors to attach to fibronectin and other proteins in the extracellular matrix (ECM) and to break it down.
(7) Fourth key step is for malignant cells to produce cytokines that stimulate locomotion, so that they can move through basement membranes and the intracellular and extracellular matrices.
(8) When malignant cells encounter capillaries, they must penetrate the blood vessels (called intravasation) in order to enter the microcirculation.
(9) While in the circulation, some malignant cells encounter host defense cells (e.g., cytotoxic T cells, killer cells; see Chapter 4) and are destroyed, whereas other cells escape destruction.
   • In cancer surgery, most malignant cells that enter the circulation produce metastasis.
(10) Those tumor cells that escape destruction form tumor cell emboli that are coated by platelets and fibrin.
(11) Tumor emboli enter capillaries of a target organ, attach to the blood vessel wall, and repeat the four-step process of invasion (called extravasation) to set up a metastatic focus that will grow and continue to spread throughout the target organ.
(12) Where these tumor emboli eventually settle depends on several factors.
   (a) Sometimes the metastatic site is the first capillary bed it encounters.
   (b) Sometimes it travels through the Batson paravertebral plexus and ends up in the vertebral column (discussed later).
   (c) Sometimes the primary cancer releases chemokines that go specifically to sites that have chemokine receptors similar to those in the primary tumor.
   (d) Sometimes target organs release chemotaxattractants that signal tumor cells to deposit at that site.

J. Types of metastasis
1. Benign tumors do not metastasize.
2. Malignant tumors metastasize.
   a. Most important criterion for malignancy
      b. Basal cell carcinoma (BCC) is a notable exception to the rule, because these cells invade tissue (a criteria of malignancy) but do not metastasize.
3. Pathways of dissemination
   a. Lymphatic spread of cancer
      (1) Lymphatic spread to regional lymph nodes is the first step for dissemination in carcinomas.
         • Lymph nodes are the first line of defense against the spread of carcinomas.
      (2) Using the model of invasion and metastasis discussed in Figure 9-5, in carcinomas, the vessel that is invaded is an afferent lymphatic vessel. The tumor emboli enter the sinuses of the regional lymph nodes and invade the parenchymal tissue of the lymph node.
      (3) Tumor cells that invade efferent lymphatics send tumor emboli into the thoracic duct, and from there they enter the systemic circulation, where they disperse to capillaries in target organs to form metastatic foci.
         • This is the hematogenous phase of cancer dissemination in carcinomas.
   b. Hematogenous spread of cancer
      (1) Sarcomas initially invade capillaries and/or venules and directly spread to distant sites without involving the lymph nodes.
Malignant cells in portal vein → metastasize to liver
Malignant cells in vena cava → metastasize to lungs
Both carcinomas/sarcomas have hematogenous spread

Seeding: exfoliation from serosal surface and invade tissue in a body cavity
Seeding: malignant surface-derived ovarian cancers; omental implants
Peripheral located lung adenocarcinomas seed pleural cavity
GBM uses spinal fluid to seed distant sites (brainstem, spinal cord)

Bone metastasis: vertebrae MC site
Breast cancer MC cancer metastatic to bone
Paravertebral venous plexus: connections with vena cava and vertebral bodies
Prostate cancer MCC osteoblastic metastases, followed by breast cancer
Osteoblastic metastasis: ↑serum ALP; radiodensities in radiographs
Osteolytic metastases: radiolucencies in bone
PGE₂, IL-1 produced by tumor locally activate osteoclasts
Osteolytic cancers: lung, kidney, breast
Osteolytic metastasis: hypercalcemia, pathologic fractures
Bone pain: localized radiation

(2) Malignant cells entering the portal vein metastasize to the liver, whereas those that enter the vena cava metastasize to the lungs.
(3) Both carcinomas and sarcomas have hematogenous dissemination; however, carcinomas invade regional lymph nodes before entering the systemic circulation.

Renal cell carcinomas (RCCs) commonly invade the renal vein, where the tumor has the potential for extending into the vena cava to as far as the right side of the heart. RCCs also have lymphatic spread to regional lymph nodes. Hepatocellular carcinomas (HCCs) invade the portal and hepatic veins. Tumor obstruction of either vein produces portal hypertension, splenomegaly, and ascites. HCCs also spread to regional lymph nodes. Follicular carcinomas of the thyroid invade blood vessels and have hematogenous spread. Lymph nodes are usually spared.

c. Seeding of malignant cells
(1) Definition—malignant cells exfoliate from a serosal surface and implant and invade tissue in a body cavity (pleural, pericardial, peritoneal)
  • Analogous to a farmer spreading seeds in a field, which develop roots and grow
(2) Primary surface-derived ovarian cancers (e.g., serous cystadenocarcinoma) commonly seed the omentum and produce malignant effusions in the peritoneal cavity.
(3) Peripherally located lung cancers (usually adenocarcinomas) commonly seed the parietal and visceral pleurae, causing malignant pleural effusions.
(4) A variant of seeding is a glioblastoma multiforme (GBM), a high-grade cancer arising in the brain that commonly exfoliates malignant cells into the cerebrospinal fluid (CSF) and seeds the brainstem and spinal cord.

4. Bone metastasis
a. Vertebral column
   (1) Most common metastatic site in bone (Fig. 9-6A)
     • Breast cancer is the most common cancer metastatic to bone; second most common is prostate cancer.
   (2) Batson paravertebral venous plexus is responsible for the predilection of bone metastases to this site.
     (a) This plexus has connections with the vena cava and the vertebral bodies.
     (b) Using breast cancer as an example, a tumor embolus in the intercostal vein can enter the vena cava and from there enter the paravertebral venous plexus, which has tributaries that enter the vertebral bodies.

b. Osteoblastic metastases
(1) Malignant cells in metastatic sites secrete cytokines that specifically activate osteoblasts, which initiate reactive bone formation (see Fig. 9-6B).
   (a) Prostate cancer is the most common cancer producing osteoblastic metastases; second most common is breast cancer.
   (b) Serum alkaline phosphatase (ALP) is elevated, because osteoblasts use this enzyme in bone formation.
(2) Bone formation in metastatic sites produces radiodensities that are identified in radiographs (e.g., prostate cancer; see Fig. 9-6C).

c. Osteolytic metastases
(1) Osteolytic metastases produce radiolucencies in bone that are identified in radiographs (see Fig. 9-6D).
(2) Pathogenesis
   (a) Malignant cells in metastatic sites produce chemicals (e.g., prostaglandin E₂, interleukin [IL]-1) that locally activate osteoclasts.
   (b) Cancers that commonly produce lytic metastases include lung cancer, renal cell carcinomas, and breast cancer.
(3) Clinical findings
   (a) Pathologic fractures
   (b) Hypercalcemia, possible if osteolytic lesions are extensive

d. Bone pain from metastasis
  • Requires localized radiation
9-6: A, Radionuclide scan. Radionuclide uptake is increased throughout the skeleton, with a very heavy uptake in the vertebral column. The patient had a primary breast cancer, which is the most common cancer metastatic to bone. B, Prostate cancer metastatic to the vertebral column. Multiple white foci of metastatic prostate cancer produce an osteoblastic response in the bone. C, Multiple osteolytic metastases and a pathologic fracture of the right femoral neck in a woman with breast cancer. Lytic lesions are scattered throughout the pelvis and in the proximal femoral bones. D, Radiograph showing osteolytic lesions. Note the radiolucent areas in the midshaft of the fibula (arrow) in metastatic breast cancer. E, Metastasis to the liver. The liver contains multiple nodules that have a depressed central area ("umbilicated") and stellate-shaped borders. (A from Bouloux P: Self-Assessment Picture Tests: Medicine, Vol. 1, London, Mosby-Wolfe, 1997, p 70, Fig. 140; B from Kumar V, Fausto N, Abbas A: Robbins and Cotran's Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 1052, Fig. 21-35; C from Forbes C, Jackson W: Color Atlas and Text of Clinical Medicine, 3rd ed, London, Mosby, 2004, p 145, Fig. 3.156; D from Rosai J, Ackerman LV: Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 2187, Fig. 24-92; E from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 303, Fig. 11-18.)

5. Metastasis is more common than a primary cancer in the following sites:
   a. Lymph nodes (e.g., metastatic breast and lung cancer most common)
   b. Lungs (e.g., metastatic breast cancer most common)
   c. Liver (e.g., metastatic lung cancer most common) (see Fig. 9-6E)
   d. Bone (e.g., metastatic breast cancer most common)
   e. Brain (e.g., metastatic lung cancer most common)

III. Cancer Epidemiology
   A. General epidemiology
      1. Second most common cause of death in the United States
      2. Causes of cancer
         a. External factors
            • Tobacco (#1), alcohol, chemicals, radiation, microbial pathogens
b. Internal factors
   • Hormones, immune conditions, inherited mutations
   c. Geographic and ethnic factors
3. Age is an important risk factor for cancer.
   a. Cancer incidence increases with age.
      • Majority of cancers are in persons 55 years or older.
   b. Colorectal, lung, and prostate cancer progressively increase in incidence with age, whereas others reach a peak and begin to decline (e.g., malignant melanoma).
   a. African-Americans have a greater risk for developing prostate cancer than white Americans.
   b. Skin cancer is more common in fair-skinned people than dark-skinned people, because of the protective effect of melanin against ultraviolet (UV) light.
   c. Breast cancer has a low incidence in Japanese and Asian women, while the incidence is high in North American and European women.

B. Cancer incidence by age and sex
1. Cancers in children
   a. Malignant neoplasms are the leading cause of disease-related (noninjury) mortality among children 1 to 14 years of age.
   b. Top three cancers in children in decreasing order are:
      (1) Leukemia (acute lymphoblastic leukemia is the most common leukemia)
      (2) Central nervous system (CNS; cerebellar tumors most common)
      (3) Neuroblastoma
   c. Other common cancers in children that are not common in adults include embryonal rhabdomyosarcoma, Wilms tumor, retinoblastoma, osteogenic sarcoma, and Ewing sarcoma.
   d. Epithelial tumors of organs, such as lung, colon, and breast are common in adults but uncommon in children.
2. Top three cancer sites in men in decreasing order are:
   a. Prostate
   b. Lung
   c. Colon/rectum
3. Top three cancer sites in women in decreasing order are:
   a. Breast
   b. Lung
   c. Colon/rectum
4. Top three sites for gynecologic cancers in decreasing order are:
   a. Uterine corpus (endometrium)
   b. Ovary
   c. Cervix

C. Sites for cancer-related deaths
1. Top three sites for cancer-related deaths in men in decreasing order are:
   a. Lung
   b. Prostate
   c. Colon/rectum
2. Top three sites for cancer-related deaths in women in decreasing order are:
   a. Lung
   b. Breast
   c. Colon/rectum
3. Top three gynecologic sites for cancer-related deaths in women in decreasing order are:
   a. Ovary
   b. Uterine corpus (endometrium)
   c. Cervix

D. Cancer and heredity
1. Inherited predisposition to cancer accounts for 5% of all cancers.
2. Categories of inherited cancers (Table 9-1; Figs. 9-7 and 9-8)
   a. Autosomal dominant cancer syndromes
   b. Autosomal recessive disorders involving DNA repair
   c. Familial cancers
### Table 9-1 Selected Inherited Cancer Syndromes

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>CANCER</th>
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<tr>
<td>Autosomal dominant (AD) cancer syndromes</td>
<td><strong>Retinoblastoma</strong>: malignancy of the eye in children under 5 years of age. Of all cases, 60% are nonhereditary and are usually unilateral, 15% are AD and have unilateral retinoblastomas, and 25% are AD and have bilateral retinoblastomas. In the AD type, one of the RB1 genes on chromosome 13 is mutated in germ cells, and a second mutation of the RB1 gene on the remaining chromosome 13 (deletion or recombination mutation) is necessary after birth (“two hits”) to produce a unilateral retinoblastoma or a bilateral retinoblastoma. In the sporadic type, the two somatic mutations of the RB1 suppressor gene on chromosome 13 occur in early childhood and produce unilateral retinoblastomas. In the AD type of retinoblastoma, there is an additional risk for developing second malignancies, which include osteogenic sarcoma (most common), soft tissue sarcoma, or malignant melanoma. <strong>Familial adenomatous polyposis</strong>: colorectal cancer from malignant transformation of polyps develops by age 50 years. There is inactivation of APC suppressor gene and increased incidence of desmoid tumors (fibromatosis of anterior abdominal wall). <strong>Li-Fraumeni syndrome</strong>: increased risk for brain tumors, sarcomas, leukemia, carcinomas (e.g., breast, colon, ovary) before 50 years of age. There is inactivation of the p53 suppressor gene. <strong>Hereditary nonpolyposis colon cancer (HNPCC; Lynch syndrome)</strong>: increased risk for colorectal cancers without previous polyps. It is caused by a germ line mutation that inactivates DNA mismatch repair (MMR) genes, which causes a microsatellite repeat replication error (called microsatellite instability, MSI). Microsatellites are repeated sequences that predispose to replication errors if there are mutations in DNA repair enzymes (e.g., mismatch repair genes). The microsatellites become unstable (become longer or shorter) and produce frameshift mutations that inactivate or alter tumor suppressor gene function leading to cancer. MSI is found in the majority of patients with HNPCC. <strong>BRCA1 and BRCA2 genes</strong>: inactivation of these genes increases the risk for developing breast (sometimes bilateral) and ovarian cancer.</td>
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<tr>
<td>Autosomal recessive (AR) syndromes with defects in DNA repair</td>
<td><strong>Xeroderma pigmentosum</strong>: increased risk at an early age for developing skin cancers (basal cell carcinoma, squamous cell carcinoma, malignant melanoma) due inability to repair pyridine dimers produced by exposure to ultraviolet light. <strong>Chromosome instability syndromes</strong>: in these syndromes, chromosomes are susceptible to damage by ionizing radiation and drugs. In <em>ataxia telangiectasia</em>, there is an increased risk for developing malignant lymphomas. In <em>Bloom syndrome</em>, there is an increased risk for developing gastrointestinal tumors and malignant lymphoma. In <em>Fanconi syndrome</em>, there is an increased risk for developing malignant lymphomas, squamous cell carcinoma, and hepatocellular carcinomas.</td>
</tr>
<tr>
<td>Familial cancer syndromes</td>
<td>There is no clearly defined pattern of inheritance, but cancers (e.g., breast, ovary, colon) develop with increased frequency in families. This syndrome sometimes involves the BRCA1 and BRCA2 suppressor genes.</td>
</tr>
</tbody>
</table>

![Image of RETINOBLASTOMA](image)

**9-7**: Retinoblastoma (RB1) tumor suppressor gene. A. Patients with the autosomal dominant (AD) type of retinoblastoma are born with only one normal RB1 gene; the other one is deleted in germ cells (first “hit”). After birth, the normal RB1 gene is mutated in retinoblasts as a result of a spontaneous somatic mutation (second “hit”), which allows oncogenes in those cells to express themselves and produce a retinoblastoma either in one or both eyes. B. Patients with the sporadic type of retinoblastoma have normal RB1 genes at birth, and both of the normal RB1 genes must undergo a spontaneous somatic mutation in the same retinoblast (“two hits”), causing a retinoblastoma to develop in one eye. Retinoblastomas usually develop before 5 years of age; hence the importance of genetic counseling of the parents. (Modified from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 89, Fig. 4-21.)
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9-8: Xeroderma pigmentosum. This is an autosomal recessive disease with defects in DNA repair. Note the numerous hyperpigmented lesions, and nodular and scaly growths on the face. Many of these lesions are precancerous or ultraviolet light–related cancers. (Courtesy R.A. Marsden, MD, St. George’s Hospital, London.)

TABLE 9-2 Acquired Preneoplastic Disorders*

<table>
<thead>
<tr>
<th>PRECURSOR LESION</th>
<th>CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinic (solar) keratosis (see Fig. 25-8A)</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Atypical hyperplasia of ductal epithelium of breast</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Chronic irritation at sinus orifice, third-degree burn scars</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Chronic ulcerative colitis (see Fig. 18-22B)</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Complete hydatidiform mole (see Fig. 22-16A)</td>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Dysplastic nevus (see Fig. 25-6G)</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>Endometrial hyperplasia (see Fig. 22-10D)</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Glandular metaplasia of esophagus (Barrett esophagus; see Fig. 18-10B)</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Glandular metaplasia of stomach (Helicobacter pylori)</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>Acute leukemia</td>
</tr>
<tr>
<td>Regenerative nodules in cirrhosis (see Fig. 19-7B)</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Scar tissue in lung (see Fig. 17-16E)</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Squamous dysplasia of oropharynx, larynx, bronchus, cervix (see Fig. 2-14H)</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Tubular adenoma of colon (see Fig. 9-1A)</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Vaginal adenosis (diethylstilbestrol exposure)</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Villous adenoma of rectum (see Fig. 18-24C,D)</td>
<td>Adenocarcinoma</td>
</tr>
</tbody>
</table>

*Metaplastic and hyperplastic cells become dysplastic before progressing to cancer.

E. Cancer and geography

1. Worldwide
   - Malignant melanoma increasing at most rapid rate of all cancers
2. China
   a. Nasopharyngeal (NP) carcinoma
      - Associated with Epstein-Barr virus (EBV)
   b. SCC of the esophagus
      - Associated with alcohol abuse, smoking, and unknown factors
3. Japan
   - Stomach adenocarcinoma associated with smoked foods
4. Southeast Asia
   - Hepatocellular carcinoma (HCC) associated with hepatitis B virus (HBV) postnecrotic cirrhosis plus aflatoxins (produced by Aspergillus) in food
5. Sub-Saharan Africa
   a. Burkitt lymphoma
      - Associated with EBV
   b. Kaposi sarcoma (KS)
      - Associated with human herpesvirus 8 (HHV-8)

F. Acquired preneoplastic disorders (Table 9-2)

G. Prevention modalities in cancer

1. Modify lifestyle
   a. Stop smoking cigarettes
      - Most important lifestyle modification to prevent cancer (refer to Chapter 7 for the list of cancers)
b. Increase dietary fiber and decrease dietary saturated animal fat
   • Decreases the risk for developing colorectal cancer
c. Reduce alcohol intake (refer to Chapter 7 for the list of cancers)
d. Reduce weight
   (1) More adipose tissue increases aromatase conversion of androgens to estrogen.
   (2) Higher estrogen level increases the risk for developing endometrial and breast cancer.
e. Sunscreen protection
   • Decreases risk for developing BCC, SCC, and malignant melanoma (refer to Chapter 25)

2. Immunization
a. HBV vaccination
   • Immunization against HBV decreases the risk for developing HCC due to HBV-induced postnecrotic cirrhosis.
b. Human papillomavirus (HPV) immunization
   • Decreases the risk for developing SCC of the cervix and penis

3. Screening procedures to detect cancer
a. Cervical Papanicolaou (Pap) smears
   (1) Decrease the risk for cervical cancer due to HPV 16, 18 subtypes
      • Explains why cervical cancer is the least common gynecologic cancer and the least common gynecologic cancer causing death
   (2) Pap smears detect cervical squamous dysplasia, which is the precursor lesion for cervical SCC.
      • Cervical dysplasia is treated by cervical conization and other interventions (refer to Chapter 22).
b. Colonoscopy
   • Detects and removes polyps that are precancerous
c. Mammography
   • Detects nonpalpable breast masses
d. Prostate-specific antigen (PSA)
   (1) More sensitive than specific for diagnosing prostate cancer
   (2) Specificity is decreased, because of increased false positive results due to benign prostatic hyperplasia.

4. Treatment of conditions that predispose to cancer decreases the risk for cancer.
   a. Treatment of *Helicobacter pylori* infections (peptic ulcer disease, gastritis)
      (1) Decreases risk for developing malignant lymphoma (lymphoid hyperplasia → malignant lymphoma)
      (2) It does not decrease the risk for developing adenocarcinoma of stomach.
   b. Treatment of gastroesophageal reflux disease (GERD)
      • Decreases risk for developing distal adenocarcinoma arising from Barrett esophagus (glandular metaplasia → adenocarcinoma; refer to Chapters 2 and 18)

IV. Carcinogenesis

A. Overview
   • Cancer is a multistep process involving gene mutations, telomerase activation, angiogenesis, invasion, and metastasis.

B. Types of gene mutations producing cancer
   1. Point mutations (most common mutation)
   2. Balanced translocations (Fig. 9-10)
   3. Insertion of a viral genome (insertional mutagenesis)
      • Disrupts normal chromosome structure and genetic dysregulation
   4. Other mutations
      • Deletion, gene amplification (multiple copies of a gene), and overexpression (increased gene transcription resulting in the production of too much protein product)

C. Genes involved in cancer
   1. Mutations involving proto-oncogenes
      a. Proto-oncogenes are involved in normal growth and repair.
      b. Functions of proto-oncogene protein products include:
         • Synthesis of growth factors, growth factor receptors, signal transducers, and nuclear transcribers
      c. Mutations of proto-oncogenes cause *sustained activity* of the genes (Table 9-3; Fig. 9-9).
   2. Mutations involving suppressor genes (antioncogenes)
      a. Suppressor genes protect against unregulated cell growth.
### Table 9-3 Some Proto-oncogenes and Their Functions, Mutations, and Associated Cancers

<table>
<thead>
<tr>
<th>PROTO-ONCOGENE</th>
<th>FUNCTION</th>
<th>MUTATION</th>
<th>CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABL</strong> (see Fig. 9-9)</td>
<td>Nonreceptor tyrosine kinase activity</td>
<td>Translocation t(9;22); forms fusion gene (BCR-ABL)</td>
<td>Chronic myelogenous leukemia (chromosome 22 with the translocation in the Philadelphia chromosome), acute lymphoblastic leukemia</td>
</tr>
<tr>
<td><strong>ERBB2</strong> (also called Her-2/Neu)</td>
<td>Receptor synthesis</td>
<td>Amplification or overexpression</td>
<td>Breast carcinoma (marker of aggressiveness; amplified or overexpression in 25% of breast cancers)</td>
</tr>
<tr>
<td><strong>C-MYC</strong> (see Fig. 9-10)</td>
<td>Nuclear transcription</td>
<td>Translocation t(8;14)</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td><strong>N-MYC</strong></td>
<td>Nuclear transcription</td>
<td>Amplification</td>
<td>Neuroblastoma, small cell carcinoma of lung</td>
</tr>
<tr>
<td><strong>RAS</strong></td>
<td>Guanosine triphosphate signal transduction</td>
<td>Point mutation</td>
<td>Accounts for 15%–20% of all cancers; pancreatic carcinomas (90%); ~50% of endometrial, colon, thyroid cancers; 30% lung adenocarcinoma and myeloid leukemias; bladder cancer; infrequent in breast and cervical cancer</td>
</tr>
<tr>
<td><strong>RET</strong></td>
<td>Receptor synthesis</td>
<td>Point mutation</td>
<td>Multiple endocrine neoplasia lla/llb syndromes; leukemia</td>
</tr>
<tr>
<td><strong>SIS (PBGFB)</strong></td>
<td>Growth factor synthesis</td>
<td>Overexpression</td>
<td>Osteogenic sarcoma, astrocytoma</td>
</tr>
</tbody>
</table>

**9-9**: The Philadelphia chromosome translocation, t(9;22). The Philadelphia chromosome (Ph1) is the derivative of chromosome 22, which has exchanged part of its long arm for a segment of material from chromosome 9q that contains the ABL oncogene (nonreceptor tyrosine kinase). Formation of the BCR-ABL fusion gene on the Ph1 chromosome is the critical genetic event in the development of chronic myelogenous leukemia. (From Nussbaum R, McInnes R, Willard H: Thompson & Thompson Genetics in Medicine, 7th ed, Philadelphia, Saunders Elsevier, 2007, p 466, Fig. 16-4.)

**9-10**: Translocation of the MYC oncogene from chromosome 8 to chromosome 14 activates the MYC oncogene and produces Burkitt lymphoma. The immunoglobulin (Ig) gene juxtaposed to the MYC gene on chromosome 14 acts as a promoter. (Adapted from Kumar V, Abbas AK, Fausto N, Aster JC: Robbins and Cotran Pathologic Basis of Disease, 8th ed, Philadelphia, Saunders, 2010.)

**Mutations in suppressor genes → unregulated cell growth**

**BCL2** gene family: antiapoptosis genes; prevent cytochrome c from leaving mt

**t(14;18) translocation in B cells: overexpression mutation → B cell follicular lymphoma**

b. Main sites of control in the cell cycle are the G1 to S phase and nuclear transcription (refer to Chapter 3).

c. Mutations cause **unregulated cell proliferation** (Table 9-4).

3. Mutations involving antiapoptosis genes; **BCL2** family of genes (refer to Chapter 3)

a. **BCL2** gene family located on chromosome 18 produces gene products that prevent mitochondrial (mt) leakage of cytochrome c (antiapoptosis gene).
   - Cytochrome c in the cytosol activates caspases initiating apoptosis.

b. Translocation t(14;18) in B cells causes an overexpression type of mutation of the **BCL2** protein product.
   - Prevents apoptosis of B lymphocytes (cytochrome c cannot enter the cytosol), which produces a B-cell follicular lymphoma (refer to Chapter 14).
TABLE 9-4 Some Tumor Suppressor Genes, Their Functions, and Associated Cancers

<table>
<thead>
<tr>
<th>GENE</th>
<th>FUNCTION</th>
<th>ASSOCIATED CANCERS 1</th>
</tr>
</thead>
</table>
| APC        | Prevents nuclear transcription (degrades catenin, an activator of nuclear transcription) | Inherited mutation (AD): familial polyposis (colorectal carcinoma)  
Somatic mutations: colon and stomach cancer     |
| BRCA1/BRCA2| Regulates DNA repair                         | Inherited mutation: female breast, ovary carcinomas; carcinoma male breast |
| NF1        | Inhibits RAS signal transduction; cell cycle inhibitor | Inherited mutation (AD): neurofibromatosis type 1: pheochromocytoma, Wilms tumor, neurofibrosarcomas  
Somatic mutation: neuroblastoma                  |
| NF2        | Cytoskeletal stability                       | Inherited mutation (AD): neurofibromatosis type II: bilateral acoustic neuromas (schwannoma), meningioma  
Somatic mutation: schwannoma, meningioma         |
| p53        | Inhibits G1 to S phase                       | Inherited mutation (AD): Li-Fraumeni syndrome: breast carcinoma, brain tumors, leukemia, sarcomas  
Somatic mutation: most human cancers (p53 gene is the most common gene producing cancer) |
| RB1        | Inhibits G1 to S phase                       | Inherited mutation (AD): retinoblastoma, osteogenic sarcoma  
Somatic mutation: retinoblastoma, osteogenic sarcoma, carcinomas of breast, lung, colon  |
| TGF-β      | Inhibits G1 to S phase                       | Inherited mutation: familial stomach cancer  
Somatic mutation: pancreatic and colorectal carcinomas     |
| VHL        | Regulates nuclear transcription              | Inherited mutation (AD): von Hippel–Lindau syndrome: cerebellar hemangioblastoma, retinal angioma, renal cell carcinoma (bilateral), pheochromocytoma (bilateral)  |
| WT1        | Regulates nuclear transcription              | Inherited mutation (AD): Wilms tumor  
Sporadic mutation: Wilms tumor                    |

AD, Autosomal dominant; APC, adenomatous polyposis coli; BRCA, breast cancer; RB1, retinoblastoma; TGF-β, transforming growth factor β; VHL, von Hippel–Lindau; WT1, Wilms tumor.

4. Mutations involving DNA repair genes (see Tables 9-1 and 9-4)
   a. Examples of DNA repair
      (1)Mismatch repair genes produce proteins that correct errors in nucleotide pairing.
          • Associated with hereditary nonpolyposis colon cancer syndrome (Lynch syndrome; see Table 9-1)
      (2)Nucleotide excision repair pathway removes pyrimidine dimers in UV-damaged skin (Fig. 9-11).
   b. Effect of mutations involving DNA repair genes
      • Mutations in repair genes, allows cells with nonlethal damage to proliferate, which increases the risk for cancer.

V. Carcinogenic Agents
   A. Chemical carcinogens (Table 9-5; refer to Chapter 7)
      1. Polycyclic hydrocarbons in tobacco smoke
         • Most common group of carcinogens in the United States
      2. Mechanism of action
         a. Direct-acting carcinogens
            • Contain electron-deficient atoms that react with electron-rich atoms in DNA (e.g., alkylating agents, nickel)
         b. Indirect-acting carcinogens
            (1) Require metabolic conversion to a carcinogen before they become active
            (2) For example, polycyclic hydrocarbons from cigarette smoke, smoked meats, or meats cooked at a high temperature over an open flame are metabolized in the liver cytochrome P-450 system and converted into DNA-binding epoxides that are carcinogenic.
      3. Sequence of chemical carcinogenesis
         a. Initiation
            (1) Produces an irreversible mutation
            (2) Examples of initiators include ionizing radiation, UVB light, nitrosamines, asbestos, polycyclic hydrocarbons, and HPV.
         b. Promotion
            (1) Stimulate mutated cells to enter the cell cycle
            (2) Cannot induce cancer on their own
            (3) Example of promoter—estrogen

   Repair genes: correct errors nucleotide pairing; excise pyrimidine dimers

   Enzymes in DNA repair: endonuclease, exonuclease, polymerase, ligase

   Mutations DNA repair genes: allow cells with nonlethal damage to proliferate

   Polycyclic hydrocarbons in tobacco smoke MC carcinogen

   Direct-acting carcinogens react with DNA (e.g., alkylating agents)

   Indirect-acting carcinogens require metabolic conversion (e.g., polycyclic hydrocarbons)

   Chemical carcinogenesis: initiation → promotion → progression

   Initiation: irreversible mutation; e.g., ionizing radiation

   Promotion: proliferation mutated cell; promoters (e.g., estrogen) cannot induce cancer
### Table 9-5 Chemical Carcinogens

<table>
<thead>
<tr>
<th>CARCINOGEN</th>
<th>MEANS OF EXPOSURE/SOURCES</th>
<th>ASSOCIATED CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxin (from Aspergillus)</td>
<td>Ingestion of maize and peanuts grown in hot/humid climates</td>
<td>Hepatocellular carcinoma in association with hepatitis B virus</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Oncology chemotherapy</td>
<td>Malignant lymphoma</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Herbicides (common in vineyard workers), fungicides, animal dips; metal smelting; intentional/accidental poisoning</td>
<td>Squamous cell carcinoma of skin, lung cancer, liver angiosarcoma</td>
</tr>
<tr>
<td>Azo dyes</td>
<td>Used in paints, printing inks, varnishes, leather products, carpets, food products</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Roofing material (roofers with over 20 years of experience have had contact with this); insulation for pipes in ships in shipyards, old homes; old cars with brake liners</td>
<td>Bronchogenic carcinoma (most common), pleural mesothelioma</td>
</tr>
<tr>
<td>Benzene</td>
<td>Component of light oil; used in printing industry, dry cleaning, paint, adhesives and coatings</td>
<td>Acute leukemia, Hodgkin lymphoma</td>
</tr>
<tr>
<td>Beryllium</td>
<td>Used in the space industry (missile fuel and space vehicles; metal alloys in aerospace appliances and nuclear reactors)</td>
<td>Bronchogenic carcinoma</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Industrial industries where ore is being smelted; electroplating; welders who have welded on cadmium-containing alloys or worked with silver solders; found in some batteries</td>
<td>Prostate and lung cancer</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Chemotherapy agent</td>
<td>Transitional cell carcinoma of urinary bladder</td>
</tr>
<tr>
<td>Diethylstilbestrol (DES)</td>
<td>Once used to treat women with threatened abortions</td>
<td>Daughters exposed to mothers who took DES may develop clear cell carcinoma of vagina/cervix</td>
</tr>
<tr>
<td>β-Naphthylamine (aniline dyes) and aromatic amines</td>
<td>Workers in the rubber, chemical, leather, textile, metal, and printing industries</td>
<td>Transitional cell carcinoma of urinary bladder</td>
</tr>
<tr>
<td>Nickel</td>
<td>Nickel plating, by-product of stainless steel welding, ceramics, batteries, spark plugs</td>
<td>Bronchogenic carcinoma, nasal cavity cancer</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Birth control pill</td>
<td>Breast and cervical cancer; hepatic adenoma (tendency to rupture)</td>
</tr>
<tr>
<td>Polycyclic hydrocarbons</td>
<td>These are formed when coal, soot (chimney sweeper), wood, gasoline, oil, tobacco, or other organic materials are burned; also formed in food when fish or meats are charbroiled on an open flame</td>
<td>Squamous cell carcinoma: skin (scrotum with soot in chimney sweeper), oral cavity, midesophagus, larynx, lung Adenocarcinoma: distal esophagus, pancreas, kidney Transitional cell carcinoma: urinary bladder, renal pelvis</td>
</tr>
<tr>
<td>Polyvinyl chloride</td>
<td>Found in plastic piping material, adhesive plastics, refrigerant</td>
<td>Liver angiosarcoma</td>
</tr>
<tr>
<td>Radon and decay products</td>
<td>By-product of decay of uranium, hazard in quarries and underground mines</td>
<td>Bronchogenic carcinoma</td>
</tr>
<tr>
<td>Silica</td>
<td>Chemical of silicon dioxide, rock quarries, sandblasting</td>
<td>Bronchogenic carcinoma</td>
</tr>
</tbody>
</table>

**Progression:**
- Development of tumor heterogeneity
- Example—clonal production of cells that invade or metastasize (see Fig. 9-5)

**B. Microbial agents**
1. Oncogenic viruses (Table 9-6)
2. Oncogenic bacteria
   - Examples—stomach cancer and low-grade malignant lymphoma due to *H. pylori*
3. Oncogenic parasites
   a. *Schistosoma haematobium*
   b. *Clonorchis sinensis* and *Opisthorchis viverrini*
   - Cause cholangiocarcinoma of the bile ducts (refer to Chapter 19)

**C. Radiation**
1. Ionizing radiation–induced cancers
   a. Mechanism
      - Produces hydroxyl free radical injury of DNA
b. Examples

(1) Acute myeloblastic leukemia (AML) and chronic myelogenous leukemia (CML)
- Increased risk of leukemia in radiologists and individuals exposed to radiation in nuclear reactors
(2) Papillary thyroid carcinoma
(3) Lung, breast, and bone cancers
(4) Liver angiosarcoma
- Due to radioactive thorium dioxide used to visualize the arterial tree

2. UVB light–induced cancers
a. Mechanism
- Produces pyrimidine dimers that distort DNA structure (Fig. 9-11)

2. UVB light–induced cancers
a. Mechanism
- Produces pyrimidine dimers that distort DNA structure (Fig. 9-11)

b. BCC (see Fig. 25-8B), SCC (see Fig. 25-8D), and malignant melanoma (see Fig. 25-6H)

D. Physical injury
1. SCC may develop in third-degree burn scars.
2. SCC may develop at the orifices of chronically draining sinuses (e.g., chronic osteomyelitis).

VI. Clinical Oncology
A. Host defenses against cancer (refer to Chapter 4)
1. Humoral immunity
- Involves antibodies and complement

Leukemia: MC cancer due to ionizing radiation; AML/CML

Ionizing radiation: papillary cancer thyroid; lung, breast, bone cancers; liver angiosarcoma

UVB light produces pyrimidine dimers that distort DNA

BCC: MC cancer due to excessive UV light exposure; others—SCC, melanoma

SCC: 3rd-degree burn scars; orifice of draining sinus

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### Table 9-6 Oncogenic RNA and DNA Viruses

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>MECHANISM</th>
<th>ASSOCIATED CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>Produces postnecrotic cirrhosis</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>Activates TAX gene, stimulates polyclonal T-cell proliferation, inhibits p53 suppressor gene</td>
<td>T-cell leukemia and lymphoma</td>
</tr>
<tr>
<td><strong>DNA Viruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>Promotes polyclonal B-cell proliferation, which increases risk for t(8;14) translocation</td>
<td>Burkitt lymphoma, CNS lymphoma in AIDS, mixed cellularity Hodgkin lymphoma, nasopharyngeal carcinoma</td>
</tr>
<tr>
<td>HBV</td>
<td>Activates proto-oncogenes, inactivates p53 suppressor gene</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Acts via cytokines released from HIV and HSV</td>
<td>Kaposi sarcoma in AIDS</td>
</tr>
<tr>
<td>HPV types 16 and 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 16 (~50% of cancers): E6 gene product inhibits p53 suppressor gene</td>
<td>Squamous cell carcinoma of vulva, vagina, cervix, anus (associated with anal intercourse), larynx, oropharynx</td>
<td></td>
</tr>
<tr>
<td>Type 18 (~10% of cancers): E7 gene product inhibits RB1 suppressor gene</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EBV,** Epstein-Barr virus; **HBV,** hepatitis B virus; **HCV,** hepatitis C virus; **HHV,** human herpesvirus; **HPV,** human papillomavirus; **HSV,** herpes simplex virus; **HTLV,** human T-cell lymphotropic virus.

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9-11: Excision-repair mechanism of a thymidine dimer. (Modified from McKee PH, Calonje E, Granter SR: Pathology of the Skin with Clinical Correlations, 3rd ed, St. Louis, Elsevier Mosby, 2005, p 1228, Fig. 22.193.)
2. Type IV cell-mediated immunity (CMI)
   a. Most efficient mechanism for killing cancer cells
   b. Cytotoxic CD8 T cells
      - Recognize altered class I antigens on neoplastic cells and destroy them
3. Natural killer (NK) cells
   - Directly kill malignant cells (type IV hypersensitivity) or use indirect killing of cells via type II hypersensitivity reactions
4. Macrophages kill cancer cells; however, they are not as effective a host defense as cytotoxic T cells and NK cells.

B. Grading and staging of cancer

1. Grading criteria for cancer
   a. Degree of differentiation (e.g., low, intermediate, or high grade [anaplastic]; see II.B.2.)
   b. Nuclear features, invasiveness
2. Staging criteria
   a. Most important prognostic factor for survival
   b. TNM system for staging cancer
      (1) TNM progresses from the least to the most important prognostic factor.
      (2) T refers to tumor size.
         - Malignant tumor ≥2 cm inherently able to metastasize
      (3) N refers to whether lymph nodes are involved.
      (4) M refers to extranodal metastases (e.g., liver, lung).
         - For a carcinoma to reach M, it already has passed through N (lymph nodes) and spread to other organ sites via the bloodstream.
         - If there are no extranodal metastases, then N (lymph nodes) is the most important prognostic factor for survival.

C. Cancer effects on the host

1. Cachexia (wasting disease)
   a. Epidemiology
      (1) Very common complication of disseminated cancer (weight loss syndrome)
      (2) Definition—generalized catabolic reaction that is associated with anorexia, muscle wasting, loss of subcutaneous fat, and fatigue
      (3) Accounts for ~30% of deaths due to cancer
   b. Pathogenesis
      (1) Cancer cells release cachectic agents, which include:
         (a) Proteolysis-inducing factor (PIF)
         (b) Lipolysis-mobilizing factor (LIF)
      (2) PIF uses NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) to activate the ubiquitin-proteasome pathway (refer to Chapter 2).
         - Activation of this pathway causes degradation of myosin heavy chains in skeletal muscle.
      (3) LIF has multiple functions
         (a) Activates hormone-sensitive lipase in adipose cells, which reduces body fat and increases free fatty acids
         (b) Increases release of TNF from macrophages and monocytes
            - Suppresses the appetite center in the hypothalamus, which leads to weight loss.
            - Stimulates apoptosis (refer to Chapter 2)
2. Anemia in cancer (refer to Chapter 12)
   a. Anemia of chronic disease (ACD) is the most common anemia in malignancy.
   b. Iron deficiency is most often due to gastrointestinal blood loss (e.g., colorectal cancer).
   c. Macrocytic anemia is most often due to folic acid deficiency from rapid tumor growth and use of folic acid for DNA synthesis.
   d. Cold autoimmune hemolytic anemia (AIHA) due to IgM cold agglutinins produced by chronic lymphocytic leukemia (CLL) or certain types of malignant lymphoma
   e. Myelophthisic anemia
      (1) Definition—metastasis to bone and replacement of normal marrow with malignant cells and/or fibrosis
      (2) Presence of immature, normal hematopoietic cells in the peripheral blood (i.e., leukoerythroblastic smear; see Fig. 13-1)
         (a) Nucleated RBCs, immature neutrophils (e.g., metamyelocytes) are present in peripheral blood.
         (b) Presence of teardrop RBCs indicate that myelofibrosis secondary to bone metastasis has occurred.
3. Hemostasis abnormalities (refer to Chapter 15)
   a. Increased risk for vessel thrombosis in malignancy
      (1) Due to thrombocytosis and/or increased synthesis of coagulation factors (e.g., fibrinogen, factors V and VIII).
      (2) Due to release of procoagulants from cancer cells (e.g., pancreatic carcinoma)
   b. Disseminated intravascular coagulation (DIC)
      • Due to excessive release of tissue thromboplastin from cancer cells, which activates the coagulation system to form fibrin clots in microcirculation (refer to Chapter 15).
4. Fever in malignancy
   a. Most often due to infection rather than pyrogens secreted from cancer cells
   b. Gram-negative sepsis from *Escherichia coli* or *Pseudomonas aeruginosa* is a common cause of death in cancer (refer to Chapter 5).
5. Paraneoplastic syndromes
   a. Definition—distant effects of a tumor unrelated to metastasis
      • May predate the onset of metastasis
   b. Occur in 10% to 15% of cancer patients
   c. Involve multiple organ systems and mimic metastatic disease (Table 9-7; Fig. 9-12)
   d. May ectopically secrete hormones (Table 9-8)

**D. Tumor markers (biomarkers) in cancer**
1. Biological markers of cancer (Table 9-9)
   • Markers include hormones, enzymes, oncofetal antigens, immunoglobulins, and glycoproteins.
**TABLE 9-8 Paraneoplastic Syndrome Endocrinopathies**

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>ASSOCIATED CANCER</th>
<th>ECTOPIC HORMONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing syndrome</td>
<td>Small cell carcinoma of lung, medullary carcinoma of thyroid, pancreatic cancer</td>
<td>ACTH</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Choriocarcinoma (testis), seminoma</td>
<td>hCG</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Renal cell carcinoma, primary squamous cell carcinoma of lung, breast carcinoma, adult T-cell leukemia/lymphoma Malignant lymphomas (contain 1α-hydroxylase)</td>
<td>PTH-related protein Calcitriol (vitamin D)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Medullary carcinoma of thyroid</td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Hepatocellular carcinoma, ovarian carcinoma, fibrosarcoma</td>
<td>Insulin-like factor</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Small cell carcinoma of lung</td>
<td>Antidiuretic hormone</td>
</tr>
<tr>
<td>Secondary polycythemia</td>
<td>Renal cell carcinoma, hepatocellular carcinoma, cerebellar hemangioma</td>
<td>Erythropoietin</td>
</tr>
</tbody>
</table>

ACTH, Adrenocorticotropic hormone; hCG, human chorionic gonadotropin; PTH, parathyroid hormone.

**TABLE 9-9 Tumor Markers and Associated Cancers**

<table>
<thead>
<tr>
<th>TUMOR MARKER</th>
<th>ASSOCIATED CANCER</th>
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</thead>
<tbody>
<tr>
<td>AFP</td>
<td>Hepatocellular carcinoma, yolk sac tumor (endodermal sinus tumor) of ovary or testis</td>
</tr>
<tr>
<td>Bence Jones protein</td>
<td>Multiple myeloma, Waldenström macroglobulinemia (represent light chains in urine)</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>CA19-9</td>
<td>Pancreatic, colorectal carcinomas</td>
</tr>
<tr>
<td>CA125</td>
<td>Surface-derived ovarian cancer (e.g., serous cystadenocarcinoma; helpful in distinguishing benign from malignant tumors)</td>
</tr>
<tr>
<td>CEA</td>
<td>Colorectal and pancreatic carcinomas (monitor for recurrences); cancers of lung, stomach, heart</td>
</tr>
<tr>
<td>LDH</td>
<td>Malignant lymphoma (prognostic factor for response to standard therapy)</td>
</tr>
<tr>
<td>Neuron specific enolase</td>
<td>Small cell carcinoma of lung</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate carcinoma (also increased in prostate hyperplasia)</td>
</tr>
</tbody>
</table>

AFP, α-Fetoprotein; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

Cytokeratin +: epithelial tissue origin  
Vimentin +: connective tissue origin  
CD45 +: malignant lymphoma  
Markers: Dx cancer, estimate tumor burden, detect recurrences, follow tumor response to therapy

2. Pathologists use special stains and techniques that help define different types of cancer.  
   a. Cytokeratin stain positive—epithelial tissue origin  
   b. Vimentin stain positive—connective tissue origin  
   c. CD45 positive—malignant lymphoma.  
3. Tumor markers are used to diagnose cancer, estimate tumor burden, detect recurrences, and indicate tumor response to treatment.
I. Lipoprotein Disorders
   A. Lipoprotein fractions
      1. Chylomicrons
         a. Transport \textit{diet-derived} triglycerides (TGs) in the blood
            • Absent during fasting
         b. Composition
            (1) Protein (2%)
            (2) TG (87%)
            (3) Cholesterol (CH; 3%)
            (4) Phospholipid (8%)
         c. Formation in the small intestine
            (1) Enterocytes lining the villi reabsorb monoglycerides and fatty acids (FAs), which are then converted into TG in the cytosol (refer to Chapters 8 and 18).
            (2) TG is packaged into a chylomicron, which requires apolipoprotein (apo) B48 for assembly and secretion.
               • All lipoprotein fractions must be coated by protein so they can be carried in the water phase of plasma (Fig. 10-1).
            (3) Nascent (newly made) chylomicrons enter intestinal lymphatics that drain into the thoracic duct, which empties into the blood stream.
         d. Circulation phase (Fig. 10-2A)
            (1) Nascent chylomicrons obtain apoCII and apoE from high density lipoprotein (HDL) and become mature chylomicrons.
            (2) TG in chylomicrons is hydrolyzed by capillary lipoprotein lipase (CPL) into FAs and glycerol.
               • They are used to synthesize TGs in the liver (see later) and in adipose tissue, the latter location being a storage site for fat.
            (3) Hydrolysis of chylomicrons by CPL leaves \textit{chylomicron remnants}, which contain much less TG than mature chylomicrons.
               (a) Insulin is responsible for synthesis of CPL in the fed state.
               • CPL is located in capillaries in adipose, muscle, and myocardium.
               (b) ApoCII is responsible for activating CPL during the fed state.
            (4) Chylomicron remnants are removed from the circulation by apoE receptors in the liver.
      2. Very low density lipoprotein (VLDL) (see Fig. 10-2B)
         a. TG in the liver is synthesized by adding three FAs to glycerol 3-phosphate (G3P; refer to Chapter 2).
            • G3P is a three-carbon intermediate of glucose metabolism.
         b. With the aid of apoB100, TG is packaged into VLDL and secreted into blood as nascent VLDL.
         c. Composition
            (1) Protein (9%)
            (2) TG (55%)
10-1: Lipoprotein structure. Lipoproteins are spherical particles with a hydrophobic core and an amphophilic surface. The surface consists of a single layer of phospholipids. This surface layer also contains proteins and free cholesterol. The hydrophobic core mainly contains triglycerides and cholesterol esters. (From McPherson, R, Pincus, M: Henry’s Clinical Diagnosis and Management by Laboratory Methods, 21st ed, Philadelphia, Saunders, 2007, p 227, Fig. 17-1.)

10-2: Schematics of lipid metabolism and hyperlipoproteinemias. A, Chylomicron metabolism. Chylomicrons are synthesized in the enterocytes of the small intestine and enter the circulation with apoB48 (nascent chylomicron). HDL puts apoCII and apoE on the surface and they are now mature chylomicrons. CPL hydrolyzes TG in the mature chylomicron releasing FAs and glycerol. The chylomicron remnant is removed by apoE receptors in the liver. Deficiency of apoE produces a type III hyperlipoproteinemia (chylomicron remnants accumulate). B, VLDL, IDL, LDL, and HDL metabolism. Nascent VLDL (liver-synthesized TGs), when it enters the circulation from synthesis in the liver, has apoCII and apoE tags placed by HDL. When CPL is activated by apoCII, it hydrolyzes the TG in VLDL, and as it loses FAs and glycerol, it becomes IDL, a remnant of VLDL. LDL is the primary carrier of cholesterol. Most tissue cells have receptors for LDL, because they all need cholesterol for cell membrane synthesis, or in some cases, for hormone synthesis (e.g., vitamin D and adrenal cortex hormones). CEPT transfers TG to HDL in exchange for CH from HDL. This lowers HDL-CH and the amount of CH that can be taken up by the liver and excreted or converted into bile salts/acids. Hence the higher the VLDL, the lower the HDL-CH level, which increases the risk for coronary artery disease. CEPT, Cholesterol ester transport protein; CH, cholesterol; CPL, capillary lipoprotein lipase; HDL, high density lipoprotein; IDL, intermediate density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; VLDL, very low density lipoprotein. (From Pelley J, Goljan F: Rapid Review Biochemistry, 2nd ed, Philadelphia, Mosby, 2007, pp 126, 127, Figs. 7-8, 7-9, respectively.)
(3) CH (17%)
(4) Phospholipid (19%)
d. VLDL is a source of FAs and glycerol.
(1) TG in VLDL is hydrolyzed by CPL into FAs and glycerol.
  • They are used to synthesize TGs in the liver (see later) and adipose tissue.
(2) Hydrolysis of nascent VLDL by CPL first produces intermediate density lipoprotein (IDL), and further hydrolysis produces low density lipoprotein (LDL).
(3) Some of the IDL is removed from blood by apo E receptors in the liver.
e. Cholesterol ester transport protein (CETP)
(1) Transfers CH from HDL to VLDL and TG from VLDL to HDL.
  • This interferes with HDL’s main function of transferring CH from peripheral tissue to the liver for excretion in bile or synthesis of bile salts/acid.
(2) Increase in VLDL always causes a decrease in HDL-CH, which explains why increased VLDL is a risk for coronary artery disease.
f. VLDL concentration is calculated with the following formula: VLDL = TG / 5
g. Clinically important serum TG levels
(1) Optimal level: <150 mg/dL
(2) Borderline high level: 150 to 199 mg/dL
(3) High level: 200 to 499 mg/dL
(4) Very high level: >500 mg/dL
3. Causes of increased plasma turbidity (Fig. 10-3).
a. Increased turbidity, or a milky appearance of plasma, is due to very high levels of TGs in the serum (usually >1000 mg/dL).
b. Increase in serum TG is due to an increase in chylomicrons and/or VLDL.
c. Standing chylomicron test distinguishes which lipoprotein component is increased.
   (1) A test tube is left upright in a refrigerator overnight to give the TG a chance to settle, based on the density of the lipoprotein (percent protein) that is present.
   (2) If in the morning, milky material is floating on the surface of the plasma (supranate), chylomicrons are increased.
     • Person did not fast before the lipid study (most common cause) or has a type I hyperlipoproteinemia (discussed later).
VLDL: turbid infranate; more protein than chylomicrons

LDL: derives from VLDL; transports CH

Small dense LDL particles: Risk for atherosclerosis, CAD

HDL-CH: “good CH”

Fasting not required for accurate serum CH

The intensity of treatment to lower CH is directly related to the degree of risk for coronary heart disease (CHD). Risk groups include high risk, moderately high risk, moderate risk, and low risk. The risk factors include age (male >45 years, female ≥55 years); family history of premature CHD (e.g., family member with myocardial infarction before 55 years of age); LDL >160 mg/dL; current cigarette smoking; blood pressure ≥140/90 mm Hg (or on antihypertensive medicine); and HDL <40 mg/dL (if ≥60 mg/dL, subtract 1).

4. Low density lipoprotein (LDL) (see Fig. 10-2B)
   a. Transports CH in the blood
   b. Derives from continued hydrolysis of IDL by CPL
   c. Removed from blood by LDL receptors in peripheral tissue
   d. Small, dense LDL particles
      (1) Associated with increased atherosclerosis risk and coronary artery disease (CAD)
          • Small particle size allows them to penetrate endothelium easier
      (2) Increased in diets that are high in carbohydrates
   e. Composition
      (1) Protein (22%)
      (2) TG (10%)
      (3) CH (47%)
      (4) Phospholipid (21%)
   f. Calculated LDL = CH – HDL – TG ÷ 5 (VLDL)
      (1) Chylomicrons falsely lower the calculated LDL by increasing diet-derived TG; therefore fasting is required for an accurate calculated LDL.
      (2) Chylomicrons falsely increase the calculated VLDL.
   g. Functions of CH
      (1) Major component of the cell membrane
      (2) Synthesis of vitamin D, adrenal cortex hormones (e.g., cortisol), and bile salts and acids in the liver
   h. Clinically important serum LDL levels
      (1) Optimal level <100 mg/dL
          • Risk for coronary heart disease (CHD) is markedly reduced
      (2) Near optimal level: 100 to 129 mg/dL
      (3) Borderline high level: 130 to 159 mg/dL
      (4) High level: 160 to 189 mg/dL
      (5) Very high level: >190 mg/dL
          • Greatest risk for CH
   i. Fasting is not required for an accurate serum CH.
      • CH content in chylomicrons is <3%; therefore fasting does not have a medically significant effect on serum level.

5. High density lipoprotein (HDL) (see Fig. 10-2B)
   a. Factors that increase HDL (“good cholesterol”)
      (1) Nicotinic acid, exercise
          • Nicotinic acid is the best lipid lowering agent for increasing HDL.
      (2) Dietary alterations are not effective
   b. Composition
      (1) Protein (50%)
      (2) TG (3%; unless VLDL is increased)
      (3) CH (20%)
      (4) Phospholipid (27%)
   c. Synthesized by the liver and small intestine
   d. Functions
      (1) Source of apolipoproteins (apoE, apoCII) for other lipoprotein fractions
      (2) Removes CH from fatty streaks and atherosclerotic plaques
          (a) HDL delivers CH from peripheral tissue to the liver.
          (b) CH is either excreted into bile or converted into bile acids/salts.
e. Laboratory measurement
   (1) Reported as HDL-CH
   (2) Increased HDL-CH, decreased risk for CHD
   (3) Decreased HDL-CH if VLDL increased (see I.A.2.e.)
   (4) Ranges of HDL-CH
      (a) High level (optimal): >60 g/dL
      (b) Low level (suboptimal): <40 mg/dL

B. Lipoprotein disorders (Table 10-1; Fig. 10-4)

<table>
<thead>
<tr>
<th>TYPE</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| Type I | Familial chylomicronemia: AR inheritance, childhood disease  
Pathogenesis: deficiency of CPL or apoCII (normally activates CPL)  
Chylomicrons are primarily increased in early childhood. VLDL also increases later in life.  
Clinical findings: presents with acute pancreatitis (chylomicrons block the circulation and cause rupture of pancreatic vessels)  
Laboratory findings: increase in serum CH (>1000 mg/dL; primarily chylomicrons). Turbid supranate (chylomicrons) and clear infranate with refrigeration. Normal (usual case) to moderately increased serum CH. |

| Type II | Type IIa: increase in serum CH (>260 mg/dL) and LDL (>190 mg/dL). Serum TG <300 mg/dL.  
Type IIb: increase in serum CH (>260 mg/dL) and LDL (>190 mg/dL). Serum TG >300 mg/dL.  
Acquired causes of type II hyperlipoproteinemia  
Primary hypothyroidism: decreased synthesis of LDL receptors  
Blockage of bile flow: bile contains CH  
Nephrotic syndrome: increased liver synthesis of CH  
Genetic causes of type II hyperlipoproteinemia  
Polygenic hypercholesterolemia (type IIa): most common type (85% of cases). Multifactorial (polygenic) inheritance. Alteration in regulation of LDL levels with primary increase in serum LDL and TG <300 mg/dL.  
Familial combined hypercholesterolemia (type IIb): AD inheritance. CH and TG begin to increase around puberty. Associated with metabolic syndrome (refer to Chapter 23). Increase in CH and TG >300 mg/dL. Decrease in HDL.  
Familial hypercholesterolemia (type IIa): AD inheritance. Deficiency of LDL receptors. Achilles tendon xanthoma (diagnostic; see Fig. 10-4A), xanthelasma (yellow plaques on eyelid; see Fig. 10-4B). Premature CAD and stroke. Increase in serum CH and HDL. Serum TG <300 mg/dL. Decrease in HDL. |

| Type III | Familial dysbetalipoproteinemia or “remnant disease”: AR inheritance  
Pathogenesis: deficiency of apoE. Decreased liver uptake of IDL and chylomicron remnants.  
Palmar xanthomas in flexor creases (see Fig. 10-4C). Increased risk for CAD and peripheral vascular disease.  
Both serum CH and LDL >300 mg/dL. LDL <190 mg/dL. Confirm diagnosis with ultracentrifugation to identify remnants, lipoprotein electrophoresis, identify apoE gene defect. |

| Type IV | Acquired causes of type IV hyperlipoproteinemia  
Excess alcohol intake: most common cause; increased production of VLDL, decreased activity of CPL.  
Oral contraceptives: estrogen increases synthesis of VLDL.  
Diabetes mellitus: decreased adipose and muscle CPL (decreased VLDL clearance; decreased insulin responsible for decreased synthesis of CPL). Increased LDL; decreased HDL.  
Chronic renal failure: increased synthesis of VLDL and decreased clearance of VLDL.  
Thiazide diuretics, β-blockers: inhibition of CPL (decreases clearance of VLDL).  
Familial hypertriglyceridemia: AD inheritance. Most common hyperlipoproteinemia.  
Pathogenesis: increased production of VLDL (most common), decreased clearance of VLDL.  
Increased risk for CAD and peripheral vascular disease.  
Eruptive xanthomas (yellow, papular lesions; see Fig. 10-4D).  
Increase in TG (>300 mg/dL). Serum CH normal to moderately increased (250–500 mg/dL). Serum LDL <190 mg/dL. Decrease in HDL. Inverse relationship with VLDL. Turbid infranate after refrigeration. |

| Type V | Most commonly familial hypertriglyceridemia + an exacerbating disorder: e.g., diabetic ketoacidosis, alcoholism.  
Pathogenesis: increase in chylomicrons and VLDL due to decreased activation and release of CPL.  
Hyperchylomicronemia syndrome.  
Eruptive xanthomas (same as those in type IV).  
Increased incidence of acute pancreatitis.  
Lipemia retinalis: retinal vessels look like milk, blurry vision.  
Dyspnea and hypoxemia: impaired gas exchange in pulmonary capillaries.  
Hepatosplenomegaly  
Increase in serum TG (usually >1000 mg/dL). Normal serum CH and LDL.  
Turbid supranate and infranate after refrigeration. |

AD, Autosomal dominant; AR, autosomal recessive; CAD, coronary artery disease; CH, cholesterol; CPL, capillary lipoprotein lipase; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein.
II. Arteriosclerosis

A. Definition

- Thickening and loss of elasticity of arterial walls

B. Medial calcification

1. Definition—dystrophic calcification in the wall of muscular arteries
   a. Can be seen in plain radiographs
   b. Examples—calcification in uterine arteries and radial arteries

2. No clinical consequence unless it is associated with atherosclerosis

C. Atherosclerosis

1. Epidemiology
   a. More common in men than women
   b. Increases with age
   c. Risk factors
      (1) Hypertension (HTN)
         - Accelerates atherosclerosis by producing endothelial cell dysfunction
      (2) Diabetes mellitus (DM)
         (a) Associated with hyperlipidemias and HTN, which are risk factors for atherosclerosis

Nonpharmacologic treatment of type II hyperlipoproteinemia includes dietary modification, increasing activity with aerobic exercises, and cessation of smoking. Dietary modification consists of a low CH, low-fat diet (fat intake <30% of total caloric intake); polyunsaturated fat up to 10% of total calories; monounsaturated fat up to 20% of total calories; saturated fat <7% of total calories; no more than 200 mg/day of CH; and dietary fiber 20 to 30 g/day. Pharmacologic treatment includes HMG (Hydroxy Methyl Glutaryl)-CoA reductase inhibitors (“statins”; most effective); nicotinic acid (least expensive lipid-lowering agent; also decreases TG, and increases HDL greater than other drugs); bile salt sequestrants; and cholesterol absorption inhibitors.

Nonpharmacologic treatment of type IV hyperlipoproteinemia is to reduce alcohol intake and carbohydrate intake and increase intake of ω-3 fatty acids from fish, flaxseed oil, or other sources (up to 3 g/day). Pharmacologic therapy consists of nicotinic acid or fibric acid derivatives.
b. Associated with abnormalities of coagulation, platelet adhesion and aggregation, increased oxidative stresses, and functional changes in the endothelium

3. Cigarette smoking, hyperlipoproteinemias, previous *Chlamydia pneumoniae* infection (second most common cause of atypical pneumonia; refer to Chapter 17)

2. Pathogenesis (Fig. 10-5)

a. Due to endothelial cell damage of muscular and elastic arteries
   - Veins under increased pressure (e.g., pulmonary venous hypertension, saphenous veins used in coronary artery bypass) undergo atherosclerosis.

b. Causes of endothelial cell injury
   - Stress areas in the vasculature (e.g., bifurcations), HTN, smoking tobacco, homocysteine, oxidized LDL, small dense LDL

c. Cell response to endothelial injury (“reaction to injury” theory)
   - Macrophages infiltrate the intima, and platelets adhere to damaged endothelium.
     - (a) Platelets induce inflammatory responses in both leukocytes and endothelial cells.
     - (b) Platelet-mediated inflammatory responses occur even with the widespread use of platelet-inhibiting drugs.

2. Inflammatory cells release cytokines and growth factors (e.g., platelet-derived growth factor), the latter causing hyperplasia of smooth muscle cells (SMCs).

3. SMCs migrate to the tunica intima.

4. CH enters SMCs and macrophages, producing foam cells.
   - Grossly, these early lesions have the appearance of fatty streaks.

5. SMCs and macrophages release cytokines that produce extracellular matrix.
   - Matrix components include collagen, proteoglycans, and elastin.

d. Development of a fibrous plaque (cap)
   - Components include:
     - SMCs, foam cells, inflammatory cells, and extracellular matrix
   - Overlies a necrotic center
     - Necrotic center consists of cellular debris, CH crystals (slit-like spaces), and foam cells

Atherosclerosis: endothelial cell injury; platelets/macrophages pivotal roles

Endothelial injury: HTN, smoking, homocysteine, oxidized LDL

Macrophages infiltrate intima; release cytokines

Platelets induce inflammatory responses in leukocytes/endothelial cells

Foam cells: macrophages, SMCs with CH

Fibrous plaque: pathognomonic lesion atherosclerosis

Fibrous plaque overlies necrotic core
(3) Disrupted (inflammatory) plaques may extrude underlying necrotic material, which extends to the endothelial surface serving as a nidus for thrombus formation (see Fig. 5-15).

**Serum C-reactive peptide** (CRP) is increased in patients with disrupted (inflammatory) plaques (refer to Chapter 3). Plaques may rupture and produce vessel thrombosis, which leads to acute myocardial infarction (MI). CRP may be a stronger predictor of cardiovascular events than LDL.

(4) Frequently becomes dystrophically calcified and ulcerated (complicated plaque)

3. Sites (descending order)
   a. Abdominal aorta
   b. Coronary artery
   c. Popliteal artery
   d. Internal carotid artery

4. Complications
   a. Vessel weakness (e.g., vessel aneurysms; discussed later)
   b. Vessel thrombosis (platelet thrombus overlying atheromatous plaques; refer to Chapter 5)
      1. Acute MI (coronary artery; refer to Chapter 11)
      2. Stroke (internal carotid artery, middle cerebral artery; refer to Chapter 26)
      3. Small bowel infarction (superior mesenteric artery; refer to Chapter 26)
   c. Hypertension
      • Renal artery atherosclerosis may activate the renin-angiotensin-aldosterone system (discussed later), producing HTN.
   d. Cerebral atrophy
      • Atherosclerosis may involve circle of Willis vessels or internal carotid artery (refer to Chapter 26).
   e. Peripheral arterial disease (PAD)
      1. Epidemiology
         (a) Prevalence increases with age and is equal in men and women
         (b) Black Americans are at greater risk than white Americans
      2. Signs and symptoms
         (a) Claudication—pain (buttocks, hips, legs), weakness, numbness, or cramping in muscles due to decreased arterial blood flow
            • Symptoms just mentioned are often precipitated by walking and relieved by cessation of walking (similar to angina pectoris).
         (b) Sores, wounds, or ulcers that heal slowly
         (c) Danger of gangrene (dry and wet; see Fig. 2-15D and F)
         (d) Cool skin temperature
         (e) Diminished hair and nail growth on limb digits
         (f) Diminished pedal pulses, bruits over the femoral/popliteal arteries
         (g) Acute peripheral artery vessel occlusion—the five Ps:
            • Pain—shooting pain followed by numbness and weakness
            • Pallor—progresses from pale to a mottled cyanosis
            • Paresthesias—portends serious consequences if it rapidly progresses
            • Paralysis—weakness of dorsiflexion of the foot or toe (peroneal nerve distribution)
            • Pulselessness—below the area of occlusion
            • Other findings—collapsed superficial veins, cold skin

(3) Diagnosis
   (a) Measurement of the resting ankle-brachial index (ABI ratio <0.9 is consistent with PAD)
   (b) Angiography, duplex ultrasonography

(4) Treatment
   (a) Management of the risk factors for PAD
   (b) Revascularization surgical procedures
   (c) Cilostazol (platelet aggregation inhibitor)
D. Arteriolosclerosis
1. Definition—hardening of the arterioles
   • Two types—hyaline arteriolosclerosis and hyperplastic arteriolosclerosis
2. Hyaline arteriolosclerosis
   a. Pathogenesis
      • Increased protein is deposited in the vessel wall and occludes the lumen (Fig. 10-6).
   b. Causes
      (1) Diabetes mellitus
         (a) In poorly controlled diabetes, glucose combines with proteins in the basement membrane of arterioles, a process called nonenzymatic glycosylation (NEG).
         (b) NEG causes the basement membrane to leak proteins from the plasma into the vessel wall (pink-staining material on H&E stain).
      (2) Hypertension
         • Increased intraluminal pressure in arterioles pushes plasma proteins into the vessel wall.
3. Hyperplastic arteriolosclerosis
   a. Pathogenesis
      • Acute increase in blood pressure (e.g., malignant HTN) causes basement membrane duplication and smooth muscle hyperplasia in the renal arterioles (e.g., afferent and efferent arterioles).
   b. Renal arterioles have an "onion skin" appearance (see Fig. 20-7B).

III. Vessel Aneurysms
A. Definition
   • Weakening of the vessel wall, followed by dilation due to increased wall stress
B. Abdominal aortic aneurysm (AAA)
   1. Epidemiology
      a. Most common vessel aneurysm
      b. Usually occurs in men >60 years old (4:1 male/female ratio)
      c. Tenth leading cause of death in men >65 years old
      d. Usually located below the renal artery orifices
   2. Pathogenesis
      a. Atherosclerosis weakens the vessel wall.
         (1) Vessel wall stress increases with vessel diameter (law of Laplace).
         (2) Vessel lumen fills with atheromatous debris and blood clots (Fig. 10-7)
      b. Other factors—familial, structural defects in connective tissue, absence of vasa vasorum in abdominal aorta (vessel that supplies the blood vessel)
   3. Clinical findings
      a. Usually asymptomatic
      b. Pulsatile epigastric mass that may or may not be tender
      c. Bruit (harsh sound) is heard if renal artery stenosis or visceral arterial stenosis is present.
      d. Atherosclerotic plaques can chip off and embolize to distal extremities.
      e. Rupture is the most common complication; rupture triad is:
         (1) Sudden onset of severe left flank pain (bleed is initially retroperitoneal), followed by hypotension from blood loss into the retroperitoneum; and presence of a pulsatile mass on physical examination
         (2) Greatest predictor of rupture is the diameter of the aneurysm.
            • Surgical repair is beneficial for AAAs that are 5.0 to 5.4 cm in diameter.

10-6: Hyaline arteriolosclerosis. The arrow depicts eosinophilic material representing protein that has leaked through the basement membrane and deposited in the wall of an arteriole. Other neighboring arterioles demonstrate similar changes. Diabetes mellitus and hypertension are the most common causes.
(From Damjanov I, Linder J: Pathology: A Color Atlas. St. Louis, Mosby, 2000, p 32, Fig. 2-1A.)
4. Diagnosis
   a. Ultrasound is 100% accurate (excellent initial screen).
   b. CT scan is used preoperatively to localize extent into renal vessels and evaluate the integrity of the vessel wall to exclude rupture.
   c. Angiography gives detailed arterial anatomy.

5. Treatment
   • Endovascular or open surgery

C. Popliteal artery aneurysm
   1. Predominantly seen in males in >95% of cases
   2. Most common peripheral artery aneurysm
   3. Pulsatile mass behind the knee
   4. Treated surgically

D. Mycotic aneurysm
   1. Pathogenesis
      a. Definition—vessel wall weakening due to an infection
         • Does not have to be a fungal infection
      b. Fungi that commonly invade vessels and weaken them include:
         • Aspergillus, Candida, and Mucor
      c. Bacteria that invade vessels and weaken them include:
         • Bacteroides fragilis, Pseudomonas aeruginosa, and Salmonella species

2. Clinical findings
   a. Thrombosis with or without infarction
   b. Rupture

3. Treated surgically

E. Berry (saccular) aneurysm of cerebral arteries (also refer to Chapter 26)
   1. Epidemiology
      a. Definition—saccular dilatation typically found around the circle of Willis and base of the brain
      b. Risk factors
         (1) Normal hemodynamic stress
         (2) Presence of HTN of any cause
         (3) Coarctation of aorta
         (4) Atherosclerosis
      c. Most common site is at the junction of the communicating branches with the anterior cerebral artery (ACA)
2. Pathogenesis
   a. At the junction of the communicating branches with the main cerebral vessels, the vessel normally lacks an internal elastic lamina and smooth muscle (see Fig. 26-12A).
   b. Rupture of the aneurysm releases blood into the subarachnoid space or into the brain parenchyma (see Fig. 26-12B).
3. Clinical findings of ruptured aneurysm
   a. Sudden onset of severe occipital headache
      • Described as the "worst headache I ever had"
   b. Nuchal rigidity from irritation of the meninges
4. Complications of ruptured aneurysm
   a. Death occurring shortly after the bleed
   b. Rebleeding, hydrocephalus, neurologic deficits
5. Diagnosis of ruptured aneurysm
   • CT scan and angiography (definitive test)
6. Treatment is immediate surgical repair.

F. Syphilitic aneurysm

1. Epidemiology
   a. Complication of tertiary syphilis due to Treponema pallidum (spirochete)
   b. Usually occurs in men 40 to 55 years of age
2. Pathogenesis
   a. T. pallidum infects the vasa vasorum of the ascending and transverse portions of aortic arch (Fig. 10-8).
      (1) Vasculitis is called endarteritis obliterans.
      (2) Characteristic plasma cell infiltrate is present in the vessel wall.
      (3) Inflammation is intense and often occludes the lumen of the vessel.
   b. Vessel ischemia of the medial tissue leads to weakness and subsequent dilation of the aorta and aortic valve (AV) ring.
3. Clinical findings
   a. AV regurgitation (see shaded area)

**AV regurgitation** is a problem in closing the AV. Because the AV closes in diastole, the murmur occurs in early diastole as blood leaks back into the ventricle. The increase in left ventricular end-diastolic volume results in an increase in stroke volume (increased systolic pressure). Blood rapidly draining back into the left ventricle decreases the diastolic pressure. The wide pulse pressure (difference between the systolic and diastolic pressure) is manifested by a hyperdynamic circulation (e.g., pulsating uvula, bounding pulses). Excessive blood dripping back onto the anterior mitral valve (MV) leaflet produces another diastolic murmur called the Austin Flint murmur. This finding indicates the need for aortic valve replacement.

10-8: Syphilitic aortitis. Note the dilated aortic valve root and the irregular intimal wrinkling ("tree barking") due to scarring in the wall of the aorta from inflammation and repair of the vasa vasorum. The inset shows a silver stain with spirochetes. (From Klatt F: Robbins and Cotran Atlas of Pathology, Philadelphia, Saunders, 2006, p 9, Figs. 1-22 [gross picture] and 1-24 [inset].)
Aortic dissection: MCC
death in Marfan syndrome/EDS

Marfan syndrome: AD, missense mutation in fibrillin synthesis
Marfan syndrome: arachnodactyly, dislocated lens, MVP, AV regurgitation, eunuchoid

Aortic dissection: CMD; elastic tissue fragmentation
Risk factors: Marfan/EDS, HTN, pregnancy, coarctation of aorta

Aortic dissection: pain radiates into back; absent pulse

Aortic dissection: AV regurgitation, cardiac tamponade MCC death

Superficial saphenous → perforator branch → deep veins → back to right heart

Locations: superficial saphenous vein, distal esophagus, anorectal region, left scrotal sac

b. Brassy cough
   - Left recurrent laryngeal nerve is stretched by the aneurysm.
4. Linear calcifications are usually seen in the aortic wall on a plain radiograph.
   - Definitive diagnosis with aortography
5. Treatment is antibiotics for tertiary syphilis and surgery, if warranted.

G. Aortic dissection
1. Epidemiology
   a. Most often occurs in men (3:1 male/female ratio) with a mean age of 40 to 60 years and a history of antecedent HTN.
   b. Commonly occurs in young people with an underlying connective tissue disorder, usually Marfan syndrome (see shaded area) or Ehlers-Danlos syndrome (EDS; refer to Chapter 3).

Marfan syndrome is an autosomal dominant disorder resulting in the production of weak elastic tissue due to a defect in synthesizing fibrillin (missense mutation). Cardiovascular abnormalities dominate. Dilation of the ascending aorta may progress to aortic dissection and/or AV regurgitation. Mitral valve prolapse (MVP) is the most common valvular defect and is often associated with conduction defects causing sudden death. Skeletal defects include hypermobile joints, eunuchoid proportions (lower body length > upper body length, arm span > height), and arachnodactyly (spider hands; Fig. 10-9A). Dislocation of the lens is another finding, because the suspensory ligament holding the lens is composed of elastic tissue.

2. Pathogenesis
   a. Cystic medial degeneration (CMD)
      (1) Elastic tissue fragmentation in the media weakens the elastic artery.
      (2) Degraded matrix material collects in areas of fragmentation in the media.
   b. Risk factors for CMD
      (1) Increased wall stress; causes include:
         - HTN, pregnancy (increased plasma volume), and coarctation of aorta
      (2) Defects in connective tissue; diseases include:
         - Marfan syndrome (defect in elastic tissue) and EDS (defect in collagen)
   c. Intimal tear in the aorta
      (1) Tear is due to HTN or underlying structural weakness in the media.
      (2) Usually occurs within 10 cm of AV (see Fig. 10-9B)
      (3) Blood dissects under arterial pressure through areas of weakness.
      (4) Blood dissects proximally and/or distally (see Fig. 10-9C and D).

3. Clinical findings
   a. Acute onset of severe retrosternal chest pain radiating to the back
      - In an acute MI, the pain usually radiates down the inner arms (refer to Chapter 11).
   b. AV regurgitation
      (1) Due to AV ring dilation
      (2) Radiograph or echocardiogram shows widening of the AV root (see Fig. 10-9E).
      (3) Axial CT shows true and false lumen of dissection (see Fig. 10-9F).
   c. Loss of upper extremity pulse
      - Compression of subclavian artery by blood in the false lumen
   d. Rupture sites include:
      - Pericardial sac (most common), pleural cavity, and peritoneal cavity

IV. Venous System Disorders
A. Saphenous venous system
1. Superficial saphenous veins drain blood into the deep veins via perforating branches.
2. Valves in perforator branches prevent reversal of blood flow into the superficial system.
3. Deep veins direct blood back to the heart.

B. Varicose veins
1. Epidemiology
   a. Definition—veins that are abnormally distended (>3 mm) and often tortuous underneath the skin surface
   b. Locations
      (1) Superficial saphenous veins (most common site)
      (2) Distal esophagus (due to portal hypertension; refer to Chapter 18)
      (3) Anorectal region (e.g., internal hemorrhoids; refer to Chapter 18)
      (4) Left scrotal sac (e.g., varicocele; refer to Chapter 21)
2. Superficial varicosities in the lower extremities
   a. Most common clinical manifestation of chronic venous insufficiency
   b. Risk factors
      (1) Female gender
      (2) Family history of varicose veins
      (3) Multiple pregnancies, jobs with prolonged standing, obesity, advanced age
   c. Pathogenesis
      (1) Valve incompetence of perforator branches with reversal of blood flow from the high-pressure deep venous system into the superficial system
      (2) May be secondary to deep venous thrombosis (DVT; Fig. 10-10)
         • Retrograde blood flow through the perforating branches into the superficial system causes increased pressure and dilation of the vessels.
   d. Treatment
      (1) Nonpharmacologic treatment
         • Graded compression stockings
Rapid Review Pathology

Chronic treatment
(a) Compression sclerotherapy
(b) Ligation and stripping
(c) Endovenous obliteration using radiofrequency (diathermy) or laser

C. Venous thromboses (also refer to Chapter 5)

1. Causes
   a. Stasis of blood flow (e.g., prolonged immobilization [$\geq$ 3 days], postoperative state)
   b. Hypercoagulability (e.g., antithrombin III deficiency, oral contraceptives; pancreatic cancer, factor V deficiency, protein C and S deficiencies)

2. Locations
   a. Most often occurs in the deep veins of the lower extremity (e.g., veins in the calf [anterior, posterior, peroneal veins; calf venous sinusoids]; popliteal vein; femoral vein).
   b. Less common sites include periprostatic plexus, ovarian and periuterine veins, portal vein, hepatic vein, and dural sinuses in the brain.

3. DVT in the calf (refer to Chapter 5)
   a. Acute signs of DVT include:
      (1) Swelling of the affected leg relative to the other leg ($>3$ cm in circumference)
      (2) Pain on dorsiflexion of the foot (Homans sign) and compression of the calf
      (3) Pitting edema distal to the thrombosis due to increased hydrostatic pressure
   b. Chronic signs of DVT in lower leg
      (1) Stasis dermatitis (Fig. 10-11)
         (a) Definition—hemorrhagic or orange discoloration of the skin and ischemic ulcers (poor O$_2$ perfusion) located around the medial malleolus of the ankles
            • Orange discoloration is due to hemosiderin deposited in the skin from ruptured blood vessels.
         (b) Caused by rupture of the perforating branches due to pressure backup (retrograde blood flow) from chronic deep vein insufficiency (related to DVT, trauma, pregnancy)
         (c) Treatment
            • Topical high potency corticosteroids and antibiotics if infection is present
   (2) Secondary varicosities may develop in the superficial system (see Fig. 10-10).
c. Diagnosis
   • Venous duplex ultrasonography (95% sensitivity/specificity) + serum d-dimer assay
     (88%–97% sensitivity; refer to Chapter 15)

d. Treatment
   (1) Low-molecular-weight heparin
   (2) Compression stockings
   (3) Long-term treatment (3–6 months) to prevent recurrent DVT—warfarin therapy
   (4) Serum d-dimer assays are useful in predicting recurrence after withdrawal of
     anticoagulation (<250 mg/mL, low risk for recurrence; >250 mg/dL, high risk for
     recurrence).

D. **Superficial thrombophlebitis**

1. Epidemiology
   • 10% to 20% are associated with occult DVT.

2. Pathogenesis
   a. Intravenous cannulation of veins
   b. Infection (*Staphylococcus aureus* in 65%–78% of cases)
   c. Carcinoma of the pancreatic head
   d. Hypercoagulable state (see IV.C.1.b.; also refer to Chapter 15)

3. Clinical findings
   a. Pain and tenderness along the course of a superficial vein
   b. Erythema and edema of the overlying skin and subcutaneous tissue

4. Treatment
   a. Warm, moist compresses
   b. Nonsteroidal antiinflammatory drugs (NSAIDs), dicloxacillin, or cephalaxin

E. **Superior vena cava (SVC) syndrome**

1. Pathogenesis
   a. Extrinsic compression of SVC due to a primary lung cancer (90% of cases)
   b. Small cell carcinoma of the lung is the most common cause.

2. Clinical findings
   a. "Puffiness" and blue to purple discoloration of the face, arms, and shoulders
      (see Fig. 17-18B)
   b. Retinal hemorrhage, stroke

3. Treatment
   • Radiation, stent to bypass the obstruction

F. **Thoracic outlet syndrome (TOS)**

1. Pathogenesis
   a. Compression of the neurovascular compartment in the neck
   b. Causes
      • Cervical rib, spastic anterior scalene muscles, or positional change in the neck and
        arms, particularly in muscular individuals

2. Clinical findings
   a. Vascular signs (e.g., arm "falls asleep" while the person is sleeping)
   b. Nerve root signs (e.g., numbness, paresthesias)
   c. Positive Adson test
      • Pulse disappears/diminished when the arm is outstretched and the patient looks to
        the side of the outstretched arm.

3. Treatment
   • Manipulation therapy, home exercise, surgery if there is an anatomic cause

V. Lymphatic Disorders

A. **Structure of lymphatic vessels**
   • Lymphatic vessels have incomplete basement membranes, which predisposes them to
     infection and tumor invasion.

B. **Acute lymphangitis**

1. Definition—inflammation of lymphatics ("red streak"; Fig. 10-12A)
2. Cellulitis is most often caused by *Streptococcus pyogenes*.
3. Treatment is with clindamycin or erythromycin.

C. **Nodular lymphangitis**
   • Sporotrichosis (refer to Chapter 25; Fig. 25-4K)
10-12: A, At the base of the index finger is an ulceration from the bite of a brown recluse spider. Redness of the skin extends around the bite and down the lymphatics on the medial side of the wrist and forearm. B, Lymphedema. Note the swelling of the entire right arm. The patient had a modified radical mastectomy followed by radiation. C, Elephantiasis (lymphedema) of the right leg due to filariasis (Wuchereria bancrofti). (A courtesy Edward Goljan MD. B from Swartz M: Textbook of Physical Diagnosis History and Examination, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 444, Fig. 15-3; C from Cohen J, Powderly W, Opal S: Infectious Diseases, 3rd ed, Philadelphia, Elsevier, 2010, Fig. 115.1a.)

D. Lymphedema (also refer to Chapter 5)
1. Definition—collection of lymphatic fluid in interstitial tissue or body cavities
2. Causes
   a. In the United States, it is most often post–radical mastectomy followed by irradiation of the axilla (see Fig 10-12B).
   b. Other causes include filariasis (most common cause of lymphedema in the world; see Fig. 10-12C), congenital origin (birth, teenager, >30 years old), and Turner syndrome (refer to Chapter 6, Fig. 6-21A,B).
3. Clinical findings
   a. Early in interstitial edema, there is pitting with compression; however, in advanced cases it is nonpitting, due to increased fibrosis.
   b. Usually painless and progressive
4. Treatment
   - Complex decongestive therapy including extremity elevation, limb massage, and pneumatic compression
5. Chylous effusions (e.g., pleural cavity)
   a. Definition—contain chylomicrons with TG (milky appearance)
   b. Causes in the thoracic cavity
     • Damage to the thoracic duct by malignant lymphoma or trauma

VI. Vascular Tumors and Tumor-like Conditions (Table 10-2; Fig. 10-13)
- Most tumors derive from small vessels or arteriovenous anastomoses in glomus bodies.

VII. Vasculitic Disorders
A. Definition
- Inflammation of small vessels (arterioles, venules, capillaries), medium-sized vessels (muscular arteries), large vessels (elastic arteries), or combinations of these vessel types (Fig. 10-14).

B. Pathogenesis
1. Type III hypersensitivity (immunocomplex)
   • Example—Henoch-Schönlein purpura
2. Type II hypersensitivity (antigen–antibody)
   • Example—Goodpasture syndrome (anti–basement membrane antibodies)
3. Antineutrophil cytoplasmic antibodies (ANCA)
   a. Antibodies activate neutrophils, causing release of their enzymes and free radicals resulting in vessel damage.
   b. c-ANCA type of vasculitides
      (1) Antibodies are directed against proteinase 3 in cytoplasmic granules.
      (2) Example—Wegener granulomatosis
   c. p-ANCA type of vasculitides
      (1) Antibodies are directed against myeloperoxidase in neutrophils.
      (2) Examples—microscopic polyangiitis, Churg-Strauss syndrome
4. Direct invasion by all classes of microbial pathogens
### Table 10-2 Vascular Tumors and Tumor-Like Conditions

<table>
<thead>
<tr>
<th>TUMOR/CONDITION</th>
<th>CLINICAL FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiomyolipoma</td>
<td>Kidney hamartoma: composed of blood vessels, muscle, and mature adipose tissue. Associated with tuberous sclerosis (refer to Chapter 26)</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Liver angiosarcoma is associated with exposure to polyvinyl chloride, arsenic, or thorium dioxide</td>
</tr>
<tr>
<td>Bacillary angiomatosis</td>
<td>Benign capillary proliferation involving skin and visceral organs in AIDS patients. Simulates Kaposi sarcoma in AIDS. Caused by Bartonella henselae, a gram-negative bacillus (also causes cat-scratch disease)</td>
</tr>
<tr>
<td>Capillary hemangioma</td>
<td>Facial lesion in newborns. Advise parents that these normally regress with age.</td>
</tr>
<tr>
<td>Cavernous hemangioma</td>
<td>Most common benign tumor of the liver and spleen. May rupture if large and produce a hemoperitoneum</td>
</tr>
<tr>
<td>Cystic hygroma</td>
<td>Lymphatic cyst in the neck that may be associated with Turner syndrome (responsible for the webbed neck)</td>
</tr>
<tr>
<td>Glomus tumor</td>
<td>Painful red subungual nodule in a digit. Derive from arteriovenous shunts in glomus bodies.</td>
</tr>
<tr>
<td>Hereditary telangiectasia (AD)</td>
<td>Dilated vessels on the skin and mucous membranes in the mouth and throughout the gastrointestinal tract. Chronic iron deficiency anemia may occur because of bleeding from telangiectasias in the gastrointestinal tract.</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>Malignant tumor arising from endothelial cells or primitive mesenchymal cells. It is an AIDS-defining lesion and the most common cancer in AIDS. Associated with human herpesvirus type 8. Raised, red-purple discoloration that progresses from a flat lesion to a plaque to a nodule that ulcerates. Common sites include skin (most common site), mouth (2nd most common site), and gastrointestinal tract.</td>
</tr>
<tr>
<td>Lymphangiosarcoma</td>
<td>Malignancy of lymphatic vessels. Arises out of long-standing chronic lymphedema (e.g., after a modified radical mastectomy).</td>
</tr>
<tr>
<td>Pyogenic granuloma</td>
<td>Vascular, red pedunculated mass that ulcerates and bleeds easily. Posttraumatic or associated with pregnancy (caused by increased estrogen; usually regress postpartum without a scar).</td>
</tr>
<tr>
<td>Spider telangiectasia</td>
<td>Arteriovenous fistula (disappears when the body is compressed). Associated with hyperestrinism (e.g., cirrhosis, normal pregnancy).</td>
</tr>
<tr>
<td>Sturge-Weber syndrome</td>
<td>Nevus flammeus (“birthmark”) on the face in the distribution of the ophthalmic branch and/or maxillary branch of cranial nerve V (trigeminal). Some cases show ipsilateral malformation of pia mater vessels overlying the occipital and parietal lobes. These can bleed and produce a subarachnoid hemorrhage.</td>
</tr>
<tr>
<td>Von Hippel–Lindau syndrome (AD)</td>
<td>Cavernous hemangiomas in the cerebellum and retina. Increased incidence of bilateral pheochromocytoma and bilateral renal cell carcinomas.</td>
</tr>
</tbody>
</table>

**AD**, Autosomal dominant.

#### C. Clinical Findings

1. Small vessel vasculitis
   a. Called leukocytoclastic vasculitis or hypersensitivity vasculitis
   b. Gross appearance
      1. Skin overlying the vasculitis is hemorrhagic, raised, and painful to palpation.
         - Called palpable purpura (“tumor” of acute inflammation; refer to Chapter 15)
      2. Examples—Henoch-Schönlein purpura and microscopic polyangiitis
   c. Microscopic appearance
      - Vessel is disrupted and contains a neutrophilic infiltrate associated with nuclear debris and fibrinoid necrosis.
2. Medium-sized vessel vasculitis
   a. Muscular artery vasculitis
   b. Presents with vessel thrombosis and infarction or aneurysms
   c. Examples—polyarteritis nodosa and Kawasaki disease
3. Large vessel vasculitis
   a. Elastic artery vasculitis
   b. Presents with loss of a pulse or a stroke
   c. Examples—Takayasu arteritis and giant cell (temporal arteritis)
4. Summary table of vasculitides (Table 10-3; Fig. 10-15)
10-13: A, Bacillary angiomatosis. Note the nodular red mass and satellite lesions at the periphery. B, Capillary hemangioma. Note the raised, red lesion above the right eyelid in this child. C, Cystic hygroma in the neck of a newborn that did not have Turner syndrome. D, Hereditary telangiectasia. Note the telangiectasias scattered over the dorsal surface of the tongue. E, Pyogenic granuloma. Note the nodular, bleeding, red mass erupting from the skin surface. F, Sturge-Weber syndrome. Nevus flammeus (“birthmark”) on the face in distribution of ophthalmic and maxillary branch of cranial nerve V (trigeminal). (A courtesy Richard Johnson, MD, Beth Israel Deaconess Medical Center, Boston; B from Habif T: Clinical Dermatology, 4th ed, St. Louis, Mosby, 2004; C from Townsend C: Sabiston Textbook of Surgery, 18th ed, Philadelphia, Saunders Elsevier, 2008, p 2052, Fig. 71.3; D and F from Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, pp 333, 770, Figs. 12-11, 24-8, respectively; E from Fitzpatrick JE, Morelli JG: Dermatology Secrets Plus, 4th ed, Philadelphia, Elsevier Mosby, 2011, p 303, Fig. 42.7.)

10-14: Arrangement of blood vessels in the cardiovascular system. Vasculitis may occur in any of these vessels. (From Costanzo LS: Physiology, 3rd ed, Philadelphia, Saunders Elsevier, 2006, p 114, Fig. 4.2.)
VIII. Hypertension

A. Epidemiology

1. Essential HTN accounts for 85% of cases of hypertension.
   - Remaining 15% represent a group called secondary hypertension.
2. In the United States, 25% to 30% of adult population has HTN.

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>VASCULITIS</th>
<th>EPIDEMIOLOGY/ETIOLOGY</th>
<th>CLINICAL/LABORATORY FINDINGS/TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takayasu arteritis (&quot;pulseless disease&quot;)</td>
<td>Granulomatous large vessel vasculitis involving aortic arch vessels</td>
<td>Young Asian women and children</td>
<td>Absent upper extremity pulse Discrepancy in blood pressure between the arms is &gt;10 mm Hg Visual defects, stroke Treatment: corticosteroids</td>
</tr>
<tr>
<td>Giant cell (temporal) arteritis</td>
<td>Granulomatous large vessel vasculitis involving superficial temporal and ophthalmic arteries</td>
<td>Adults &gt;50 years of age</td>
<td>Temporal headache, jaw claudication (pain when chewing stretches the inflamed artery) Blindness on the ipsilateral side due to ophthalmic artery vasculitis Polymyalgia rheumatica (muscle and joint pain; normal serum creatine kinase) is commonly associated with temporal arteritis Increased ESR (useful screening test) Treatment: corticosteroids</td>
</tr>
<tr>
<td>Polyarteritis nodosa (see Fig. 10-15A)</td>
<td>Necrotizing medium-sized vessel vasculitis involving renal, coronary, mesenteric arteries (spares pulmonary arteries)</td>
<td>Middle-aged men Association with HBsAg (30% of cases), HCV less commonly Hepatitis B associated polyarteritis is immunocomplex disease (type III hypersensitivity); otherwise the cause for polyarteritis nodosa is unknown</td>
<td>Vessels are at all stages of acute and chronic inflammation Fever is commonly present (often presents as a fever of unknown origin) Focal vasculitis produces aneurysms (detected with angiography) Organ infarction in kidneys (renal failure, hematuria), heart (acute MI), bowels (bloody diarrhea), skin (ischemic ulcer), testicle (testicular pain) Angiography and biopsy of lesions confirm the diagnosis. Treatment: corticosteroids; cyclophosphamide in resistant cases</td>
</tr>
<tr>
<td>Kawasaki disease (see Fig. 10-15B and C)</td>
<td>Necrotizing medium-sized vessel vasculitis involving coronary arteries (e.g., thrombosis, aneurysms)</td>
<td>Children &lt;5 years of age Boys &gt; girls Cause unknown (probably infectious etiology precipitating an immune reaction in genetically susceptible individuals) Leading cause of acquired heart disease in children in developed countries Children of Asian descent have highest incidence (highest incidence in Japan) Surpassed acute rheumatic heart disease as most common acquired heart disease in children</td>
<td>Fever, erythema and edema of hands and feet convalescing with desquamated rash; cervical adenopathy; oral erythema and cracking of the lips; strawberry-appearing tongue (glossitis) Abnormal ECG (e.g., acute MI) Treatment: intravenous immunoglobulin; aspirin; corticosteroids indicated only if two courses of IV immunoglobulin are unsuccessful</td>
</tr>
<tr>
<td>Thromboangiitis obliterans (Buerger disease)</td>
<td>Medium-sized vessel vasculitis with digital vessel thrombosis and damage to neurovascular compartment</td>
<td>Genetic mechanism has been proposed Most commonly occurs in Jews of Ashkenazi ancestry living in Israel; high morbidity in India, Korea, and Japan Typically occurs in men 25–50 years of age who smoke cigarettes; may occur in females (10%)</td>
<td>Lower extremity is involved in 100% of cases: resting pain on the forefoot is characteristic, with possible ischemic ulcers or gangrene of foot/toes Upper extremity is involved in 40%–50% of cases: upper limb ischemia with ulceration and gangrene (amputation is common); Raynaud phenomenon Treatment: smoking cessation essential; intravenous iloprost (prostaglandin analog), vasodilators (α-blockers, calcium channel blockers)</td>
</tr>
<tr>
<td>Raynaud disease</td>
<td>Medium-sized vessel vasculitis involving digital vessels in fingers and toes; also tip of nose and ears in some cases</td>
<td>Young women Exaggerated vasomotor response to cold or stress</td>
<td>Paroxysmal digital color changes (white-blue-red sequence) Ulceration and gangrene in chronic cases Treatment: avoid cold temperatures (wear gloves); calcium channel blockers (e.g., nifedipine)</td>
</tr>
</tbody>
</table>
### Table 10-3: Vasculitic Disorders: Elastic Artery, Muscular Artery, and Small Vessel—cont’d

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>VASCULITIS</th>
<th>EPIDEMIOLOGY/ETIOLOGY</th>
<th>CLINICAL/LABORATORY FINDINGS/TREATMENT</th>
</tr>
</thead>
</table>
| Raynaud phenomenon (see Fig. 10-15D)          | Medium-sized vessel vasculitis involving digital vessels in fingers and toes; also tip of nose and ears in some cases | Adult men and women Secondary to other diseases (e.g., systemic sclerosis, CREST syndrome, SLE) | Systemic sclerosis and CREST syndrome (refer to Chapter 4): digital vasculitis with vessel fibrosis, dystrophic calcification, ulceration, gangrene  
**Treatment:** same as for Raynaud disease |
| Wegener granulomatosis (see Fig. 10-15E)       | Necrotizing medium and small-sized vessel vasculitis involving lung (infarctions) and renal vessels (glomerulonephritis) | Mean age 41 years Incidence equal in men and women Approximately 90% present with symptoms involving the upper or lower airways or both | Necrotizing granulomas in skin, upper respiratory tract (nasopharynx–saddle nose deformity, chronic sinusitis, collapse of trachea), and lower respiratory tract (cavitating nodular lesions)  
**Treatment:** corticosteroids, cyclophosphamide  
**C-ANCA** antibodies (>90% of cases) correlate erratically with therapy  
**Treatment:** corticosteroids, cyclophosphamide |
| Microscopic polyangiitis                      | Small vessel vasculitis involving skin, lung, brain, GI tract, kidneys (postcapillary venules and glomular capillaries) | Children and adults Precipitated by drugs (e.g., penicillin), infections (e.g., streptococci), immune disorders (e.g., SLE) | Vessels at same stage of inflammation  
Palpable purpura, glomerulonephritis ( crescentic type)  
P-ANCA antibodies (>80% of cases)  
**Treatment:** corticosteroids and cyclophosphamide |
| Churg-Strauss syndrome                        | Small vessel vasculitis involving skin, lung, heart vessels                | Usually occurs at a mean age of 51 years Probably an autoimmune disease             | Allergic rhinitis, asthma  
p-ANCA antibodies (70% of cases), eosinophilia  
**Treatment:** corticosteroids; with treatment, 1-year survival 90%, 5-year survival ~60% |
| Henoch-Schönlein purpura (see Fig. 10-15F)    | Small vessel vasculitis involving skin, GI tract, renal, joint vessels    | Usually seen in children 1–15 years of age; some cases in young adults Peak incidence is in the spring, rarely the summer  
Males > females  
Most common vasculitis in children  
More common in whites and Asians than in blacks  
IgA–anti-IgA immunocomplexes (type III hypersensitivity) | Often follows a viral URI, group A streptococcal pharyngeal infection. Pathogens may act as an antigen trigger that causes antibody formation leading to immunocomplex formation (type III hypersensitivity)  
Palpable purpura of buttocks and lower extremities is a characteristic finding (95%–100%)  
Polyarthritis (80%), glomerulonephritis (80%), abdominal pain and vomiting (85%), and GI bleeding may occur. Recurrence occurs in one third of cases.  
Most have spontaneous recovery in 4 months without therapy.  
**Treatment:** corticosteroids are mainly used if severe GI disease or renal disease are present |
| Cryoglobulinemia                              | Small vessel vasculitis involving skin, GI tract, renal vessels Different types of cryoglobulinemia (mixed, monoclonal, polyclonal) | Adults; female more common than male (3:1 ratio) Association with HCV (>50%), type 1 MPGN, multiple myeloma (monoclonal type), lymphoproliferative disorders, connective tissue disorders | Cryoglobulins: they are proteins in plasma that gel at cold temperatures, particularly in those areas that are exposed to the cold temperature (i.e., nose, fingers, ears)  
Palpable purpura, acral cyanosis of nose and ears and Raynaud phenomenon (reverses when in warm room); glomerulonephritis ( crescentic type); arthritis; abdominal pain  
**Treatment:** immunosuppressive agents |
| Infectious vasculitis (see Fig. 10-15G and H) | Small vessel vasculitis involving skin vessels rocky Mountain spotted fever (RMSF): most prevalent in Southeast, followed by the south central states | Children and adults involves all microbial pathogens Rocky Mountain spotted fever (RMSF): most prevalent in Southeast, followed by the south central states | RMSF: dog tick (Dermaentor variabilis) or wood tick (Dermacentor andersoni) transmission of Rickettsia rickettsii (present in the tick’s salivary glands)  
Organisms invade endothelial cells producing vasculitis Fever is present in 100% of cases  
Petechiae (vasculitis) begin on the palms and spread to the trunk; petechiae appear in the first days in 50% of cases and by the 5th day, in 80% of cases; there are no petechiae in 10% of cases.  
**Treatment:** oral doxycycline; can treat children up to 10 days (no permanent teeth discoloration)  
Disseminated meningococcemia is due to Neisseria meningitidis  
**Capillary thromboses, usually in the setting of DIC, produce minute hemorrhages into the skin (petechiae) that become confluent ecchymoses as the disease progresses. Hemorrhagic infarctions of both adrenal glands commonly occurs producing acute hypocortisolism and death (Waterhouse-Friderichsen syndrome)  
**Treatment:** intravenous penicillin G |

* c-ANCA, Cytoplasmic antineutrophil cytoplasmic antibodies; DIC, disseminated intravascular coagulation; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; Ml, myocardial infarction; MPGN, membranoproliferative glomerulonephritis; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies; SLE, systemic lupus erythematosus; URI, upper respiratory infection.
10-15: A, Mesenteric angiogram in polyarteritis nodosa. Note the numerous small aneurysms (arrows) in the medium-sized vessels. B, Kawasaki disease. Note the desquamation of the skin of the toes, which is a characteristic skin finding in this disease. C, Kawasaki disease. Note the swollen, erythematous lips and the erythema in the angles of the lips (angular cheilosis). The child also had glossitis. The tongue had an erythematous appearance resembling the surface of a strawberry (“strawberry” tongue). D, Raynaud phenomenon. Note the extreme pallor of the digits in both hands in this patient with systemic lupus erythematosus. E, Saddle nose deformity in Wegener granulomatosis. Note the concavity (arrow) below the bridge of the nose having the appearance of a saddle. F, Henoch-Schönlein purpura. Multiple erythematous, raised, palpable lesions around the ankles show areas of hemorrhage into the skin overlying areas of immunocomplex vasculitis involving small vessels. The lesions extended up to the buttocks. G, Rocky Mountain spotted fever. The palm shows a few petechial lesions in this patient with a history of a tick bite. H, Disseminated meningococcemia showing confluent ecchymoses. (A from Goldman L, Ausiello D: Cecil’s Textbook of Medicine, 2nd ed, Philadelphia, Saunders Elsevier, 2008, p 2054, Fig. 291-2A; B courtesy J. Ross, MD, Lewisham Hospital, London; C from McKee PH, Calonje E, Granter RS: Pathology of the Skin with Clinical Correlations, 3rd ed, St. Louis, Elsevier Mosby, 2005, p 736, Fig. 15.63; D from Savin JA, Hunter JAA, Hepburn NC: Diagnosis in Color: Skin Signs in Clinical Medicine, London, Mosby-Wolfe, 1997, p 205, Fig. 8.42; E, F, and H from Boulloux P-M: Self-Assessment Picture Tests: Medicine, Vol. 3, London, Mosby-Wolfe, 1996, pp 41, 66, and 96, Figs. 92, 75, and 191, respectively; G courtesy Department of Dermatology, University of North Carolina at Chapel Hill, Chapel Hill, NC.)
3. Definitions
   a. Normal blood pressure: <120 mm Hg systolic, <80 mm Hg diastolic
   b. Prehypertension: 120 to 139 mm Hg systolic, 80 to 90 mm Hg diastolic
   c. Stage 1 hypertension: 140 to 159 mm Hg systolic, 90 to 99 mm Hg diastolic
   d. Stage 2 hypertension: ≥160 mm Hg systolic, ≥100 mm Hg diastolic

B. Pathophysiology
   1. Systolic blood pressure (SBP)
      a. SBP correlates with stroke volume (SV) and the compliance of the aorta.
         (1) Primary determinants of SV include:
            (a) Preload, or the volume of blood in the left ventricle (LV)
            (b) Afterload, or the resistance the LV contracts against to eject blood from the heart
               • Example—aortic stenosis is an afterload that is present at the level of the AV.
            (c) Contractility of the heart
         (2) Vessel elasticity determines the compliance of the aorta, or the ability of the aorta to expand with blood during systole.
            (a) Compliance decreases with age because of reduced elasticity in the aorta.
            (b) Decreased compliance is the mechanism for systolic hypertension in people >60 years of age
      b. Increased SBP is caused by:
         • Increased preload, increased contractility, and decreased compliance of the aorta
      c. Decreased SBP is caused by:
         • Decreased preload, decreased contractility, or increased afterload (e.g., severe aortic stenosis)
   2. Diastolic blood pressure (DBP)
      a. DBP correlates with the volume of blood in the aorta during diastole.
      b. Primarily depends on the state of contraction (tonicity) of the SMCs in the peripheral vascular resistance (PVR) arterioles, the viscosity of blood, and the heart rate (HR).
      c. Increased DBP is caused by:
         (1) Vasoconstriction of the PVR arterioles
            • A greater volume of blood is present in the artery while the heart is filling up in diastole.
         (2) Increase in blood viscosity (e.g., polycythemia)
         (3) Increase in heart rate
            • Increasing heart rate decreases filling of the coronary arteries, leaving a greater volume of blood in the aorta during diastole.
      d. Decreased DBP is caused by:
         (1) Vasodilation of the PVR arterioles
         (2) Severe anemia, which decreases the viscosity of blood
         (3) Decreasing the heart rate
            • Decreasing heart rate, increases filling of the coronary arteries leaving a less volume of blood in the aorta during diastole.

Factors that contract arteriole smooth muscle cells causing vasoconstriction include α-adrenergic stimuli, catecholamines, angiotensin II, vasopressin, endothelin, and increased total body sodium.

3. Role of sodium in HTN
   a. Excess sodium increases plasma volume (PV).
      • Excess PV increases SV, which in turn increases SBP.
   b. Excess sodium produces vasoconstriction of PVR arterioles.
      • An increase of sodium in smooth muscle increases calcium-mediated contraction of the muscle, causing an increase in the DBP.

C. Essential hypertension
   1. Epidemiology
      • Essential HTN is more common in black Americans than white Americans.
   2. Pathogenesis
      a. Genetic factors reduce renal sodium excretion.
      b. Decreased sodium excretion increases PV, which increases SV, which increases SBP.
      c. Decreased sodium excretion increases vasoconstriction of PVR arterioles, which increases the DBP.
      d. Additional important factors include obesity, stress, smoking, increased salt intake, and lack of physical exercise.
**Table 10-4 Causes of Secondary Hypertension**

<table>
<thead>
<tr>
<th>SYSTEM OR SOURCE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
</table>
| Adrenal          | Cushing syndrome: increased mineralocorticoids  
|                  | Pheochromocytoma: increased catecholamines  
|                  | Neuroblastoma: increased catecholamines  
|                  | 11-Hydroxylase deficiency: increased mineralocorticoids (i.e., deoxytocorticosterone)  
|                  | Primary aldosteronism (Conn syndrome): increased aldosterone |
| Aorta            | Postductal coarctation: activation of RAA system  
|                  | Elderly: systolic hypertension due to decreased elasticity of the aorta |
| CNS              | Intracranial hypertension: release of catecholamines |
| Drugs            | Oral contraceptives: increased synthesis of angiotensinogen; most common cause of hypertension in young women (resolves with discontinuing contraceptive)  
|                  | Cocaine: increased sympathetic activity |
| Parathyroid      | Primary hyperparathyroidism: calcium increases peripheral resistance arteriole smooth muscle cell contraction |
| Pregnancy        | Preeclampsia: increased angiotensin II |
| Renal            | Renovascular disease: atherosclerosis (elderly men; see Fig. 10-16A), fibromuscular hyperplasia (women; see Fig. 10-16B). In both conditions, there is an epigastric bruit due to blood being forced through a narrow lumen. In both conditions, there is activation of the renin-angiotensin-aldosterone system (high renin hypertension). ATII causes vasoconstriction of peripheral vascular resistance arterioles and it increases sodium reabsorption in the kidneys (increases plasma volume → stroke volume; increases calcium-mediated vasoconstriction of peripheral vascular resistance arterioles). Increased aldosterone increases renal reabsorption of sodium. The increased plasma volume from sodium retention increases renal blood flow in the unaffected renal artery, causing suppression of plasma renin activity. Medical treatment of renovascular hypertension includes ACE inhibitors, β-blockers, and diuretics used in combination with ACE inhibitors. Treatment of the atherosclerotic type of hypertension involves open surgical approaches or percutaneous interventions with stent implantation. Balloon angioplasty is used for treating fibromuscular hyperplasia. Renal parenchymal disease: e.g., diabetic nephropathy, adult polycystic kidney disease, glomerulonephritis; retention of sodium |
| Thyroid          | Graves disease: systolic hypertension from increased cardiac contraction  
|                  | Hypothyroidism: diastolic hypertension due to retention of sodium |

RAA, Renin-angiotensin-aldosterone.

**10-16:** A, Angiogram showing right renal artery stenosis with poststenotic dilatation (arrow). B, Angiogram showing bilateral renal artery fibromuscular hyperplasia. Note the beading effect in both vessels. (A from Katz D, Math K, Groskin S: Radiology Secrets, Philadelphia, Hanley & Belfus, 1998, p 184, Fig. 7; B from Katz D, Math K, Groskin S: Radiology Secrets, Philadelphia, Hanley & Belfus, 1998, p 180, Fig. 27.)

Reduced renal sodium excretion is the primary mechanism of essential HTN in black Americans and the elderly. Increased PV suppresses renin release from the juxtaglomerular apparatus, producing a low renin type of HTN.

D. Secondary hypertension
1. Secondary HTN accounts for 15% of cases of HTN.
2. Causes of secondary HTN (Table 10-4; Fig. 10-16)

E. Complications of hypertension (Table 10-5; Box 10-1)

2° HTN: 15% of cases; renovascular HTN and drugs are leading causes

Complications of HTN, descending order: acute MI, stroke, renal failure
### TABLE 10-5 Complications of Hypertension

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Left ventricular hypertrophy: most common overall complication</td>
</tr>
<tr>
<td></td>
<td>Acute myocardial infarction: most common cause of death</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Central nervous</td>
<td>Intracerebral hematoma: due to rupture of Charcot-Bouchard aneurysms</td>
</tr>
<tr>
<td></td>
<td>Berry aneurysm: rupture produces a subarachnoid hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Lacunar infarcts: small infarcts due to hyaline arteriolosclerosis</td>
</tr>
<tr>
<td>Renal</td>
<td>Benign nephrosclerosis: kidney disease of hypertension. Due to hyaline arteriolosclerosis.</td>
</tr>
<tr>
<td></td>
<td>Atrophy of tubules and sclerosis of glomeruli. Progresses to renal failure</td>
</tr>
<tr>
<td></td>
<td>Malignant hypertension: rapid increase in blood pressure accompanied by renal failure and cerebral edema</td>
</tr>
<tr>
<td>Eyes</td>
<td>Hypertensive retinopathy: arteriovenous nicking, hemorrhage of retinal vessels, exudates (increased vessel permeability, retinal infarction), papilledema</td>
</tr>
</tbody>
</table>

### BOX 10-1 Hypertensive Retinopathy

The sequence of events in hypertensive retinopathy involves focal spasm of the arterioles followed by progressive sclerosis and narrowing of the arterioles, leading eventually to flame hemorrhages from rupture of the vessels, formation of exudates (soft and hard), and papilledema (swelling of the optic disk). Normal arteriole walls are transparent; hence the column of blood is visible and the light reflex is narrow. Sclerotic changes in the vessels are first described as “copper wiring,” because blood is still visible through the vessel wall. The light reflex becomes wider. When the vessel wall is thickened enough to prevent visualization of the blood, the light reflects back from the vessel wall to produce a “silver wiring” effect. In some cases, no blood is visible in portions of the vessel. Because arterioles cross over the veins (normal ratio of arteriole/venous diameters is 3:4), as arterioles thicken they create a depression in the wall of the venule, which is called an arteriovenous nicking defect. The distal vein becomes slightly distended owing to the backup of blood. More advanced nicking literally cuts off the blood flow, and the veins appear to end abruptly. Hemorrhages in the retina are usually the result of rupture of microaneurysms that develop from increased pressure on the arterioles. Grayish-white exudates that are soft, like cotton wool, are due to microinfarctions; whereas exudates that have clear margins (hard exudates) are due to leakage of protein from increased vessel permeability. A brief summary of the Keith-Wagener-Barker classification of hypertensive retinopathy follows (other classification schema are also available):

- **Grade I:** focal narrowing of the arterioles, mild arteriovenous nicking
- **Grade II:** arteriole narrowing, copper wiring present, arteriovenous nicking more accentuated
- **Grade III:** arteriole narrowing, silver wiring present, hemorrhages, soft and hard exudates, disappearance of the vein under the arteriole, disk normal
- **Grade IV:** arterioles are fine fibrous cords; same as grade III except papilledema is present

### Nonpharmacologic treatment of HTN

Control of HTN has greatest benefit in reducing incidence of strokes

- **Control of HTN has greatest benefit in reducing incidence of strokes**
- **Control of HTN has greatest benefit in reducing incidence of strokes**
- **Control of HTN has greatest benefit in reducing incidence of strokes**

**Nonpharmacologic treatment** of HTN includes weight loss (most important), limited alcohol intake, aerobic exercise (30 min/day), reduced sodium intake (<1 mmol/day or <2.3 g/day), adequate potassium intake (>3500 mg/day), cessation of smoking, and a CH lowering diet. For prehypertension, the lifestyle modifications just listed are recommended to bring the blood pressure under 130/80 mm Hg. For stage 1 HTN, diuretics are preferred for initial therapy. More selective therapy is used if different disorders are present (e.g., congestive heart failure or diabetes—angiotensin-converting enzyme [ACE] inhibitor). For stage 2 HTN, two drug combinations are required (e.g., diuretic + angiotensin II inhibitor). For pregnant women with HTN (>130/80 mm Hg), the following drugs can be used: methyldopa, hydralazine, labetalol, or atenolol.

Control of HTN has its greatest benefit in reducing the incidence of strokes; however, it also significantly reduces the risk for developing CHD and renal disease.
I. **Cardiac Physical Diagnosis** (Box 11-1)

II. **Ventricular Hypertrophy**

A. **Definition**

- Ventricular hypertrophy is a compensatory change related to alterations in pressure and/or volume imposed on the wall of the ventricle.

B. **Pathogenesis of left and right ventricular hypertrophy**

1. Sustained pressure in the ventricles increases wall stress.
2. Changes in wall stress alter gene expression in the muscle.
3. Changes in gene expression lead to duplication of sarcomeres.
   - Definition—contractile element of muscle
4. Changes occur in wall stress when there is an increase in afterload.
   a. Definition—resistance the ventricle contracts against to eject blood in systole
   b. Increased afterload produces concentric thickening of the ventricular wall (Fig. 11-1A).
      - Sarcomeres duplicate parallel to the long axis of the cells causing the individual muscle fibers to be thicker.
   c. Causes of concentric left ventricular hypertrophy (LVH) due to increased afterload include:
      (1) Essential hypertension (HTN; most common).
      (2) Aortic valve (AV) stenosis
      (3) Hypertrophic cardiomyopathy
   d. Causes of concentric right ventricular hypertrophy (RVH) due to increased afterload include:
      (1) Pulmonary hypertension (PH; see Fig. 17-9)
      (2) Pulmonary valve (PV) stenosis
5. Changes occur in wall stress when there is an increase in preload.
   a. Definition—volume of blood in the ventricle that must be expelled during systole
   b. Correlates with the left and right ventricle end-diastolic volumes (LVEDV, RVEDV).
   c. Increased preload increases stroke volume (volume of blood ejected) via the Frank-Starling pressure relationship.
   d. Increased preload causes dilation and hypertrophy (eccentric hypertrophy) of the ventricular wall (see Fig. 11-1B).
      - Sarcomeres duplicate in series, causing the individual muscle fibers to increase in length and width.
   e. Causes of eccentric hypertrophy of the left ventricle (LV) due to increased preload include:
      (1) Mitral valve (MV) or AV regurgitation
      (2) Left-to-right shunting of blood (e.g., ventricular septal defect)
         - In left-to-right shunting, more blood returns to the left side of the heart, because the right side of the heart is receiving more blood than usual.
BOX 11-1  Cardiac Physical Diagnosis

Valve Locations for Auscultation
Locations where heart sounds are best heard do not always correlate with their anatomic location. The mitral valve (MV) is best heard at the apex; the tricuspid valve (TV), at the left parasternal border; the pulmonary valve (PV), at the left second and third intercostal spaces (ICS); and the aortic valve (AV), at the left sternal border for regurgitation murmurs and right second ICS for ejection murmurs.

Cardiac Cycle Relationships with Heart Sounds
The P wave represents atrial depolarization; the PR interval, atrioventricular conduction time; the QRS, ventricular depolarization; and, the T wave, ventricular repolarization, or recovery. The S1 heart sound co-occurs with the QRS complex and marks the beginning of systole, whereas the S2 heart sound occurs after the T wave and marks the beginning of diastole.

Heart Sounds
The S1 heart sound corresponds with closure of the MV and TV during systole. The MV closes before the TV. It is best heard at the apex and corresponds with the carotid/radial pulse. The S2 heart sound is caused by closure of the AV and PV (doors make noise when they close) and marks the beginning of diastole. It is best heard at the left second or third ICS. The aortic component (A2) normally precedes the pulmonary component (P2) of the S2 heart sound. Unlike the S1 heart sound, the S2 heart sound splits on inspiration. As the diaphragm descends, it causes a further decrease in negative intrathoracic pressure, which increases the flow of blood out of the vena cava into the right side of the heart. This causes flattening of the jugular neck veins. The excess amount of blood in the right side of the heart delays closure of the PV, causing P2 to separate more from A2 (see schematic). This physiologic split is best heard over the PV area. A2 and P2...
An **S₃** heart sound (see schematic) is the most clinically significant extra heart sound. It is a normal finding in children and young adults, where it reflects a more energetic expansion and filling of the left ventricle. However, it is considered a pathologic finding after 40 years of age. It is thought to be due to a sudden rush of blood entering a volume overloaded left or right ventricle. This is analogous to a river emptying into a large volume of water. Turbulence occurs where the two bodies of water interact. The S₃ heart sound is best heard at the apex with the patient in the left lateral decubitus position. It commonly occurs with regurgitant types of murmurs involving any of the valves. It is the first cardiac sign of congestive heart failure, where increased ventricular volume stretches the MV or TV ring, causing volume overload from mitral/tricuspid regurgitation. An S₃ heart sound produces a ventricular gallop. An **S₄** heart sound (see schematic) coincides with atrial contraction in late diastole and the a wave in the jugular venous pulse (JVP; see later). It is never a normal finding and is due to increased resistance to filling (decreased compliance) in the left or the right heart following a vigorous atrial contraction. It is heard best at the apex. Causes of decreased ventricular compliance include concentric ventricular hypertrophy (left/right) and a volume overloaded ventricle (no more room to expand). In a volume overloaded left or right ventricle, it is commonly present along with an S₃ heart sound. An S₃ heart sound and the a wave of a JVP are absent in atrial fibrillation. Presence of an S₃ heart sound produces an atrial gallop. Presence of an S₃ and S₄ heart sound is called a summation gallop (see schematic) and sounds like a galloping horse.

Heart Murmurs

Heart murmurs may occur in systole and diastole. They may be caused by structural valve disease (e.g., damage due to rheumatic fever) or stretching of the valve ring (e.g., volume overload in left- or right-sided heart failure). Murmurs due to stretching of valve rings are often called functional murmurs. Murmurs often radiate. For example, AV stenosis radiates into the neck and MV regurgitation radiates into the axilla. They are graded 1 to 6 in terms of their intensity. Grade 1 and 2 murmurs are very hard to hear, whereas grade 3 murmurs are easy to hear. Grade 4 to 6 murmurs are often accompanied by a palpable precordial thrill. Grade 6 murmurs are audible without a stethoscope. Murmurs and abnormal heart sounds (e.g., S₃ and S₄ heart sounds) change their intensity with respirations. Right-sided murmurs and abnormal heart sounds have increased intensity when the patient takes a deep inspiration and holds the breath for 3 to 5 seconds. This is due to the increase in negative intrathoracic pressure drawing blood out of the venous system into the right side of the heart, hence accentuating the murmur and abnormal heart sound on that side. In contradistinction, left-sided heart murmurs and abnormal heart sounds do not change their intensity with deep held inspiration. Continuous murmurs occur through systole and diastole. The most common cause of a continuous murmur in children is a cervical venous hum. A patent ductus arteriosus also produces a continuous murmur. Innocent murmurs occur in children from 3 to 7 years old. They are usually grade 2 systolic murmurs that are caused by increased blood flow through the PV. They are best heard in the PV area, and as expected, their intensity increases with deep, held inspiration. Stenosis murmurs occur when there is a problem in opening the valves. Because the AV and PV normally open in systole, the murmurs of AV and PV stenosis occur in systole. They produce an ejection type of murmur (schematic A), which has a diamond-shaped (crescendo-decrescendo) configuration. The MV and TV normally open in diastole; therefore, the murmurs of MV and TV stenosis are heard in diastole. MV stenosis is accompanied by an opening snap (schematic B), which occurs when the thickened valve is forced open by a strong atrial contraction. An opening snap is usually absent in TV stenosis. Regurgitant (insufficiency) murmurs occur when there is a problem in closing a valve. Because the MV and TV normally close in systole, these murmurs occur in systole. They are even-intensity pansystolic murmurs (schematic C) that often obliterate
the $S_1$ and $S_2$ heart sounds. AV and PV regurgitant murmurs occur in diastole immediately after the $S_2$ heart sound (schematic D).

**Jugular Venous Pulses (JVPs)**

*Normal JVPs* (see schematic) have three positive waves ($a$, $c$, and $v$) and two negative waves ($x$ and $y$). The **a wave** is a positive wave due to atrial contraction in late diastole. It occurs after the P wave in an electrocardiogram. It disappears in atrial fibrillation. A **giant a wave** occurs when there is restricted filling of the right side of the heart (e.g., TV stenosis, pulmonary hypertension, right ventricular hypertrophy). The **c wave** is a positive wave due to right ventricular contraction in systole causing bulging of the TV into the right atrium producing increased pressure in the atrium and jugular vein. It correlates with the $S_1$ heart sound and the upstroke of the carotid pulse. The **x wave** is a large negative wave occupying most of systole. It is due to downward displacement of the TV when blood is ejected out of the RV into the pulmonary artery. The **v wave** is a positive wave that correlates with right atrial filling in systole when the TV is closed. The peak of the v wave marks the end of systole and beginning of diastole. A **giant c-v wave** occurs in TV regurgitation as blood refluxes back into the right atrium during systole. The **y wave** is a negative wave occupying most of diastole. It is due to opening of the TV with rapid flow of blood into the right ventricle in diastole.

**BOX 11-1 Cardiac Physical Diagnosis—cont’d**

11-1: Left ventricular hypertrophy. The heart in the middle has a normal thickness of the left ventricle (LV). The heart on the left (A) has concentric hypertrophy of the LV that is related to an increase in afterload, whereas the heart on the right (B) has eccentric hypertrophy of the LV that is related to an increase in preload. (Reproduced with permission from Allen HD, Driscoll DJ, Shaddy RE, Feltes TF [eds]: Moss and Adams Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adults, 7th ed, Philadelphia, Williams & Wilkins, 2008, Fig. 1.12B.)
f. Causes of eccentric hypertrophy of the right ventricle (RV) due to increased preload include:
   • Tricuspid valve (TV) and PV regurgitation

C. Consequences of ventricular hypertrophy
1. Left- and right-sided heart failure
   a. Excess work is imposed upon the ventricles (LVH or RVH).
   b. Excess work is caused by either an increase in afterload or an increase in preload.
2. Angina pectoris with exercise (only a complication of LVH)
   a. In the normal LV, the subendocardium receives the least amount of blood from the coronary arteries.
   b. Therefore, if the muscle is concentrically thickened, angina may occur with exercise, because the muscle wall is so thick that the subendocardial tissue receives dangerously low levels of O₂, causing chest pain.
   • Recall that with exercise the heart rate increases, which decreases the time for diastole and the filling of the coronary arteries.
3. S₄ heart sound is commonly present in either LVH or RVH
   a. Abnormal heart sound that correlates with atrial contraction in late diastole
      • Produces an atrial gallop (see schematic in Box 11-1)
   b. Caused by blood entering a noncompliant ventricle (problem in filling the ventricle).
      (1) Noncompliant ventricle is present in concentric hypertrophy involving either the LV or RV.
      (2) Noncompliant ventricle is also present in left- or right-sided eccentric hypertrophy, because the ventricles are volume overloaded and resist receiving more blood in late diastole.
         • Analogous to eating pumpkin pie for dessert when the stomach is already filled up with turkey
   c. Examples of a noncompliant ventricle producing an S₄ heart sound include:
      (1) Concentric LVH in essential HTN or AV stenosis
      (2) Concentric RVH in PH or PV stenosis
      (3) Volume overload in MV or TV regurgitation
      (4) Volume overload in AV or PV regurgitation
4. Pathologic S₃ heart sound is commonly present in either left- or right-sided eccentric hypertrophy.
   a. Due to blood entering a volume overloaded chamber in early diastole (see Box 11-1).
      • Analogous to the Mississippi river emptying into the Gulf of Mexico
   b. Examples of volume overloaded ventricles producing an S₃ heart sound include:
      (1) Volume overload in MV or TV regurgitation
      (2) Volume overload in AV or PV regurgitation

III. Congestive Heart Failure (CHF)
A. Definition
   • The heart fails when it is unable to eject blood delivered to it by the venous system.
B. Epidemiology
1. Most common hospital admission diagnosis for persons >65 years old
2. Types
   a. Left-sided heart failure (LHF; most common type)
   b. Right-sided heart failure (RHF)
   c. Biventricular heart failure (LHF, RHF)
   d. High-output heart failure (least common heart failure)
3. Blood builds up behind the failed heart.
   a. In LHF, blood backs up in the lungs (pulmonary congestion).
   b. In RHF, blood builds up in the systemic venous system.
C. Left-sided heart failure (LHF)
1. Definition—LV cannot efficiently eject blood into the aorta
   a. Causes an increase in the LVEDV and LV end-diastolic pressure (LVEDP)
   b. Increased LVEDV and LVEDP (i.e., hydrostatic pressure) leads to a backup of blood into the lungs producing pulmonary edema (refer to Chapter 5).
2. Pathogenesis
   a. Decrease in ventricular contraction
      (1) Decreased LV contraction defines systolic heart failure (SHF).
         • SHF is the most common type of LHF.
Causes of SHF include:
(a) Ischemia, due to coronary artery atherosclerosis (most common cause)
(b) Post–myocardial infarction (MI), myocarditis, and dilated cardiomyopathy

b. Noncompliant LV (stiff ventricle) with impaired relaxation
(1) Noncompliant LV with impaired relaxation defines diastolic heart failure (DHF).
   • In DHF, there is an increased LVEDP.
(2) Causes of DHF
   (a) Concentric LVH due to essential HTN is the most common cause of DHF.
   (b) Other causes include AV stenosis, hypertrophic cardiomyopathy, and restrictive cardiomyopathy (amyloidosis or glycogenosis).

**Systolic heart failure (SHF)** is characterized by a low ejection fraction (EF <40%; some use <50%). The EF equals the stroke volume (SV) divided by the left ventricular end-diastolic volume (LVEDV). The normal value ranges from 55% to 80%. **Diastolic heart failure (DHF)** is characterized by a normal EF (>60%) at rest. In addition, there is usually an S₄ atrial gallop, due to increased resistance to filling in late diastole. There is an increase in left atrial and left ventricular end-diastolic pressure. Pulmonary congestion commonly occurs when the heart cannot meet the metabolic demands of peripheral tissue (e.g., when the patient exercises) at which point the EF is decreased.

3. Gross and microscopic findings in LHF
   a. Lungs are heavy, congested, and exude a frothy pink transudate (edema) on the cut surface or in the airways.
   b. Alveoli are filled with a pink-staining fluid (Fig. 11-2A) and alveolar macrophages often contain hemosiderin (“heart failure” cells).
      (1) Presence of hemosiderin implies that the pulmonary capillaries have ruptured under pressure, and RBCs entered the alveoli and were phagocytosed by alveolar macrophages.
      (2) Excess iron in the macrophage binds to ferritin, which degrades into hemosiderin (rust-colored granules with H&E stain or blue with Prussian blue stain), producing a rust-colored sputum.

4. Clinical and laboratory findings
   a. Difficulty with breathing (dyspnea)
      (1) Definition—the patient cannot take a full inspiration
      (2) Interstitial fluid stimulates juxtacapillary (J)-receptors that are innervated by the vagus nerve, the latter inhibiting the patient from taking a full inspiration.
   b. Pulmonary edema
      (1) An increase in LVEDV leads to an increase in hydrostatic pressure (HP) in the LV that is transmitted back into the pulmonary capillaries.
      (a) Once pulmonary capillary HP overrides oncotic pressure (OP), a transudate enters the interstitial space and then the alveoli, producing pulmonary edema (refer to Chapter 5).
(b) Peribronchiolar edema narrows the airway and produces expiratory wheezing (called cardiac asthma).

(2) Bibasilar inspiratory crackles (rales)
   • Inspiratory crackles are due to air expanding alveoli filled with fluid.

(3) Rust-colored sputum
   • Presence of hemosiderin in alveolar macrophages (heart failure cells)

(4) Chest radiograph findings include:
   (a) Congestion in the upper lobes (early finding)
   (b) Perihilar congestion ("bat-wing configuration" or "angel-wing configuration"; see Fig. 11-2B)
   (c) Fluffy alveolar infiltrates (see Fig. 11-2B)
   (d) Kerley lines (septal edema)
   (e) Air bronchograms (air visible in the bronchus or small airways because fluid surrounds the airways)

(c) Left-sided S₃ (first cardiac sign of LHF) and S₄ heart sounds (see Box 11-1)

(d) Functional MV regurgitation
   • Stretching of MV ring by the increased LVEDV causes the regurgitant murmur.

(e) Paroxysmal nocturnal dyspnea (PND)
   (1) Definition—choking sensation that occurs at night when the patient is supine
   (2) Without the effect of gravity, fluid from the interstitial space moves into the vascular compartment.
   (3) This increases venous return to the right side of the heart and then to the failed left side of the heart.
   (4) Failed left heart cannot handle the excess load and blood backs up into the lungs, producing dyspnea and pulmonary edema.

(f) Dyspnea is relieved by standing or placing pillows under the head (pillow orthopnea).
   (a) Both standing and raising the head on pillows increase gravity, which reduces venous return to the heart (decreases preload).
   (b) The number of pillows that causes symptomatic relief should be quantitated (e.g., three-pillow orthopnea is worse than one-pillow orthopnea).

(f) Increased serum brain natriuretic peptide (BNP)
   (1) Definition—cardiac neurohormone secreted from the ventricles when they are volume overloaded (refer to Chapter 5)
   (2) BNP is useful in:
      (a) Diagnosing LHF (increased)
      (b) Excluding LHF (normal)
      (c) Predicting survival (remains high; bad prognostic sign)

(3) Serum atrial natriuretic peptide (ANP) is also increased in LHF because of left atrial dilatation.

D. Right-sided heart failure (RHF)

1. Definition—RV cannot effectively pump venous blood into the lungs.
   • Blood pools under pressure in the venous system (blood builds up behind the failed heart).

2. Pathogenesis
   a. Increase in RV afterload (increased resistance to blood flow out of the RV)
      • Examples—LHF (most common cause RHF), PH, PV stenosis, saddle embolus (refer to Chapters 5 and 17)
   b. Decrease in RV contraction
      • Example—RV infarction, myocarditis
   c. RV is noncompliant (cannot fill properly)
      • Example—restrictive cardiomyopathy (e.g., amyloidosis or glycogenosis), concentric RVH
   d. Increase in RV preload (this increases work in pumping blood out of the RV)
      • Examples—TV/PV regurgitation, left-to-right shunt

3. Clinical and laboratory findings
   a. Prominence of internal jugular veins (see Fig. 11-2C)
      • Increased volume in venous system
   b. Functional TV regurgitation
      • Stretching of the TV ring from RV volume overload
   c. Right-sided S₃ and S₄ heart sounds
      • Both are due to RV volume overload.

Cardiac asthma: peribronchiolar edema
LHF: bibasilar inspiratory crackles (edema)
LHF X-ray: bat-wing configuration, fluffy alveolar infiltrate, Kerley lines, air bronchograms
S₃: first cardiac sign LHF
LHF: functional sign LHF
PND/orthopnea: ↑venous return to right side of heart at night → failed left heart → pulmonary edema
Pillow orthopnea: pillows ↑gravitational effect → ↓venous return to right heart
BNP: useful in confirming/excluding LHF; predicting survival
ANP: ↑with left atrial dilatation in LHF
RHF: ↑venous hydrostatic pressure
MCC RHF: ↑afterload from LHF
RHF: ↓RV contraction; e.g., myocarditis, RV infarction
RHF: RV noncompliant; e.g., restrictive cardiomyopathy, concentric RVH
RHF: ↑RV preload; e.g., valvular regurgitation; left-to-right shunt
RHF: prominence internal jugular veins; function TV regurgitation
RHF: S₃/S₄ heart sounds
d. Painful hepatomegaly
   (1) Due to centrilobular hemorrhagic necrosis
      (a) Systemic venous blood backs up into the hepatic veins and then into the central venules, which expand with blood and cause hepatic cell necrosis in zone III hepatocytes (refer to Chapter 2; see Fig. 19-5B and Fig. 2-7B).
      • Serum transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] are markedly increased; refer to Chapter 19)
      (b) Increase in pressure is transmitted into the sinusoids of the liver and eventually the portal vein.
      • An increase in portal vein pressure produces ascites (refer to Chapters 5 and 19).
   (2) Compression of the congested liver increases jugular neck vein distention (hepatojugular reflux).

e. Dependent pitting edema (see Fig. 5-3D)
   • Increase in venous hydrostatic pressure (refer to Chapter 5).

f. Cyanosis of the mucous membranes
   (1) Cyanosis is more likely to occur in RHF than LHF.
   (2) Backup of blood in the venous system in RHF increases time available for peripheral tissue to extract O₂, which decreases O₂ saturation enough to produce cyanosis (refer to Chapter 2).

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Nonpharmacologic therapy in CHF involves restricting sodium (<2 g/day) and water (<2 L/day), both of which are increased because of the decreased cardiac output and renal retention of sodium and water (refer to Chapter 5). Systolic heart failure (SHF) is treated with drugs that reduce the workload of the left ventricle. This is accomplished by decreasing afterload and preload. A first-line treatment for SHF is an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor inhibitor if the patient develops chronic cough. ACE inhibitors decrease afterload by decreasing angiotensin II (normally constricts peripheral vascular resistance arterioles) and decrease preload by decreasing aldosterone. Diuretics (e.g., loop diuretics, aldosterone blockers) compliment ACE inhibitors by decreasing preload. β-Blockers decrease sympathetic tone, which reduces myocardial O₂ consumption. It is considered first-line therapy for SHF. Digitalis may be useful because of its inotropic and vagotonic effects, particularly in those with severe heart failure or atrial arrhythmias. Direct vasodilating drugs (e.g., hydralazine) reduce systemic vascular resistance and pulmonary venous pressure. Therapeutic options for treating diastolic heart failure (DHF) include the use of an ACE inhibitor and β-blocker, the latter decreasing heart rate, which prolongs diastolic filling. Diuretics must be used with caution, because excessive diuresis may produce volume depletion and decrease the cardiac output.

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E. High-output heart failure (HOF)
   1. Definition
      • Form of heart failure in which cardiac output is increased compared with values for the normal resting state.
   2. Pathogenesis
      a. Increase in stroke volume (SV)
         • Example—hyperthyroidism
      b. Decrease in blood viscosity
         (1) A decrease in blood viscosity, decreases peripheral vascular resistance (PVR), which increases venous return to the heart.
         (2) Example—severe anemia
      c. Vasodilation of PVR arterioles
         (1) Vasodilation increases venous return to the heart.
         • An analogy is opening all the flood gates in a dam to release water into a river.
         (2) Examples—thiamine deficiency (decrease ATP synthesis; refer to Chapter 8), early phase of endotoxic shock (increased release of nitric oxide; refer to Chapter 5)
      d. Arteriovenous fistula
         (1) Arteriovenous communications bypass the microcirculation, which increases venous return to the heart.
         (2) Causes
            (a) Trauma from a knife wound (most common cause)
            (b) Surgical shunt for hemodialysis
            (c) Mosaic bone in Paget disease (refer to Chapter 24)
IV. Ischemic Heart Disease (IHD)

A. Definition
- Imbalance between myocardial O$_2$ demand and supply from the coronary arteries

B. Coronary artery blood flow
1. Coronary arteries provide O$_2$ to cardiac muscle.
   a. Normally fill during diastole
   b. Tachycardia (>180 bpm) decreases filling time, leading to ischemia.
2. Left anterior descending (LAD) coronary artery (Fig. 11-3A)
   a. Distribution includes:
      (1) Anterior portion of the LV
      (2) Anterior two thirds of the interventricular septum (IVS)
      (3) Apex of the heart
   b. Site for 40% to 50% of coronary artery thromboses
3. Right coronary artery (RCA) (see Fig. 11-3B)
   a. Distribution includes:
      (1) Posterobasal wall of the LV
      (2) Posterior one third of IVS
      • Sometimes perfused by the left circumflex artery
      (3) Right ventricle (80% of individuals)
      (4) Posteromedial papillary muscle in LV
      (5) Atroventricular and sinoatrial (SA) nodes
   b. Site for 30% to 40% of coronary artery thromboses
4. Left circumflex coronary artery (see Fig. 11-3C)
   a. Supplies the lateral wall of the LV (80% of individuals)
   b. Site for 15% to 20% of coronary artery thromboses
5. Collateral circulation may develop over time if there is slow occlusion of the vessels by atherosclerosis.
   • Protective effect on preventing an acute myocardial infarction (AMI)

C. Epidemiology
1. Major cause of death in the United States
   a. IHD is more common in men than women.
   b. Incidence peaks in men after age 60 years and in women after age 70 years.
2. Types
   a. Angina pectoris (most common type)
   b. Chronic ischemic heart disease (CIHD)
   c. Sudden cardiac death
   d. Acute myocardial infarction (AMI)
3. Risk factors
   a. Age
      (1) Men ≥45 years old, women ≥55 years old
      (2) Most important risk factor
   b. Family history of premature coronary artery disease or stroke
   c. Lipid abnormalities
      (1) Low-density lipoprotein (LDL) >160 mg/dL
      (2) High-density lipoprotein (HDL) <40 mg/dL
d. Smoking tobacco, HTN, diabetes mellitus (DM)
e. Subtract 1 from the total number of risk factors if HDL >60 mg/dL.

D. Angina pectoris

1. Epidemiology
   a. Most common in middle-aged and elderly males
   b. Women are usually affected after menopause.
   c. Within 1 year of a diagnosis of stable angina, 10% to 20% of people with angina pectoris will develop an AMI or unstable angina.

2. Chronic (stable) angina pectoris
   a. Most common variant of angina
   b. Causes
      (1) Fixed, atherosclerotic coronary artery disease (most common cause)
         (a) One or more vessels are obstructed.
         (b) Severity of stenosis is usually >70%.
      (2) AV stenosis or HTN with concentric LVH
         • O₂ supply is not adequate for the thickened muscle wall.
      (3) Hypertrophic cardiomyopathy
      (4) Cocaine-induced coronary artery vasoconstriction
   c. Pathogenesis
      • Subendocardial ischemia due to decreased coronary artery blood flow (most common cause) or a thick muscle wall (concentric hypertrophy)
   d. Clinical findings
      (1) Exercise-induced substernal chest pain lasting 30 seconds to 30 minutes
         • Other precipitating events include sexual intercourse, climbing stairs, eating a heavy meal, emotional stress, and cold temperature.
      (2) Often accompanied by shortness of breath, diaphoresis, numbness, and pain in the left inner arm, shoulder, or jaw
      (3) Relieved by resting or nitroglycerin
      (4) Stress test shows ST-segment depression >1 mm (Fig. 11-4).

3. Prinzmetal variant angina
   a. Pathogenesis
      (1) Intermittent coronary artery vasospasm at rest with or without superimposed coronary artery atherosclerotic disease.
      (2) Vasoconstriction, in some cases, may be due to:
         (a) An increase in platelet thromboxane A₂ originating from thrombus material overlying an atherosclerotic plaque or, in 10% of cases, a thrombus not overlying an atherosclerotic plaque
         (b) An increase in endothelin
   b. Clinical findings
      • Stress test shows ST-segment elevation (transmural ischemia).

4. Unstable angina
   a. Pathogenesis
      (1) Severe, fixed, multivessel atherosclerotic disease
      (2) Disrupted plaques, with or without platelet nonocclusive thrombi, invariably present (refer to Chapters 5 and 10)
   b. Clinical findings
      (1) Frequent bouts of chest pain occur at rest or with minimal exertion.
      (2) It may progress to an AMI.

**11-4: Electrocardiogram with ST segment depression.** Tracing in A is the patient at rest. 1, The PQ junction (baseline reference); 2, the J point, where the QRS complex joins the ST segment; 3, the ST segment 80 msec from the PQ point. Tracing in B shows the amount of ST segment depression measured 80 msec past the J point is 4 mm. *(From Goldman L, Ausiello D: Cecil's Textbook of Medicine, 23rd ed, Philadelphia, Saunders Elsevier, 2008, p 481, Fig. 70-2.)*
5. Diagnostic tests
   a. Resting electrocardiogram
   b. Exercise test with electrocardiogram (ECG) monitoring alone (without imaging)
   c. Stress echocardiography or stress testing with myocardial perfusion imaging
   d. Coronary angiography
   e. Multidetector computed tomography

Nonpharmacologic therapy of angina pectoris includes losing weight, cessation of smoking, placing the patient on a low cholesterol diet, and encouraging daily aerobic exercise. Pharmacologic therapy for angina involves the use of antiischemic agents. Nitrates (release nitric oxide) cause venodilation (reduces preload and wall tension in the ventricles), vasodilation of the coronary arteries, and vasodilation of peripheral resistance arterioles (reduces afterload). β-Blockers decrease myocardial O2 consumption by reducing heart rate and systolic blood pressure (initial therapy for all patients with stable angina). Calcium channel blockers cause vasodilation of the coronary arteries and peripheral resistance arterioles. They are the drug of choice for treating Prinzmetal variant angina. Aspirin inhibits platelet aggregation, which decreases the risk for developing a platelet thrombus (refer to Chapters 5 and 15). Clopidogrel (inhibits platelet aggregation) should be used if patients are allergic to aspirin. Heparin plus aspirin is used for patients with unstable angina and reduces the risk for developing a myocardial infarction and refractory angina. Ranolazine is indicated for chronic angina that is inadequately controlled by other antiangiinal drugs. If homocysteine levels are increased, the patient should be placed on pharmacologic doses of folic acid. If C-reactive protein is increased, the patient should be placed on statin drugs to lower the LDL levels to 70 mg/dL or less. This stabilizes disrupted plaques and reduces the risk for thrombosis. Revascularization procedures include percutaneous transluminal coronary angioplasty (PTCA) and stenting. Balloon angioplasty dilates and ruptures the atheromatous plaque to improve blood flow (restenosis commonly occurs) and intracoronary stents (the most common procedure) bypass the obstruction (restenosis less common). Complications are associated with either procedure (e.g., thrombosis, localized dissection). To prevent platelet thrombosis in these revascularization procedures, abciximab (inhibits the GpIIb-IIIa fibrinogen receptor in platelets; refer to Chapter 15) is used. Coronary artery bypass graft (CABG) is reserved for patients with left main coronary artery disease and for those patients with symptomatic three-vessel disease. Internal mammary artery grafts have the best graft patency after 10 years, whereas saphenous vein grafts commonly show “arterialization” of the vessels with fibrosis after 10 years.

E. Chronic ischemic heart disease (CIHD)
   1. Definition—progressive CHF resulting from long-term ischemic damage to myocardial tissue
   2. Due to replacement of myocardial tissue with noncontractile scar tissue
   3. Clinical findings include:
      a. Biventricular CHF
      b. Angina pectoris
      c. Evolution into a dilated cardiomyopathy

F. Sudden cardiac death (SCD)
   1. Epidemiology
      a. Definition—unexpected death from cardiac causes in persons without symptomatic heart disease or within 1 hour after the onset of symptoms
      b. Approximately 70% of sudden natural deaths have a cardiac cause, and 80% of those are attributable to CIHD.
      c. Risk factors
         (1) Ischemic heart disease (most important risk factor)
         (2) Obesity, glucose intolerance, hyperlipidemia, LVH, HTN, smoking, recent non–Q wave (NSTEMI [non–ST elevation myocardial infarction]) myocardial infarction
      d. Most frequently occurs in the morning hours (8 AM to 11 AM) and late afternoon to evening hours (4 PM to 7 PM).
      e. Non–coronary artery causes of SCD syndrome include:
         (1) Cardiomyopathy (all types)
         (2) AV stenosis
         (3) Mitral valve prolapse, cocaine, myocarditis, conduction defects (Wolff-Parkinson-White syndrome)
f. Causes of SCD in children include:
   (1) AV stenosis (most common cause)
   (2) Cardiomyopathies (hypertrophic cardiomyopathy is the most common cause)
   (3) Wolff-Parkinson-White syndrome

2. Pathogenesis of SCD in adults
   a. Lethal arrhythmia occurs (e.g., ventricular tachycardia in 75% of cases).
   b. Severe atherosclerotic coronary artery disease with disrupted plaques is commonly present.
      • Occlusive vessel thrombosis is usually not present in 80% of cases.

G. Acute myocardial infarction (AMI)
1. Epidemiology
   a. Most common cause of death in adults in the United States
   b. Prominent in males between 40 and 65 years old
   c. No predominant sex predilection after 65 years old
   d. At least 25% of AMIs are clinically unrecognized.

2. Pathogenesis
   a. Sequence for developing an AMI
      (1) An atheromatous plaque is suddenly disrupted (see Fig. 5-15).
      (2) Subendothelial collagen and thrombogenic necrotic material are exposed.
      (3) Platelets adhere to the exposed material and eventually form an occlusive platelet thrombus.
   b. Role of thromboxane A₂ in an AMI (refer to Chapter 15)
      (1) Platelet aggregating agent that contributes to the formation of the platelet thrombus
      (2) Acts as vasoconstrictor and causes vasospasm of the artery to reduce blood flow

3. Less common causes of an AMI include:
   a. Vasculitis (e.g., polyarteritis nodosa, Kawasaki disease)
   b. Cocaine use (the coronary arteries are normal)
   c. Embolization of plaque material from the aorta or coronary artery
   d. Thrombosis syndromes
      • Examples—antithrombin III deficiency, polycythemia vera
   e. Dissection of blood into the wall of a coronary artery
      • Examples—revascularization procedure, aortic dissection

4. Types
   a. STEMI (ST segment elevation myocardial infarction)
      (1) Full thickness of the myocardium is involved.
      (2) New Q waves develop in an ECG.
   b. Non-STEMI (NSTEMI)
      (1) Inner third of the myocardium (subendocardium) is involved.
      (2) Q waves are absent.

5. Ischemia/reperfusion injury in AMI
   a. Reperfusion may occur spontaneously or, most commonly, after percutaneous coronary intervention (PCI) and/or thrombolytic (fibrinolytic) therapy.
      (1) Reperfusion may have beneficial effects if previously ischemic myocardial cells are salvaged, and those myocardial cells that are already irreversibly damaged are destroyed. These two processes limit the size of the infarction.
      (2) Reperfusion may have deleterious effects if ischemic myocardial cells that were not irreversibly injured are damaged by reperfusion and then destroyed (this is called the reperfusion injury).
        • Up to 50% of infarction size may be secondary to reperfusion injury.
   b. Tissue effects of reperfusing ischemic tissue depend on when reperfusion occurs after myocardial blood flow has ceased.
      (1) If reperfusion occurs <3 hours after cessation of blood flow, there is a greater chance of salvaging ischemic but not irreversibly damaged tissue.
        (a) Salvaged tissue is biochemically altered, which may interfere with normal function for several days or longer (called myocardial stunning) and also predispose tissue to reperfusion dysrhythmias.
        (b) Reperfusion of previously irreversibly damaged cells results in their death and the formation of contraction bands due to the entry of Ca²⁺ into the cytosol causing hypercontraction of the myocytes (Fig. 11-5). Contraction bands: calcium-mediated sign of reperfusion.
(2) If reperfusion occurs >3 hours, there is a much greater chance that previously ischemic cells are irreversibly damaged (called reperfusion injury).
- Overall size of the infarction will increase.

c. **Mechanism of irreversible myocardial injury**
   (1) Superoxide free radicals (FRs) are locally produced by xanthine oxidase and irreversibly damage myocytes.
   (2) Acute inflammation occurs with an infiltration of tissue by neutrophils (refer to Chapter 3).
      (a) Neutrophils occlude capillary lumens, which decreases blood flow to the ischemic tissue.
      (b) Neutrophils release proteolytic enzymes and increase the production of reactive O₂ species (refer to Chapter 2).
   (3) Other factors include platelet activation, complement system activation, and apoptosis.

6. **Gross and microscopic findings**
   a. During the first 24 hours
      (1) No gross changes are evident until 24 hours.
      (2) Coagulation necrosis is present within 12 to 24 hours.
      (3) Neutrophils begin to enter the area of infarction from the periphery.
   b. From 1 to 3 days
      (1) Pallor of the infarcted tissue is apparent.
      (2) Myocyte nuclei and striations disappear (see Fig. 2-15A).
      (3) Neutrophils are abundant and lyse dead myocardial cells.
   c. During days 3 to 7
      (1) Red granulation tissue surrounds the area of infarction.
      (2) Macrophages begin to remove necrotic debris.
      (3) This period is the most dangerous time for rupture.
   d. From 7 to 10 days
      (1) Necrotic area is bright yellow (Fig. 11-6; see Fig. 2-15B).
      (2) Granulation tissue and collagen formation are well developed.
   e. During the first 2 months
      (1) Infarcted tissue is replaced by white, patchy, noncontractile scar tissue.
      (2) If the amount of scar tissue is increased, CIHD is likely to occur (see earlier).

7. **Clinical findings**
   a. Sudden onset of severe, crushing retrosternal pain
      (1) Usually lasts >30 minutes.
      (2) Not relieved by nitroglycerin
      (3) Usually radiates down the inner left (most common) or right arm (less common), into the shoulders, or into the jaw or epigastrium
         (a) Nerves to the heart are T1 to T5.
         (b) Radiation to the inner arm and shoulder is in the T1 distribution.
         (c) Radiation to the epigastrium is in the T4 to T5 distribution.
      (4) Associated with sweating (diaphoresis), anxiety, and hypotension

Reperfusion injury: previously ischemic cells become irreversibly damaged
Irreversible injury: superoxide FRs
Neutrophils contribute to irreversible myocardial injury
AMI: coagulation necrosis within 24 hours
AMI: heart softest 3–7 days; danger of rupture
AMI: retrosternal pain >30 minutes, radiation to left inner arm/shoulder, diaphoresis
Nerves to heart: T1–T5
Inner arm pain: T1 distribution
Epigastrium radiation: T4–T5 distribution
b. “Silent” AMIs occur in ~20% of cases.
   (1) Often occur in the elderly and in individuals with diabetes mellitus, who frequently have neuropathies and cannot feel pain.
   (2) May also occur in people who have a high pain threshold.
c. STEMI infarctions have an increased early mortality rate compared to NSTEMI infarctions.
d. NSTEMI infarctions
   (1) Increased risk of reinfarction
   (2) Increased risk for SCD post-MI
8. Complications of STEMI AMIs
a. Cardiogenic shock occurs in ~7% of cases.
   • Revascularization improves survival.
b. Arrhythmias
   (1) Ventricular premature contractions are the most common arrhythmia.
   (2) Most common cause of death is ventricular fibrillation.
   (3) Heart block
      (a) Occurs in 5% of inferior AMIs
      (b) Occurs in 3% of anterior AMIs
c. Congestive heart failure
   • Usually occurs within the first 24 hours
d. Rupture
   (1) Most commonly occurs between days 3 and 7 (range is 1–10 days)
   (2) Anterior wall rupture (Fig. 11-7)
      (a) Produces cardiac tamponade
      (b) Associated with thrombosis of the LAD coronary artery
   (3) Posteromedial papillary muscle rupture or dysfunction
      (a) Most often associated with inferior AMIs due to thrombosis of the RCA
      (b) Presents with an acute onset of MV regurgitation and LHF
   (4) Interventricular septum (IVS) rupture
      (a) Most often associated with a thrombosis in the LAD coronary artery
      (b) Produces a left-to-right shunt, causing RHF
         • Diagnosis is made by finding an increased O₂ saturation and pressure in the RV.
e. Mural thrombus
   (1) Occurs in ~10% of AMIs.
   (2) Most often associated with LAD coronary artery thrombosis.
   (3) Danger of peripheral embolization (refer to Chapter 5).
f. Fibrinous pericarditis with or without effusion (see Fig. 3-8B)
   (1) Most often occurs between day 1 to 7 of a STEMI.
      (a) Presents with substernal chest pain that is relieved by leaning forward and aggravated by leaning backward
      (b) Precordial friction rub is present on auscultation (see later)
         • Due to increased vessel permeability in the pericardium (exudate of acute inflammation)

11-7: Acute myocardial infarction with rupture of the free wall of the left ventricle (arrow). This rupture is unusual in that it occurred 3 weeks after an acute myocardial infarction. (From Klatt F: Robbins and Cotran Atlas of Pathology, Philadelphia, Saunders, 2006, p 25, Fig. 2-30.)
Autoimmune pericarditis (Dressler syndrome)
(a) Usually occurs 1 to 8 weeks after a STEMI infarction.
(b) Autoantibodies are directed against the damaged pericardial antigens (type II hypersensitivity reaction; refer to Chapter 4).
(c) Fever and a precordial friction rub are present.

Ventricular aneurysm (Fig. 11-8)
(1) Clinically recognized within 4 to 8 weeks after a STEMI.
   • Begins to develop in the first 48 hours
(2) Precordial bulge occurs during systole
   • Blood enters the aneurysm, causing anterior chest wall movement.
(3) Complications
   (a) SHF occurs because of the lack of contractile tissue.
   (b) Clot material may embolize.
   (c) Rupture is uncommon.
      • Scar tissue has good tensile strength.

h. Right ventricular AMI
(1) Associated with RCA thrombosis.
(2) Occurs in one third of inferior AMIs.
   • Clinically significant in 30% of cases
(3) Clinical findings include:
   (a) Hypotension
   (b) RHF
   (c) Preserved LV function

9. Laboratory diagnosis of AMI (Fig. 11-9)
a. Serial testing for creatine kinase isoenzyme MB (CK-MB)
(1) CK-MB appears within 4 to 8 hours, peaks at 24 hours, and disappears within 1.5 to 3 days.
   (a) Sensitivity and specificity is 95%.
   (b) Increased in myocarditis, muscular dystrophy, rhabdomyolysis (rupture of muscle), and polymyositis.
      • Decreases the test’s specificity; however, they are not common disorders and are easy to differentiate from an AMI.
Reinfarction: reappearence of CK-MB after 3 days

cTnI, cTnT: cannot diagnose reinfarction

cTnI, cTnT: gold standard for diagnosis of AMI

ECG findings in STEMI: inverted T waves, elevated ST segments, Q waves

Inverted T waves: correlates with ischemia at periphery of infarct

ST elevation: correlates with injured myocardial cells surrounding area of necrosis

Q waves: correlates with area of coagulation necrosis

10. Correlation of ECG changes with pathologic changes (Fig. 11-10)

a. Inverted T waves
   • Correlates with areas of ischemia at the periphery of the infarct

b. Elevated ST segments
   • Correlates with injured myocardial cells surrounding the area of necrosis

c. New Q waves
   • Correlates with the area of coagulation necrosis

11. Classic ECG patterns in AMI

a. LAD coronary artery anterior wall infarction
   • Q waves in leads V₁–V₂

b. Anteroseptal infarction due to proximal LAD coronary artery occlusion
   • Q waves in leads V₁–V₂

c. Anterolateral infarction due to mid-LAD or circumflex coronary artery occlusion
   • Q waves in leads V₄–V₆, I, aVL

d. Lateral wall infarction due to left circumflex coronary artery occlusion
   • Q waves in leads I, aVL

e. Inferior wall infarction due to RCA occlusion
   • Q waves in leads II, III, aVF
V. Congenital Heart Disease (CHD)

A. Fetal circulation (Fig. 11-11)

1. Chorionic villi in the placenta (refer to Chapter 22)
   a. Derived from the fetus
   b. Primary site for O\textsubscript{2} exchange
   c. Umbilical vein derived from villus vessels
2. Umbilical vein
   - Vessel with the highest PO\textsubscript{2} in the fetal circulation
3. Inferior vena cava blood drains into the right atrium.
   - Most blood is directly shunted into the left atrium through the foramen ovale.
4. Superior vena cava (SVC) blood
   - Most blood from the SVC is directed from the right atrium into the RV.
5. Pulmonary artery blood
   a. Blood from the pulmonary artery is shunted through a patent ductus arteriosus (PDA) into the aorta.
      - Ductus arteriosus is kept open by prostaglandin E\textsubscript{2}, a vasodilator synthesized by the placenta.

Nonpharmacologic therapy of an AMI includes limiting patient activity, cessation of smoking, and placing the patient on a diet that is low in cholesterol and salt. Pharmacologic therapy includes antiplatelet therapy (aspirin, clopidogrel if allergic to aspirin); nitrates (reduce coronary artery spasm; venodilation decreases ventricular preload, hence reducing myocardial O\textsubscript{2} consumption); pain medication (morphine); nasal O\textsubscript{2} (2–4 liters/minute); \(\beta\)-blockers (decrease sympathetic tone, hence decreasing myocardial O\textsubscript{2} consumption; they also prevent tachyarrhythmias); ACE inhibitors (reduce LV dysfunction and dilation, hence slowing the progression of CHF); warfarin (often used along with aspirin); and myocardial reperfusion, which markedly improves survival. In STEMI, percutaneous coronary artery intervention is more effective than fibrinolytic therapy. CABG is necessary in some patients. It is important to measure the ejection fraction before discharge to evaluate the severity of damage and to provide an index of prognosis.

11-11: Fetal circulation. The umbilical veins have the highest oxygen content. The ductus venosus shunts most of the blood past the liver, and the foramen ovale and the ductus arteriosus act as shunts to bypass the pulmonary circulation. All of these shunts normally close at or shortly after birth, as do the umbilical vein and distal part of umbilical arteries. Arrows indicate blood flow. (From Moore NA, Ray WA: Rapid Review Cross and Developmental Anatomy, 3rd ed, Philadelphia, Mosby Elsevier, 2010, p 50, Fig. 2-30.)
Rapid Review Pathology

Fetal pulmonary arteries
b. Hypertrophied from chronic vasoconstriction due to decreased \( P_O_2 \).
(1) Prevents blood from entering the pulmonary capillaries and left atrium

6. Descending aorta
a. Blood flows toward the placenta via two umbilical arteries.
   - Increased risk for congenital abnormalities with a single umbilical artery (refer to Chapter 6)

b. Umbilical arteries have the lowest \( O_2 \) concentration.

7. Changes in the fetal circulation at birth
a. Ductus arteriosus closes
   (1) Anatomic closure should occur within 2 to 8 weeks.
   (2) It becomes the ligamentum arteriosum
b. Gas exchange occurs in the lungs.
   - Pulmonary artery opens up because of the increase in \( P_a O_2 \).
c. Foramen ovale functionally closes in 24 hours.

B. Congenital heart diseases (CHDs)

1. Epidemiology
a. Most common heart disease in children
b. Incidence is higher in premature than full-term newborns.
c. No identifiable cause for CHD in \( \sim 90\% \) of cases
d. Most common known causes of CHD are:
   (1) Genetic-environmental interactions (i.e., multifactorial inheritance; \( 85\% \) of cases)
   (2) Primary genetic factors (single gene disorders, chromosome disorders; [see later] \( 10\% \) of cases)
   (3) Environmental factors (e.g., isotretinoin, alcohol, viruses [rubella], maternal factors; \( 3\%–5\% \) of cases [see later])
e. Examples of maternal risk factors
   (1) Increased age (>45 years old)
   (2) Previous child with CHD (1:50 chance of having second child with CHD)
   (3) Poorly controlled DM during pregnancy
      (a) Left-ventricular outflow obstruction (e.g., AV stenosis, hypertrophied IVS)
      (b) Transposition of the great arteries, ventricular septal defect (VSD)
   (4) Alcohol intake during pregnancy
      - PV stenosis, VSD
   (5) Congenital infection (e.g., rubella) during pregnancy
      - PDA, PV stenosis
   (6) Aspirin intake
      - Persistent PH syndrome
   (7) Diphenylhydantoin intake
      - AV stenosis, PV stenosis
   (8) Systemic lupus erythematosus (SLE)
      - Heart block, pericarditis, endomyocardial fibrosis
f. Spectrum of CHD
   (1) Valvular diseases (e.g., PV stenosis)
   (2) Shunts (acyanotic and cyanotic types)
g. Systemic complications
   (1) Secondary polycythemia with clubbing of the fingers
      (a) Occurs in cyanotic CHD.
      (b) Decreased \( P_a O_2 \) stimulates the release of erythropoietin, which increases RBC production by the bone marrow.
   (2) Increased risk for developing infective endocarditis before or after corrective surgery
   (3) Metastatic abscesses may occur particularly in cyanotic CHD.
2. \( O_2 \) saturation (\( S_a O_2 \)) findings that help distinguish cyanotic versus noncyanotic shunts
a. Left-to-right shunts: step up of \( S_a O_2 \) in right heart
   (1) Unoxgenated blood from the right side of the heart (\( S_a O_2 \), 75%) is mixed with oxygenated blood on the left side of the heart (\( S_a O_2 \), 95%).
   (2) \( S_a O_2 \) is increased in the right side of the heart (step up) from 75% to 80% or more in affected chambers/vessels.

b. Right-to-left shunts: step up of \( S_a O_2 \) in right heart
   (1) Oxygenated blood from the left side of the heart (\( S_a O_2 \), 95%) is mixed with unoxgenated blood on the right (\( S_a O_2 \), 75%).
Heart Disorders

(2) Sao₂ is decreased in the left side of the heart (step down) from 95% to 80% or less in affected chambers/vessels.
   (a) Whether cyanosis occurs depends on how low the Sao₂ is in the left side of the heart.
   (b) If Sao₂ is above 85%, cyanosis is not present, because only a small volume of blood is shunted between the two sides of the heart.
   (c) If Sao₂ is below 80%, cyanosis is present, because a large volume of blood is shunted between the two sides of the heart.

3. Left-sided to right-sided heart shunts
   a. Volume overload occurs in the right side of the heart, which may have several complications, such as:
      (1) Pulmonary hypertension (PH)
      (2) RVH, due to PH
          • PH increases the afterload the RV must contract against to eject blood, which causes concentric hypertrophy of the RV.
      (3) LVH, due to more blood returning to the left heart than normal.
          • Increases LV volume (preload) and produces an eccentric type of LVH.
      (4) Reversal of the shunt, because the pressure in the right side of the heart is greater than the pressure in the left side
          (a) Signs of reversal of the shunt include cyanosis (called Eisenmenger syndrome) and clubbing of the fingers (Fig. 11-12).
          (b) Another term is tardive cyanosis (late-onset cyanosis)
   b. Ventricular septal defect (VSD; Fig. 11-13A)
      (1) Most common CHD (30% of all CHDs)
      (2) Accounts for ~25% of CHD in children and ~10% of CHD in adults
      (3) Defect in the membranous part of the IVS (75%–80% of the cases), the muscular or trabecular part of the septum (5%–20% of cases), or in less common sites
      (4) Equal frequency in males and females
      (5) Associations of VSD with other CHDs include:
          (a) Atrial septal defect (35% of cases)
          (b) PDA (22%)
          (c) Coarctation of the aorta (17% of cases)
          (d) Subvalvular AV stenosis (4% of cases)
      (6) Multiple VSDs are more likely to be associated with tetralogy of Fallot.
      (7) Associations of VSD with other congenital diseases include:
          (a) Cri du chat syndrome (refer to Chapter 6).
          (b) Fetal alcohol syndrome (refer to Chapter 6).
      (8) Acquired in an AMI with rupture of the IVS
      (9) Harsh pansystolic murmur is present along the lower left sternal border.
      (10) Increased Sao₂ in the RV and pulmonary artery (PA)
      (11) Spontaneously closes in 30% to 50% of cases
          • Criteria have been established as to whether corrective surgery is necessary.
      (12) Lifetime risk for developing infective endocarditis ranges from 5% to 30%.
   c. Atrial septal defect (ASD; see Fig. 11-13B)
      (1) Accounts for 8% to 10% of all CHDs.
      (2) Incidence greater in females than males
11-13: A, Ventricular septal defect (VSD). B, Atrial septal defect (ASD). C, Patent ductus arteriosus (PDA). D, Tetralogy of Fallot. E, Complete transposition of the great vessels. F, Postductal coarctation. Ao, Aorta; AV, aortic valve; DA, ductus arteriosus; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; LVH, left ventricular hypertrophy; MV, mitral valve; PA, pulmonary artery; PH, pulmonary hypertension; PV, pulmonary valve; RA, right atrium; RV, right ventricle; RVH, right ventricular hypertrophy; SVC, superior vena cava; TV, tricuspid valve. (A to F from Goljan EF: Star Series: Pathology, Philadelphia, Saunders, 1998.)
(3) Most common CHD in adults
(4) Patent foramen ovale (secundum type) is the most common cause in 80% of cases.
(5) Associations of ASD with other CHDs include:
   (a) Fetal alcohol syndrome (refer to Chapter 6)
   (b) Down syndrome (primum type in 25% of cases; refer to Chapter 6)
(6) Soft mid systolic murmur along the upper sternal border associated with increased PA blood flow.
   • Characteristic wide and fixed split of the S₂ heart sound
(7) Paradoxical embolism may occur (venous clot material in the systemic circulation; refer to Chapter 5)
(8) Increase in SaO₂ in the right atrium (RA), RV, and PA.
(9) Criteria have been established as to whether surgical closure is required.
d. Patent ductus arteriosus (PDA; see Fig. 11-13C)
   (1) PDA accounts for 10% of all CHDs.
   (2) Ductus arteriosus remains open at birth (normal in a fetus to be open).
      • Isolated defect in 90% of cases
(3) Associations of PDAs include:
      (a) Congenital rubella
      (b) Respiratory distress syndrome (due to persistence of a decreased PaO₂)
      (c) Complete transposition of the great vessels
      (d) Tetralogy of Fallot
(4) Machinery murmur is heard continuously through systole and diastole.
(5) Increased SaO₂ in the PA
(6) Reversal of the shunt may occur if PH develops from the increase in PA blood flow.
      (a) In a reversal of the shunt, unoxygenated blood enters the aorta below the subclavian artery.
      (b) Child has a pink upper body and a cyanotic lower body, which is called differential cyanosis.
(7) Treatment
      (a) Intravenous indomethacin (inhibits prostaglandin E₂, a vasodilator)
      (b) Surgical closure (e.g., banding)
4. Right-sided to left-sided heart shunts
   a. Cyanotic CHD
   b. Complications (see earlier)
   c. Tetralogy of Fallot
      (1) Most common cyanotic CHD after the age of 1 year (see Fig. 11-13D)
         (a) Accounts for 10% of all cases of CHD
         (b) Accounts for 50% to 70% of cyanotic CHD
         (c) Accounts for 85% of adults with cyanotic CHD
      (2) Defects in tetralogy of Fallot
         (a) VSD
         (b) Infundibular (most common) or PV stenosis
            • Degree of PV stenosis determines whether the infant develops cyanosis or not after birth (see later).
         (c) RVH
         (d) Dextorotated aorta with a right-sided aortic arch (25% of cases)
      (3) Onset of cyanosis usually after 3 months of age
      (4) Harsh systolic crescendo/decrescendo murmur that results from RV outflow tract obstruction
      (5) Minimal infundibular PV stenosis or PV stenosis
         (a) Leads to increased oxygenation of blood in the lungs
         (b) Less right-to-left shunting of blood through the VSD
         (c) Absence of cyanosis (SaO₂ >80%; acyanotic tetralogy).
      (6) Severe infundibular stenosis or PV stenosis
         (a) Less oxygenation of blood in the lungs
         (b) Increased right-to-left shunting of blood through the VSD
         (c) Cyanosis is present (SaO₂ <80%).
      (7) Decrease in SaO₂ in the LV and aorta (Ao)
      (8) Cardioprotective shunts increase oxygenation in tetralogy of Fallot.
         (a) Presence of an ASD steps up SaO₂ in the RA; therefore the blood that is shunting into the left side of the heart has a higher SaO₂.
A PDA shunts unoxygenated blood from the Ao to the PA for oxygenation in the lungs.

9. Tet spells (hypoxic spells)
   - Spells are caused by a sudden increase in hypoxemia and cyanosis related to crying, fever, hypotension, anemia, or by events that exacerbate RV outflow obstruction.
   - Squatting increases PVR, causing temporary reversal of the shunt.
   - Unoxygenated blood is forced back into the PA for oxygenation.

D. Complete transposition of the great arteries (see Fig. 11-13E)
   1. Definition—embryologic defect results from abnormal formation of the truncal and aortopulmonary septa
   2. Defects in complete transposition
      - Ao arises from the RV.
      - PA arises from the LV.
      - Left and right atria (LA, RA) are normal (the vena cava empties into the RA and the pulmonary vein empties into the LA).

3. Cardioprotective shunts
   - ASD steps up $\text{Sa}_2$ in the RA.
     - Increases $\text{Sa}_2$ in the RV for delivery to tissue via the transposed Ao
   - VSD shunts blood into the LV for oxygenation in the lungs via the transposed PA.
   - PDA shunts blood into the transposed PA for oxygenation in the lungs.

E. Other types of cyanotic CHD include:
   1. Total anomalous pulmonary venous return
      - Pulmonary vein empties oxygenated blood into the RA.
   2. Truncus arteriosus
      - Ao and the PA share a common trunk and intermix their blood.
   3. TV atresia
      - In addition to the TV atresia, there is usually an ASD with a right-to-left shunt.

C. Coarctation of the aorta (Fig. 11-14A and B; see Fig. 11-13F)
   1. Accounts for 6% to 8% of all CHDs
   2. Infantile (preductal) coarctation
      a. This type accounts for 70% of all coarctations.
      b. Constriction in the Ao is between the subclavian artery and the ductus arteriosus.
      c. It is associated with other congenital heart defects (e.g., VSD) and Turner syndrome.
      d. Infants usually develop CHF and can die unless corrective surgery is performed.
3. Adult coarctation of the aorta
   a. Accounts for 30% of all coarctations
   b. Develops in children (most common) and adults (less common)
   c. Constriction of the Ao distal to the ligamentum arteriosum (see Fig. 11-13F)
      (1) Blood flow into the proximally located branch vessels is increased, which increases
          the blood pressure.
      (2) Blood flow below the constriction is decreased.
      (3) Constriction in the Ao produces a systolic ejection murmur posteriorly in the
          midthorax.
      (4) An additional defect that is often present is a bicuspid AV (50% of cases), which
          also produces a systolic ejection murmur along the sternal border.
   d. Clinical findings and possible complications proximal to the coarctation
      (1) Increase in the upper extremity blood pressure, due to increased blood flow
          particularly in the subclavian arteries.
      (2) Dilation of the Ao, which increases the risk for developing an aortic dissection
          (occurs in 2% to 6% of patients; refer to Chapter 10).
      (3) Increased cerebral blood flow, which increases the risk for developing berry
          aneurysms (refer to Chapters 10 and 26).
   e. Clinical findings and possible complications distal to the coarctation
      (1) Decrease in the SBP and pulse amplitude in the lower extremity (>10 mm Hg
          difference in blood pressure from the upper extremities).
      (2) Leg claudication (pain in calf or buttocks when walking) may be present
          along with slight underdevelopment of the musculature compared to the
          upper body.
      (3) Decreased renal blood flow, which activates the renin-angiotensin-aldosterone
          (RAA) system, causing hypertension.
   f. Development of collateral circulations (see Fig. 11-14A)
      (1) Collaterals develop between the intercostal arteries (ICAs) above and below the
          constriction.
         (a) Anterior ICAs arise from the internal thoracic artery.
         (b) Posterior ICAs arise from the Ao.
         (c) Increased pressure in the aorta extends into the subclavian artery \(\rightarrow\) into the
             internal thoracic artery \(\rightarrow\) into the anterior ICAs, which stimulates the
             formation of a collateral circulation. The posterior ICAs reverse blood flow into
             the Ao.
      (2) Collaterals develop between the superior epigastric artery and the inferior
          epigastric artery.
         (a) Internal thoracic artery becomes the superior epigastric artery.
         (b) Superior epigastric artery forms collaterals with the inferior epigastric artery,
             which is a branch of the external iliac artery.
         (c) Reversal of blood flow in the inferior epigastric artery forces blood into the
             external iliac artery.
      (3) Chest radiograph shows rib notching on the undersurface of the ribs (see
          Fig. 11-14B).
         • Increased blood flow through the enlarged, pulsating ICA in the neurovascular
           bundle in the costal groove of the rib wears the bone away, producing rib
           notching.
   g. Surgical removal of a coarctation corrects the hypertension.

VI. Acquired Valvular Heart Disease
A. Rheumatic fever (RF)

1. Epidemiology
   a. First attack of RF usually occurs between 5 and 15 years of age.
   b. Develops over 1 to 5 weeks (average 20 days) after a group A streptococcal
      \((\text{Streptococcus pyogenes})\) pharyngitis.
      (1) Pharynx is the only site for infection leading to RF.
      (2) Nephrogenic strains of group A streptococcus that produce poststreptococcal
          glomerulonephritis, lack the types of matrix (M) proteins (virulence factors)
          in their cell wall that are present in pharyngeal strains; hence they never
          produce RF.
   c. Risk factors for developing streptococcal pharyngitis
      (1) Crowding, poverty
      • RF is common in impoverished countries.
(2) Young age
(3) Living in Salt Lake City, Utah
  - For unexplained reasons, this area in the United States has the highest incidence and prevalence of RF.
d. Recurrent RF produces chronic valvular disease.

2. Pathogenesis
   a. Antibody-mediated disease that follows a group A streptococcal infection of the pharynx.
   b. Host develops antibodies against group A streptococcal M proteins.
      (1) Antibodies that are produced cross-react with similar proteins in human tissue (called mimicry).
      - Type II antibody-mediated hypersensitivity reaction (HSR; refer to Chapter 4).
      (2) Some evidence that cell-mediated immunity (type IV HSR) is also involved; however, this has not been confirmed.

3. Clinical findings in acute RF
   a. Migratory polyarthritis (~75% of cases)
      (1) Most common initial presentation of acute RF
      (2) Involves the large joints (knees), ankles, and wrists
      (3) No permanent joint damage
   b. Carditis (~35% of cases)
      (1) Most serious complication
      (2) Fibrinous pericarditis presents with precordial chest pain with or without a friction rub.
      (3) Myocarditis usually presents with signs of CHF.
         (a) Most common cause of death in acute RF
         (b) Aschoff bodies are present in myocardial tissue (a postmortem finding).
            - Lesions have a central area of fibrinoid necrosis surrounded by Anitschkow cells (reactive histiocytes).
      (4) Endocarditis refers to inflammation of cardiac valves.
         (a) It most commonly involves the MV, followed by the AV, followed by the TV.
         (b) Sterile, verrucous vegetations develop along the line of closure of the valve (Fig. 11-15A).
            - Embolism is uncommon, but does occur rarely.

**Migratory polyarthritis**
MC initial presentation

**Carditis:** pericarditis, myocarditis, endocarditis (valves)

**Myocarditis** MCC death in acute RF

**Endocarditis:** MV most often involved, followed by AV; sterile vegetations

(c) MV regurgitation or AV regurgitation occurs depending upon which valve is inflamed.
   • LHF may occur (systolic heart failure).
(d) Recurrent infection of the MV or AV over many years leads to stenosis of the respective valves.

  c. Subcutaneous nodules (~10% of cases) occur on the extensor surfaces of the forearms.
     (1) Nodules are very similar to those seen in rheumatoid arthritis.
     (2) Centers of the nodules have fibrinoid necrosis (refer to Chapter 2).

d. Erythema marginatum presents as evanescent circular rings or C-shaped areas of erythema around normal skin (~10% of cases; see Fig. 11-15B).

e. Sydenham chorea is characterized by reversible rapid, involuntary movements affecting all the muscles (~10% of cases).
   • Late manifestation of acute RF.

4. Diagnosis (revised Jones criteria)
   a. One major criterion and two minor criteria if supported by evidence of an antecedent group A streptococcal pharyngitis
   b. Major criteria include:
      • Carditis, migratory polyarthritis, chorea, erythema marginatum, or subcutaneous nodules
   c. Minor criteria include:
      (1) Previous RF or rheumatic heart disease
      (2) Arthralgia (pain without joint swelling)
      (3) Fever
      (4) Increased acute phase reactants (refer to Chapter 3)
         a. Increased erythrocyte sedimentation rate (ESR)
         b. Increased C-reactive protein
         c. Absolute neutrophilic leukocytosis
      (5) Prolonged PR interval (first-degree heart block)
   d. Laboratory tests
      (1) Increased antistreptolysin O (ASO) titers >400 Todd units
         a. Titers peak at 4 to 5 weeks after a streptococcal pharyngitis.
         b. High titers are supportive but not diagnostic for acute RF.
      (2) Increased anti-DNase B titers (less reliable than ASO titers)
      (3) Throat cultures possibly positive
   e. Treatment for acute RF
      (1) Bed rest
      (2) Course of penicillin to eradicate throat carriage of group A streptococcus
         • Continue penicillin for years if severe carditis is present.
      (3) Aspirin with or without presence of a murmur
      (4) Carditis and heart failure
         • Corticosteroids are added to the antibiotic regimen if a murmur is present.
   f. Treatment for chronic RF
      • Monthly treatment with intramuscular benzathine penicillin to prevent recurrences

B. Mitral valve stenosis
1. Epidemiology
   a. Most commonly caused by recurrent attacks of RF
   b. Twice as common in women than men
2. Pathophysiology
   a. Narrowing of the MV orifice (<2.5 cm² [normal 4–6 cm²]; Fig. 11-16)
   b. LA becomes dilated and hypertrophied because of increased work imposed on the LA in filling the LV during diastole.
3. Clinical findings
   a. Dyspnea and hemoptysis with rust-colored sputum (heart failure cells)
      • Due to pulmonary capillary congestion and hemorrhage into the alveoli as blood builds up behind the LA
   b. Atrial fibrillation
      (1) Atrial fibrillation (irregularly irregular pulse) is a complication of LA dilation and hypertrophy.
      (2) Intra-atrial thrombi in the LA develop from blood stasis (refer to Chapter 5).
         • Systemic embolization occurs in 80% of cases when atrial fibrillation is present.
c. Pulmonary venous hypertension
   (1) Due to chronic backup of LA blood in the pulmonary vein
   (2) RHF and concentric RVH from the increase in afterload

d. Dysphagia for solids
   (1) LA is the most posteriorly located chamber in the heart.
   (2) When markedly dilated, it compresses the esophagus, causing difficulty in
      swallowing solid food.

e. Murmur of MV stenosis is an opening snap followed by an early to mid diastolic
   rumble (see Box 11-1)
   (1) LA must exert a lot of pressure to open valves that are fibrosed and calcified.
   (2) Thickened valves open with a snap and blood from the LA, which should already
      have been emptied into the LV , gushes into the chamber and produces a diastolic
      rumble.
   (3) Deep held inspiration for 3 to 5 seconds does not alter the intensity of the opening
      snap or middiastolic rumble (Box 11-1).

4. Diagnosis is confirmed by echocardiography.
5. Treatment is replacement of the valve.

C. Mitral valve regurgitation

1. Epidemiology
   a. Definition—incompetent closure of MV causes retrograde blood flow into the LA
      during systole
   b. Causes
      (1) Mitral valve prolapse (MVP; most common cause)
      (2) Rupture/dysfunction of the posteroemedial papillary muscle (e.g., posterior AMI;
         second most common cause)
      (3) Functional MV regurgitation (stretching of MV ring)
         • Example—LHF
      (4) Infective endocarditis
      (5) Other causes—acute RF, dilated cardiomyopathy, myocarditis, Libman-Sacks
         endocarditis in SLE, and nonbacterial thrombotic endocarditis

2. Pathophysiology (Fig. 11-17A)
   a. Retrograde blood flow into the LA during systole
      (1) In acute MV regurgitation cardiac output is decreased.
      (2) If left uncorrected, LA becomes dilated/hypertrophied with the excess blood.
         (a) Pulmonary venous pressure increases, leading to pulmonary vein
             hypertension.
         (b) Pulmonary vein hypertension leads to RVH and a potential for RHF
   b. Volume overload occurs in the LV. There is more blood entering the LV in diastole
      because of the increase in LA blood volume.
      • Produces eccentric LVH
   c. In chronic compensated MV regurgitation, the LA and LV have time to dilate and
      accommodate the regurgitant volume, which eventually normalizes the stroke volume
      and cardiac output.
      • LA pressure is often normal or only slightly elevated.
d. In the chronic decompensated phase of mitral regurgitation, muscle dysfunction occurs, which increases LV and LA pressure. This ultimately leads to pulmonary edema and, potentially, cardiogenic shock.

3. Clinical findings
   a. Dyspnea, inspiratory crackles, and cough from LHF (usually systolic dysfunction type)
   b. Pansystolic murmur with $S_3$ and $S_4$ heart sounds (see Box 11-1)
      • Deep held inspiration for 3 to 5 seconds does not alter the intensity of the murmur or the abnormal heart sounds.

4. Diagnosis is confirmed by echocardiography.

5. Surgery is the only definitive treatment of severe MV regurgitation.

D. Mitral valve prolapse (MVP)

1. Epidemiology
   a. Most common MV lesion and cause of MV regurgitation
   b. More common in women than men
   c. Commonly associated with Marfan, Ehlers-Danlos, and Klinefelter syndromes
   d. Caused by defective embryogenesis in cells of mesenchymal origin

2. Pathophysiology
   a. Bulging of the anterior and/or posterior leaflets into the LA occurs during systole (see Fig. 11-17B).
      • Analogous to air underneath a parachute, the latter representing the MV.
   b. Redundancy of MV tissue
      • Excess of dermatan sulfate in the MV leaflet (called myxomatous degeneration)

3. Clinical findings
   a. Most patients are asymptomatic.
   b. Heart murmur of MVP is present.
      (1) Midsystolic click
         • Click is due to sudden restraint by the chordae tendineae of the prolapsed MV.
      (2) Mid to late systolic, MV regurgitant murmur follows the click
(3) Decreased preload causes the click and murmur to move closer to the \( S_1 \) heart sound (length of systole is decreased); examples of maneuvers or conditions that decrease preload include:

(a) Anxiety  
- Anxiety increases the heart rate, which decreases the time for diastolic filling of the LV.
(b) Standing  
- Standing decreases venous return to the right side of the heart.
(c) Valsalva maneuver (holding breath with epiglottis closed)  
- Produces an increase in positive intrathoracic pressure, which decreases venous return to the heart (compression of the vena cava and right side of the heart)

(4) Increased preload causes the click and murmur to move closer to the \( S_2 \) heart sound (the length of systole is increased); examples of maneuvers or conditions that increase preload include:

(a) Reclining  
- Increases venous return to the right side of the heart, which, in turn, increases volume in the left side of the heart.
(b) Squatting or sustained hand grip  
- Increase PVR, which impedes emptying of the LV.

c. Other findings include palpitations, chest pain, and rupture of the chordae producing acute MV regurgitation (see Fig. 11-17B).

4. Diagnosis is confirmed by echocardiography.

5. Treatment in symptomatic patients  
- \( \beta \)-Blocker decreases the heart rate and force of contraction, leading to less stretch and trauma to the prolapsed leaflets

E. Aortic valve (AV) stenosis

1. Epidemiology  
   a. Most common valve lesion of adults in Western countries
   b. Etiology
      (1) Calcific AV stenosis is the most common cause of stenosis in persons >60 years old (Fig. 11-18A).
      - Calcification may involve a normal or a congenital bicuspid AV (1%–2% of the population).

![Aortic stenosis. The superior view shows a tricuspid aortic valve with severe stenosis due to fibrocalcific involvement of the three valve cusps. B, Aortic stenosis. The stenotic valve causes concentric hypertrophy of the left ventricle. The pulse pressure is diminished; hence the pulse is diminished on physical exam. The cardiac output decreases with exercise, leading to syncope with exercise and angina. The latter is due to decreased filling of the coronary arteries in diastole, because of the increased heart rate from exercise. Less blood is delivered to the left ventricular muscle and subendocardial ischemia leads to angina. Ao, Aorta; AV, aortic valve; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; LVH, left ventricular hypertrophy; MV, mitral valve; PA, pulmonary artery; PH, pulmonary hypertension; PMI, point of maximal impulse; PV, pulmonary valve; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve. (A from Damjanov I, Linder J: Anderson's Pathology, 10th ed, St. Louis, Mosby, 1996, p 1268, Fig. 45.6B; B from Goljan EF: Star Series: Pathology, Philadelphia, Saunders, 1998.)
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(2) Congenital AV stenosis
   • Major cause of AV stenosis in persons <30 years old
(3) Other causes include age-related sclerosis of the AV and chronic RF (uncommon).

2. Pathophysiology (see Fig. 11-18B)
   a. Normal AV orifice is 3 cm².
      (1) Symptoms and signs appear when the orifice is <1 cm².
      (2) Severe AV stenosis is present when the orifice is <0.5 cm².
   b. Obstruction of LV outflow during systole
      • Reduction in the AV orifice area produces concentric LVH and poststenotic dilatation of the aorta, due to the jet stream of blood impacting on the wall of the vessel.
   c. At rest, the cardiac output is normal; however, with exercise, it may be decreased, particularly with severe AV stenosis.

3. Clinical findings
   a. Harsh systolic ejection murmur in the right second intercostal space with radiation into the neck
      • Deep held inspiration for 3 to 5 seconds does not increase the intensity of the murmur (see Box 11-1).
   b. Left-sided S₄ heart sound, due to decreased compliance of the LV (Box 11-1)
   c. Decreasing preload lessens the volume the LV must eject.
      • Murmur intensity decreases
   d. Increasing preload increases the volume the LV must eject.
      • Murmur intensity increases
   e. Angina with exercise
      (1) Decreased blood flow through the stenotic AV leads to reduced filling of the coronary arteries during diastole.
      (2) Subendocardial of the concentrically hypertrophied LV receives less blood, leading to subendocardial ischemia and angina.
   f. Syncope with exercise
      • Decreased blood flow through the stenotic AV leads to decreased blood flow to the brain and syncope.
   g. Hemolytic anemia (microangiopathic) with schistocytes (refer to Chapter 12)
      • Indication for AV replacement. Diminished pulse pressure (difference between SBP and DBP) with severe stenosis
      • Decreased cardiac output may occur in severe aortic stenosis.

4. Diagnosis is confirmed by echocardiography

5. Treatment in severe disease is AV replacement.

F. Aortic valve regurgitation

1. Epidemiology
   a. Most common cause of isolated AV regurgitation is aortic root dilatation.
   b. Other causes include:
      (1) Infective endocarditis
      • Most common infectious cause of acute AV regurgitation
      (2) Chronic RF
      • Most common cause of AV regurgitation in developing countries
      (3) Aortic dissection (refer to Chapter 10)
      (4) Coarctation of the aorta
      (5) Dilated AV ring, syphilitic aortitis (refer to Chapter 10), aortitis in ankylosing spondylitis (refer to Chapter 24), and Takayasu arteritis (refer to Chapter 10)

2. Pathophysiology (Fig. 11-19)
   a. Incompetent closure of AV leading to retrograde blood flow into the LV in diastole
      (1) In acute AV regurgitation, this leads to a markedly increased LVEDP; a normal left ventricular size, decreased SBP (decreased stroke volume), normal to decreased pulse pressure (see Box 11-1), and decreased cardiac output.
      (2) In chronic AV regurgitation, the LVEDP returns to normal, left ventricular size is increased, SBP is increased, DBP is decreased (drop of arterial volume as blood drips back into the LV), the pulse pressure is increased (see Box 11-1), and the cardiac output is normal.
   b. Volume overload in the LV leads to eccentric LVH.
3. Clinical findings
   a. Early diastolic murmur, due to blood dripping back into the LV right after the second heart sound
      (1) $S_1$ and $S_2$ heart sounds are present (Box 11-1)
      (2) Deep held inspiration for 3 to 5 seconds does not increase the intensity of the murmur or the abnormal heart sounds (see Box 11-1).
   b. In chronic AV regurgitation, signs of a hyperdynamic circulation are caused by a widened pulse pressure (see earlier); hyperdynamic signs include
      (1) Bounding pulses (Corrigan water-hammer pulse)
      (2) Head nodding with systole (de Musset sign)
      (3) Pulsating nail bed with elevation of the nail (Quincke pulse)
   c. Austin Flint murmur
      (1) Regurgitant stream from the incompetent AV hits the anterior leaflet of the mitral valve, producing a diastolic murmur.
      (2) Presence of this murmur is an indication for AV replacement.
   d. Normalization of the cardiac output occurs in chronic aortic regurgitation

4. Diagnosis is confirmed by echocardiography

5. Treatment in severe disease is AV replacement.

G. Tricuspid valve (TV) regurgitation

1. Epidemiology
   a. Most common cause of TV regurgitation in the adult population is functional regurgitation due to stretching of the ring in RHF.
   b. In adolescents and young adults, most cases of TV regurgitation are due to CHD.
   c. Small degree of TV regurgitation (not clinically significant) occurs in ~70% of adults.
   d. In intravenous drug abusers (IVDA), infective endocarditis affecting the TV is the most common cause of regurgitation.
   e. Other less common causes include:
      * Pulmonary hypertension, dilated cardiomyopathy, RV infarction, and carcinoid heart disease

2. Pathophysiology
   a. Retrograde blood flow into the RA during systole due to stretching of the TV ring or damage to the TV
b. Causes RA dilatation and hypertrophy and backup of pressure into the venous system
c. Eccentric RVH due to volume overload of the RV

3. Clinical findings
   a. Pulsating liver
      • Blood backs up into the venous system and increases hepatic vein blood flow
to the central venules, leading to an increase in pressure in the sinusoids and portal vein.
   b. Dependent pitting edema from increased venous hydrostatic pressure
c. Ascites due to increased portal vein pressure
d. Giant c-v wave is present in the jugular venous pulse (see Box 11-1).
   • Sign of severe TV regurgitation
e. Pansystolic murmur heard best along the left parasternal border
   (1) S₃ and S₄ heart sounds are present (see Box 11-1).
   (2) Deep held inspiration for 3 to 5 seconds increases the intensity of the murmur and
the abnormal heart sounds (see Box 11-1).

4. Diagnosis is confirmed by echocardiography.
5. Treatment is directed at the cause of the TV regurgitation.
   • Surgical replacement of the TV is uncommon.

H. Pulmonary valve (PV) stenosis
1. Uncommon valvular lesion
2. Associated with CHD and carcinoid heart disease
3. Systolic ejection murmur in the left second intercostal space (see Box 11-1).
4. Concentric RVH
5. Diagnosis is confirmed by echocardiography.
6. PV replacement is required in severe cases.

I. Pulmonary valve regurgitation
1. Most often a functional murmur from stretching of the PV ring
   • Example—pulmonary hypertension (called a Graham Steell murmur)
2. Volume overload of the RV, which leads to eccentric RVH
3. Produces a diastolic murmur heard after the second heart sound
4. S₃ and S₄ heart sounds are present (see Box 11-1).
5. Diagnosis is confirmed by echocardiography.

J. Carcinoid heart disease
1. Liver metastasis from a primary carcinoid tumor of the small intestine (refer to Chapter 18) is the most common cause.
2. Serotonin is produced by the metastatic foci in the liver and gains access to the hepatic vein → inferior vena cava → right side of the heart.
3. In the right side of the heart, serotonin increases fibrosis of the TV and PV, producing TV regurgitation and PV stenosis.

K. Infective endocarditis (IE)
1. Epidemiology
   a. Definition—infection of the endocardial surface of the heart, which may encompass
      one or more valves or a septal defect in CHD
   b. Most frequently occurs in adults between 45 and 65 years of age
   c. Risk factors
      (1) Diabetes mellitus, HIV infection
      (2) Poor dental hygiene, CHD
      (3) MVP, AV stenosis
      (4) Hemodialysis, prosthetic heart valve
      (5) Intravenous catheters, IVDA
d. Microbial pathogens associated with infective endocarditis
   (1) Acute endocarditis
      • Staphylococcus aureus (most common), streptococcal species groups A through
       G, Haemophilus influenzae, and Streptococcus pneumoniae
   (2) Endocarditis in IVDAs
      • Staphylococcus aureus (most common), Pseudomonas aeruginosa, Candida spp.,
       and enterococci
   (3) Subacute endocarditis
      • Viridans group of Streptococcus (most common overall pathogens
       causing endocarditis), Streptococcus bovis, enterococci, Staphylococcus aureus

RA dilatation/hypertrophy; eccentric RVH; ↑ pressure in venous system
Pulsating liver; ascites; ↑ portal vein pressure
Giant c-v wave; pansystolic murmur + S₃/S₄; ↑ in intensity with deep held inspiration
PV stenosis: CHD, carcinoid heart disease
PV regurgitation: MCC stretching of ring from PH
Must be liver metastasis to produce carcinoid heart disease; serotonin causes valve fibrosis
Carcinoid heart disease: PV stenosis, TV regurgitation
IE most frequent at age 45–65 years
Acute IE: Staphylococcus aureus MCC
IVDA IE: Staphylococcus aureus MCC
Subacute endocarditis: viridans Streptococcus MCC
Viridans group of Streptococcus: overall MCC IE
(4) Endocarditis associated with artificial heart valves (early; <60 days)
   • *Staphylococcus epidermidis* (coagulase negative; most common cause), *Candida* species, gram-negative bacilli

(5) Endocarditis associated with artificial heart valves (late; >60 days)
   • *Staphylococcus aureus*, enterococci, group D streptococci

(6) Nosocomial endocarditis
   (a) *Staphylococcus aureus* is the most common cause in patients with intravenous catheters
   (b) Enterococci are the most common cause in patients with indwelling urinary catheters.

(7) Endocarditis associated with ulcerative lesions in the colon (e.g., ulcerative colitis, colon cancer)
   • *Streptococcus bovis (gallolyticus)*

   e. Valves involved
   (1) Majority of the valves involved are left-sided (>90% of cases)
   • Right-sided valves with IE are usually associated with IVDA.
   (2) MV is the most common overall valve involved in IE.
   (3) TV and AV are the most common valves involved in IE due to IVDA.

2. Pathogenesis
   a. Turbulent blood flow damages the valve → adherence of fibrin and platelets to the areas of damage → trapping of circulating bacteria/fungi → proliferation of the pathogens + laying down of fibrin to encase the vegetation
   b. Viridans group of streptococci infect previously damaged valves.
   c. *Staphylococcus aureus* infects normal or previously damaged valves.

3. Pathology
   a. Vegetations destroy the valve leaflet and chordae tendineae (Fig. 11-20A).
   b. Valve destruction leads to regurgitation murmurs.

4. Clinical findings
   a. Fever is the most consistent sign (90% of cases).
   • IE is a common cause of fever of unknown origin.

**11-20:** A, Acute bacterial endocarditis. Large, friable, and irregular vegetation (arrow) is present on the margin of the mitral valve. Smaller vegetations are present along the line of closure of the valve. B, Roth spots. Note the areas of hemorrhage with white dots in the center (white arrows). C, Splinter hemorrhages in the nail bed. Note the longitudinal red hemorrhages in the nail bed. D, Osler nodes on the pads of the toes. These represent areas of microembolization of vegetation material and are usually painful. (A from Damjanov I, Linder J: *Pathology: A Color Atlas*, St. Louis, Mosby, 2000, p 11, Fig. 1-16; B from Bouloux P: *Self-Assessment Picture Tests Medicine*, Vol. 1, London, Mosby-Wolfe, 1997, p 63, Fig. 125; C from Swartz MH: *Textbook of Physical Diagnosis*, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 747, Fig. 8-10; D from Bouloux P: *Self-Assessment Picture Tests Medicine*, Vol. 3, London, Mosby-Wolfe, 1997, p 45, Fig. 89.)
b. Immunocomplex vasculitis (if IE is subacute)
   - Examples—glomerulonephritis (nephritic type), Roth spot (irregular red area with central white dot; 2%–10% of cases; see Fig. 11-20B)

c. Microembolization findings (occurs in >50% of cases)
   1. Splinter hemorrhages are linear hemorrhages that are present in the nail beds (see Fig. 11-20C; 10%–23% of cases).
   2. Janeway lesions are painless areas of hemorrhage on the palms and soles of the feet (10% of cases).
   3. Osler nodes are painful hemorrhagic nodules on the pads of the fingers or toes (see Fig. 11-20D; 10%–23% of cases).
      a. Although most references state that Osler nodes are an example of an immunocomplex vasculitis, more recent studies have contradicted that belief.
      b. Early biopsies frequently demonstrate bacteria within microabscesses without any evidence of a vasculitis, which favors microembolization as the initial process.
      c. However, as time progresses, the microabscess becomes sterile and an immune-mediated vasculitis develops.
   4. Infarctions may occur in different tissue sites (e.g., digits, brain).

d. Heart murmurs (regurgitant types) may change in intensity because of microembolization and progressive damage to the valve (85% of cases).

e. Splenomegaly is present if IE is subacute.

5. Laboratory findings
   a. Positive blood cultures are present in 80% of cases.
      - Low percentage reflects the fact that many patients are taking antibiotics when the cultures are drawn.
   b. Neutrophilic leukocytosis occurs in acute IE.
   c. Monocytosis occurs in subacute IE.
   d. Mild anemia is most frequently due to anemia of chronic disease (refer to Chapter 12).

6. Diagnosis
   a. Blood cultures (three sets in the first 24 hours)
   b. Echocardiography or transesophageal echocardiography to detect vegetations on the valves

7. Treatment
   a. Initial treatment is directed at the most likely organism.
   b. Antibiotic that is used after identification of the pathogen is guided by susceptibility testing.

L. Libman-Sacks endocarditis
   1. Definition—endocarditis associated with SLE
   2. Occurs in 30% to 50% of patients with SLE
   3. Sterile vegetations are located over the MV surface and chordae.
      - Produces valve deformity and MV regurgitation

M. Nonbacterial thrombotic endocarditis (NBTE; marantic endocarditis)
   1. Paraneoplastic syndrome (occurs in 20% of cases; refer to Chapter 9).
   2. Sterile, nondestructive vegetations present on the MV
      - Most often due to the procoagulant effect of circulating mucin from mucin-producing tumors of the colon/pancreas
   3. Complications
      a. Embolization of vegetation material to distant sites
      b. Vegetations may be secondarily infected.

VII. Myocardial and Pericardial Disorders
A. Myocarditis
   1. Epidemiology
      a. Major cause of sudden death (15%–20% of cases) in adults <40 years of age
      b. Etiology
         1. Microbial pathogens
            a. Viruses
               - Adenovirus (most common), group B coxsackieviruses, HIV, parvovirus B19, human herpesvirus 6
            b. Parasites
               - Trypanosoma cruzi (Chagas disease; Fig. 11-21A to C), Trichinella spiralis, and Toxoplasma gondii
            c. Bacteria
               - Borrelia burgdorferi, Mycoplasma, and Rickettsia rickettsii
            d. Fungi
               - Candida, Mucor, and Aspergillus
         2. Noninfectious causes
            a. Mechanical
            b. Autonomic nervous system disorders
            c. Cardiac surgery
            d. Hypertension
            e. Myocardial infarction
            f. Cardiac transplant rejection
   2. Complications
      a. Myocardial infarction
      b. Pericardial effusion
      c. Arrhythmia
      d. Heart failure
      e. Perimyocarditis
      f. Myocardial rupture
      g. Cardiac arrest
   3. Prognosis
      - Acute: 50% survival at 1 year
      - Chronic: 80% survival at 5 years

   Viruses: MCC acute myocarditis U.S.
   Chagas disease: MCC myocarditis leading to CHF in Central/South America

American trypanosomiasis (Chagas disease) is caused by *Trypanosoma cruzi*, a protozoan (hemoflagellate). It is transmitted by a bite around the eye or mouth that is contaminated with the feces of a reduviid bug (*Triatoma*, or kissing bug). Facial edema occurs near the bite site (called Romaña sign). The flagellated trypomastigotes circulate in the blood and the amastigotes (lack flagella) invade tissue. Common clinical findings are myocarditis causing chronic heart failure (most common cause of death) and arrhythmias; acquired achalasia, a motility disorder due to destruction of ganglion cells in the lower esophageal sphincter; and acquired Hirschsprung disease (large bowel motility disorder), due to destruction of ganglion cells in the rectosigmoid. The diagnosis is secured by finding trypomastigotes in the peripheral blood and/or amastigotes in tissue. Xenodiagnosis is used in some cases. An uninfected reduviid bug is allowed to feed on a patient and after a short period of time, the intestine of the bug is examined for the parasite. Serologic tests are also available. Nifurtimox is the treatment of choice.
2. Pathology
   a. Global enlargement of the heart and dilation of all chambers
   b. Lymphocytic infiltrate with focal areas of necrosis is highly predictive of a viral myocarditis (see Fig. 11-21D).

3. Clinical findings
   a. Dyspnea (most common symptom)
   b. Fever (20% of cases)
   c. Chest pain (35% of cases)
   d. Arrhythmias
      • Persistent tachycardia out of proportion to fever is a characteristic finding in myocarditis.
   e. Pericardial friction rub (see later)
   f. Biventricular heart failure with S₂ and S₄ heart sounds
   g. Heart murmurs
      • MV regurgitation is the most common murmur and is due to stretching of the MV ring from volume overload in the left ventricle.

4. Diagnosis
   a. Echocardiogram, ECG, cardiac catheterization
   b. Laboratory findings
      (1) Increased troponin T and/or I (a normal value does not exclude myocarditis)
      (2) Increased CK-MB (a normal value does not exclude myocarditis)
      (3) Detection of antibodies of the suspected pathogen

5. Treatment
   a. Treat the underlying cause.
   b. Approximately 50% of patients will die within 5 years.

B. Pericarditis

1. Epidemiology
   a. Definition—inflammation (or infiltration) of the pericardium
   b. Etiology
      (1) Most cases are idiopathic (>40% of cases).
      (2) Infectious (similar to the pathogens producing myocarditis)
         • Examples—adenovirus, coxsackievirus, and HIV
      (3) Drugs (similar to those listed for myocarditis)
      (4) SLE (pericarditis with effusion is a common presentation), acute RF, post-MI pericarditis, autoimmune pericarditis post-MI, systemic sclerosis, uremia, metastasis (e.g., breast, lung, leukemia)

2. Pathology
   a. Fibrinous type of pericardial exudate (see Fig. 3-8B)
      • Often accompanied by an effusion
   b. Dense scar tissue with dystrophic calcification may cause constrictive pericarditis.

3. Clinical and laboratory findings
   a. Fever
   b. Tachycardia
   c. Precordial chest pain
      (1) Pain is relieved when leaning forward.
      (2) Pain increases when leaning back.
   d. Precordial friction rub
      (1) Scratchy, three-component rub (systole, early, and late diastole)
         • Best heard with the patient leaning forward
         • All three components are heard in ~50% of cases.
      (2) Does not disappear when the person holds their breath, which distinguishes it from a pleural friction rub.
   e. Often accompanied by a pericardial effusion.
      (1) Normal heart sounds are muffled.
         • Fluid surrounding the heart makes heart sounds difficult to hear (Fig. 11-22A).
         • All pressures are equal in all chambers of the heart.
      (2) Cardiac output is decreased, because less blood is entering the right heart.
      (3) Neck vein distention occurs on inspiration
         • Blood cannot easily enter the RA on inspiration, because of fluid surrounding the heart.
         • Some blood reflexes back into the jugular vein on inspiration, causing distention (this is called Kussmaul sign).

Effusion: muffled heart sounds
Effusion: ↓cardiac output; neck vein distention with inspiration
Young woman with pericarditis and effusion most likely has SLE
Hypotension is associated with pulsus paradoxus.
- On inspiration there is a further increase in pressure of blood in the RV, which displaces the IVS to the left, causing a decrease in the LV volume and a corresponding drop in SBP that is >10 mm Hg (called pulsus paradoxus).

f. Serum CK-MB is usually normal.
g. Troponins I and T are increased in 35% to 50% of cases.
- Usually indicates that a myocarditis is also present

4. Diagnosis
a. If an effusion is present, a chest radiograph shows a “water bottle” configuration (see Fig. 11-22B).
b. Echocardiogram is useful in detecting a pericardial effusion.
c. ECG is useful in identifying changes that occur with the PR interval, ST wave, and T wave in different phases of pericarditis.

5. Treatment
a. Treatment is aimed at the cause of pericarditis.
b. Pericardiocentesis is required if an effusion is present.

6. Constrictive pericarditis
a. Etiology
   (1) Tuberculosis is the most common cause of constrictive pericarditis worldwide.
   (2) Most cases in the United States are idiopathic or secondary to scarring from previous open heart surgery.
   (3) Pericardial calcification is seen on a chest radiograph in ~25% of cases.
b. Pathophysiology
   - There is incomplete filling of the cardiac chambers due to thickening of the parietal pericardium.
c. Clinical findings
   - Pericardial knock is heard due to the ventricles hitting the thickened parietal pericardium.
d. Chest radiograph usually shows dystrophic calcification in the parietal pericardium.

VIII. Cardiomyopathy
A. Epidemiology
1. Definition—group of diseases that primarily involve the myocardium and produce myocardial dysfunction
2. Types
   a. Dilated (congestive)
   b. Hypertrophic
   c. Restrictive

B. Dilated cardiomyopathy

1. Most common cardiomyopathy in young people (accounts for 25% of cases).
2. Causes
   a. Idiopathic (most common)
   b. Genetic causes (25%–35% of cases)
   c. Previous myocarditis
      • Most common known cause of dilated cardiomyopathy
   d. Alcohol (15%–40% of cases)
      • Direct toxic effect of alcohol or thiamine deficiency with a decrease in ATP (refer to Chapter 8).
   e. Drugs
      • Examples—doxorubicin, daunorubicin, and cocaine
   f. Postpartum state
      • May occur in the last trimester or within 6 months postpartum
   g. Organic solvents (“glue sniffer’s heart”)
   h. Acromegaly, myxedema heart in severe hypothyroidism

3. Pathophysiology
   • Generalized decrease in contractility leading to global enlargement of the heart (Fig. 11-23A).

4. Clinical findings
   a. Signs and symptoms of LHF (see III.C.4.)
   b. Signs and symptoms of RHF (see III.D.3.)
   c. Narrow pulse pressure due to a decreased stroke volume
   d. Arrhythmias
      (1) Bundle branch blocks
      (2) Atrial and ventricular arrhythmias

5. Diagnosis
   a. Echocardiography shows an ejection fraction <40% (normal >55%).
   b. Chest x-ray shows global enlargement of the heart (see Fig. 11-23B)

6. Treatment
   • If medical therapy is ineffective, cardiac transplantation is the only other option.
C. Hypertrophic cardiomyopathy (HCM)

1. Epidemiology
   a. Most common cause of sudden death in young athletes
   b. Prevalence in the general population is 1 in 500.
   c. Familial form (60% to 70% of cases)
      (1) It is autosomal dominant (AD) with nearly complete penetrance (refer to Chapter 6).
      (2) Young individuals are affected.
      (3) Genes involved are mapped to chromosomes 11 (most common) and 14q.
      (4) A missense mutation occurs in multiple genes, causing a single amino acid substitution in one of the contractile proteins of the cardiac sarcomere.
   d. Sporadic form
      • Primarily occurs in elderly people

2. Pathophysiology
   a. Hypertrophy of the myocardium
      (1) Proportionately greater hypertrophy of the IVS than the free LV wall
      (2) IVS hypertrophy may obstruct blood flow through the LV outflow tract.
      (3) Most patients do not have severe obstruction of the LV outflow tract.
   b. Obstruction to blood flow, if present, is below the AV (Fig. 11-24A and B).
      • As blood exits the LV, the anterior leaflet of the MV is drawn against the asymmetrically hypertrophied IVS.
   c. Aberrant myofibers are present in the conduction system, which may cause fatal arrhythmias and sudden death (see Fig. 11-24C).
   d. LV is noncompliant.
      • Muscle thickening restricts filling and produces diastolic dysfunction.

3. Clinical findings
   a. Harsh systolic ejection murmur
      • Best heard along the left sternal border
   b. Palpable double apical impulse
   c. Murmur intensity increases (obstruction worsens) with decreased preload (note that these changes are the opposite of those that occur with AV stenosis).
      • Examples—standing up, Valsalva maneuver (increases positive intrathoracic pressure), and use of inotropic drugs (e.g., digitalis)
   d. Murmur intensity decreases (obstruction lessens) with increased preload (note that these changes are the opposite of those that occur with AV stenosis).
      (1) Examples—reclining, drugs decreasing cardiac contractility (e.g., β-blockers), sustained clenching of hands, and squatting
      (2) Increasing preload opens the outflow track.
   e. Angina or syncope with exercise
      • Similar in pathophysiology to AV stenosis (see VI.E.)
   f. Sudden death is due to ventricular tachycardia/fibrillation.

4. Diagnosis of hypertrophic cardiomyopathy
   • Two-dimensional echocardiography

5. Treatment
   a. Avoid strenuous exertion.
   b. Avoid drugs that decrease preload (e.g., diuretics) or increase force of contraction (e.g., digitalis).
   c. β-Blockers are the mainstay of therapy.
      (1) Decreased heart rate prolongs diastole.
      • Increases preload
      (2) Decreases myocardial contractility
   d. Implantable cardioverter defibrillator
      • Prevents ventricular tachycardia/fibrillation and sudden cardiac death
   e. Surgery in selected cases
   f. Screen all first-degree relatives.
      (1) Two-dimensional echocardiography is used.
      (2) Screening for mutations is likely in the future.

D. Restrictive cardiomyopathy

1. Epidemiology
   a. Most frequently caused by the following:
      (1) Amyloidosis (most common)
      (2) Myocardial fibrosis after open heart surgery
      (3) Radiation
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11-24: A. Schematic of hypertrophic cardiomyopathy. Note the asymmetric hypertrophy of the IVS causing it to obstruct the outflow tract. When systole occurs, the anterior leaflet is drawn against the septum causing a marked decrease in blood flow. B. Hypertrophic cardiomyopathy. The heart shows asymmetric hypertrophy of the interventricular septum (black arrow) with marked narrowing of the outflow tract. The histologic section of the conduction system in the septum (C) shows aberrant myofibers. Ao, Aorta; AV, aortic valve; IVC, inferior vena cava; IVS, interventricular septum; LA, left atrium; LV, left ventricle; LVH, left ventricular hypertrophy; MV, mitral valve; PA, pulmonary artery; PV, pulmonary valve; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve. (A from Goljan EF: Star Series: Pathology, Philadelphia, Saunders, 1998; B from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles, Philadelphia, Saunders, 1989; C from Kumar V, Abbas AK, Fausto N, Mitchell RN: Robbins Basic Pathology, 8th ed, Philadelphia, Saunders Elsevier, 2007, p 413, Fig. 11-25.)

b. Infiltrative diseases
   - Examples—Pompe glycogenosis, hemochromatosis
c. Endocardial fibroelastosis in a child
   - Thick fibroelastic tissue in the endocardium
d. Sarcoidosis
e. Systemic sclerosis

2. Pathophysiology
   a. Decreased ventricular compliance
   b. Diastolic dysfunction type of LHF

3. Clinical findings
   a. Progressive LHF and RHF
   b. ECG is low voltage with nonspecific ST-T wave changes

4. Diagnosis
   - Echocardiography and cardiac catheterization

5. Treatment
   a. Treat the underlying cause.
      - Examples—treat hemochromatosis with phlebotomy; treat sarcoidosis with corticosteroids
   b. No effective therapy for most causes of restrictive cardiomyopathy
IX. Tumors of the Heart

A. Epidemiology
1. Metastasis is more common than primary tumors.
   - Example—extension of a primary lung cancer
2. Pericardium is the most common site for metastasis.
   - Leads to pericarditis and effusions
3. Primary tumors or tumor-like conditions include:
   - Cardiac myxoma and rhabdomyoma

B. Cardiac myxoma
1. Most common primary tumor of the heart in adults
2. Pathology
   a. This primary mesenchymal tumor is benign.
   b. Approximately 90% arise from the LA (Fig. 11-25).
   c. The tumor is sessile or pedunculated.
   d. “Ball-valve” effect blocks the MV orifice.
      - Blocks diastolic filling of the LV, simulating MV stenosis
3. Clinical findings
   a. Nonspecific findings include:
      - Fever, fatigue, malaise, and anemia
   b. Complications include:
      - Embolization and syncopal episodes (blocks mitral valve orifice)
4. Diagnosis
   - Transeosophageal ultrasound is the most useful study for viewing the LA, which is the most posteriorly located chamber.

C. Rhabdomyoma
1. Most common primary tumor of the heart in infants and children
2. Hamartoma (nonneoplastic) arising from cardiac myocytes

Fig. 11-25: Cardiac myxoma in the left atrium. Note the large red mass in the left atrium. (From Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 27, Fig. 1-65A.)
CHAPTER 12
Red Blood Cell Disorders

I. Erythropoiesis

A. Erythropoiesis and erythropoietin

1. Definition of erythropoiesis
   a. Production of red blood cells (RBCs) in the bone marrow
   b. Dependent on the release of erythropoietin (EPO) from the kidneys

2. EPO synthesized in the renal cortex by interstitial cells in the peritubular capillary bed

3. Stimuli for EPO release include:
   - Hypoxemia (arterial $P_{O_2}$), severe anemia, left-shifted $O_2$-binding curve (OBC), high altitude, and decreased $O_2$ saturation ($S_aO_2$; carbon monoxide poisoning, methemoglobinemia)

4. Increased $O_2$ content suppresses EPO release (e.g., polycythemia vera).

EPO increases the $O_2$-carrying capacity of blood by stimulating erythroid stem cells to divide (RBC hyperplasia; Fig. 12-1). Epoetin alfa, a form of EPO produced by recombinant DNA technology, is frequently abused by athletes to increase their energy level. It also is used in the treatment of anemia associated with renal failure, chronic disease, and chemotherapy.

5. Other sources of EPO
   - Ectopically produced in renal cell carcinoma and hepatocellular carcinoma (refer to Chapter 9)

B. Reticulocytes and the reticulocyte count

1. Importance of reticulocytes
   a. Newly released RBCs from the bone marrow
   b. Peripheral blood markers of effective erythropoiesis
   c. Effective erythropoiesis refers to a good bone marrow response to anemia.
      - Correlates with an increase in synthesis/release of reticulocytes from the bone marrow

2. Easily identified in the peripheral blood with supravital stains
   - Stains detect thread-like RNA filaments in the cytoplasm of young RBCs (Fig. 12-2A).

3. In 24 hours, a reticulocyte becomes a mature RBC.
   - Maturation occurs with the help of splenic macrophages.

4. Reticulocyte count is reported as a percentage (normal <3%).
   a. Using the percentage reticulocyte count in anemia gives a falsely increased percentage (see Fig. 12-2B).
   b. Initial percentage must be corrected for the degree of anemia
   c. Corrected reticulocyte count = (actual Hct/45) $\times$ reticulocyte count, where 45 represents the normal hematocrit (Hct).
   d. Example calculation
      (1) Hct 15%, reticulocyte count 18%
      (2) Corrected reticulocyte count is 6% ($15/45 \times 18\% = 6\%$)

Reticulocyte count: must correct for degree of anemia

Correction = Hct/45 \times reticulocyte count

Other EPO sources:
- renal cell carcinoma, hepatocellular carcinoma

Effective erythropoiesis:
- good bone marrow response to anemia; $\uparrow$reticulocyte synthesis/release

EPO: synthesized in interstitial cells of peritubular capillary bed

EPO stimuli: ↓PaO2/↓SaO2, left-shifted OBC, high altitude
12-1: Morphology and lineage of hematopoietic cells. Pluripotent stem cells and colony-forming units (CFU) are long-lived cells capable of replenishing the more differentiated functional and terminally differentiated cells. Erythropoietin (EPO) directly stimulates the erythroid CFU, leading to increased production of mature RBCs. (From Murray PR, Rosenthal KS, Pfaller MA: Medical Microbiology, 6th ed, Philadelphia, Mosby Elsevier, 2009, p 90, Fig. 9.1.)

12-2: A, Peripheral blood reticulocytes with a methylene blue stain. Red blood cells with thread-like material in the cytosol represent residual RNA filaments and protein (arrow). The patient has a hemolytic anemia; therefore the number of reticulocytes are increased. B, Correction of the reticulocyte count for degree of anemia. Note that the normal reticulocyte count is 3% when 3 reticulocytes (pale blue RBCs) are expressed as a percentage of 100 RBCs in the microscopic field. However, the same 3 reticulocytes account for 10% of the RBCs in the patient with anemia, who has only 30 RBCs in the microscopic field. C, Polychromasia. The arrow indicates a blue discolored RBC without a central area of pallor. These cells are younger than reticulocytes and require anywhere from 2 to 3 days to become a mature RBC. (A from Naeim F: Atlas of Bone Marrow and Blood Pathology, Philadelphia, Saunders, 2001, p 12, Fig. 1-15B; B from Goljan EF, Sloka KI: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 146, Fig. 5-3; C from Naeim F: Atlas of Bone Marrow and Blood Pathology, Philadelphia, Saunders, 2001, Fig. 1-15A.)

Polychromasia: original correction ÷ 2

Corrected reticulocyte count: <3% ineffective erythropoiesis; ≥3% effective erythropoiesis

12-2: A, Peripheral blood reticulocytes with a methylene blue stain. Red blood cells with thread-like material in the cytosol represent residual RNA filaments and protein (arrow). The patient has a hemolytic anemia; therefore the number of reticulocytes are increased. B, Correction of the reticulocyte count for degree of anemia. Note that the normal reticulocyte count is 3% when 3 reticulocytes (pale blue RBCs) are expressed as a percentage of 100 RBCs in the microscopic field. However, the same 3 reticulocytes account for 10% of the RBCs in the patient with anemia, who has only 30 RBCs in the microscopic field. C, Polychromasia. The arrow indicates a blue discolored RBC without a central area of pallor. These cells are younger than reticulocytes and require anywhere from 2 to 3 days to become a mature RBC. (A from Naeim F: Atlas of Bone Marrow and Blood Pathology, Philadelphia, Saunders, 2001, p 12, Fig. 1-15B; B from Goljan EF, Sloka KI: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 146, Fig. 5-3; C from Naeim F: Atlas of Bone Marrow and Blood Pathology, Philadelphia, Saunders, 2001, Fig. 1-15A.)
In the fetus, hematopoiesis (blood cell formation) begins in the yolk sac and subsequently moves to the liver and finally the bone marrow by the fifth to sixth months of gestation.

II. Complete Blood Cell Count and Other Studies

A. Components of a complete blood cell count (CBC)

1. Hemoglobin (Hb), Hct, RBC count
2. RBC indices, RBC distribution width (RDW)
3. WBC count with a differential count and platelet count
4. Evaluation of the peripheral blood morphology

B. Hb, Hct, and RBC counts

1. Factors (age, sex, pregnancy) affecting the normal range (refer to Chapter 1)
2. Anemia
   a. Definition—decrease in Hb, Hct, or RBC concentration
   b. O₂ saturation (SaO₂) and PaO₂ (partial pressure of arterial O₂) are normal.
      • O₂ exchange in the lungs is normal; therefore the PaO₂ and SaO₂ are normal in anemia.
   c. O₂ content, which includes the Hb concentration, SaO₂, and PaO₂, is decreased, because the Hb concentration is decreased (refer to Chapter 2).
   d. Anemia is a sign of an underlying disease rather than a specific diagnosis.
   e. General clinical findings:
      (1) Fatigue, dyspnea with exertion, inability to concentrate, and dizziness
      (2) Pulmonary valve flow murmur, due to decreased blood viscosity in severe anemia
      (3) Pallor of the skin, conjunctivae, and palmar creases
         • Indicators of severe anemia

(b) Examples of effective erythropoiesis include:
   • Hemolytic anemia (e.g., sickle cell anemia) and the reticulocyte count after treatment of iron deficiency with iron.

(7) Corrected reticulocyte count <3%

(a) Indicates a poor bone marrow response to anemia, which is called ineffective erythropoiesis

(b) Examples of ineffective erythropoiesis include:
   • Untreated iron deficiency, anemia of chronic disease, folic acid deficiency, and aplastic anemia

C. Extramedullary hematopoiesis (EMH)

1. Definition—RBC, white blood cell (WBC), and platelet production that occurs outside the confines of the bone marrow
2. Common sites for EMH are the liver and spleen.
3. Pathogenesis
   a. Intrinsic bone marrow disease (e.g., myelofibrosis)
   b. Accelerated erythropoiesis (e.g., severe hemolysis in sickle cell disease)
      (1) The process expands the bone marrow cavity.
      (2) Radiograph of the skull shows a “hair-on-end” appearance, due to expansion of the bone marrow within the skull bones (Fig. 12-3).
4. EMH produces hepatosplenomegaly.

EMH: erythropoiesis outside bone marrow

EMH: most often occurs in liver and spleen

EMH: hepatosplenomegaly

Fetus: hematopoiesis begins in yolk sac

12-3: This lateral radiograph of the skull shows the typical “hair-on-end” appearance, with thinning of the cortical bone and widening of the marrow cavity from accelerated erythropoiesis (e.g., severe hemolysis in sickle cell disease). (From Bouloux P: Self-Assessment Picture Tests Medicine, Vol. 1, London, Mosby-Wolfe, 1997, p 49, Fig. 97.)
12-4: Classification of anemia using mean corpuscular volume (MCV). An intrinsic RBC defect indicates a structural or biochemical flaw in the RBCs. An extrinsic RBC defect indicates that the RBCs are structurally normal, but that other factors cause the anemia. G6PD, Glucose-6-phosphate dehydrogenase.

- High output failure; anemia ↓blood viscosity
- MCV: classification of anemias
  - Microcytic MCV <80 µm³
  - Normocytic MCV 80–100 µm³
  - Macrocytic MCV >100 µm³
- MCHC: ↓microcytic anemias, Hereditary spherocytosis
- RDW: measure RBC size variation

C. Red blood cell indices

1. Mean corpuscular volume (MCV)
   a. Definition—average volume of RBCs
   b. Frequently used to classify anemia (Fig. 12-4).
      1. Microcytic anemia: MCV <80 µm³
      2. Normocytic anemia: MCV 80–100 µm³
      3. Macrocytic anemia: MCV >100 µm³

2. Mean corpuscular hemoglobin concentration (MCHC)
   a. Definition—average Hb concentration in RBCs
   b. Decreased MCHC
      1. Decrease correlates with decreased synthesis of Hb, which is a feature of all the microcytic anemias (e.g., iron deficiency).
      2. Central area of pallor is greater than normal, because there is less Hb in the cell.
         - Called hypochromasia (compare Fig. 12-5 with Fig. 12-10D)
   c. Increased mean corpuscular hemoglobin concentration
      1. Correlates with the presence of spherical RBCs, which occurs in hereditary spherocytosis
      2. Spherocytes lack the central area of pallor, which is called hyperchromasia (see Fig. 12-22B).

3. Red blood cell distribution width (RDW)
   a. Definition—reflects any significant variation in size of the peripheral blood RBCs
      1. Size variation is called anisocytosis.
      2. The value is only significant if it is increased.
   b. Increased if RBCs are not uniformly the same size
      • Example—mixture of microcytic and normocytic cells (see Fig. 12-10D)
   c. Useful in distinguishing iron deficiency from other causes of microcytic anemia
      1. Iron deficiency is the most common microcytic anemia with an increased RDW.
         • Due to a mixture of normocytic and microcytic RBCs in the peripheral blood in iron deficiency
(2) With other microcytic anemias, particularly anemia of chronic disease (ACD) and thalassemia, RBCs appear more uniform.

D. Characteristics of mature RBCs (see Fig. 12-5)

1. Lack mitochondria; therefore there is:
   • No citric acid cycle, no β-oxidation of fatty acids, and no ketone body synthesis
2. Lack a nucleus; therefore they cannot synthesize DNA or RNA
3. Use anaerobic glycolysis as their primary source of adenosine triphosphate (ATP)
   a. Lactic acid is the end product of RBC anaerobic metabolism.
   b. Lactic acid is converted by the liver into glucose via gluconeogenesis.
   c. Glucose derived from gluconeogenesis is used by RBCs to synthesize ATP (Cori cycle).
4. Use the pentose phosphate pathway
   a. Synthesizes glutathione (GSH)
      (1) GSH is an antioxidant that converts hydrogen peroxide (H₂O₂) to water (refer to Chapter 2).
      (2) GSH also neutralizes acetaminophen free radicals (FRs).
   b. H₂O₂ is a product of oxidative metabolism in every living cell; therefore this pathway must be functional to prevent destruction of RBCs by H₂O₂.
5. Use a methemoglobin (metHb) reductase pathway (refer to Chapter 2).
   a. The heme iron in metHb is oxidized (Fe³⁺).
      • It cannot bind O₂.
   b. Reductase system converts iron back to its ferrous (Fe²⁺) state so that heme groups can bind O₂.
6. Use the Luebering-Rapoport pathway
   a. This pathway synthesizes 2,3-bisphosphoglycerate (2,3-BPG).
   b. Pathway is required for shifting the O₂C to the right (i.e., release O₂ to tissue; refer to Chapter 2).
7. Lack human leukocyte antigens (HLAs) on their membranes (refer to Chapter 4)
8. Fate of senescent RBCs
   a. Normal life span is 110 to 120 days in the peripheral blood.
   b. Senescent RBCs are phagocytosed in the cords of Billroth by splenic macrophages.
   c. Heme degradation by macrophages produces unconjugated bilirubin (UCB).
      • Most of the UCB in blood in a normal individual derives from destruction of senescent RBCs.

E. WBC count and differential

A 100-cell differential count divides leukocytes by percentage (neutrophils, lymphocytes, etc.) and further subdivides neutrophils into segmented and band neutrophils. Multiplication of the percentage and the total WBC count gives the absolute number of a particular leukocyte. Example—lymphocytes 30%, total WBC count 10,000/mm³; absolute lymphocyte count is 0.30 × 10,000 = 3000 cells/mm³.
**Platelets:** pinch off megakaryocyte cytoplasm

**Ferritin:** soluble iron-binding protein; keeps iron in non-toxic form

**Serum ferritin:** ↓ iron deficiency; ↑ ACD, iron overload disease

**Hemosiderin:** degradation product of ferritin; Prussian blue +

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F. **Platelet count**
1. Anucleate cells
2. Derived from cytoplasmic budding of megakaryocytes in the bone marrow (refer to Fig. 15-1)
3. Have human leukocyte antigens on their membranes

G. **Iron studies (Fig. 12-6)**
1. **Serum ferritin**
   a. Definition—soluble iron-binding storage protein
      (1) Synthesized by bone marrow macrophages and hepatocytes
      (2) Keeps iron in a non-toxic form
      (3) Macrophages are the primary storage site for ferritin in the bone marrow.
         (a) See shaded area in the small box in Figure 12-6A.
         (b) Most macrophage iron comes from phagocytosis of senescent RBCs.
      (4) Serum levels directly correlate with ferritin stores in the macrophages.
         • 1 µg/L of serum ferritin correlates with 8 mg of storage iron.
      (5) Synthesis of ferritin in macrophages (and hepatocytes) increases in inflammation.
         • Due to the release of interleukin-6 (refer to Chapter 3)
   b. Decrease in serum ferritin is diagnostic of iron deficiency (see Fig. 12-6B).
   c. Increase in serum ferritin is present in ACD (see Fig. 12-6C) and iron overload disease (see Fig. 12-6D).
   d. Hemosiderin is an insoluble product of ferritin degradation in lysosomes (refer to Chapter 2).
      (1) Decreased and increased levels of hemosiderin correlate with changes in the ferritin stores in the bone marrow macrophages.
      (2) Hemosiderin stains blue with Prussian blue stain.
2. Serum iron
   a. Definition—iron that is bound to transferrin
   - Transferrin is the binding protein of iron and is synthesized in the liver.
   b. Serum iron is the shaded area of the column in Figure 12-6A.
   - Note that the normal serum iron level is ~100 µg/dL.
   c. Iron shown coming into the macrophages in Figure 12-6A is coming from the degradation of senescent macrophages, not from transferrin.
   - Amount of iron coming into the macrophage is equal to the amount of iron leaving the macrophage to bind with transferrin.
   d. Decreased serum iron occurs in iron deficiency (see Fig. 12-6B) and ACD (see Fig. 12-6C).
   e. Increased serum iron occurs in iron overload diseases (see Fig. 12-6D).
      - Examples of iron overload diseases include the sideroblastic anemias and hemochromatosis.

3. Serum total iron-binding capacity (TIBC)
   a. Definition—correlates with the concentration of transferrin
      (1) Height of the column in Figure 12-6A correlates with serum transferrin and TIBC.
      (2) Note that the normal TIBC is ~300 µg/dL.
   b. Relationship of transferrin synthesis with ferritin stores in macrophages
      (1) Decreased ferritin stores leads to increased liver synthesis of transferrin
         (see Fig. 12-6B).
         - Increase in transferrin and TIBC is present in iron deficiency.
      (2) Increased ferritin stores leads to decreased liver synthesis of transferrin
         (see Fig. 12-6C and D).
         - Decrease in transferrin and TIBC occurs in ACD (see Fig. 12-6C) and iron overload disease (see Fig. 12-6D).
   c. Primary function of transferrin is to deliver ferric iron (Fe³⁺) to erythroid precursors in the bone marrow.
      - Iron on transferrin comes from bone marrow macrophages and from the duodenum, the primary site for iron reabsorption.

4. Iron saturation (%)
   a. Definition—percentage of binding sites on transferrin that are occupied by iron
      (1) Formula for calculating iron saturation: Iron saturation (%) = serum iron/TIBC × 100
      (2) In Figure 12-6A, the normal % saturation is 100/300 × 100, or 33%.
   b. Decreased iron saturation is present in iron deficiency (see Fig. 12-6B) and ACD (see Fig. 12-6C).
   c. Increased iron saturation is present in iron overload diseases (see Fig. 12-6D).

H. Hemoglobin (Hb) electrophoresis
   1. Hb electrophoresis is used to detect hemoglobinopathies (Fig. 12-7), which include:
      a. Abnormalities in globin chain structure (e.g., sickle cell disease)
      b. Abnormalities in globin chain synthesis (e.g., thalassemia)
   2. Types of normal Hb detected (see Fig. 12-7A)
      a. HbA has 2α/2β globin chains (97% in adults).
      b. HbA₂ has 2α/2δ globin chains (2% in adults).
      c. HbF has 2α/2γ globin chains (1% in adults).
   3. Examples of abnormal Hb detected include:
      - Sickle Hb, HbH, and Hb Bart

III. Microcytic Anemias
A. Types
   1. Iron deficiency (most common)
   2. Anemia of chronic disease (ACD)
   3. Thalassemia (thal; α and β)
   4. Sideroblastic anemias (least common)
B. Pathogenesis (Fig. 12-8)
   1. All are defects in Hb synthesis
      - Hemoglobin = heme + globin chains
   2. Defects in heme synthesis (i.e., iron + protoporphyrin) include:
      - Iron deficiency, ACD, and sideroblastic anemias
   3. Defects in globin chain synthesis (i.e., α or β) include α- and β-thal.
<table>
<thead>
<tr>
<th>Pattern</th>
<th>Type of Anemia</th>
<th>Interpretation and Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. $A_2$ S F A</td>
<td>None</td>
<td>Normal Hb electrophoresis</td>
</tr>
<tr>
<td>2% 1% 97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. $A_2$ S F A</td>
<td>Microcytic</td>
<td>$\alpha$-Thal trait. Note that the proportion of the Hb types remains the same; however, the patient has a microcytic anemia.</td>
</tr>
<tr>
<td>2% 1% 97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. $A_2$ S F A</td>
<td>Microcytic</td>
<td>$\beta$-Thal minor. Note that HbA is decreased, because $\beta$-globin chain synthesis is decreased. There is a corresponding increase in HbA$_2$ and HbF.</td>
</tr>
<tr>
<td>5% 2% 93%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. $A_2$ S F A</td>
<td>Microcytic</td>
<td>$\beta$-Thal major. Note that there is no synthesis of HbA.</td>
</tr>
<tr>
<td>10% 90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. $A_2$ S F A</td>
<td>No anemia</td>
<td>Sickle cell trait. Note that there is not enough HbS to cause spontaneous sickling in the peripheral blood.</td>
</tr>
<tr>
<td>2% 45% 1% 52%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. $A_2$ S F A</td>
<td>Normocytic</td>
<td>Sickle cell disease. Note that there is no HbA. There is enough HbS to cause spontaneous sickling.</td>
</tr>
<tr>
<td>2% 90% 8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12-7: Hemoglobin electrophoresis in various hemoglobinopathies. See text for discussion. (From Goljan EF, Sloka KJ: Rapid Review Laboratory Testing in Clinical Medicine, London, Mosby Elsevier, 2008, p 159, Fig. 5-12.)

12-8: Pathophysiology of microcytic anemias. All microcytic anemias have a decrease in hemoglobin synthesis. A decrease in hemoglobin synthesis could be due to a decrease in the synthesis of heme or a decrease in the synthesis of globin chains. ALA, Aminolevulinic acid.

![Pathophysiology of microcytic anemias](image-url)
12-9: Iron absorption. The reabsorption of iron is dependent on total iron stores in the body, which is reflected in the amount of iron that is bound to transferrin. Transferrin with iron binds to immature precursor cells of normal enterocytes, which serve as iron sensors in the duodenum. The HFE hemochromatosis gene (HFE gene) protein product in these sensor cells acting together with the transferrin receptor causes the precursor cells to differentiate into mature enterocytes that can actively reabsorb iron. Absorptively active enterocytes absorb ferrous iron (Fe$^{2+}$) directly via heme carrier protein 1 or through the divalent metal transporter (DMT1). Absorbed iron is either stored in the cytoplasm as mucosal ferritin or transferred to the ferroportin 1 port where it is converted to ferric iron (Fe$^{3+}$) by hephaestin and ceruloplasmin. Plasma transferrin then binds the iron and carries it to erythroid precursors in the bone marrow. The HFE protein also regulates the production of another protein called hepcidin, which is the “master” iron regulatory hormone. Hepcidin is produced by the liver and determines how much iron is absorbed from the diet and released from storage sites in the body. For example, if there is less transferrin iron bound to the receptor (decreased iron stores), then there is decreased transcription of hepcidin in the liver and more iron is allowed to enter the circulation via the ferroportin 1 port to bind to transferrin and more iron is released from bone marrow macrophages to bind to transferrin. If there is increased transferrin iron bound to the receptor (excess iron stores), there is increased transcription of hepcidin, and iron is trapped in the mucosal cell because of downregulation of ferroportin 1. Furthermore, bone marrow macrophages cannot release iron (iron blockade). Enterocytes with excess iron are then shed, and the iron is lost in the stool. (Modified from Kumar V, Fausto N, Abbas A, Aster J: Robbins and Cotran Pathologic Basis of Disease, 8th ed, Philadelphia, Saunders Elsevier, 2010, p 661, Fig. 14-22; from Damjanov I: Pathophysiology, Philadelphia, Saunders Elsevier, 2009, p 69, Fig. 3-1.)

Types of iron: reduced Fe$^{2+}$ (heme iron in meat), oxidized Fe$^{3+}$ (nonheme iron in plants)

C. Iron deficiency anemia
1. Iron distribution
   a. Functional iron is present in Hb, enzymes, and myoglobin.
   • Amount of functional iron in men is ~2500 mg and in women, ~2000 mg.
   b. Iron is primarily stored as ferritin and hemosiderin in bone marrow macrophages.
   • Amount of stored iron in men is ~1000 mg and in women, 400 mg (decreased due to menses).
   c. Total iron stores in men is ~3500 mg and in women ~2400 mg.
2. Iron absorption and regulation (Fig. 12-9)
   a. Gastric acid frees elemental iron from heme and nonheme products.
   • Underscores why achlorhydria (absent stomach acid) decreases the availability of iron for absorption.
   b. Iron from plants is in a nonheme or oxidized form (ferric, Fe$^{3+}$).
   (1) Cannot be absorbed in the duodenum
   (2) Converted by cytochrome B in the duodenal mucosa into reduced iron (Fe$^{2+}$)
   (3) Reduced iron absorbed by divalent metal transporter 1 (DMT1) into the mucosal cell
Reduced Fe\(^{2+}\) directly reabsorbed in duodenum

Iron bound to transferrin regulates iron absorption

\[ \text{HFE protein product} \rightarrow \text{transferrin receptors differentiate sensor cells to enterocytes} \]

Hepcidin: master iron regulator

\[ \downarrow \text{Transferrin-bound iron} \rightarrow \downarrow \text{hepcidin synthesis} \rightarrow \uparrow \text{Iron bound to transferrin} \rightarrow \uparrow \text{Iron released from macrophages} \]

\[ \uparrow \text{Transferrin bound iron} \rightarrow \uparrow \text{hepcidin synthesis} \rightarrow \downarrow \text{Iron bound to transferrin} \rightarrow \downarrow \text{Iron released from macrophages (iron blockade)} \]

c. Iron from meat is in a heme or reduced form (ferrous, Fe\(^{2+}\)).
   • Ferrous form of iron is directly absorbed in the duodenum by heme carrier protein 1.

d. Absorbed iron is stored as mucosal ferritin or it enters the ferroportin 1 port and is immediately converted by hephaestin or ceruloplasmin to ferric iron (Fe\(^{3+}\)) so that it can bind to transferrin in the blood.
   • Transferrin brings iron to developing erythroid precursors in the marrow.

e. The amount of iron absorbed is regulated.
   (1) Absorption is dependent on total iron stores in the body, which is reflected by the amount of iron bound to transferrin.
   (2) Transferrin with iron binds to transferrin receptors in immature precursor cells of normal enterocytes, which serve as iron sensors in the duodenum.
   (3) HFE gene (hemochromatosis gene) protein product in the sensor cells acting with the transferrin receptor causes differentiation of these cells into mature enterocytes that absorb iron.
   (4) HFE protein product also regulates the production of hepcidin, a hormone synthesized in the liver.
      (a) Hepcidin is the “master” iron regulatory hormone and determines whether iron is absorbed or not absorbed in the duodenum and whether iron is released from macrophages or not released.
      (b) A decreased level of transferrin-bound iron binding to transferrin receptors in enterocytes indicates iron depletion, which leads to reduced hepcidin synthesis in the liver.
         • This upregulates ferroportin 1, causing more iron to be reabsorbed in the duodenum to bind to transferrin and more iron to be released from bone marrow macrophages to bind to transferrin for erythropoiesis.
      (c) An increased level of transferrin-bound iron binding to transferrin receptors in enterocytes indicates iron excess, which leads to increased hepcidin synthesis in the liver.
         • This downregulates ferroportin 1, causing iron accumulation in enterocytes, which are eventually shed into the bowel. A reduced level of ferroportin 1 also causes iron blockade in bone marrow macrophages, so less is released for binding to transferrin.

3. Percentage of iron absorbed from the diet is increased (i.e., decreased hepcidin) in the following conditions:
   a. Normal menstrual cycle
   b. Pregnancy and lactation
   c. Any anemia, regardless of type
      • Underscores the danger of iron overload, if iron supplements are improperly prescribed.

4. Epidemiology
   a. Most common overall anemia
   b. Most common nutritional deficiency worldwide
   c. Greatest prevalence of the anemia is found in:
      (1) Toddlers aged 1 to 2 years
         • Due to inadequate intake of iron
      (2) Females aged 12 to 49 years
         • Due to menstrual loss
   d. Causes of iron deficiency (Table 12-1)

5. Pathogenesis
   • Decreased synthesis of heme (iron + protoporphyrin) leads to a decreased synthesis of Hb (see Fig. 12-8).

6. Clinical and laboratory findings
   a. Chronic iron deficiency
      (1) Esophageal web (Plummer-Vinson syndrome)
         • Produces dysphagia for solids but not liquids
      (2) Achlorhydria
         • Absence of hydrochloric acid in the stomach
      (3) Glossitis and angular cheilosis
         • Inflammation of the tongue and corner of the mouth, respectively
      (4) Spoon nails (koilonychia; Fig. 12-10C)
   b. Pallor of the conjunctivae and palmar skin creases (see Fig. 12-10A and B)
   c. Craving (pica) for ice
### TABLE 12-1 Causes of Iron Deficiency Anemia

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>CAUSES</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss</td>
<td>Gastrointestinal loss</td>
<td>Peptic ulcer in a Meckel diverticulum (older children) PUD (most common cause in adult men) Hemorrhagic gastritis (e.g., NSAID) Hookworm infestation Polyps/colorectal cancer (most common cause in adults &gt;50 years of age). There will be a positive stool for blood.</td>
</tr>
<tr>
<td>Increased utilization</td>
<td>Menorrhagia Pregnancy/lactation</td>
<td>Most common cause in women &lt;50 years of age. Daily iron requirement is 3.4 mg in pregnancy and 2.5–3 mg in lactation; therefore, if the woman does not continue taking prenatal vitamins, she will become iron deficient. Normal iron stores are ~400 mg. The net loss of iron in pregnancy is 500 mg; therefore, if the woman is not taking prenatal vitamins, she will become iron deficient. Iron is required for tissue growth and expansion of blood volume in the developing fetus.</td>
</tr>
<tr>
<td>Decreased intake</td>
<td>Prematurity</td>
<td>There is a loss of iron each day a fetus is not in utero. Due to blood loss from repeated phlebotomy for laboratory testing. Decreased intake of iron is the most common cause of iron deficiency in young children. Restricted diets with very little meat intake decreases the intake of heme iron.</td>
</tr>
<tr>
<td>Decreased absorption</td>
<td>Celiac sprue Post–gastric surgery</td>
<td>Absence of the villous surface in the duodenum decreases absorption of iron. There is a rapid transit of food, which decreases iron absorption; and there is absent acid, which is required to release elemental iron from food.</td>
</tr>
<tr>
<td>Intravascular hemolysis</td>
<td>Microangiopathic hemolytic anemia Paroxysmal nocturnal hemoglobinuria</td>
<td>Intravascular hemolysis produces a chronic loss of hemoglobin in the urine (hemoglobinuria), which ultimately leads to iron deficiency. Intravascular hemolysis of RBCs due to complement destruction of RBCs at night.</td>
</tr>
</tbody>
</table>

*Hb, Hemoglobin; NSAID, nonsteroidal antiinflammatory drug; PUD, peptic ulcer disease.*

**12-10:** A, Note the generalized pallor of the face in this woman with severe anemia. B, Note the pallor of the hand in the patient with anemia (left) when compared to a normal hand (right). C, Koilonychia. Note the spoon shape of the nail bed. D, Peripheral blood smear in iron deficiency anemia. The enlarged central area of pallor (arrows) indicates a decrease in hemoglobin synthesis, which is characteristic of the microcytic anemias. The mean corpuscular hemoglobin concentration is decreased. Also note the size variation, which explains the increased red blood cell distribution width. (A and B from Forbes C, Jackson W: Color Atlas and Text of Clinical Medicine, 3rd ed, London, Mosby, 2004, pp 405, 406, respectively, Fig. 10.3, 10.4, respectively, C from Savin JAA, Hunter JAA, Hepburn NC: Diagnosis in Color: Skin Signs in Clinical Medicine, London, Mosby-Wolfe, 1997, p 118, Fig. 4.60; D from Wickramasinghe SE, McCullough J: Blood and Bone Marrow Pathology, London, Churchill Livingstone, 2003, Fig. 11-6.)
d. Laboratory findings
   (1) Decreased MCV
   (2) Decreased serum iron and iron saturation
   (3) Decreased serum ferritin
   (4) Increased TIBC and RDW

The stages of iron deficiency in sequence are as follows: absent iron stores; decreased serum ferritin; decreased serum iron, increased TIBC, and decreased iron saturation; normocytic normochromic anemia; and microcytic hypochromic anemia.

(5) Microcytic and normocytic cells are present with increased central area of pallor (see Fig. 12-10D).

(6) Increased serum level of free erythrocyte protoporphyrin (FEP)
   - Less iron to combine with protoporphyrin to form heme

(7) Thrombocytosis
   - Common finding in chronic iron deficiency
   - Reactive phenomenon to increase blood viscosity and prevent high-output heart failure (refer to Chapter 11)

(8) WBC count is usually normal
   - Eosinophilia occurs in hookworm infestations.

7. Treatment
   a. Ferrous sulfate, given orally
   b. Hct should increase 0.5% to 1%/day after the initial lag period.
   c. Lack of response indicates:
      (1) Noncompliance (most common)
      (2) Continued blood loss
      (3) Iron is not being absorbed

D. Anemia of chronic disease (ACD)

1. Epidemiology
   a. Most common anemia in hospitalized patients
   b. Common causes
      (1) Chronic inflammation
         - Examples—rheumatoid arthritis, tuberculosis (TB), and Crohn disease
      (2) Alcoholism
         - ACD is the most common anemia in alcoholism.
      (3) Malignancy
         - ACD is the most common anemia in malignancy.

2. Pathogenesis
   a. Decreased heme synthesis (see Fig. 12-8).
   b. Decreased renal production and/or response to EPO
   c. Increased liver synthesis and release of hepcidin (refer to II.C.2.e.)

3. Laboratory findings
   a. Normal to decreased MCV
      (1) ACD, in some cases, presents as a normocytic anemia.
      (2) It is most likely to present as a microcytic anemia in the setting of rheumatoid arthritis and Crohn disease.
   b. Decreased serum iron, TIBC, and percent iron saturation
   c. Increased serum ferritin
   d. Increased serum FEP
      - Less iron to combine with protoporphyrin to form heme
   e. Anemia rarely <9 g/dL

4. Treatment
   a. Treat the underlying disease causing the inflammation.
   b. In some cases, giving EPO increases the Hb concentration.
   c. Hepcidin antagonists (recent treatment modality)

E. Thalassemia (thal)

1. Epidemiology
   a. Definition—decrease in α- or β-globin chain synthesis
   b. Autosomal recessive disorders
c. α-thal is common in Southeast Asians, people who live on the African west coast, and in blacks (prevalence of 5%).
d. β-thal is common in blacks, Greeks (prevalence 15% to 30%), and Italians.

2. Pathogenesis of α-thal
   a. Decrease in α-globin chain synthesis is due to gene deletions (Fig. 12-11).
      • Four genes control α-globin chain synthesis (Fig. 12-11, Normal).
   b. One gene deletion produces a silent carrier.
      • Not associated with anemia
   c. Combination of two gene deletions is called α-thal trait (see Fig. 12-11A and B).
      (1) Produces a mild anemia with a normal to increased RBC count.
          • There is no consensus as to why the RBC count is normal to increased, when the Hb and Hct are decreased; however, it is a very useful clinical finding.
      (2) In the black population, it is associated with a loss of one gene on each chromosome (trans: α/~ α/~; see Fig. 12-11A)
      (3) In the Southeast Asian population, it is associated with a loss of both genes on the same chromosome (cis: ~~/~ α/α; see Fig. 12-11B)
          • Increased risk for developing more severe types of α-thal, because one chromosome completely lacks α-globin genes
   d. Combination of three gene deletions is called HbH (four β-chains) disease
      (1) Associated with a severe hemolytic anemia
          • Excess β-chain inclusions cause macrophage destruction of RBCs (hemolytic anemia).
      (2) Hb electrophoresis detects HbH.
e. Combination of four gene deletions is called Hb Bart (four γ-chains) disease
      (1) This combination is incompatible with life.
      (2) Hb electrophoresis shows an increase in Hb Bart.
f. Laboratory findings in α-thal trait
      (1) Decreased MCV, Hb, and Hct
      (2) Increased RBC count
      (3) MCV/RBC count ratio <13.
      (4) Target cells inconsistently present
      (5) Teardrop RBCs inconsistently present
      (6) Normal RDW, serum ferritin, serum FEP, and Hb electrophoresis

Hemoglobin electrophoresis is normal in α-thal trait, because all Hb types require α-globin chains. The Hb concentration is decreased; however, the relative proportions of the normal Hbs remains the same (see Fig. 12-7B).
g. α-thal trait is a diagnosis of exclusion.
   - Usually there is a family history of members with a mild microcytic anemia, normal Hb electrophoresis, and normal iron studies.

h. There is no treatment.

3. Pathogenesis of β-thal
   a. Decrease in β-globin chain synthesis (see Fig. 12-8)
      (1) Mild anemia is most often due to DNA splicing defects.
      (2) Severe anemia is due to a nonsense mutation with formation of a stop codon.
         - Premature termination of β-globin chain synthesis or absent β-globin chain synthesis
   b. Normal synthesis of α-, δ-, and γ-globin chains

Normal β-globin chain synthesis is designated β; some β-globin chain synthesis is designated β⁺; absence of β-globin chain synthesis is designated β⁻.

c. β-thal minor (β/β⁺)
   (1) Mild microcytic anemia
   (2) Decreased MCV, HB, and Hct
   (3) Increased RBC count
   (4) MCV/RBC count ratio <13
   (5) Target cells consistently present (Fig. 12-12A)
   (6) Teardrop RBCs present (see Fig. 12-12B)
      - Due to damage of the RBC membrane from removal of excess globin chains by splenic macrophages
   (7) Normal RDW, serum ferritin, and serum FEP
      - Serum FEP is normal because heme synthesis is normal.
   (8) Hb electrophoresis (see Fig. 12-7C)
      (a) HbA (2α/2β) is decreased, because β-globin chains are decreased.
      (b) Corresponding increase in HbA₂ (2α/2δ) and HbF (2α/2γ)
   (9) No treatment

d. β-Thal major (Cooley anemia; β⁺/β⁺ or β⁺/β⁺)
   (1) Severe hemolytic anemia
      (a) RBCs with α-chain inclusions are removed by splenic macrophages
         - Marked increase in unconjugated bilirubin (UCB; jaundice)
      (b) RBCs with α-chain inclusions undergo apoptosis in the bone marrow (ineffective erythropoiesis).
   (2) EMH and accelerated erythropoiesis
      (a) Hepatosplenomegaly from excessive hematopoiesis
      (b) Radiographs of the skull show a hair-on-end appearance (see Fig. 12-3).
   (3) Increased RDW due to increased size variation (see Fig. 12-12B)

12-12: A, β-Thalassemia trait. Note the uniform size of the RBCs, which explains why the red blood cell distribution width is normal. Target cells are commonly seen in all hemoglobinopathies. The arrow points to a teardrop RBC. B, β-Thalassemia major. A few cells contain hardly any hemoglobin (Hb). What little is present is often precipitated at the membrane. Howell-Jolly bodies (solid arrows; nuclear remnants), poorly hemoglobinated nucleated red blood cells (two nucleated cells), and a poorly hemoglobinated teardrop cell (interrupted arrow) are present. (From McPherson R, Pincus M: Henry's Clinical Diagnosis and Management by Laboratory Methods, 21st ed, Philadelphia, Saunders, 2007, pp 587, 586, respectively, Figs. 31-27, 31-26, respectively.)
(4) Increase in reticulocytes, teardrop cells, Howell-Jolly bodies (nuclear remnants), and nucleated RBCs (see Fig. 12-12B)
(5) Hb electrophoresis (see Fig. 12-7D)
   (a) No synthesis of HbA
   (b) Corresponding increase in HbA₂ and HbF
(6) Treatment
   (a) Blood transfusion
   • Danger of iron overload (called hemosiderosis)
   • Requires chelation therapy with desferrioxamine
   (b) Bone marrow transplantation (only curative approach)

F. Sideroblastic anemia

1. Epidemiology
   a. Chronic alcoholism (most common cause)
   b. Pyridoxine (vitamin B₆) deficiency
   c. Lead (Pb) poisoning
   d. X-linked recessive (XR) disease

2. Pathogenesis
   a. Definition—defect in heme synthesis within the mitochondria of developing RBCs in the bone marrow (see Fig. 12-8)
      (1) Heme is end product of porphyrin synthesis.
      (2) Heme has a negative feedback relationship with δ-aminolevulinic acid synthase.
   b. Iron accumulates in mitochondria, which produces ringed sideroblasts (Fig. 12-13).
   c. It is classified as an iron-overload type of anemia.
      (1) Iron stores increase markedly in the bone marrow macrophages.
      (2) Sideroblasts die in the marrow (ineffective erythropoiesis)
         • Phagocytosed by macrophages, which leads to excess iron stores

3. Chronic alcoholism
   a. Alcohol is a mitochondrial toxin (poison).
      • Damages heme biosynthetic pathways in the mitochondria
   b. Sideroblastic anemia is present in ~30% of hospitalized chronic alcoholics.

4. Pyridoxine deficiency
   a. Vitamin B₆ is a cofactor for δ-aminolevulinic acid synthase, the rate-limiting reaction of heme synthesis (see Fig. 12-8).
   b. Most common cause of deficiency is isoniazid (INH) therapy for TB.
      • INH inactivates pyridoxine.

5. Lead (Pb) poisoning
   a. Epidemiology
      (1) Most common in children ages 1 to 5 years old
      (2) May occur in utero, because it crosses the placenta
      (3) Uncommon cause of sideroblastic anemia
      (4) Causes of lead poisoning
         (a) Pica (abnormal craving) for eating lead-based paint
            • Common cause of childhood lead poisoning in inner cities where there are apartments built before 1950, when lead-based paints were primarily used.
            • Lead-based paints are primarily used for painting the exterior of homes.
         (b) Pottery glazes that are used commercially or are homemade

β-thal major: no HbA; ↑HbA₂, HbF, RDW, reticulocytes

Sideroblastic anemia: chronic alcoholism MCC, ↓pyridoxine, Pb poisoning, XR

Pyridoxine deficiency: INH MCC

12-13: Ringed sideroblasts in a bone marrow aspirate. Dark blue iron granules around the nucleus of developing normoblasts (arrows) represent iron trapped within mitochondria and indicate a defect in mitochondrial heme synthesis (sideroblastic anemia). (From Porwitt A, McCullough J, Erber WN: Blood and Bone Marrow Pathology, 2nd ed, London, Churchill Livingstone Elsevier, 2011, p 402, Fig. 27.8C)
Pb poisoning: paint, batteries, pottery glazes, radiator repair, moonshine

Pb denatures ferrochelatase, ALA dehydrase, ribonuclease

Pb poisoning: coarse basophilic stippling (persistent ribosomes)

(5) Working in a battery or ammunition factory
(6) Radiator repair mechanics
(7) Air contamination from a smelter (form of extractive metallurgy)
(8) Other sources of lead include jewelry, moonshine, traditional medicines (e.g., Chinese tea), lead plumbing, and imported toys (e.g., from China).

b. Lead denatures enzymes.
(1) Ferrochelatase is denatured (heme synthase; see Fig. 12-8).
   (a) Iron cannot bind with protoporphyrin to form heme.
   (b) FEP, which is proximal to the enzyme block, is increased.
(2) Aminolevulinic acid (ALA) dehydrase is denatured.
   • Causes an increase in δ-ALA, which is proximal to the enzyme block
(3) Ribonuclease is denatured.
   (a) Ribosomes cannot be degraded and therefore persist in the RBC.
   (b) Result of denaturation is coarse basophilic stippling (Fig. 12-14A).

c. Lead interferes with iron absorption and utilization in heme pathways (see earlier).
   • Some authors state that the microcytosis in lead poisoning is due to iron deficiency.

d. Clinical and laboratory findings
(1) Abdominal colic with constipation (children)
   • Lead is visible in the gastrointestinal tract on plain abdominal radiographs (see Fig. 12-14B).

12-14: A, Peripheral blood with coarse basophilic stippling of red blood cells in lead poisoning. Note the mature red blood cell containing numerous dots representing ribosomes (arrow). Lead denatures ribonuclease; hence the ribosomes persist in the cytoplasm. B, Abdominal radiograph showing numerous metallic foci representing lead chips. C, Bone radiograph showing densities (lead deposits; arrows) in the epiphysis of the distal femur and proximal tibia. D, Lead poisoning produces a blue line at the margin of the gum and teeth. (A from Naeim F: Atlas of Bone Marrow and Blood Pathology, Philadelphia, Saunders, 2001, p 27, Fig. 2-22M; B and C from Katz D, Math K, Groskin S: Radiology Secrets, Philadelphia, Hanley & Belfus, 1998, p 310, Fig. 6 and Fig. 5, respectively; D from Forbes C, Jackson W: Color Atlas and Text of Clinical Medicine, 3rd ed, London, Mosby, 2004, p 345, Fig. 8.27.)
(2) Encephalopathy (children)
(a) Cerebral edema and papilledema
   • Lead damages capillary endothelium, causing leakage into the brain parenchyma.
   • Lead also damages myelin and induces demyelination.
(b) Learning disabilities (children)
(3) Growth retardation (children)
(a) Lead is deposited in the epiphysis of growing bone.
(b) Radiographs show increased density in the epiphyses (see Fig. 12-14C).
(4) Peripheral neuropathy in adults (children to a lesser extent)
   • Examples—foot drop (peroneal nerve palsy), wrist drop (radial nerve palsy), and claw hand (ulnar nerve palsy)
(5) Nephrotoxic damage to proximal renal tubules (adults)

Tubular damage by lead causes Fanconi syndrome. The syndrome includes proximal renal tubular acidosis (loss of bicarbonate in urine), aminoaciduria, phosphaturia, and glucosuria.

(6) Lead line in the gums (see Fig. 12-14D)
   • Usually occurs in adults who have preexisting gingivitis
(7) Reduced RBC survival time († hemolytic anemia).
(8) Increased whole blood and urine lead levels
   • Best screen and confirmatory tests
d. Treatment
   • Chelation therapy—succimer, dimercaprol, ethylenediaminetetraacetic acid (EDTA)
6. Laboratory findings in sideroblastic anemias
   a. Increased serum iron, iron saturation, and ferritin
   b. Normal to decreased MCV and decreased TIBC
   c. Ringed sideroblasts in a bone marrow aspirate
7. Summary table of microcytic anemias (Table 12-2)

IV. Macrocytic Anemias
A. Overview
   • Subdivided into megaloblastic (e.g., folic acid or vitamin B₁₂ deficiency) and nonmegaloblastic anemia (e.g., macrocytosis related to alcohol intoxication)
B. Vitamin B₁₂ (cobalamin) metabolism
   1. Water-soluble vitamin present in meat, eggs, and dairy products
   2. Parietal cells synthesize intrinsic factor (IF) and hydrochloric acid (HCl).
      a. Gastric acid converts pepsinogen to pepsin.
      b. Pepsin frees vitamin B₁₂ from ingested proteins.
   3. Free vitamin B₁₂ binds to R-binders (haptocorrins) synthesized in salivary glands.
      • Protects vitamin B₁₂ from acid destruction

<table>
<thead>
<tr>
<th>TABLE 12-2 Laboratory Findings in Microcytic Anemias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEST</strong></td>
</tr>
<tr>
<td>MCV</td>
</tr>
<tr>
<td>Serum iron</td>
</tr>
<tr>
<td>TIBC</td>
</tr>
<tr>
<td>Percent saturation</td>
</tr>
<tr>
<td>Serum ferritin</td>
</tr>
<tr>
<td>RDW</td>
</tr>
<tr>
<td>RBC count</td>
</tr>
<tr>
<td>Hb electrophoresis</td>
</tr>
<tr>
<td>β-Thal trait: ↑HbA, ↑HbA₂/F</td>
</tr>
<tr>
<td>Ringed sideroblasts</td>
</tr>
<tr>
<td>Coarse basophilic stippling</td>
</tr>
</tbody>
</table>

Hb, Hemoglobin; MCV, mean corpuscular volume; RDW, red blood cell distribution width; Thal, thalassemia; TIBC, total iron-binding capacity.
### TABLE 12-3 Causes of Vitamin B₁₂ Deficiency

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>CAUSES</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased intake</td>
<td>Pure vegan diet Malnutrition</td>
<td>Breast-fed infants of pure vegans may develop deficiency. Malnutrition may occur in elderly patients.</td>
</tr>
<tr>
<td>Impaired absorption</td>
<td>↓Intrinsic factor ↓Gastric acid ↓Terminal ileum absorption</td>
<td>Autoimmune destruction of parietal cells: this occurs in pernicious anemia, the most common cause of vitamin B₁₂ deficiency. Gastric acid and intrinsic factor are both decreased, the former interfering with activation of pepsinogen and the latter the absorption of vitamin B₁₂ in the terminal ileum. Proton blockers inhibit the synthesis of gastric acid. Gastrectomy decreases both acid and intrinsic factor. Bacterial overgrowth: bacteria use available vitamin B₁₂. Bacterial overgrowth occurs in small bowel diverticulosis, blind loops, and with defects in small bowel motility (diabetes mellitus; systemic sclerosis). Fish tapeworm: the worms absorb more than 80% of the vitamin B₁₂ intake. Chronic pancreatitis: enzyme deficiency leads to inability to cleave R-binder from the vitamin B₁₂–R-binder complex. Crohn disease, celiac disease, small bowel resection involving the terminal ileum: these disorders interfere with reabsorption of vitamin B₁₂.</td>
</tr>
<tr>
<td>Increased requirement</td>
<td>Pregnancy/ lactation</td>
<td>Deficiency is more likely to occur in a pure vegan, because their liver iron stores are depleted.</td>
</tr>
</tbody>
</table>

### TABLE 12-4 Causes of Folic Acid Deficiency

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>CAUSES</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased intake</td>
<td>Malnutrition Infants/elderly Chronic alcoholics Goat milk</td>
<td>Decreased intake is the most common cause of folic acid deficiency. Alcoholics with a poor diet are likely to have folic acid deficiency. Goat milk lacks folic acid, unless it is fortified.</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Celiac disease</td>
<td>In celiac disease, villi in the jejunum may be destroyed, leading to folic acid deficiency.</td>
</tr>
<tr>
<td>Drug inhibition</td>
<td>5-Fluorouracil Methotrexate, trimethoprim-sulfamethoxazole Phenytoin Oral contraceptives, alcohol</td>
<td>Inhibits thymidylate synthase Inhibit dihydrofolate reductase Inhibits intestinal conjugase Inhibit uptake of monoglutamate in jejunum Alcohol also inhibits the release of folic acid from the liver.</td>
</tr>
<tr>
<td>Increased utilization</td>
<td>Pregnancy/ lactation Disseminated malignancy Severe hemolytic anemia</td>
<td>There is increased utilization of folic acid in DNA synthesis.</td>
</tr>
</tbody>
</table>

4. Pancreatic enzymes in the duodenum cleave off the R-binders.
   - Vitamin B₁₂ binds to IF to form a complex.
5. Vitamin B₁₂–IF complex is absorbed in the terminal ileum.
6. Vitamin B₁₂ binds to transcobalamin II and enters the plasma.
   - Delivered to metabolically active cells or stored in the liver (6- to 9-year supply)

### C. Causes of vitamin B₁₂ deficiency (Table 12-3)

### D. Folic acid metabolism

1. Polyglutamate form is present in green vegetables and animal proteins
2. Converted to monoglutamates by intestinal conjugase in the jejunum
   - Intestinal conjugase is inhibited by phenytoin.
3. Monoglutamate is absorbed in the jejunum (active and passive transport).
   a. Monoglutamate is converted to methyltetrahydrofolate, the circulating form of folic acid.
   b. Absorption of monoglutamate is blocked by alcohol and oral contraceptives (OCPs).
   c. The liver contains only a 3- to 4-month supply of folic acid.

### E. Causes of folic acid deficiency (Table 12-4)

### F. Pathogenesis of macrocytic anemia in folic acid and vitamin B₁₂ deficiency

1. Impaired DNA synthesis delays nuclear maturation.
   a. Causes a block in cell division in all rapidly dividing cells, leading to large, nucleated hematopoietic cells with an open chromatin pattern
   - Cells that are affected include RBCs, leukocytes, megakaryocytes, and intestinal epithelium.
b. Cellular RNA synthesis and protein synthesis are not affected.
   • Cytoplasmic volume continues to expand.
2. Ineffective hematopoiesis
   a. Megaloblastic precursors outside the bone marrow sinusoids are phagocytosed and
destroyed by bone marrow macrophages.
   b. Megaloblastic precursors undergo apoptosis, causing pancytopenia (anemia, neutropenia,
and thrombocytopenia).

G. Vitamin B₁₂ and folic acid in conversion of homocysteine to methionine and in DNA
synthesis (Fig. 12-16)
1. Methionine synthase removes the methyl group (-CH₃) from 5-methyltetrahydrofolate
(N⁵-methyl-FH₄), the circulating form of folic acid in the blood, to produce tetrahydrofolate
(FH₄) and methyl-B₁₂ (methylcobalamin).
   • Key point—folic acid and folic acid derivatives are important in single carbon transfer
reactions from methyl groups (-CH₃) and methylene groups (-CH₂).
   a. Methionine synthase transfers the methyl group of methyl-B₁₂ to homocysteine, which
regenerates vitamin B₁₂ (cobalamin) and releases the product methionine.
   • Deficiency of vitamin B₁₂ traps N⁵-methyl-FH₄ in its circulating form, which falsely
increases the serum folic acid in 30% of cases (methyltetrahydrofolate trap).
   b. Deficiency of folic acid and/or vitamin B₁₂ increases plasma homocysteine.

Folic acid deficiency is the most common cause of increased serum homocysteine levels in the
United States. Homocysteine acts as an atherogenic factor by converting a stable atherosclerotic
plaque into an unstable plaque that leads to thrombosis.

2. Tetrahydrofolate combines with serine to produce N⁵,N¹⁰-methylene-FH₄; glycine is a
by-product of the reaction.
   • Tetrahydrofolate receives a methyl group (-CH₃) from serine to produce N⁵,N¹⁰-
methylenetetrahydrofolate and glycine.
   a. In the conversion of N⁵,N¹⁰-methylene-FH₄ to dihydrofolate reductase (FH₂) by
thymidylate synthase, the carbon from the methylene group is transferred to
deoxyuridine monophosphate (dUMP) to produce deoxyctidylate monophosphate
(dTMP).
   • Thymidylate synthase is irreversibly inhibited by 5-fluorouracil.
   b. Dihydrofolate reductase converts dihydrofolate to FH₄.
   • Dihydrofolate reductase is inhibited by methotrexate and trimethoprim.

H. Vitamin B₁₂ in odd-chain fatty acid metabolism
1. Vitamin B₁₂ is involved in odd-chain fatty acid (FA) metabolism, which explains the
neurologic problems that are unique to vitamin B₁₂ deficiency (Fig. 12-17).
2. Propionyl CoA is converted to methylmalonyl CoA, which, in turn, is converted to methylmalonyl CoA by methylmalonyl CoA mutase using vitamin B₁₂ as a cofactor.
   a. When vitamin B₁₂ is deficient, there is an increase in propionyl CoA and methylmalonyl CoA and their corresponding acids proximal to the enzyme block.
   b. Propionyl CoA replaces acetyl CoA in neuronal membranes, which causes demyelination in the spinal cord, brain, and peripheral nerves.

I. **Clinical findings in vitamin B₁₂ deficiency**

1. Pernicious anemia (PA), the most common cause of vitamin B₁₂ deficiency, has clinical findings that are not present in other causes of vitamin B₁₂ listed in **Table 12-3**.
   a. Three antibodies that are associated with the pathophysiology of PA and its clinical findings include:
      (1) Antibodies directed against the proton pump in parietal cells (85%–90% of cases)
      (2) Antibodies that block the binding of vitamin B₁₂ to intrinsic factor (60%–75% of cases)
         • Most specific test for PA
      (3) Antibodies that prevent the binding of vitamin B₁₂–intrinsic factor complexes to ileal receptors (30%–50% of cases)
   b. Antibodies that attack parietal cells in the body/fundus (type II hypersensitivity reaction) produce a chronic atrophic gastritis that is associated with achlorhydria (lack of gastric acid) and a loss of IF:
      (1) Loss of acid prevents proper digestion of food in the stomach, which interferes with the release of vitamin B₁₂ from food.
      (2) Loss of IF decreases absorption of vitamin B₁₂ in the terminal ileum.
      (3) Achlorhydria leads to a corresponding increase in serum gastrin (hypergastrinemia; negative feedback).
      (4) Intestinal metaplasia in the chronic atrophic gastritis (refer to **Chapter 2**), increases the risk for developing adenocarcinoma of the body/fundus.
   c. Other antibodies associated with PA also contribute to producing vitamin B₁₂ deficiency.
   d. Another clinical finding in PA unrelated to the previously mentioned antibodies is a peculiar lemon yellow appearance of the skin (Fig. 12-18A).
   e. PA is often associated with other autoimmune disease (e.g., type 1 diabetes mellitus, Graves disease, Addison disease) and *Helicobacter pylori* infection.

2. Clinical problems associated with **all** causes of vitamin B₁₂ deficiency include:
   a. Glossitis associated with a smooth, sore tongue and atrophy of the papillae (see Fig. 12-18B)
   b. Neurologic disease associated with demyelination
      (1) Peripheral neuropathy with sensorimotor dysfunction
      (2) Subacute combined degeneration (demyelination) of spinal cord (see Fig. 12-18C)
         a. Posterior column dysfunction decreases vibratory sensation and proprioception (joint sense).
         b. Lateral corticospinal tract dysfunction produces spasticity.
         c. Dorsal spinocerebellar tract dysfunction causes ataxia.
      (3) Dementia from involvement of the brain
      (4) Possible to have neurologic disease **without** anemia in 20% of patients

J. **Laboratory findings in vitamin B₁₂ deficiency**

1. Decreased serum vitamin B₁₂
2. Increased serum homocysteine and methylmalonic acid (95% of cases)
3. Peripheral blood findings include:
   a. Pancytopenia
   b. Oval (egg-shaped) macrocytes
Red Blood Cell Disorders

Hypersegmented neutrophils (see Fig. 12-18D)
- Hypersegmented neutrophils have more than five nuclear lobes.

4. Bone marrow findings
- Megaloblastic nucleated cells are present with a primitive open (lacy) chromatin pattern (see Fig. 12-15).

5. Schilling test localizes some of the causes of vitamin B₁₂ deficiency.
- Although it is not routinely performed anymore, it is a good review of causes of vitamin B₁₂ deficiency.

The Schilling test has been used in the past to demonstrate impaired absorption of vitamin B₁₂. This is achieved indirectly by combining orally administered radioactive vitamin B₁₂ with IF, or with pancreatic extract, or alone after pretreatment with antibiotics followed by a 24-hour urine collection to measure radioactive vitamin B₁₂. Lack of absorption of radioactive vitamin B₁₂ excludes a potential cause of impaired absorption, whereas the presence of absorption confirms the cause of the impaired absorption. For example, if the combination of radioactive vitamin B₁₂ + IF leads to an increase in radioactive vitamin B₁₂ in the urine, the patient has PA; if it does not, the diagnosis of PA is excluded. Similarly, correction with pancreatic extract implicates chronic pancreatitis as the cause or bacterial overgrowth as the cause, if antibiotics correct the absorption. To ensure that the oral radioactive vitamin B₁₂ enters the kidney for excretion, the person is given a massive intramuscular dose of nonradioactive vitamin B₁₂ so that all available transcobalamin II sites are occupied by the vitamin B₁₂. Therefore if radioactive vitamin B₁₂ is absorbed in the terminal ileum, it cannot bind to transcobalamin II and must be excreted in the urine.
K. Clinical findings in folic acid deficiency
1. Similar to vitamin B₁₂ deficiency with the exception of neurologic disease
2. Increased risk for open neural tube defects in the fetus if there is decreased maternal intake of folic acid before conception (see Fig. 26-4A, B, D and E

L. Laboratory findings in folic acid deficiency
1. Peripheral blood and bone marrow findings similar to vitamin B₁₂ deficiency
2. Decreased serum folic acid and RBC folic acid level
   a. RBC folic acid level is the best screening test; however, both tests are usually ordered.
   b. RBC folic acid best correlates with folic acid stores.

M. Treatment of vitamin B₁₂ and folic acid deficiency
1. Treatment of vitamin B₁₂ deficiency
   a. Intramuscular injections of vitamin B₁₂ are given.
   b. Treatment is indefinite in PA.
2. Treatment of folic acid deficiency
   • Oral administration of monoglutamic folic acid

It is important to distinguish folic acid deficiency from vitamin B₁₂ deficiency. Pharmacologic doses of folic acid correct the hematologic findings in both folic acid and vitamin B₁₂ deficiency; however, neurologic disease is not corrected.

N. Comparison table of vitamin B₁₂ and folic acid deficiency (Table 12-5)
O. Nonmegaloablastic macrocytosis
1. General differences of nonmegaloablastic macrocytosis from megaloblastic macrocytic anemias include:
   a. Macrocytes are round rather than oval or egg-shaped.
   b. Hypersegmented neutrophils are not present in the peripheral blood.
   c. Leukocytes and platelets are quantitatively normal.
   d. Glossitis and neuropathy are absent.
   e. Anemia may not be present.
   f. Alcohol excess is the most common cause for all types of the macrocytosis.
2. Liver disease associated with alcohol is a common cause of nonmegaloablastic macrocytosis without anemia.
   a. MCV range is 105 ± 10 µm³.
   b. Peripheral blood has thin, round, macrocytic target cells (Fig. 12-19).
      • Target cells are due to excess RBC membrane lipid, which bunches the membrane up in the middle and causes the targetoid appearance.
   c. Life span of the RBCs is not decreased
3. Direct toxic effect of alcohol on RBC precursors produces a nonmegaloablastic macrocytosis and mild anemia.
   a. MCV ranges from 100 to 110 µm³.
   b. Vacuolization of RBC precursors is present in the bone marrow.
   c. Abstinence from alcohol reverses the macrocytosis and anemia.

### Table 12-5 Clinical and Laboratory Findings in Vitamin B₁₂ and Folic Acid Deficiencies

<table>
<thead>
<tr>
<th>LABORATORY/CLINICAL FINDING</th>
<th>PERNICIOUS ANEMIA</th>
<th>OTHER VITAMIN B₁₂ DEFICIENCIES</th>
<th>FOLIC ACID DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achlorhydria</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Chronic atrophic gastritis</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Gastric carcinoma risk</td>
<td>↑</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hypersegmented neutrophils</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>Present</td>
<td>Present</td>
<td>None</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Plasma homocysteine</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Serum gastrin level</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Urine methylmalonic acid</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
Red Blood Cell Disorders

V. Normocytic Anemias: Corrected Reticulocyte Count or Index <3% (see Table 12-5)

A. Acute blood loss
   1. Epidemiology
      a. External blood loss
         • Examples—open fractures, knife wound
      b. Internal blood loss
         • Examples—ruptured abdominal aortic aneurysm, ruptured spleen
      c. Acute blood loss is the most common cause of hypovolemic shock
   2. Clinical and laboratory findings in hypovolemic shock (refer to Chapter 5)
   3. Hb, Hct, and RBC count are initially normal in acute blood loss, because whole blood is lost.
      a. Once plasma begins to be replaced by fluid from the interstitial space entering the vascular compartment, the RBC deficit becomes apparent and the Hb, Hct, and RBC count decrease.
      b. If the patient is receiving intravenous (IV) saline, the RBC deficit is immediately uncovered, because the saline is acting like plasma.
      c. It takes 5 to 7 days before a reticulocyte response is observed in acute blood loss.

B. Early iron deficiency or ACD
   1. In both iron deficiency and ACD, the anemia is normocytic before it becomes microcytic.
      • In ACD, it is microcytic in only 10% to 30% of cases, usually in the setting of rheumatoid arthritis or Crohn disease.
   2. Serum ferritin is most useful in distinguishing the two anemias as previously discussed.

C. Aplastic anemia
   1. Epidemiology
      a. Two peaks of presentation—between 15 and 25 years or >60 years
      b. Causes (Table 12-6)
   2. Pathogenesis
      a. Immunologic alterations occur in the myeloid stem (progenitor) cells, causing T-cell activation and release of cytokines that suppress or destroy the myeloid stem cells (see Fig. 12-1).

Table 12-6 Causes of Aplastic Anemia

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>EXAMPLES AND DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>Approximately 50%–70% of cases are idiopathic</td>
</tr>
<tr>
<td>Drugs</td>
<td>Most common known cause of aplastic anemia</td>
</tr>
<tr>
<td></td>
<td>Dose-related causes are usually reversible (e.g., alkylating agents, antimetabolites)</td>
</tr>
<tr>
<td></td>
<td>Idiosyncratic reactions are frequently irreversible (e.g., chloramphenicol, phenylbutazone)</td>
</tr>
<tr>
<td>Chemical agents</td>
<td>Toxic chemicals in industry and agriculture (e.g., benzene, insecticides-DDT, parathion)</td>
</tr>
<tr>
<td>Infection</td>
<td>May involve all hematopoietic cell lines (pancytopenia) or only erythroid cell line (pure RBC aplasia)</td>
</tr>
<tr>
<td></td>
<td>Examples—EBV, CMV, parvovirus; non-A, non-B hepatitis, HCV</td>
</tr>
<tr>
<td>Physical agents</td>
<td>Whole-body ionizing radiation (therapeutic or nuclear accident)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Thymoma (may be associated with pure RBC aplasia)</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
</tbody>
</table>

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus.

12-19: Round macrocytes and target cells in chronic alcoholism. Note the round macrocytes with target cell formation (arrows). [From Wickramasinghe SN, McCullough J: Blood and Bone Marrow Pathology, London, Churchill Livingstone, 2003, Fig. 6-2F.]
Aplastic anemia: fever, bleeding, fatigue

RBC aplasia: suppression/destruction
erythroid colony-forming unit

RBC aplasia: Diamond-Blackfan syndrome, thymomas, leukemia, drugs, parvovirus

Complete recovery <10%

Anemia CRF: ↓EPO + ACD

CRF: platelet dysfunction (reversible with dialysis), burr cells

**12-20**: Bone marrow biopsy in aplastic anemia. The biopsy shows a marrow largely replaced by adipose cells. Scattered lymphocytes are present in between adipose cells. (From Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, Fig. 13-27B.)

<table>
<thead>
<tr>
<th>Lab finding</th>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Due to infection associated with neutropenia</td>
<td>Discontinue drug</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Due to thrombocytopenia</td>
<td>Broad-spectrum antibiotics</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Due to anemia</td>
<td>Prevent infection</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>Due to bone marrow transplant candidate</td>
<td>Transfusions, if required, should be with irradiated blood</td>
</tr>
<tr>
<td>Reticulocytopenia</td>
<td>Due to bone marrow transplantation</td>
<td>Irradiated blood kills donor T cells</td>
</tr>
<tr>
<td>Hypocellular bone marrow</td>
<td>Due to graft-versus-host reaction</td>
<td>Immunosuppressive therapy</td>
</tr>
</tbody>
</table>

5. Complete recovery occurs in <10% of cases.

6. Treatment

b. Mutations in TERT, the gene for the RNA component of telomerase, cause short telomerases in congenital aplastic anemia and some acquired causes.

3. Clinical findings include:

a. Fever, due to infection associated with neutropenia
b. Bleeding, due to thrombocytopenia
c. Fatigue, due to anemia

4. Laboratory findings include:

a. Pancytopenia
b. Reticulocytopenia
c. Hypocellular bone marrow (Fig. 12-20)
   - Lymphocytes are present in the marrow and peripheral blood, because the pluripotential stem cell is proximal to the myeloid progenitor stem cell (see Fig. 12-1).

7. Pure RBC aplasia

a. Uncommon type of aplasia that only involves suppression or destruction of RBC precursor cells (erythroid colony-forming unit; see Fig. 12-1).

b. Causes include:
   - Congenital problems (e.g., Diamond-Blackfan syndrome), thymomas, certain types of leukemia (e.g., B- and T-cell chronic lymphocytic leukemia), drugs (e.g., phenytoin, azathioprine, sulfonamides), and parvovirus
c. Treatment
   - (1) Blood transfusions
   - (2) Corticosteroids
   - (3) Autologous and allogeneic peripheral stem cell transplantation

D. **Chronic renal failure (CRF)**

1. Pathogenesis
   - Combination of a decrease in EPO and ACD (see previous discussion)

2. Laboratory findings include:
   a. Normocytic anemia
   b. Presence of burr cells (i.e., RBCs with an undulating membrane)
   c. Prolonged bleeding time (refer to Chapter 15)
   - Defect in platelet aggregation that is reversible with dialysis

E. **Malignancy; causes of anemia include:**

1. ACD is the overall most common anemia.
2. Gastrointestinal bleeding (e.g., colorectal cancer) produces a normocytic or microcytic anemia from loss of iron.
3. Metastasis to the bone marrow
   a. Malignant cells displace normal marrow hematopoietic cells into the peripheral blood (myelophthitic anemia).
   b. Presence of nucleated RBCs and immature myeloid cells in the peripheral blood is also called a leukoerythroblastic reaction (see Fig. 13-1).
4. Immune hemolytic anemia (IHA)
   - Example—a cold type of IHA occurs in chronic lymphocytic leukemia

VI. Normocytic Anemias: Corrected Reticulocyte Count >3% (see Table 12-5)
A. Pathogenesis of hemolytic anemias
1. Intrinsic or extrinsic types
   a. Intrinsic refers to a defect in the RBC causing the anemia.
      - Examples—membrane defects (hereditary spherocytosis), abnormal hemoglobin (sickle cell anemia), and enzyme deficiency (glucose-6-phosphate dehydrogenase deficiency)
   b. Extrinsic refers to factors outside the RBC causing hemolysis.
      - Examples—stenotic aortic valve and immune destruction
2. Mechanisms of hemolysis (Fig. 12-21)
   a. Extravascular hemolysis
      (1) RBC phagocytosis by macrophages in the spleen (most common site) and/or the liver
      (2) Reasons for RBC phagocytosis
         a. RBCs coated by IgG with or without C3b
            - Macrophages have receptors for IgG and C3b.
         b. Abnormally shaped RBCs that cannot get back into the peripheral circulation (e.g., spherocytes, sickle cells).
         c. Contain inclusions (e.g., Heinz bodies in glucose-6-phosphate dehydrogenase deficiency [G6PD])
      (3) Increase in serum UCB produces jaundice if >2.5 mg/dL.
         - UCB is the end product of macrophage degradation of Hb.
      (4) Increased serum lactate dehydrogenase (LDH) from hemolyzed RBCs
      (5) May be a decrease in serum haptoglobin (see later)

![Diagram](https://via.placeholder.com/150)

**12-21:** Extravascular (A) and intravascular (B) hemolysis of red blood cells. In extravascular hemolysis, macrophage destruction of RBCs produces unconjugated hyperbilirubinemia and, in some cases, a decrease in serum haptoglobin. In intravascular hemolysis, hemoglobinuria, hemosiderinuria, and a decrease in serum haptoglobin are the key findings. There is some overlap in the two types of hemolysis, but these are the exception rather than the rule. (From Goljan EF: Star Series: Pathology, Philadelphia, Saunders, 1998, Fig. 12-2.)
b. Intravascular hemolysis
   (1) Hemolysis occurs within blood vessels
   (2) Causes of intravascular hemolysis include:
       (a) Enzyme deficiency (e.g., G6PD)
       (b) Complement destruction (e.g., IgM-mediated hemolysis; IgG-mediated in some cases)
       (c) Mechanical damage (e.g., calcific aortic valve stenosis)
   (3) Laboratory findings include:
       (a) Increased plasma and urine Hb
       (b) Hemosiderinuria (proximal renal tubule cells convert iron in Hb into hemosiderin)
       (c) Decreased serum haptoglobin
   (4) Increased serum LDH from hemolyzed RBCs

Haptoglobin is an acute phase reactant that combines with Hb to form a complex that is phagocytosed and degraded by macrophages, causing a decrease in serum haptoglobin. The amount of Hb in the complexes may increase UCB, leading to jaundice. Because the serum UCB level must be >2.5 mg/dL to produce visible evidence of jaundice, the increase in UCB from macrophage removal of the haptoglobin-Hb complex may not be enough to cause jaundice.

B. Hereditary spherocytosis (HS)
   1. Epidemiology
      a. Predominantly an autosomal dominant disorder
         • Some cases are autosomal recessive.
      b. Common in people of Northern European descent
      c. Intrinsic defect with extravascular hemolysis
   2. Pathogenesis
      a. Membrane protein defect results in the loss of RBC membrane and volume, leading to spherocyte formation (Fig. 12-22A).
         (1) Mutation in spectrin is the most common defect.
            • Mutations in ankyrin, band 2 or band 3, account for other defects.
         (2) Microvesicles that form on the surface of the RBCs in the areas of membrane weakness are lost (Fig. 12-22A).
         (3) In addition, the membrane defect leads to a loss of both potassium and water, which produces cellular dehydration.
         (4) Combination of microvesicle loss of cell membrane plus cellular dehydration yields spherocytes with a decreased surface to volume ratio.
      b. Spherocytes are extravascularly removed by splenic macrophages, which causes normocytic anemia.
   3. Clinical findings
      a. Jaundice commonly occurs because of increased UCB from splenic macrophage destruction of RBCs.
         • In newborns, 30% to 50% develop a hemolytic anemia with unconjugated hyperbilirubinemia leading to jaundice.
      b. Incidence of calcium bilirubinate gallstones is increased (see Fig. 19-9C).
         (1) Due to increased liver conversion of excess amounts of UCB to conjugated bilirubin (CB), which is excreted in the bile.
         (2) CB is converted back to UCB in the gallbladder and combines with calcium to form the stones.
      c. Splenomegaly (due to hypertrophy from RBC hemolysis) is present in 75% of cases.
      d. Aplastic crisis is uncommon but may occur in children, especially after a viral infection (e.g., parvovirus).
   4. Laboratory findings
      a. Normocytic anemia with spherocytosis (see Fig. 12-22B)
         • Other causes of spherocytosis: warm IHA and ABO hemolytic disease of newborn
      b. Increased MCHC
         (1) Due to cellular dehydration from the loss of potassium and water
         (2) Only anemia with an increase in MCHC
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12-22: A, Schematic showing the formation of microvesicles on the RBC membrane from areas of weakness in the RBC membrane. These are removed by macrophages in the spleen. Eventually, so much membrane has been lost that the RBC forms a spherocyte, which is phagocytosed and destroyed by splenic macrophages. B, Peripheral blood with spherocytes in hereditary spherocytosis. Numerous, round, dense red blood cells without central areas of pallor represent spherocytes (arrows). The mean corpuscular hemoglobin concentration is increased. C, Osmotic fragility test. Comparison of red cell lysis in severe hereditary spherocytosis (interrupted line) and in normal blood (shaded area). The curve is shifted to the right of the normal range. (B From Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 75, Fig. 5-7; C from McPherson R, Pincus M: Henry’s Clinical Diagnosis and Management by Laboratory Methods, 22nd ed, Philadelphia, Saunders, 2011, p 573, Fig. 32-11.)

c. Increased RBC osmotic fragility (see Fig. 12-22C)
   (1) When compared to normal RBCs, there is increased osmotic fragility when spherocytes are placed in saline solutions of different tonicity.
   (2) Hemolysis is primarily due to the decreased surface to volume ratio of spherocytes.

d. Increased RDW (dense, round spherocytes plus normal-sized RBCs)

5. Treatment is splenectomy,
   - Spherocytes remain in the peripheral blood.

C. Hereditary elliptocytosis
   1. Pathogenesis
      a. Autosomal dominant disorder
      b. Mutation in spectrin and band 4.1
      c. Intrinsic defect with extravascular hemolysis
   2. Clinical findings
      a. Majority have no anemia or a mild hemolytic anemia
      b. Splenomegaly
   3. Laboratory findings
      a. Elliptocytes account for >25% of the RBCs (Fig. 12-23).
      b. Osmotic fragility is increased.
   4. Treatment is splenectomy in symptomatic patients.

D. Paroxysmal nocturnal hemoglobinuria (PNH)
   1. Epidemiology
      - Intrinsic defect with intravascular hemolysis

---

HS: ↑MCHC, ↑RBC osmotic fragility (↓surface to volume ratio), ↑RDW
HS: Rx splenectomy

Elliptocytosis: AD disorder; mutation spectrin and band 4.1

Hereditary elliptocytosis: >25% elliptocytes in peripheral blood
PNH: intrinsic defect with intravascular hemolysis
PNH: mutation in PIG group A gene in myeloid stem cell clone

PNH: defect in anchoring inhibitors of complement (CD55 [decay accelerating factor], CD59)

Inhibitors normally degrade C3/C5 convertase to prevent MAC activation; prevent lysis in RBCs, neutrophils, and platelets

PNH: episodic hemoglobinuria, 

†vessel thrombosis, acute myeloblastic leukemia

PNH: pancytopenia; -LAP stain; hemoglobinuria

PNH Dx: flow cytometry best test; sucrose hemolysis test and acidified serum test outdated

2. Pathogenesis
   a. Acquired stem cell disease with a somatic mutation after birth in the PIG (phosphatidylinositol glycan) group A gene in a myeloid stem cell clone
   b. Mutation results in a defect in the anchoring of inhibitors of complement (CD55 [decay accelerating factor] and CD59) on the surface of RBCs, neutrophils, and platelets.
      - The inhibitors just mentioned normally degrade C3 and C5 convertase on hematopoietic cell membranes, which prevents activation of the membrane attack complex (MAC) and subsequent lysis of RBCs, neutrophils, and platelets.
   c. Intravascular complement-mediated lysis of RBCs, neutrophils, and platelets
      - Occurs at night, because respiratory acidosis enhances complement attachment to these cells

3. Clinical findings
   a. Iron deficiency possible because of episodic hemoglobinuria (microcytic anemia)
   b. Increased incidence of vessel thrombosis (e.g., hepatic vein)
      - Due to the release of aggregating agents from destroyed platelets (e.g., adenosine diphosphate)
   c. Increased risk for developing acute myeloblastic leukemia

4. Peripheral blood findings
   a. Normocytic anemia with pancytopenia
      - Microcytic if iron deficiency develops from hemoglobinuria
   b. Negative leukocyte alkaline phosphatase (LAP) stains
   c. Decreased serum haptoglobin
   d. Increased serum and urine Hb

5. Diagnosis
   a. Test of choice is flow cytometry detecting granulocytes missing the anchor for the inhibitors of complement
   b. Older tests for diagnosing PNH
      (1) Screening test using the sucrose hemolysis test (sugar water test)
         - Sucrose enhances complement destruction of RBCs.
      (2) Confirmatory test using the acidified serum test (Ham test)
         - Acidified serum activates the alternative pathway causing hemolysis.

6. Treatment
   a. Corticosteroids
   b. Eculizumab to inhibit activation of the terminal complement components
      - Significantly reduces intravascular hemolysis and the need for blood transfusions
   c. Anticoagulation to prevent thromboses
   d. Bone marrow transplantation

E. Paroxysmal cold hemoglobinuria (PCH)
1. Epidemiology
   a. Extrinsic defect with intravascular hemolysis
   b. Transient hemolytic anemia in children with measles, mumps, influenza, and chickenpox
   c. Associated with syphilis
2. Pathogenesis
   a. IgG cold antibody develops that has bithermal activity (Donath-Landsteiner antibody).
   b. Antibody is directed against the P blood group antigen on RBCs.
      (1) At cold temperatures, it binds to RBCs and fixes complement.
      (2) At 37° C, it detaches from RBCs and activates complement, causing intravascular hemolysis.
   c. Hemolytic anemia usually occurs when moving from a cold to warm environment.
   d. Clinical findings
      a. Within minutes after exposure to cold temperatures, there is fever, rigors, and chills followed by red to brown urine (hemoglobinuria).
      b. The anemia produces back, leg, and abdominal pain.
      c. It may be associated with Raynaud phenomenon (refer to Chapter 10).
      d. Transient hepatosplenomegaly with jaundice may occur.
      e. Oliguria and renal failure may occur.
      f. Symptoms and hemoglobinuria usually resolve within hours, especially when moving into a warm environment.

4. Diagnosis
   • Special laboratory tests detect the bithermal antibody.

5. Treatment
   a. Blood transfusion may be necessary, especially in children.
   b. Plasma exchange removes the bithermal antibody.

F. Sickle cell disease
   1. Epidemiology
      a. Autosomal recessive disorder
      b. Most common hemoglobinopathy in individuals of African descent
         • Highest prevalence (~30%–40%) is in sub-Saharan Africa
      c. Intrinsic defect with predominantly extravascular hemolysis of sickle cells
         • Mild component of intravascular hemolysis
      d. Missense point mutation with substitution of valine for glutamic acid at the sixth position of the β-globin chain
      e. Heterozygote condition (sickle cell trait, HbAS) has no anemia.
         • Present in ~10% of the black population
      f. Homozygous condition (HbSS) produces severe anemia.
      g. Using an example of a pedigree with two people with sickle cell trait:
         (1) Normal child 25%
         (2) Sickle cell trait 50%
         (3) Sickle cell disease 25%
      h. Protective against Plasmodium falciparum malaria

2. Pathogenesis
   a. Hemoglobin S molecules aggregate and polymerize into long needle-like fibers when deoxygenated.
      (1) RBCs assume a sickle or boat-like shape (Fig. 12-24A).
      (2) O₂ inhibits sickling.
   b. Causes of sickling
      (1) Sickle hemoglobin (HbS) concentration >60% is the most important factor for sickling.
         • HbS concentration is too low in HbAS (<50%) to produce sickling in the peripheral blood.
      (2) Factors that increase the concentration of deoxyHb and increase the risk for sickling include:
         (a) Acidosis, which shifts the OBC to the right, causing O₂ release from RBCs and leading to an increase in deoxyHb
         (b) Volume depletion, where intracellular dehydration causes an increase in concentration of deoxyHb
         (c) Hypoxemia, where a decrease in arterial P0₂ decreases the O₂ saturation of Hb, which increases the amount of deoxyHb
   c. Reversible and irreversible sickling
      (1) Initial sickling is reversible with administration of O₂.
         • O₂ inhibits sickling.
      (2) Recurrent sickling causes irreversible sickling due to membrane damage.
         (a) Influx of calcium ions cross-links membrane proteins, causing the egress of K⁺ and H₂O and leaving the cell dehydrated.
Irreversibly sickled cells: dehydrated; correlate with degree of severity of hemolysis; extravascular removal

Sickle cells: ↑ expression of adhesion molecules; stick to and damage endothelial cells in microvasculature

HbF prevents sickling: hydroxyurea ↑ HbF synthesis

HbSS anemia: severe hemolytic anemia; vasoocclusive crises

Dactylitis: aseptic necrosis in metacarpal bones; MC presentation in infants

(b) Number of irreversibly sickled cells correlates with the severity of hemolysis.

(c) Irreversibly sickled cells are sequestered and are extravascularly removed by macrophages in the spleen and liver.

d. Microvascular occlusions (vasoocclusive crises) produce ischemic damage.
   (1) Sickled cells are sticky because of increased expression of adhesion molecules on their surface; this enables them to stick to and damage endothelial cells in the microvasculature.
   (2) Microvascular occlusion leads to ischemic damage of tissue.

e. HbF prevents sickling
   (1) Increased HbF at birth prevents sickling in HbSS until 5 to 6 months of age.
   (2) Hydroxyurea increases the synthesis of HbF.
   (3) HbF has a high affinity for O₂, which inhibits sickling.

f. Key pathologic processes in homozygous sickle cell disease include:
   (1) Severe hemolytic anemia
   (2) Painful vasoocclusive crises

3. Clinical findings in homozygous sickle cell disease (HbSS)

a. Dactylitis (hand-foot syndrome)
   (1) Painful swelling of the hands (see Fig. 12-24B) and feet
      • Infarctions in the metacarpal bones (aseptic necrosis)
   (2) Occurs in infants (usually 6–9 months old) and is rarely seen after 2 years of age

b. Acute chest syndrome
   (1) Definition
      • New segmental lung infiltrate associated with chest pain
   (2) Most common cause of death in young people with sickle cell disease
(3) Causes include:
   (a) Pneumonia
      • *Streptococcus pneumoniae, Mycoplasma, Chlamydia*, viruses
   (b) Bone infarction with fat embolism
(4) Clinical findings include:
   • Chest pain, wheezing, dyspnea, pleuritic chest pain, pleural effusion, and cough
(5) Arterial blood gas shows hypoxemia
(6) Chest x-ray shows lung infiltrates

(c) Avascular necrosis of femoral head

(d) Autosplenectomy
   (1) Spleen is enlarged but dysfunctional by age 10 to 12 months.
      • Nuclear remnants (Howell-Jolly bodies) appear in RBCs, indicating loss of
        macrophage function in the spleen (see Fig. 12-24C).
   (2) Spleen is fibrosed and smaller in young adults.
      • Most authors refer to this stage as “autosplenectomy.”

(e) Increased susceptibility to infections
   (1) Risk for infection is due to a dysfunctional spleen with impaired opsonization of
       encapsulated bacteria.
   (2) Children are at risk for *S. pneumoniae* sepsis.
      (a) This is a common cause of death in children.
      (b) Prophylactic penicillin is recommended.

(3) Increased risk for osteomyelitis
   • Most often due to *Salmonella paratyphi* and less frequently to *Staphylococcus aureus*

(f) Aplastic crisis
   (1) Most frequently associated with a parvovirus infection
   (2) No reticulocytes in the peripheral blood (reticulocytopenia)

(g) Sequestration crisis
   (1) Associated with rapid splenic enlargement and entrapment of sickled RBCs (drop in
       hemoglobin) and blood causing hypervolemia
   (2) Usually occurs in the first 2 years of life
   (3) Reticulocytosis present in the peripheral blood

(h) Increased risk for calcium bilirubinate gallstones (see previous discussion)

(i) Strokes may occur in children between ages 2 and 5 years.
   (1) Common cause of death in children
   (2) 70% recurrence rate

(j) Recurrent leg ulcers
   • Commonly occur above the medial or lateral malleolus

(k) Proliferative retinopathy
   • Commonly leads to blindness

(l) End-stage renal failure occurs after 40 years of age.

4. Renal findings in sickle cell trait (HbAS; also in HbSS)
   a. Sickling occurs in peritubular capillaries in the medulla
      • O₂ tension is normally low enough in the medulla to induce sickling in trait and
        disease.
   b. Microhematuria occurs because of microinfarctions in the kidneys.
      • Always order a sickle cell screen in any black person with unexplained hematuria.
   c. Renal papillary necrosis may occur (refer to Chapter 20).
      • Loss of the renal papillae results in a loss of concentration and dilution of urine.

5. Laboratory findings in sickle cell trait and disease
   a. Sickle cell screen
      • Sodium metabisulfite reduces O₂ tension, which induces sickling in a test tube.
   b. Hb electrophoresis (see Fig. 12-7E and F)
      (1) HbAS (trait) profile: HbA 55% to 60%, HbS 40% to 45%
      (2) HbSS (disease) profile: HbS 90% to 95%, HbF 5% to 10%, no HbA
   c. Peripheral blood findings
      (1) Normal peripheral blood smear in HbAS
      (2) Sickle cells, target cells, nucleated RBCs, and Howell-Jolly bodies in HbSS
         (see Fig. 12-24A)
   d. Prenatal screening
      • Analysis of fetal DNA is used to detect the point mutation.
6. Treatment of sickle cell disease
   a. Treat infections
   b. Pain relief (e.g., morphine)
   c. Transfusion of blood
      • Acute chest syndrome, aplastic crisis
7. Preventive measures in sickle cell disease
   a. Hydroxyurea to increase hemoglobin F
   b. Routine immunizations all current
   c. Pneumococcal vaccine
   d. Folic acid supplementation
      • Often decreased because accelerated erythropoiesis depletes supply.

G. Glucose-6-phosphate dehydrogenase (G6PD) deficiency

1. Epidemiology
   a. X-linked recessive (XR) disorder
   b. Highest prevalence is in tropical Africa (most common location), the Middle East, Greece, Italy, and Asia
   c. Intrinsic defect with predominantly intravascular hemolysis
   d. Most common enzyme deficiency causing hemolysis
   e. Subtypes of G6PD deficiency
      (1) Mediterranean variant
      (2) Black variant (occurs in 10% of blacks)
   f. Protective against *P. falciparum* malaria

2. Pathogenesis
   a. Decreased synthesis of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione (GSH) in the pentose phosphate pathway (Fig. 12-25A)
      (1) GSH normally neutralizes *H₂O₂*, an oxidant product in RBC metabolism.
      (2) In G6PD deficiency, *H₂O₂* oxidizes Hb, which precipitates in the form of Heinz bodies (see Fig. 12-25B).
         (a) Heinz bodies damage the RBC membranes, causing intravascular hemolysis.
         (b) Heinz bodies removed from RBC membranes by splenic macrophages, producing bite cells.
   b. Half-life of G6PD in Mediterranean variant is markedly reduced (<10% activity).
      (1) Enzyme is highest in young RBCs and decreases in old RBCs, so the old RBCs with the least amount of enzyme are preferentially destroyed.
      • In this variant, there are a lot more old RBCs that lack the enzyme.

**Figure 12-25:** A, Pentose phosphate pathway. The enzyme glucose-6-phosphate dehydrogenase catalyzes the irreversible reaction that converts glucose 6-phosphate to 6-phosphogluconate. NADPH (reduced form of nicotinamide adenine dinucleotide phosphate [NADP]) is produced in this reaction and reduces oxidized glutathione (GSSG) to glutathione (GSH), which neutralizes peroxide and converts it to water. B, Peripheral blood smear with a bite cell and inset showing Heinz bodies in glucose-6-phosphate dehydrogenase deficiency. The arrow shows a bite cell with part of the red blood cell membrane removed. The inset shows a peripheral blood smear with a supravital stain visualizing punctate inclusions representing denatured hemoglobin (Heinz bodies). (A from Goljan EF: Pathology: Saunders Text and Review Series, Philadelphia, Saunders, 1998, Fig. 12-10; B from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, Fig. 13-8; inset from Wickramasinghe SN, McCullough J: Blood and Bone Marrow Pathology, London, Churchill Livingstone, 2003, Fig. 8-8.)
The person has either a severe, chronic hemolytic anemia or one with severe hemolysis associated only with an oxidant stress (see later).

- Half-life of G6PD in black variant is moderately reduced (10%–60% activity).
  - Produces an episodic type of hemolytic anemia after exposure to an oxidant stress.
- Oxidant stresses inducing hemolysis include:
  1. Infection (most common)

**A decrease in NADPH** impairs neutrophils and monocyte killing of bacteria by the O₂-dependent myeloperoxidase (MPO) system (refer to Chapter 3), which requires NADPH as a cofactor for NADPH oxidase. This explains why infection is the most important oxidant stress initiating hemolysis.

**2. Drugs**
   - Examples—primaquine, chloroquine, dapsone, sulfonamides, and nitrofurantoin

**3. Fava beans** (mainly in the Mediterranean variant)

**3. Clinical findings**
   a. Sudden onset of back pain with hemoglobinuria 2 to 3 days after an oxidant stress
   b. Jaundice possible in both neonates and adults

**4. Laboratory findings**
   a. Normocytic anemia
   b. Heinz bodies (see Fig. 12-25B)
     1. Identified with a supravital stain
     2. Best screen during active hemolysis
   c. RBC enzyme analysis
     - Confirmatory test after hemolysis has subsided
   d. Peripheral blood findings
     - Bite cells (macrophage removal of membrane; see Fig. 12-25B)

**H. Pyruvate kinase (PK) deficiency**

1. Epidemiology
   a. Autosomal recessive (AR) disease
   b. Intrinsic defect with extravascular hemolysis
   c. Most common enzyme deficiency producing hemolysis in the glycolysis pathway (Fig. 12-26A)
      - Normally converts phosphoenolpyruvate (PEP) to pyruvate, leading to a net gain of 2 ATP

   ![Diagram of pyruvate kinase reaction](image)

   **12-26: A** Schematic of pyruvate kinase reaction. Note that pyruvate kinase is involved in the key reaction that generates a net gain of 2 ATP per glucose molecule in anaerobic glycolysis in RBCs. However, there is a proximal increase in 1,3-BPG, which is then converted to 2,3-BPG. This shifts the O₂-binding curve to the right, allowing more O₂ to enter tissue, even though there is an anemia. This offsets the clinical severity of the anemia.

   **B** Peripheral blood smear in pyruvate kinase deficiency. The arrow shows one of many red blood cells with thorny projections (echinocytes) extending from the red blood cell membrane. **BPG, Bisphosphoglycerate.**
   ![Image of blood smear](image)
2. Pathogenesis

a. Membrane damage from chronic lack of ATP
   - Results in dehydration of the RBC and formation of echinocytes (see Fig. 12-26B)
   - Increase in 2,3-BPG synthesis proximal to the enzyme block
   - Right shift of the OBC increases release of O₂ to tissue, which somewhat offsets the clinical effects of the anemia.

3. Clinical findings

a. Hemolytic anemia with jaundice beginning at birth
b. Splenomegaly

4. Laboratory findings

a. Normocytic anemia
b. RBCs with thorny projections (echinocytes)
c. Confirmatory test—RBC enzyme assay

I. Immune hemolytic anemias (IHA)

1. Epidemiology

a. Definition
   - Group of extrinsic hemolytic anemias with extravascular or intravascular hemolysis

b. Classification (Table 12-7)
   - Autoimmune hemolytic anemia (AIHA)
     a. Most common type of IHA
     b. More common in women than men
     - Systemic lupus erythematosus (SLE) is the most common cause of AIHA.
   - Drug-induced IHA (see Table 12-7)
   - Alloimmune hemolytic anemia (refer to Chapter 16)

2. Pathogenesis

a. IgG-mediated hemolysis
   - RBCs coated by IgG are phagocytosed by splenic macrophages.
     a. Predominantly extravascular hemolysis
     b. Small element of intravascular hemolysis with some IgG types
   - Spherocytes are produced if a small portion of the membrane is removed by macrophages.

b. Complement-mediated hemolysis
   - RBCs coated by C₃b alone are phagocytosed by liver macrophages.
     - Predominantly extravascular hemolysis

---

**Table 12-7 Classification of Immune Hemolytic Anemias**

<table>
<thead>
<tr>
<th>TYPE OF IMMUNE HEMOLYTIC ANEMIA</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune</td>
<td>Primary or idiopathic (no underlying cause)</td>
</tr>
<tr>
<td></td>
<td>Secondary (e.g., SLE)</td>
</tr>
<tr>
<td>Cold antibodies (IgM)</td>
<td>Mycoplasma pneumoniae (anti-l antibodies)</td>
</tr>
<tr>
<td></td>
<td>Infectious mononucleosis (anti-l antibodies)</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal cold hemoglobinuria (IgG antibodies produce hemolysis, not IgM antibodies; bithermal antibody)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>Warm and cold immune hemolytic anemia</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Drug adsorption (e.g., penicillin, 2nd and 3rd generation cephalosporins): IgG antibody directed against the drug attached to the RBC membrane; with cephalosporins, IgG or IgM antibodies may be involved.</td>
</tr>
<tr>
<td></td>
<td>Immunocomplex (e.g., quinidine): drug-IgM immunocomplex deposits on the RBC, causing intravascular hemolysis</td>
</tr>
<tr>
<td></td>
<td>Autoantibody induction (e.g., α-methyldopa): drug alters Rh antigens on RBCs, inducing synthesis of autoantibodies against altered Rh antigens</td>
</tr>
<tr>
<td>Alloimmune</td>
<td>Hemolytic transfusion reaction (refer to Chapter 16)</td>
</tr>
<tr>
<td></td>
<td>ABO hemolytic disease of newborn (refer to Chapter 16)</td>
</tr>
<tr>
<td></td>
<td>Rh hemolytic disease of newborn (refer to Chapter 16)</td>
</tr>
</tbody>
</table>

PK def: loss ATP damages RBC membranes (echinocytes)

PK deficiency:

↑2,3-BPG shifts OBC to right; offsets clinical effects of anemia

Extrinsic hemolytic anemias with extravascular or intravascular hemolysis

AIHA: MC IHA

AIHA: warm type (IgG; MC), cold type (IgM)

IgG-mediated:

- Predominantly extravascular IHA; spherocytosis

Complement-mediated:

- Intravascular or extravascular IHA

SLE: Systemic lupus erythematosus.
(2) RBCs coated by C5 through C9 (MAC)
   • Predominantly intravascular hemolysis
(3) RBCs coated by IgG and C3b are phagocytosed by liver and splenic macrophages
   (e.g., SLE).
   • Predominantly extravascular hemolysis
c. IgM-mediated hemolysis
   (1) Extravascular or intravascular hemolysis depending on the degree of complement activation
   (2) In most cases, it is intravascular hemolysis.
3. Clinical findings
   a. Jaundice due to unconjugated hyperbilirubinemia
      • Occurs in extravascular types of hemolysis
b. Hepatosplenomegaly
   • Due to work hypertrophy of splenic and liver macrophages in extravascular hemolytic anemias
c. Raynaud phenomenon (refer to Chapter 10)
   • Cold types of AIHA
4. Laboratory findings
   a. Positive direct antihuman globulin test (DAT; Coombs test)
      • Direct Coombs test detects RBCs sensitized with IgG, C3b, or C3d (Fig. 12-27A).
   b. Positive indirect antihuman globulin test (indirect Coombs test; see Fig. 12-27B).
      • Indirect Coombs test detects antibodies in the serum (e.g., anti-D antibodies).
c. Unconjugated hyperbilirubinemia, if extravascular hemolysis is present.
d. Hemoglobinuria
e. Decreased serum haptoglobin if intravascular hemolysis is present (less common with extravascular hemolysis)
f. Peripheral blood findings
   (1) Normocytic anemia
   (2) Spherocytosis
      • Due to macrophage removal of RBC membrane in the IgG type of IHAs
   (3) Reticulocytosis
   (4) RBC agglutination
      • Occurs in the IgM types of IHAs (Fig. 12-28)

12-27: Schematic of the direct Coombs test (A) and indirect Coombs test (B). A, In the direct Coombs test, red blood cells (RBCs) sensitized with IgG antibodies (or C3b, C3d) are agglutinated when Coombs reagent (rabbit anti-IgG antibody) is added to the test tube. B, In the indirect Coombs test, IgG antibodies (e.g., anti-D) in the serum must first bind to blood group type O test RBCs added to the test tube. Addition of Coombs reagent causes the sensitized type O test RBCs to agglutinate, indicating that IgG antibodies are present in the serum. The specificity of the antibodies (e.g., anti-D IgG antibodies) is determined by other tests performed in the blood bank. (From Goljan EF: Pathology: Saunders Text and Review Series, Philadelphia, Saunders, 1998, p 289, Fig. 12-11.)
5. Treatment
   a. Discontinue any offensive drug
   b. Corticosteroids
   c. Immunosuppressive agents if corticosteroids are not effective
   d. Splenectomy in selected cases
   e. Intravenous immunoglobulin
      1. IgG coats all the macrophage receptors so they cannot phagocytose RBCs.
      2. This is only used when most of the treatments just mentioned are not working.

J. **Microangiopathic and macroangiopathic hemolytic anemias (MHA)**

1. **Epidemiology**
   a. Causes (Table 12-8)
   b. Extrinsic defect with intravascular hemolysis
   c. Aortic valve (AV) stenosis is the most common cause of MHA.

2. **Pathogenesis**
   a. Microangiopathic hemolytic anemias
      - Microcirculatory lesions (e.g., fibrin or platelet thrombi) cause RBC fragmentation (schistocytes; Fig. 12-29).
   b. Macroangiopathic
      - Valvular defects (e.g., AV stenosis) mechanically damage the RBCs.

3. **Laboratory findings**
   a. Normocytic anemia
      - Long-standing hemoglobinuria causes iron deficiency anemia and a microcytic anemia.
   b. Decreased serum haptoglobin
   c. Hemoglobinuria, hemosiderinuria
   d. Schistocytes in the peripheral blood

K. **Malaria**

1. **Epidemiology**
   a. Female *Anopheles* mosquito transmits *Plasmodia* to humans.
b. Malaria life cycle (Fig. 12-30)

1. Bite of an infected female *Anopheles* species mosquito injects sporozoites into the host's blood.
   a. Sporozoites infect the liver (exoerythrocytic phase) and develop into merozoites (motile, infective stage), which are released and invade erythrocytes. Asexual reproduction within erythrocytes proceeds through several stages (ring form, trophozoite, and schizont), culminating in rupture of the cell and release of more merozoites. Some gametocytes are also produced within erythrocytes. Ingestion of male and female gametocytes by a mosquito during a blood meal initiates sexual reproduction of plasmodia within the mosquito, leading to production of more sporozoites that can infect humans. (From Rosenthal K, Tan M: Rapid Review Microbiology and Immunology, 3rd ed, Philadelphia, Mosby, 2011, Fig. 29-2.)

2. Pathogenesis
   a. Intraerythrocytic parasite causes intravascular hemolysis.
      1. Hemolysis correlates with the fever spikes
      2. Minor component of extravascular hemolysis
   b. Fever and splenomegaly
   c. *Plasmodium vivax*
Most common cause of malaria worldwide

Duffy (Fy) antigen on RBCs is the binding site for the parasite.

• Fy antigen is often absent in blacks, which provides a modicum of protection.

Simple tertian fever pattern (every 48 hours; see Fig. 12-31C)

c. \textit{P. falciparum} (malignant tertian malaria)

(1) Most lethal type of malaria

(2) Quotidian (malignant tertian) fever pattern (daily spikes with no pattern; see Fig. 12-31C)

d. \textit{Plasmodium malariae}

(1) Association with nephrotic syndrome

(2) Simple quartan fever pattern (every 72 hours; see Fig. 12-31C)

4. Laboratory findings

a. Thick smears identify organisms in RBCs.

b. Immunologic tests have excellent sensitivity (98%) and specificity (99%).

5. Medications

a. Prophylaxis (prevention)

(1) Chloroquine

(a) Safe during pregnancy

(b) Kills blood schizonts

(c) Gametocidal to all malaria species except \textit{P. falciparum}

(2) Prophylaxis for resistant strains of \textit{P. falciparum}

(a) Atovaquone-proguanil is recommended.

(b) Mefloquine is an alternative drug.

b. Treatment \textit{P. vivax/ovale}

• Chloroquine plus primaquine

c. Treatment \textit{P. falciparum}

(1) Chloroquine sensitive: chloroquine without primaquine

(2) Chloroquine resistant: quinine sulfate + doxycycline

L. Summary table of normocytic anemias (Table 12-9)
### TABLE 12-9 Summary of Normocytic Anemias

<table>
<thead>
<tr>
<th>ANEMIA</th>
<th>PATHOGENESIS</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reticulocytosis &gt;3%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute blood loss</td>
<td>Loss of whole blood</td>
<td>Initial Hb and Hct normal Infusion of normal saline uncovers anemia Signs of volume depletion (e.g., absolute neutrophilic leukocytosis) commonly present; positive tilt test (refer to Chapter 4)</td>
</tr>
<tr>
<td>Early iron deficiency</td>
<td>Decreased iron stores</td>
<td>Normocytic before microcytic Iron studies abnormal (↓Serum ferritin)</td>
</tr>
<tr>
<td>Early ACD</td>
<td>Iron trapped in macrophages by hepcidin</td>
<td>Normocytic before microcytic Iron studies abnormal (↓Serum ferritin)</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Suppression or deficiency of myeloid stem cells</td>
<td>Pancytopenia Hypocellular marrow</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Deficiency of EPO</td>
<td>Presence of burr cells</td>
</tr>
<tr>
<td><strong>Reticulocytosis ≥3%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary spherocytosis</td>
<td>AD disorder Defect in spectrin/ankyrin Extravascular hemolysis</td>
<td>Increased osmotic fragility Treat with splenectomy</td>
</tr>
<tr>
<td>Hereditary elliptocytosis</td>
<td>AD disorder Defect in spectrin and band 4.1 Extravascular hemolysis</td>
<td>Elliptocytes &gt;25%</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Acquired loss of anchor for complement inhibitors (e.g., decay accelerating factor) in clone of myeloid stem cell Complement destruction of hematopoietic cells Intravascular hemolysis Detect defect on hematopoietic cells</td>
<td>Pancytopenia Flow cytometry best test Positive sugar water test (screen) and acidified serum test (confirmatory test)</td>
</tr>
<tr>
<td>Paroxysmal cold hemoglobinuria</td>
<td>IgG cold antibody with bithermal activity Attaches to RBCs in cold temperature and fixes complement Detaches in warm temperature and activates complement producing intravascular hemolysis</td>
<td>Special test to identify bithermal antibody (Donath-Landsteiner antibody)</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>AR disorder Valine substitution for glutamic acid β-globin chain Extravascular hemolysis</td>
<td>HbAS: HbA 55%–60%; HbS 40%–45%; HbSS: HbS 90%–95%; HbF 5%–10%; no HbA</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>XR disorder GSH deficiency causes oxidant damage to Hb and RBC membrane Intravascular hemolysis</td>
<td>Bite cells in peripheral blood Heinz body preparation: screen during active hemolysis Enzyme assay: confirmatory test when hemolysis subsides</td>
</tr>
<tr>
<td>Pyruvate kinase deficiency</td>
<td>AR disease ↓ATP synthesis Extravascular hemolysis</td>
<td>↑2,3-BPG shifts OBC to right Dehydrated RBCs with thorny projections (echinocytes)</td>
</tr>
<tr>
<td>Acute blood loss</td>
<td>Loss of whole blood Reticulocytosis 5–7 days</td>
<td>↓Hb, Hct, RBC count</td>
</tr>
<tr>
<td>Warm AIHA</td>
<td>IgG with or without C3b Extravascular hemolysis</td>
<td>Positive direct Coombs test SLE most common cause</td>
</tr>
<tr>
<td>Cold AIHA</td>
<td>IgM with C3b Extravascular or intravascular hemolysis (most common)</td>
<td>Association with Mycoplasma pneumoniae; EBV Positive direct Coombs test</td>
</tr>
<tr>
<td>Alloimmune hemolytic anemia</td>
<td>Antibodies against foreign RBC antigens Extravascular hemolysis</td>
<td>Hemolytic transfusion reaction ABO and Rh HDN Positive direct Coombs test</td>
</tr>
<tr>
<td>Microangiopathic and macroangiopathic hemolytic anemia</td>
<td>Mechanical destruction of RBCs with formation of schistocytes Intravascular hemolysis</td>
<td>Calcific aortic stenosis most common cause; TTP, HUS Chronic hemoglobinuria causes iron deficiency</td>
</tr>
<tr>
<td>Malaria</td>
<td>Transmitted by female Anopheles mosquito Intravascular hemolysis</td>
<td>Rupture of RBCs corresponds with fever</td>
</tr>
</tbody>
</table>

ACD, Anemia of chronic disease; AD, autosomal dominant; AIHA, autoimmune hemolytic anemia; AR, autosomal recessive; ATP, adenosine triphosphate; BPG, bisphosphoglycerate; DAF, decay accelerating factor; EBV, Epstein-Barr virus; EPO, erythropoietin; G6PD, glucose-6-phosphate dehydrogenase; GSH, glutathione; Hb, hemoglobin; HbAS, sickle cell trait; HbSS, homozygous for sickle cell disease; Hct, hematocrit; HUS, hemolytic uremic syndrome; OBC, oxygen-binding curve; Rh HDN, Rhesus hemolytic disease of the newborn; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura; XR, X-linked recessive.
I. Benign Qualitative White Blood Cell Disorders

A. Definition
- Defects in structure and/or function of white blood cells (WBCs)

B. Pathogenesis
1. Defects in leukocyte structure
   - Example—membrane fusion defect in Chédiak-Higashi syndrome (refer to Chapters 2 and 3)
2. Defects in leukocyte function
   a. Leukocyte adhesion defect (LAD)
      - Examples—deficient selectin or CD11a/CD18 adhesion molecules (refer to Chapter 3)
   b. Phagocytosis defect
      - Example—decreased opsonins in Bruton agammaglobulinemia (refer to Chapters 3 and 4)
   c. Microbicidal defect
      - Example—deficiency myeloperoxidase (MPO) or NADPH oxidase (refer to Chapter 3)

C. Clinical findings
1. Unusual pathogens (e.g., *Serratia marcescens*)
2. Frequent infections and growth failure in children
3. Lack of an inflammatory response (e.g., production of "cold" abscesses)
4. Severe gingivitis

---

**Job syndrome** is an autosomal dominant (sometimes recessive) disorder of neutrophils. Most patients have unaffected parents. It is due to mutation in STAT3, whose protein products act as transcription activators. There is also a reduction in T17 helper T cells, which produce interleukin 17, a chemotactic agent for monocytes and neutrophils. Therefore neutrophils and monocytes in these patients have abnormal chemotaxis, leading to “cold” soft tissue abscesses and recurrent pneumonias. The most common pathogens are *Staphylococcus aureus* and *Candida* species. Patients have red hair, a leonine face (increased width of the nose, full lower lip), chronic eczema, eosinophilia, and increased serum IgE (hyperimmunoglobulin E syndrome). Genetic testing is available to secure the diagnosis.

---

D. Unusual benign leukocyte reactions
1. Leukemoid reaction
   a. Definition—absolute leukocyte count usually >25,000 to 30,000 cells/mm³
      - May involve neutrophils, lymphocytes, or eosinophils
   b. Normal bone marrow response to cytokines released by cells (e.g., lymphocytes, stromal cells, macrophages) to infection (most common) or trauma
   c. Examples include:
      - (1) Neutrophilic leukocytosis associated with perforated appendicitis

---

**Absolute count = % leukocytes × total WBC count**
2. Lymphocytosis associated with whooping cough

3. Eosinophilia associated with cutaneous larva migrans

d. Pathogenesis
   - Normal albeit exaggerated response to an infection

2. Leukoerythroblastosis (leukoerythroblastic reaction) (Fig. 13-1)
   a. Definition—presence of immature bone marrow WBCs and nucleated red blood cells (RBCs) in the peripheral blood ("peripheralization" of the bone marrow), irrespective of the total leukocyte count
   b. Causes
      (1) Normal bone marrow
         • Example—severe acute hemolytic anemia (e.g., sickle cell disease)
      (2) Abnormal bone marrow
         (a) Bone marrow infiltrative disease (e.g., amyloidosis)
         (b) Metastatic malignancy (e.g., breast cancer)
         (c) Granulomatous disease (e.g., tuberculosis [TB], systemic fungal disease, sarcoidosis)
         (d) Hematologic malignancies (e.g., acute leukemia, multiple myeloma) chronic myeloproliferative diseases (e.g., myelofibrosis with myeloid metaplasia)
      (3) Other causes include:
         • Massive trauma with multiple fractures, Paget disease of bone, and extramedullary hematopoiesis (EMH)
   c. Peripheral blood findings
      (1) Myeloblasts, progranulocytes, and other leukocyte precursors
      (2) Nucleated RBCs and teardrop RBCs (if fibrosis is present)

II. Benign Quantitative WBC Disorders

A. Disorders involving neutrophils

1. Neutrophilic leukocytosis
   a. Definition—absolute neutrophil count >7500 cells/mm³ (see Fig. 3-16)
   b. Causes
      (1) Bacterial infection (e.g., acute appendicitis)
      (2) Sterile inflammation with necrosis (e.g., acute myocardial infarction)
      (3) Drugs (e.g., corticosteroids)
   c. Pathogenesis
      (1) Increased bone marrow production or release of neutrophils
      (2) Decreased activation of neutrophil adhesion molecules
         (a) Fewer neutrophils adhere to endothelial cells
         (b) Examples—corticosteroids, catecholamines, and lithium

2. Neutropenia
   a. Definition—absolute neutrophil count <1500 cells/mm³
   b. Causes
      (1) Aplastic anemia
      (2) Immune destruction
         • Examples—systemic lupus erythematosus (SLE), and paroxysmal nocturnal hemoglobinuria
      (3) Septic shock
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(4) Drugs
   - Penicillin, cephalosporins, quinidine, and sulfonamides

(5) Tick-borne diseases
   - Ehrlichiosis, anaplasmosis, and babesiosis

(6) Viral infections
   - Hepatitis, infectious mononucleosis

(7) Bacterial infections
   - Typhoid fever, brucellosis, and tuberculosis

(8) Fungal infections
   - Systemic fungal infections (e.g., histoplasmosis)

(9) Ionizing radiation

c. Pathogenesis
(1) Decreased production
   - Aplastic anemia, ionizing radiation, and drugs

(2) Increased destruction
   - Destruction by complement, macrophages, and antibodies

(3) Activation of neutrophil adhesion molecules
   (a) Increase the number of neutrophils adhering to endothelium
   (b) Example—endotoxins

B. Disorders involving eosinophils
1. Eosinophilia (Fig. 13-2A)
   a. Definition—absolute eosinophil count >400 cells/mm³

   b. Causes
      (1) Type I hypersensitivity reaction
         - Examples—bronchial asthma, reaction to penicillin, hay fever, and atopic dermatitis

      (2) Protozoal disease
         - *Dientamoeba fragilis* (only protozoal infection with eosinophilia)

      (3) Invasive helminthic infection
         (a) Examples—strongyloidiasis and hookworm infection
(b) Pinworms and adult ascariasis are not accompanied by eosinophilia (noninvasive).

(4) Polyarteritis nodosa, Churg-Strauss syndrome
(5) Addison disease (cortisol deficiency)
(6) Job syndrome (see previous discussion)

c. Pathogenesis
(1) Release of eosinophil chemotactic factor from mast cells
   - Type I hypersensitivity reaction (HSR)
(2) No sequestering of eosinophils in lymph nodes
   - Example—hypocortisolism

2. Eosinopenia
a. Causes
   - Hypercortisolism (Cushing syndrome, corticosteroids)
b. Pathogenesis
   - Corticosteroids sequester eosinophils in lymph nodes and trigger apoptosis.

C. Disorders involving basophils; basophilia
1. Definition—absolute basophil count >110 cells/mm³ (see Fig. 13-2B)
2. Causes
   - Chronic myeloproliferative disorders (e.g., polycythemia vera)

D. Disorders involving lymphocytes
1. Lymphocytosis
   a. Definition—absolute lymphocyte count >5000 cells/mm³ in adults or >8000 cells/mm³ in children (see Fig. 13-2C)
b. Causes
   (1) Viral
      - Examples—mononucleosis and cytomegalovirus (CMV)
(2) Bacterial
   - Examples—whooping cough (Bordetella pertussis) and tuberculosis
(3) Drugs
   - Examples—phenytoin and tetracycline
(4) Graves disease
(5) Neoplasia
   - Example—chronic lymphocytic leukemia (CLL)
c. Pathogenesis
   (1) Increased production
   (2) Decreased entry into lymph nodes
      - Example—lymphocytosis-promoting factor produced by Bordetella pertussis

2. Atypical lymphocytosis
a. Causes of atypical lymphocytosis
   (1) Infection
      - Examples—mononucleosis, viral hepatitis, CMV infection, and toxoplasmosis
(2) Drugs (e.g., phenytoin)
b. Pathogenesis of atypical lymphocytosis
   - Definition—antigen-stimulated lymphocytes with prominent nucleoli and abundant blue cytoplasm

3. Infectious mononucleosis (mono)
   a. Epidemiology
      (1) Caused by the Epstein-Barr virus (EBV)
      (2) Most common between the ages of 15 and 24 years old
   b. Pathogenesis
      (1) Primarily transmitted by kissing
         - Virus initially replicates in epithelial cells in the oropharynx.
      (2) Infection spreads to B cells in lymph nodes.
         (a) Virus attaches to CD21 receptors on B cells.
         (b) B cells become antigenically stimulated (Fig. 13-3A), proliferate, and increase the synthesis of IgM antibodies (heterophile antibodies).
            - Cytotoxic T cells are important in controlling the proliferation of infected B cells to prevent relapses and circulate as atypical lymphocytes.
         (c) Virus remains dormant in B cells; therefore mononucleosis may recur.
   c. Clinical findings
      (1) Severe fatigue and malaise

Causes: type I HSR, invasive helminths, D. fragilis, hypocortisolism

Eosinopenia: hypercortisolism

Basophilia: consider myeloproliferative disease

Lymphocytosis: >5000 cells/mm³ (adult); >8000 cells/mm³ (child)

Causes: viruses (mononucleosis, CMV), bacteria (whooping cough, TB)

Causes: drugs (phenytoin, tetracycline); Graves disease, CLL

Atypical: infection (mononucleosis, CMV, toxoplasmosis, viral hepatitis); drugs (phenytoin)

Atypical lymphocytes: antigenically stimulated

Mononucleosis: EBV

B cells have CD21 receptor sites for EBV; atypical B cells

Mono: cytotoxic T cells control infected B cells; atypical lymphocytes

Mono: EBV dormant in B cells; relapses may occur
(2) Exudative tonsillitis (see Fig. 13-3B)
   (a) May be complicated by a group A streptococcus infection in 30% of cases, which emphasizes the importance of culture or other diagnostic tests to rule out group A streptococcal infection.
   (b) Petechiae in posterior palate
(3) Tender hepatosplenomegaly
   (a) Danger of liver/splenic rupture in contact sports
   (b) Hepatitis not chronic
(4) Generalized painful lymphadenopathy
(5) Generalized, erythematous, prolonged pruritic rash may occur if the patient is treated with ampicillin or amoxicillin (see Fig. 13-3C).
   (a) Rash does not mean that the patient is allergic to ampicillin or amoxicillin.
   (b) Rash that commonly accompanies infectious mononucleosis is also generalized; however, it is faint, evanescent, and nonpruritic.
(6) Other findings include:
   • Encephalitis, pancreatitis, Guillain-Barré syndrome, cranial nerve palsies, and myositis
d. Laboratory findings
   (1) Atypical lymphocytosis
      • Atypical lymphocytes usually account for >20% of the total WBC count.
   (2) Positive heterophil antibody test
      (a) Heterophil antibody test is the initial screening test for infectious mononucleosis.
      (b) Test detects IgM antibodies against horse (most common), sheep, and bovine RBCs.
      (c) Test sensitivity is 87% and the specificity is 91%.
   (3) Anti–viral capsid antigen (VCA) antibodies
      (a) High sensitivity and specificity
      (b) Develops early in the infection and persists for life
   (4) Anti–early antigen (EA) antibodies
      • Increased with chronic infections
   (5) Anti–Epstein-Barr nuclear antigen (EBNA) antibodies
      (a) High sensitivity and specificity
      (b) Develops late in the infection and persists for life
   (6) Serum transaminases from hepatitis are markedly increased.
      • Jaundice occurs in <10% of cases.

4. Lymphopenia
   a. Definition—absolute lymphocyte count <1500 cells/mm³ in adults or <3000 cells/mm³ in children
b. Causes
   (1) Human immunodeficiency virus
   (2) Immunodeficiency disorders
      (a) DiGeorge syndrome (T-cell deficiency)
      (b) Severe combined immunodeficiency (B- and T-cell deficiency)
      (c) Bruton agammaglobulinemia (B-cell deficiency)
   (3) Immune destruction (e.g., systemic lupus erythematosus)
   (4) Drugs
      • Corticosteroids, cyclophosphamide, quinine, and cytotoxic chemotherapy
   (5) Ionizing radiation
      • Lymphocytes are the most sensitive cells to destruction by radiation (refer to Chapter 7).

c. Pathogenesis
   (1) Increased destruction
      • Examples—lysis of CD4 helper T cells by the human immunodeficiency virus; apoptosis by corticosteroids
   (2) Decreased production
      • Example—Bruton agammaglobulinemia

E. Disorders involving monocytes; monocytosis
1. Definition—absolute monocyte count >800 cells/mm³ (see Fig. 13-2D)
2. Causes
   a. Chronic inflammation
      • Examples—tuberculosis, subacute infective endocarditis, and cirrhosis
   b. Autoimmune disease
      • Example—rheumatoid arthritis
   c. Malignancy
      • Examples—carcinoma and malignant lymphomas
3. Pathogenesis
   • Immune response to chronic inflammation, autoimmune disease, or malignancy

III. Acute and Chronic Leukemias
A. Epidemiology
1. Malignant diseases arising from bone marrow stem cells
   • May involve all cell lines
2. More common in males than females
3. Risk factors
   a. Chromosomal abnormalities
      • Examples—Down syndrome and chromosome instability syndromes
   b. Ionizing radiation
      • Example—nuclear plant explosion
   c. Chemicals
      • Example—benzene for myeloid and lymphoid leukemias
   d. Alkylating agents
      • Example—busulfan
   e. Chronic myeloproliferative diseases
      • Example—polycythemia vera
   f. Paroxysmal nocturnal hemoglobinuria (PNH)
   g. Cigarette smoking
   h. Immunodeficiency diseases
      • Example—Wiskott-Aldrich syndrome
4. Age ranges for common leukemias
   a. More common in adults than children
   b. Newborn to 14 years old
      • Acute lymphoblastic leukemia (ALL) is the most common leukemia and most common overall cancer in children.
   c. Persons 40 to 60 years old
      (1) Acute myeloblastic leukemia (AML)
      (2) Chronic myelogenous leukemia (CML)
   d. Persons >60 years of age
      (1) Chronic lymphocytic leukemia (CLL)
      (2) Chronic myelogenous leukemia

Lymphopenia in HIV: lysis CD4 helper T cells by virus
Corticosteroids produce neutrophilic leukocytosis, eosinopenia, and lymphopenia
Monocytosis: >800 cells/mm³
Monocytosis: chronic infection, autoimmune disease, malignancy
Leukemia: malignant transformation marrow stem cells
Risk factors: Down syndrome; ionizing radiation; benzene; alkylating agents
Risk factors: chronic myeloproliferative disorders, PNH, smoking, immunodeficiency disease
ALL: MC leukemia/ cancer in children
AML/CML: 40–60 years old
CLL: MC >60 years
CLL MC overall type of leukemia
B. Pathogenesis

1. Block in stem cell differentiation leading to a monoclonal proliferation of neoplastic leukocytes behind the block
   a. Acute leukemia—block occurs at an early stage of stem cell development
   b. Chronic leukemia—block occurs at a later stage in stem cell development
      • Some evidence of maturation in chronic leukemia
2. Leukemic cells:
   a. Replace most of the bone marrow and crowd out normal hematopoiesis
   b. Enter the peripheral blood
   c. Metastasize throughout the body

C. Clinical findings in acute leukemia

1. Abrupt onset of signs and symptoms
2. Clinical findings
   a. Fever is common and usually indicates infection.
   b. Bleeding is common and is most often caused by thrombocytopenia.
   c. Anemia causes fatigue.
3. Signs of metastatic disease
   a. Hepatosplenomegaly
   b. Generalized painless lymphadenopathy
   c. Headache from central nervous system (CNS) involvement
      • Especially common in ALL
   d. Skin involvement
      • Especially common in T-cell leukemias
   e. Testicles
      • Especially common in ALL
4. Bone pain and tenderness
   • Pain is due to bone marrow expansion by the leukemic cells.

D. Laboratory findings in acute leukemia

1. Peripheral WBC count
   a. Ranges from <10,000 cells/mm³ (normal) to >100,000 cells/mm³
   b. Blast cells are usually present.
      • Examples—myeloblasts, lymphoblasts, and monoblasts
2. Normocytic to macrocytic anemia
   • Macrocytic if folic acid is depleted due to increased production of leukemic cells
3. Thrombocytopenia
   • Usually <100,000 cells/mm³
4. Bone marrow findings
   a. Hypercellular with >20% blast cells
   b. Usually completely replaced by blast cells

E. Clinical findings in chronic leukemia

1. Insidious onset of signs and symptoms
2. Hepatosplenomegaly
3. Generalized painless lymphadenopathy

F. Laboratory findings in chronic leukemia

1. Peripheral WBC count
   a. Count is similar to that of acute leukemia
   b. Blast cells are usually <10% of the total WBC count.
   c. Leukemic cells show evidence of maturation.
2. Normocytic to macrocytic anemia
   • Macrocytic if folic acid is depleted because of increased production of leukemic cells
3. Thrombocytopenia
   a. Usually <100,000 cells/mm³
   b. Exception is CML, in which thrombocytosis occurs in 35% of cases
4. Bone marrow findings
   • Hypercellular with <10% blast cells

IV. Neoplastic Myeloid Disorders

A. Overview of neoplastic myeloid disorders

1. All myeloid disorders are neoplastic stem cell disorders.
   • May involve one or more stem cell lines
2. Classification
   a. Chronic myeloproliferative disorders
   b. Myelodysplastic syndrome
   c. Acute myeloblastic leukemia (AML)
B. Chronic myeloproliferative disorders

1. Classification
   a. Polycythemia vera (most common)
   b. Chronic myelogenous leukemia (CML)
   c. Myelofibrosis with myeloid metaplasia (MMM)
   d. Essential thrombocythemia (ET)

2. General characteristics
   a. Splenomegaly
   b. Propensity for reactive bone marrow fibrosis (“spent phase”)
   c. Propensity for transformation to acute leukemia

3. Polycythemia (Fig. 13-4)
   a. Definition—increased hemoglobin (Hb), hematocrit (Hct), and RBC count
   b. Plasma volume (PV) varies with the type of polycythemia.
   c. RBC count versus RBC mass
      (1) RBC count is the number of RBCs per microliter (µL) of blood.
      (2) RBC mass is the total number of RBCs in the peripheral blood in mL/kg.
      (3) Figure 13-4A shows the normal relationship between RBC count, RBC mass, plasma volume (PV), erythropoietin (EPO), and O2 saturation (SaO2).
   d. Relative polycythemia (see Fig. 13-4B)
      (1) Overall, relative polycythemia is the most common type.
      (2) Definition—increased RBC count is due to a decrease in plasma volume (PV)
         • Example—volume depletion from sweating
      (3) RBC mass is normal.
         • No increase in bone marrow production of RBCs
      (4) EPO and SaO2 are normal.
      (5) Simple fluid replacement corrects the polycythemia.
   e. Absolute polycythemia
      (1) Definition—increase in bone marrow production of RBCs
         • Increase in RBC count and RBC mass
      (2) Appropriate absolute polycythemia (see Fig. 13-4C)
         (a) Hypoxic stimulus for EPO release
         (b) Examples—primary lung disease, cyanotic congenital heart disease, and high altitude
         (c) Decreased SaO2
         (d) Increased RBC count, RBC mass, and EPO level
         (e) Normal PV
      (3) Inappropriate absolute polycythemia: ectopic production of EPO (see Fig. 13-4D)
         (a) No hypoxic stimulus for EPO release; therefore it is an inappropriate absolute polycythemia
            • Ectopic release of EPO may occur in renal cell carcinoma (most common) and hepatocellular carcinoma.

---

**Fig. 13-4:** Schematic showing RBC count, RBC mass, plasma volume (PV), erythropoietin (EPO) concentration, and O2 saturation (SaO2) in polycythemia and the normal (N) state. A, Normal. B, Relative polycythemia. C, Appropriate absolute polycythemia D, Inappropriate absolute polycythemia due to ectopic production of EPO. E, Polycythemia vera. See text for discussion.
4. Polycythemia vera (see Fig. 13-4E)

- **Definition**—malignant inappropriate absolute polycythemia
- **Pathogenesis**
  1. Myeloid stem cell undergoes clonal expansion.
  2. Most cases are due to mutation of the JAK2 gene on the short arm of chromosome 9.
     a. This gene plays a role in the signaling pathways that tell the body to generate hematopoietic cells.
     b. Same mutation may manifest as myelofibrosis with myeloid metaplasia or essential thrombocythemia (discussed later).
  3. In polycythemia vera, there is increased production of RBCs, granulocytes (neutrophils, eosinophils, basophils), mast cells, and platelets (Fig. 13-5).

- **Clinical findings**
  1. Hepatosplenomegaly
  2. Ruddy (plethoric) face due to vessel congestion
  3. Thrombotic events
     a. Hyperviscosity related to the increased RBC count/mass
     b. Sites of thrombosis—hepatic vein, dural sinus, and retinal vein
  4. Impaired CNS circulation leads to:
     - Headache, blurred vision, retinal vein engorgement, vertigo, transient ischemic attacks, and strokes
  5. Signs of increased histamine released from mast cells
     a. Pruritus after bathing
        - Very common initial complaint
        - Mast cells in the skin degranulate with changes in skin temperature.
     b. Peptic ulcer disease
        - Histamine stimulates production of gastric acid.
  6. Gout
     - Due to increased breakdown of nucleated cells with release of purines, which are converted to uric acid

- **Laboratory findings**
  1. Increased RBC count, RBC mass, and PV
  2. Decreased EPO
     a. EPO is decreased because O\textsubscript{2} content is increased (refer to Chapter 2).
     b. Measuring serum levels of EPO is an excellent initial screen in diagnosing polycythemia vera.
  3. Normal Sa\textsubscript{O\textsubscript{2}}
  4. Hypercellular bone marrow with fibrosis that develops in later stages

- **Major and minor criteria**
  1. Parameters that are measured for major criteria include:
     - Hb, Hct, RBC count, RBC mass, and a test for the JAK2 V617F mutation in exon 14
  2. Parameters that are evaluated for minor criteria include:
     - A bone marrow exam, EPO level, and in vitro demonstration of erythroid colony formation
COPD, Chronic obstructive pulmonary disease; EPO, erythropoietin; SaO₂, oxygen saturation.

### Table 13-1 Laboratory Findings in Polycythemias

<table>
<thead>
<tr>
<th>Polycythemia vera</th>
<th>RBC Mass</th>
<th>Plasma Volume</th>
<th>SaO₂</th>
<th>EPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↑</td>
<td>Normal</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Appropriate polycythemia (e.g., COPD, cyanotic congenital heart disease)</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Inappropriate polycythemia: ectopic EPO (e.g., renal cell carcinoma)</td>
<td>↑</td>
<td>Normal</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Relative polycythemia (e.g., volume depletion)</td>
<td>Normal</td>
<td>↓</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

f. Treatment
- Nonpharmacologic treatment
  - Phlebotomy to reduce hyperviscosity
- Pharmacologic treatment
  - Hydroxyurea + phlebotomy
  - Interferon-α-2b

g. Prognosis
- Without treatment, the median survival is 6 to 18 months after diagnosis.
- With treatment, the average survival time is 12 years.

h. Summary table of the polycythemias (Table 13-1)

5. Chronic myelogenous leukemia
a. Epidemiology
- Median age for CML is 45 to 55 years old
- Accounts for 15% of adult leukemias
- Risk factor—exposure to ionizing radiation

b. Pathogenesis
- Neoplastic clonal expansion of the pluripotential stem cell
  - This stem cell has the capacity to differentiate into a lymphoid or myeloid stem cell (see Fig. 13-1).
- t(9;22) translocation of the ABL proto-oncogene
  - Proto-oncogene fuses with the break cluster region (BCR) on chromosome 22 (BCR-ABL fusion gene; Fig. 13-6).
  - Chromosome 22 with the translocation is called the Philadelphia chromosome.

c. Clinical findings
- Generalized findings of fatigue and weight loss are common.
- Splenomegaly is the most consistent finding (50% to 60% of cases).
  - Due to metastasis
- Hepatomegaly (8% of cases) and painless lymphadenopathy (6% of cases) may occur.

d. Laboratory findings
- Initial peripheral WBC count ranges from 10,000 to 500,000 cells/mm³ (Fig. 13-7).
  - Myeloid series is in all stages of development (sign of maturation).
  - Basophilia is a consistent finding.
- Normocytic to macrocytic anemia
  - Macrocytic if folic acid is depleted in the production of leukemic cells
- Thrombocytosis occurs in ~35% of cases (uncommon in leukemia).
- Bone marrow findings in the initial phase of CML
  - Myeloblasts account for <10% of the myeloid cells.
  - Marrow is hypercellular with marked myeloid hyperplasia.
- Philadelphia chromosome is present in 95% of cases.
  - This chromosome is not specific for CML and is present in other leukemias (e.g., AML).
  - Chromosome is not lost during therapy unless α-interferon is used.
- BCR-ABL fusion gene is present in 100% of cases (Fig. 13-6).
  - Fusion gene is the most sensitive and specific test for chronic myelogenous leukemia.
- Decreased leukocyte alkaline phosphatase (LAP) score
  - Stain for alkaline phosphatase in neoplastic granulocytes shows little to no uptake of the stain in the cytoplasm.
  - In benign granulocytes, the stain is strongly positive.
- Blast crisis in CML
  - Usually occurs in ~5 years
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CML blast crisis: myeloblasts/lymphoblasts; no Auer rods

(b) Increase in numbers of myeloblasts or lymphoblasts (25% of cases)
(c) No Auer rods in myeloblasts (see later)

e. Treatment
(1) Imatinib mesylate
   (a) Oral tyrosine kinase inhibitor
   (b) More than 75% of patients have a major cytogenetic response (<35% of cells are positive for Philadelphia chromosome after treatment)
(2) Allogeneic stem cell transplantation is the only curative treatment.

f. Prognosis
   • ~90% 5-year survival rate

6. Myelofibrosis with myeloid metaplasia (MMM)
a. Epidemiology
   (1) Primarily occurs in persons >50 years old
   (2) Most common cause of massive splenomegaly in this group

b. Pathogenesis
   (1) MMM is a clonal myeloproliferative disease.
   (2) Most cases are due to mutation of the JAK2 gene.
   (3) Ineffective erythropoiesis, dysplastic megakaryocytes, increased numbers of immature granulocytes, and early onset of reactive myelofibrosis
      • Marrow fibrosis occurs earlier than in the other chronic myeloproliferative diseases.
   (4) Hematopoiesis moves to the spleen, liver, and other sites (EMH).

c. Clinical findings
   (1) Massive splenomegaly occurs with portal hypertension.
   (2) Splenic infarcts commonly occur and are associated with left-sided pleural effusions.

d. Laboratory findings
   (1) Bone marrow fibrosis (Fig. 13-8)
   (2) Peripheral WBC count range: 10,000 to 50,000 cells/mm³
   (3) Normocytic anemia
      (a) Teardrop cells (damaged RBCs) are commonly present (see Fig. 13-1).
      (b) Leukerythroblastosis is present (see Fig. 13-1).
   (4) Platelet count is variable.
      • Platelets are morphologically abnormal.
   (5) Leukocyte alkaline phosphatase score is normal to increased.
      • Recall that it is decreased in CML and increased in polycythemia vera.

13-6: Schematic of t(9:22) translocation of the ABL (abl) proto-oncogene on chromosome 9 and its fusion with the break cluster region (bcr) on chromosome 22. Chromosome 22 with this translocation is called the Philadelphia chromosome. (From Damjanov I, Linder J: Anderson’s Pathology, 10th ed, St. Louis, Mosby, 1996, p 253, Fig. 12-40.)

13-7: Peripheral blood in chronic myelogenous leukemia. Marked leukocytosis shows neutrophils at different stages of development (segmented and band neutrophils, metamyelocytes, and myelocytes). The cell in the center (arrow) depicts a basophil with dark granules in the cytosol and overlying the nucleus. Basophilia is prominent in chronic myeloproliferative diseases. (From Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 80, Fig. 5-26.)
e. Treatment
   (1) Hydroxyurea
   (2) Interferon-α

7. Essential thrombocythemia (ET)
   a. Pathogenesis
      (1) Clonal myeloproliferative disease with excess formation of dysplastic and defective platelets
      (2) Most cases are due to mutation of the JAK2 gene.
         • Recall that polycythemia vera and MMM have the same mutation.
   b. Clinical findings
      (1) Bleeding is the most common finding, because the platelets are nonfunctional.
         (a) Usually the bleeding is gastrointestinal and associated with iron deficiency.
         (b) Vessel thrombosis may also occur.
      (2) Splenomegaly
   c. Laboratory findings
      (1) Thrombocytosis
         (a) Platelet count is >600,000 cells/mm³ and is frequently >1 million cells/mm³.
         (b) Platelet morphology is abnormal.
      (2) Mild neutrophilic leukocytosis
      (3) Basophilia is common.
      (4) Bone marrow is hypercellular and contains numerous megakaryocytes that appear abnormal (dysplastic).
   d. Treatment
      • Hydroxyurea

C. Myelodysplastic syndromes (MDSs)
   1. Epidemiology
      • Usually occur in men between 50 and 80 years old
   2. Pathogenesis
      a. Group of acquired clonal disorders that affect stem cells
      b. Characteristically have cytopenias and hypercellular bone marrows
      c. Classification
         (1) Refractory anemia
         (2) Refractory anemia with ringed sideroblasts
         (3) Chronic myelomonocytic leukemia
         (4) Refractory anemia with excess blast cells in transformation
      d. Frequently progresses to AML (30% of cases)
   3. Laboratory findings
      a. Severe pancytopenia is common.
         (1) Normocytic to macrocytic anemias
            • Dimorphic RBC population (microcytic and macrocytic) is commonly present, which increases the RBC distribution width (RDW).
         (2) Leukoerythroblastosis
      b. Bone marrow findings
         (1) Ringed sideroblasts (nucleated RBCs with excess iron) are present.
         (2) Myeloblasts account for <20% of the granulocytes.
            • If myeloblasts are >20%, it has progressed to AML.
D. Acute myeloblastic leukemia

1. Epidemiology
   a. Median age of presentation is 50 years old, with a range from 30 to 60 years old.
   b. French-American-British (FAB) classification (Table 13-2).
   c. Risk factors
      (1) Genetic factors—Down syndrome, Turner syndrome, and Klinefelter syndrome
      (2) Chemicals/drugs—benzene and alkylating agents
      (3) Miscellaneous—ionizing radiation and MDS
   d. Cytogenetic abnormalities include:
      (1) Mutations on chromosome 8
      (2) t(8;21) translocation

2. Clinical findings
   a. Weakness, fatigue, bleeding, and fever (infection)
   b. Hepatosplenomegaly, painless generalized lymphadenopathy
   c. Gum infiltration (common in acute monochytic leukemia [M5])

3. Laboratory findings
   a. Findings include normocytic anemia, thrombocytopenia, and leukocytosis.
   b. Auer rods present in certain AML subtypes
      (1) Splinter-shaped to rod-shaped structures in the cytosol of myeloblasts (Fig. 13-9)
      • Fused azurophilic granules
      (2) Only present in AML (M2 and M3 subtypes)
      • Not present in myeloblasts in CML, even when they go into a blast crisis
   c. Disseminated intravascular coagulation commonly occurs in AML (refer to Chapter 15).

4. General treatment strategy
   • Induction therapy, followed by consolidation therapy with or without radiation, followed by maintenance therapy

5. Five-year survival rate is ~20%.

V. Lymphoid Leukemias

A. Acute lymphoblastic leukemia (ALL)

1. Epidemiology
   a. Most common leukemia and cancer in children (newborn to 14 years of age)
      (1) Adults can also develop ALL.
      (2) Adults have a poorer prognosis than children with ALL.
   b. Peak incidence is 2 to 10 years of age.
   c. Risk factors include:
      • Antineoplastic agents, Hodgkin lymphoma, ionizing radiation, benzene exposure, and multiple myeloma

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**Table 13-2: French-American-British Classification of Acute Myeloblastic Leukemia (AML)**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0: Minimally differentiated AML</td>
<td>No Auer rods</td>
</tr>
<tr>
<td>M1: AML without differentiation: 20%</td>
<td>Rare Auer rods</td>
</tr>
<tr>
<td>M2: AML with maturation</td>
<td>Most common type (30%–40% of cases) Auer rods present 15–59-yr-old age bracket</td>
</tr>
<tr>
<td>M3: Acute promyelocytic</td>
<td>Numerous Auer rods DIC is invariably present There is a t(15;17) translocation causing abnormal retinoic acid metabolism. High doses of all-trans retinoic acid may induce remission by causing cells to differentiate into neutrophils, which subsequently undergo apoptosis and die.</td>
</tr>
<tr>
<td>M4: Acute myelomonocytic</td>
<td>Auer rods uncommon</td>
</tr>
<tr>
<td>M5: Acute monocytic</td>
<td>No Auer rods Gum infiltration</td>
</tr>
<tr>
<td>M6: Acute erythroleukemia</td>
<td>Bizarre, multinucleated erythroblasts Myeloblasts present</td>
</tr>
<tr>
<td>M7: Acute megakaryocytic</td>
<td>Myelofibrosis in bone marrow Increased incidence in Down syndrome in children &lt;3 years old</td>
</tr>
</tbody>
</table>

DIC, Disseminated intravascular coagulation.
**d. Immunologic classification for ALL is:**

1. Early pre-B-cell acute lymphoblastic leukemia (80% of cases)
2. Pre-B-, B-, and T-cell acute lymphoblastic leukemia

**2. Pathogenesis**

a. Clonal lymphoid stem cell disease
b. Majority have numerical or structural chromosome changes (e.g., hyperploidy [>50 chromosomes]).

**3. Early pre-B-cell ALL**

a. Marker studies for common acute lymphoblastic leukemia antigen (CALLA; CD10) are positive.
b. Marker studies for terminal deoxynucleotidyl transferase (TdT) are positive
c. t(12;21) translocation offers a favorable prognosis.
d. Greater than 95% with this subtype achieve complete remission.
   - At least 75% to 85% of patients are considered cured.

**4. T-cell ALL**

- CD10 negative and TdT positive

**5. Clinical findings**

a. Metastatic sites are similar to those of AML.
b. B-cell types commonly metastasize to the CNS and testicles

c. T-cell types commonly present as an anterior mediastinal mass or as an acute leukemia.

**6. Laboratory findings**

a. Peripheral WBC count ranges from 10,000 to 100,000 cells/mm³ (Fig. 13-10)
   - Majority of cells are lymphoblasts.
b. Normocytic anemia with thrombocytopenia
c. Bone marrow findings
   - Usually totally replaced by lymphoblasts

**7. General treatment strategy is similar to AML.**

- Bone marrow transplantation is an option.

**B. Adult T-cell leukemia**

1. Epidemiology
   - Associated with the human T-cell lymphotropic virus type 1 (HTLV-1)

2. Pathogenesis
   - Activation of the TAX gene inhibits the p53 suppressor gene.
   - Neoplastic CD4 helper T cells undergo monoclonal proliferation.

3. Clinical findings
   - Hepatosplenomegaly and generalized painless lymphadenopathy are present.
   - Skin infiltration is a common finding in all T-cell malignancies.
   - Lytic bone lesions
     1. Lymphoblasts release osteoclast-activating factor.
     2. Lytic lesions may produce hypercalcemia.
4. Laboratory findings
   a. Peripheral WBC count ranges from 10,000 to 50,000 cells/mm$^3$
      (1) Numerous lymphoblasts
      (2) Lymphoblasts are positive for CD4 marker and negative for TdT.
   b. Normocytic anemia and thrombocytopenia
   c. Bone marrow is replaced by CD4 lymphoblasts

C. Chronic lymphocytic leukemia (CLL)

1. Epidemiology
   a. Primarily occurs in individuals >60 years old
      • Median age for CLL is 65 years old.
   b. Most common overall leukemia in Western countries
   c. Most common cause of generalized lymphadenopathy in the same age bracket

2. Pathogenesis
   • Neoplastic disorder of virgin B cells (B cells that cannot differentiate into plasma cells)

3. Clinical findings
   a. Generalized painless lymphadenopathy (Fig. 13-11A)
   b. Metastatic sites similar to those of AML
   c. Increased incidence of immune hemolytic anemia
      • Warm (IgG) or cold (IgM) immune hemolytic anemia may occur (refer to Chapter 12).

4. Laboratory findings
   a. Peripheral WBC count ranges from 15,000 to 200,000 cells/mm$^3$ (see Fig. 13-11B)
   b. Lymphoblasts are <10% of the total lymphocyte count.
   c. Neutropenia
   d. Numerous "smudge" cells (fragile leukemic cells)
   e. Normocytic anemia (50% of cases) and thrombocytopenia (40% of cases)
   f. Bone marrow findings
      (1) Usually completely replaced by neoplastic B cells
      (2) Lymphoblasts account for <10% of the lymphoid cells that are present.
   g. Hypogammaglobulinemia
      • Neoplastic B cells do not develop into plasma cells.

5. Five-year survival rate is 75%.

D. Hairy cell leukemia (HCL)

1. Epidemiology
   a. Type of B-cell leukemia
   b. Occurs predominantly in men between ages 40 and 60 years
   c. Overexpression of cycli D1 protein (important cell regulator)
2. Clinical findings
   a. Splenomegaly is common (90% of cases).
   b. Lymphadenopathy is very uncommon (<10%).
   c. Hepatomegaly (20% of cases)
   d. Autoimmune vasculitis and arthritis
3. Laboratory findings
   a. Pancytopenia
   b. Leukemic cells have hair-like projections (Fig. 13-12A and B)
   c. Bone marrow
      1. Marrow is packed with neoplastic cells.
      2. Reticulin fibers are increased.
   d. Neoplastic cells stain positive for tartrate-resistant acid phosphatase (TRAP) stain
4. Treatment
   a. Drugs of choice are the purine analogs (e.g., 2-chloro-2-deoxyadenosine).
   b. Complete remission is induced in 85% of cases.

E. Summary table of the lymphoid leukemias (Table 13-3)
CHAPTER 14  Lymphoid Tissue Disorders

Lymphadenopathy, 334  Mast Cell Disorders, 344
Non-Hodgkin Lymphoma, 339  Plasma Cell Dyscrasias (Monoclonal
Hodgkin Lymphoma, 341  Gammopathies), 345
Langerhans Cell Histiocytoses, 343  Spleen Disorders, 347

I. Lymphadenopathy

A. Locations of lymphoid tissue

1. Normal locations
   a. Regional lymph nodes
   b. Tonsils and adenoids (Waldeyer tonsillar ring)
   c. Peyer patches and appendix
   d. White pulp of the spleen

2. Locations of B cells (Fig. 14-1)
   a. Germinal follicles in lymph nodes
   b. Peripheral areas of the spleen white pulp

3. Location of T cells (see Fig. 14-1)
   a. Paracortex (parafollicular) in the lymph nodes
   b. Periarteriolar sheath in the spleen
   c. Thymus (primary site for T cell synthesis)

4. Locations for histiocytes
   a. Sinuses in lymph nodes (see Fig. 14-1)
   b. Skin (called Langerhans cells)

5. Locations of selected lymphoid disorders (Fig. 14-2)

B. Lymphadenopathy

1. Epidemiology
   a. Age and lymphadenopathy
      (1) Persons <30 years old
         • Lymph node enlargement is usually a benign disease (~80% of cases).
      (2) Persons >30 years old
         (a) Lymph node enlargement is usually a malignant disease (~60% of cases; Fig. 14-3).
         (b) Malignant disease may be metastatic cancer (most common) or a primary
             lymph node malignancy (e.g., malignant lymphoma).
   b. Causes
      (1) Reactive lymphadenitis
         • Hyperplasia of B cells, T cells, or histiocytes
      (2) Infiltrative disease
         • Examples—metastasis (most common) and malignant lymphoma

2. Clinical findings
   a. Painful lymph nodes imply inflammation (e.g., infection, autoimmune disease).
      (1) Localized painful lymphadenopathy
          (a) Localized lymphadenopathy occurs when nodes drain sites of infection (e.g., tonsillitis).
          (b) Most common sites are the anterior cervical nodes (e.g., tonsillitis) and the
              inguinal nodes (e.g., lymphogranuloma venereum, chancroid).
      (2) Generalized painful lymphadenopathy
          (a) Primarily seen in systemic disease
          (b) Examples—infectious mononucleosis, SLE
14-1: Lymph node cortex, light micrograph. The white asterisk shows a germinal follicle containing B cells; the solid arrow shows the paracortex containing T cells; and the interrupted arrow shows the subcapsular sinus where histiocytes are located. (From Gartner L, Hiatt J: Color Textbook of Histology, 3rd ed, Philadelphia, Saunders, 2001, p 292, Fig. 12-8.)

14-2: Sites of pathologic processes in lymph nodes. Some lymphoid disorders initially localize in the germinal follicles, where B cells are located; others localize in the paracortex, where T cells are located. Mixed B- and T-cell reactions also may occur. Histiocytic disorders involve the sinuses.

14-3: Patient with cervical lymph node. Painful nodes are usually inflammatory, whereas painless nodes are usually malignant. (From Bouloux P: Self-Assessment Picture Tests: Medicine, Vol. 1, London, Mosby-Wolfe, 1997, p 41, Fig. 81.)

b. Painless nodes imply a malignancy.
   (1) Lymph nodes usually indurated and often fixed to the surrounding tissue
   (2) Localized painless lymphadenopathy
      (a) Occurs when lymph nodes are draining a primary cancer site
         • Examples—axillary lymph nodes in breast cancer and inguinal lymph nodes in vulvar squamous cell carcinoma
      (b) Also occurs in Hodgkin lymphoma (HL) and other types of malignant lymphoma
   (3) Generalized painless lymphadenopathy
      (a) Occurs in the majority of acute and chronic leukemias except hairy cell leukemia
      (b) Occurs in follicular B-cell lymphoma and other types of malignant lymphoma

c. Key lymph node groups involved in primary or metastatic cancer
   (1) Submental lymph nodes (Fig. 14-4)
      • Metastatic squamous cell carcinoma in the floor of the mouth
   (2) Cervical lymph nodes (see Fig. 14-4)
      (a) Metastatic head and neck tumors (e.g., larynx; thyroid, nasopharynx)
      (b) Hodgkin lymphoma
   (3) Left supraclavicular lymph nodes (Virchow nodes)
      • Metastatic abdominal cancers (e.g., stomach; pancreas)
   (4) Right supraclavicular lymph nodes (see Fig. 14-4)
      (a) Metastatic lung and esophageal cancers
      (b) Hodgkin lymphoma
   (5) Axillary lymph nodes (Fig. 14-5)
      • Metastatic breast cancer
   (6) Epitrochlear lymph nodes
      • Non-Hodgkin lymphoma (NHL)
   (7) Hilar lymph nodes
      • Metastatic lung cancer

Germinal follicle: reactive lymphadenitis, follicular B-cell lymphoma
Sinus: metastasis, sinus histiocytosis, Langerhans cell histiocytosis, histiocytic lymphoma
Paracortex: reactive hyperplasia, T-cell lymphomas

Painless lymphadenopathy: metastasis or primary malignant lymphoma
Painless axillary nodes woman: metastatic breast cancer

Generalized painless adenopathy: acute/ chronic leukemia; follicular B-cell lymphoma

Left supraclavicular node metastasis: stomach/pancreatic carcinoma

Hilar node metastasis: lung cancer
14-4: Lymph nodes of the neck and their drainage. (From Swartz M: Textbook of Physical Diagnosis History and Examination, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 197, Fig. 9-5.)

14-5: Regional lymph nodes draining the breast. (From Drake RL, Vogl AW, Mitchell AWM: Gray's Anatomy for Students, 2nd ed, Philadelphia, Churchill Livingstone Elsevier, 2010, p 138, Fig. 3.16.)

(8) Mediastinal lymph nodes
(a) Metastatic lung cancer
(b) Hodgkin lymphoma (particularly the nodular sclerosing type)
(c) T-cell lymphoblastic lymphoma

(9) Tonsillar (superior jugular node)
- Metastatic squamous cancers in the oral cavity
(10) Pre-aortic lymph nodes (Fig. 14-6)
   (a) Metastatic testicular cancer
      • Testicles migrate to the scrotum from the abdomen.
   (b) Burkitt lymphoma

(11) Inguinal lymph nodes (see Fig. 14-6)
   • Metastatic vulvar and penis squamous cancers

C. Types of reactive lymphadenitis
1. Follicular hyperplasia
   a. Definition—B-cell antigenic response (see Fig. 14-1)
      (1) Germinal follicles are sharply demarcated from the paracortex.
      (2) Lymphocytes are in different stages of development.
   b. Examples
      (1) Early stages of HIV infection
      (2) Other examples—rheumatoid arthritis and SLE

2. Paracortical hyperplasia
   a. Definition—T-cell antigenic response
   b. Dermatopathic lymphadenitis
      (1) Lymph nodes are draining areas with a chronic dermatitis (e.g., psoriasis).
      (2) Lymph nodes contain macrophages with phagocytosis of melanin pigment.
         • Because of the black pigment, it is confused with metastatic malignant melanoma.
   c. Other examples—phenytoin and viral infections

3. Mixed B- and T-cell hyperplasia
   a. Cat-scratch disease
      (1) Granulomatous microabscesses are present in regional lymph nodes (e.g., axillary, cervical).
      (2) Bartonella henselae is the cause.
      (3) Treatment is azithromycin.
   b. Toxoplasmosis
      (1) Approximately 50% of the population has been infected with Toxoplasma gondii.
      (2) It causes a syndrome like mononucleosis, with painful cervical lymphadenopathy.
c. Tularemia
   (1) Epidemiology
      (a) Caused by *Francisella tularensis*, a gram-negative intracellular coccobacillus
      (b) Zoonosis (infection transmitted from animals to humans) often seen in hunters and trappers
      (c) Reservoirs of the bacteria include rodents, deer, and rabbits (90%).
      (d) Transmission
         - Bites by *Dermacentor* ticks
         - Skin contact with an animal hide
         - Aerosol
   (2) Ulceroglandular type of tularemia
      (a) Most common presentation in the United States
      (b) Localized papular lesion develops at the point of inoculation (tick bite) →
      (c) Ulceration of the papule →
      (d) Regional lymphadenitis (noncaseating granulomatous inflammation) →
      (e) Sepsis leading to dissemination throughout the body (e.g., spleen, liver)
   (3) Treatment is gentamicin.

d. Plague
   (1) Epidemiology
      (a) Caused by *Yersinia pestis*, a gram-negative facultative intracellular bacterium
         - *Yop* gene protein products inhibit phagocytosis of the bacterium and kill phagocytes.
         - Similar to all *Yersinia* species, it requires iron for growth.
      (b) Transmission
         - Bite of infected fleas that have bitten infected ground squirrels, prairie dogs, wood rats, or chipmunks, which are the reservoir of the bacterium
         - Droplet infection from a patient with the disease
      (c) Three main presentations
         - Bubonic plague (most common presentation)
         - Septicemic plague (second most common presentation)
         - Pneumonic plague (transmits to others by aerosol [uncommon] or as a secondary complication of septicemic plague)
      (d) Plague mainly occurs in the Western United States (most commonly in Arizona, New Mexico, and Colorado).
      (e) Bubonic plague may be limited to lymph node involvement or spread into the bloodstream (secondary septicemic plague), with or without spread to the lungs (secondary pneumonic plague).
   (2) Natural history of the infection
      (a) Organism enters the body at the site of a flea bite, usually the lower leg.
      (b) Infection spreads into the inguinal lymph nodes, where it produces buboes, which appear edematous and congested early in the disease.
      (c) Within the lymph nodes there is massive proliferation of the organisms accompanied by an exudate without inflammatory cells causing the nodes to swell to the size of hen’s eggs (Fig. 14-7).
(d) Eventually the nodes exhibit hemorrhagic necrosis and vessel thrombosis with abscess formation, often leading to spontaneous rupture of the nodes.
(e) Bacteria often escape from the nodes and enter the bloodstream (secondary septicemic phase), causing widespread necrosis within organs throughout the body.
   • Disseminated intravascular coagulation is a common complication in this phase.
   • Endotoxemia produces septic shock (refer to Chapter 5).
(f) If the lungs are involved (secondary pneumonic phase), hemorrhagic and necrotizing bronchopneumonia develops in all lobes, along with fibrinous pleuritis.

(3) Clinical findings
(a) Bubonic plague findings include:
   • Fever, chills, myalgia, arthralgia, headache, and prostration
(b) Septicemic plague findings are those of septic shock from endotoxemia and include:
   • Vomiting, abdominal pain, refractory hypotension, and renal failure
(c) Pneumonic plague findings include:
   • Chest pain, dyspnea, and productive cough (Gram stain reveals numerous organisms)

(4) Treatment
(a) Gentamicin is effective and has replaced streptomycin for treatment.
(b) Tetracycline is effective in uncomplicated bubonic plague.

4. Sinus histiocytosis
   a. Definition—benign histiocytic response in lymph nodes draining a tumor
   b. Favorable sign in the axillary lymph nodes in breast cancer

II. Non-Hodgkin Lymphoma (NHL)
   A. Epidemiology
   1. Account for ~60% of adult lymphomas
      • Greater than 80% are of B-cell origin and derive from the germinal follicle.
   2. Second most common cancer in AIDS
   3. Median age in adults is 50 years old
   4. Approximately one-third arise from extranodal sites.
      • Extranodal sites include the stomach (most common site), Peyer patches, and central nervous system (CNS; particularly in AIDS).
   5. Childhood NHL
      a. Account for 60% of cases of malignant lymphoma
         • T-cell lymphoblastic lymphoma or a Burkitt lymphoma
      b. NHL is generally more aggressive in children than adults.
   6. Risk factors
      a. Viruses
         (1) Epstein-Barr virus (EBV)
            • Burkitt lymphoma
         (b) Diffuse large B-cell lymphoma
         (c) Primary CNS lymphoma (HIV)
            • Associated with AIDS
      (2) Human T-cell lymphotropic virus (HTLV) type I
         • Adult T-cell lymphoma or leukemia
      (3) Hepatitis C virus (HCV)
         • B-cell lymphoma
      b. Helicobacter pylori
         (1) Malignant lymphoma of the stomach
            • Derives from mucosa-associated lymphoid tissue in the stomach
         (2) Treatment of peptic ulcer disease caused by H. pylori reduces the risk for developing this lymphoma.
   c. Autoimmune disease
      (1) Sjögren syndrome
         • Commonly associated with salivary gland and gastrointestinal lymphomas
      (2) Hashimoto thyroiditis
         • Associated with malignant lymphoma arising within the thyroid gland
   d. Immunodeficiency syndromes
      • Chromosome instability syndromes (e.g., Bloom syndrome), AIDS

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**Lymphoid Tissue Disorders**

- **Immunodeficiency**
- **Autoimmune**

**Helicobacter pylori**

- **Viruses**
  - **Definition**—benign
  - **Associated**—bacteria
    - **Endotoxemia**—massive
    - **Septicemic**—massive

- **Clinical findings**
  - **Bubonic plague**—chills, myalgia, arthralgia, headache, and prostration
  - **Septicemic plague**—vomiting, abdominal pain, refractory hypotension, and renal failure
  - **Pneumonic plague**—chest pain, dyspnea, and productive cough

- **Treatment**
  - **Gentamicin**—effective and has replaced streptomycin
  - **Tetracycline**—effective in uncomplicated bubonic plague

- **Sinus histiocytosis**
  - Definition—benign histiocytic response
  - Favorable sign in axillary lymph nodes in breast cancer

**Non-Hodgkin Lymphoma (NHL)**

- **Epidemiology**
  - Account for ~60% of adult lymphomas
    - Greater than 80% are of B-cell origin
  - Second most common cancer in AIDS
  - Median age in adults is 50 years old
  - Approximately one-third arise from extranodal sites
    - Stomach, Peyer patches, central nervous system

- **Childhood NHL**
  - Account for 60% of cases of malignant lymphoma
    - T-cell lymphoblastic lymphoma
    - Burkitt lymphoma
  - Generally more aggressive in children than adults

- **Risk factors**
  - **Viruses**
    - Epstein-Barr virus (EBV)
      - Burkitt lymphoma
    - Diffuse large B-cell lymphoma
    - Primary CNS lymphoma (HIV)
      - Associated with AIDS
  - **Human T-cell lymphotropic virus (HTLV) type I**
    - Adult T-cell lymphoma
  - **Hepatitis C virus (HCV)**
    - B-cell lymphoma
  - **Helicobacter pylori**
    - Malignant lymphoma of the stomach
      - Derived from mucosa-associated lymphoid tissue
    - Treatment of peptic ulcer disease reduces risk

- **Autoimmune disease**
  - **Sjögren syndrome**
    - Commonly associated with salivary gland and gastrointestinal lymphomas
  - **Hashimoto thyroiditis**
    - Associated with malignant lymphoma within the thyroid gland

- **Immunodeficiency syndromes**
  - Chromosome instability syndromes (e.g., Bloom syndrome), AIDS
e. Immunosuppressive therapy used to prevent rejection in recipients of organ or bone marrow transplants

f. High-dose radiation used in the treatment of Hodgkin lymphoma

**B. Pathogenesis**

1. Mutation produces a block at a specific stage in the development of B or T cells

2. Example—accumulation of small cleaved B cells in follicular lymphoma

**C. B-cell lymphomas** *(Table 14-1; Fig. 14-8)*

**D. T-cell lymphomas**

1. Precursor T-cell lymphoblastic leukemia/lymphoma
   a. Accounts for 40% of childhood lymphomas
      (1) Primarily involves the anterior mediastinal and cervical nodes
      (2) Bone marrow and CNS involvement is common

---

**Table 14-1 Common Types of B-Cell Non-Hodgkin Lymphoma**

<table>
<thead>
<tr>
<th>TYPE</th>
<th>EPIDEMIOLOGY</th>
<th>DESCRIPTION/IMMUNOPHENOTYPE</th>
<th>CLINICAL FINDINGS</th>
</tr>
</thead>
</table>
| Burkitt lymphoma (see Fig. 14-8A and B) | 30% of children with NHL            | EBV relationship with t(8;14) “starry sky” appearance with neoplastic B cells (dark of night) and reactive histiocytes with phagocytic debris (stars) | American type: gastrointestinal tract, para-aortic nodes
African type: jaw
Bone marrow involvement
Leukemic phase common |
| Diffuse large B-cell lymphoma | 50% of adults with NHL; elderly and childhood populations | Derives from the germinal center                                 | Localized disease with extranodal involvement: gastrointestinal tract, brain (EBV association with AIDS) |
| Extranodal marginal zone lymphoma | Association with Helicobacter pylori gastritis | Derives from MALT                                                | Low-grade malignant lymphoma of the stomach                                     |
| Follicular lymphoma (see Fig. 14-9) | 40% of adults with NHL; elderly patients | Derives from germinal center t(14;18), causing overexpression of BCL-2 antipoptosis gene | Generalized lymphadenopathy
Bone marrow involvement |
| Small lymphocytic lymphoma (SLL) | Patients usually >60 years of age | Neoplasm of small, mature B lymphocytes
SLL if confined to lymph nodes
CLL if leukemic phase is present | Generalized lymphadenopathy |

ClL, Chronic lymphocytic leukemia; EBV, Epstein-Barr virus; MALT, mucosa-associated lymphoid tissue; NHL, non-Hodgkin lymphoma.

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14-8: A, Burkitt lymphoma. Note the swelling of the jaw, a very characteristic location for this type of malignant lymphoma. B, Lymph node biopsy in Burkitt lymphoma. The lymph node is completely effaced with a monomorphic infiltrate of lymphocytes. Interspersed are clear spaces with reactive histiocytes containing phagocytic debris. At low power the node has a “starry sky” appearance, with the stars represented by the reactive histiocytes. This type of lymphoma is associated with a t(8;14) translocation. (A from Hoffbrand I, Pettit J, Vyas P. Color Atlas of Clinical Hematology, 4th ed, St. Louis, Mosby Elsevier, 2010, p 358, Fig. 19-82; B from Rosai J, Ackerman LV. Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 1595, Fig. 21-103.)
b. Precursor T-cell lymphoblastic leukemia
   • Leukemic variant of the lymphoma

2. Mycosis fungoides and Sézary syndrome
   a. Epidemiology
      (1) Both conditions involve neoplastic peripheral CD4 helper T (T₄) cells.
      (2) They usually occur in adults 40 to 60 years of age.
   b. Mycosis fungoides (MF)
      (1) Begins in the skin (rash to plaque to nodular masses)
         • Progresses to the lymph nodes, lung, liver, and spleen
      (2) Groups of neoplastic cells that invade the epidermis are called Pautrier microabscesses.
   c. Sézary syndrome
      (1) MF with a leukemic phase
      (2) Circulating malignant T cells are called Sézary cells.

 E. Survival statistics
   • Survival rate varies with the type of NHL

III. Hodgkin Lymphoma (HL)
   A. Epidemiology
      1. Accounts for ~40% of adult lymphomas
      2. Age and sex differences
         a. Slightly more common in men than women
         • Exception—nodular sclerosing type is more common in women
         b. More common in adults than children
         c. More common in whites than blacks
      3. Bimodal age distribution
         a. First large peak is 15 to 34 years old
         b. Second smaller peak is >50 years old
         c. Occurs in a younger age bracket than NHL
      4. Most common site of initial involvement is the neck region
      5. EBV has been identified in certain types of HL (e.g., 60%-70% of cases of mixed cellularity HL).
      6. Persons with HIV infections have a higher incidence of HL relative to an uninfected population.
      7. Defects in cell-mediated immunity (CMI)
         • Example—defects in skin reactions to injection of common antigens (anergy; refer to Chapter 4)
      8. Classification (Table 14-2; Fig 14-9)
         a. Lymphocyte rich classical
         b. Nodular sclerosing classical (most common type)
         c. Mixed cellularity classical
         d. Lymphocyte depleted classical
         e. Nodular lymphocyte predominant

   B. Pathogenesis
      2. Activation of the transcription factor NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is common in classical HL.
         a. NF-κB is activated by EBV or other factors.
         b. Once activated, it turns on genes that promote proliferation of B cells.

   C. Pathologic findings
      1. Involves localized groups of nodes and has contiguous spread to other lymph node groups
         a. Most frequently involves cervical, supraclavicular, and anterior mediastinal lymph nodes
         b. Cut section of involved lymph nodes has a bulging “fish-flesh” appearance
      2. Reed-Sternberg (RS) cell
         a. Neoplastic cell of HL
         (1) Immunophenotype markers are positive for CD15 and CD30.
         (2) Most (not all) RS cells are of B-cell origin, derived from lymph node germinal centers.
b. Classic RS cell
   - Two mirror image nuclei, each with an eosinophilic nucleolus surrounded by a clear halo (Fig. 14-10A)

c. RS variant: lacunar cell
   (1) Not a “classical” Reed-Sternberg cell
   (2) Monolobated or multinucleated cell with small nucleoli and abundant, pale cytoplasm
   (3) Cell lies in a clear space (artifact of fixation in formalin-fixed tissue)
   (4) Present in the nodular sclerosis type of HL (Fig. 14-10B)

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**TABLE 14-2 Types of Hodgkin Lymphoma (HL)**

<table>
<thead>
<tr>
<th>TYPE</th>
<th>EPIDEMIOLOGY/CLINICAL</th>
<th>HISTOLOGIC FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte rich classical HL</td>
<td>Uncommon Epstein-Barr virus association 40% of cases Males greater than females; older adults Very good to excellent prognosis</td>
<td>Classic RS cells are present. Reactive lymphocytes often completely efface the lymph node architecture.</td>
</tr>
<tr>
<td>Nodular sclerosis classical HL</td>
<td>60% to 80% of cases Equal frequency in young adult males and females Epstein-Barr virus association infrequent. Usually involves anterior mediastinal nodes (seen on chest x-ray) and either cervical or supraclavicular nodes Excellent prognosis</td>
<td>Classic RS cells infrequent Lacunar type RS cells (called RS variants) present: monolobated or multilobated nucleus, small nucleolus, abundant pale cytoplasm Collagen separates nodular areas</td>
</tr>
<tr>
<td>Mixed cellularity classical HL</td>
<td>15% to 30% of cases Men &gt;55 years of age Epstein-Barr virus association (60%-70% of cases) Type that most commonly occurs in HIV-positive patients (all are EBV positive) Commonly affects abdominal lymph nodes and spleen. Advanced stage-disease and systemic signs are usually present. Overall prognosis is good.</td>
<td>Numerous classic RS cells Eosinophils, plasma cells, histiocytes</td>
</tr>
<tr>
<td>Lymphocyte depleted classical HL</td>
<td>Least common HL (&lt;1% of cases) Men &gt;50 years of age Epstein-Barr virus association especially if associated with HIV-positive individuals. Most aggressive Hodgkin’s lymphoma. Poorest survival statistics. Usually present with advanced-stage disease.</td>
<td>RS cells are frequently present some of which have bizarre features.</td>
</tr>
<tr>
<td>Nodular lymphocyte-predominant HL</td>
<td>“Non-classical” type of HL 5% of cases ~75% are male with one peak in children and the other with a median age of 30 to 40 years Good prognosis</td>
<td>Classical RS cells infrequent Lymphocytic and histiocytic (L&amp;H) cells or “popcorn” cells (nuclei resemble an exploded kernel of corn) are present. These cells are positive for B-cell antigens (CD19 and CD20) but are negative for CD15 and CD30.</td>
</tr>
</tbody>
</table>
Lymphoid Tissue Disorders

14-10: A, Classic Reed-Sternberg cell. The large, multilobed cell with prominent nucleoli is surrounded by a halo of clear nucleoplasm. Classic Reed-Sternberg cells are more easily found in mixed-cellularity classical Hodgkin lymphoma than in lymphocyte-predominant and nodular-sclerosing Hodgkin lymphoma. B, Nodular-sclerosis classical Hodgkin lymphoma. The lymphoid nodule is encased by fibrous tissue. Note the clear spaces in the nodule within which are Reed-Sternberg variants called lacunar cells (cytoplasm shrinks during formalin fixation). (A from Damjanov I, Linder J: Anderson’s Pathology, 10th ed, St. Louis, Mosby, 1996, p 1145, Fig. 42-47A; B from Rosai J, Ackerman LV: Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 1924, Fig. 21-56.)

3. Diagnosis
   - Presence of a classic Reed-Sternberg cell is required
4. Differences of HL from NHL
   - HL less commonly involves Waldeyer tonsillar ring, mesenteric lymph nodes, and extranodal sites than NHL.
D. Clinical findings and prognosis
   1. Constitutional signs
      a. Fever, unexplained weight loss, night sweats (40% of cases)
      b. Pruritus
      c. Pel-Ebstein fever—uncommon variant of fever
         • Characterized by alternating bouts of fever followed by remissions
   2. Hematologic findings
      a. Normocytic anemia (presenting symptom 40% of cases)
         • Anemia of chronic disease, immune hemolytic anemia
      b. Painless enlargement of single groups of lymph nodes in the neck region
         • Become painful if the patient drinks alcohol
   3. Chest pain, cough, and dyspnea usually indicate the presence of a large mediastinal mass or metastasis to the lungs.
4. Primary factors that determine the prognosis in HL
   a. Clinical stage is more important than the type of HL
   b. Majority have lymphadenopathy above the diaphragm (stages I and II), which correlates with an excellent prognosis.
5. Increased risk for developing second malignancies, usually acute myeloblastic leukemia (AML) or NHL
   • Increased risk is related to treatment with radiation and alkylating agents.
E. Treatment
   • Radiotherapy and chemotherapy are used depending on the stage of the disease.
F. Survival statistics
   1. Cure rate for persons with stage I or IIA disease is over 90%.
   2. In moreadvanced disease (e.g., stage IVA or IVB), the 5-year survival rate is 60% to 70%.
IV. Langerhans Cell Histiocytoses (Histiocytosis X)
A. Epidemiology
   1. Characteristics
      a. Histiocytes are CD1 positive.
      b. Cells contain Birbeck granules (tennis racket appearance; Fig. 14-11A).
         • Only visible with electron microscopy
   2. Primarily occurs in children and young adults
   3. Types of histiocytes
      a. Letterer-Siwe disease
      b. Hand-Schüller-Christian disease
      c. Eosinophilic granuloma

RS cell required to diagnose HL
HL: fever, weight loss, night sweats; pruritus
Prognosis: stage more important than type of HL
Nodular sclerosis HL: anterior mediastinal mass + single group of nodes above diaphragm
Rx HL: Titik 2nd malignancies (AML, NHL)
Histocytes: CD1+; Birbeck granules
B. **Letterer-Siwe disease**
1. Epidemiology
   a. Malignant histiocytosis
   b. Occurs in infants and children that are <2 years old
2. Clinical findings
   a. Diffuse eczematous rash (see Fig. 14-11B)
   b. Multiple organ involvement
   c. Lytic lesions in the skull, pelvis, and long bones
3. Rapidly fatal

C. **Hand-Schüller-Christian (HSC) disease**
1. Epidemiology
   a. Malignant histiocytosis
   b. Mainly affects children
2. Clinical findings
   a. General findings
      (1) Fever
      (2) Localized rash on the scalp and in the ear canals
   b. Classic triad due to infiltrative disease
      (1) Lytic lesions are present in the skull.
      (2) Central diabetes insipidus (CDI), due to invasion of the posterior pituitary stalk
      (3) Exophthalmos from infiltration of the orbit
3. Intermediate prognosis

D. **Eosinophilic granuloma**
1. Epidemiology
   a. Benign histiocytosis
   b. Occurs in adolescents and young adults
2. Clinical findings
   a. Unifocal lytic lesions are present in bone (skull, ribs, and femur).
   b. Bone pain and pathologic fractures are common.
3. Prognosis is excellent

V. **Mast Cell Disorders**
A. **Overview**
1. Epidemiology
   - Localized (urticaria pigmentosa and solitary mastocytoma) or systemic
2. Signs and symptoms relate to mast cell release of histamine—pruritus and swelling of tissue
B. Urticaria pigmentosa (UP)

1. Epidemiology
   a. Majority of persons with UP are children
   b. In adolescents and adults, UP is more likely to persist.
2. Skin lesions
   a. Multiple oval, red-brown, nonscaling macules (flat lesions) or papules are present
   b. Scratching of the lesions results in erythematous swelling and pruritus.
      • Called Darier sign
   c. Dermatographism
      • Dermal edema occurs when apparently normal skin is stroked with a pointed object.
   d. Lesions remain hyperpigmented when they regress.
   e. Skin biopsy findings
      • Mast cells have metachromatic granules that stain positive with toluidine blue and Giemsa stain.
3. Pruritus and flushing are triggered by foods, alcohol, or drugs (e.g., codeine).
4. Other findings include:
   a. Abdominal pain with diarrhea
   b. Headaches with flushing of the skin
   c. Anaphylactic reactions if envenomated by a bee, hornet, or wasp
5. Treatment
   • H1 and H2 antihistamines decrease pruritus, flushing, and gastrointestinal symptoms.

VI. Plasma Cell Dyscrasias (Monoclonal Gammopathies)

A. Overview of monoclonal gammopathies (MG; plasma cell dyscrasias)
1. All are monoclonal B-cell disorders
   • Definition—increase in a single immunoglobulin (M protein) and its corresponding light chain
2. Clinical significance of M proteins
   a. Most MGs are due to an increase in IgG.
      • All other plasma cell clones are immunologically suppressed.
   b. Bence Jones (BJ) protein
      (1) Definition—free κ or λ light chains that are excreted in urine
      (2) Associated with plasma cell malignancies and Waldenström macroglobulinemia
3. Test used to detect MGs
   a. Serum protein electrophoresis (SPE; also refer to Chapter 3)
      (1) Useful in quantitating the M protein and shows a monoclonal spike (M protein; Fig. 14-13)
      (2) Does not specify which M protein is increased (e.g., IgG, IgA, IgM)
   b. Serum immunofixation electrophoresis
      (1) More sensitive than SPE and provides a characterization of the M protein (heavy and light chain subclass; e.g., IgGk or IgGλ; IgMk or IgMλ)
      (2) Does not quantitate the M protein

14-13: Serum protein electrophoresis (SPE) showing a schematic of a monoclonal gammopathy. (From Goljan EF, Sloka KI: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 284, Fig. 9-1C.)

14-12: Urticaria pigmentosa. Note the numerous red-brown, round to oval macules and papules that are distributed over the trunk. These lesions are pruritic as a result of the release of histamine from the dermal mast cells. The lesions gradually darken over time because of increased melanin pigmentation. (Courtesy R.A. Marsden, MD, St. George’s Hospital, London.)
plasma cell

MM: MM: normal one lesions

b.  Inemia, and

c.  IgG

MM: vertebrae MC bone

pathologic fractures,

plasma cells

MM: lytic lesions,

chain myeloma

CRAB: calcium elevation,

renal insufficiency,

anemia, and

bone lesions

MM: MGUS

MM: MM: normal plasma cell → MGUS → myeloma

MM: lytic lesions, plasma cells >10%, pathologic fractures, hypercalcemia

MM: vertebræ MC bone site

c.  Urine protein electrophoresis
   (1) Identifies BJ protein (free light chains) and quantitates the amount of light chains in the urine
   (2) Does not specify whether the light chains are κ or λ

d. Urine immunofixation electrophoresis
   (1) Characterizes whether BJ protein is κ or λ
   (2) More sensitive in detecting BJ protein than the standard urine protein electrophoresis

e. Serum for free light chains
   (1) Detects and quantitates κ and λ light chains in serum
   (2) More sensitive for detecting light chains than any of the urine methodologies listed above

4. Classification
   a. Monoclonal gammopathy of undetermined significance (MGUS)
   b. Multiple myeloma
   c. Light chain amyloidosis
   d. Solitary plasmacytoma
   e. Waldenström macroglobulinemia
   f. Heavy chain disease

B. Multiple myeloma (MM)

1. Epidemiology
   a. Accounts for 10% of all hematologic malignancies
   b. Two times more common in blacks than whites
   c. Median age at onset is 66 years
      • Rare under 40 years of age
   d. Increased risk with radiation or benzene exposure
   e. M-spike occurs in 80% to 90% of cases
      (1) IgGκ myeloma (60% of cases) followed by IgA (20% of cases) and pure light chain myeloma (20% of cases)
         • Serum M protein is >3g/dL.
      (2) Urinalysis for BJ protein is positive in 60% to 80% of cases.
   f. Evidence of end-organ damage includes calcium elevation, renal insufficiency, anemia, and bone lesions (CRAB).
   g. Nonsecretory multiple myeloma
      (1) Accounts for 1% to 3% of all cases
      (2) No serum or urine M protein
      (3) Bone marrow plasma cells are >10%
      (4) CRAB present

2. Pathogenesis
   a. Chromosome abnormalities (deletions, translocations)
      • Detected with fluorescence in-situ hybridization (FISH) and have prognostic significance for detecting high-risk patients
   b. Possible evolution from normal plasma cells → MGUS → multiple myeloma

3. Pathologic findings
   a. Sheets of malignant plasma cells are present in a bone marrow aspirate/biopsy (Fig. 14-14A).
   b. Malignant plasma cells account for >10% of cells in the aspirate.

4. Skeletal system findings
   a. Bone pain occurs in ~60% of cases.
      (1) “Punched out” lytic lesions occur in the bone (see Fig. 14-14B and C).
         (a) Myeloma cells produce an inhibitor of osteoblast differentiation (DKK1).
         (b) Myeloma cells release interleukin-1 (osteoclast activating factor), which activates osteoclasts.
      (2) Vertebræ are the most common sites of bone involvement.
      (3) Other sites include ribs, skull, femur, and pelvis.
      (4) Pain commonly presents with pathologic fractures, particularly if rib lesions are present.
   b. Hypercalcemia (25% of cases)

5. Renal findings
   a. Renal failure (30%–50% of cases)
   b. Different renal presentations
1. Proteinaceous tubular casts
   (a) Casts are composed of BJ protein.
   (b) BJ protein is nephrotoxic and damages tubular epithelium.
   (c) Biopsy reveals an intratubular multinucleated giant cell reaction.

2. Nephrocalcinosis
   (a) Hypercalcemia leads to metastatic calcification of the tubular basement membranes in the collecting ducts (refer to Chapter 2).
   (b) Calcium deposits are a common cause of acute renal failure in multiple myeloma.

3. Metastatic disease to interstitial tissue

4. Primary amyloidosis (10% of cases)
   • Light chains are converted into amyloid (refer to Chapter 4 and produce a nephrotic syndrome (refer to Chapters 4 and 20).

6. Hematologic findings
   a. Normocytic anemia with rouleaux (Fig. 3-19)
   b. Markedly increased erythrocyte sedimentation rate (ESR) (refer to Chapter 3)
   c. Prolonged bleeding time (refer to Chapter 15)
      (1) Defect in platelet aggregation
      (2) Dialysis restores the bleeding time to normal.

7. Radiculopathy may occur from bone compression and vertebral fractures.

8. Recurrent infection is a common cause of death.
   • Sepsis is commonly due to Haemophilus influenzae or Streptococcus pneumoniae.

9. Treatment
   a. High-dose chemotherapy
   b. Autologous stem cell transplantation
      • Dramatically improved survival

10. Prognosis
    • Median survival after diagnosis is 3 years.

C. Other plasma cell dyscrasias (Table 14-3)

VII. Spleen Disorders
   A. Clinical anatomy and physiology
      1. Red pulp of spleen
         • Contains the cords of Billroth with fixed macrophages and sinusoids

BJ renal disease in MM: proteinaceous casts with multinucleated giant cell reaction

MM: association with primary (AL) amyloidosis

MM: anemia with rouleaux, ↑ bleeding time (platelet aggregation defect)

MM: sepsis/renal failure common causes of death

MGUS: MC monoclonal gammopathy

Red pulp: fixed macrophages
**Table 14-3 Additional Plasma Cell Dyscrasias**

<table>
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<th>TYPE</th>
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| Monoclonal gammopathy of undetermined significance (MGUS) | Most common monoclonal gammopathy (50%–65% of all monoclonal gammopathies)  
MGUS is found in ~3% of individuals aged 50 years  
Small IgG M-spike in elderly patients (serum M protein ≤3 g/dL)  
Plasma cells ≤10% in bone marrow  
No serum or urine BJ protein or CRAB  
1% lifelong risk per year of progression to multiple myeloma  
Treatment: none required; close follow-up to detect appearance of malignancy |
| Solitary skeletal plasmacytoma             | Accounts for 3%–5% of all monoclonal gammopathies  
Twice as common in women  
Single lytic lesion with clonal plasma cells in the following bone sites: vertebrae, ribs, pelvis  
Low or no serum and urine M protein  
Bone marrow is not consistent with multiple myeloma  
Approximately 50% progress to multiple myeloma over 4 to 5 years |
| Extramedullary plasmacytoma                | Sites: upper respiratory tract (nasopharynx, sinuses, larynx)  
Low to no serum and urine M protein  
No malignant plasma cells in the bone marrow  
Small percentage may develop multiple myeloma |
| Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia) | Neoplastic lymphoplasmacytoid B cells in bone marrow  
Primarily elderly males (median age 65 years)  
Main risk factor is MGUS  
M spike with IgM  
BJ protein is present (80% of cases)  
Generalized lymphadenopathy (~30% of cases; not present in myeloma)  
Anemia and bone marrow (no lytic lesions like myeloma), liver, and spleen involvement (hepatosplenomegaly; not common in myeloma)  
Hyperviscosity syndrome due to increased IgM: retinal hemorrhages, strokes, platelet aggregation defects; plasmapheresis important to remove IgM  
Unlike multiple myeloma, renal disease and amyloidosis are rare  
Poor response to therapy  
Median survival is 5 years  
Patients with a malignant lymphoma associated with an IgM M-spike but who do not meet the diagnostic criteria for Waldenström macroglobulinemia (<3 g M-spike) are classified as having lymphoplasmacytic lymphoma with an IgM M protein. |
| Heavy-chain diseases                       | M protein heavy chain without light chains  
Absence of BJ protein  
α-Heavy-chain disease: neoplastic infiltration of the jejunum, leading to malabsorption or localized upper respiratory tract disease  
γ-Heavy-chain disease: presents as a lymphoma  
μ-Heavy-chain disease: often associated with chronic lymphocytic leukemia or lymphoma |
| POEMS syndrome                             | Paraneoplastic syndrome including polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes |

BJ, Bence Jones; CRAB, calcium elevation; renal insufficiency, anemia, and bone lesions.

2. White pulp of spleen
   - Contains B and T cells

3. Important functions
   a. Blood filtration; macrophages remove:
      (1) Hematopoietic elements (e.g., senescent red blood cells)  
      (2) Intraerythrocytic parasites (e.g., malaria)  
      (3) Encapsulated bacteria (e.g., S. pneumoniae)  
   b. Antigen trapping and processing in macrophages  
   c. Reservoir for one third of the peripheral blood platelet pool  
   d. Site for extramedullary hematopoiesis (EMH; refer to Chapter 12)

B. Splenomegaly
1. Basic mechanisms and causes
   a. Immune response work hypertrophy; examples include:
      • Infectious mononucleosis, subacute bacterial endocarditis, and malaria  
   b. Congestion; examples include:
      • Splenic vein thrombosis and portal hypertension
c. RBC destruction work hypertrophy; examples include:
- Hereditary spherocytosis, pyruvate kinase deficiency, and β-thalassemia major

d. Myeloproliferative disease; examples include:
- Polycythemia vera, myelofibrosis, and myeloid metaplasia, and essential thrombocytthemia

e. Neoplastic disease; examples include:
- Acute and chronic leukemias, and malignant lymphoma

f. Infiltrative disease; examples include:
(1) Primary and secondary amyloidosis, sarcoidosis, Gaucher disease, and Niemann-Pick disease.
(2) Gaucher disease
   (a) Autosomal recessive lysosomal storage disease with a deficiency of glucocerebrosidase and lysosomal accumulation of glucocerebrosides
   (b) Macrophages with a fibrillary appearance (Fig. 14-15A)
(3) Niemann-Pick disease
   (a) Autosomal recessive lysosomal storage disease with a deficiency of sphingomyelinase and lysosomal accumulation of sphingomyelin
   (b) Macrophages with a soap bubble appearance (see Fig. 14-15B)

2. Clinical findings
a. Left upper quadrant pain
- Pain may be due to splenic infarctions causing friction rubs and a left-sided pleural effusion.

b. Hypersplenism (see later discussion)

C. Spleen in portal hypertension (PH)

1. Gross findings
- Spleen is covered by a thickened (“sugar-coated”) capsule from perisplenitis

2. Microscopic findings
- Calcium and iron concretions called Gamma-Gandy bodies are deposited in collagen.

D. Hypersplenism

1. Definition
a. Normal splenic function is exaggerated.
b. RBCs, WBCs, and platelets, either singly or in combination, are sequestered and destroyed.

2. Most common cause is PH associated with cirrhosis

3. Clinical findings
a. Splenomegaly
b. Peripheral blood cytopenias
   - Anemia, thrombocytopenia, and neutropenia, alone or in combination
   - Attempt by the marrow to replace lost hematopoietic cells
   - Correction of cytopenias with splenectomy

Gaucher disease: ↓glucocerebrosidase, ↑glucocerebroside, macrophages fibrillary appearance

Niemann-Pick: ↓sphingomyelinase, ↑sphingomyelin, macrophages soap bubble appearance

Massive splenomegaly: infarctions with pain, friction rub, and left-sided pleural effusion

Splenomegaly in cirrhosis with portal hypertension: sugar-coated spleen

Hypersplenism: destruction of hematopoietic cells produces cytopenias

PH MCC hypersplenism
E. Splenic dysfunction and splenectomy

1. Signs of splenic dysfunction
   a. Howell-Jolly (HJ) bodies (nuclear remnants) in the peripheral blood RBCs (Fig. 12-24C)
      • With a functioning spleen, macrophages would have removed RBCs with HJ bodies.
   b. Predisposition to infections by encapsulated pathogens
      (1) Infections include septicemia, peritonitis, and osteomyelitis.
      (a) Pathogens include S. pneumoniae (most common), Haemophilus influenzae, Salmonella, and Neisseria meningitidis.
      (b) Immunization helps prevent infectious complications of splenic dysfunction.
      (2) Mechanisms causing infections by the pathogens just listed
        (a) Concentration of IgM drops, leading to a decrease in complement system activation (less C3b for opsonization).
        • Spleen is a site for IgM synthesis.
        (b) Splenic macrophages are not present in sufficient numbers to phagocytose the opsonized encapsulated pathogens.
        (c) Tuftsin, which is normally synthesized in the spleen, is lost.
        • Tuftsin activates receptors on macrophages to increase their phagocytic activity.

2. Splenectomy
   a. Increases the risk for infections (see previous discussion)
   b. Hematologic findings
      (1) Nucleated RBCs
      (2) HJ bodies
      (3) Target cells (excess membrane cannot be removed)
      (4) Thrombocytosis
        • Platelets normally sequestered in the spleen are now circulating.
I. Normal Hemostasis and Hemostasis Testing

A. Definition of hemostasis
- Prevention of blood loss requiring the interaction of the blood vessels, platelets, coagulation factors, and fibrinolytic agents

B. Factors preventing thrombus formation in small blood vessels
1. Small blood vessels include capillaries, venules, and arterioles.
2. Thrombus formation is prevented by heparin-like molecules.
   a. Enhance antithrombin III (ATIII) activity
   b. Neutralize activated serine protease coagulation factors
      - Factors VII, IX, X, XI, and XII; thrombin (activated prothrombin)
3. Prostaglandin (PG) I$_2$ (prostacyclin)
   a. Synthesized by intact endothelial cells (refer to Chapter 3)
   b. PGH$_2$, the precursor prostaglandin, is converted by prostacyclin synthase to PGI$_2$.
      (1) PGI$_2$ is a vasodilator; and inhibits platelet aggregation.
      (2) Aspirin does not inhibit the synthesis of PGI$_2$ by endothelial cells.
4. Proteins C and S
   a. These proteins are vitamin K–dependent coagulation factors
   b. Protein S acts a cofactor for protein C.
   c. Thrombin binds to thrombomodulin on the surface of endothelial cells.
      (1) Thrombin-thrombomodulin complex activates protein C, which inhibits clotting by inactivating factors Va and VIIIa.
      (2) Demonstrates an anticoagulant function rather than a procoagulant function of thrombin
5. Tissue plasminogen activator (tPA)
   a. tPA is synthesized by endothelial cells.
   b. It activates plasminogen to release plasmin.
   c. Plasmin degrades coagulation factors and lyses fibrin clots (thrombi).

C. Factors enhancing thrombus formation in small vessel injury
1. Thromboxane A$_2$ (TXA$_2$)
   a. Synthesized by platelets
      (1) PGH$_2$ is converted into TXA$_2$ by thromboxane synthase.
      (2) Aspirin irreversibly inhibits platelet cyclooxygenase (refer to Chapter 3).
         (a) Prevents formation of PGH$_2$, the precursor for TXA$_2$
         (b) Platelets are functional 48 hrs after discontinuing aspirin intake.
      (3) Other nonsteroidal antiinflammatory drugs (NSAIDs) reversibly inhibit platelet cyclooxygenase.
         - Platelet function is restored 12 to 24 hours after discontinuing NSAIDs.
      (4) Prostacyclin synthase in endothelial cells is minimally affected by NSAIDs.
   b. Functions of TXA$_2$ in hemostasis
      - Vasoconstrictor and enhances platelet aggregation
vWF: platelet adhesion molecule; synthesized in Weibel-Palade bodies in endothelial cells

vWF complexes with factor VIII:c in plasma to prevent its degradation

vWF: ↓vWF causes ↓VIII:c

Factor VIII:c is synthesized by the liver and reticuloendothelial tissues. When factor VIII:c is activated by thrombin, it dissociates from the factor VII:vWF complex and performs its procoagulant function in the intrinsic coagulation cascade system.

Tissue thromboplastin: activates VII in extrinsic coagulation system

Platelet receptors: GpIb (binds to vWF); GpIIb-IIIa (binds to fibrinogen)

Ticlopidine, clopidogrel, abciximab: interfere with GpIIb-IIIa receptor function

2. von Willebrand factor (vWF)
   a. Synthesized by endothelial cells and megakaryocytes in the bone marrow
      (1) Synthesized in the Weibel-Palade bodies in the endothelial cells
      (2) Platelets carry some vWF in their α-granules.
   b. Functions of vWF
      (1) Platelet adhesion molecule
         (a) Binds platelets to exposed collagen so that a platelet thrombus is formed to stop bleeding from damaged small blood vessels
         (b) Platelets have glycoprotein (Gp) Ib receptors that bind to vWF, causing platelet adhesion to the damaged site.
      (2) vWF complexes with factor VIII coagulant (factor VIII:c) in the circulation (VIII:vWF).
         (a) Complexes prevent degradation of factor VIII:c in the circulation.
         (b) Decrease in vWF (e.g., von Willebrand disease) secondarily decreases factor VIII:c activity.

3. Tissue thromboplastin (factor III)
   a. Definition—noncirculating ubiquitous substance that is released from injured tissue
   b. Activates factor VII in the extrinsic coagulation system

4. Extrinsic and intrinsic coagulation systems (discussed later)

D. Platelet structure and function

1. Derivation of platelets
   a. Platelets are formed through cytoplasmic fragmentation of megakaryocytes.
   b. Approximately 1000 to 3000 platelets are produced per megakaryocyte (Fig. 15-1).

2. Locations of platelets
   a. Present in the peripheral blood and live for ~8 to 10 days
   b. Approximately one-third of the total platelet pool is stored in the spleen.

3. Platelet receptors
   a. Glycoprotein receptors for vWF are designated GpIb.
   b. Glycoprotein receptors for fibrinogen are designated GpIIb-IIIa.
      (1) Ticlopidine and clopidogrel
         (a) Inhibit adenosine diphosphate (ADP)-induced expression of platelet GpIIb-IIIa receptors
         (b) Prevent fibrinogen binding to the receptor, which inhibits platelet aggregation
      (2) Abciximab
         • Monoclonal antibody directed against the GpIIb-IIIa receptor that prevents platelets from aggregating

15-1: Megakaryocyte showing budding of platelets (arrow) along the periphery of the cell. (Electron micrograph courtesy William Meek, Ph.D., Professor of Anatomy and Cell Biology, Oklahoma State University, Center for Health Sciences, Tulsa, Oklahoma.)
4. Platelet factor 3 (PF3)
   a. Located on the platelet membrane
   b. Phospholipid substrate that is required for the clotting sequence

5. Platelet structure
   a. Contractile element called thrombosthenin helps in clot retraction.
      • Deficient in Glanzmann disease
   b. Dense bodies contain:
      (1) ADP, an aggregating agent
      (2) Calcium, a binding agent for vitamin K–dependent factors
   c. α-Granules contain:
      • vWF, fibrinogen, platelet-derived growth factor (PDGF), and platelet factor 4 (PF4), which is a heparin-neutralizing factor

6. Platelet functions
   a. Stabilize the vascular endothelial–cadherin complex at intercellular adherens junctions, particularly in postcapillary venules
      (1) The process is accomplished by platelet release of cytokines and growth factors stored within the platelet granules.
      (2) Stabilizing these junctions prevents the leakage of RBCs into the interstitium.
      (3) If the platelet count falls below critical levels, these junctions disassemble, causing extravasation of RBCs into the interstitium.
         • This induces formation of petechiae, a hallmark of thrombocytopenia.
   b. Important in the formation of the hemostatic plug (fibrin thrombus) in small vessel injury
   c. PDGF stimulates smooth muscle hyperplasia.
      • Important in the pathogenesis of atherosclerosis (refer to Chapter 10)

E. Coagulation system (Fig. 15-2)
1. Coagulation cascade
   a. Extrinsic system (factor VII)
   b. Intrinsic system (factors VIII, IX, XI, and XII)

2. Extrinsic coagulation system
   a. Factor VII is activated (factor VIIa) by tissue thromboplastin released from damaged tissue.
   b. Factor VIIa activates factors IX and X (intrinsic system and the final common pathway, respectively).

3. Intrinsic coagulation system
   a. Factor XII (Hageman factor) is activated by:
      (1) Exposed subendothelial collagen
      (2) High-molecular-weight kininogen (HMWK)

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**Extrinsic system**

- Tissue thromboplastin
- Factor VII
- Factor VIIa
- Factor X

**Intrinsic system**

- Factor XII (Hageman factor)
- Factor Xa
- Factor Xa + PF3 + Ca2+

**Final common pathway**

- Factor X to fibrin clot
- Coagulation cascade. Both the extrinsic and intrinsic coagulation systems use the final common pathway for the formation of a fibrin clot. a. Activated; HMWK, high-molecular-weight kininogen; PF3-platelet factor 3.
b. Functions of factor XIIa
   - Activates factor XI, plasminogen (produces plasmin), and the kininogen system (produces kallikrein and bradykinin)


4. Final common pathway
   a. Pathway includes factors V and X, prothrombin (II), and fibrinogen (I)
   b. Prothrombin complex
      (1) The complex is a four-component system consisting of factor Xa, factor V, PF3, and calcium.
      (2) Calcium binds factor Xa, a vitamin K-dependent coagulation factor.
      (3) Prothrombin complex cleaves prothrombin into thrombin (an enzyme).
   c. Functions of thrombin
      (1) Acts on fibrinogen to produce fibrin monomers plus fibrinopeptides A and B
      (2) Activates fibrin-stabilizing factor XIII
         (a) Factor XIIa converts soluble fibrin monomers to insoluble fibrin.
         (b) It enhances protein-protein cross-linking of insoluble fibrin to strengthen the fibrin clot.
            • Cross-links are detected in the d-dimer assay (discussed later).
            • Cross-links are analogous to those between tropocollagen molecules, which give collagen its tensile strength.
      (3) Activates factor VIIIa in the intrinsic coagulation system
      (4) Complexes with thrombomodulin on endothelial cells to activate protein C, which inactivates factors Va and VIIIa

5. Vitamin K-dependent factors include:
   a. Factors II, VII, IX, and X; protein C and protein S.
   b. Synthesized in the liver as nonfunctional precursor proteins
   c. Function of vitamin K (also refer to Chapter 8)
      (1) Majority of vitamin K is synthesized by colonic bacteria
         • Vitamin K is activated in the liver by epoxide reductase.
      (2) Activated vitamin K γ-carboxylates each of the vitamin K-dependent factors.
         • Carboxylated factors are now able to bind to calcium and PF3 in the cascade sequence.

6. Some of the coagulation factors are consumed in the formation of a fibrin clot.
   • Consumed factors include fibrinogen (factor I), factor V, factor VIII, and prothrombin (II).

When blood is drawn into a clot tube (no anticoagulant is added), a fibrin clot is formed. When the tube is spun down in a centrifuge, the supranate is called serum, which, unlike plasma, is missing fibrinogen (factor I), prothrombin (factor II), factor V, and factor VIII. When blood is drawn into a tube that has an anticoagulant (e.g., heparin), a clot does not form. When the tube is spun down in a centrifuge, the supranate is called plasma and contains all of the coagulation factors.

F. Fibrinolytic system

1. Activation of the fibrinolytic system
   a. Tissue plasminogen activator (tPA) activates plasminogen to release the enzyme plasmin.
      • Alteplase and reteplase are recombinant forms of tPA that are used in thrombolytic therapy.
   b. Other activators of plasminogen include:
      (1) Factor XIIa
      (2) Streptokinase
         • Derived from streptococci
      (3) Anistreplase
         • Complex of streptokinase and plasminogen
      (4) Urokinase
         • Derived from human urine
   c. Aminocaproic acid
      • Competitively blocks plasminogen activation, thereby inhibiting fibrinolysis
2. Functions of plasmin
   a. Cleaves insoluble fibrin monomers and fibrinogen into fibrin (ogen) degradation products (FDPs)
      • Fragments of cross-linked insoluble fibrin monomers are called D-dimers.
   b. Degrades factors V and VIII, and fibrinogen
3. α2-Antiplasmin, which is synthesized in the liver, inactivates plasmin.

G. Small vessel hemostasis response to injury (Fig. 15-3A and B)
1. Sequence: vascular, platelet, coagulation, and fibrinolytic phases
2. Vascular phase
   a. Transient vasoconstriction occurs directly after injury.
   b. Factor VII (extrinsic coagulation system) is locally activated by tissue thromboplastin.
   c. Exposed collagen activates factor XII (intrinsic coagulation system).
3. Platelet phase
   a. Platelet adhesion
      (1) Platelet GpIb receptors adhere to exposed vWF in damaged endothelial cells (see Fig. 15-3B).
      (2) Platelet adhesion is defective in von Willebrand disease (no vWF) and Bernard-Soulier disease (absent GpIb receptor for vWF).
   b. Platelet release reaction
      (1) Platelets release ADP from dense bodies.
      (2) ADP produces conformational changes in the GpIIb-IIIa fibrinogen receptor, which makes it functional for the next platelet phase.
Table 15-1 Causes of Increased Bleeding Time

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>NATURE OF DEFECT</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin or NSAIDs</td>
<td>Platelet aggregation defect</td>
<td>Normal platelet count</td>
</tr>
<tr>
<td></td>
<td>Inhibition of platelet COX, which ultimately inhibits synthesis of TXA₂</td>
<td></td>
</tr>
<tr>
<td>Bernard-Soulier</td>
<td>Platelet adhesion defect</td>
<td>Thrombocytopenia, giant platelets</td>
</tr>
<tr>
<td>syndrome</td>
<td>Autosomal recessive disease</td>
<td>Lifelong bleeding problem</td>
</tr>
<tr>
<td></td>
<td>Absent GpIIb-IIIa receptors for vWF</td>
<td></td>
</tr>
<tr>
<td>Glanzmann disease</td>
<td>Platelet aggregation defect</td>
<td>Lifelong bleeding problem</td>
</tr>
<tr>
<td></td>
<td>Autosomal recessive disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absent GpIIb-IIIa fibrinogen receptors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absent thrombosthenin (contractile protein)</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>Platelet aggregation defect</td>
<td>Reversed with dialysis and desmopressin acetate</td>
</tr>
<tr>
<td></td>
<td>Inhibition of platelet phospholipid by toxic products</td>
<td></td>
</tr>
<tr>
<td>Scurvy (see Fig. 8-9B,</td>
<td>Vascular defect</td>
<td>May cause ecchymoses, hemarthroses, perifollicular hemorrhages, bleeding gums</td>
</tr>
<tr>
<td>C, and D)</td>
<td>Caused by vitamin C deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Defective collagen resulting from poor cross-linking of tropocollagen molecules</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Decreased platelet number</td>
<td>Increased bleeding time when the platelet count is &lt;90,000 cells/mm³</td>
</tr>
<tr>
<td>von Willebrand disease</td>
<td>Platelet adhesion defect</td>
<td>Combined platelet and coagulation factor disorder</td>
</tr>
<tr>
<td></td>
<td>Autosomal dominant disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absent or defective vWF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased factor VIII: c</td>
<td></td>
</tr>
</tbody>
</table>

COX, Cyclooxygenase; NSAIDs, nonsteroidal antiinflammatory drugs; TXA₂, thromboxane A₂; vWF, von Willebrand factor.
15-4: Prothrombin time (PT) and partial thromboplastin time (PTT). The PT evaluates in sequential order factors VII, V, II, and I. The PTT evaluates in sequential order factors XII, XI, IX, VIII, X, V, II, and I.

b. vWF antigen assay
   (1) Measures the quantity of vWF that is present in serum regardless of function
   (2) Decreased in classic vWD

I. Coagulation tests (Fig. 15-4)
   1. Prothrombin time (PT)
      a. Evaluates the extrinsic coagulation system down to the formation of the fibrin clot
         • Factors that are evaluated include VII, X, V, II, I (separate test).
      b. Normal reference is 11 to 15 seconds; however, this varies in different laboratories.
         • The time is only prolonged when a factor level is 30% to 40% of normal; hence it is not a very sensitive test.
      c. International normalized ratio (INR)
         (1) INR standardizes the PT for use in monitoring warfarin anticoagulation therapy.
         (2) Results are the same regardless of the reagents used to perform the test.
         (3) Usual range for the international normalized ratio is 2 to 3.
      d. Uses of the PT
         (1) Monitoring persons who are taking warfarin for anticoagulation
         (2) Evaluates liver synthetic function
            • Increased PT indicates severe liver dysfunction (e.g., cirrhosis of the liver, chronic hepatitis).
         (3) Used to detect factor VII deficiency if the PTT is normal
   2. Partial thromboplastin time (PTT)
      a. Evaluates the intrinsic coagulation system down to formation of a fibrin clot
         • Factors that are evaluated include XII, XI, IX, VII, X, V, II, I (separate test).
      b. Normal reference interval is 25 to 40 seconds; however, this varies in different laboratories.
         • Time is only prolonged when a factor level is 30% to 40% of normal.
      c. Uses of the PTT
         (1) Most commonly used to monitor heparin anticoagulation therapy
            (a) Heparin enhances antithrombin III activity.
            (b) PTT is not required to follow low-molecular-weight heparin therapy.
         (2) Used to detect factor deficiencies in the intrinsic coagulation system if the PT is normal

Whether the patient is receiving heparin or warfarin anticoagulation therapy, both the PT and PTT are increased, because both inhibit factors in the final common pathway. Experience has shown that the PT performs better in monitoring warfarin, whereas the PTT performs better in monitoring heparin.

J. Fibrinolytic system tests
   1. Fibrin(ogen) degradation products (FDPs)
      • Detects fragments associated with plasmin degradation of fibrinogen and/or insoluble fibrin in fibrin clots
II. Platelet Disorders

A. Classification of platelet disorders

1. Quantitative platelet disorders
   a. Thrombocytopenia (decreased)
   b. Thrombocytosis (increased)

2. Qualitative (functional) platelet disorders

B. Pathogenesis of platelet disorders

1. Thrombocytopenia (Table 15-2, Figure 15-8)
   a. Definition—decreased number of platelets
   b. Pathogenesis
      (1) Decreased production of platelets
         • Examples—aplastic anemia and leukemia
      (2) Increased destruction of platelets
         (a) Immune destruction
            • Examples—idiopathic thrombocytopenic purpura and drugs
         (b) Nonimmune destruction
            • Examples—thrombotic thrombocytopenic purpura and DIC
      (3) Sequestration in the spleen
         • Example—hypersplenism in portal hypertension

2. Thrombocytosis
   a. Definition—increase in the platelet count
   b. Pathogenesis
      (1) Primary thrombocytosis
         • Examples—essential thrombocythemia and polycythemia vera (refer to Chapter 13)
      (2) Secondary (reactive) thrombocytosis
         • Examples—chronic iron deficiency, infections, splenectomy, and malignancy

3. Qualitative platelet disorders
   a. Definition—platelets do not function properly with or without an alteration in platelet number
   b. Pathogenesis
      (1) Acquired (e.g., aspirin, chronic renal failure)
      (2) Hereditary (e.g., Glanzmann disease, Bernard-Soulier disease)

C. Clinical findings associated with platelet dysfunction (Table 15-3)

1. Epistaxis (nosebleeds) is the most common sign.
   • Kiesselbach area is the most common site for bleeding in epistaxis (Fig. 15-5)

2. Petechiae and multiple small ecchymoses (purpura); most commonly caused by thrombocytopenia
   a. Petechiae are pinpoint areas of hemorrhage in subcutaneous tissue (Fig. 15-6).
   b. Ecchymoses are areas of bleeding that are the size of a quarter.
   c. Other less common causes of petechiae are seen in Rocky Mountain spotted fever (rickettsiae invade endothelial cells in small vessels causing them to rupture), and excessive mechanical compression (e.g., blood pressure cuff is pumped up too high).
**Hemostasis Disorders**

**TABLE 15-2 Disorders Producing Thrombocytopenia**

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute idiopathic thrombocytopenic purpura (ITP)</td>
<td>It is the most common cause of thrombocytopenia in children 2 to 6 years of age. IgG antibodies are directed against the GpIIb-IIIa receptors on platelets (type II hypersensitivity reaction). It has an abrupt onset, 1 to 3 weeks after a viral infection. Patients present with epistaxis, easy bruising, and petechiae. Lymphadenopathy and splenomegaly are not present. Treatment varies with the platelet count. ITP responds well to corticosteroid therapy or intravenous immunoglobulin.</td>
</tr>
<tr>
<td>Chronic idiopathic thrombocytopenic purpura</td>
<td>It is the most common cause of thrombocytopenia in adults. It is most common in women 20 to 40 years of age. IgG antibodies are directed against the GpIIb-IIIa fibrinogen receptors (type II hypersensitivity reaction). It has an insidious onset and presents with epistaxis, easy bruising, and petechiae. Newborn infants of mothers with chronic ITP may have transient thrombocytopenia due to transplacental passage of IgG antibodies. Secondary causes of chronic ITP: SLE, HIV, lymphoproliferative diseases Treatment: It is often resistant to corticosteroid therapy and requires splenectomy. Intravenous γ-globulin temporarily stops serious bleeding (IgG blocks macrophage Fc receptors).</td>
</tr>
<tr>
<td>Neonatal alloimmune thrombocytopenia (NAIT)</td>
<td>NAIT accounts for 20% of cases of thrombocytopenia in neonates. There is a fetomaternal incompatibility for platelet-specific antigens (e.g., PlA1). PlA1 is absent from 2% of the population; therefore, if a PlA1-negative mother is exposed to PlA1-positive platelets during pregnancy or from a previous pregnancy or transfusion, she will develop IgG antibodies against the PlA1 antigen. Transplacental passage of IgG antibodies targets fetal PlA1-positive platelets, leading to macrophage destruction of those platelets (type II hypersensitivity reaction). In the neonate, it may produce petechial hemorrhages in the first few days of life or CNS hemorrhages in severe cases.</td>
</tr>
<tr>
<td>Post-transfusion purpura</td>
<td>This type of purpura primarily occurs in multiparous women, because they are more likely to have been exposed to fetal blood from each of their pregnancies that contained fetal PlA1-positive platelets. If these women with IgG antibodies directed against PlA1 antigen receive a blood transfusion with PlA1-positive platelets, they will develop a severe thrombocytopenia 7 to 10 days after the transfusion. Both the donor platelets and her PlA1-negative platelets will be destroyed.</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia (HIT)</td>
<td>HIT is a common cause of thrombocytopenia in hospitalized patients. The type I variant of HIT is mild and occurs early in the course of heparin therapy. It is non–immune mediated and is self-limited. The type II variant of HIT is uncommon; however, it produces a severe thrombocytopenia and vessel thrombosis 5 to 14 days after heparin therapy. Heparin attaches to PF4 (heparin neutralizing factor) on platelets. Then IgG antibodies attach to the heparin-PF4 complex and produce immune complexes that destroy the platelets. The complexes break free from platelets and damage endothelial cells, leading to activation of the coagulation system and vessel thrombosis. Heparin must be stopped immediately, and thrombin antagonists like the hirudin analogues lepirudin and bivalirudin should be used to prevent thrombosis. Low-molecular-weight heparin should not be used because of cross-reactivity.</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura (TTP)</td>
<td>TTP occurs in females between ages 10 and 50 years. It is an acquired or genetic deficiency in von Willebrand factor–cleaving metalloprotease (ADAMTS13) in endothelial cells. Absence of this enzyme results in an increase in circulating multimers of vWF that promote platelet activation and aggregation. Superimposed on this, there is endothelial injury at arteriole-capillary junctions (? direct effect, production of neoantigens leading to production of autoantibodies) associated with drugs (e.g., cyclosporine, chemotherapy agents, oral contraceptives, ticlopidine, penicillin), the postpartum state, infection (e.g., HIV, Streptococcus pneumoniae sepsis), hypertension, autoimmune disease (e.g., SLE), malignancy (e.g., lymphoid leukemias/lymphomas), radiation, and bone marrow transplantation. Platelets are consumed owing to production of numerous platelet thrombi that develop in the areas of endothelial injury at the arteriole-capillary junctions. Patients with TTP may have a clinical pentad including fever, thrombocytopenia, renal failure, microangiopathic hemolytic anemia with schistocytes (damage by platelet thrombi; see Fig. 15-8), and CNS deficits. One or more of the findings in this pentad may be absent. Recurrence rate is 20%–40% of cases. Treatment: plasma exchange therapy (most responsible for excellent survival rates), corticosteroids; splenectomy in refractory cases. Mortality rate is 10%–20%.</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome (HUS)</td>
<td>HUS primarily occurs in children &lt;10 years old. It may be epidemic, most commonly during the summer months in rural populations. It can be transmitted person-to-person. It is the most common cause of acute renal failure in children. It is most often caused by Escherichia coli serotype O157:H7. Activation of platelets and endothelial damage at the arteriole-capillary junctions may be related to the Shiga-like toxin and defects in complement regulatory proteins. Organisms proliferate in undercooked red meat, unpasteurized milk or milk products, water, fruits, and vegetables. Other causes of HUS in children and adults are drugs (many of them are similar to those listed for TTP), infections (e.g., Shigella, Salmonella, Yersinia, Campylobacter, coxsackievirus, influenza virus), complement disorders (e.g., defects in complement factor H, membrane cofactor protein, or factor I), these are the main causes in nondiarrheal atypical HUS). Clinical findings are similar to TTP; however, CNS findings are less frequent. Bloody diarrhea occurs in 75% of cases. In HUS, there may be a clinical triad including thrombocytopenia, (used up in forming thrombi at the arteriole-capillary junctions), acute renal failure, and microangiopathic hemolytic anemia (see Fig. 15-8). Treatment: blood transfusion for severe anemia. Platelet transfusion only for severe thrombocytopenia. Antibiotics should not be used if HUS is due to E. coli serotype O157:H7. Mortality rate is &lt;5%.</td>
</tr>
</tbody>
</table>

CNS, Central nervous system; DIC, disseminated intravascular coagulation; PF4, platelet factor 4; Rx, treatment; SLE, systemic lupus erythematosus; vWF, von Willebrand factor.
**TABLE 15-3 Clinical Findings in Platelet and Coagulation Disorders**

<table>
<thead>
<tr>
<th></th>
<th>PLATELET DYSFUNCTION</th>
<th>COAGULATION FACTOR DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding from superficial scratches</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Yes (thrombocytopenia)</td>
<td>No</td>
</tr>
<tr>
<td>Late rebleeding</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemarthroses</td>
<td>No</td>
<td>Yes (only very severe factor deficiencies)</td>
</tr>
<tr>
<td>Epistaxis, menorrhagia, gastrointestinal/ genitourinary bleeding, easy bruising</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ecchymoses/purpura</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**15-5:** The Kiesselbach area is the most common site for bleeding in epistaxis. (From Marx J: Rosen’s Emergency Medicine Concepts and Clinical Practice, 7th ed, Philadelphia, Mosby Elsevier, 2010, p 884, Fig. 70-1.)

**15-6:** Petechiae in idiopathic thrombocytopenic purpura showing pinpoint hemorrhages in the skin over the thorax and shoulders. Petechiae are most frequently caused by thrombocytopenia. When compressed, petechiae do not blanch with pressure. (From Forbes C, Jackson W: Color Atlas and Text of Clinical Medicine, 2nd ed, London, Mosby, 2002, Fig. 10-10.)

**15-7:** Senile purpura showing the large, irregular areas of hemorrhage on the backs of both hands. This benign condition primarily occurs in body areas that are frequently traumatized. It is due to the normal vessel instability that is associated with aging. (From Forbes C, Jackson W: Color Atlas and Text of Clinical Medicine, 2nd ed, London, Mosby, 2002, Fig. 10-112.)

**15-8:** Peripheral blood in a patient with thrombotic thrombocytopenic purpura showing schistocytes (fragmented RBCs) and absence of platelets. (From Porwit A, McCullough J, Erber WN: Blood and Bone Marrow Pathology, 2nd ed, London, Churchill Livingstone Elsevier, 2011, p 167, Fig. 10.6.)

**Ecchymoses (purpura)** are caused by a variety of disorders unrelated to thrombocytopenia. Palpable purpura (purpura that can be felt) is a sign of a small vessel vasculitis (refer to Chapter 10). Because vasculitis is a type of acute inflammation, the lesions are palpable due to increased vessel permeability. Ecchymoses are also present in scurvy (vitamin C deficiency) and are due to vessel weakness related to lack of cross-bridges between tropocollagen molecules (refer to Chapter 8). Senile purpura is a normal finding in elderly patients and is due to vessel instability normally associated with aging (Fig. 15-7). Ecchymoses develop in areas of trauma (e.g., back of the hands, shins).
3. Bleeding from superficial scratches
   • No temporary platelet thrombus is present to stop bleeding from injury to small vessels.
4. Other findings in platelet dysfunction
   a. Menorrhagia, hematuria
   b. Bleeding from tooth extraction sites
   c. Easy bruising
   d. Gastrointestinal and intracranial bleeding

III. Coagulation Disorders
A. Classification of coagulation disorders
   1. Acquired coagulation disorders
      • Single or multiple coagulation factor deficiencies may occur.
   2. Hereditary coagulation disorders
      • There is usually a single coagulation factor deficiency.

B. Pathogenesis
   1. Decreased production
      • Examples—hemophilia A and cirrhosis
   2. Pathologic inhibition
      • Example—acquired circulating antibodies (inhibitors) against coagulation factors
   3. Excessive consumption
      • Example—DIC.

C. Clinical findings (see Table 15-3)
   1. Late rebleeding after surgery or wisdom tooth extraction
      a. Lack of thrombin prevents formation of a stable platelet thrombus held together by fibrin.
      b. Temporary platelet thrombi are the only mechanical block preventing bleeding from damaged small vessels.
         • Moving around after surgery or rinsing the mouth out with water after a wisdom tooth extraction dislodges the temporary platelet thrombi (held together by fibrinogen), leading to late rebleeding.
   2. Findings in severe coagulation factor deficiencies
      a. Hemarthroses
      b. Retroperitoneal and deep muscular bleeding
   3. Clinical findings in coagulation factor deficiency that also occur in qualitative platelet disorders or thrombocytopenia
      a. Ecchymoses, epistaxis
      b. Menorrhagia, hematuria
      c. Bleeding from tooth extraction sites
      d. Easy bruising
      e. Gastrointestinal and intracranial bleeding

D. Hemophilia A
   1. Epidemiology and pathogenesis
      a. X-linked recessive (refer to Chapter 6)
         (1) Females are asymptomatic carriers.
         (2) Females transmit the abnormal X chromosome to 50% of their sons.
         (3) Affected males have a deficiency of factor VIII:c, a coagulation factor in the intrinsic coagulation system.
            • Deficiency of VIII:c also decreases activation of factor X by activated factor VII, because it is part of the factor VIII, IXa, PF3, calcium complex.
      b. If there is no family history of hemophilia and a person in that family has hemophilia, it is most likely due to a new mutation (30% of cases).
      c. In rare cases, female carriers may have symptomatic disease.
         (1) Disease in affected females is due to inactivation of more normal X chromosomes than X chromosomes with the mutation.
         (2) Females become "homozygous" for the abnormal X chromosome.
   2. Clinical findings
      a. Signs and symptoms correlate with the level of factor VIII:c activity.
         (1) Mild disease occurs when factor VIII:c activity is 5% to 25% of normal.
         (2) Moderate disease occurs when factor VIII:c activity is 1% to 4% of normal.
         (3) Severe disease occurs when factor VIII:c activity is <1% of normal.
      b. Bleeding problems may occur in newborns (10% to 15% of cases).
         • Excessive bleeding may occur in male newborns after circumcision or umbilical cord separation.
### Hemophilia B

Hemophilia B (Christmas disease) is an X-linked recessive disorder involving a deficiency of factor IX. It is clinically indistinguishable from hemophilia A.

- Laboratorv findings
  1. PTT is increased.
  2. Factor VIII:c activity is decreased.
  3. Detection of female carriers is best accomplished with DNA technology.

#### 3. Treatment

- Mild cases of hemophilia A respond to desmopressin acetate.
  - VWF released from Weibel-Palade bodies stabilizes circulating VIII:c (circulates as multimeric complexes) so that it does not degrade.
- Severe cases require infusion of recombinant factor VIII.
  - No risk for contracting HIV infection from this infusion.

### E. Classic von Willebrand disease (vWD)

#### 1. Epidemiology

- Autosomal dominant (AD) disorder
- Most common hereditary bleeding disorder
  - Prevalence is 1/100 people.
- Several subtypes of vWD
  - Type I (80%; only one discussed), type IIA, type IIB, and type III vWD
- Associations
  1. Angiodysplasia (refer to Chapter 18)
    - Persons who have angiodysplasia are more likely to bleed if they have vWD.
  2. Severe aortic valve (AV) stenosis (refer to Chapter 11) may produce acquired vWD.
    - Large circulating multimeric complexes of vWF complexed with VIII:c are destroyed by the high shear stress in severe AV stenosis, which decreases both VWF and VIII:c.
    - AV replacement corrects the problem.

#### 2. Clinical findings

- Menorrhagia
- Easy bruising
- Mucosal bleeding
  - Gingival bleeding, epistaxis, gastrointestinal bleeding
- Postpartum bleeding, bleeding after surgery or dental extraction

#### 3. Laboratory findings are variable (may require repeat testing)

- Increased PTT is only present in 25% to 50% of cases; therefore a normal PTT does not exclude the diagnosis.
- Increased BT is only present in 50% of cases; therefore a normal BT does not exclude the diagnosis.
- Ristocetin cofactor activity assay, vWF antigen, and factor VIII:c activity tests have variable findings.
- Gene analysis is available to secure the diagnosis.

#### 4. Treatment

- Mainstay of treatment is to replace the deficient protein at the time of spontaneous bleeding or before invasive procedures are performed.
- Desmopressin acetate increases the release of vWF from Weibel-Palade bodies, which in turn stabilizes circulating VIII:c by preventing its degradation.
  - Oral contraceptives (OCPs) have a similar activity as desmopressin acetate.
- In severe cases, infusion of cryoprecipitate is recommended (refer to Chapter 16).
- Factor VIII concentrate that is rich in vWF (Humate-P) is also recommended in severe cases.

### F. Circulating anticoagulants (inhibitors)

#### 1. Pathogenesis

- Coagulation factor or factors are destroyed by antibodies.
- Most common antibody is directed against factor VIII:c.
  - Most often occurs postpartum or in hemophiliacs receiving recombinant factor VIII

#### 2. Clinical findings

- Similar to those with coagulation factor deficiencies due to decreased production
Hemostasis Disorders

3. Laboratory findings
   a. Increased PT and/or increased PTT, depending on the factor deficiency
      • These tests do not differentiate immune destruction from decreased production of the
        coagulation factor deficiency.
   b. Mixing studies differentiate decreased production from increased destruction of a
      coagulation factor.
      (1) Normal plasma is mixed with patient plasma in a test tube.
      (2) No correction of PT and/or the PTT indicates immune destruction.
      • Antibody is also destroying the coagulation factor in the normal plasma.
      (3) Correction of the PT and/or PTT indicates decreased production.

G. Vitamin K deficiency (refer to Chapter 8)

H. Hemostasis disorders in cirrhosis

1. Pathogenesis
   a. Decreased synthesis of coagulation factors
      (1) Multiple coagulation factor deficiencies
      (2) Decreased γ-carboxylation of vitamin K–dependent coagulation factors
   b. Decreased synthesis of anticoagulants such as antithrombin III, and proteins
      C and S
   c. Decreased synthesis of fibrinolytic agents (e.g., plasminogen)
   d. Decreased clearance of fibrinogen/fibrin degradation products and D-dimers
      • Interferes with platelet aggregation and polymerization of fibrin
   e. Decreased clearance of tPA and decreased synthesis of α2-antiplasmin
      • May produce primary fibrinolysis (see section IV)

2. Laboratory findings
   a. Increased PT and PTT
   b. Increased fibrinogen/fibrin degradation products and D-dimers
   c. Increased BT

I. Disseminated intravascular coagulation (DIC)

1. Overview
   a. Definition—thrombohemorrhagic disorder
   b. Fibrin thrombi occlude the microcirculation throughout the body, producing ischemic
      damage.
      • Fibrin thrombi in the microcirculation are primarily composed of RBCs, with trapped
        leukocytes and platelets (refer to Chapter 5).
   c. Bleeding occurs from the gastrointestinal tract, nose (epistaxis), and every puncture site,
      producing anemia.

2. Etiology and pathogenesis
   a. Activation of the intrinsic and/or extrinsic coagulation system
      (1) Activation of the extrinsic system occurs by the release of tissue thromboplastin from
          damaged tissue; examples include:
          (a) Massive trauma (car accident; extensive surgery)
          (b) Hypovolemic or cardiogenic shock (refer to Chapter 5)
          (c) Malignancies (acute promyelocytic leukemia, adenocarcinomas [pancreas,
              prostate, lung, breast])
          (d) Obstetrical problems (amniotic fluid embolism, abruptio placenta, toxemia of
              pregnancy, dead retained fetus)
          (e) Acute pancreatitis, rattlesnake envenomation, acute respiratory distress
              syndrome
      (2) Activation of the intrinsic system is by activation of factor XII by surface
          contact with collagen secondary to injury to endothelial cells; examples include:
          (a) Gram-negative sepsis with release of endotoxins (most common cause
              of DIC >50% of cases; refer to Chapter 5)
          (b) Deposition of immunocomplexes (e.g., systemic lupus erythematosus
              [SLE])
          (c) Severe temperature alterations (heatstroke, third-degree burns)
   b. With activation of either the intrinsic or extrinsic coagulation system, fibrin thrombi
      develop in the microcirculation; fibrin thrombi:
      (1) Obstruct blood flow, causing ischemia and the potential for infarction (e.g.,
          hemorrhagic infarction of the adrenal glands in Waterhouse-Friderichsen syndrome
          in Neisseria meningitidis sepsis; Chapter 23)
      (2) Consume coagulation factors (I, II, V, VIII) causing bleeding problems

Cirulating anticoagulant: PT and/or PTT not corrected with mixing study

Cirrhosis: multiple hemostasis abnormalities; some bleeding problems, others thrombosis problems

Cirrhotic: ↑PT, PTT, BT, FDPs, and D-dimers

DIC: thrombohemorrhagic disorder (produce fibrin thrombi and bleeding)

Fibrin thrombi contain RBCs with trapped WBCs/platelets

DIC: activation intrinsic/extrinsic system with release tissue thromboplastin

Gram-negative sepsis: MCC DIC
(3) Trap platelets, causing thrombocytopenia, which also contributes to bleeding
   • Petechiae and ecchymoses develop on the skin and mucous membranes.
(4) Damage circulating RBCs, producing microangiopathic hemolytic anemia (MHA) with schistocytes (refer to Chapter 12)
c. Activation of the fibrinolytic system (secondary fibrinolysis) due to activation of plasminogen by factor XII
   • FDPs interfere with platelet aggregation, which also contributes to bleeding.

3. Laboratory findings
   a. Coagulation abnormalities
      (1) Increases PT and PTT
      (2) Decreases serum fibrinogen
   b. Platelet abnormalities
      (1) Thrombocytopenia
      (2) Increased BT
   c. Fibrinolysis abnormalities
      • Presence of FDPs and d-dimers
   d. Normocytic anemia due to:
      (1) Extensive bleeding from the skin and gastrointestinal tract
      (2) Mechanical damage to RBCs by fibrin thrombi causing a microangiopathic hemolytic anemia with schistocytes

4. Treatment
   a. Most important treatment is to correct the underlying cause of DIC!
   b. Blood components used in treating DIC include:
      (1) Fresh frozen plasma to correct the multiple coagulation factor deficiencies
      (2) Packed RBCs to correct the anemia
      (3) Platelet concentrates to correct the thrombocytopenia and platelet dysfunction
      (4) Cryoprecipitate to correct fibrinogen deficiency (if warranted)
   c. Low-dose heparin is given in selected cases (e.g., acute promyelocytic leukemia).

IV. Fibrinolytic Disorders
   A. Primary fibrinolysis
      1. Causes
         a. Open heart surgery
            • Cardiopulmonary bypass causes a decrease in α2-antiplasmin and an increase in tissue plasminogen activator.
         b. Radical prostatectomy
            • Surgery causes increased release of urokinase, which activates plasminogen.
         c. Cirrhosis
            • Decrease in the synthesis of α2-antiplasmin

      2. Pathogenesis of bleeding problems
         a. FDPs interfere with platelet aggregation.
         b. Plasmin degrades coagulation factors, causing multiple factor deficiencies.

      3. Clinical findings
         • Severe bleeding

      4. Laboratory findings
         a. Increased PT and PTT due to multiple coagulation factor deficiencies
         b. Increased BT due to interference with platelet aggregation
         c. Positive test for FDPs
         d. Negative d-dimer assay, because no fibrin thrombi are present
         e. Normal platelet count

      5. Treatment
         • Aminocaproic acid competitively blocks plasminogen activation, thereby inhibiting fibrinolysis.

   B. Secondary fibrinolysis
      1. Definition—compensatory reaction in the presence of DIC
      2. Increase in both FDPs and d-dimers
         • In primary fibrinolysis, D-dimers are not present
      3. Platelets decreased (trapped in fibrin clots)
         • In primary fibrinolysis, platelets are not decreased.

V. Summary of Laboratory Test Results in Hemostasis Disorders (Table 15-4)

VI. Thrombosis Syndromes
   A. Acquired thrombosis syndromes
      1. Antiphospholipid syndrome (APLS)
a. Epidemiology
(1) APLS is commonly associated with SLE.
(2) Other disease associations include rheumatoid arthritis, Sjögren syndrome, idiopathic thrombocytopenic purpura, and HIV infection.
(3) Most persons are young to middle-aged adults.
(4) Both venous (most common) and arterial thrombi may occur.

b. Pathogenesis
(1) Presence of antiphospholipid antibodies (APAs). Antibodies are directed against phospholipids bound to plasma proteins
(2) APAs include:
   • Anticardiolipin antibody (ACA)
   • Also reacts with the cardiolipin reagent in the rapid plasma reagin test for syphilis, causing a false positive syphilis serology
   (b) Lupus anticoagulant (LA)
   (c) Anti–β2-glycoprotein 1 antibody
(3) Produce arterial and venous thrombosis syndromes
   (a) Venous thrombi are more common than arterial thrombi.
   (b) Mechanism by which APAs produce vessel thrombosis is not fully understood
   (c) Possible mechanisms include resistance to protein C, impaired fibrinolysis, and endothelial cell injury with activation of platelets.

c. Clinical findings
(1) Venous thrombosis; vessels commonly involved include:
   (a) Deep veins in the calf (most common site)
   (b) Renal, hepatic, axillary, subclavian, and retinal veins; venae cavae; and the placental bed (recurrent spontaneous abortions)
(2) Arterial thrombosis sites include:
   (a) Cerebral vessels (most common site; produces strokes)
   (b) Coronary, renal, mesenteric, and bypass arteries

d. Laboratory findings
(1) False positive syphilis serologic test
   (a) Occurs if ACAs are present
   (b) ACAs react with beef cardiolipin in the test system for RPR (Rapid Plasma Reagin) and VDRL (Venereal Disease Research Laboratory); however, the FTA-ABS test (Fluorescent Treponema Antibody-absorption test) is negative.
(2) LA
   • Increased PTT that does not correct with mixing studies (see previous discussion)
(3) ACAs
   • Most sensitive and specific test (positive in >80% of cases)
(4) Anti–β2-glycoprotein 1 antibodies

e. Treatment
(1) Treatment depends on the clinical presentation.
(2) In general, initiate anticoagulation with heparin and keep on lifelong warfarin treatment.

2. Other acquired causes of thrombosis (also refer to Chapter 5)
a. Postoperative state with stasis of blood flow
b. Malignancy
(1) Increased synthesis of coagulation factors
(2) Thrombocytosis
(3) Release of procoagulants from tumors, particularly pancreatic cancers
c. Folic acid or vitamin B₁₂ deficiency
   • Increased plasma homocysteine levels, increase the risk for thrombosis.

d. OCPs
   • Estrogen increases the synthesis of coagulation factors and decreases the concentration of antithrombin III.

e. Hyperviscosity syndromes (refer to Chapter 13)
   (1) Polycythemia
   (2) Waldenström macroglobulinemia

B. Hereditary thrombosis syndromes

1. Epidemiology
   a. Autosomal dominant syndromes
   b. Deep venous thrombosis (DVT) and pulmonary emboli (PE) commonly occur at an early age.
   c. Venous thromboses often occur in unusual places.
      • Examples—hepatic vein and dural sinus

2. Factor V Leiden
   a. Most common hereditary thrombosis syndrome
      • Occurs in 2% to 8% of the white population
   b. Mutant form of factor V that cannot be degraded by activated protein C
   c. Heterozygotes for the disease have increased risk for thrombosis by a factor of 5 to 10, whereas the risk for thrombosis in homozygotes is increased by a factor of 50 to 100.
   d. Treatment for acute venous thrombosis or pulmonary embolism
      • Begin heparin and warfarin. Discontinue heparin after 5 days and continue warfarin for at least 6 months.

3. Antithrombin III (ATIII) deficiency
   a. ATIII activity is normally enhanced by heparin and heparin-like molecules.
   b. It normally neutralizes activated serine proteases, which include:
      • Factors II, VII, IX, X, XI, and XII
   c. Therefore, when ATIII is deficient, the above factors are not neutralized and the person is thrombogenic.
   d. In ATIII deficiency, there is no increase in PTT after injecting a standard dose of heparin.
   e. Treatment is similar to that described for factor V Leiden.

4. Proteins C and S deficiency
   a. Pathogenesis
      • Activated factors V and VIII cannot be inhibited.
   b. Treatment
      (1) Begin with heparin and a very low dose of warfarin to reduce the risk for developing hemorrhagic skin necrosis.
      (2) Send the patient home on warfarin.

Hemorrhagic skin necrosis: associated with warfarin therapy in protein C or S deficiency

There is a potential for heterozygote carriers of protein C deficiency to develop hemorrhagic skin necrosis when placed on warfarin. Heterozygote carriers have ~50% protein C activity. Protein C has a short half-life (~6 hours). When these patients are placed on warfarin, protein C activity falls to zero in 6 hours, causing a hypercoagulable state due to increased activity of factors V and VIII. This causes cutaneous vessel thrombosis and concomitant skin necrosis. This complication is not likely to occur in normal people.
I. ABO Blood Group Antigens
   A. Definition of ABO blood group antigens
      • Glycoproteins attached to the red blood cell (RBC) surface as well as other tissues throughout the body
   B. Blood group O characteristics
      1. Most common blood group
         • No blood group antigens (A or B) are present on the RBC membrane.
      2. Natural antibodies (isoagglutinins) in serum
         a. All O individuals have anti-A IgM and anti-B IgM natural antibodies.
         b. Most O individuals have anti-A and anti-B IgG antibodies for unknown reasons.

Blood group antibodies are natural antibodies that are synthesized in Peyer patches after birth. A and B antigens that are normally present in food are trapped by M cells, which are specialized epithelial cells that overlie Peyer patches. M cells transport the A and/or B antigens to lymphocytes in Peyer patches, resulting in the development of natural antibodies against the antigens. Natural antibodies develop against antigens that are not present on the RBC, which explains why blood group O persons have antibodies against both A and B antigens.

3. Increased incidence of duodenal ulcers
   • May relate to the absence of A or B antigens on the mucosal cells, which have a protective effect on preventing acid injury.

C. Blood group A characteristics
   1. Anti-B IgM natural antibodies
   2. Increased incidence of gastric carcinoma for unknown reasons

D. Blood group B characteristics
   • Anti-A IgM natural antibodies

E. Blood group AB characteristics
   1. Least common ABO blood group
   2. No natural antibodies

F. Newborns
   1. Do not have natural antibodies at birth
   2. Begin to develop these antibodies 3 to 6 months after birth

G. Elderly individuals
   • Frequently lose their natural antibodies

Elderly individuals may not have a hemolytic transfusion reaction if they are transfused with the wrong blood group, because they frequently lose their natural antibodies. This does not mean that elderly individuals can safely receive blood from any blood group.

H. Paternity issues in newborns
   1. Blood group AB parents cannot have an O child.
   2. Blood group O parents cannot have an AB, A, or B child.
Rh: D antigen

16-1: Possible phenotypes of children if the father is BO and the mother is AO. AB parents cannot have an blood group O child. O parents cannot have an A, B, or AB child. (Adapted from Goljan EF: Star Series: Pathology, Philadelphia, Saunders, 1998.)

- B O Father
- A AB AO
- O BO OO

16-2: Forward and back type to identify ABO blood groups. Forward type identifies the blood group antigen by reacting test anti-A and anti-B antibodies against patient RBCs. Back type identifies the natural antibodies in the patient serum by reacting test blood group A RBCs and B RBCs against the patient serum. Refer to the text for discussion of the blood groups and their natural antibodies.

16-3: Possible Rh phenotypes in children if the father is cde/CDE and the mother is cDE/CDE. (Adapted from Goljan EF: Star Series: Pathology, Philadelphia, Saunders, 1998.)

**Table:**

<table>
<thead>
<tr>
<th>Blood group</th>
<th>Forward Type</th>
<th>Back Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>A</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>AB</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

- Blood group AB parents: cannot have O child
- Blood group O parents: cannot have AB, A, or B child

**Blood group Anti-A Anti-B**

- A RBCs B RBCs
- O – – + +
- A – – + +
- B – – + –
- AB + + – –

**Forward typing:** identifies blood group antigen

**Back typing:** identifies natural antibodies

**I. Determining an individual’s ABO group (Fig. 16-2)**

1. Forward type
   - a. Identifies an individual’s blood group antigen
     - An individual’s RBCs are added to test tubes that contain either anti-A or anti-B test serum.
   - b. If an agglutination reaction occurs with anti-A test serum but not anti-B test serum, the individual is blood group A.
   - c. If an agglutination reaction occurs with anti-B test serum but not anti-A test serum, the individual is blood group B.
   - d. If an agglutination reaction occurs with both anti-A test serum and anti-B test serum, the individual is blood group AB.
   - e. If an agglutination reaction does not occur with either anti-A test serum or anti-B test serum, the individual is blood group O.

2. Back type
   - a. Identifies natural antibodies
     - An individual’s serum is added to test tubes containing either A or B test RBCs.
   - b. If serum agglutinates B test RBCs but not A test RBCs, the individual is blood group A, who normally have anti-B IgM natural antibodies.
   - c. If serum agglutinates A test RBCs but not B test RBCs, the individual is blood group B, who normally have anti-A IgM natural antibodies.
   - d. If serum does not agglutinate either A test RBCs or B test RBCs, the individual is blood group AB, who do not have natural antibodies.
   - e. If serum agglutinates both A test RBCs and B test RBCs, the individual is blood group O, who normally have anti-A IgM and anti-B IgM natural antibodies.

**II. Rh and Non-Rh Antigen Systems**

**A. Rh antigen system**

1. It has three adjoining gene loci coding for:
   - a. D antigen (no d antigen)
   - b. C and c antigen
   - c. E and e antigen

2. It has an autosomal codominant inheritance pattern.
   - a. One of the sets of three Rh antigens from each parent is transmitted to each child.

**Rh antigen system: autosomal codominant inheritance**

- Absence of D antigen on a chromosome is designated d even though the antigen does not exist.

- b. Possible Rh antigen profiles include:
  - (1) DD, Dd, or dd
  - (2) CC, Cc, or cc
  - (3) EE, Ee, or ee

3. An individual who is Rh positive is D antigen positive.
   - a. Approximately 85% of the population has D antigen.
   - b. Individual lacking D antigen is considered Rh negative.
4. Testing for an individuals Rh phenotype
   a. RBCs are reacted with test antisera against each of the Rh antigens.
   b. Example—Rh phenotype that is positive for C, c, D, and E antigens but negative for e antigen (phenotype is CcDE)

B. Alloimmunization
   1. Definition—production of an antibody against a foreign antigen that is not present on a individual's RBCs
      a. For example, an individual may be exposed to an Rh antigen they are lacking (e.g., D antigen).
      b. For example, an individual may be exposed to non-Rh antigens they are lacking (e.g., Kell antigen).
   2. Antibodies that develop against foreign antigens are called atypical antibodies.
      • An individual is considered sensitized if atypical antibodies are present in their serum.
   3. Clinical significance of atypical antibodies
      a. May produce a life-threatening hemolytic transfusion reaction (HTR) during or shortly after a blood transfusion
         (1) HTRs occur when blood containing a foreign RBC antigen is infused into an individual that has been previously sensitized against that antigen.
         (2) Example—an individual with anti-Kell antibodies is exposed to Kell antigen positive RBCs in a blood transfusion
      b. Transfusion requirements in an individual with single or multiple atypical antibodies
         (1) Individual must receive blood that is negative for all of the foreign RBC antigens
         (2) Example—an individual with anti-Kell antibodies must receive blood that is negative for Kell RBC antigen

C. Clinically important non-Rh antigens
   1. Duffy (Fy) antigens
      a. Fy antigens are the binding site for infestation of RBCs by Plasmodium vivax.
      b. Majority of the black population lack the Fy antigen
         • Offers protection from contracting P. vivax malaria
   2. I and i antigen systems
      a. IgM antibodies (cold agglutinins) from an infection may develop against I or i antigens, which are natural antigens on the surface of RBCs.
         • When these antibodies react against the I or i antigens on the RBCs, they produce a cold immune hemolytic anemia (IHA) with intravascular hemolysis.
      b. Two infections that may induce production of these antibodies are infectious mononucleosis (may produce anti-i IgM antibodies) and Mycoplasma pneumoniae pneumonia (anti-I IgM antibodies; cold agglutinins).

III. Blood Transfusion Therapy
A. Blood donors
   1. Autologous transfusion
      a. Definition—process of collection, storage, and reinfusion of a persons own blood
      b. Safest form of blood transfusion
   2. Tests performed in blood banks on donor blood
      a. Group (ABO) and type (Rh)
      b. Antibody screen (indirect Coombs test)
         • Detects atypical RBC antibodies that may be present in the serum (e.g., anti-D, anti-Kell)
      c. Screening tests for infectious disease
         • Screening tests available for syphilis, hepatitis B and C, HIV-1 and HIV-2, West Nile virus, and human T-lymphotropic virus type 1 (HTLV-1), to name a few

There is a risk for transmitting infection when transfusing blood, because there is an incubation period before specific antibodies are developed against the pathogen. The risk for developing an infection per unit of blood in the post–nucleic acid testing era has markedly reduced the risk for transmission of hepatitis B, hepatitis C, and HIV. The most common infectious agent transmitted by blood transfusion is cytomegalovirus (CMV), which is present in donor lymphocytes. When newborns receive transfusions, the blood must be irradiated to destroy lymphocytes that may be carrying cytomegalovirus. Because a newborn's cellular immunity is not fully developed, a cytomegalovirus infection would likely be disseminated.
B. Patient crossmatch for a blood transfusion

1. Components of a standard crossmatch for blood
   a. ABO group and Rh type
   b. Antibody screen (ABS) to detect atypical RBC antibodies
   c. Direct Coombs test to identify atypical IgG antibodies on the patient's RBCs
   d. Major crossmatch

2. Major crossmatch
   a. Purpose—detects atypical antibodies in the patient receiving the blood that are directed against foreign antigens on donor RBCs
   b. Patient serum is mixed with a sample of RBCs from a donor unit.
      (1) Each unit of donor blood must have a separate crossmatch.
      (2) Lack of RBC agglutination or hemolysis indicates a compatible crossmatch (i.e., there are no atypical antibodies in the patient directed against donor RBCs).

   If a patient has a negative ABS for atypical RBC antibodies, the major crossmatch should be compatible. However, a compatible crossmatch does not guarantee that the recipient will not develop atypical antibodies, a transfusion reaction, or an infection.

3. Use of packed RBCs of blood group O for transfusion
   a. Blood group O packed RBCs (refer to Table 16-1) can be transfused into any patient, regardless of the blood group.
      (1) Blood group O RBCs lack A and B antigens; therefore blood recipients with anti-A IgM and/or anti-B IgM natural antibodies cannot destroy O RBCs.
      (2) Blood group O individuals are considered universal donors.
      (3) However, as a general rule group A, B, and AB patients who require a transfusion should receive blood that matches their blood group.

4. Blood group AB patients can be transfused with blood from any blood group.
   a. Blood group AB patients lack natural antibodies.
   b. Blood group AB individuals are considered universal recipients.
   c. However, as a general rule, AB patients who require a transfusion should receive AB blood, if it is available.

Before blood is transfused into newborns or patients with T-cell deficiencies, it must be irradiated to kill donor lymphocytes. This prevents the patient from developing a graft-versus-host reaction (refer to Chapter 4) or a disseminated cytomegalovirus infection.

C. Blood component therapy (Table 16-1)

D. Blood transfusion reactions

1. Allergic transfusion reactions
   a. Definition—type I IgE-mediated hypersensitivity reaction (HSR) against proteins (allergens) that are present in the donor blood
   b. Pathophysiology
      (1) Since the patient has been previously sensitized to an allergen that is present in donor blood, IgE antibodies are already present on the patient's mast cells (refer to Chapter 4).
      (2) Exposure to the allergen from the donor blood leads to cross-linking of IgE antibodies specific for the allergen on the mast cell membranes.
      (3) IgE triggering causes an early phase reaction that is characterized by mast cell release of preformed mediators.
         • Preformed chemicals include histamine, eosinophil chemotactic factor, and serotonin.
   c. Most common transfusion reaction
   d. Clinical findings
      (1) Urticaria with pruritus
      (2) Fever, tachycardia, wheezing
      (3) Potential for anaphylactic shock
Immunohematology Disorders

**TABLE 16-1 Blood Components**

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed RBCs</td>
<td>Purpose: increase O₂ transport to tissues. Packed RBCs have less volume and a higher Hct than whole blood. Each unit of packed RBCs should raise the Hb by 1 g/dL and the Hct by 3%. Lack of an increment implies a hemolytic transfusion reaction or continued blood loss in the patient. Yersinia enterocolitica, a pathogen that thrives on iron, is the most common contaminant of stored blood.</td>
</tr>
<tr>
<td>Platelets</td>
<td>Purpose: stop medically significant bleeding related to thrombocytopenia or qualitative platelet defects (e.g., aspirin). Platelets have HLA antigens and ABO antigens on their surface; however, they lack Rh antigens. Each unit of platelets should raise the platelet count by 5000–10,000 cells/mm³.</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>Purpose: treatment of multiple coagulation deficiencies (e.g., DIC, cirrhosis) or treatment of warfarin over-anticoagulation if bleeding is life-threatening. It contains previously γ-carboxylated vitamin K–dependent factors as well as all the other coagulation factors.</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Purpose: treatment of coagulation factor deficiencies involving fibrinogen or factor VIII (e.g., DIC). Cryoprecipitate contains fibrinogen, factor VIII, and factor XIII. Desmopressin acetate is used instead of cryoprecipitate in treating mild hemophilia A and von Willebrand disease.</td>
</tr>
</tbody>
</table>

*DIC,* Disseminated intravascular coagulation; *Hb,* hemoglobin; *Hct,* hematocrit.

3. Acute hemolytic transfusion reaction (HTR)
   a. Intravascular acute HTRs
      (1) Most frequently due to ABO blood group incompatibility.
      (2) Example—a group B person receives group A donor blood.
         (a) In this case, anti-A IgM in the recipient attaches to A positive donor RBCs, producing intravascular hemolysis.
         (b) This is a type II HSR.
   b. Extravascular acute HTRs
      (1) These are most frequently due to an atypical IgG antibody in the recipient’s blood that is reacting against a foreign antigen on donor RBCs.
         (a) This type of reaction rarely occurs, because the recipient has had an antibody screen and major crossmatch with the donor unit, which should have detected the atypical IgG antibody.
         (b) In this reaction, splenic macrophages phagocytose and destroy donor RBCs coated by the atypical IgG antibody (type II HSR).
      (2) Jaundice commonly occurs.
         • Recall that unconjugated bilirubin (UCB) is the end product of macrophage degradation of Hb.

**Anti-HLA antibodies** develop when individuals are exposed to foreign HLA antigens (e.g., leukocytes from a previous blood transfusion or organ transplant). Women commonly have these reactions owing to pregnancy, where there is an increased risk for exposure to fetal blood leukocytes during delivery or after a spontaneous abortion. Recall that there are no HLA antigens on RBCs.

**Febrile transfusion reaction** (type II HSR)

**Anti-HLA antibodies:** previous exposure to HLA antigens (blood transfusion, transplant)

**Intravascular HTR:** transfusion of ABO incompatible blood; e.g., group A person receives group B blood; type II HSR

**Extravascular HTR:** recipient atypical IgG antibody reacts against foreign antigen on donor RBCs; macrophage removal; type II HSR
Individuals who have been infused with blood in the past may have been exposed to a foreign blood group antigen and developed atypical antibodies that are no longer circulating. In this case, the pretransfusion antibody screen is negative. However, memory B cells are present and reexposure to the foreign antigen causes them to produce antibodies, resulting in an extravascular hemolytic anemia. This reaction may occur within hours or as long as 3 to 10 days after the transfusion.

c. Clinical findings
   (1) Fever
   (2) Back pain
   (3) Hypotension

d. Potential complications include:
   (1) Disseminated intravascular coagulation (DIC)
   (2) Acute renal failure (ARF)

e. Laboratory findings
   (1) Positive direct Coombs test on the recipient’s RBCs (refer to Chapter 12)
      (a) IgG antibody and/or C3b is coating the donor RBCs.
      (b) Present in either intravascular or extravascular hemolysis
   (2) Positive indirect Coombs test of the recipient’s serum (refer to Chapter 12)
      (a) Detects the atypical antibody in the recipient’s serum
      (b) Present in either intravascular or extravascular hemolysis
   (3) No significant increase in Hb over pretransfusion levels
      • Present in either intravascular or extravascular hemolysis
   (4) Hemoglobinuria
      • Mainly present in intravascular hemolysis (refer to Chapter 12).
   (5) Jaundice
      • Mainly present in extravascular hemolysis (refer to Chapter 12)

4. Actions that should be taken with suspected transfusion reactions
   a. Immediately stop the blood transfusion.
   b. Keep the intravenous line in place.
      • Keep the intravenous line open with normal saline.
   c. Send the unit of blood STAT to the blood bank.
   d. A transfusion reaction workup is performed to identify the type of transfusion reaction.

IV. Hemolytic Disease of the Newborn (HDN)
   A. Definition
      • HDN results from the transplacental passage of maternal IgG antibodies (e.g., anti-D antibodies, anti-A and anti-B IgG antibodies in group O mothers) resulting in an extravascular hemolytic anemia with unconjugated hyperbilirubinemia in the newborn.

   B. ABO HDN (Fig. 16-4A)
      1. Epidemiology
         a. Most common HDN
            • Present in 20% to 25% of all pregnancies; however, only 10% of the neonates develop hemolytic anemia requiring treatment.
         b. Mothers are usually blood group O and the fetus is either blood group A or B.

      2. Pathogenesis
         a. Most blood group O individuals have anti-A and anti-B IgG antibodies.
            (1) IgG antibodies cross the placenta and attach to fetal A or B RBCs.
               (a) IgG antibodies also attach to A and B antigens in other tissues; therefore fewer antibodies attach to fetal A or B RBCs, which reduces the risk for hemolysis.
               (b) Because fetal expression of A and B antigen is poor, there are fewer attachment sites for the IgG antibody, which also reduces the risk for hemolysis.
            (2) Fetal splenic macrophages phagocytose antibody-coated RBCs, causing a mild anemia or no anemia.
            (3) UCB is the end product of extravascular hemolysis by the splenic macrophages; however, it is readily metabolized by the placenta.
         b. ABO HDN may affect the firstborn or any future pregnancy where ABO incompatibility exists.
            • No protection against developing ABO hemolytic disease
3. Clinical and laboratory findings
   a. Jaundice is not present at birth; however, mild jaundice develops within the first 24 hours after birth.
      (1) ABO HDN is the most common cause of jaundice in this period of time.
         • Newborn liver cannot handle the excess bilirubin load, because of low levels of glucuronosyltransferase, which is required for conversion of unconjugated to conjugated (water soluble) bilirubin.
      (2) Risk for developing severe hemolytic anemia requiring exchange transfusion and risk for developing bilirubin encephalopathy (kernicterus) is very small when compared to Rh HDN.
   b. The neonate liver and/or spleen may be slightly enlarged or not enlarged at all, depending on the degree of RBC hemolysis requiring RBC production in other sites (accelerated erythropoiesis; refer to Chapter 12).
   c. Anemia
      (1) Mild normocytic anemia or no anemia at all in most cases
         • If hemolysis is severe, Hb may be as low as 10 to 12 g/dL.
      (2) Reticulocytes may be increased depending upon the severity of the anemia.
   d. Weakly positive direct Coombs test on fetal cord blood RBCs
      • Positive test is due to the presence of anti-A or anti-B IgG antibodies coating fetal A or B RBCs.
   e. Spherocytes are present in the cord blood peripheral smear.
      • Due to fetal splenic macrophage removal of a portion of the RBC membrane in RBCs that are not completely phagocytosed
4. Treatment
   a. Jaundice is treated with phototherapy (discussed later).
   b. Exchange transfusion is sometimes indicated.

C. Rh HDN
1. Epidemiology
   • Preventive measures in Rh-negative women have greatly reduced the incidence of Rh HDN due to anti-D antibodies.
2. Pathogenesis
   a. Mother is Rh (D antigen) negative and the fetus is Rh positive
   b. Exposure of the Rh-negative mother to Rh-positive fetal RBCs occurs as a result of asymptomatic fetomaternal hemorrhage, usually at the time of delivery, or less commonly, during the third trimester when the cytotrophoblast in the placenta is absent.

16-4: ABO hemolytic disease of the newborn. Mother is blood group O and the baby is blood group A or B. Anti-A and anti-B IgG cross the placenta, attach to fetal blood group A or B RBCs, and sensitized RBCs are phagocytosed and destroyed by splenic macrophages, producing anemia and unconjugated hyperbilirubinemia. B, Rh hemolytic disease of the newborn. The mother is Rh negative and the baby Rh positive. Anti-D IgG antibodies from a previously sensitized mother cross the placenta and attach to the fetal Rh-positive RBCs. Fetal RBCs are destroyed by lysozymes from macrophages or natural killer cells (not shown), or they are phagocytosed and destroyed by macrophages, producing anemia and unconjugated hyperbilirubinemia. (From Goljan EF: Star Series: Pathology; Philadelphia, Saunders, 1998, Fig. 14-1.)
c. Once the mother is exposed to D antigen, she develops anti-D IgG antibodies and is now sensitized for life.
   • Since maternal exposure occurs in the first Rh incompatible pregnancy, the firstborn child is not affected.
d. Subsequent Rh incompatible pregnancies are at risk for developing Rh HDN (see Fig. 16-4B).
   (1) Anti-D IgG antibodies cross the placenta and strongly attach to fetal Rh-positive RBCs.
   (2) Sensitized fetal RBCs attach to Fc receptors for IgG on macrophages in the reticuloendothelial system, particularly those in the spleen.
   (3) Numerous fetal RBCs are attached to these macrophages, forming rosettes.
      (a) Fetal RBCs are lysed by lysosomal enzymes released by the macrophages and/or natural killer cells.
      (b) Fetal RBCs are phagocytosed and destroyed by the macrophages.
   (4) Macrophage destruction of RBCs produces a severe anemia and an increase in UCB.
      (a) Prolonged hemolysis stimulates fetal erythropoiesis in the liver, spleen, bone marrow (normal sites for erythropoiesis in the fetus), and extramedullary sites, such as the skin and placenta.
      • Hepatosplenomegaly may occur.
      (b) Placenta effectively metabolizes the UCB, unless it is overwhelmed
3. Clinical manifestations
   a. A wide spectrum of clinical manifestations may occur depending on the severity of the hemolysis.
   b. Hydrops fetalis is the most serious manifestation of Rh HDN (Fig. 16-5).
      (1) Marked erythropoiesis in the liver produces hepatic dysfunction manifested as a decrease in albumin synthesis.
         • This decreases plasma oncotic pressure (refer to Chapter 5), which causes peripheral edema, ascites, and pleural effusions.
      (2) Severe anemia produces high-output cardiac failure, leading to left-sided heart failure with pulmonary edema and right-sided heart failure, with increased venous pressures contributing to peripheral edema and ascites.
   c. Jaundice with unconjugated hyperbilirubinemia
      (1) Jaundice develops shortly after birth.
      (2) Level of UCB is much higher than with ABO HDN
         (a) Most of the UCB is not bound to albumin and circulates free in the blood.
         (b) Albumin levels are low because of hepatic dysfunction.
(3) Increased risk for developing bilirubin encephalopathy (kernicterus), when bilirubin levels are >20 mg/dL.
   (a) Free, unbound, lipid-soluble UCB poses the greatest risk for bilirubin entry into the neonate brain through the poorly developed blood-brain barrier (Fig. 16-6).
   (b) Bilirubin is neurotoxic and binds to lipids in the brain, imparting a yellow discoloration of the basal ganglia, thalamus, cerebellum, gray matter of the cerebral cortex, and spinal cord.

4. Laboratory findings
   a. Degree of anemia is more severe than with ABO HDN.
      • Reticulocytosis and nucleated RBCs are commonly present in the peripheral blood, which are signs of accelerated erythropoiesis.
   b. Cord bilirubin is generally 3 to 5 mg/dL.
   c. Both direct and indirect Coombs tests on fetal cord RBCs are strongly positive.
   d. Spherocytes are not present in the cord blood.
      • Splenic macrophages phagocytose the entire RBC.

5. Treatment of Rh HDN requires exchange transfusions.
   a. The newborn’s blood is removed and replaced with fresh blood.
   b. Transfusion corrects anemia and removes antibodies and UCB.

6. Table 16-2 compares Rh HDN and ABO HDN.
7. Prevention of Rh HDN in Rh-negative mothers without anti-D
   a. Women receive anti-D globulin (Rh immune globulin [RhGAM]) during the 28th week of pregnancy.
   b. It does not cross the placenta.
   c. It protects the mother from sensitization to fetal Rh-positive cells that may enter her circulation during the last trimester.
   d. It lasts ~3 months in the mother’s blood.
   e. Additional anti-D globulin is given to the mother after delivery if the baby is Rh positive.

Special tests (Kleihauer-Betke acid dilution technique) are performed on the mother’s blood that detect fetal RBCs. The amount of fetal blood is quantified so that the appropriate amount of additional anti-D globulin is given to the mother. Anti-D globulin masks the antigenic sites on the fetal RBCs or destroys the fetal RBCs so that the mother does not host an antibody response against the D antigen. If the patient develops anti-D antibodies, there is no indication for giving the globulin either during or after delivery, because its main purpose is to prevent sensitization.
8. Tests performed on sensitized (anti-D positive) women
   a. Sequential antibody titers and periodic amniocentesis are used to monitor sensitized
      women.
   b. Amniotic fluid is submitted to spectrophotometric analysis to identify bilirubin pigment.
      (1) Bilirubin has absorbance at a wavelength of 450 nm.
      (2) $\Delta \text{OD}_{450}$ (optical density) 450 value is obtained on the amniotic fluid (AF).
         • $\Delta \text{OD}_{450}$ is the height of the bilirubin spike on the spectrophotometer reading
           from the baseline.
      (3) $\Delta \text{OD}_{450}$ is sequentially plotted on a Liley chart.
      (4) The chart provides an indication of the severity of RBC hemolysis in the affected
           fetus.
      (5) Very severe cases at an early gestational age may require an in utero exchange
           transfusion.

D. Blue fluorescent light or sunlight
1. Light is used as a treatment of jaundice in the newborn.
2. UCB in the skin absorbs light energy from blue fluorescent light or sunlight.
3. Photoisomerization converts UCB to a nontoxic water-soluble dipyrrrole (called lumirubin).
   • Lumirubin is excreted in bile or urine.

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TABLE 16-2 Comparison of Rh Hemolytic Disease of the Newborn and ABO Hemolytic Disease of the Newborn

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>RH HEMOLYTIC DISEASE OF NEWBORN</th>
<th>ABO HEMOLYTIC DISEASE OF NEWBORN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Blood group association</td>
<td>Mother can be any blood group</td>
<td>Mother must be group O and the</td>
</tr>
<tr>
<td></td>
<td>baby must be group A or B</td>
<td>baby must be group A or B</td>
</tr>
<tr>
<td>Rh association</td>
<td>Mother must be Rh negative and</td>
<td>ABO HDN is protective against</td>
</tr>
<tr>
<td></td>
<td>the baby must be Rh positive</td>
<td>Rh sensitization with the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exception of an O Rh-positive</td>
</tr>
<tr>
<td>Anemia at birth</td>
<td>Frequent and often severe</td>
<td>Mild to no anemia at birth;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>severe anemia uncommon</td>
</tr>
<tr>
<td>Jaundice first 24 hours</td>
<td>Frequent; moderate to severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>Common; sign of accelerated</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>erythrocytosis causing EMH</td>
<td></td>
</tr>
<tr>
<td>First pregnancy</td>
<td>If the mother is Rh negative</td>
<td>Baby can be affected if the</td>
</tr>
<tr>
<td></td>
<td>and has an Rh-positive baby,</td>
<td>mother is blood group O and</td>
</tr>
<tr>
<td></td>
<td>the baby is not affected, but</td>
<td>the baby is blood group A or B</td>
</tr>
<tr>
<td></td>
<td>the mother is at great risk for</td>
<td></td>
</tr>
<tr>
<td></td>
<td>developing anti-D antibodies.</td>
<td></td>
</tr>
<tr>
<td>Later pregnancies</td>
<td>If the mother has anti-D and</td>
<td>Each pregnancy is at risk for ABO</td>
</tr>
<tr>
<td></td>
<td>the baby is Rh positive, the</td>
<td>HDN if the mother is blood group</td>
</tr>
<tr>
<td></td>
<td>baby is at risk for Rh HDN</td>
<td>O</td>
</tr>
<tr>
<td>Direct Coombs test on cord blood</td>
<td>Strongly positive</td>
<td>Weakly positive</td>
</tr>
<tr>
<td>Indirect Coombs test on cord blood</td>
<td>Positive</td>
<td>Usually positive</td>
</tr>
<tr>
<td>Spherocytes in the peripheral blood</td>
<td>Not present (RBCs fully</td>
<td>Present (part of the RBC</td>
</tr>
<tr>
<td></td>
<td>phagocytosed)</td>
<td>membrane is removed by</td>
</tr>
<tr>
<td></td>
<td></td>
<td>macrophages)</td>
</tr>
</tbody>
</table>

*EMH, Extramedullary hematopoiesis; HDN, hemolytic disease of the newborn.*
I. Symptoms and Signs of Respiratory Disease (Tables 17-1 and 17-2)

II. Alveolar-Arterial (A-a) Gradient

A. Definition

1. A-a gradient is the difference in partial pressure of oxygen (P\textsubscript{aO\textsubscript{2}}) between the alveolar P\textsubscript{aO\textsubscript{2}} (P\textsubscript{aO\textsubscript{2}}) and arterial P\textsubscript{aO\textsubscript{2}} (P\textsubscript{aO\textsubscript{2}}).
2. Normally, there is a mismatch between ventilation and perfusion in the lungs.
   • P\textsubscript{aO\textsubscript{2}} and arterial P\textsubscript{aO\textsubscript{2}} are not the same.
3. Calculation of A-a gradient is useful in differentiating causes of hypoxemia (decreased P\textsubscript{aO\textsubscript{2}}; refer to Chapter 2).
   a. Hypoxemia due to pulmonary cause (e.g., acute respiratory distress syndrome) increases the A-a gradient.
   b. Hypoxemia due to an extrapulmonary cause (e.g., paralysis of the diaphragm) does not increase the A-a gradient.

B. Calculation of the A-a gradient

1. \[ \text{P\textsubscript{aO\textsubscript{2}}} = \%\text{O}_2 \times (713) - 40/0.8 = 100 \text{ mm Hg} \]
   • \%O\textsubscript{2} is the percentage of O\textsubscript{2} the patient is breathing; 713 is the atmospheric pressure (760 mm Hg) minus the water vapor pressure (47 mm Hg); and 0.8 is the respiratory quotient.
2. Example of an A-a calculation using normal values
   a. Normal P\textsubscript{aO\textsubscript{2}} = 0.21(713) = 40/0.8 = 100 mm Hg
   b. Normal P\textsubscript{aO\textsubscript{2}} = 95 mm Hg
   c. Normal A-a gradient = 100 mm Hg − 95 mm Hg = 5 mm Hg
   d. Medically significant A-a gradient is \geq 30 mm Hg.
3. Medically significant A-a gradient normally increases with age.
4. A-a \geq 30 mm Hg is set for the highest specificity.
5. Normal value for A-a gradient varies with age and can be approximated with the following formula: A-a = (age/4) + 4.

C. Hypoxemia with an increased A-a gradient (refer to Chapter 2)

1. Ventilation defect
   a. Alveoli are perfused; however, there is impaired O\textsubscript{2} delivery to alveoli (see Fig. 2-3B).
   b. Example—airway collapse (atelectasis) due to the respiratory distress syndrome (RDS)
2. Perfusion (P) defect
   a. Alveoli are ventilated but there is no perfusion of the alveoli (see Fig. 2-3C).
   b. Example—pulmonary embolus
3. Diffusion defect
   a. O\textsubscript{2} cannot diffuse through the alveolar-capillary interface.
   b. Examples—interstitial fibrosis, pulmonary edema
4. Right-to-left cardiac shunt
   • Example—tetralogy of Fallot
### Table 17-1 Common Symptoms of Respiratory Disease

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>CAUSES/DISCUSSION</th>
</tr>
</thead>
</table>
| Dyspnea         | Difficulty with breathing  
Due to stimulation of J receptors causing decrease in full inspiration  
Causes:  
Decreased compliance (e.g., interstitial fibrosis)  
Increased airway resistance (e.g., chronic bronchitis)  
Chest bellows disease (e.g., obesity, kyphoscoliosis)  
Interstitial inflammation/fluid accumulation (e.g., left-sided heart failure) |
| Cough           | Cough receptors: located at bifurcations in airways, larynx, distal esophagus  
Cough with a normal chest x-ray:  
Postnasal discharge is the most common cause  
Nocturnal cough with:  
GERD: due to acid reflux in tracheobronchial tree at night  
Bronchial asthma: due to bronchoconstriction  
Productive cough with:  
Chronic bronchitis: due to smoking cigarettes  
Typical bacterial pneumonia  
Bronchiectasis  
Drugs causing cough:  
ACE inhibitors: inhibit degradation of bradykinin; causes mucosal swelling and irritation in tracheobronchial tree  
Aspirin: causes an increase in LT C-D-E4 (bronchoconstrictors) |
| Hemoptysis      | Coughing up blood-tinged sputum  
Mechanisms:  
Parenchymal necrosis  
Bronchial and/or pulmonary vessel damage  
Causes:  
Chronic bronchitis (most common cause)  
Pneumonia, bronchogenic carcinoma  
TB, bronchiectasis, aspergiloma (fungus living in a cavitary lesion) |

ACE, Angiotensin-converting enzyme; GERD, gastroesophageal reflux disease; LT, leukotriene; TB, tuberculosis.

### Table 17-2 Signs of Respiratory Disease

<table>
<thead>
<tr>
<th>SIGN</th>
<th>DISCUSSION</th>
</tr>
</thead>
</table>
| Tachypnea       | Normal respiratory rate: 14–20 breaths per minute (bpm) in adults; up to 44 bpm in children  
Tachypnea: rapid shallow breathing (>20 bpm)  
Causes: restrictive lung disease; pleuritic chest pain; pulmonary embolus with infarction (key finding) |
| Chest Palpation | Tracheal shift:  
Causes:  
Pressure in contralateral lung: large tension pneumothorax, large pleural effusion  
Decreased volume in ipsilateral lung: large spontaneous pneumothorax, resorption atelectasis |
| Vocal tactile fremitus | Palpable thrill (vibration) transmitted through chest when patient says “E” or “1, 2, 3” or “99”  
Decreased vocal tactile fremitus with emphysema or asthma, with increased AP diameter from an increased in total lung capacity  
Absent vocal tactile fremitus with atelectasis (collapse of airways); fluid (effusion); air (pneumothorax) in pleural space  
Increased tactile fremitus (sound travels well through consolidations) with alveolar consolidation (e.g., lobar pneumonia) |
| Percussion      | Dull percussion with pleural effusion; lung consolidation; atelectasis (no air in the alveoli)  
Hyperresonant percussion with pneumothorax; asthma; emphysema |
| Lung Sounds     | General breath sounds: trachea  
Mechanism: air velocity and turbulence induce vibrations in airway walls  
Sites modifying breath sound: terminal airway and alveolar disease modify breath sounds; sounds heard with the stethoscope are produced in more central (hilar) regions and are altered in intensity and tonal quality as they pass through pulmonary tissue to the periphery  
Site for normal airway resistance: segmental bronchi (turbulent air flow)  
Site for laminar airflow: begins at the bronchioles—“small airway”  
Parallel branching: increases cross-sectional area of airways; converts turbulence into laminar airflow  
Effects of inflammation of small airways (e.g., asthma, chronic bronchitis): air trapping, wheezing, increased airway resistance |
### TABLE 17-2 Signs of Respiratory Disease—cont’d

<table>
<thead>
<tr>
<th>SIGN</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tubular breath sounds</strong></td>
<td>Sound is like blowing air through a tube. Tracheal breath sound: normal sound over lateral neck or suprasternal notch. Bronchial breath sounds: always an abnormal sound. Loud, high-pitched sound with a peculiar hollow or tubular quality. Expiratory sounds longer than inspiratory. Significance: consolidation (e.g., lobar/bronchopneumonia). Mechanism: bronchi must be patent and partially collapsed.</td>
</tr>
<tr>
<td><strong>Vesicular breath sounds</strong></td>
<td>Normal breath sounds: tracheal sounds that are modified (filtered) in alveoli. Sites: most lung fields except trachea and central bronchi. Inspiratory/expiratory ratio is 3:1. Present in: normal lungs; chronic bronchitis, emphysema. Diminished in: emphysema and asthma due to increased AP diameter. Absent in: pneumothorax; atelectasis; effusion.</td>
</tr>
<tr>
<td><strong>Bronchovesicular breath sounds</strong></td>
<td>Normal breath sounds heard over main bronchi. Abnormal if heard in lung periphery. Inspiratory and expiratory breath sounds are equal in length.</td>
</tr>
<tr>
<td><strong>Adventitial sounds</strong></td>
<td>Extra sounds that are normally absent in respiratory cycle. Crackles: usually inspiratory. Early and mid inspiratory crackles: due to secretions in proximal large to medium-sized airways (e.g., chronic bronchitis); clear with coughing. Late inspiratory crackles: due to reopening of distal airways partially occluded by increased interstitial pressure (e.g., interstitial fluid—pus, transudate in CHF); do not clear with coughing; vary from fine to coarse. Causes: pulmonary edema; lobar pneumonia; interstitial fibrosis (e.g., sarcoidosis).</td>
</tr>
<tr>
<td><strong>Wheezeing</strong></td>
<td>Wheezing: high-pitched musical sound usually heard in expiration; sometimes inspiration and expiration longer than inspiration. Causes: inflammation of segmental bronchi, small airways (e.g., asthma, chronic bronchitis); pulmonary edema constricting airway (called cardiac asthma); pulmonary infarction (release of TXA2 from platelets in embolus causes bronchoconstriction).</td>
</tr>
<tr>
<td><strong>Rhonchi</strong></td>
<td>Rhonchi: low-pitched snoring sound heard during inspiration or expiration; due to secretions in large airways (bronchus, trachea); usually clear with coughing; common in chronic bronchitis.</td>
</tr>
<tr>
<td><strong>Inspiratory stridor</strong></td>
<td>Inspiratory stridor: high-pitched inspiratory sound; sign of upper airway obstruction. Causes: epiglottitis (Haemophilus influenzae); croup (parainfluenza virus).</td>
</tr>
<tr>
<td><strong>Pleural friction rub</strong></td>
<td>Pleural friction rub: two inflamed surfaces (pleural and parietal) rubbing against each other. Timing: end of inspiration and early part of expiration. Disappears: large effusion is present (separates inflamed surfaces); holding breath (continues with pericardial friction rub). Causes: pleuritis due to cancer, infarction, pneumonia, serositis (SLE).</td>
</tr>
<tr>
<td><strong>Grunting in newborns</strong></td>
<td>Grunting in newborns: always abnormal after 24 hours; common finding in RDS. Bronchophony (sound of bronchi). Normal lung: spoken syllables or numbers (e.g., “99”) are indistinctly heard. Alveolar consolidation: syllables/numbers heard louder and more distinctly. Whispeered pectoriloquy (Latin for “voice of chest”): clear and intelligible words (e.g., patient whispering “1, 2, 3?”). Egophony (Greek for “voice of goat”): patient saying “E” sounds like “A.”</td>
</tr>
</tbody>
</table>

**AP**: Anteroposterior; **bpm**: breaths per minute; **CHF**: congestive heart failure; **RDS**: respiratory distress syndrome; **SLE**: systemic lupus erythematosus; **TXA2**: thromboxane A2.
Calculation of the A-a gradient in a patient breathing 0.30 O₂ who has a PCO₂ of 80 mm Hg and PaO₂ of 40 mm Hg: \[ P_{A\text{O}_2} = 0.30(713) - 80/0.8 = 114 \text{ mm Hg}. \] A-a gradient = 114 − 40 = 74 mm Hg, which is medically significant and indicates one or more of the above-mentioned lung disorders or a right-to-left shunt in the heart.

D. Hypoxemia with a normal A-a gradient
1. Depression of the respiratory center in the medulla; examples include:
   • Barbiturate overdose, brain injury.
2. Upper airway obstruction; examples include:
   a. Epiglottitis due to Haemophilus influenzae
   b. Croup due to parainfluenza virus
      • Mucosal edema narrows the trachea.
3. Chest bellows (muscles of respiration) dysfunction; examples include:
   a. A paralyzed diaphragm
   b. Amyotrophic lateral sclerosis with degeneration of anterior horn cells

Calculation of the A-a gradient in a patient breathing room air who has a PCO₂ of 80 mm Hg and PaO₂ of 40 mm Hg: \[ P_{A\text{O}_2} = 0.21(713) - 80/0.8 = 50 \text{ mm Hg}. \] A-a gradient = 50 − 40 = 10 mm Hg, which excludes the lung as the cause of the hypoxemia and indicates an extrapulmonary cause of hypoxemia.

III. Upper Airway Disorders
A. Choanal atresia
1. Most common congenital anomaly of the nose
   • ~50% to 70% affected infants have other congenital anomalies, particularly if the choanal atresia is bilateral.
2. Unilateral or bilateral bony (90% of cases) or membranous (10% of cases) septum between the nose and the pharynx
3. Newborn (NB) turns cyanotic when breast-feeding
   • Crying causes the child to “pink up” again.

B. Nasal polyps
1. Nonneoplastic tumefactions
   • Develop as a response to chronic inflammation
2. Allergic polyps are the most common polyp.
   a. Most often seen in adults with a history of IgE-mediated allergies
   b. Nasal smear shows numerous eosinophils
3. Nasal polyps are often associated with cystic fibrosis (CF; Fig. 17-1).
   a. Thick secretions in CF cause inflammatory polyps to develop in the nose.
   b. A sweat test to rule out CF is indicated whenever a child has a nasal polyp (see IX.D.5.).

17-1: Nasal polyp. Note the gray-white mass in the left nasal cavity. (From Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 312, Fig. 11-24.)
C. Obstructive sleep apnea (OSA)

1. Epidemiology
   a. Definition—excessive snoring with intervals of breath cessation (apnea)
   b. Causes
      (1) Obesity is the most common cause of OSA.
      • Pharyngeal muscles collapse due to the weight of tissue in the neck.
      (2) Other causes—tonsillar hypertrophy, nasal septum deviation, hypothyroidism, and acromegaly

2. Pathogenesis
   • Airway obstruction causes CO₂ retention (respiratory acidosis), leading to hypoxemia (↓PaO₂).

3. Clinical findings
   a. Excessive snoring with episodes of apnea
   b. Daytime somnolence often simulating narcolepsy

4. Laboratory findings
   • PaO₂ and O₂ saturation (SaO₂) decrease and Paco₂ increases (respiratory acidosis) during apneic episodes.

5. Complications
   a. Pulmonary hypertension (PH) occurs followed by right ventricular hypertrophy (RVH).
      (1) Hypoxemia and respiratory acidosis cause smooth muscle cells in pulmonary vessels to vasoconstrict, which leads to PH.
      (2) Once PH develops, the right ventricle becomes hypertrophied (called cor pulmonale).
   b. Secondary polycythemia
      • Hypoxemic stimulus for erythropoietin release leads to RBC hyperplasia and secondary polycythemia.

6. Nocturnal polysomnography documents periods of apnea during sleep.

7. Treatment
   a. Nasal continuous positive airway pressure (CPAP)
      • Provides a pneumatic splint that relieves upper airway obstruction
   b. Surgical correction of any obstructive lesions and weight loss

D. Sinusitis

1. Epidemiology
   a. Definition—inflammation of the mucous membranes lining one or more of the paranasal sinuses.
   b. In adults, sinusitis most often occurs in the maxillary sinus, whereas in children, it is most common in the ethmoid sinus.
   c. Causes
      (1) Upper respiratory infections (URIs); e.g., viral, bacterial
      (2) Deviated nasal septum
      (3) Allergic rhinitis, barotrauma, and smoking cigarettes
   d. Pathogens
      (1) Principal pathogens are *Streptococcus pneumoniae* (most common), nontypeable *Haemophilus influenzae*, and *Moraxella catarrhalis*.
      (2) Rhinoviruses, anaerobes (chronic sinusitis), *Staphylococcus aureus* (nosocomial infections), systemic fungi (e.g., *Mucor* or *Aspergillus* species) may also be the cause.
      • Diabetics may have sinusitis due to *Mucor* species.

2. Pathogenesis
   • Blockage of sinus drainage into the nasal cavity

3. Clinical findings
   a. Fever
   b. Nasal congestion with or without purulent discharge
   c. Pain over the affected sinuses
   d. Painful teeth (associated with maxillary sinusitis), cough from postnasal discharge, peri orbital cellulitis (extension of an infection from ethmoid sinus)

4. Diagnosis
   a. Four-view sinus radiographs are obtained.
   b. CT scan is the most sensitive test.

5. Treatment
   a. Decongestants
   b. Antimicrobial therapy
Recommendation is *not to* use antibiotics, because most cases are viral and resolve within 2 weeks.

If resolution does *not* occur, first-order antibiotics include:
- Amoxicillin (most common drug), erythromycin, and trimethoprim-sulfamethoxazole (TMP-SMX)

**E. Nasopharyngeal (NP) carcinoma**
1. Epidemiology
   a. Most common malignant tumor of the nasopharynx
   b. Male dominant
   c. Increased in Chinese (common in adults) and African populations (common in children)
2. Pathogenesis
   - Causal relationship with Epstein-Barr virus (EBV)
3. Pathologic findings
   a. Squamous cell carcinoma (SCC), nonkeratinizing squamous carcinoma, or undifferentiated cancer
   b. Metastasizes to cervical lymph nodes (70% of cases)
4. Treatment is radiotherapy.
5. Approximately 60% 3-year survival rate

**F. Laryngeal carcinoma**
1. Epidemiology and pathogenesis
   a. Risk factors
      1. Cigarette smoking (most common cause)
      2. Alcohol (synergistic effect with smoking)
      3. Squamous papillomas and papillomatosis
         - Human papillomavirus types 6 and 11 association
   b. Majority located on true vocal cords (Fig. 17-2)
2. Majority are keratinizing SCCs
3. Clinical findings
   - Persistent hoarseness often associated with cervical lymphadenopathy
4. Treatment is surgery.

**IV. Atelectasis**
   **A. Definition**
   - Loss of lung volume due to inadequate expansion of the airspaces (collapse)

   **B. Resorption atelectasis**
   1. Pathogenesis
      a. Airway obstruction by thick secretions prevents air from reaching the alveoli.
         - Obstruction occurs in bronchi, segmental bronchi, or terminal bronchioles.
      b. Causes of obstruction
         1. Mucus or mucopurulent plugs after surgery
         2. Aspiration of foreign material
         3. Centrally located bronchogenic carcinoma

**17-2: Laryngeal squamous cell carcinoma involving the right vocal cord (arrow).** (From Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 47, Fig. 3-16.)
c. Cause of alveolar collapse
   (1) Lack of air and distal resorption of preexisting air
   (2) Following obstruction, circulating blood in the pulmonary capillary absorbs the
       preexisting air in the peripheral alveoli, leading to alveolar collapse and an airless
       state within a few hours.

d. Collapse may involve all or part of a lung.

2. Clinical findings
a. Fever and dyspnea
   • Symptoms occur within 24 to 36 hours of collapse.
b. Absent breath sounds
c. Absent vocal vibratory sensation (tactile fremitus)
   • Alveoli are collapsed.

3. Treatment
a. Incentive spirometry after surgery
b. CPAP by face mask
c. Positive end-expiratory pressure (PEEP) on mechanical ventilation

C. Compression atelectasis
1. Definition—air or fluid in the pleural cavity under increased pressure collapses small
   airways beneath the pleura

2. Examples
a. Tension pneumothorax where air compresses the lung
b. Pleural effusion where fluid compresses the lung

D. Atelectasis due to loss of surfactant
1. Surfactant
   a. Surfactant reduces surface tension in the small airways.
      • Prevents collapse on expiration, when collapsing pressure is greatest
   b. Type II pneumocytes synthesize surfactant.
      (1) Surfactant is stored in lamellar bodies (Fig. 17-3A).
      (2) Synthesis begins in 28th week of gestation.

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**17-3:** A, Electron micrograph of a type II pneumocyte showing a lamellar body (arrow) containing surfactant. B, Neonatal respiratory distress syndrome. Some of the dilated respiratory bronchioles and alveolar ducts are lined with a fibrin-rich membrane (hyaline membrane) (arrow). The subjacent alveoli are collapsed. C, Chest radiograph in respiratory distress syndrome. Note the fine, uniform granularity distributed throughout both lungs (“ground glass” appearance). (A from Corrin B: Pathology of the Lungs, London, Churchill Livingstone, 1999, p 15, Fig. 1-26; B from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 128, Fig. 5-25; C from Katz D, Math K, Groskin S: Radiology Secrets, Philadelphia, Hanley & Belfus, 1998, p 380, Fig. 2.)
Surfactant: cortisol/thyroxine ↑synthesis, insulin ↓synthesis
Surfactant: ↓surface tension
RDS: ↓surfactant
RDS: prematurity (MCC), maternal DM, C-section
RDS: ↑tension

LHF: MCC pulmonary edema

V. Acute Lung Injury
A. Pulmonary edema (refer to Chapters 5 and 11)

1. Edema due to alterations in Starling pressure (transudate)
   a. Increased hydrostatic pressure (HP) in pulmonary capillaries
      • Left-sided heart failure (LHF; see Fig. 11-2A), volume overload, and mitral stenosis
   b. Decreased oncotic pressure (OP)
      • Nephrotic syndrome and cirrhosis

2. Edema due to microvascular or alveolar injury (exudate)
   a. Infections
      • Examples—sepsis, pneumonia
   b. Aspiration
      • Examples—drowning (refer to Chapter 7) and gastric contents
   c. Drugs
      • Example—heroin (refer to Chapter 7)
   d. High altitude (refer to Chapters 2 and 7)
   e. Acute respiratory distress syndrome (ARDS; see later)
B. ARDS
1. Definition—noncardiogenic pulmonary edema resulting from acute alveolar-capillary damage
2. Epidemiology
   a. Due to direct injury to the lungs or systemic diseases
   b. Causes
      (1) Gram-negative sepsis (>40% of cases)
      (2) Gastric aspiration (>30% of cases)
      (3) Severe trauma with shock (>20% of cases)
      (4) Diffuse pulmonary infections
         • Severe acute respiratory syndrome (SARS), hantavirus
      (5) Other causes: heroin, smoke inhalation, acute pancreatitis, cardiopulmonary bypass, disseminated intravascular coagulation, amniotic fluid embolism, and fat embolism
3. Pathogenesis
   a. Acute damage occurs in alveolar capillary walls and epithelial cells.
   b. Alveolar macrophages and other cells release cytokines.
      (1) Cytokines are chemotactic to neutrophils.
      (2) Neutrophils transmigrate into the alveoli through pulmonary capillaries.
      (3) Capillary damage causes leakage of a protein-rich exudate producing hyaline membranes.
      (4) Neutrophils damage type I and II pneumocytes.
         • Decrease in surfactant causes atelectasis with intrapulmonary shunting.
   c. Late findings
      (1) Repair by type II pneumocytes
      (2) Progressive interstitial fibrosis (restrictive lung disease)
4. Clinical findings
   a. Dyspnea/tachypnea
   b. Late inspiratory crackles
5. Laboratory findings
   a. Severe hypoxemia not responsive to O2 therapy
      • \( \text{PaO}_2 < 50 \text{ mm Hg} \)
   b. Pulmonary artery wedge pressure <18 mm Hg
      • Important to distinguish ARDS from cardiogenic pulmonary edema, where PA wedge pressure is >18 mm Hg
   c. Respiratory acidosis or normal PaCO2
   d. Increased A-a gradient, due to:
      (1) Intrapulmonary shunting related to atelectasis
      (2) Diffusion abnormalities related to hyaline membranes, alveolar infiltrate
   e. Chest x-ray
      (1) Bilateral interstitial infiltrates initially
      (2) Progresses to widespread alveolar consolidation with air bronchograms (80%)
6. Treatment
   a. Treat underlying disease
   b. Hemodynamic monitoring
   c. Mechanical ventilation
   d. Nitric oxide inhalation, corticosteroids
7. Poor prognosis (40%–50% mortality rate)

VI. Pulmonary Infections
A. Pneumonia
1. Epidemiology
   a. Pneumonia is classified as community-acquired or nosocomial (hospital-acquired).
   b. Community-acquired pneumonia is further subdivided into typical and atypical.
2. Typical community-acquired pneumonia
   a. Epidemiology
      (1) Sixth leading cause of death in the United States
      (2) Majority are caused by bacterial pathogens.
      (3) Most often due to \textit{Streptococcus pneumoniae} (50%–75% of cases; Fig. 17-4A)
   b. Pathogenesis
      (1) Microaspiration of oropharyngeal contents during sleep (most common cause)
      (2) Inhalation of aerosol drops ranging in size from 0.5 to 1 \( \mu \text{m} \) (second most common cause)
      (3) Bloodstream infection (least common cause)
Bronchopneumonia

1. It begins as an acute bronchitis and spreads locally into the lungs.
2. The lower lobes or right middle lobe are usually involved.
3. The lung has patchy areas of consolidation (see Fig. 17-4B).
   - Microabscesses are present in the areas of consolidation.

Lobar pneumonia

- Complete or almost complete consolidation of a lobe of lung (see Fig. 17-4C)

Complications

1. Lung abscesses, empyema (pus in the pleural cavity)
2. Sepsis

Clinical findings

1. Sudden onset of high fever with productive cough
2. Chest pain
3. Tachycardia
4. Signs of consolidation (alveolar exudate)
   - Dullness to percussion
   - Increased vocal tactile fremitus
   - Sound is transmitted well through alveolar consolidations.
   - Late inspiratory crackles
   - Bronchial breath sounds, bronchophony and egophony
5. Chest radiograph (gold standard screen)
   - Patchy infiltrates (bronchopneumonia) or lobar consolidation (see Fig. 17-4D)
   - Sensitivity 50% to 85%
6. Laboratory findings
   - Positive Gram stain
     - Stain is more useful than culture (still obtained)
     - Sensitivity is 80%.
   - Neutrophilic leukocytosis
   - Blood cultures positive in 20% of cases.

3. Table 17-3 summarizes important respiratory microbial pathogens.
### TABLE 17-3 Summary of Respiratory Microbial Pathogens

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Rhinovirus | Most common cause of the common cold  
Transmitted by hand to eye-nose contact  
Other causes of colds—coronaviruses, adenoviruses, influenza C virus, coxsackievirus |
| Coxsackievirus | Acute chest syndrome: fever with pleuritis  
Parainfluenza (see Fig. 17-5A) | Most common cause of croup (laryngotraceobronchitis) in infants  
Inspiratory stridor (upper airway obstruction) due to submucosal edema in trachea; brassy cough; signs of respiratory distress  
Anterior x-ray of neck shows “steeple sign,” representing mucosal edema in the trachea (site of obstruction)  
Bronchiolitis in infants  
Treatment: cold water humidifiers and aerosolized racemic epinephrine |
| CMV (see Fig. 17-5B) | Common pneumonia in immunocompromised hosts (e.g., bone marrow transplants, AIDS)  
Enlarged alveolar macrophages/pneumocytes, contain eosinophilic intranuclear inclusions surrounded by a halo  
Treatment: cidofovir, foscarnet, ganciclovir |
| Influenzavirus | Type A viruses are most often involved  
Hemagglutinins bind virus to cell receptors in the nasal passages  
Neuraminidase dissolves mucus and facilitates release of viral particles  
Influenza A: worldwide epidemics; pneumonia may be complicated by a superimposed bacterial pneumonia (usually Staphylococcus aureus)  
Influenza B: causes major outbreaks  
Antigen drift: minor mutation; does not require new vaccine  
Antigen shift: major mutation in hemagglutinin or neuraminidase; new vaccine required  
Clinical: fever, headache, cough, myalgias, chest pain  
Vaccination: mandatory for people >65 years old, people with chronic illnesses  
Treatment: neuraminidase inhibitors (e.g., oseltamivir)  
Associations: Reye syndrome with salicylate ingestion; Guillain-Barré syndrome |
| Rubeola | Fever, cough, conjunctivitis, and excessive nasal mucus production  
Koplik spots in the mouth precede onset of the rash.  
Warthin-Finkeldey multinucleated giant cells are a characteristic-finding |
| Respiratory syncytial virus (RSV) | Most common cause of pneumonia and bronchiolitis (wheezing) in infants  
Causes otitis media in older children  
Hand washing and use of gloves prevents nosocomial outbreaks in nurseries  
Fusion protein causes cells to fuse, producing multinucleated giant cells  
Infections primarily occur in winter  
Rapid diagnosis by detection of antigen in nasopharyngeal wash  
Passive immunization (high risk children): palivizumab (monoclonal antibody) reduces hospitalization rates between November and April |
| SARS | First transmitted to humans through contact with masked palm civets (China) and then from human-to-human contact through respiratory secretions (e.g., hospitals, families)  
Develop severe respiratory infection  
Diagnose with viral detection by PCR assay or detection of antibodies  
Children: no therapy or vitamin A |
| Hantavirus pulmonary syndrome | Transmission: inhalation of urine/feces from deer mice in Southwestern United States  
Pulmonary syndrome: ARDS, hemorrhage, renal failure  
Diagnosis: detect viral RNA in lung tissue  
No effective treatment  
High mortality rate |
| **Bacteria** | |
| Chlamydia | Second most common cause of atypical pneumonia  
Seroepidemiologic association with coronary artery disease  
Treatment: doxycycline  
Chlamydophila pneumoniae | Newborn pneumonia (passage through birth canal)  
Afebrile, staccato cough (choppy cough), conjunctivitis, wheezing  
Treatment: erythromycin |
| Chlamydia trachomatis | | |
| Mycoplasma M. pneumoniae | Most common cause of atypical pneumonia  
Common in adolescents and military recruits (closed spaces)  
Risk factor for Guillain-Barré syndrome  
Insidious onset with low-grade fever  
Cold agglutinins in blood  
Complications: bullous myringitis, cold autoimmune hemolytic anemia due to anti-I IgM antibodies  
Treatment: erythromycin; azithromycin; clarithromycin |
| Coxiella burnetii | Usually transmitted without a vector  
Contracted by dairy farmers, veterinarians  
Associated with the birthing process of infected sheep, cattle, and goats, and handling of milk or excrement  
Atypical pneumonia, myocarditis, granulomatous hepatitis  
Treatment: doxycycline |

Continued
**Streptococcus pneumoniae**
(see Fig. 17-4A)
Gram-positive lancet-shaped diplococcus
Most common cause of typical community-acquired pneumonia
Rapid onset, productive cough, signs of consolidation
Urine antigen test excellent screen
Treatment: penicillin G (penicillin sensitive); vancomycin +/- rifampin (penicillin resistant)

**Staphylococcus aureus**
(see Fig. 17-5C)
Gram-positive cocci in clumps
Yellow sputum
Commonly superimposed on influenza pneumonia and measles pneumonia
Major lung pathogen in cystic fibrosis and IV drug abusers
Hemorrhagic pulmonary edema, abscess formation, and pneumatoceles (thin-walled air-filled cysts that develop in the lung parenchyma, usually after pneumonia)
Treatment of pneumonia: methicillin-sensitive: nafcillin or oxacillin; methicillin resistant: vancomycin

**Corynebacterium diphtheriae**
(see Fig. 17-5D)
Gram-positive rod
Toxin inhibits protein synthesis by ADP-ribosylation of elongation factor 2 involved in protein synthesis
Toxin also impairs β-oxidation of fatty acids in the heart
Toxin-induced pseudomembranous inflammation produces shaggy gray membranes in the oropharynx and trachea; toxic myocarditis (death)
Treatment: erythromycin

**Bacillus anthracis**
(see Fig. 17-5E)
Gram-positive rod
Habitat: soil
Capsule inhibits phagocytosis
Exotoxins: edema factor (activates adenylate cyclase); lethal factor (inhibits a signal transduction protein involved in cell division); protective antigen (assists entry of above toxins into cells)
Transmission: direct contact with animal skins or products (most commonly sheep and cattle) and entry of the organisms through abrasions or cuts; inhalation (use in germ warfare)
Cutaneous anthrax (90%–95% of cases): occurs through direct contact with infected or contaminated animal products; resembles insect bite but eventually swells to form a black scab, or eschar, with a central area of necrosis (malignant pustule); if untreated, death occurs in 20% of patients
Pulmonary anthrax: “first sign of the disease is death”; inhalation of spores present in contaminated hides or biological weapon; necrotizing pneumonia, meningitis, pronounced splenomegaly, and dissemination throughout the rest of the body
Prevention: vaccine available for high-risk patients; e.g., veterinarians, soldiers entering developing countries
Treatment: ciprofloxacin

**Actinomyces israelii**
Gram-positive filamentous bacteria; strict anaerobe; normal flora in tonsils and adenoids
Produces draining sinuses in the jaw, chest cavity, and abdomen; pus contains sulfur granules (yellow specks) that contain the bacteria
Treatment: ampicillin or penicillin G

**Nocardia asteroides**
Gram-positive filamentous bacteria; strict aerobe; partially acid-fast
Produces granulomatous microabscesses in the lungs
Frequently disseminates to the CNS and kidneys
Treatment: TMP-SMX

**Bordetella pertussis**
Gram-negative rod
Pili attach to cilia in upper respiratory tract; toxin stimulates adenylate cyclase, which catalyzes the addition of ADP-ribose to the inhibitory subunit of the G protein complex; toxin also produces absolute lymphocytosis (normal-appearing lymphocytes) often in leukemoid reaction range
Produces whooping cough, transmitted by droplet infection
Catarhal phase: lasts 1–2 weeks; mild coughing, rhinorrhea, conjunctivitis
Paroxysmal coughing phase: lasts 2–5 weeks; characteristic 4–5 coughs in succession on expiration followed by an inspiratory whoop; absolute lymphocytosis (20,000–50,000 cells/mm³)
Convalescence phase: lasts 1–2 weeks; slow decline in coughing and lymphocytosis
Complications: hemorrhage into skin, conjunctiva, bronchus, brain from coughing; otitis media; meningoencephalitis (10%); rectal prolapse from coughing; pneumonia (most common cause of death in children <3 years old; children <1 year old have no protection from mother’s immunoglobulins)
Diagnosis: nasopharyngeal swabs using special cough plate; direct immunofluorescence of swab material
Treatment: erythromycin

**Haemophilus influenzae**
Gram-negative rod
Common cause of sinusitis, otitis media, conjunctivitis (pink-eye)
Inspiratory stridor may be due to acute epiglottitis
Swelling of epiglottis produces “thumbprint sign” on lateral x-ray of the neck
Most common bacterial cause of acute exacerbation of COPD
Treatment: cefotaxime; ceftriaxone

**Moraxella catarrhalis**
Gram-negative diplococcus
Common cause of typical pneumonia, especially in the elderly
Second most common pathogen causing acute exacerbation of COPD
Common cause of chronic bronchitis, sinusitis, otitis media
Treatment: amoxicillin-clavulanate
**Table 17-3 Summary of Respiratory Microbial Pathogens—cont’d**

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Green sputum (pyocyanin)</td>
</tr>
<tr>
<td></td>
<td>Water-loving bacteria most often transmitted by respirators</td>
</tr>
<tr>
<td></td>
<td>Most common cause of nosocomial pneumonia and death due to pneumonia in cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Pneumonia often associated with infarction due to vessel invasion</td>
</tr>
<tr>
<td></td>
<td>Treatment: antipseudomonal β-lactam + aminoglycoside + antipseudomonal quinolone or macrolide</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>Gram-negative fat rod surrounded by a mucoid capsule</td>
</tr>
<tr>
<td></td>
<td>Common gram-negative organism causing lobar pneumonia and typical pneumonia in elderly patients in</td>
</tr>
<tr>
<td></td>
<td>nursing homes</td>
</tr>
<tr>
<td></td>
<td>Common cause of pneumonia in alcoholics; however, <em>S. pneumoniae</em> is still the most common pneumonia</td>
</tr>
<tr>
<td></td>
<td>Typical pneumonia associated with blood-tinged, thick, mucoid sputum</td>
</tr>
<tr>
<td></td>
<td>Lobar consolidation and abscess formation are common</td>
</tr>
<tr>
<td></td>
<td>Treatment: varies with susceptibility</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>Gram-negative rod (requires IF stain or Dieterle silver stain to identify in tissue)</td>
</tr>
<tr>
<td></td>
<td>Antigens can also be detected in urine</td>
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<tr>
<td></td>
<td>Water-loving bacterium (water coolers; mists in produce section of grocery stores; outdoor restaurants</td>
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<tr>
<td></td>
<td>in summer; rain forests in 2005)</td>
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<tr>
<td></td>
<td>Risk factors: alcoholic, smoker, immunosuppression</td>
</tr>
<tr>
<td></td>
<td>Atypical pneumonia associated with high fever, dry cough, flu-like symptoms</td>
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<tr>
<td></td>
<td>May produce tubulointerstitial disease with destruction of the JG apparatus leading to hyporeninemic</td>
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<tr>
<td></td>
<td>hypoaldosteronism (type IV renal tubular acidosis—hyponatremia, hyperkalemia, metabolic acidosis)</td>
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<tr>
<td></td>
<td>Urine antigen test excellent screen</td>
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<td></td>
<td>Treatment: fluoroquinolone; azithromycin</td>
</tr>
<tr>
<td><em>Yersinia pestis</em></td>
<td>Gram-negative rod</td>
</tr>
<tr>
<td></td>
<td>Cause of plague</td>
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<tr>
<td></td>
<td>Transmitted by bite of rat flea; primary reservoir for bacteria are ground squirrels in the Southwest</td>
</tr>
<tr>
<td></td>
<td>Also transmitted person-to-person by droplet infection</td>
</tr>
<tr>
<td></td>
<td>Macrophages cannot kill bacteria because V and W antigens provide protection</td>
</tr>
<tr>
<td></td>
<td>Three types of disease: bubonic (most common), pneumonic (transmitted by aerosol), septicemic</td>
</tr>
<tr>
<td></td>
<td>Bubonic type: bite by rat flea that has recently bitten an infected ground squirrel; infected lymph</td>
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<td>nodes enlarge (usually in the groin), mat together, and drain to the surface (buboes)</td>
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<tr>
<td></td>
<td>Treatment: pneumatic type: gentamicin</td>
</tr>
<tr>
<td><strong>Systemic Fungi</strong></td>
<td></td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Budding yeast with narrow-based buds; surrounded by a thick capsule. Found in pigeon excreta (around</td>
</tr>
<tr>
<td>(see Fig. 17-5F)</td>
<td>buildings, outside office windows, under bridges)</td>
</tr>
<tr>
<td></td>
<td>Primary lung disease (40%): granulomatous inflammation with caseation. Do not have to be</td>
</tr>
<tr>
<td></td>
<td>immunocompromised.</td>
</tr>
<tr>
<td></td>
<td>Treatment: fluconazole</td>
</tr>
<tr>
<td><em>Aspergillus fumigatus</em></td>
<td>Fruiting body and narrow-angled (&lt;45 degrees), branching septate hyphae</td>
</tr>
<tr>
<td>(see Fig. 17-5G)</td>
<td>Aspergilloma: fungus ball (visible on x-ray) that develops in a preexisting cavity in the lung (e.g.,</td>
</tr>
<tr>
<td></td>
<td>old TB site); cause of massive hemoptysis (invades blood vessels)</td>
</tr>
<tr>
<td></td>
<td>Allergic bronchopulmonary aspergillosis: type I and type III hypersensitivity reactions; IgE levels</td>
</tr>
<tr>
<td></td>
<td>increased; eosinophilia. Intense inflammation of airways and mucus plugs in terminal bronchioles.</td>
</tr>
<tr>
<td></td>
<td>Repeated attacks may lead to bronchiectasis and interstitial lung disease; treatment with corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Vessel invader with hemorrhagic infarctions and a necrotizing bronchopneumonia</td>
</tr>
<tr>
<td></td>
<td>Treatment: voriconazole</td>
</tr>
<tr>
<td><em>Mucor species</em></td>
<td>Wide-angled hyphae (&gt;45 degrees) without septa</td>
</tr>
<tr>
<td></td>
<td>Clinical settings: diabetes, immunosuppressed patients</td>
</tr>
<tr>
<td></td>
<td>Vessel invader and produces hemorrhagic infarcts in the lung</td>
</tr>
<tr>
<td></td>
<td>Invades the frontal lobes in patients with diabetic ketoacidosis (rhinocerebral mucormycosis)</td>
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<tr>
<td></td>
<td>Treatment: liposomal amphotericin B</td>
</tr>
<tr>
<td><em>Coccidioides immitis</em></td>
<td>Spherules with endospores in tissues</td>
</tr>
<tr>
<td>(see Fig. 17-5H)</td>
<td>Contracted by inhaling arthrospores in dust while living or passing through arid desert areas in the</td>
</tr>
<tr>
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<td>Southwest (valley fever); increased after earthquakes (increased dust)</td>
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<td></td>
<td>Flu-like symptoms and erythema nodosum (painful nodules on lower legs; inflammation of subcutaneous</td>
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<tr>
<td></td>
<td>fat)</td>
</tr>
<tr>
<td></td>
<td>Treatment: usually self-limited; if severe: itraconazole or fluconazole</td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>Most common systemic fungal infection</td>
</tr>
<tr>
<td>(see Fig. 17-5I and J)</td>
<td>Endemic in Ohio and central Mississippi river valleys</td>
</tr>
<tr>
<td></td>
<td>Inhalation of microconidia in dust contaminated with excreta from bats (increased incidence in cave</td>
</tr>
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<td></td>
<td>explorers, spelunkers, starlings, or chickens (common in chicken farmers)</td>
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<tr>
<td></td>
<td>Granulomatous inflammation with caseous necrosis</td>
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<td>Yeast forms are present in macrophages</td>
</tr>
<tr>
<td></td>
<td>Simulates TB lung disease; produces coin lesions, consolidations, miliary spread, and cavitation</td>
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<td></td>
<td>Marked dystrophic calcification of granulomas; most common cause of multiple calcifications in the</td>
</tr>
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<td>spleen</td>
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<tr>
<td></td>
<td>Treatment: usually self-limited; if severe: itraconazole or liposomal amphotericin B</td>
</tr>
</tbody>
</table>

Continued
### PATHOGEN DISCUSSION

**Blastomyces dermatitidis** *(see Fig. 17-5K)*

- Yeasts have broad-based buds and nuclei
- Occurs in Great Lakes region, central, and southeastern United States
- Most often associated with fishing (most common), hunting, gardening, exposure to beaver dams (beavers are reservoirs for the fungus)
- Male dominant disease
- Produces skin and lung disease; skin lesions simulate squamous cell carcinoma
- Granulomatous inflammation with caseous necrosis
- **Treatment:** liposomal amphotericin B

**Pneumocystis jiroveci** *(see Fig. 4-15A)*

- Similar to fungi but have no ergosterol in plasma membrane
- Cysts and trophozoites present; cysts attach to type I pneumocytes
- Primarily an opportunistic infection; occurs when CD4 count < 200 cells/mm³.
- Common initial AIDS-defining infection
- **Treatment:** TMP-SMX given prophylactically when CD4 count < 200 cells/mm³

#### Table 17-3 Summary of Respiratory Microbial Pathogens—cont’d

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blastomyces dermatitidis</strong> <em>(see Fig. 17-5K)</em></td>
<td>Yeasts have broad-based buds and nuclei. Occurs in Great Lakes region, central, and southeastern United States. Most often associated with fishing (most common), hunting, gardening, exposure to beaver dams (beavers are reservoirs for the fungus). Male dominant disease. Produces skin and lung disease; skin lesions simulate squamous cell carcinoma. Granulomatous inflammation with caseous necrosis. <strong>Treatment:</strong> liposomal amphotericin B.</td>
</tr>
<tr>
<td><strong>Pneumocystis jiroveci</strong> <em>(see Fig. 4-15A)</em></td>
<td>Similar to fungi but have no ergosterol in plasma membrane. Cysts and trophozoites present; cysts attach to type I pneumocytes. Primarily an opportunistic infection; occurs when CD4 count &lt; 200 cells/mm³. Common initial AIDS-defining infection. Predominantly produces pulmonary disease. Patients develop fever, dyspnea, and severe hypoxemia. Diffuse intra-alveolar foamy exudates with cup-shaped cysts best visualized with silver or Giemsa stains. Chest x-ray shows diffuse alveolar and interstitial infiltrates. <strong>Treatment:</strong> TMP-SMX given prophylactically when CD4 count &lt; 200 cells/mm³.</td>
</tr>
</tbody>
</table>

**M. pneumoniae:** MCC atypical pneumonia

- Atypical pneumonia: interstitial pneumonia; no signs of consolidation

**Pseudomonas aeruginosa:** nosocomial pneumonia; contracted from respirators

**Aspergillus fumigatus:** MC pathogen causing pneumonia in AIDS

**P. jiroveci:** MC pathogen causing pneumonia in AIDS

#### Notes
- ARDS, Acute respiratory distress syndrome; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; IF, immunofluorescent; JG, juxtaglomerular; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome; TB, tuberculosis; TMP-SMX, trimethoprim-sulfamethoxazole.
17-6: A, Primary tuberculosis. Note the tan-yellow subpleural granuloma with caseation necrosis and the tan-yellow area of caseation necrosis in the hilar lymph node in the mid-lung field. The two of these together is called a Ghon complex. The inset shows an acid-fast stain with numerous Mycobacterium tuberculosis organisms. B, Reactivation tuberculosis. The apices of both lungs show gray-white areas of caseation necrosis and multiple areas of cavitation. (A from Klatt E: Robbins and Cotran Atlas of Pathology. Philadelphia, Saunders, 2006, p 197, Fig. 8-4; inset from Hoffbrand AV: Color Atlas: Clinical Hematology, 3rd ed, St. Louis, Mosby, 2000, p 136, Fig. 7-85B; B from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 386, Fig. 8-32.)

TB: acid-fastness due to mycolic acid
TB: cord factor is virulence factor

PPD: does not distinguish active vs inactive TB

1° TB: upper part of lower lobes; lower part of upper lobes; Ghon complex

Reactivation TB: upper lobe cavitary lesion(s)
TB: drenching night sweats, fever, weight loss

Kidneys: MC extrapulmonary site TB
TB in vertebrae: Pott disease

(3) Characteristics
(a) Strict aerobe, acid-fast (due to mycolic acid in cell wall)
(b) Cord factor is virulence factor

(4) Screening
(a) Purified protein derivative (PPD) intradermal skin test
(b) Does not distinguish active from inactive disease

(5) Protein in cell wall
• Responsible for positive PPD

(6) Drug resistance
(a) Chromosome mutations involving mycolic acid
(b) Chromosome mutations involving catalase peroxidase
• Enzyme is required to activate isoniazid.

b. Primary TB
(1) Subpleural location (Fig. 17-6A)
(a) Upper part of the lower lobes or lower part of the upper lobes
(b) Ghon focus (caseous necrosis) in periphery
(c) Ghon complex (caseous necrosis) in hilar lymph nodes

(2) Usually resolves
(a) Produces a calcified granuloma or area of scar tissue
(b) May be a nidus for secondary TB

c. Secondary (reactivation) TB
(1) Due to reactivation of a previous primary TB site
(2) Involves one or both apices in upper lobes (see Fig. 17-6B)
(a) Ventilation (oxygenation) is greatest in the upper lobes.
(b) M. tuberculosis is a strict aerobe.

(3) Cavitary lesion due to release of cytokines from memory T cells

d. Clinical findings
• Fever, drenching night sweats, weight loss

e. Complications
(1) Miliary spread in lungs due to invasion into the bronchus or lymphatics
(2) Miliary spread to extrapulmonary sites
(a) Spread is due to invasion of pulmonary vein tributaries.
(b) Kidney is the most common extrapulmonary site.
(c) Adrenal involvement may result in Addison disease.

(3) Massive hemoptysis, bronchiectasis, scar carcinoma
(4) Granulomatous hepatitis, spread to vertebrae (Pott disease)

f. Diagnosis
(1) Bronchoalveolar lavage best for staining and culture
(2) Sputum cultures
g. Treatment
   (1) Isoniazid + rifampin + pyrazinamide
   (2) Noninfectious in 2 to 3 weeks
   (3) Treat for additional 9 to 12 months
      • Kills metabolically inactive persisters in lesions

8. *Mycobacterium avium-intracellulare* complex (MAC)
   a. Atypical mycobacterium
   b. Most common TB in AIDS (often disseminates)
      • Occurs when CD4 helper T cell (T₄) count falls <50 cells/mm³
   c. Treatment
      • Clarithromycin + rifabutin + ethambutol

9. Systemic fungal infections (see Fig. 17-5F to K)
   a. Contracted from inhalation of the pathogen
   b. Produce a granulomatous inflammatory reaction with or without caseation

B. Lung abscess
1. Causes of lung abscesses
   a. Most often due to aspiration of oropharyngeal material (e.g., tonsillar material)
      (1) Risk factors
         (a) Alcoholism
         (b) Loss of consciousness
         (c) Recent dental work
      (2) Microbial pathogens
         (a) Aerobic and anaerobic streptococci
         (b) *Staphylococcus*
         (c) *Prevotella*
         (d) *Fusobacterium*
         (e) Anaerobes in 60% of cases
   b. Complication of bacterial pneumonia
      • Examples—*Staphylococcus aureus, Klebsiella pneumoniae*
   c. Septic embolism
      • Example—infected endocarditis
   d. Obstructive lung neoplasia
      • From 10% to 15% of abscesses are behind a bronchus obstructed by cancer.

2. Gross findings
   a. Abscesses vary in size and location (Fig. 17-7A).
   b. Those due to aspiration are primarily located on the right side (Box 17-1).

3. Clinical findings
   a. Spiking fever and productive cough (foul-smelling sputum) are common.
   b. Chest imaging shows cavitation with an air-fluid level (see Fig. 17-7B).

4. Treatment
   a. Clindamycin
   b. Bronchoscopy if it does not resolve

17-7: A, Lung abscess. Note the large abscess spanning the right upper and lower lobes. It is filled with necrotic material. B, Lung abscess. The chest computed tomographic scan shows an abscess in the right lower lobe with an air-fluid level. (A from Corrin B: *Pathology of the Lungs*, London, Churchill Livingstone, 2000, p 172, Fig. 5.5.16; B from Klatt E: *Robbins and Cotran Atlas of Pathology*, Philadelphia, Saunders, 2006, p 121, Fig. 5-74.)
VII. Vascular Lung Lesions

A. Pulmonary thromboembolism (PE)

1. Epidemiology and pathogenesis

   a. Third most common cardiovascular cause of death after acute myocardial infarction and stroke

   b. Source

      (1) Majority (90%) originate from the lower extremities.

      (2) Thrombi usually start in the calf veins and propagate into the popliteal and femoral vein, from which they embolize to the lungs.

   c. Risk factors (also refer to Chapter 5)

      • Stasis of blood flow (e.g., prolonged bed rest), hypercoagulable states

   d. Size of the embolus determines the pulmonary vessel that is occluded.

      (1) Large emboli occlude the major vessels (saddle embolus) (Fig. 17-8A).

      (2) Small emboli occlude medium-sized and small pulmonary arteries (see Fig. 2-15C).

   e. Potential consequences of pulmonary artery occlusion

      (1) Increase in pulmonary artery pressure

      (2) Decrease blood flow to pulmonary parenchyma

      • May cause hemorrhagic infarction

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**BOX 17-1 Aspiration Sites in the Lungs**

Foreign material localizes to different portions of the lung, depending on the position of the patient. In the standing or sitting position, material localizes in the posterobasal segment of the right lower lobe; in the supine position, the superior segment of the right lower lobe; and in the right-sided position, the right middle lobe or the posterior segment of the right upper lobe. The most common aspiration site is the superior segment of the right lower lobe.

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**17-8:** A, Saddle embolus occluding the main branches of the pulmonary artery. B, Radionuclide perfusion scan in the lung. The radionuclide scan shows multiple perfusion defects in both lungs (arrows) due to multiple pulmonary emboli. (A from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 57, Fig. 4-26; B from Forbes C, Jackson W: Color Atlas and Text of Clinical Medicine, 2nd ed, London, Mosby, 2002, Fig. 4-49.)
In a patient with normal bronchial artery blood flow (originates from thoracic aorta and intercostal arteries) and ventilation, a pulmonary embolus produces a hemorrhagic infarction in ~10% of cases. However, if the patient has decreased bronchial artery blood flow (e.g., decreased cardiac output) or previously damaged lungs (e.g., obstructive lung disease), then occlusion of the pulmonary vessel will likely result in a hemorrhagic infarction, which significantly increases risk of morbidity and death.

2. Red-blue, raised, wedge-shaped area that extends to the pleural surface (see Fig. 2-15C)
   a. Pleural surface has a fibrinous exudate (produces pleural friction rub).
      • Hemorrhagic pleural effusion may also occur.
   b. Majority are located in the lower lobes.
      • Perfusion is greater than ventilation in the lower lobes.

3. Clinical findings
   a. Saddle embolus
      (1) Sudden increase in pulmonary artery pressure
      (2) Produces acute right ventricular strain and sudden death
   b. Pulmonary infarction
      (1) Sudden onset of dyspnea and tachypnea
      (2) Fever
      (3) Pleuritic chest pain (pain on inspiration), friction rub, effusion
      (4) Expiratory wheezing
         • Due to release of thromboxane A2 (bronchoconstrictor) from platelets

4. Laboratory findings
   a. Respiratory alkalosis (arterial Pco₂ <33 mm Hg)
   b. PaO₂ <80 mm Hg (90% of cases; perfusion defect [refer to Chapter 2])
   c. Increase in a-a gradient (100% of cases)
   d. Increase in D-dimers (refer to Chapter 15)

5. Diagnosis
   a. Chest x-ray
      (1) Elevation of ipsilateral hemidiaphragm (most common finding)
      (2) Pleural effusion (usually hemorrhagic)
      (3) "Cut-off" sign of one or more pulmonary arteries
         • Hypovascularity behind the blocked vessel
      (4) Hampton hump
         • Wedge-shaped area of consolidation
   b. Abnormal perfusion radionuclide scan
      (1) Ventilation scan is normal, but the perfusion scan is abnormal (see Fig. 17-8B).
      (2) Pulmonary angiogram is gold standard confirmatory test.
         • Expensive and not clinically available in smaller hospitals
      (3) Spiral (helical) CT is excellent if preexisting lung disease is present.
   c. Positive D-dimers (refer to Chapter 15)
      (1) Test is usually performed with ventilation/perfusion (V/Q) scan or spiral CT.
      (2) Sensitivity ranges from 85% to 98% for the diagnosis of a PE.
         • Most useful in excluding PE if the test returns normal
      (3) Specificity is poor.

6. Treatment
   a. Reperfusion therapy is recommended for severe PE associated with hypotension or shock.
   b. Anticoagulation is the cornerstone of therapy.
      • Heparin or low-molecular-weight heparin; warfarin for extended therapy
   c. Inferior vena cava filters

7. Prognosis
   a. Case fatality 1 month after diagnosis is 12%.
   b. Recurrence rate is ~6% during the first 6 months.

**B. Pulmonary hypertension (PH)**

1. Definition
   a. Mean pulmonary artery pressure >25 mm Hg at rest (normal mean pressure 15 mm Hg)
   b. Mean pulmonary artery pressure >30 mm Hg with exercise (normal mean pressure 20 mm Hg)
2. Epidemiology and pathogenesis
   a. Primary PH
      (1) Primary type is more common in women than men.
      (2) Genetic predisposition
      (3) Vascular hyperreactivity with proliferation of smooth muscle
   b. Secondary PH
      (1) Endothelial cell dysfunction
         (a) Loss of vasodilators (e.g., nitric oxide)
         (b) Increase in vasoconstrictors (e.g., endothelin)
      (2) Hypoxemia and respiratory acidosis stimulate vasoconstriction of pulmonary arteries.
         • Causes smooth muscle hyperplasia and hypertrophy
      (3) Causes
         (a) Chronic hypoxemia
            • Examples—chronic lung disease, living at high altitude
         (b) Chronic respiratory acidosis
            • Chronic bronchitis (CB); obstructive sleep apnea
         (c) Loss of pulmonary vasculature
            • Increases workload for remaining vessels; emphysema, recurrent pulmonary emboli
         (d) Left-to-right cardiac shunts (refer to Chapter 11)
            • Volume overloading pulmonary vasculature
         (e) Left-sided valvular disease (e.g., mitral stenosis)
            • Backup of blood into pulmonary veins; pulmonary venous hypertension
            • Most common type seen in practice
         (f) Drugs
            • Anorexigens (e.g., aminorex, fenfluramine), amphetamines

3. Pathologic findings
   a. Atherosclerosis of main elastic pulmonary arteries (PAs)
      • Due to increased pressure on the endothelium leading to injury
   b. Proliferation of myointimal cells and smooth muscle cells

4. Clinical findings
   a. Exertional dyspnea most common presenting sign
   b. Chest pain
   c. Chest radiograph shows tapering of the pulmonary arteries
   d. Accentuated P₂ (sign of PH)
   e. Left parasternal heave (sign of right ventricular hypertrophy [RVH])
      • PH imposes an increased afterload on the right ventricle.
   f. Right-sided heart failure due to cor pulmonale

5. Diagnosis
   a. Catheterization to measure pressures
      • Can also use transthoracic Doppler echocardiogram
   b. Chest x-ray
      (1) Enlargement of main pulmonary arteries
      • Rapid tapering of distal vessels
      (2) Right ventricular enlargement
   c. Electrocardiogram
      • Right axis deviation, right ventricular enlargement, right atrial enlargement, and ST and T wave changes that reflect right ventricular strain

6. Treatment
   a. Treat the underlying condition
   b. Warfarin (international normalized ratio 1.5–2.5)
   c. Diuretics (e.g., furosemide)
   d. Oxygen
   e. Vasodilators
      • Calcium channel blockers, prostanoids, endothelin receptor antagonists
   f. Bilateral lung or heart-lung transplant

7. Cor pulmonale (Fig. 17-9)
   • Combination of PH and RVH leading to right-sided heart failure (RHF)
C. **Goodpasture syndrome (refer to Chapter 20)**

1. Antibodies are directed against basement membrane in pulmonary capillaries and glomerular capillaries (type II hypersensitivity reaction).
2. Pulmonary hemorrhage with hemoptysis often precede renal failure.

VIII. **Restrictive Lung Diseases**

A. **Spirometry (Fig. 17-10)**

1. Spirometry is helpful in distinguishing restrictive from obstructive lung disease.
2. Important volumes and capacities
   a. Total lung capacity (TLC)—total amount of air in a fully expanded lung
   b. Residual volume (RV)—volume of air left over in the lung after maximal expiration
   c. Tidal volume (TV)—volume of air that enters or leaves the lungs during normal quiet respiration
   d. Forced vital capacity (FVC)—total amount of air expelled after a maximal inspiration
      - Normal FVC is 5 L (see Fig. 17-10A).
   e. Forced expiratory volume in 1 second (FEV₁)—amount of air expelled from the lungs in 1 second after a maximal inspiration.
      - Normal FEV₁ is 4 L (see Fig. 17-10A).
   f. Ratio of FEV₁/FVC is normally 4/5, or 80%

B. **Epidemiology of restrictive lung disease (RLD)**

1. Definition—disorders characterized by reduced total lung capacity (TLC) in the presence of a normal or reduced expiratory flow rate
2. More common in men than women
3. Causes
   a. Chest wall disorders in the presence of normal lungs
      - Examples—kyphoscoliosis (refer to Chapter 24), pleural disease (e.g., mesothelioma), obesity (refer to Chapter 8)
   b. Acute or chronic interstitial lung diseases (ILDs)
      (1) Acute interstitial lung disease (e.g., ARDS)
      (2) Chronic interstitial lung disease
         (a) Fibrosing disorders (e.g., idiopathic pulmonary fibrosis [most common cause of RLD]; pneumoconiosis)
         (b) Granulomatous disease (e.g., sarcoidosis)

C. **Pathogenesis of interstitial fibrosis**

1. Earliest manifestation is an alveolitis.
   - Leukocytes release cytokines, which stimulate fibrosis.
2. Effects of interstitial fibrosis
   a. Decreases lung compliance
      (1) Decreased expansion of the lung parenchyma during inspiration
      (2) Damage to type I/II alveolar cells and endothelial cells
         • Functional loss of alveolar and capillary units
   b. Increases lung elasticity
      • Recoil of the lung on expiration is increased.

3. Clinical and laboratory findings in all RLDs
   a. Dry cough and exertional dyspnea
   b. Late inspiratory crackles in lower lung fields
   c. Potential for cor pulmonale
   d. Pulmonary function test findings and arterial blood gases
      (1) All volumes and capacities are equally decreased.
      (2) Decreased FEV₁ (see Fig. 17-10B)
         • Example—3 L (normal 4 L)
      (3) Decreased FVC (see Fig. 17-10B)
         • Often the same value as FEV₁ (3 L) because of increased lung elasticity
      (4) Increased ratio of FEV₁/FVC
         • Example—3/3 = 100% (normal is 80%)
      (5) Respiratory alkalosis (arterial Pco₂ <33 mm Hg)
      (6) Decreased Pao₂
   e. Chest radiograph findings
      • Diffuse bilateral reticulonodular infiltrates

D. Pneumoconioses
1. Epidemiology
   a. Inhalation of mineral dust into the lungs leading to interstitial fibrosis
      (1) Mineral dust includes coal dust, silica, asbestos, and beryllium.
      (2) Accounts for ~25% of cases of chronic interstitial lung disease
   b. Particle size determines site of lung deposition
      (1) 1- to 5-μm particles
         • Reach the bifurcation of the respiratory bronchioles and alveolar ducts
      (2) Smaller than 0.5-μm particles
         • Reach the alveoli and are phagocytosed by alveolar macrophages
   c. Coal dust is the least fibrogenic particle.
   d. Silica, asbestos, and beryllium are very fibrogenic.

2. Coal worker's pneumoconiosis (CWP)
   a. Sources of coal dust (anthracotic pigment)
      • Coal mines, large urban centers, tobacco smoke
   b. Pulmonary anthracosis
      (1) Usually asymptomatic
      (2) Anthracotic pigment in interstitial tissue and hilar nodes
         • Alveolar macrophages with anthracotic pigment are called "dust cells."
   c. Simple CWP
      (1) Fibrotic opacities are smaller than 1 cm in upper lobes and upper portions of lower lobes.
      (2) Coal deposits adjacent to respiratory bronchioles produce centrilobular (centrilobular; element of obstructive lung disease).
   d. Complicated CWP (progressive massive fibrosis)
      (1) Fibrotic opacities larger than 1 to 2 cm with or without necrotic centers (Fig. 17-11A)
      (2) Crippling lung disease ("black lung" disease)
      (3) No increased incidence of TB or primary lung cancer
      (4) Cor pulmonale may occur.
      (5) Caplan syndrome may occur.
         • CWP plus large cavitating rheumatoid nodules in the lungs

3. Silicosis
   a. Epidemiology
      (1) Most common occupational disease in the world
      (2) Quartz (crystalline silicon dioxide) is most often implicated.
         • Sources: foundries (casting metal), sandblasting, working in mines
b. Pathogenesis
   (1) Quartz is highly fibrogenic and deposits in the upper lungs.
   (2) Quartz activates and is cytolytic to alveolar macrophages.
      • Macrophages release cytokines that stimulate fibrogenesis.
c. Acute exposure: chest x-ray findings
   • Ground glass appearance in all lung fields
d. Chronic exposure: chest x-ray findings:
   (1) Nodular opacities in the lungs
      • Concentric layers of collagen with or without central cavitation (see Fig. 17-11B)
Silicosis: egg-shell calcification hilar nodes
Silicosis:  
<table>
<thead>
<tr>
<th>Risk lung cancer/TB</th>
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Asbestos fibers deposit in respiratory unit

Ferruginous bodies: iron coated asbestos fibers

Benign pleural plaques: most common asbestos lesions

Lung carcinoma: MC asbestos-related cancer

Mesothelioma: arises from pleura serosa; encases lung

Asbestos: no TB risk

Berylliosis: risk lung cancer

Sarcoidosis: MC noninfectious granulomatous lung disease

Sarcoidosis: blacks > whites; women > men

Sarcoidosis: CD4 T<sub>h</sub> cells interact with unknown antigen (? mycobacterial KatG protein)

(2) “Egg-shell” calcification in hilar nodes
  - Rim of dystrophic calcification in the nodes
  e. Complications
    (1) Cor pulmonale, Caplan syndrome
    (2) Increased risk for developing lung cancer and TB

4. Asbestos-related disease
   a. Geometric forms of asbestos
      (1) Serpentine
          (a) Curly and flexible fibers (e.g., chrysotile)
          (b) Produces interstitial fibrosis and lung cancer
      (2) Amphibole
          (a) Straight and rigid (e.g., crocidolite)
          (b) Produces interstitial fibrosis, lung cancer, mesothelioma
      (3) Deposition sites
          - Respiratory bronchioles, alveolar ducts, alveoli
   b. Sources
      (1) Insulation around pipes in old naval ships
      (2) Roofing material, ceiling tiles, floor tiles used >20 years ago
      (3) Demolition of old buildings
      (4) Automobile shops
   c. Appearance in tissue
      (1) Fibers are coated by iron and protein (called ferruginous bodies)
          - Macrophages phagocytose and coat the fibers with ferritin (synthesized by macrophages)
      (2) Golden, beaded appearance in sputum or in distal, small airways (see Fig. 17-11C)
   d. Asbestos-related disease
      (1) Benign pleural plaques
          (a) Most common asbestos lesions (asymptomatic)
          (b) Calcified plaques on the pleura and dome of the diaphragm
          (c) Not a precursor lesion for a mesothelioma
      (2) Diffuse interstitial fibrosis with/without pleural effusions
      (3) Primary bronchogenic carcinoma
          (a) Risk further increases if the patient smokes cigarettes
          (b) Latency period ~20 years after exposure
      (4) Malignant mesothelioma of pleura
          (a) No etiologic relationship with smoking
          (b) Arises from the serosal cells lining the pleura
          (c) Encases and locally invades the subpleural lung tissue (see Fig. 17-11D)
          (d) Latency period 25 to 40 years after first exposure
      (5) No increased risk for TB
   e. Complications
      - Cor pulmonale, Caplan syndrome

5. Berylliosis
   a. Exposure in the nuclear and aerospace industry
   b. Diffuse interstitial fibrosis with noncaseating granulomas
   c. Increased risk for cor pulmonale and primary lung cancer

E. Sarcoidosis
   1. Epidemiology
      a. Definition—multisystem noninfectious granulomatous disease that produces chronic interstitial fibrosis
      b. Accounts for ~25% of cases of chronic ILD
      c. Common in blacks and nonsmokers
      d. More common in women than men
      e. Incidence peaks between 20 to 39 years
   2. Pathogenesis
      a. Disorder in immune regulation
         - Major histocompatibility complex (MHC) genes and non-MHC genes have been located on the short arm of chromosome 6 that are genetic risk factors.
      b. CD4 T<sub>h</sub> cells interact with unknown airborne antigens (e.g., mold or mildew, pesticides, mycobacterial KatG protein).
         - Releases cytokines causing formation of noncaseating granulomas
c. Diagnosis of exclusion
   - Must rule out other granulomatous diseases
3. Lung disease
   a. Primary target organ
      (1) Granulomas located in the interstitium and mediastinal and hilar nodes
      (2) Granulomas contain multinucleated giant cells (see Fig. 17-11E).
      - Contain laminated calcium concretions (Schaumann bodies) and stellate inclusions (called asteroid bodies)
   b. Dyspnea is the most common symptom.
4. Skin lesions
   a. Nodular lesions containing granulomas (see Fig. 17-11F)
   b. Violaceous rash on the nose and cheeks (called lupus pernio)
   c. Erythema nodosum
      (1) Painful nodules on lower extremities
      (2) Inflammation of subcutaneous fat
5. Eye lesions: produces uveitis
   - Blurry vision, glaucoma, and corneal opacities
6. Liver lesions
   - Granulomatous hepatitis (most common non-infectious cause)
7. Other multisystem findings
   a. Enlarged salivary and lacrimal glands
   b. Central diabetes insipidus (CDI; hypothalamic and posterior pituitary disease)
   c. Granulomas in the bone marrow and spleen
   d. Calcium renal stones, nephrocalcinosis
8. Laboratory findings
   a. Increased angiotensin-converting enzyme (ACE; 60% of cases)
      - Nonspecific finding
   b. Hypercalcemia (5% of cases)
      - Increased synthesis of 1-α-hydroxylase in macrophages in the granulomas (hypervitaminosis D)
   c. Other findings
      (1) Polyclonal gammopathy
      (2) Cutaneous anergy to common skin antigens (e.g., Candida)
      - Due to consumption of CD4 T H cells in granulomas and loss of cells in alveolar secretions
9. Chest radiograph
   a. Enlarged hilar and mediastinal lymph nodes (called “potato nodes”)
   b. Reticulonodular densities throughout the lung parenchyma
10. Treatment
    a. Majority (>50%) have spontaneous remission in 3 years and do not require treatment
    b. Corticosteroids if treatment is required
    c. Tumor necrosis factor inhibitors
    d. Hydroxychloroquine useful if skin involvement is present
11. Prognosis
    - Approximately 5% of patients die (particularly black Americans).

F. Idiopathic pulmonary fibrosis
   1. Epidemiology
      a. Accounts for ~30% of cases of RLD
      b. More common in smoking males than in females
      c. Usually occurs in individuals 40 to 70 years old
   2. Pathogenesis
      a. Repeated cycles of alveolitis are triggered by an unknown agent.
      b. Release of cytokines produces interstitial fibrosis.
      c. Alveolar fibrosis leads to proximal dilatation of the small airways.
      - Lung has a honeycomb appearance.
   3. Clinical findings
      a. Fever
      b. Dyspnea with exertion
      c. Chronic, nonproductive cough
      d. Late inspiratory crackles
4. Treatment
   • None very useful; however, corticosteroids are generally prescribed
   5. Poor prognosis (median survival 3 to 5 years after diagnosis)

G. Collagen vascular diseases
   1. Account for ~10% of cases of chronic ILD
   2. Systemic sclerosis (refer to Chapter 4)
      • Most common cause of death is lung disease.
   3. Systemic lupus erythematosus (SLE; refer to Chapter 4)
      a. Interstitial lung disease occurs in 50% of patients.
      b. Pleuritis with pleural effusions

Any unexplained pleural effusion in a young woman is SLE until proved otherwise. Pleural fluid contains an inflammatory infiltrate (exudate), and lupus erythematosus cells (neutrophils with phagocytosed DNA) are sometimes present. One of the key criteria for diagnosing SLE is the presence of serositis, pleuritis with a pleural effusion being an example of this type of inflammation.

4. Rheumatoid arthritis (RA; refer to Chapter 24)
   a. Rheumatoid nodules in lungs plus a pneumoconiosis is called Caplan syndrome.
   b. Pulmonary findings in RA
      (1) Interstitial fibrosis with/without intrapulmonary rheumatoid nodules
         • Nodules often cavitating
      (2) Pleuritis with pleural effusions

H. Hypersensitivity pneumonitis
   1. Definition—extrinsic allergic alveolitis associated with exposure to a known inhaled antigen
      • Does not involve IgE antibodies (type I hypersensitivity) or have eosinophilia
   2. Farmer’s lung
      a. Exposure to *Saccharopolyspora rectivirgula* (thermophilic actinomycetes) in moldy hay
      b. First exposure
         • Patient develops precipitating IgG antibodies (present in serum)
      c. Second exposure
         (1) Antibodies combine with inhaled allergens to form immune complexes.
            • Type III hypersensitivity reaction (HSR)
         (2) Immuno complexes produce an inflammatory reaction in lung tissue.
      d. Chronic exposure
         • Additional component of granulomatous inflammation (type IV HSR)
      e. Treatment
         (1) Use of facial mask to prevent contact with antigen
         (2) Corticosteroids
   3. Silo filler’s disease
      a. Inhalation of gases (oxides of nitrogen) from plant material
      b. Causes an immediate hypersensitivity reaction associated with dyspnea
      c. Treatment
         • Corticosteroids
   4. Byssinosis
      a. Epidemiology
         (1) Occurs in workers in textile factories
         (2) Contact with cotton, linen, hemp products
            • Exposure to bacterial endotoxin from gram-negative bacteria growing on the cotton
      b. Clinical findings
         (1) Dyspnea develops upon exposure to cotton, linen, or hemp products.
         (2) Workers feel better over the weekend (no exposure to antigens).
            • Depression occurs when returning to work on Monday (“Monday morning blues”)
      c. Treatment
         • Improve dust removal
I. Drugs associated with interstitial fibrosis
   1. Amiodarone
   2. Bleomycin and busulfan
   3. Cyclophosphamide
   4. Methotrexate and methysgeride
   5. Nitrosourea and nitrofurantoin

J. Radiation-induced lung disease
   1. Acute pneumonitis may occur 1 to 6 months after therapy.
   2. Clinical findings
      a. Fever, dyspnea
      b. Pleural effusions
      c. Chest x-ray shows infiltrates
   3. Some patients develop chronic radiation pneumonitis.

IX. Chronic Obstructive Pulmonary Disease (COPD)
   A. Epidemiology
      1. Definition—progressive, largely irreversible obstruction to airflow out of the lungs
      2. Cigarette smoking is the principal cause of COPD (refer to Chapter 7).
      3. Greater than 10% of the population >45 years old has airflow obstruction.
      4. Majority of patients with COPD have both emphysema (air space destruction) and chronic bronchitis (CB; conducting airway inflammation).

   B. Emphysema
      1. Definition—permanent enlargement of all or part of the respiratory unit
         a. Respiratory unit includes respiratory bronchioles, alveolar ducts, and alveoli
      2. Epidemiology
         a. Causes
            (1) Smoking cigarettes is the most common cause.
            (2) \( \alpha \)-Antitrypsin (AAT) deficiency
         b. Types of emphysema associated with smoking or loss of AAT
            (1) Centriacinar (centrilobular) emphysema
            (2) Panacinar emphysema
      3. Pathogenesis
         a. Increased compliance and decreased elasticity
            (1) There is an imbalance between elastase and antielastases (e.g., AAT)
            (2) There is an imbalance between oxidants (free radicals [FRs]) and antioxidants (e.g., glutathione [GSH])
            (3) Elastase and oxidants derive from neutrophils and macrophages.
            (4) Net effect of the preceding is destruction of elastic tissue.
         b. Cigarette smoke is chemotactic to neutrophils and macrophages.
            • Neutrophils/macrophages accumulate in the respiratory unit and release FRs and elastases.
            c. FRs in cigarette smoke inactivate AAT and antioxidants.
               • Produces a functional AAT deficiency
         d. Normal function of elastic tissue
            (1) Fibers attach to the outside wall of the small airways (Fig. 17-12A).
            (2) Fibers apply radial traction to keep the airway lumens open.
         e. Destruction of elastic tissue causes loss of radial traction.
            • Small airways collapse, particularly on expiration.
         f. Sites of elastic tissue destruction in emphysema
            (1) Distal terminal bronchiole at its junction with the respiratory bronchiole (RB)
            (2) All or part of the respiratory unit
         g. Site of obstruction and air trapping in emphysema
            (1) During expiration the distal terminal bronchioles collapse, which prevents egress of air from the respiratory unit.
            (2) Trapped air distends parts of the respiratory unit that have lost their elastic tissue support.
      4. Centriacinar (centrilobular) emphysema
         a. Epidemiology
            • Most common type of emphysema in smokers
         b. Pathogenesis
            (1) It primarily involves the apical segments of the upper lobes.
            (2) Distal terminal bronchioles and the RBs (see Figs. 17-12B and 17-13A) are the sites of elastic tissue destruction.
17-12: Types of emphysema. A. The schematic shows a normal distal airway, including a terminal bronchiole (TB) leading into the respiratory unit consisting of a respiratory bronchiole (RB), alveolar duct (AD), and alveoli (ALV). Elastic fibers apply radial traction to keep these airways open. B, Centriacinar (centrilobular) emphysema is characterized by trapping of air in the respiratory bronchioles. Note how the elastic fibers of the distal TB are destroyed, causing obstruction to airflow. This causes the trapped air to distend the RBs, whose elastic tissue support is destroyed. C, Panacinar emphysema is characterized by trapping of air in the entire respiratory unit behind the collapsed TB.

(3) Air trapped behind the collapsed distal terminal bronchioles distends the RBs.
   • Trapped air increases RV and TLC.

5. Panacinar emphysema
   a. Epidemiology
      (1) Associated with AAT deficiency
         • Genetic or acquired causes (cigarette smoke inactivates AAT)
      (2) Genetic type of AAT deficiency
         (a) It is an autosomal dominant disorder.
         (b) MM phenotype is normal.
         (c) Normal amounts of AAT are synthesized in the liver.
         (c) Homozygous ZZ type has decreased synthesis of AAT by the liver.
      (3) Emphysema develops at an early age in the genetic type.
   b. Pathogenesis
      (1) Primarily affects the lower lobes
      (2) Distal terminal bronchioles and all parts of the respiratory units are the sites of elastic tissue destruction (see Figs. 17-12C and 17-13B).
      (3) Air trapped behind the collapsed terminal bronchioles distends the entire respiratory unit.
   c. Laboratory finding
      • Absent α₁-globulin peak in a serum protein electrophoresis (SPE)

6. Clinical findings in centriacinar and panacinar emphysema
   a. Progressive dyspnea and hyperventilation
      (1) Dyspnea is severe and occurs early in the disease.
      (2) Hypoxemia occurs late in the disease (takes time for destruction of respiratory units).
      (3) Sometimes patients are called “pink puffers.”
   b. Centriacinar type frequently coexists with CB.
   c. Breath sounds are diminished because of hyperinflation.
   d. Cor pulmonale is uncommon.

7. Chest radiograph (see Fig. 17-13C and D)
   a. Hyperlucent lung fields
   b. Increased anteroposterior diameter
   c. Vertically oriented heart
   d. Depressed diaphragms due to hyperinflated lungs

8. Pulmonary function tests and arterial blood gases
   a. Increased TLC due to an increase in RV
   b. Decreased FEV₁ (e.g., 1 L versus 4 L; see Fig. 17-10C)
   c. Decreased FVC (e.g., 3 L versus 5 L; see Fig. 17-10C)
      • Decreased FEV₁/FVC ratio (e.g., 1/3 = 33%)
   d. Decreased Pao₂ develops late in the disease.
      • Destruction of the capillary bed matches destruction of the respiratory unit.
   e. Normal to decreased arterial Pco₂ (respiratory alkalosis; “pink puffer”)
Upper and Lower Respiratory Disorders

17-13: A, Centriacinar (centrilobular emphysema). The enlarged spaces in the lung parenchyma are air-filled respiratory bronchioles that have lost their elastic tissue support. B, Panacinar emphysema. The enlarged spaces in the lung parenchyma are air-filled respiratory bronchioles, alveolar ducts, and alveoli that have lost their elastic tissue support. C, Chest radiograph in emphysema showing a vertically-oriented heart (arrow) and depressed diaphragm. D, Radiograph of the thorax in a patient with emphysema. There is an increase in lung volume, darkness of the lungs (increased air relative to tissue), and an increase in space between the sternum and the heart. (A and B reproduced by permission of the late Professor B.E. Heard, Brompton, UK; C from Forbes C, Jackson W: Color Atlas and Text of Clinical Medicine, 2nd ed, London, Mosby, 2002, p 186, Fig. 4-94; D from Goldman L, Schafer AI: Cecil's Medicine, 24th ed, Philadelphia, Saunders Elsevier, 2012, p 540, Fig. 88-3B.)

9. Treatment
   a. Cessation of smoking most important
   b. Pulmonary rehabilitation program
   c. Oxygen, using 1 to 2 L/minute, through nasal prongs
      • Maintain O₂ saturation of 90%
   d. Bronchodilators
      (1) Catecholamine inhalers/nebulizers
      (2) Steroid inhalers controversial
   e. Anticholinergics
10. Other types of emphysema unrelated to smoking or AAT deficiency
   a. Paraseptal emphysema
      (1) Localized disease in a subpleural location
      • Primarily targets the alveolar ducts and alveoli
      (2) Does not produce obstructive airway disease
      (3) Increased incidence of spontaneous pneumothorax
         • Due to rupture of subpleural blebs
   b. Irregular emphysema
      (1) Localized disease associated with scar tissue
      (2) Does not produce obstructive airway disease

C. Chronic bronchitis (CB)
1. Epidemiology
   a. Productive cough for at least 3 months for 2 consecutive years
   b. Causes
      (1) Smoking cigarettes
      (2) Cystic fibrosis
2. Pathogenesis
   a. Hypersecretion of mucus occurs in the bronchus and its subdivisions.
   b. Obstruction to airflow occurs from mucus plugs located in the segmental bronchi and proximal bronchioles.
   c. Irreversible fibrosis may occur in chronically inflamed segmental bronchi and bronchioles.
   d. Changes in the bronchi
      (1) Hypersecretion of submucosal mucus-secreting glands in trachea and bronchi
         • Primarily responsible for sputum overproduction
      (2) Acute inflammation (neutrophils) often superimposed on chronic inflammation
      (3) Loss of ciliated epithelium and presence of squamous metaplasia
   e. Changes in the bronchioles
      (1) Mucus plugs in lumens (block the exodus of CO₂)
      (2) Goblet cell metaplasia
      (3) Chronic inflammation and fibrosis narrowing the lumen

Turbulent airflow in the bronchus and its subdivisions is converted to laminar airflow primarily in the nonrespiratory bronchioles (<1 mm diameter). These bronchioles undergo parallel branching, which reduces airway resistance and spreads air out over a large cross-sectional area. In CD, mucus plugs located in the small diameter segmental bronchi and proximal nonrespiratory bronchioles allow air to move around them on inspiration (airways expand). However, on expiration when airway diameter is reduced, the mucus plugs prevent the exodus of large amounts of CO₂ arising from the distally located branching-airways. This produces respiratory acidosis (refer to Chapter 5). Furthermore, expiratory wheezing may also occur as air under pressure is forced past these areas of obstruction.

3. Clinical findings
   a. Productive cough
   b. Dyspnea occurs late in the disease.
   c. Hypoxemia and respiratory acidosis occur early in the disease.
   d. Cyanosis of skin and mucous membranes
      (1) O₂ saturation is decreased from hypoxemia (refer to Chapter 2).
      (2) Patients are called “blue bloaters” due to cyanosis of skin and mucous membranes.
   e. Tend to be stocky or obese
   f. Expiratory wheezing and sibilant rhonchi
   g. Cor pulmonale is commonly present.
4. Chest radiograph
   a. Large, horizontally oriented heart
   b. Increased bronchial markings
5. Pulmonary function tests and arterial blood gases
   a. Less increase in TLC and RV than emphysema
   b. Chronic respiratory acidosis
      (1) Arterial PCO₂ >45 mm Hg
      (2) Bicarbonate >30 mEq/L
   c. Moderate to severe hypoxemia early in the disease
TABLE 17-4 Comparison of Emphysema and Chronic Bronchitis

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>EMPHYSEMA</th>
<th>CHRONIC BRONCHITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>Normal to decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>pH</td>
<td>Normal to increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Habitus</td>
<td>Thin</td>
<td>Stocky</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Onset of hypoxemia</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Onset of dyspnea</td>
<td>Early</td>
<td>Late</td>
</tr>
</tbody>
</table>

6. Treatment (see IX.B.9.)
7. Summary of findings in emphysema and chronic bronchitis (Table 17-4)

D. Bronchial asthma
1. Epidemiology
   a. Episodic and reversible airway disease (most cases)
   b. Primarily targets the bronchi and its subdivisions and nonrespiratory bronchioles
   c. Most common chronic respiratory disease in children
      (1) More common in children than adults
      (2) Majority (50%–80%) develop symptoms before 5 years of age.
   d. Extrinsic and intrinsic types

2. Extrinsic asthma
   a. Pathogenesis
      (1) Type I HSR with exposure to extrinsic allergens
         • Typically develops in children with an atopic family history to allergies
      (2) Initial sensitization to an inhaled allergen
         (a) Stimulate induction of subset 2 helper T cells (CD4 T₃₋₂) that release interleukin (IL)-4 and IL-5
         (b) IL-4 stimulates isotype switching to IgE production.
         (c) IL-5 stimulates production and activation of eosinophils.
      (3) Inhaled antigens cross-link IgE antibodies on mast cells on mucosal surfaces.
         (a) Release of histamine and other preformed mediators
         (b) Functions of mediators
            • Stimulate bronchoconstriction, mucus production, influx of leukocytes
      (4) Late phase reaction (4–8 hours later)
         (a) Eotaxin is produced.
            • Chemotactic for eosinophils and activates eosinophils
         (b) Eosinophils release major basic protein (MBP) and cationic protein.
            • Damage epithelial cells and produce airway constriction
   b. Other mediators involved
      (1) Leukotrienes LTC-D-E₄ causes prolonged bronchoconstriction.
      (2) Acetylcholine causes airway muscle contraction.
   c. Histologic changes in bronchi
      (1) Thickening of the basement membrane
      (2) Edema and a mixed inflammatory infiltrate
      (3) Hypertrophy of submucosal glands
      (4) Hypertrophy/hyperplasia of smooth muscle cells
   d. Histologic changes in the bronchioles
      (1) Formation of spiral-shaped mucus plugs
         (a) Contain shed epithelial cells called Curschmann spirals
         (b) Pathologic effect of MBP and cationic protein
      (2) Crystalline granules in eosinophils coalesce to form Charcot-Leyden crystals.
      (3) Patchy loss of epithelial cells, goblet cell metaplasia
      (4) Thick basement membrane
      (5) Smooth muscle cell hypertrophy and hyperplasia
   e. Clinical findings
      (1) Episodic expiratory wheezing (inspiratory as well when severe)
      (2) Nocturnal cough

Asthma: episodic and reversible airway disease of bronchi, subdivisions, and bronchioles
Extrinsic asthma: type I HSR
IL-4: stimulates isotype switching to IgE production
IL-5: production/activation of eosinophils
Eosinophils: MBP/cationic protein damage epithelial cells
LTC-D-E₄/acetylcholine: potent bronchoconstrictors
Curschmann spirals: shed epithelial cells
Eosinophils: granules produce Charcot-Leyden crystals
Asthma: expiratory wheezing; nocturnal cough; ↑AP diameter
### Bronchial asthma: initially present with respiratory alkalosis

- Clubbing
- Productive cough

### Bronchiectasis:

- Periphery bronchi extend to dynein arm dyskinesia: cilia lack

### Intrinsic asthma:

- Nonimmune; viruses, air pollutants, aspirin/NSAIDs

### CF: MCC bronchiectasis

- U.S.; TB MCC worldwide

### E. Bronchiectasis

#### 1. Epidemiology and pathogenesis

- Definition—permanent dilation of the bronchi and bronchioles causing repeated episodes of airway infection and inflammation
  - Due to destruction of cartilage and elastic tissue by chronic necrotizing infections

- Causes
  
  1. Cystic fibrosis (CF)
    - Most common cause in the United States
  
  2. Infections
    - (a) TB is the most common cause worldwide.
    - (b) *Mycobacterium avium-intracellulare* (typically involves the right middle lobe and lingula), adenovirus, *Staphylococcus aureus*, *Haemophilus influenzae*
  
  3. Bronchial obstruction
    - Example—proximally located bronchogenic carcinoma occludes the lumen.
  
  4. Primary ciliary dyskinesia
    - (a) Dynein arm in cilia is absent.
    - (b) Dynein arm contains ATPase (adenosine triphosphatase) for movement of the cilia.
  
  5. Allergic bronchopulmonary aspergillosis

#### 2. Gross findings

- Most commonly occurs in the lower lobes

- Dilated bronchi and bronchioles are filled with pus (Fig. 17-14A)
  - (1) Dilated airways extend to the lung periphery.
  - (2) Dilations are tube-like and/or saccular.

#### 3. Clinical findings

- Cough productive of copious sputum (often cupfuls)
- Hemothysis that is sometimes massive
- Digital clubbing
- Cor pulmonale

#### 4. Chest radiograph, CT scan findings

- Crowded bronchial markings extend to the lung periphery (see Fig. 17-14B).
### TABLE 17-5 Tumors and Tumor-like Disorders of the Lung

<table>
<thead>
<tr>
<th>TYPE OF TUMOR OR DISORDER</th>
<th>LOCATION IN LUNG</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma (see Fig. 17-16E and F)</td>
<td>Peripheral</td>
<td>Most common primary cancer (35%–40%)&lt;br&gt;Most common in nonsmokers&lt;br&gt;More common in women&lt;br&gt;Grow slowly but metastasize early&lt;br&gt;High frequency of KRAS mutations&lt;br&gt;Scar carcinomas: develop in scars (e.g., old tuberculous granuloma); no relationship to smoking&lt;br&gt;Bronchioloalveolar carcinoma: derives from Clara cells (nonciliated epithelium; most common), mucin-secreting bronchiolar cells, or type II pneumocytes; malignant cells spread along alveolar walls (look like pegs); radiologically mimics lobar pneumonia; no relationship to smoking</td>
</tr>
<tr>
<td>Squamous cell carcinoma (see Fig. 17-16A)</td>
<td>Central</td>
<td>Account for 20%–30% of primary cancers&lt;br&gt;More common in men than women&lt;br&gt;Strong association with cigarette smoking&lt;br&gt;High frequency of p53 mutations&lt;br&gt;Tend to cavitate&lt;br&gt;May ectopically secrete PTH-related protein (peptide)</td>
</tr>
<tr>
<td>Small cell carcinoma (see Fig. 17-16B)</td>
<td>Central</td>
<td>Account for 20% of primary cancers&lt;br&gt;Slightly more common in men than women&lt;br&gt;Strong association with cigarette smoking&lt;br&gt;Arise from neuroendocrine cells (Kulchitsky cells); neurosecretory granules are noted on EM&lt;br&gt;High frequency of p53, RB1 mutations&lt;br&gt;Rapidly growing cancer that metastasizes early&lt;br&gt;May ectopically secrete ADH or ACTH</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>Central or peripheral</td>
<td>Account for 10%–15% of primary cancers&lt;br&gt;More common in men than women&lt;br&gt;Undifferentiated cancer (adenocarcinoma or squamous cell carcinoma) that metastasizes early; strong relationship with smoking</td>
</tr>
<tr>
<td>Bronchial carcinoid</td>
<td>Central or peripheral</td>
<td>Account for 1%–5% of primary lung cancers&lt;br&gt;Most common primary lung tumor in children&lt;br&gt;No sex predilection or association with smoking&lt;br&gt;Usually present in persons &lt;40 years old&lt;br&gt;Low-grade cancer of neuroendocrine origin&lt;br&gt;Intraluminal mass that penetrates bronchial wall and fans out (sometimes called iceberg tumor)&lt;br&gt;Approximately 20% locally metastasize&lt;br&gt;Present with hemoptysis (most common), cough, carcinoid syndrome (&lt;1%; does not have to metastasize to the liver)</td>
</tr>
<tr>
<td>Carcinoma metastatic to the lung (see Fig. 17-17A to C)</td>
<td>Multifocal</td>
<td>More common than primary cancer&lt;br&gt;Sites of metastasis: parenchyma (most common), pleura/pleural space, endobronchial mucosa, lymphatics (causes dyspnea)</td>
</tr>
<tr>
<td>Bronchial hamartoma</td>
<td>Peripheral (90%)&lt;br&gt;Central (10%)</td>
<td>Nonneoplastic proliferation of cartilage and adipose tissue&lt;br&gt;Appears as solitary “coin” lesion on chest radiograph; popcorn calcifications</td>
</tr>
</tbody>
</table>

ACTH, Adrenocorticotropic hormone; ADH, antidiuretic hormone; EM, electron microscopy; PTH, parathyroid hormone.

17-14: A, Bronchiectasis showing dilated airways filled with pus. B, Computed tomographic scan showing bronchiectasis in both lungs. Note the dilated airways with cystic to saccular appearance. (A from Corrin B: Pathology of the Lungs, London, Churchill Livingstone, 1999, p 85, Fig. 3-5; B from Goldman L, Ausiello D: Cecil’s Textbook of Medicine, 23rd ed, Philadelphia, Saunders Elsevier, 2008, p 633, Fig. 90-2.)
17-15: Schematic showing the normal function of cystic fibrosis transmembrane regulator (CFTR) in sweat glands (A) and epithelial cells (B) and what happens in cystic fibrosis. Note that in sweat glands, CFTR normally increases chloride ion reabsorption and, indirectly, sodium reabsorption. Absence of CFTR in cystic fibrosis, leads to a loss of both sodium and chloride ions. In epithelial cells, CFTR pumps chloride ions into secretions to maintain their viscosity, whereas in cystic fibrosis, absence of CFTR leads to a loss of sodium and chloride ions into secretions, causing them to be less viscous (dehydrated).

5. Cystic fibrosis (CF)
   a. Epidemiology
      (1) Autosomal recessive disease
      (2) Primarily affects whites (>98% of cases)
         - Uncommon in Asians and blacks
      (3) Most common fatal hereditary disorder in whites in the United States
      (4) Median age of diagnosis is ~5 months
      (5) Median survival is 30 years of age.
   b. Pathogenesis
      (1) Most common mutation is a three-nucleotide deletion on chromosome 7 that normally codes for phenylalanine (70% of cases).
      (2) Mutation causes defective protein folding in the cystic fibrosis transmembrane conductance regulator (CFTR).
         (a) CFTR is normally regulated by cyclic adenosine monophosphate (cAMP)-dependent phosphorylation and by intracellular ATP
         (b) Its function in cells is to regulate chloride ion permeability in sweat glands (Fig. 17-15A left schematic) and other secretions (Fig. 17-15B left schematic)
      (3) Defective CFTR is degraded in the Golgi apparatus.
      (4) Loss of CFTR causes decreased Cl⁻ reabsorption in the sweat glands (Fig. 17-15A right schematic).
         - Basis of the chloride sweat test, which is used to diagnose CF
      (5) Effect of loss of CFTR in other secretions (see Fig. 17-15B right schematic)
         (a) Increased Na⁺ and water reabsorption from luminal secretions
         (b) Decreased Cl⁻ secretion out of epithelial cells into luminal secretions
         (c) Net effect of these electrolyte alterations is dehydration of body secretions due to lack of NaCl.
         - Secretions are dehydrated (thickened) in bronchioles, pancreatic ducts, bile ducts, meconium, cervix, and seminal fluid.
   c. Clinical findings
      (1) Nasal polyps (25% of cases)
      (2) Heat exhaustion
         - Loss of sodium-containing fluid from skin
      (3) Respiratory infections/failure
         (a) *Pseudomonas aeruginosa* is the most common respiratory pathogen.
            - Other common pathogens—*S. aureus*, *H. influenzae*, *Burkholderia*, and *Aspergillus*
         (b) Cor pulmonale commonly occurs.
      (4) Pneumothorax (20% of cases)
         - Rupture of blebs that develop from infection
(5) Malabsorption (80% of cases)
   (a) Pancreatic exocrine deficiency
   (b) Atrophy of glands from dehydrated secretions blocking the lumens
   (c) Chronic pancreatitis
(6) Type 1 diabetes mellitus (20% of cases)
   • Due to chronic pancreatitis
(7) Infertility in males (95% of cases)
   • Atresia of vas deferens
(8) Infertility in females (20% of cases)
(9) Meconium ileus (20% of cases)
   • Small bowel obstruction in newborn (thick meconium)
(10) Rectal prolapse
   • Straining at stool
(11) Gallstones (>50% of cases)
   (a) Usually in older CF patients
   (b) Stasis of thickened bile
   (c) Common bile duct obstruction (15%–20% of cases)
(12) Secondary biliary cirrhosis
   • Due to obstruction of bile ductules by thick secretions
d. Screen infants
   • Increased serum immunoreactive trypsin levels
e. Sweat test findings diagnostic for CF
   (1) Sweat chloride >40 mmol/L in infants
   (2) Sweat chloride >60 mmol/L in children and adults
f. Treatment
   (1) Antibiotics for documented respiratory infections
   (2) Bronchodilators
   (3) Pancreatic enzyme replacement
   (4) Corticosteroids in children (alternate day)
   (5) Vitamin supplements
   • Fat-soluble vitamins important
   (6) Recombinant human deoxyribonuclease aerosol
   • Improves mucociliary clearance of viscid sputum

X. Lung Tumors
A. Epidemiology
1. Primary lung cancer is the most common fatal cancer in both men and women worldwide.
   a.Accounts for >30% of cancer deaths in men
   b. Accounts for >25% of cancer deaths in women
2. Incidence of lung cancer is declining in men but increasing in women.
3. Peak incidence is at 55 to 65 years of age.
4. Causes
   a. Cigarette smoking most common cause
      (1) Tobacco smoking accounts for 85% of cases and secondhand smoke for 15% of cases
      (2) Risk increases with quantity and duration of smoking
      (3) Men who smoke have greater risk than women who smoke
      (4) Non–smoking related lung cancer is more common in women than men
   b. Radon gas (uranium mining)
   c. Asbestos
d. Certain metals
   • Chromium, cadmium, beryllium, and arsenic
   e. Secondhand smoke, ionizing radiation, air pollution, and history of tuberculosis
5. Molecular genetics in lung cancer
   a. Most common oncogenes—KRAS, MYC family, HER-2/neu, BCL-2, EGFR (epidermal growth factor receptor)
   b. Most common suppressor genes—p53 (most common), RB1, p16
6. Classified as small cell or non–small cell (most common) cancers
7. Primary lung cancer by specific type in decreasing incidence:
   a. Adenocarcinoma (most common primary cancer)
   b. Squamous cell carcinoma (SCC; Fig. 17-16A)

10. Common sites for metastasis
   a. Hilar lymph nodes most common site
   b. Adrenal gland (50% of cases)
   c. Liver (30% of cases)
   d. Brain (20% of cases)
   e. Bone (usually osteolytic)

B. Tumors and tumor-like disorders (Table 17-6)
### Table 17-6 Pleural Fluid Transudates Versus Exudates

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>TRANSUDATE</th>
<th>EXUDATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF protein/serum protein</td>
<td>&lt;0.5</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>PF LDH/serum LDH</td>
<td>&lt;0.6</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>PF LDH</td>
<td>&lt;200 U/L</td>
<td>&gt;200 U/L</td>
</tr>
</tbody>
</table>

LDH, Lactate dehydrogenase; PF, pleural fluid.

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17-17: A, Metastatic renal cell carcinoma showing multiple nodular lesions scattered throughout the lung parenchyma. B, Chest radiograph showing multiple metastatic nodules throughout both lung fields. C, Computerized tomography showing multiple discrete metastatic nodules in the lungs (arrows) from a colon adenocarcinoma. (A from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 766, Fig. 15-47; B from Goldman L, Ausiello D: Cecil's Textbook of Medicine, 23rd ed, Philadelphia, Saunders Elsevier, 2008, p 600, Fig. 84-9; C from Herring W: Learning Radiology: Recognizing the Basics, 2nd ed, Philadelphia, Elsevier Saunders, 2012, p 25, Fig. 3.18A.)

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A **solitary pulmonary nodule** or coin lesion (e.g., see Fig. 17-15I) is the term applied to a peripheral lung nodule <5 cm. Causes of a solitary pulmonary nodule in descending order include granulomas (e.g., TB, histoplasmosis), malignancy (usually primary cancer), and a bronchial (chondroid) hamartoma. Patients <35 years old have a 1% risk of a solitary coin lesion representing a malignancy, but patients ≥50 years old have a 50% to 60% risk of malignancy, usually a primary cancer. In evaluating solitary coin lesions, comparing previous chest x-rays for changes in size of the nodule is the most important initial step.

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C. **Metastatic cancer**

1. Epidemiology
   a. Most common lung cancer
   b. Cancers most often responsible for metastasis
      (1) Primary breast cancer most common cause
      (2) Colon cancer and renal cell carcinoma

2. Sites of lung metastasis
   a. Parenchyma (Fig. 17-17A, B, and C)
   b. Pleura and pleural space (malignant effusions)
   c. Lymphatics (causes severe dyspnea)

3. Dyspnea is the most common symptom.
D. Clinical findings for primary lung cancer

1. Cough
   • Most common symptom (75% of cases)
2. Weight loss (40% of cases)
3. Chest pain (30% of cases)
4. Hemoptysis (25%–30% of cases)
5. Dyspnea
6. Pancoast tumor (superior sulcus tumor)
   a. Tumor is usually a primary SCC located at the extreme apex of the lung.
   b. Destruction of superior cervical sympathetic ganglion produces Horner syndrome
      (Fig. 17-18A).
      (1) Ipsilateral lid lag
      (2) Miosis (pinpoint pupil)
      (3) Ipsilateral anhydrosis (lack of sweating)
7. Superior vena cava syndrome (refer to Chapter 9; see Fig. 17-18B)
8. Paraneoplastic syndromes (refer to Chapter 9)
   a. Digital clubbing
      • Due to reactive periosteal changes in the underlying bone (see Fig. 9-12)
   b. Muscle weakness (Eaton-Lambert syndrome)
      (1) Antibody directed against calcium channel in muscle
      (2) Usually associated with small cell carcinoma
   c. Ectopic hormone secretion (see earlier)

E. Diagnosis of lung cancer

1. Chest x-ray
   a. Central masses
      (1) Squamous cell carcinoma
      (2) Small cell carcinoma
   b. Peripheral masses
      (1) Adenocarcinoma
      (2) Scar carcinoma
2. Sputum cytologic examination
3. Fine needle aspiration
4. Bronchoscopy with lavage
5. New techniques for early detection
   a. Low-dose spiral (helical) CT scan
   b. Positron emission tomography (PET)
      • More sensitive than CT
   c. Molecular markers in sputum

F. Treatment

1. Surgery
2. Radiation
3. Chemotherapy
4. Targeted biologic therapies
   • Bevacizumab and erlotinib
G. Prognosis
1. Non–small cell cancers fare better than small cell carcinoma.
2. Overall combined 5-year survival rate is ~15%.

XI. Mediastinum and Pleural Disorders
A. Mediastinal masses
1. Epidemiology
   a. Usually metastatic primary lung cancer in older patients
   b. Usually primary disease in younger patients
   c. Anterior mediastinum is the most common site (>50% of cases).
   d. Most common primary mediastinal masses, in descending order:
      (1) Neurogenic tumors
          a. Located in the posterior mediastinum
          b. Usually malignant in children
             • Neuroblastoma
          c. Usually benign in adults
             • Ganglioneuroma
      (2) Thymomas
      (3) Pericardial cyst
          • Located in the middle mediastinum
      (4) Malignant lymphomas
          a. Located in the anterior mediastinum
          b. Usually nodular sclerosing Hodgkin lymphoma in a woman
      (5) Teratoma
          a. Located in the anterior mediastinum
          b. Majority are benign cystic teratomas
          c. Small percentage are malignant teratomas

2. Thymoma
   a. Epidemiology
      (1) Located in the anterior mediastinum
      (2) Benign (70%), malignant (30%)
   b. Epithelium, not lymphoid tissue, is the neoplastic component.
   c. Majority express systemic symptoms of myasthenia gravis (refer to Chapter 24).
      (1) Less than 15% of myasthenia patients have a thymoma.
      (2) Majority (65%–75%) have follicular B-cell hyperplasia in the thymus.
         • Site for synthesis of anti–acetylcholine receptor antibodies
   d. Other thymoma associations
      (1) Hypogammaglobulinemia
      (2) Pure RBC aplasia
      (3) Increased incidence of autoimmune disease (e.g., Graves disease)

B. Pleural effusions
1. Movement of pleural fluid (PF)
   a. Fluid moves from parietal pleura to pleural space to lungs.
   b. Movement depends upon the balance of Starling pressures (refer to Chapter 5).
      • Example—normally, the parietal capillary hydrostatic pressure (HP) > visceral capillary HP

2. Etiology and pathogenesis
   a. Increased HP in visceral pleura
      • Example—congestive heart failure (CHF)
   b. Decreased oncotic pressure (OP)
      • Example—nephrotic syndrome

3. Increased vessel permeability of visceral pleural capillaries
   • Examples—pulmonary infarction, pneumonia

4. Metastasis to the pleura
   • Example—metastatic breast cancer

5. Types of pleural effusions
   a. Transudates (refer to Chapter 5)
      (1) Ultrafiltrate of plasma involving disturbances in Starling pressures
      (2) Examples
         a. Increased HP in CHF
         b. Decreased OP in nephrotic syndrome
b. Exudates (refer to Chapters 3 and 5)
   (1) Protein-rich and cell-rich fluid
       - Due to increased vessel permeability in acute inflammation
   (2) Examples—pneumonia, tuberculosis, infarction, metastasis

c. Chylous effusions
   (1) Indicates interruption of the thoracic duct
   (2) Etiology
       (a) Malignancy (most common)
           - Blocks lymphatic drainage
       (b) Trauma
           - Iatrogenic tear that occurs during surgery or is pathologic
   (3) Turbid, milky appearance
       (a) Due to chylomicrons (diet-derived triglyceride; refer to Chapter 10)
       (b) Chylomicrons form a supranate in a test tube after refrigeration.
   (4) PF triglyceride >110 mg/dL is diagnostic.

d. Pseudochylous effusions
   (1) Turbid, milky appearance
   (2) Caused by inflammation with increased amount of necrotic debris
       - PF cholesterol increased
   (3) Most commonly caused by rheumatoid lung disease

6. Laboratory distinction of transudates versus exudates (see Table 17-6)
   a. PF and serum concentrations of lactate dehydrogenase (LDH) and protein are most useful.
       - Ratios of PF protein and LDH to serum protein and LDH increase test sensitivity and specificity.
   b. Test sensitivity is 99%, and specificity is 98% if at least one of the three criteria for an exudate is present.
   c. Additional criteria
       (1) pH >7.4 indicates a transudate.
       (2) pH <7.4 indicates an exudate.

7. Clinical findings
   a. Dullness to percussion
   b. Absent breath sounds
   c. Absent vocal tactile fremitus
   d. Contralateral shift of the mediastinum
       - Only large effusions

8. Imaging (Fig. 17-19)
   a. Blunting of the costophrenic angle
   b. Obscuration of the diaphragm

C. Spontaneous pneumothorax
   1. Epidemiology
      a. More common in men than women
      b. Commonly seen in tall, thin, young men aged 20 to 40 years

17-19: Frontal chest radiograph showing a right pleural effusion. Note the blunting of the right costophrenic angle and obscuration of the right hemidiaphragm. (From Pretorius ES, Solomon JA: Radiology Secrets, 2nd ed, Philadelphia, Mosby, 2006, p 539, Fig. 66-2A.)
c. Risk increases with smoking

d. Approximately 25% recurrence rate within 2 years

2. Causes

a. Primary (idiopathic; most common)
   (1) Rupture of apical subpleural bleb(s)
   (2) Blebs are secondary to high negative intrapleural pressures.
   (3) Most patients are male smokers between 30 and 40 years old.
   (4) Recurrence in the contralateral lung is common.

b. COPD
   (1) Most common secondary cause
   (2) Paraseptal emphysema

c. Marfan syndrome

d. Scuba diving

e. Insertion of subclavian catheter
   • Always order a chest x-ray after insertion!

3. Pathogenesis

a. Rupture of a subpleural or intrapleural bleb produces a hole in the pleura.

b. Pleural cavity pressure is the same as the atmospheric pressure.
   (1) Loss of the negative intrathoracic pressure
   (2) Causes a portion of lung or the entire lung to collapse

4. Clinical findings

a. Sudden onset of dyspnea with pleuritic type of chest pain (90% of cases)

b. Physical examination
   (1) Tympanic percussion note
   (2) Absent breath sounds
   (3) Trachea deviated to the side of the collapse if there is total lung collapse

5. Upright chest x-ray

a. White visceral pleural line

b. Absence of vessel markings peripheral to line

6. Treatment

a. Observation alone if asymptomatic and pneumothorax <15%

b. One hundred percent oxygen administration
   • Reduces partial pressure of nitrogen; hence increasing rate of pneumothorax absorption

c. Chest tube insertion or thoracoscopy may be required.

D. Tension pneumothorax

1. Causes

a. Penetrating trauma to the lungs (e.g., knife wound)

b. Rupture of tension pneumato cysts (seen with S. aureus pneumonias)
2. Pathogenesis
   a. Flap-like pleural tear (check valve) allows air into the pleural cavity but prevents its exit.
      - Similar in concept to filling a tire up with air
   b. Increased pleural cavity pressure
   c. Produces compression atelectasis (see section IV)

3. Clinical findings
   a. Sudden onset of severe dyspnea and pleuritic chest pain
   b. Physical examination
      (1) Tympanitic percussion note and absent breath sounds
      (2) Trachea and mediastinal structures deviate to contralateral side if tension pneumothorax is large (Fig. 17-20A and B).
         - Compromised venous return to the heart, if the pneumothorax is located on the left side
   c. Treatment
      (1) Relieve pressure first.
         - Insert a needle into the second intercostal space on the midclavicular line.
      (2) Insert a chest tube.
I. Oral Cavity and Salivary Gland Disorders

A. Cleft lip and palate
   1. Epidemiology
      a. Most common congenital disorder of oral cavity
         (1) ~1:800 live births
         (2) Cleft lip and palate (50%)
         (3) Cleft lip alone (25%)
            • Male > female
         (4) Cleft palate alone (25%; Fig. 18-1)
            • Female > male
      b. Genetic factors involved
         • Presence in subsequent siblings (3%)
      c. More common in whites than blacks
      d. Complications
         (1) Malocclusion
         (2) Eustachian tube dysfunction
            • Chronic otitis media
         (3) Speech problems
   2. Pathogenesis
      • Failure of fusion of facial processes
   3. Treatment is surgery

B. Common infections in the oral cavity (Table 18-1)

C. Oral manifestation of HIV
   1. Candidiasis (Fig. 18-2)
      • Most common oral infection
   2. Aphthous ulcers (stomatitis; canker sores)
      a. Unknown origin
         (1) Virus versus immunologic
         (2) Often stress-induced
      b. Painful ulcers covered by a shaggy gray membrane (Fig. 18-3)
   3. Hairy leukoplakia (see Fig. 18-2B)
      • Glossitis due to Epstein-Barr virus (EBV)
   4. Kaposi sarcoma
      a. Hard palate is the most common location.
      b. Due to human herpesvirus 8 (HHV-8)

D. Dental caries
   1. Streptococcus mutans produces acid from sucrose fermentation.
      • Acid erodes enamel and exposes underlying dentine.
   2. Fluoride prevents dental caries (refer to Chapter 8).
      • Excess fluoride causes a chalky discoloration of the teeth.

E. Noninfectious ulcerations in the oral cavity
   1. Pemphigus vulgaris and mucous membrane pemphigoid
      • Both are immunologic skin disorders (refer to Chapter 25).
18-1: Cleft palate. Note the defect in the palate (arrow). (From Grieg JD: Color Atlas of Surgical Diagnosis, London, Mosby-Wolfe, 1996, p 68, Fig. 10-7.)

**Table 18-1 Infections of the Oral Cavity**

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>PATHOGEN</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exudative tonsillitis</td>
<td>Viruses: most cases</td>
<td>Culture is necessary to differentiate bacterial versus viral infection</td>
</tr>
<tr>
<td>Hairy leukoplakia</td>
<td>EBV</td>
<td>Glossitis associated with bilateral white excrescences on lateral border of tongue Pre-AIDS-defining lesion (refer to Chapter 4)</td>
</tr>
<tr>
<td>Herpes labialis</td>
<td>HSV type 1</td>
<td>Recurrent vesicular lesions on the lips (virus remains dormant in cranial sensory ganglia) Reactivated by stress, sunlight, and menses</td>
</tr>
<tr>
<td>Mumps</td>
<td>Paramyxovirus</td>
<td>Bilateral parotitis (70%) with increased serum amylase Complications: meningogencephalitis, unilateral orchitis or oophoritis, pancreatitis</td>
</tr>
<tr>
<td>Herpangina</td>
<td>Coxsackievirus</td>
<td>Occurs in children Typically occurs in epidemics during the summer Painful vesicles or small white papules occur on an erythematous base typically at the junction of the soft and hard palate</td>
</tr>
<tr>
<td>Hand-foot-and-mouth disease</td>
<td>Coxsackievirus</td>
<td>Occurs in young children Vesicles located in mouth and distal extremities</td>
</tr>
<tr>
<td><strong>Bacterial disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervicofacial actinomycosis</td>
<td>Actinomyces israelii</td>
<td>Draining sinus tract from facial or cervical area “Sulfur granules” in pus contain gram-positive, branching filamentous anaerobic bacteria Often follows extraction of an abscessed tooth</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Corynebacterium diphtheriae</td>
<td>Toxin produces “shaggy” gray pseudomembrane in posterior pharynx and upper airways Treatment: erythromycin Complication due to tonsillitis</td>
</tr>
<tr>
<td>Peritonsillar abscess</td>
<td>Streptococcus pyogenes</td>
<td>Uvula deviates to contralateral side; “hot potato” voice; foul-smelling breath Complication due to tonsillitis Treatment: surgical drainage of pus; penicillin G or V, add clindamycin for serious invasive infections</td>
</tr>
<tr>
<td>Ludwig angina</td>
<td>Aerobic/anaerobic</td>
<td>Cellulitis involving the submaxillary and sublingual space. Follows fascial planes and may spread into pharynx, carotid sheath, superior mediastinum. Causes: dental extraction (most common), trauma to floor of mouth Treatment: surgical drainage; clindamycin + metronidazole</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td><em>S. pyogenes</em></td>
<td>Associated with tonsillitis Potential for acute rheumatic fever and glomerulonephritis Treatment: penicillin V</td>
</tr>
<tr>
<td>Scarlet fever</td>
<td><em>S. pyogenes</em></td>
<td>Pharyngitis, tonsillitis, glossitis Erthrogenic toxin produces rash on skin and tongue (initially white and then strawberry colored) Increased risk for glomerulonephritis Nephritogenic strains pose no risk for acute rheumatic fever Treatment: penicillin G or V</td>
</tr>
<tr>
<td>Sialadenitis</td>
<td><em>Staphylococcus aureus</em></td>
<td>Bacterial inflammation of major salivary gland Secondary to a calculus, which obstructs the duct in postoperative patients Treatment: oxacillin, nafcillin if methicillin susceptible; TMP-SMX if community-acquired methicillin resistant; vancomycin if methicillin resistant in hospital</td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td><em>Treponema pallidum</em> (spirochete)</td>
<td>Abnormalities involving incisors (notched and tapered like a peg) and molar teeth (resemble mulberries) Treatment: aqueous crystalline penicillin G</td>
</tr>
<tr>
<td>Acute necrotizing gingivitis</td>
<td>Anaerobes: <em>Prevotella, Fusobacterium</em> spirochetes</td>
<td>Anaerobic bacterial infection of gingiva. Necrosis of interdental papilla with punched out lesions covered by a grayish pseudomembrane. Treatment: penicillin or metronidazole</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral thrush</td>
<td><em>Candida albicans</em> (yeast)</td>
<td>May occur in neonates, immunocompromised patients (common pre-AIDS–defining lesion), diabetes mellitus, and following antibiotic therapy Treatment: fluconazole, itraconazole</td>
</tr>
</tbody>
</table>

*EBV,* Epstein-Barr virus; *HSV,* herpes simplex virus; *TMP-SMX,* trimethoprim-sulfamethoxazole.
2. Erythema multiforme (refer to Chapter 25)
   a. Hypersensitivity reaction against *Mycoplasma* or drugs (e.g., sulfonamides)
   b. Called Stevens-Johnson syndrome when it involves the mouth
3. Aphthous ulcers (stomatitis; see Fig. 18-3)
4. Behçet syndrome
   a. Epidemiology
      (1) Combination of environmental + genetic factors
      • Human leukocyte antigen (HLA)-B51, HLA-B27 associations
      (2) May be precipitated by herpes simplex virus or parvovirus
      (3) High incidence in Turkey and eastern Mediterranean
   b. Pathophysiology
      • Immune complex small vessel vasculitis
   c. Clinical findings
      (1) Recurrent aphthous ulcers, genital ulcerations
      (2) Uveitis, erythema nodosum
      (3) Attacks last 1 to 4 weeks
   d. Treatment
      (1) Antiinflammatory medications
      (2) Corticosteroids
      (3) Colchicine, thalidomide

F. Pigmentation abnormalities
1. Peutz-Jeghers syndrome (see section IV)
   • Melanin pigmentation of the lips and oral mucosa (Fig. 18-4)
2. Addison disease (see Fig. 23-16A)
   a. Increased adrenocorticotropic hormone (ACTH) stimulates melanocytes.
   b. Melanin pigmentation is present on the buccal mucosa.
3. Lead poisoning
   • Lead deposits along the gingival margins in adults with gingivitis (see Fig. 12-14D)

G. Tooth discoloration
1. Tetracycline
   a. Drug discolors newly formed teeth.
   b. Not recommended in a child <12 years of age.
2. Excess fluoride
   • Mottled, chalky white discoloration
3. Congenital erythropoietic porphyria
   a. Porphyrin deposits in the teeth
   b. Reddish-brown discoloration

H. Macroglossia (enlarged tongue)
1. Myxedema
   • Severe primary hypothyroidism
2. Down syndrome
3. Acromegaly
4. Systemic amyloidosis
5. Mucosal neuromas in multiple endocrine neoplasia (MEN) syndrome IIb

I. Glossitis (inflammation of tongue)

1. Definition—sore, beefy red tongue with or without papillary atrophy
2. Causes
   a. Long-standing iron deficiency
   b. Vitamin B12 or folate deficiency
   c. Scurvy (vitamin C deficiency)
   d. Pellagra (niacin deficiency)
   e. Scarlet fever
   f. EBV-associated hairy leukoplakia

J. Leukoplakia and erythroplakia

1. Definitions
   a. Leukoplakia literally means “white patch” (Fig. 18-5A).
   b. Erythroplakia is a red patch (see Fig. 18-5B).
   c. Combination of leukoplakia and erythroplakia is called leukoerythroplakia
2. These lesions initially show squamous hyperplasia of the epidermis.
   a. May progress into squamous dysplasia or invasive squamous cell carcinoma (SCC)
   b. Leukoplakia has an ~30% rate of progression to oral cancer.
   c. Erythroplakia has an ~60% rate of progression to oral cancer.


Macroglossia: myxedema, Down syndrome, acromegaly, amyloidosis, MEN IIb

Glossitis: deficient in iron, vitamin B12, folic acid, vitamin C, niacin; scarlet fever; hairy leukoplakia

Leuko/erythroplakia: possible dysplasia → SCC
3. **Locations**
   a. Vermilion border lower lip (most common site)
   b. Buccal mucosa, hard and soft palates, floor of the mouth
4. **Causes**
   a. Chronic irritation (e.g., dentures)
   b. All forms of tobacco use
   c. Alcohol abuse
   d. Human papillomavirus (HPV)
5. **Always biopsy these lesions because of the high risk for progression to oral cancer.**

**K. Lichen planus (refer to Chapter 25)**
1. Often associated with Wickham striae on the buccal mucosa
   - Fine, white, lacy lesions (see Fig. 18-5C)
2. May be associated with SCC

**L. Dentigerous cyst**
1. Derives from epithelial elements of dental origin (odontogenic origin)
2. Associated with the crown of an unerupted or impacted third molar
3. Associated with ameloblastomas in 15% to 30% of cases

**M. Benign tumors of the oral cavity (excluding salivary gland)**
1. Squamous papillomas
   a. Most common benign tumor in oral cavity
   b. Exophytic tumor with a fibrovascular core
   c. May occur on the tongue, gingiva, palate, or lips
2. Ameloblastoma
   a. Arise from enamel organ epithelium or a dentigerous cyst
   b. Located in the mandible
      1. Produces a radiolucency in bone that has a "soap bubble" appearance
      2. Locally invasive but do not metastasize

**N. Malignant tumors of the oral cavity (excluding salivary gland)**
1. **Epidemiology**
   a. Majority are well-differentiated SCCs
   b. More common in men than women
   c. Risk factors
      1. HPV most common risk factor.
         - Approximately 50% of cases have HPV oncogenic variants.
      2. Use of tobacco products
         - Pipe tobacco, cigarettes, chewing tobacco
      3. Alcohol abuse (synergistic with smoking)
         a. Synergism between smoking and alcohol excess
         b. Increases relative risk 30-fold
      4. Chronic irritation from dentures
      5. Lichen planus
   d. Cancer sites in descending order
      1. Lower lip (vermilion border; see Fig. 18-5D)
      2. Floor of mouth
      3. Lateral border of tongue
   e. Metastasis
   f. Tonsillar node (superior jugular node)
   g. Verrucous carcinoma
      - Associated with smokeless tobacco
   h. Basal cell carcinoma (BCC)
      1. Most common cancer of the upper lip
      2. Associated with exposure to ultraviolet light B
2. **Treatment**
   a. Surgery and radiation; chemotherapy in advanced cases
   b. HPV vaccination is protective against developing HPV oropharyngeal cancers.

**O. Salivary gland disorders**
1. Sjögren syndrome (refer to Chapter 24)
   a. Female dominant autoimmune disease associated with rheumatoid arthritis
   b. Autoimmune destruction of minor salivary glands and lacrimal glands
II. Esophageal Disorders

A. Signs and symptoms of esophageal disease

1. Heartburn
   - Most commonly due to gastroesophageal reflux disease (GERD)

2. Dysphagia (difficulty swallowing) for solids alone
   a. Symptom of an obstructive lesion
   b. Examples—esophageal cancer, esophageal web, stricture

3. Dysphagia for solids and liquids
   a. Symptom of a motility disorder
   b. Oropharyngeal (upper esophageal) dysphagia
      (1) Striated muscle dysmotility
      (2) Examples—dermatomyositis, myasthenia gravis, stroke
   c. Lower esophageal dysphagia
      (1) Smooth muscle dysmotility
      (2) Examples—systemic sclerosis, CREST syndrome (calcinosis/centromere antibodies, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia), achalasia

Parotid gland: MC site salivary gland tumors

Pleomorphic adenoma: MC salivary gland tumor

Warthin tumor: heterotopic salivary gland tissue in lymph node

Mucopidermoid carcinoma: MC malignant salivary gland tumor

Heartburn: GERD

Dysphagia for solids: obstructive lesion

Dysphagia of solids and liquids: motor disorder
B. **Tracheoesophageal (TE) fistula**

1. **Epidemiology**
   a. Most common congenital anomaly of esophagus
   b. Characteristics of the most common type
      1. Proximal esophagus ends blindly (Fig. 18-7).
      2. Distal esophagus arises from the trachea.
   c. Risk factors include:
      - Advanced maternal age, smoking, and obesity
2. **Pathogenesis** is unknown
3. **Clinical findings**
   a. Maternal polyhydramnios (excess amniotic fluid)
      - Swallowed amniotic fluid cannot be reabsorbed in the small intestine.
   b. Abdominal distention in newborn (NB)
      - Air in the stomach from tracheal fistula
   c. Frothing and bubbling around the mouth at birth
   d. Difficulty with feeding
      1. Food is regurgitated out of the mouth.
      2. NB develops chemical pneumonia from aspiration.
   e. **VATER syndrome**
      1. Vertebral abnormalities
      2. Anorectal (usually anal atresia)
      3. TE fistula
      4. Renal disease and absent radius
   f. **VACTERL syndrome**
      - Same as VATER syndrome except C stands for cardiac and L stands for limb abnormalities

C. **Plummer-Vinson syndrome** (refer to Chapter 12)

1. Due to chronic iron deficiency
2. Leukoplakia in oral mucosa and esophagus
3. Intermittent dysphagia for solids
   - Due to an esophageal web or stricture

D. **Esophageal diverticulum**

1. **Types of diverticulum**
   a. True diverticulum
      - Outpouching lined by mucosa, submucosa, muscularis propria, and adventitia
   b. False, or pulsion diverticulum
      1. Weakness in underlying muscle wall
      2. Outpouching of mucosa and submucosa into area of weakness
2. **Zenker diverticulum**
   a. Pulsion type is located in upper esophagus.
      - Area of weakness is the cricopharyngeus muscle (Fig. 18-8A and B).
   b. **Clinical findings**
      1. Painful swallowing
      2. Halitosis
         - Due to entrapped food
      3. Regurgitate food through the mouth
      4. Diverticulitis possible
   c. Treatment is surgery
E. Hiatal hernia

1. Epidemiology
   a. Found in 50% of persons over 50 years old
      • Likelihood increases with age
   b. More common in women than men
   c. Associations
      (1) Sigmoid diverticulosis (25% of cases)
      (2) Esophagitis (25% of cases)
      (3) Duodenal ulcers (20% of cases)
      (4) Gallstones (18% of cases)

2. Sliding hernia
   a. Most common type of hiatal hernia (99%)
   b. Herniation of proximal stomach into thoracic cavity through the diaphragmatic esophageal hiatus
   c. Clinical findings
      (1) Heartburn
      (2) Nocturnal epigastric distress from acid reflux
      (3) Hematemesis (vomiting blood)
      (4) Ulceration, stricture
      (5) Bowel sounds heard over left lung base
   d. Treatment
      (1) Nonpharmacologic
         (a) Reduce intake of foods/drugs that decrease lower esophageal sphincter tone
         • Examples—coffee, chocolate, calcium channel blockers
         (b) Avoid eating large quantities of food
         (c) Sleep with head of the bed elevated
      (2) Pharmacologic
         (a) H₂ antagonists
         (b) Proton pump inhibitors
         (c) Prokinetic agents
      (3) Surgery if indicated

3. Paraesophageal (rolling) hernia (1%)
   a. Gastroesophageal junction remains at the level of the diaphragm.
   b. Part of the stomach bulges into the thoracic cavity.

18-8: A, Schematic of a Zenker diverticulum (pulsion diverticulum). The area of weakness is the cricopharyngeus muscle. B, Solid white arrow shows dye in the diverticular sac. (A from Townsend C: Sabiston Textbook of Surgery, 18th ed, Philadelphia, Saunders Elsevier, 2008, p 1061, Fig. 41-20; B from Herring W: Learning Radiology Recognizing the Basics, 2nd ed, Philadelphia, Elsevier Saunders, 2012, p 175, Fig. 18.3A.)

A pleuroperitoneal diaphragmatic hernia (Bochdalek hernia) accounts for 90% of the hernias seen in newborns (Fig. 18-9). The visceral contents extend through the posterolateral part of the diaphragm on the left into the chest cavity causing severe respiratory distress at birth. Loops of bowel are present in the left pleural cavity on a radiograph.
F. Gastroesophageal reflux disease (GERD)

1. Epidemiology
   a. Approximately 10% of adults have GERD daily.
   b. Approximately 80% of pregnant women have GERD.
   c. Hiatal hernia present in ~70% of people with GERD.
   d. Risk factors
      (1) Smoking, alcohol
      (2) Caffeine, fatty foods, chocolate
      (3) Pregnancy, obesity
      (4) Hiatal hernia

2. Pathogenesis
   a. Transient relaxation of lower esophageal sphincter (LES)
      • Reflux of acid and bile into the distal esophagus (Fig. 18-10A)
   b. Ineffective esophageal clearance of reflux material

3. Clinical findings
   a. Noncardiac chest pain
      • Heartburn, indigestion
b. Nocturnal cough, nocturnal asthma  
c. Acid injury to enamel  
d. Early satiety, abdominal fullness  
e. Bloating with belching  
f. Barrett esophagus  

4. Diagnostic tests with atypical presentation  
a. Esophageal pH monitoring for 24 hours  
   • Sensitivity/specificity 80% to 90%  
b. Esophageal endoscopy  
c. Manometry  
   • LES pressure <10 mm Hg  

5. Treatment  
a. Nonpharmacologic  
   • Similar to hiatal hernia (see earlier)  
b. Pharmacologic  
   • Similar to hiatal hernia (see earlier)  
c. Surgery if indicated  
   (1) Fundoplication procedure  
   (2) Involves putting a gastric wrap around the gastroesophageal junction  

G. Barrett esophagus  
1. Complication of GERD  
2. Glandular (intestinal) metaplasia in distal esophagus due to acid injury  
   • Gastric type of columnar cells and small intestine type of cells (goblet cells; see Fig. 2-14F and Fig. 18-10B)  

3. Complications  
a. Ulceration with stricture formation (most common)  
b. Glandular dysplasia with increased risk for distal adenocarcinoma (see later)  

H. Infectious esophagitis  
1. Usually a complication of AIDS  
2. Pathogens  
a. Herpes simplex virus (HSV)  
   • Multinucleated squamous cells with intranuclear inclusions  
b. Cytomegalovirus (CMV)  
   • Eosinophilic intranuclear inclusions  
c. Candida  
   • Yeasts and pseudohyphae (extended yeast forms)  
3. Presents with painful swallowing (i.e., odynophagia)  

I. Corrosive esophagitis  
1. Ingestion of strong alkali (e.g., lye) or acid (e.g., HCl)  
2. Complications  
a. Stricture formation  
b. Perforation  
c. SCC  

J. Esophageal varices  
1. Epidemiology and pathogenesis  
a. Definition—dilated submucosal left gastric veins (Fig. 18-11)  
b. Complication of portal hypertension (PH) from cirrhosis  
   • Alcohol abuse is the most common cause.  
2. Clinical findings  
a. Rupture with massive hematemesis (vomiting blood)  
b. Most common cause of death in cirrhosis  
3. Diagnosis  
   • Endoscopy  
4. Initial management  
a. Endoscopy  
   (1) Most important diagnostic procedure  
   (2) Value in treatment of the bleed as well  
b. Assess/maintain intravascular volume  
c. Insert nasogastric tube for gastric aspirate/lavage.  
   (1) Confirms upper gastrointestinal source of bleeding  
   (2) Assesses rate of bleeding  

GERD: nocturnal cough/asthma; acid injury to enamel; Barrett esophagus.  
GERD atypical presentation: esophageal pH monitoring, endoscopy, manometry.  
Barrett esophagus: complication of GERD.  
Barrett esophagus complications: distal adenocarcinoma, stricture.  
AIDS-related esophagitis: HSV, CMV, Candida.  
Corrosive esophagitis: strictures, perforation, SCC.  
Left gastric vein drains blood from distal esophagus and proximal stomach into the portal vein.  
Esophageal varices: PH dilates left gastric veins.  
Ruptured esophageal varices: MCC death in cirrhosis.  
Ruptured esophageal varices: endoscopy most important diagnostic procedure.
5. Prevention/treatment of bleeds
   a. β-Blockers and isosorbide
      (1) Decrease rate of recurrent bleeding
      (2) Increase survival by 5% to 10%
   b. Transjugular intrahepatic portasystemic stent (TIPS)
      • Used for treatment of both bleeding and intractable ascites
   c. Octreotide intravenous drip (somatostatin analog) for bleeding
   d. Endoscopic ligation, endoscopic sclerotherapy, open surgery with stapling

K. **Mallory-Weiss syndrome**
   1. Definition—mucosal tear in the proximal stomach and distal esophagus
   • Due to severe retching, most often associated with alcoholism or bulimia
   2. Causes

L. **Boerhaave syndrome**
   1. Definition—rupture of the distal esophagus
   2. Causes
      a. Endoscopy (~75% of cases)
      b. Retching, bulimia
   3. Complications
      a. Pneumomediastinum
         (1) Air dissects subcutaneously into the anterior mediastinum.
         (2) Crunching sound (Hamman sign) is heard on auscultation.
      b. Pleural effusion contains food, acid, and amylase.

M. **Motor disorders**
   1. Systemic sclerosis and CREST syndrome (refer to Chapter 4)
   2. Achalasia
      a. Epidemiology
         (1) Bimodal age distribution
            (a) Occurs in those 20 to 40 years old
            (b) Occurs after 60 years of age
         (2) Men and women affected equally
         (3) Most common neuromuscular disorder of esophagus
         (4) Risk for esophageal cancer
      b. Pathogenesis
         (1) Normal relaxation of the smooth muscle in the LES is due to nitric oxide (NO) and vasoactive intestinal peptide (VIP).
         (2) In achalasia, there is incomplete relaxation of the LES.
            (a) Loss of myenteric nerve fibers and inhibitory neurons in the myenteric plexus producing nitric oxide synthase
               • Probably autoimmune destruction
            (b) Decrease in both NO and VIP
(3) Dilation of esophagus occurs proximal to LES, but peristalsis is absent.
(4) Acquired cause is Chagas disease.
   • Destruction of ganglion cells by amastigotes (lack flagella)

c. Clinical findings
   (1) Nocturnal regurgitation of undigested food
   (2) Dysphagia for solids and liquids
   (3) Chest pain and heartburn
   (4) Frequent hiccups
   (5) Nocturnal cough from aspiration
   (6) Difficulty belching

d. Diagnosis
   (1) Abnormal findings with barium swallow
      • Dilated, aperistaltic esophagus with a beak-like tapering at distal end
         (Fig. 18-12)
   (2) Abnormal findings with esophageal manometry
      • Detects aperistalsis and failure of LES relaxation

e. Treatment
   (1) Nonpharmacologic
      (a) Pneumatic dilation
      (b) Esophagomyotomy
   (2) Pharmacologic (short-term)
      (a) Long-acting nitrates
      (b) Calcium channel blockers
      (c) Botulinum toxin injection

N. Esophageal tumors

1. Leiomyoma
   • Most common benign tumor of esophagus

2. Adenocarcinoma of distal esophagus (Fig. 18-13A)
   a. Most common primary cancer of the esophagus in the United States
   b. Barrett esophagus is most common predisposing cause.
      • Prevention of GERD decreases risk for developing adenocarcinoma.

3. SCC
   a. Epidemiology
      (1) Most common primary cancer in developing countries
         • Caspian Sea to Northern China

Acquired achalasia: Chagas disease
Achalasia: nocturnal regurgitation undigested food
Achalasia barium swallow: dilated, aperistaltic esophagus; beak-like tapering at distal end
Leiomyoma: MC benign tumor esophagus
Distal adenocarcinoma esophagus: MC esophageal cancer; Barrett esophagus is precursor lesion
More common in blacks than whites
(3) Occurs in men more often than women
(4) Risk factors
  (a) Smoking most common cause
  (b) Alcohol abuse, lye strictures
  (c) Achalasia, Plummer-Vinson syndrome
(5) Locations
  (a) Upper third (~15%)  
  (b) Middle third (~50%) (see Fig. 18-13B and C)  
  (c) Lower third (~35%)
(6) Spreads to local nodes first and then to liver and lungs
b. Clinical findings
(1) Dysphagia for solids initially
(2) Weight loss of short duration
(3) Painless enlarged supraclavicular nodes
(4) Dry cough and hemoptysis
  • Suggests tracheal invasion
(5) Hoarseness
  • Probable invasion of recurrent laryngeal nerve
(6) Odynophagia
(7) Hypercalcemia
  • Parathyroid hormone–related peptide similar to SCC in the lungs (refer to Chapter 17)
c. Diagnosis
(1) Esophagogram
(2) Endoscopy
d. Treatment
  • Surgery, radiation therapy, chemotherapy
e. Prognosis
  • Overall 5-year survival rate is 13%.
III. Stomach Disorders

A. Signs and symptoms of stomach disease

1. Hematemesis (vomiting blood)
   a. Most commonly due to peptic ulcer disease (PUD)
   b. Other causes—esophageal varices, hemorrhagic gastritis

2. Melena (dark, tarry stools)
   a. Hemoglobin (Hb) is converted into hematin (black pigment) by acid.
   b. It signifies a bleed proximal to duodenojejunal junction (90% of cases).
      (1) Duodenojejunal junction is the fourth part of the duodenum.
      (2) It is surrounded by a peritoneal fold containing muscle fibers called the ligament of Treitz.

3. Gastric analysis

B. Congenital pyloric stenosis (CPS)

1. Epidemiology
   a. Probable genetic basis
   b. Occurs in males > females
   c. Affected fathers or mothers
      • Increased risk for child with CPS
   d. Acquired pyloric obstruction
      • Complication of chronic duodenal ulcer disease with pyloric scarring

2. Pathophysiology
   a. It is caused by progressive hypertrophy of the circular muscles in the pyloric sphincter.
      • Not present at birth but occurs over the ensuing 3 to 5 weeks
   b. Deficiency of NO synthase precipitates the disease.

3. Clinical findings
   a. Projectile vomiting occurs; fluid is not bile stained.
   b. Hypertrophied pylorus is palpated in the epigastrium (70% of cases).
      • Called an “olive”
   c. Visible hyperperistalsis

4. Treatment
   • Myotomy if it does not resolve

C. Gastroparesis

1. Definition—decreased stomach motility
   a. Autonomic neuropathy (e.g., diabetes mellitus [DM])
   b. Previous vagotomy

2. Clinical findings
   a. Early satiety and bloating
   b. Vomiting of undigested food a few hours after eating

3. Treatment
   a. Frequent feeding of small meals
   b. Metoclopramide

D. Acute hemorrhagic (erosive) gastritis

1. Definitions
   a. Erosions are a breach in the epithelium of the mucosa.
   b. Ulcers are a breach in the mucosa with extension into the submucosa or deeper.

2. Causes
   a. Nonsteroidal antiinflammatory drugs (NSAIDs)
   b. Alcohol, Helicobacter pylori (see later)
   c. CMV (AIDS), smoking
   d. Burns (called Curling ulcers), CNS injury (called Cushing ulcers)
   e. Uremia, Anisakis (worm associated with eating raw fish)
3. Clinical findings
   a. Hematemesis
   b. Melena
   c. Iron deficiency
4. Treatment (excluding *H. pylori*)
   a. Nonpharmacologic
      (1) Avoid mucosal irritants (e.g., NSAIDs, alcohol)
      (2) Cessation of smoking
   b. Pharmacologic
      (1) Misoprostol
      (2) Proton pump inhibitors

E. Chronic atrophic gastritis
1. Type A chronic atrophic gastritis
   a. Involves the body and fundus
   b. Most often due to pernicious anemia (PA; refer to Chapter 12)
   c. Complications
      (1) Achlorhydria with hypergastrinemia (loss of negative feedback)
      (2) Macrocytic anemia due to vitamin B₁₂ deficiency
      (3) Increased risk for gastric adenocarcinoma
2. Type B chronic atrophic gastritis
   a. Involves the antrum and pylorus
   b. Epidemiology
      (1) Most common cause is *H. pylori*
      (2) Present in 30% to 50% of the population in the United States
      (3) Prevalence increases with age
      (4) Transmitted by fecal-oral (organism passed in stools and can live in water)/oral-oral route
         • Common in areas of poor sanitation
   c. Pathophysiology
      (1) Gram-negative, curved rod
      (2) Produces urease, proteases, cytotoxins
         (a) Urease converts amino groups in proteins to ammonia
         (b) Secretion products produce chronic gastritis and PUD.
      (3) Colonizes mucous layer lining (Fig. 18-14A)
         (a) Attaches to blood group O receptors on mucosal cells
         (b) Not an invasive bacterium
d. Microscopic findings
   (1) Chronic inflammatory infiltrate in the lamina propria
   (2) Intestinal metaplasia (similar to picture for Barrett esophagus)
      • Precursor lesion for adenocarcinoma
e. Tests to identify *H. pylori* are highly sensitive and specific.
   (1) Urea breath test
      (a) Documents active infection
      (b) Sensitivity and specificity >90%
   (2) Stool antigen test (excellent screen; cheaper than urea breath test)
      (a) Positive when there is active infection
      (b) Negative when infection has been eradicated
      (c) Sensitivity and specificity >90%
   (3) Tests to detect urease in a gastric biopsy
      • Considered to be the gold standard test albeit an invasive test
   (4) Serologic tests have been discontinued.
f. Treatment
   • Optimal therapy has not been defined.
g. Test of cure is stool antigen test
   (1) If negative 8 weeks after therapy, infection is cured.
   (2) A negative result does not imply that infection cannot recur.
h. Other disease associations with *H. pylori*
   (1) Duodenal and gastric ulcers (see later)
   (2) Gastric adenocarcinoma (see later)
   (3) Low-grade B-cell mucosa-associated lymphoid tissue lymphoma (see later)
3. Ménétrier disease (hypertrophic gastropathy)
   a. Giant rugal folds
      (1) Due to hyperplasia of mucus-secreting cells
      (2) Causes hypoproteinemia (protein-losing enteropathy)
   b. Atrophy of parietal cells (achlorhydria)
      • Increased risk for adenocarcinoma

F. Peptic ulcer disease (PUD)
   1. Epidemiology
      a. PUD is most often caused by H. pylori (70% of cases).
      • Other parts of the world >90% of cases

18-14: A, Silver stain showing Helicobacter pylori organisms in the mucus layer lining the gastric epithelial cells. B, Duodenal ulcer in the first part of the duodenum. C, Chronic gastric ulcer (arrow) in the lesser curvature. D, Plain abdominal radiograph in a supine patient with a perforated peptic ulcer. Note the presence of air under both diaphragms. E, Schematic of arterial system in the stomach. The gastroduodenal artery (black dot) and the right gastric artery (red dot) are eroded for bleeding from a duodenal ulcer and gastric ulcer, respectively. (A from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 815, Fig. 17-15; B from Damjanov I, Linder J: Anderson’s Pathology, 10th ed, St. Louis, Mosby, 1996, p 1680, Fig. 53.21B; C from Morson BC: Colour Atlas of Gastrointestinal Pathology, London, Harvey Miller Ltd, 1988, p 52, Fig. 3.27; D from Goldman L, Ausiello D: Cecil’s Textbook of Medicine, 23rd ed, Philadelphia, Saunders Elsevier, 2008, p 1015, Fig. 142-3; E from Moore A, Roy W: Rapid Review Gross and Developmental Anatomy, 3rd ed, Philadelphia, Mosby Elsevier, 2010, p 73, Fig. 3-15.)
PUD: *H. pylori* MCC worldwide

b. Eradication of *H. pylori* markedly reduces PUD recurrence.

c. Duodenal ulcers are more common than gastric ulcers.
   - Incidence of bleeding is the same in both ulcers.

d. Locations
   1. Duodenal ulcer is in the first portion of duodenum (>90% of cases; see Fig. 18-14B).
   2. Gastric ulcer is in the lesser curvature near the incisura angularis (see Fig. 18-14C).

PUD: duodenal > gastric

e. Recurrence rate for untreated PUD ~60% of cases (>70% in smokers)

2. Gross appearance of ulcers
   a. Clean, sharply demarcated, and slightly elevated around the edges
   b. Most gastric ulcers are benign.
      - Small percentage may be malignant (reason for biopsy).
   c. Duodenal ulcers are *never* malignant (reason for not taking a biopsy).
   d. Four layers in sequence are noted in histologic sections of ulcers.
      1. Necrotic debris
      2. Inflammation with a predominance of neutrophils
      3. Granulation tissue (repair tissue)
      4. Fibrosis

3. Comparison of gastric and duodenal ulcers (Table 18-2)

---

### Table 18-2 Comparison of Gastric Ulcers and Duodenal Ulcers

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>GASTRIC ULcers</th>
<th>DUODENAL ULcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of ulcer cases</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Male/female ratio 1:1 Smoking may delay healing Risk for developing gastric cancer (increased risk with blood group A individuals) Risk factors: <em>H. pylori</em> (most common), chronic intake of NSAIDs (synergism with <em>H. pylori</em>), moderate alcohol consumption</td>
<td>Male/female ratio 1:1 Risk increased with MEN I Smoking may delay healing Chronic intake NSAIDs Risk factors: <em>H. pylori</em> (most common), chronic intake of NSAIDs, type O blood group (lack blood group antigens that are protective to the mucosal surface)</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> association</td>
<td>Duodenal ulcer &gt; gastric ulcer</td>
<td>Duodenal ulcer &gt; gastric ulcer</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Defective mucosal barrier due to <em>H. pylori</em> Mucosal ischemia (reduced PGE, normally a vasodilator), bile reflux, delayed gastric emptying BAO and MAO normal to decreased</td>
<td>Defective mucosal barrier due to <em>H. pylori</em> Increased acid production (increased parietal cell mass) BAO and MAO both increased</td>
</tr>
<tr>
<td>Location</td>
<td>Single ulcer on lesser curvature of antrum (same location for cancer) (see Fig. 18-14C)</td>
<td>Single ulcer on anterior portion of first part of duodenum (see Fig. 18-14B) followed by single ulcer on posterior portion (danger of perforation into pancreas and pancreatitis)</td>
</tr>
<tr>
<td>Complications</td>
<td>Bleeding (most commonly ulceration of left gastric artery; see Fig. 18-14E). Bleeding spontaneously ceases in 80% of cases. Perforation (air under diaphragm, pain radiates to left or right shoulder; see Fig. 18-14D)</td>
<td>Bleeding (anterior ulcer; most commonly ulceration of gastroduodenal artery; see Fig. 18-14E). Bleeding spontaneously ceases in 80% of cases. Perforation (anterior ulcer; air under diaphragm, pain radiates to left or right shoulder) Gastric outlet obstruction, pancreatitis (posterior ulcer)</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Epigastric pain exacerbated by eating</td>
<td>Epigastric pain relieved by eating</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Endoscopy: 90%–95% accuracy; must biopsy gastric ulcers (1%–4% malignant) Upper GI barium study: identify 70%–80% PUD</td>
<td>Endoscopy: 90%–95% accuracy; no need to biopsy because never malignant Upper GI barium study: identify 70%–80% PUD</td>
</tr>
<tr>
<td>Treatment</td>
<td>Pharmacologic: eradication of <em>H. pylori</em> via proton pump inhibitor–based triple therapy Surgery for resistant cases uncommon: ulcer removal with antrectomy or hemigastrectomy without vagotomy</td>
<td>Pharmacologic: eradication of <em>H. pylori</em> via proton pump inhibitor–based triple therapy Surgery for resistant cases uncommon: highly selective vagotomy</td>
</tr>
</tbody>
</table>

BAO, Basal acid output; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; MAO, maximal acid output; MEN, multiple endocrine neoplasia; NSAIDs, nonsteroidal antiinflammatory drugs; PGE, prostaglandin E; PUD, peptic ulcer disease.
G. Zollinger-Ellison (ZE) syndrome
1. Epidemiology and pathogenesis
   a. Definition—malignant tumor (60%-90% of cases) that secretes excess gastrin, producing hyperacidity
      • Parietal cell mass is increased because of hyperplasia from excessive gastrin production.
   b. The majority are located in the duodenum (60% of cases) and less commonly in the pancreatic islet cells (30% of cases).
   c. The syndrome is sporadic in two-thirds of cases, and is associated with MEN type I in one-third of cases.
   d. Ulcers are single and in the usual locations or there may be multiple ulcers.
   e. Suspicious for ZE syndrome
      (1) Multiple peptic ulcers
      (2) Ulcers resistant to therapy
      (3) Ulcer distal to first portion of duodenum
      (4) PUD plus diarrhea
      (5) Family history of parathyroid or pituitary tumors (MEN type I syndrome)
      (6) PUD without H. pylori or history of NSAIDs
2. Clinical findings
   a. Epigastric pain (most common complaint) with weight loss
   b. Heartburn from GERD (60% of cases)
   c. Peptic ulceration
      • Most are solitary duodenal ulcers rather than multiple ulcers.
   d. Acid hypersecretion with diarrhea
   e. Malabsorption of food
      • Acid interferes with pancreatic enzyme activity.
3. Laboratory findings
   a. Increased BAO, MAO, and BAO/MAO ratio
   b. Serum gastrin level >1000 pg/mL (best screen)
   c. Secretin stimulation test (provocative test) shows a serum gastrin >200 pg/mL
4. Radiolabeled octreotide is used to localize the tumor.
5. Treatment
   • Chemotherapy and proton pump inhibitors

H. Gastric polyps
1. Complication of chronic gastritis and achlorhydria
2. Hyperplastic polyp
   a. Most common type
   b. Hamartoma with no malignant potential
3. Adenomatous polyp
   a. Neoplastic polyp
   b. Potential for malignant transformation

I. Gastric tumors
1. Leiomyoma
   a. Stomach is most common site
   b. May ulcerate or bleed
2. Primary stomach adenocarcinomas
   a. Epidemiology
      (1) Decreasing incidence in United States
      (2) Increasing incidence in Japan (smoked foods)
      (3) Increased incidence in blood group A people
   b. Intestinal type of gastric adenocarcinoma
      (1) Most common gastric carcinoma
      (2) Risk factors
         (a) Intestinal metaplasia due to H. pylori (type B; most important)
         (b) Nitrosamines
         (c) Smoked foods (Japan)
         (d) Diets lacking fruits/vegetables
         (e) Type A chronic atrophic gastritis (PA)
         (f) Ménétrier disease
      (3) Polypoid or ulcerated (Fig. 18-15A)
      (4) Locations
         (a) Lesser curvature of pylorus and antrum (50%-60% of cases)
         (b) Cardia (25% of cases), body and fundus
18-15: A. Gastric adenocarcinoma showing an irregular ulcer crater with piling up of the mucosa around the ulcer. B. Typical gross appearance of diffuse carcinoma of so-called linitis plastica type. Practically the entire wall of the stomach is involved by tumor. Note the prominence of rugal folds. C. Diffuse type of gastric adenocarcinoma with signet ring carcinoma cells (arrows). Mucin produced by the cancer cells pushes the nucleus to the periphery. (A and C from Kumar V, Fausto N, Abbas A; Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 825, Figs. 17-26, 17-27B, respectively; B from Rosai J: Rosai and Ackerman’s Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 664, Fig. 11.47.)

c. Diffuse type of gastric adenocarcinoma
   (1) Incidence has remained unchanged.
   (2) Not associated with H. pylori
   (3) Diffuse infiltration of malignant cells in the stomach wall (see Fig. 18-15B)
      (a) It is sometimes called linitis plastica.
      (b) Stomach does not have peristalsis.
      (c) Signet ring cells infiltrate the stomach wall (see Fig. 18-15C).
      (d) It produces Krukenberg tumors of the ovaries.
         • Signet ring cells spread hematogenously to both ovaries.

d. Clinical findings
   (1) Cachexia and weight loss (most common; 60% of cases)
   (2) Epigastric pain (50% of cases)
   (3) Vomiting, often with melena (20% of cases)
   (4) Metastasis to left supraclavicular node (Virchow node)
   (5) Paraneoplastic skin lesions (refer to Chapter 9)
      (a) Acanthosis nigricans (see Fig. 25-7B)
      (b) Multiple outcroppings of seborrheic keratoses (Leser-Trélat sign; see Fig. 25-7A)
   (6) Metastasis to umbilicus (Sister Mary Joseph nodule)

e. Common metastatic sites
   • Liver, lung, ovaries

f. Treatment
   • Surgery, local radiation, and chemotherapy

g. Approximately 10% to 15% overall 5-year survival rate

3. Primary gastric malignant lymphoma
   a. Stomach is the most common site for extranodal malignant lymphoma.
   b. Low-grade B-cell lymphoma
      (1) Related to H. pylori
      (2) MALToma (derives from mucosa-associated lymphoid tissue)
   c. High-grade B- or T-cell lymphomas
   d. 50% cure rate if H. pylori treated

IV. Small Bowel and Large Bowel Disorders
   A. Signs and symptoms of small bowel disease
      1. Colicky pain
         a. Pain followed by a pain-free interval
            • Accompanied by constipation and inability to pass gas
b. Symptom of bowel obstruction
   • Example—adhesions from previous surgery

2. Diarrhea
   a. Could be a sign of:
      • Infection, malabsorption, osmotic diarrhea
   b. If bloody, it may be a sign of:
      • Infarction, volvulus, dysentery

3. Anemia could be due to malabsorption of:
   • Iron, folic acid, vitamin B₁₂

B. Signs and symptoms of large bowel disease

1. Diarrhea
   a. Could be a sign of:
      • Infection, laxative abuse, inflammatory bowel disease
   b. If bloody, may be a sign of infarction or dysentery

2. Dysentery
   a. Refers to bloody diarrhea with mucus
   b. Infection

3. Pain occurs in:
   • Inflammatory bowel disease, ischemic colitis, diverticulitis, appendicitis, and peritonitis

4. Tenesmus
   a. Painful, ineffective straining at stool
   b. Commonly present in ulcerative colitis

5. Iron deficiency
   • Consider polyps, colorectal cancer

6. Hematochezia
   a. Massive loss of whole blood per rectum
   b. Causes
      (1) Sigmoid diverticulosis (most common)
      (2) Angiodysplasia
   c. Black mucosa (melanosis coli)
      a. Definition—chronic use of laxatives of the anthranoid group (senna and rhubarb derivatives)
      b. Bowel is black because of an increase in submucosal macrophages with lipofuscin pigment

C. Diarrheal diseases (excluding malabsorption)

1. Diarrhea
   a. Definition—more than 250 g of stool per day
   b. Acute diarrhea is defined as less than 3 weeks, chronic diarrhea over 4 weeks
   c. Invasive, osmotic, secretory types (Table 18-3)

### Table 18-3 Types Of Diarrhea

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CHARACTERISTICS</th>
<th>CAUSES</th>
<th>SCREENING TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td>Pathogens invade enterocytes</td>
<td><em>Shigella</em> spp., <em>Campylobacter jejuni</em></td>
<td>Fecal smear for leukocytes: positive in most cases Order stool culture, stool for O&amp;P, stool antigen</td>
</tr>
<tr>
<td></td>
<td>Low-volume diarrhea</td>
<td><em>Entamoeba histolytica</em></td>
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<td></td>
<td>Diarrhea with blood and leukocytes (i.e., dysentery)</td>
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<tr>
<td>Secretory</td>
<td>Loss of isotonic fluid</td>
<td>Laxatives: danger of melanosis coli (black bowel syndrome) with use of laxatives Production of enterotoxins: <em>Vibrio cholerae</em>, <em>Escherichia coli</em> Increased serotonin: carcinoid syndrome</td>
<td>Fecal smear for leukocytes: negative Increased 5-HIAA: carcinoid syndrome Stool osmotic gap &lt;50 mOsm/kg</td>
</tr>
<tr>
<td></td>
<td>High-volume diarrhea</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Mechanisms.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Enterotoxins stimulate Cl⁻ channels regulated by cAMP and cGMP</td>
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<tr>
<td></td>
<td>Serotonin increases bowel motility</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No inflammation in bowel mucosa</td>
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<tr>
<td>Osmotic</td>
<td>Osmotically active substance is drawing hypotonic salt solution out of bowel</td>
<td>Disaccharidase deficiency “Stunned gut” in giardiasis Ingestion of poorly absorbable solutes (e.g., magnesium sulfate laxatives)</td>
<td>Fecal smear for leukocytes: negative Stool osmotic gap &gt;100 mOsm/kg</td>
</tr>
<tr>
<td></td>
<td>High-volume diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No inflammation in bowel mucosa</td>
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</tbody>
</table>

*cAMP*, Cyclic adenosine monophosphate; *cGMP*, cyclic guanosine monophosphate; 5-HIAA, 5-hydroxyindoleacetic acid; O&P, ova and parasites.
2. Important screening tests
   a. Fecal smear for leukocytes (e.g., invasive diarrhea)
   b. Stool osmotic gap
      (1) 300 mOsm/kg (value used to represent normal POsm [refer to Chapter 5]) – 2 × (random stool Na⁺ + random stool K⁺)
      (2) Osmotic gap <50 mOsm/kg from POsm is a secretory diarrhea.
         • Indicates that diarrheal fluid POsm approximates normal POsm
      (3) Osmotic gap >100 mOsm/kg from POsm is an osmotic diarrhea.
         • Indicates a hypotonic loss of stool due to presence of osmotically active substances

Lactase deficiency is a common genetic defect in Native Americans, Asians, and blacks. Colon anaerobes degrade undisgested lactose into lactic acid and H₂ gas, leading to abdominal distention with explosive diarrhea. Treatment is to avoid dairy products.

3. Summary table of microbial pathogens causing diarrhea (Table 18-4; Fig. 18-16)

D. Malabsorption

1. Definition
   a. Chronic diarrhea with increased fecal excretion of fat (called steatorrhea)
   b. Concurrent deficiencies of fat-soluble vitamins, minerals, carbohydrates, and proteins may also occur

2. Etiology and pathogenesis of fat malabsorption
   a. Pancreatic insufficiency
      (1) Most often caused by chronic pancreatitis
         • Most commonly due to alcohol in adults and cystic fibrosis (CF) in children (refer to Chapter 19)
      (2) Dietary triglyceride (TG) is hydrolyzed by pancreatic lipase (refer to Chapter 8).
         (a) Hydrolysis yields monoglycerides (MGs) and fatty acids (FAs).
         (b) In chronic pancreatitis, pancreatic lipase is deficient and fats are undisgested producing a fatty stool (steatorrhea).
         • Undigested neutral fats and fat droplets are present in stool.
      (3) Maldigestion of proteins is also present.
         (a) Due to diminished pancreatic trypsin
         (b) Undigested meat fibers are in present in stool.
      (4) Carbohydrate absorption is not affected because amylase is present in the salivary glands and disaccharidases are present in the brush border of the intestinal epithelium.

   b. Bile salt/acid deficiency
      (1) Causes include:
         (a) Inadequate synthesis of bile salts/acid from cholesterol (e.g., cirrhosis)
         (b) Intrahepatic/extrahepatic blockage of bile
            • Examples—primary biliary cirrhosis, stone in common bile duct
         (c) Bacterial overgrowth in small bowel with destruction of bile salts/acid
            • Examples—small bowel diverticula, autonomic neuropathy
         (d) Excess binding of bile salts
            • Example—cholestyramine
         (e) Terminal ileal disease
            • Prevents recycling of bile salts/acid
            • Examples—Crohn disease, resection of the terminal ileum
      (2) Bile salts/acid produce micelles to enhance reabsorption of fats by the small intestinal villi.
         (a) Micelles contain MGs, FAs, fat-soluble vitamins, and cholesterol (CH) esters.
            • Note that all the fat soluble vitamins (vitamins A, D, E, and K) are packaged in micelles along with the products of fat digestion; hence any disease producing maldigestion of fats also produces deficiencies of all the fat-soluble vitamins.
         (b) In bile salt deficiency, micelles are not formed, which produces a fatty stool.

   c. Small bowel disease
      (1) Damage to the villi (e.g., celiac disease)
         (a) Villi increase the absorptive surface of the small intestine.
            • Required to reabsorb micelles into enterocytes
         (b) Loss of the villi leads to loss of micelles in the stool
### TABLE 18-4 Microbial Pathogens Causing Diarrhea

<table>
<thead>
<tr>
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<td><strong>Viruses</strong></td>
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| Cytomegalovirus              | Common cause of diarrhea in AIDS when CD4 T	extsubscript{+} count <50–100 cells/mm	extsuperscript{3}  
  *Treatment*: ganciclovir                                                   |
| Norovirus (Norwalk) virus    | Most common cause of adult gastroenteritis  
  Nausea, vomiting, diarrhea that resolves in 12–24 hours  
  Occasionally can be fatal  
  Fecal-oral transmission  
  Common infection on cruise ships  
  *Treatment*: supportive                                                     |
| Rotavirus                    | Most common cause of childhood diarrhea; particularly occurs in winter months  
  Fecal-oral transmission  
  Damages ion transport pump in small intestine; secretory diarrhea  
  Rotavirus vaccine highly effective in prevention; oral vaccine  
  *Treatment*: oral hydration; nitazoxanide                                    |
| **Bacteria**                 |                                                                                                                                             |
| *Bacillus cereus*            | Gram-positive rod  
  Food poisoning with preformed toxin  
  Associated with reheated fried rice or tacos  
  Self-limited                                                                  |
| *Campylobacter jejuni* (see Fig. 18-16A) | Curved or S-shaped gram-negative rod  
  Animal reservoirs: cattle, chicken, puppies (common source for children)  
  Transmission fecal-oral (animal to human) via contaminated water, poultry, or unpasteurized milk  
  Most common food-borne illness and invasive enterocolitis in the United States  
  Invasive and secretory enterocolitis: dysentery (bloody diarrhea) with crypt abscesses and ulcers resembling ulcerative colitis; high fever and cramping abdominal pain; organisms in stool with blood and leukocytes  
  Complications: Guillain-Barré syndrome (antibodies cross-react with neurons); hemolytic uremic syndrome; HLA-B27 positive spondylarthropathy  
  *Diagnosis*: culture, stool antigen, serology  
  *Treatment*: erythromycin                                                    |
| *Clostridium botulinum*      | Gram-positive rod  
  Adult food poisoning with preformed toxin (blocks release of acetylcholine in presynaptic terminal of neuromuscular junction in autonomic nervous system); causes descending paralysis, mydriasis, dry mouth  
  *Treatment*: trivalent antitoxin                                            |
| *Clostridium difficile* (see Figs. 3-8C and 18-16B) | Gram-positive rod  
  Associated with pseudomembranous colitis; the most common cause of nosocomial diarrhea, antibiotic-induced diarrhea, and health care–associated diarrhea; secretory type of diarrhea  
  Person-to-person induced in 30% of cases; normally present in 3% of people; carrier rate increases to >20% in hospitalized patients (related to fecal-oral contamination and contact with spores in environment to a lesser extent).  
  Antibiotic-induced in 65%–90% of cases; antibiotics (e.g., ampicillin, quinolones, clindamycin) cause overgrowth of toxin-producing *C. difficile* in colon; antibiotic increase gastrointestinal reabsorption of toxins A and B from the bacterial cell membrane; toxins release proinflammatory mediators and cytokines that attract neutrophils and stimulate excess fluid secretion (watery diarrhea).  
  Pseudomembrane covers colon mucosa; composed of cellular debris, leukocytes, fibrin, and mucin  
  Nonspecific lab findings: neutrophilic leukocytosis with left shift; fecal leukocytes; and decreased serum albumin.  
  Cytotoxin assay of diarrheal (not solid) stool has greater specificity (75%–100%) than culture of stool (75%–80%) for securing the diagnosis; glutamate dehydrogenase antigen test is also used and has excellent sensitivity and specificity (enzyme is present in all strains of *C. difficile*).  
  *Treatment*: metronidazole; vancomycin produces resistant strains  
  Increased mortality with increased age and increased virulence of antibiotic resistant strains |
| *Escherichia coli*           | Gram-negative rod  
  ETEC: certain strains produce toxin that activate adenylate or guanylate cyclase, causing secretory diarrhea (traveler’s diarrhea; no fever; no bowel inflammation; accounts for 60% of cases); other causes include *Campylobacter*, *Salmonella*, *Shigella*  
  *Treatment*: ciprofloxacin  
  STEC (O157:H7 serotype): contracted by eating undercooked beef, bean sprouts, undercooked cookies  
  Produces gastroenteritis with bloody diarrhea and hemolytic uremic syndrome (HUS; in 8% of cases; refer to Chapter 14)  
  Antibiotics *not* recommended; may enhance toxin release  
  *Diagnosis*: DNA assays; enzyme immunoassays for toxin                        |
| *Mycobacterium avium-intracellulare complex (MAC)* | Acid-fast rods  
  Causes diarrhea with malabsorption in AIDS (CD4 count <50 cells/mm	extsuperscript{3})  
  Foamy macrophages in lamina propria simulate Whipple disease  
  *Continued* |
<table>
<thead>
<tr>
<th>PATHOGEN</th>
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<tbody>
<tr>
<td><strong>Mycobacterium tuberculosis</strong></td>
<td>Acid-fast organisms swallowed from primary focus in lung In invade Peyer patches Circumferential spread in lymphatics leads to stricture formation</td>
</tr>
<tr>
<td><strong>Salmonella spp.</strong></td>
<td>Gram-negative rod Pathogenic Salmonella: S. typhi, S. paratyphi, S. enteritidis Animal reservoirs: turtles, hamsters, lizards S. enteritidis enterocolitis: Second most common food-borne illness in United States; contracted by eating raw or undercooked egg products, raw milk and milk products, drinking contaminated water, or improper washing of the hands when handling previously mentioned animal reservoirs (animal to human) Treatment: ciprofloxacin or levofloxacin Typhoid fever caused by S. typhi: Week 1: invades Peyer patches and produces sepsis (blood culture best for diagnosis) Week 2: diarrhea (positive stool culture); classic triad of bradycardia, neutropenia, splenomegaly Treatment: treat if symptomatic with fluoroquinolone; antibiotics do not shorten the illness and may increase frequency of carrier states Chronic carrier state due to gallbladder disease: cholecystectomy</td>
</tr>
<tr>
<td><strong>Shigella dysenteriae and Shigella sonnei</strong></td>
<td>Gram-negative rod No animal reservoirs Highly infectious (human to human transmission); children in day care centers; mental institutions Mucosal ulceration, pseudomembranous inflammation in rectosigmoid, dysentery Association with HLA-B27 positive seronegative spondyloarthropathy Treatment: treat if symptomatic with fluoroquinolone or azithromycin</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>Gram-positive coccus Food poisoning with preformed toxin; culture food, not stool Gastroenteritis occurs in 1–6 hours after eating Self-limited</td>
</tr>
<tr>
<td><strong>Vibrio cholerae</strong></td>
<td>Gram-negative comma-shaped rod Enterotoxin stimulates adenylate cyclase in small bowel Contracted from drinking contaminated water or eating contaminated seafood, especially crustacea No inflammation in the bowel Treatment: fluid replacement; glucose and sodium required in oral supplements (cotransport system for reabsorption); doxycycline or fluoroquinolone</td>
</tr>
<tr>
<td><strong>Yersinia enterocolitica</strong></td>
<td>Gram-negative coccobacillus with bipolar staining Enterocolitis in children; mesenteric lymphadenitis (granulomatous microabscesses) that simulates acute appendicitis Association with HLA-B27 positive seronegative spondyloarthropathy Treatment: TMP-SMX</td>
</tr>
<tr>
<td><strong>Protozoa</strong></td>
<td></td>
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<tr>
<td><strong>Balantidium coli</strong></td>
<td>Protozoan (ciliate); largest protozoan Fecal-oral transmission; ingestion of cysts in food or water Produces colonic ulcers with bloody diarrhea Treatment: tetracycline</td>
</tr>
<tr>
<td><strong>Cryptosporidium parvum</strong> (see Fig. 18-16C)</td>
<td>Protozoan (sporozoan) Fecal-oral transmission; ingestion of oocysts in food or water Responsible for outbreaks of diarrhea in water supply (e.g., Milwaukee, Wisconsin); can also be responsible with day care diarrhea in children Most common cause of diarrhea in AIDS and diarrhea from swimming in municipal swimming pools Diagnosis: stool antigen test (sensitivity/specificity 98%); oocysts partially acid-fast Treatment: if immunocompetent: nitazoxanide (less responsive to drug if immunodeficient)</td>
</tr>
<tr>
<td><strong>Cyclospora, Microsporida, Isospora belli</strong></td>
<td>Protozoan (sporozoan) Fecal-oral transmission; oocysts are the infective form of the protozoa All are common pathogens in AIDS diarrhea Cyclospora can contaminate raspberries Microsporida spores not partially acid-fast Cyclospora oocysts partially acid-fast Isospora oocysts partially acid-fast Treatment: Cyclospora: TMP-SMX double strength; Microsporida: albendazole; Isospora: TMP-SMX double strength</td>
</tr>
<tr>
<td><strong>Entamoeba histolytica</strong> (see Fig. 18-16D)</td>
<td>Protozoan (amoeba) Transmitted by ingestion of cysts in food and water Infective forms: cysts, trophozoites Cysts are nonmotile and are present in formed stool; trophozoites are motile and are present in diarrhea Produces dysentery (bloody diarrhea); cysts excyst in the cecum and become trophozoites in the cecum; trophozoites release powerful histolytic agents that produce flask-shaped ulcers; trophozoites can penetrate portal vein tributaries and drain to the liver to produce a liver abscess (“anchovy paste” abscess); trophozoites can penetrate hepatic vein tributaries and produce systemic disease Trophozoites characteristically phagocytose red blood cells Diagnosis: stool antigen test (sensitivity/specificity 100%) Treatment: metronidazole (diarrhea/dysentery, extraintestinal disease); paromomycin (asymptomatic cyst passer)</td>
</tr>
</tbody>
</table>
### Giardia lamblia
(see Fig. 18-16E)
Protozoa (flagellate)
Most common protozoal cause of diarrhea in United States
Fecal-oral transmission by ingestion of cysts in food and water; reservoirs for *Giardia* that contaminate water supplies—beavers, voles, muskrats
Common in day care centers, mental hospitals, hikers, water supplies (chlorination does not kill the cysts), men who have sex with men (anal-oral contact), IgA deficiency, common variable immunodeficiency
Produces acute and chronic diarrhea with malabsorption (cysts in formed stool; trophozoites in loose stools)
Diagnosis: stool antigen test (sensitivity/specificity 100%)
**Treatment:** tinidazole or nitazoxanide

### Helminths

#### Anisakis simplex
Intestinal nematode
Transmission: eating raw fish dishes (i.e., sushi, sashimi); eating pickled herring
Larvae penetrate gastric and intestinal mucosa
Produce cramping abdominal pain; epigastric distress with nausea, vomiting, and diarrhea within a few hours after eating
Diagnosis: endoscopy; IgE antibody test
**Treatment:** removal by endoscope or surgery

#### Enterobius vermicularis
(see Fig. 18-16F)
Intestinal nematode
Most common helminth in the United States; most contagious round worm worldwide
Fecal-oral transmission by ingestion of eggs (infective form)
Eggs deposited in anus by adult worms cause pruritus ani
Other infections: urethritis in girls; acute appendicitis
No eosinophilia because adult worms are not invasive
**Treatment:** mebendazole

#### Trichuris trichiura
(see Fig. 18-16G and H)
Intestinal nematode (whipworm)
Fecal oral transmission by ingestion of eggs (infective form)
Produces diarrhea; can produce rectal prolapse in children
Diagnosis: stool for ova and parasites; eosinophilia
**Treatment:** albendazole

#### Ascaris lumbricoides
(see Fig. 18-16I and J)
Largest intestinal nematode
Fecal oral transmission by ingestion of eggs (infective form)
Larval phase through lungs: cough, pneumonitis, eosinophilia (invasion of tissue)
Bowel obstruction or common bile duct obstruction in adult phase; no eosinophilia (no invasion of tissue)
**Treatment:** albendazole and mebendazole

#### Necator americanus
Intestinal nematode (hookworm)
Transmission by direct penetration or autoinfection; filariform larvae is infected form
Adults attach to villi, resulting in blood loss and iron deficiency
**Treatment:** albendazole or mebendazole

#### Strongyloides stercoralis
(see Fig. 18-16K)
Intestinal nematode
Transmission: filariform larvae in soil penetrate the feet → larval phase through the lungs → swallowed and molt into adults that enter the intestinal mucosa and lay eggs → eggs hatch into rhabditiform larvae, which enter the intestinal lumen and are passed in the stool (no eggs in stool) → develop into filariform larvae (infective form) in the soil
Autoinfection may occur if filariform larvae in the intestine penetrate the mucosa and migrate to the lungs to repeat the cycle
In immunocompromised patients (e.g., AIDS), massive reinfection occurs with dissemination throughout the body (hyperinfection)
Produces abdominal pain and diarrhea; can penetrate skin and migrate throughout the body (wheezing and cough with pulmonary involvement); infected for life!
**Treatment:** ivermectin

#### Diphyllobothrium latum
Intestinal cestode (tapeworm)
Transmission: ingest larvae (sparganum) in lake trout (Great Lakes)
Produce diarrhea with or without vitamin B12 deficiency; preferential uptake of vitamin B12 by the worm
Diagnosis: eggs in the stool
**Treatment:** praziquantel

#### Hymenolepis nana
Intestinal cestode
Dwarf tapeworm; common parasite of house mice; found worldwide
Fecal-oral transmission by ingestion of the egg
Eggs hatch in the small intestine → oncosphere burrows into villi and develops into cysticercoid larva → larva breaks out into lumen to become adult worm
Asymptomatic or may have abdominal pain, diarrhea
**Treatment:** praziquantel

#### Hymenolepis diminuta
Intestinal cestode
Common parasite in rats. Infected rats have droppings with eggs; flour beetles or moths ingest the eggs, and cysticercoid larvae develop in these arthropods; humans ingest the infected beetles/flour moths in the flour and larvae develop into adult worms in the human intestine.
Asymptomatic or have abdominal pain or diarrhea
**Treatment:** praziquantel

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**Table 18-4 Microbial Pathogens Causing Diarrhea—cont’d**

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ETEC, Enterotoxigenic *Escherichia coli*; STEC, Shiga toxin *E. coli*; TMP-SMX, trimethoprim-sulfamethoxazole.
Apoprotein B48 (apoB48) in enterocytes is important in resynthesizing TGs and packaging them into chylomicrons.

- Loss of enterocytes and/or deficiency of apoB48 diminishes the formation of chylomicrons.

ApoB48 is also important in transporting chylomicrons into lymphatics.

- Deficiency of apoB48 or lymphatic blockage in the intestinal cells (e.g., Whipple disease) decreases chylomicron transportation to the blood.
3. Clinical findings
   a. Steatorrhea
      • Excessive, large, sticky, stools that float
   b. Fat-soluble vitamin deficiencies (refer to Chapter 8)
      • Fat-soluble vitamins are A, D, E, K
   c. Water-soluble vitamin deficiencies (refer to Chapter 8)
      • Particularly folic acid and vitamin B₁₂
   d. Combined anemias (refer to Chapter 12)
      • Example—folic acid and iron deficiency
   e. Ascites and pitting edema (refer to Chapter 5)
      • Due to hypoproteinemia and decrease in oncotic pressure

4. General screening tests for fat malabsorption
   a. Quantitative stool for fat
      (1) Best screening test
      (2) 72-Hour collection of stool
      (3) Positive test >7 g fat/24 hours.
   b. Qualitative stool for fat
      (1) Stains are used to identify fat in stool.
      (2) Lacks sensitivity
   c. Decreased serum beta carotene
      • Precursor for fat-soluble retinoic acid (vitamin A)
   d. D-Xylose screening test
      (1) Xylose does not require pancreatic enzymes for absorption.
      (2) Lack of absorption of orally administered xylose
         • Indicates small bowel disease
   e. Tests to evaluate pancreatic insufficiency
      a. Serum immunoreactive trypsin
         (1) Trypsin is specific for the pancreas.
         (2) Concentration is decreased in chronic pancreatitis.
         (3) Concentration is increased in early cystic fibrosis
      b. CT scan of pancreas shows dystrophic calcification.
         • Sign of chronic pancreatitis
      c. Functional tests
         (1) Secretin stimulation test (requires instrumentation)
            • Tests ability of pancreas to secrete fluids and electrolytes
         (2) Bentiromide test
            • Tests ability of pancreatic chymotrypsin to cleave orally
              administered bentiromide to para-aminobenzoic acid (measured
              in urine)
   f. Tests for bile salt/acid deficiency
      • Total serum bile acids are decreased in liver disease (e.g., cirrhosis).
   g. Tests for bacterial overgrowth
      a. ¹⁴C-xylose
         (1) Most sensitive/specific test
         (2) Measures ¹⁴CO₂ in the breath
      b. Lactulose-H₂
         • Measures H₂ in the breath
      c. Bile breath test (oral radioactive test)
         • Radioactive cholyglycine is converted by bacteria into radioactive CO₂ which is
           increased in the breath.

8. Celiac disease
   a. Epidemiology
      (1) Inappropriate immune response to gluten in wheat products
         • Also related proteins in rye and barley
      (2) Prevalence of 1% in North America
      (3) Common in whites; uncommon in blacks and Asians
      (4) Occurs at any age
         (a) Highest incidence in infancy
            • First introduction to gluten products
         (b) Third decade
            • Frequent association with pregnancy
         (c) Seventh decade

Clinical: steatorrhea, fat- and water-soluble vitamin deficiencies, anemia, ascites
General screening tests: stool for fat, serum beta carotene
D-Xylose: ↓ absorption indicates small bowel disease
Serum immunoreactive trypsin: ↓ in chronic pancreatitis
Chronic pancreatitis: CT scan shows dystrophic calcification
Tests pancreatic insufficiency: secretin stimulation; bentiromide
Tests bile salt/acid deficiency: serum bile acids, bile breath test
Celiac disease: inappropriate immune response to gluten in wheat products
Celiac disease: greatest association with dermatitis herpetiformis

(5) Associations
(a) Dermatitis herpetiformis
(b) Autoimmune disease
   - Hashimoto thyroiditis, primary biliary cirrhosis
(c) Type 1 diabetes mellitus
(d) IgA deficiency
(e) Down syndrome, Turner syndrome

b. Pathogenesis
(1) Multorgan autoimmune disease
(2) Inappropriate T-cell and IgA-mediated response against gluten in genetically predisposed persons
   - Association with HLA-DQ2 (95% of cases) and HLA-DQ8 (5% of cases)
(3) Timing and dose when gluten is introduced in the diet is important.
(4) Tissue transglutaminase (tTG; deaminating enzyme) in the lamina propria has a pivotal role in producing celiac disease.
   (a) It deaminates mucosally absorbed gluten to produce deaminated and negatively charged gluten peptides.
   (b) Deaminated gluten peptides stimulate the immune system.
       - They are phagocytosed by antigen-processing cells in the lamina propria.
       - They are presented in complex with HLA-DQ2 or HLA-DQ8 to gluten-specific CD4 helper T cells.
       - CD4 T cells produce cytokines that release matrix proteases causing cell death and degradation in the epithelial cells, resulting in the loss of the villous surface in the small intestine (Fig. 18-17A and B).

c. Important diagnostic antibodies
(1) Anti–tissue transglutaminase IgA (most important), IgG antibodies
   (a) Sensitivity and specificity 98%
   (b) Excellent screening test
(2) Antiendomysial (EMA) IgA antibodies
   (a) Sensitivity and specificity 100%
   (b) Excellent screening test
(3) Antigliadin IgA, IgG antibodies
   (a) Sensitivity 80%, specificity 85%
   (b) Moderately good screening test

d. Clinical findings
(1) Steatorrhea
(2) Weight loss
(3) Failure to thrive in infants and children
(4) Pallor due to anemia (often combined anemias)
(5) Dermatitis herpetiformis (see Fig. 18-17C)
   (a) Considered to be a form of celiac disease
   (b) Villous atrophy in 75% of cases with or without diarrhea
   (c) Low levels of the diagnostic antibodies previously mentioned
(6) Findings related to water-soluble and fat-soluble vitamin deficiencies (refer to Chapter 8)
(7) Other systemic findings
   (a) Bone—osteoporosis, arthritis
   (b) CNS—seizures, depression
   (c) Reproductive—delayed puberty, miscarriages, infertility

e. Diagnosis
(1) Diagnostic antibodies discussed earlier
(2) Total IgA levels
(3) Endoscopic biopsy (see Fig. 18-17B)
   (a) Flattened villi, particularly in duodenum and jejunum
   (b) Hyperplastic glands with intense lymphocytic inflammation

f. Treatment
(1) Gluten-free diet
(2) Correct nutritional deficiencies
   - All fat-soluble vitamins; folic acid, vitamin B₁₂; calcium
(3) Corticosteroids in refractory cases
9. Whipple disease
a. Epidemiology
   (1) Occurs in men more commonly than women
   (2) Peak incidence in middle age
   (3) Caused by *Tropheryma whipplei*
      • Identified by polymerase chain reaction
   (4) Microscopic
      (a) Blunting of villi
      (b) Foamy periodic acid-Schiff (PAS) positive macrophages in lamina propria
         (see Fig. 18-17D)
      (c) Macrophages obstruct lymphatics and reabsorption of chylomicrons
         • Malabsorption of fats
   (5) Clinical findings
      (a) Steatorrhea
      (b) Fever
      (c) Recurrent polyarthritis
      (d) Generalized lymphadenopathy
      (e) Increased skin pigmentation
   (6) Treatment with antibiotics

Whipple disease: caused by *T. whipplei*
Whipple disease: foamy macrophages
E. **Bowel obstruction**

1. Small bowel (SB) is the most common site for obstruction.
   - Due to the small lumen when compared to the large bowel
2. Radiographic findings
   a. Bowel distention
   b. Air-fluid levels with a step-ladder appearance (Fig. 18-18A)
   c. Absence of air distal to obstruction
3. Causes of obstruction (Table 18-5)
4. Clinical findings
   a. Colicky pain
   - Severe pain alternating with pain-free intervals
   b. Abdominal distention
   c. No rebound tenderness

<table>
<thead>
<tr>
<th>TABLE 18-5 Small and Large Bowel Obstruction</th>
</tr>
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<tbody>
<tr>
<td><strong>ETIOLOGIC DISORDER</strong></td>
</tr>
<tr>
<td>Adhesions</td>
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<tr>
<td>Crohn disease</td>
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<td>Duodenal atresia (see Fig. 18-18C)</td>
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<td>Gallstone ileus</td>
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<td>Hirschsprung disease (see Fig. 18-18D to F)</td>
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<tr>
<td>Indirect inguinal hernia</td>
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<td>Femoral hernia</td>
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<tr>
<td>Intussusception (see Fig. 18-18G)</td>
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<td>Meconium ileus</td>
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<td>Volvulus (see Fig. 18-18H)</td>
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18-18: A, Radiograph showing small bowel obstruction. Multiple air-fluid levels are present (arrows) in dilated small bowel. There is absence of air distal to the obstruction. B, Strangulation of loops of small bowel due to adhesions (arrow). The bowel is dilated and its serosal surface is congested indicating an early stage of infarction. C, Duodenal atresia. Plain film of the abdomen showing a dilated stomach (right of the vertebra) and duodenal bulb (left of the vertebra; “double bubble” sign) in a patient with duodenal atresia. D, Hirschsprung disease. The barium enema demonstrates the zone of transition (arrows) from the dilated proximal normal colon to the reduced caliber of the distal aganglionic colon. E, Normal ganglion cells (arrows) in the myenteric plexus of the colon. F, Hirschsprung disease. Absence of ganglion cells in the myenteric plexus and thick myenteric fibers (arrow). G, Ileocecal intussusception. The beginning of the intussusception is the ileum labeled IL. A large sausage-shaped mass covered by hemorrhagic mucosal membrane with patchy necrosis is noted in the lumen of the cecum and ascending colon. This represents the intussuscepted ileum. The apex of the intussusception is located by the arrow. A length of mesentery has also been drawn into the ascending colon sufficient to cause obstruction of the vessels causing infarction and necrosis of the intussuscepted ileum. H, Schematic of sigmoid volvulus. Note how the bowel twists around itself producing obstruction and strangulation. (A from Katz DS: Radiology Secrets, Philadelphia, Hanley & Belfus, 1998, p 117, Fig. 25-1; B, E, F, and G from Morson BC: Colour Atlas of Gastrointestinal Pathology, London, Harvey Miller Ltd, 1988, pp 108, 176, 176, 107, respectively, Figs. 4.29, 6.9, 6.10, 4.26 respectively; C from Pretorius ES, Solomon JA: Radiology Secrets, 2nd ed, Philadelphia, Mosby, 2006, p 467, Fig. 58-2; D from Townsend C: Sabiston Textbook of Surgery, 18th ed, Philadelphia, Saunders Elsevier, 2008, p 2065, Fig. 71-13; from Kumar V, Abbas AK, Fausto N, Mitchell RN: Robbins Basic Pathology, 8th ed, Philadelphia, Saunders Elsevier, 2007, p 605, Fig. 15-26.)
TABLE 18-6 Hernias

<table>
<thead>
<tr>
<th>HERNIA</th>
<th>DISCUSSION</th>
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<td>Direct (see Fig. 18-19A)</td>
<td>Single layer of transversalis is stretched in the floor of the triangle of Hesselbach. medial border of triangle is rectus sheath, lateral border is inferior epigastric artery, inferior border is inguinal ligament. Hernia bulges through floor of triangle of Hesselbach. Bulge disappears when patient reclines. Small bowel cannot enter scrotal sac, therefore, there is no obstruction or incarceration. Treatment: suturing mesh covering inguinal canal and Hesselbach triangle.</td>
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<td>Indirect (see Fig. 18-19B)</td>
<td>Most common hernia. Pathogenesis in children: persistence of peritoneal connection between inguinal canal and tunica vaginalis. Pathogenesis in adults: protrusion of new peritoneal process into inguinal canal. Small bowel passes through internal inguinal ring and may enter scrotal sac. Bowel directly hits the examining finger within the inguinal canal. Complications: entrapped in inguinal canal (incarceration) or strangulated obstruction (hemorrhagic infarction). Treatment: In children: high ligation of hernia sac at the level of the internal inguinal ring + tightening of the internal inguinal ring. In adults: suturing mesh covering inguinal canal and Hesselbach triangle.</td>
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<td>Femoral</td>
<td>Most common in women. Bulge located below inguinal ligament. Highest rate of incarceration of small bowel. Treatment: transversalis fascia and conjoined tendon are sutured to Cooper ligament.</td>
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<td>Umbilical (see Fig. 18-19C)</td>
<td>Most common hernia in adults with ascites (cirrhosis), pregnancy, or obesity. Most common hernia in black newborns. Peritoneal protrusion extends into a fascial defect containing remnants of umbilical cord. Majority close spontaneously by the second year. Incarceration more likely in adults than children. Treatment: surgery.</td>
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<td>Ventral</td>
<td>Hernia develops in weakened area of previous surgical excision. Obesity most common cause.</td>
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F. Hernias
1. Mechanisms predisposing to acquired hernias
   a. Increased intra-abdominal pressure (e.g., coughing, heavy weight lifting)
   b. Weakness in the abdominal wall
2. Types of hernias (Table 18-6; Fig. 18-19)

G. Vascular disorders
1. Blood supply of the small and large bowel
   a. Areas of bowel supplied by the superior mesenteric artery (SMA; Fig. 18-20A)
      (1) Most of the small bowel (not shown in the schematic)
      (2) Ascending and transverse colon up to the left colic flexure (splenic flexure)
      (3) SMA and inferior mesenteric artery (IMA) overlap at the splenic flexure.
         • Splenic flexure is a watershed area (refer to Chapter 2).
   b. Areas of bowel supplied by the IMA
      (1) Descending and sigmoid colons (see Fig. 18-20A)
      (2) Proximal rectum (not shown)
      (3) Upper half of the anal canal (not shown)
2. Types of infarctions
   a. Transmural
      (1) Full-thickness hemorrhagic infarction
      • Usually involves all or part of the small bowel
      (2) Usually due to thrombosis of the SMA
   b. Mural and mucosal infarctions
      • Usually occur in hypoperfusion states (e.g., shock)
3. Causes of acute ischemia involving small bowel
   a. Acute mesenteric ischemia (50% of cases)
      (1) Embolism from the left side of the heart to the SMA
         a) Atrial fibrillation is the most common predisposing arrhythmia.
         b) SMA has the greatest velocity of blood flow and the most acute angle off the aorta of all the arteries originating from the abdominal aorta.
      (2) Thrombosis of the SMA (see Fig. 18-20B)
b. Nonocclusive ischemia (25% of cases)
   (1) Hypotension secondary to heart failure (most common)
   (2) Hypovolemic shock
   (3) Patient taking digitalis (? vasospasm)

c. Mesenteric vein thrombosis (25% of cases)
   (1) Thrombosis states
      (a) Polycythemia vera
      (b) Antiphospholipid syndrome
   (2) Extension of renal cell carcinoma into the vena cava

4. Clinical and radiographic findings of small bowel infarction
   a. Sudden onset of diffuse abdominal pain
      • Pain is disproportionate to the physical findings
   b. Bowel distention
   c. Bloody diarrhea
   d. Absent bowel sounds (ileus)
   e. No rebound tenderness (peritonitis) early in infarction
   f. Profound neutrophilic leukocytosis
   g. Positive stool guaiac
   h. Radiographic findings
      (1) “Thumbprint sign” due to edema in bowel wall
      (2) Bowel distention with air-fluid levels similar to bowel obstruction
   i. Abdominal CT scan has 90% sensitivity.
   j. Treatment
      (1) Surgery for embolic disease
      (2) Thrombotic disease
         • Anticoagulation and surgery if necessary

5. Ischemic colitis
   a. Splenic flexure of the large bowel (see Fig. 18-20C) is involved.
      • Watershed area where the SMA distribution ends and the IMA distribution begins
      (refer to Chapter 2)
A, Schematic of arteries of the large intestine. The superior mesenteric artery (SMA) supplies most of the small bowel, the ascending and transverse colon up to the left colic flexure (splenic flexure; interrupted circle). The inferior mesenteric artery (IMA) supplies the descending and sigmoid colons, proximal rectum (not shown), and upper half of the anal canal (not shown). Note that the colon has the benefit of two blood supplies (SMA and IMA), whereas the small intestine only has one major blood supply (SMA). This explains why the small bowel is more likely to have ischemia damage than the large bowel. B, Hemorrhagic infarction of small bowel, showing the diffuse dark discoloration of the small bowel. Arrow shows a thrombosed superior mesenteric artery attached to the aorta. C, Ischemic colitis in the splenic flexure. The mucosa is markedly hyperemic and covered by a fibrinopurulent exudate. D, Single contrast barium enema showing “thumbprinting” of the colonic mucosa (arrows) in the region of the splenic flexure in ischemic colitis. E, Angiodysplasia of the cecum with dilated venules in the mucosa/submucosa. F, Colonoscopic view of the cecum showing an area of mucosal bleeding from a ruptured telangiectatic vessel in angiodysplasia. (A from Moore A, Roy W: Rapid Review Gross and Developmental Anatomy, 3rd ed, Philadelphia, Mosby Elsevier, 2010, p 76, Fig. 3-21, B from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 124, Fig. 7-8; C from Rosai J: Rosai and Ackerman’s Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 790, Fig. 11.170; courtesy Dr. RA Cooke, Brisbane, Australia; from Cooke RA, Stewart B: Colour Atlas of Anatomical Pathology. Edinburgh, Churchill Livingstone, 2004; D and F from Grieg JD: Color Atlas of Surgical Diagnosis, London, Mosby-Wolfe, 1996, p 202, Figs. 26-9, 26-8, respectively; E from Morson BC: Colour Atlas of Gastrointestinal Pathology, London, Harvey Miller Ltd, 1988, p 178, Fig. 6.14.)
b. Atherosclerotic narrowing of SMA causes mesenteric angina.
   (1) Severe pain occurs in the splenic flexure shortly after eating.
   (2) Patient loses weight for fear of pain related to eating.
c. Clinical findings
   (1) History compatible with mesenteric angina
   (2) Pain localized to the splenic flexure
      • Accompanied by bloody diarrhea due to mucosal or mural infarction
   (3) Barium study shows thumbprinting of the colonic mucosa (see Fig. 18-20D).
      • Due to edema of the mucosa
d. Normal repair of infarction site may result in fibrosis.
   • Common cause of ischemic strictures and obstruction in the colon
6. Angiodysplasia
   a. Dilatation of mucosal and submucosal venules in cecum and right colon (see Figs. 18-20E and F)
      (1) Usually occurs in elderly individuals
      (2) Vascular ectasias in the cecum increase with age.
   b. Increased wall stress in the cecum stretches the venules.
      • Recall that the cecum has an increased diameter and according to the law of Laplace, increased diameter increases wall stress.
c. Clinical findings
   (1) Hematochezia
   (2) More likely to bleed if patient has autosomal dominant von Willebrand disease (vWD) or acquired vWD due to calcific aortic stenosis (refer to Chapter 15)
d. Diagnose with colonoscopy and angiography
e. Treatment
   (1) Colonoscopy
      (a) Identification of lesions (see Fig. 18-20F)
      (b) Cautery of lesions
   (2) Angiography localizes the disease
   (3) Right hemicolectomy
   (4) Correction of aortic stenosis (if present)
      • Bleeding often abates

H. Small bowel diverticula
1. Meckel diverticulum
   a. Vitelline (omphalomesenteric) duct remnant
      (1) True diverticulum (all layers present; Fig. 18-21A)
      (2) Mnemonic: 2 inches long, 2 feet from ileocecal valve, 2% of population, 2% symptomatic
   b. Contains pancreatic rests and heterotopic gastric mucosa
      • Increase the risk for bleeding
c. Clinical findings
   (1) Newborn finding
      • Fecal material in umbilical area due to persistence of vitelline duct
   (2) Bleeding (most common finding)
      (a) Common cause of iron deficiency in newborns and young children
      (b) Symptoms usually arise during the first and second year of life
   (3) Diverticulitis
      • Clinically impossible to distinguish Meckel diverticulitis from appendicitis
d. Diagnosis
   • 99mTc nuclear scan identifies parietal cells in ectopic gastric mucosa.
e. Treatment is surgery.
2. Small bowel pulsion diverticula
   a. Duodenum is most common site.
      • Wide-mouthed diverticula suggest systemic sclerosis.
b. Complications
   (1) Diverticulitis (danger of perforation)
   (2) Bacterial overgrowth
      • May produce bile salt deficiency and vitamin B₁₂ deficiency

I. Sigmoid colon diverticular disease
1. Epidemiology
   a. Definition—herniations of mucosa and submucosa through the muscularis
   b. Incidence in the general public is 35% to 50%.
18-21: A, Meckel diverticulum located on the antimesenteric side of the small intestine (white arrow). Mesenteric fat is located on the superior aspect of the small bowel. B, Gross section of sigmoid colon showing pulsion diverticula with fecal material (fecaliths). C, Whole mount of colon with a diverticulum (arrow shows a blood vessel). D, Double contrast barium enema showing numerous diverticula. The solid thick black arrow shows a barium filled diverticulum. The thin solid black arrow shows a small pool of barium resembling a meniscus. The open arrow shows a diverticulum with no barium in the lumen. (A from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 830, Fig. 17-31; B from Klatt E: Robbins and Cotran Atlas of Pathology, Philadelphia, Saunders, 2006, p 183, Fig. 7-94; C from Rosai J: Rosai and Ackerman’s Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 781, Fig. 11.157; D from Pretorius ES, Solomon JA: Radiology Secrets Plus, 3rd ed, Philadelphia, Mosby Elsevier, 2011, p 129, Fig. 16.20.)

c. Incidence increases with age.
d. Sigmoid colon is the most common site for diverticula in the entire gastrointestinal tract.
e. Diverticula are located on the mesenteric border where the vasa recta penetrates the muscle wall (anatomic weakness site; see Fig. 18-21B and C).

2. Pathogenesis
   a. It is due to a low-fiber diet with increased constipation.
   b. Sigmoid colon is the most common site.
   c. Area of weakness is where vasa recta penetrate the muscular propria.
      • Diverticulum is juxtaposed to a blood vessel.
   d. Associations
      (1) Marfan syndrome
      (2) Ehlers-Danlos syndrome
      (3) Adult polycystic kidney disease

3. Clinical findings
   a. Diverticulitis is the most common complication.
      (1) Caused by stool impacted (fecalith) in diverticulum sac (see Fig. 18-21B)
         • Produces ulceration and ischemia
      (2) Clinical findings
         (a) Fever
         (b) Diarrhea initially followed by constipation
         (c) Left lower quadrant pain (“left-sided appendicitis”)
         (d) Tender mass is palpated in some cases
      (3) Best diagnosed with CT scan or water-soluble barium study (see Fig. 18-21D)
      (4) Increased risk for perforation and abscess formation
      (5) Most common cause of fistula formation (connection between hollow structures)
   b. Diverticulosis
      (1) Painless bleeding, often massive (hematochezia), is characteristic.
         • Usually caused by erosion of juxtaposed vessel by a fecalith
      (2) Bleeding stops spontaneously in 60% of cases.
      (3) Sigmoid diverticulosis is the most common cause of hematochezia.
         • Scarring of the juxtaposed vessel in recurrent attacks of diverticulitis prevents bleeding.
Colovesical fistula (connection between the large bowel and the bladder) is a common fistula in the gastrointestinal tract. It is associated with pneumaturia (air in urine) and recurrent urinary tract infections.

4. Treatment
   a. Nonpharmacologic
      • Increase fiber in diet to prevent constipation
   b. Antibiotics for acute disease
   c. Colonic resection in selected cases
      • Examples—repeated episodes of diverticulitis; bleeding that does not stop; abscess/fistula formation; obstruction

J. Inflammatory bowel disease (IBD)
1. Ulcerative colitis (UC)
   a. Definition—chronic relapsing ulceroinflammatory disease of undetermined etiology
   b. Most common inflammatory bowel disease
   c. Ulcerations are in continuity (Fig. 18-22A).
      • Ulcerations are limited to the mucosa and submucosa of rectum and colon (see Fig. 18-22B).
2. Crohn disease (CD)
   a. Chronic granulomatous, ulcerocnstrictive disease
   b. Transmural inflammation (see Fig. 18-22C)
   c. Noncaseating granulomas (60% of cases; see Fig. 18-22D)
      • Discontinuous spread throughout entire gastrointestinal tract
3. Indeterminate colitis (10%)
   • Features of ulcerative colitis and Crohn disease
4. Summary of ulcerative colitis and Crohn disease (Table 18-7)

K. Irritable bowel syndrome (IBS)
1. Epidemiology
   a. Intrinsic colonic motility disorder
      (1) Possible loss of tolerance to gastrointestinal flora
      (2) Possible genetic factors
      (3) Environmental triggers (e.g., food, coffee)
   b. Most common functional bowel disorder
   c. Responsible for >50% of referrals to gastroenterologists
   d. Occurs more often in females than males
   e. Bacterial overgrowth in the small bowel may be present in some cases.
   f. Risk factors
      (1) History of childhood sexual abuse
      (2) Domestic abuse in women
      (3) Increased stress, depression, personality disorder
2. Constipation (most common) and/or diarrhea
   a. Abdominal pain and bloating relieved by defecation
   b. Stools accompanied by mucus
   c. Abnormal defecation
      (1) Straining
      (2) Sense of incomplete evacuation
   d. Normal C-reactive protein (rules out inflammation)
3. Normal flexible sigmoidoscopy/colonoscopy
4. Treatment
   a. Nonpharmacologic
      (1) Mainstay is adequate fiber intake.
      (2) Eliminate foods that aggravate
         • Examples—coffee, fatty foods, dairy products
   b. Pharmacologic
      (1) Antispasmodics-anticholinergics
         • Example—dicyclomine
      (2) Loperamide is effective for diarrhea.
         • Serotonin type 3 receptor antagonist
      (3) Lubiprostone (chloride channel activator) is effective for constipation.
      (4) Rifaximin is effective if small bowel bacterial overgrowth is documented.
18-22: A, Ulcerative colitis. The colon shows diffuse ulceration of the mucosal surface. B, Ulcerative colitis. Note the linear ulcers and islands of residual mucosa called pseudopolyps. C, Crohn disease, showing a resection of the terminal ileum with attached cecum and appendix; the appendix is to the left. The thickened terminal ileal wall (transmural inflammation) causes the narrowing (arrow) at the junction of the ileum and the cecum. The proximal ileum is dilated (due to obstruction) and the ileal mucosa has a cobblestone appearance due to linear ulcerations (aphthous ulcers) that cut into the underlying submucosa. D, Crohn disease granuloma with central necrosis (arrow; not caseation) and multinucleated giant cells. E, Crohn disease with stricture and proximal ulceration (arrow; ileocecal valve). F, Crohn disease of the anus. Note the fistulas and ulcerations and edematous tags. G, Crohn disease. The terminal ileum (solid black arrow) is markedly narrowed (string sign) and stands apart from other loops of small bowel. (A and C from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 271, Figs. 10-10A, 10-10B, respectively; B from Rosai J: Rosai and Ackerman’s Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 784, Fig. 11.161B; D, E, and F from Morson BC: Colour Atlas of Gastrointestinal Pathology, London, Harvey Miller Ltd, 1988, pp 126, 121, 272, respectively, Figs. 4.67, 4.53, 7.9, respectively; G from Herring W: Learning Radiology Recognizing the Basics, 2nd ed, Philadelphia, Elsevier Saunders, 2012, p 179, Fig. 18.12A.)
<table>
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<th>FEATURE</th>
<th>ULCERATIVE COLITIS (UC)</th>
<th>CROHN DISEASE (CD)</th>
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<tr>
<td>Epidemiology</td>
<td>More common in whites than blacks&lt;br&gt;No sex predilection&lt;br&gt;Occurs between 14 and 38 years of age&lt;br&gt;Lower incidence in smokers and other nicotine users&lt;br&gt;Lower incidence if previous appendectomy &lt;20 years old</td>
<td>More common in whites than blacks, in Jews than non-Jews. More common in children than adults.&lt;br&gt;No sex predilection&lt;br&gt;Smoking is a risk factor&lt;br&gt;Majority (&gt;75%) of cases occur between 11 and 35 years of age</td>
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<td>Extent</td>
<td>Mucosal and submucosal</td>
<td>Transmural (see Fig. 18-22C)</td>
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<td>Location</td>
<td>Mainly rectum (usually begins in this location)&lt;br&gt;Extends continuously into left colon (may involve entire colon; see Fig. 18-22A)&lt;br&gt;Does not involve other areas of GI tract</td>
<td>Terminal ileum alone (30% of cases; see Fig. 18-22E), ileum and colon (50% of cases), colon alone (20% of cases)&lt;br&gt;Involves other areas of GI tract (mouth to anus)</td>
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<td>Gross features</td>
<td>Inflammatory pseudopolyps (see Fig. 18-22B)&lt;br&gt;Ulceration and hemorrhage</td>
<td>Thick bowel wall and narrow lumen (leads to obstruction)&lt;br&gt;Aphthous ulcers in bowel (early sign)&lt;br&gt;Skip lesions, strictures, fistulas&lt;br&gt;Deep linear ulcers with cobblestone pattern&lt;br&gt;Fat creeping around serosa</td>
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<td>Microscopic features</td>
<td>Ulcers and crypt abscesses containing neutrophils&lt;br&gt;Dysplasia or cancer may be present</td>
<td>Non-caseating granulomas (60% of cases), lymphoid aggregates (see Fig. 18-22D)&lt;br&gt;Dysplasia or cancer less likely</td>
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<td>Clinical findings</td>
<td>Recurrent left-sided abdominal cramping with bloody diarrhea and mucus&lt;br&gt;Fever, tenesmus, weight loss&lt;br&gt;Toxic megacolon (up to 10% of patients). Mortality rate 50%.&lt;br&gt;Extra-gastrointestinal: primary sclerosing cholangitis (UC &gt; CD), erythema nodosum, iritis/uveitis (CD &gt; UC), pyoderma gangrenosum, HLA-B27 positive arthritis.&lt;br&gt;p-ANCA antibodies &gt;45% of cases</td>
<td>Recurrent right lower quadrant colicky pain (obstruction) with diarrhea and weight loss&lt;br&gt;Bleeding occurs only with colon or anal involvement (fistulas; abscesses)&lt;br&gt;Aphthous ulcers in mouth&lt;br&gt;Extragastrointestinal: erythema nodosum, sacroiliitis (HLA-B27 association), pyoderma gangrenosum, iritis (CD &gt; UC), primary sclerosing cholangitis (UC &gt; CD)</td>
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<td>Radiography</td>
<td>“Lead pipe” appearance in chronic disease</td>
<td>“String” sign in terminal ileum from luminal narrowing by inflammation (see Fig. 18-22G), fistulas</td>
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<td>Complications</td>
<td>Toxic megacolon (hypotonic and distended bowel)&lt;br&gt;Adenocarcinoma: greatest risks are pancolitis, early onset, duration of disease &gt;10 years</td>
<td>Anal fistulas (see Fig. 18-22F), obstruction, colon cancer (UC &gt; CD)&lt;br&gt;Calcium oxalate renal calculi (increased reabsorption of oxalate through inflamed mucosa)&lt;br&gt;Malabsorption due to bile salt deficiency&lt;br&gt;Macrocytic anemia due to vitamin B₁₂ deficiency if terminal ileum is involved</td>
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<td>Treatment</td>
<td>Sulfasalazine or mesalamine (5-ASA active metabolite; O₂ free radical scavenger; inhibits lipooxygenase pathway in arachidonic acid metabolism)&lt;br&gt;Corticosteroids for severe disease (systemically or enemas)&lt;br&gt;Nicotine patch&lt;br&gt;Immunosuppressants: azathioprine or cyclosporine&lt;br&gt;Surgery: colectomy with ileostomy usually cures</td>
<td>Sulfasalazine or mesalamine (5-ASA; oral salicylate)&lt;br&gt;Corticosteroids for moderate to severe disease&lt;br&gt;Steroid analogues that target areas of GI tract (e.g., budesonide)&lt;br&gt;Immunosuppressants: azathioprine or cyclosporine&lt;br&gt;Metronidazole for colonic fistulas&lt;br&gt;TNF inhibitors for enterocutaneous fistulas&lt;br&gt;Surgery for obstruction, fistulas, toxic megacolon, refractory disease</td>
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**ANCA**, Anti-neutrophil cytoplasmic antibodies; **ASA**, aminosalicylic acid; **GI**, gastrointestinal; **TNF**, tumor necrosis factor.

### L. Small bowel malignancy

1. Epidemiology
   - Small bowel is the least common site in the gastrointestinal tract for a primary malignancy.
2. Primary adenocarcinoma
   - Duodenum most common site
3. Carcinoid tumor
   a. Most common small bowel malignancy
   b. Neuroendocrine tumor
      1. Contains neurosecretory granules visible on electron microscopy
      2. Carcinoid tumors are malignant.
      3. Metastatic potential correlates with size and depth.
         a. Size >2 cm
         b. Depth of invasion (~50% of bowel thickness)

---

SB: least common site for malignancy in GI tract

Carcinoid tumors: MC SB tumor; malignant neuroendocrine tumors
18-23: Carcinoid tumor (CT) of the vermiform appendix. Note the yellow mass in the wall of the appendix (arrow). The lumen contains fecaliths (F). (From Greg JD: Color Atlas of Surgical Diagnosis, London, Mosby-Wolfe, 1996, p 196, Fig. 25-20.)

(4) Foregut (e.g., stomach) and hindgut (e.g., rectum) carcinoid tumors
   - Invade but rarely metastasize
(5) Midgut carcinoid tumors (e.g., terminal ileum)
   - Invade and metastasize

**c. Locations**

(1) Vermiform appendix (Fig. 18-23)
   - Most common site (40% of cases)
   - Usually <2 cm, which is too small to metastasize to liver
(2) Small bowel (20% of cases)
   - Majority occur in the terminal ileum
   - Commonly metastasize to liver
(3) In the above locations, the tumor produces bioactive compounds (e.g., serotonin)
   - Compounds are delivered to the liver by the portal vein, which empties into the sinusoids.
   - Serotonin is taken up by hepatocytes and is metabolized to 5-hydroxyindoleacetic acid (5-HIAA).
   - 5-HIAA is excreted in the urine.
   - Serotonin is completely metabolized and does not enter the systemic circulation.
   - No signs or symptoms of carcinoid syndrome
(4) Less common locations include esophagus, stomach, colon collectively (10% of cases)

**d. Bright yellow tumor**

**e. Carcinoid syndrome**

(1) Most common primary site is in the terminal ileum
(2) Liver metastasis from these tumors must occur to produce the syndrome.
   - Serotonin is secreted by metastatic tumor nodules in the liver.
   - Serotonin entering hepatic vein tributaries then accesses the systemic circulation.
   - Syndrome may occur without metastasis if it is located in the bronchus (rare).
(3) Clinical findings
   - Due to serotonin and other bioactive compounds (e.g., histamine, bradykinin)
   - Flushing of the skin (75%–90% of cases)
   - Due to vasodilation; may be triggered by emotion, alcohol, other foods
   - Diarrhea (>70% of cases)
   - Increased bowel motility from serotonin
   - Intermittent wheezing and dyspnea (25% of cases)
   - Due to bronchospasm
   - Facial telangiectasia
   - Tricuspid regurgitation and pulmonary stenosis
   - Serotonin increases collagen production in the valves.
(4) Diagnosis
   - Increase in urine 5-HIAA
   - CT scan of liver to detect metastasis
   - Scanning techniques to detect primary location and metastasis
(5) Treatment
   - Avoid alcohol
   - Surgical resection of primary tumor
   - Chemotherapy
   - Somatostatin analog
     - Effective in controlling diarrhea and flushing

**Vermiform appendix:**
- MC site for carcinoid tumor

**MC: carcinoid tumor in terminal ileum:**
- Metastasis to liver causes carcinoid syndrome

**Carcinoid tumor:**
- Bright yellow

**Carcinoid syndrome:**
- Liver metastasis necessary; serotonin must enter hepatic vein tributaries
- Flushing, diarrhea, wheezing; urine 5-HIAA
4. Malignant lymphoma  
   a. Usually occurs in Peyer patches of terminal ileum  
   b. Usually B cell origin (e.g., Burkitt lymphoma)

M. Small and large bowel polyps

1. Nonneoplastic (hamartomatous) polyps  
   a. Hyperplastic polyp (Fig. 18-24A)  
      (1) Most common type in adults  
      (2) Majority in the sigmoid colon  
      (3) No malignant potential or polyposis syndromes  
      (4) Histologically have a "sawtooth" appearance  
   b. Juvenile (retention) polyps  
      (1) Most common polyp in children  
      (2) Located in the rectum  
         • Sometimes prolapse out of the rectum and bleed  
      (3) Solitary polyp  
         • Smooth surface with enlarged cystic spaces on cut section  
      (4) Juvenile polyposis  
         • Autosomal dominant or nonhereditary  
   c. Peutz-Jeghers polyposis (PJP)  
      (1) Autosomal dominant  
      (2) Hamartomatous polyps predominate in the small bowel  
         • Less common in the stomach and colon  
      (3) Clinical findings  
         (a) Mucosal pigmentation of buccal mucosa, lips (see Fig. 18-4)  
         (b) Increased risk (>50%) for colorectal, breast, and gynecologic cancers  
            • In most cases, colorectal cancer is associated with inactivation of the serine/threonine kinase 11 (STK11) tumor suppressor gene along with interruption of other suppressor gene functions (e.g., p53).

2. Neoplastic polyps
   a. Epidemiology  
      (1) Called adenomas  
      (2) Premalignant dysplastic colonic polyps  
         (a) Increase with age  
         (b) Equal sex incidence  
   b. Tubular adenoma (adenomatous polyps)  
      (1) Most common polyp (60% of polyps)  
      (2) Sigmoid colon most common site  
      (3) Stalked polyp  
         (a) Looks like a mushroom (see Fig. 18-24B)  
         (b) Sections show complex branching of glands (adenomatous change)  
            (see Fig. 9-1A).  
   c. Tubulovillous adenoma (20%–30% of polyps)  
      (1) Usually stalked polyp  
      (2) Adenomatous and villous change (similar to small bowel villi)  
   d. Villous adenoma (10% of polyps)  
      (1) Sessile polyp (no stalk) with primarily a villous component (see Fig. 18-24C and D)  
      (2) Rectosigmoid location  
      (3) Secrete protein and potassium-rich mucus  
         • Large tumors can produce hypoalbuminemia and hypokalemia.  
   e. Risk factors for malignancy in adenomas  
      (1) Adenoma >2 cm (40% risk of malignancy)  
      (2) Multiple polyps  
      (3) Polyps with increased villous component  
         • Villous adenomas have a 30% to 40% risk for malignancy.  
   f. Familial polyposis (FP; see Fig. 18-24E)  
      (1) Autosomal dominant (AD)  
         (a) All patients develop tubular adenomas and cancer.  
         (b) Polyps begin to develop between 10 and 20 years of age.
18-24: A, Hyperplastic polyps. Arrows show numerous sessile (no stalk) polyps. B, Tubular adenoma. The head of the stalked polyp has a lobulated, mushroom-like appearance. The arrow points to the stalk. C, Villous adenoma. Note the large cauliflower-like mass in the rectosigmoid. These tumors secrete mucus rich in potassium and protein. D, Villous adenoma. The cut surface of a villous adenoma shows leaf-like villous processes. E, Familial polyposis. Note the numerous small, sessile polyps. These were present in the entire large bowel. F, Adenocarcinoma of the sigmoid colon. Resection of the rectosigmoid shows an annular and ulcerating growth, causing a stricture. G, Spot radiograph from a single contrast phase of a double contrast barium enema showing an adenocarcinoma of the rectum with circumferential narrowing of the lumen (“apple core” lesion). (A and E from Rosai J, Ackerman LV: Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, pp 805, 802, respectively, Figs. 11.201, 11-195, respectively; B from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 138, Fig. 7-55; C and D from Morson BC: Colour Atlas of Gastrointestinal Pathology, London, Harvey Miller Ltd, 1988, p 229, Figs. 6.117, 6.118, respectively; F from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 272, Fig. 10-21B; G from Pretorius ES, Solomon JA: Radiology Secrets, 2nd ed, St. Louis, Mosby, 2006, p 125, Fig. 15-9.)
(2) Pathogenesis
   • Inactivation of adenomatous polyposis coli (APC) suppressor gene

(3) Clinical findings
   (a) Malignant transformation usually occurs between 35 and 40 years of age.
      • Prophylactic colectomy is recommended.
   (b) Associated with congenital hypertrophy of retinal pigment epithelium and desmoid tumors

(4) Gardner syndrome
   (a) AD polyposis syndrome
   (b) Additional findings include benign osteomas and desmoid tumors.

(5) Turcot syndrome
   (a) Autosomal recessive (AR) polyposis syndrome
   (b) Additional finding of malignant brain tumors
      • Astrocytoma and medulloblastoma

N. Colon cancer

1. Epidemiology
   a. Second most common cancer-related death in adults
   b. Third most common cancer in men and women
   c. Incidence rates have been decreasing.
      • Increase in screening (fecal occult blood test, colonoscopy)
   d. Peak incidence in the seventh decade
   e. Rectal cancers
      • Approximately 50% are detected by digital rectal examination.
   f. Colon cancers
      • Approximately 50% are detected by flexible sigmoidoscopy.
   g. Risk factors for colon cancer
      (1) Age >50 years
      (2) Cigarette smoking
      (3) Obesity, physical inactivity, heavy alcohol intake
      (4) Hereditary polyposis syndromes (see later)
      (5) Hereditary nonpolyposis colon cancer (refer to Chapter 9)
      (6) Family cancer syndrome (refer to Chapter 9)
      (7) First-degree relatives with colon cancer
      (8) Inflammatory bowel disease
         • UC > CD
      (9) Dietary factors
         • Low-fiber diet; increased saturated fats; reduced vegetable intake

2. Carcinogenesis of colon cancer
   a. Adenoma–carcinoma sequence
      (1) Sequence-specific genetic abnormalities result in the transition from normal colonic mucosa to invasive carcinoma; genes involved include:
         • APC, KRAS, p53, BAX
      b. APC accounts for 80% of sporadic colon cancers, whereas mutations in mismatch repair genes accounts for 15% of sporadic colon cancers.
      c. Germline mutations in APC cause familial adenomatous polyposis.
      d. Germline mutations of mismatch repair genes cause hereditary nonpolyposis colon cancer (Lynch syndrome; Chapter 9).

3. Locations for colon cancer in descending order
   a. Descending colon
   b. Rectosigmoid and rectum
   c. Cecum and ascending colon
   d. Transverse colon

4. Screening tests for colon cancer
   a. Fecal occult blood (guaiac) test (FOBT)
      (1) Not very sensitive (15%–30%) or specific for colon cancer
      (2) Does not distinguish hemoglobin from myoglobin
   b. Fecal immunochemical test
      • Uses antibodies to detect globin
   c. Fecal DNA test
      (1) Human DNA is extracted from stool
      (2) Test detects DNA alteration in genes associated with colon cancer (e.g., p53, KRAS, APC, BAT26 [involved in microsatellite instability])

Colon cancer: 2nd MC cancer-related death in men and women; 3rd MC cancer

Descending colon: MC site for colon cancer

FOBT not very sensitive or specific
### Acute Appendicitis (Fig. 18-25)

#### 1. Epidemiology
- a. Occurs in 10% of the population
- b. Most common abdominal surgical emergency

#### 2. Pathogenesis in children
- a. Lymphoid hyperplasia (60% of cases) often secondary to a viral infection
- b. Examples—adenovirus, measles virus infection or immunization

#### 3. Pathogenesis in adults
- a. Fecalith obstructs the proximal lumen (similar to pathogenesis of acute diverticulitis)
  - Increased intraluminal pressure causes mucosal injury and bacterial invasion.
- b. Other causes
  - Seeds (sunflower, persimmons), pinworm infection
- c. Primary pathogens are *Escherichia coli* (most common) and *Bacteroides fragilis*.
4. Clinical findings in sequence
   a. Initial colicky periumbilical pain (50% of cases)
      (1) Irritation of unmyelinated afferent C fibers on visceral peritoneal surface
      (2) Refer pain to the midline
   b. Fever
      • Very important sign for identifying appendicitis in children with abdominal pain
   c. Nausea, vomiting, and fever
      • Pain precedes nausea and vomiting
   d. Cutaneous hyperesthesia at level of T12
   e. Pain shifts to right lower quadrant (RLQ) in 12 to 18 hours.
      (1) Irritation of Aδ fibers on parietal peritoneum
         • Localizes pain to the exact location
      (2) Rebound tenderness at McBurney point (Blumberg sign)
      (3) Pain with right thigh extension (psoas sign)
      (4) RLQ pain with palpation of left lower quadrant (Rovsing sign)
   f. Signs of a lower urinary tract infection may occur.
      • Increased frequency, dysuria
   g. Laboratory findings
      (1) Neutrophilic leukocytosis with left shift (90% of cases)
      (2) Abnormal urinalysis
         • Increased protein, hematuria, pyuria

5. Retrocecal appendicitis
   a. Radiograph shows a sentinel loop in the RLQ
   b. Due to localized ileus (lack of motility) from subjacent appendicitis

6. Complications
   a. Periappendiceal abscess with or without perforation
      (1) Most common complication
      (2) May develop subphrenic abscess
         • Usually due to Bacteroides fragilis
   b. Pyelophlebitis
      (1) Infection of the portal vein
      (2) Danger of portal vein thrombosis
      (3) Radiograph shows gas in the portal vein.
   c. Subphrenic abscess
      (1) Persistent postoperative fever
      (2) Diaphragm fixed on the right; right-sided pleural effusion
      (3) Tenderness over lateral seventh and eighth ribs
      (4) Diagnosis
         • Ultrasound, CT scan, gallium scan
      (5) Treatment
         • Extraperitoneal drainage and antibiotics

7. Diagnosis of acute appendicitis
   a. Clinical examination
   b. Spiral CT RLQ after Gastrografin enema
      • Sensitivity 90% and specificity 94%
   c. Plain CT scan with rectal contrast agent
   d. Ultrasonography
      • Sensitivity 75% and specificity 90%
8. Treatment
   a. Appendectomy
   b. Cefoxitin
     * Given prophylactically perioperatively if perforation suspected

Many disorders mimic appendicitis. These disorders include viral gastroenteritis, ruptured follicular cyst, ruptured ectopic pregnancy, mesenteric lymphadenitis, and Meckel diverticulitis.

V. Anorectal Disorders
A. Signs and symptoms of anorectal disease
   1. Bleeding
      a. Internal hemorrhoids (painless)
      b. Anorectal cancer, infection, fissure
   2. Pain
      a. Anal fissure
      b. Thrombosed external hemorrhoids
   3. Pruritus (e.g., pinworms)
   4. Anal fistula (e.g., Crohn disease)

B. Disorders
   1. Internal hemorrhoids
      a. Dilated superior hemorrhoidal veins in mucosa and submucosa
         * Located above the pectinate line (superior plexus; Fig. 18-26A)
      b. Causes
         (1) Straining at stool (most common)
            * Often associated with constipation, low-fiber diet
         (2) Pregnancy
         (3) Obesity
(4) Anal intercourse
(5) Portal hypertension
c. Clinical findings
(1) Often prolapse out of the rectum (see Fig. 18-26B)
(2) Commonly pass bright red blood with stool
   (a) Blood coats the stool.
   (b) Painless bleeding

In an adult, never assume that blood coating stool is always due to an internal hemorrhoid. Other causes include colorectal and anal cancer; therefore further investigation is necessary.

(3) Anal pruritus and soiling of underwear
d. Treatment
(1) Nonpharmacologic
   • High-fiber diet; warm soaks/sitz baths; avoid prolonged sitting or stooling
(2) Pharmacologic
   (a) Topical hydrocortisone
   (b) Stool softeners
e. Surgical
   (1) Rubber-band ligation (best overall), sclerotherapy, infrared photocoagulation
   (2) Hemorrhoidectomy
      • Overall most effective, but most painful

2. External hemorrhoids
a. Dilated inferior hemorrhoidal veins
   • Located below the pectinate line (inferior plexus; see Fig. 18-26A)
b. Painful thrombosis
c. Causes and treatment
   • See preceding internal hemorrhoid discussion

3. Rectal prolapse
a. Intussusception of the rectum through the anus (see Fig. 18-26C)
   • Due to weak rectal support mechanisms
b. Causes in children <2 years old
   (1) Whooping cough
   (2) Trichuriasis
   (3) Common sign of cystic fibrosis
c. Common in the elderly
   • Due to straining at stool
d. May occur with heavy squats in power lifters

4. Pilonidal sinus and abscess
a. Excess hair in a deep gluteal fold (see Fig. 18-26D)
   • Becomes traumatically buried into a sinus
b. Painful sacrococcygeal mass with purulent drainage
c. Treatment
   (1) Incision and drainage first episode
   (2) Chronic disease
      • Marsupialization—wide excision and wound left open

5. Pruritus ani
a. Epidemiology
   (1) More common in males than females
   (2) Occurs in 1% to 5% of population
b. Numerous causes
   (1) Anorectal diseases
      • Internal hemorrhoids (common), fissures, anal incontinence, diarrhea, cancer
   (2) Infections
      • Pinworm, Candida, venereal diseases
   (3) Local irritants
      • Soap, underwear, obesity, coffee, beer, acidic foods
   (4) Dermatologic disease
      • Psoriasis, atopic dermatitis
   (5) Diabetes mellitus
6. Anorectal fistulas
   a. Epidemiology
      (1) Common in all ages
      (2) Associated with constipation
      (3) Pediatric population
         a) More common in infants
         b) Boys > girls
      (4) Etiology
         a) Nonspecific cryptoglandular infection most common
         b) Inflammatory bowel disease
            • Crohn disease > ulcerative colitis
         c) Trauma
            • Episiotomy, prostatectomy, anal intercourse
         d) Malignancy
            • Anal carcinoma, treatment for anal carcinoma
   b. Treatment is surgery.

7. Anal fissures
   a. Epidemiology
      • Accounts for >10% of anal complaints
   b. Pathophysiology
      (1) Firm bowel movements
         • Once formed, perpetuated by bowel movements
      (2) Associated and perpetuated by spasm of the internal sphincter
   c. Clinical
      (1) Posterior (90% of cases) fissure and/or ulcer between anal verge and dentate line
         • Consider Crohn disease if not in this location
      (2) Location marked by anal tag at anal verge
      (3) Prominent proximal papilla
   d. Treatment
      (1) Nitroglycerin ointment
      (2) Botulinum toxin injection of anal sphincter
      (3) Surgery

8. Anal carcinoma
   a. Basaloid (epidermoid or cloacogenic) carcinoma
      (1) Most common type
      (2) Located in the transitional zone above the dentate line
      (3) Female dominant
      (4) Treated with surgery.
   b. SCC
      (1) Located in the anal canal
      (2) Majority occur in men who have sex with men.
         • HPV 16 and 18 association
      (3) Treatment is surgery.
I. Laboratory Evaluation of Liver Cell Injury
   A. Bilirubin metabolism and jaundice
      1. Bilirubin metabolism (Fig. 19-1A)
         a. Unconjugated bilirubin (UCB)
            (1) Senescent RBCs are phagocytosed by splenic macrophages.
            (2) UCB is the end product of heme degradation in macrophages.
               • It is lipid soluble (indirect bilirubin).
         b. UCB combines with albumin in the blood.
            (1) Taken up by hepatocytes
            (2) Conjugated to glucuronic acid by uridine glucuronosyltransferase (UGT) to
                produce conjugated bilirubin (CB)
               • CB is water soluble (direct bilirubin).
         c. CB is secreted into the intrahepatic bile ducts.
            (1) Temporarily stored in the gallbladder
            (2) Enters the duodenum via the common bile duct
         d. Intestinal bacteria convert CB to urobilinogen (UBG; some use the term
            stercolobilinogen).
            (1) UBG is spontaneously oxidized to urobilin (stercolbilin).
            (2) Urobilin produces the brown color of stool.
         e. Approximately 20% of UBG is recycled to the liver (90%) and kidneys (10%).
            • Color of urine is due to urobilin.
      2. Jaundice
         a. Jaundice is due to an increase in UCB and/or CB.
            (1) Jaundice is first noticed in the sclera (see Fig. 19-1B).
            (2) Sclera has a high affinity for bilirubin.
         b. Classification of causes of jaundice is based on the percentage of CB (Table 19-1).
            (1) Percent CB = CB/total bilirubin
            (2) It should be noted that the %CB <20% is an arbitrary cutoff for unconjugated
               hyperbilirubinemias.
         c. Common causes of jaundice (Box 19-1)
   B. Summary of liver function tests (Table 19-2)
   C. Summary of laboratory findings in selective liver disorders (Table 19-3)

II. Viral Hepatitis
   A. Phases of acute viral hepatitis
      1. Prodrome
         a. Fever
         b. Painful hepatomegaly; distaste for alcohol/cigarettes
         c. Steady increase in serum transaminases
            • Transaminases peak just before jaundice occurs.
         d. Atypical lymphocytosis (antigenically-stimulated lymphocytes)

Table 19-1 Causes Of Jaundice

<table>
<thead>
<tr>
<th>TYPE OF HYPERBILIRUBINEMIA</th>
<th>URINE BILIRUBIN</th>
<th>URINE UBG</th>
<th>EXAMPLES OF DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB &lt;20% (All UCB)</td>
<td>Absent</td>
<td>↑</td>
<td>Extravascular hemolytic anemias: e.g., spherocytosis, Rh and ABO HDN, warm AIHA</td>
</tr>
<tr>
<td>Increased production of UCB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased uptake or conjugation of UCB</td>
<td>Absent</td>
<td>Not useful</td>
<td>Gilbert syndrome (familial nonhemolytic jaundice): common AR defect; occurs in &gt;5% of population in males &gt; females. Second most common jaundice (hepatitis most common). Most common hereditary cause of jaundice. Impaired UGT activity (70%–75% decrease in activity). Jaundice occurs with fasting, volume depletion, stress, menses. Serum UCB is rarely &gt;5 mg/dL; all other liver function tests normal. Liver biopsy not necessary. No treatment required. Crigler-Najjar syndromes: rare autosomal recessive disorders with decreased to absent UGT. Type with no UGT is incompatible with life (liver transplantation necessary). Physiologic jaundice of newborn: begins on day 3 of life. Caused by normal macrophage destruction of fetal RBCs containing hemoglobin F and inability of the newborn liver to handle excess load. Breast milk jaundice: due to pregnane-3α,20α-diol, which inhibits UGT. Does not require treatment.</td>
</tr>
<tr>
<td>Mixed</td>
<td>C B 20%–50%</td>
<td>↑</td>
<td>↑ Viral hepatitis: defect in uptake, conjugation of UCB, and secretion of CB.</td>
</tr>
<tr>
<td>Obstructive</td>
<td></td>
<td></td>
<td>Decreased intrahepatic bile flow Drug-induced (e.g., OCPs) Primary biliary cirrhosis Dubin-Johnson syndrome: AR disorder in secretion into intrahepatic bile ducts (mutation in an apical canalicular membrane protein responsible for excretion of bilirubin). Black pigment present in lysosome in hepatocytes (?) etiology; see Fig. 19-1C. Rotor syndrome: AR disorder similar to Dubin-Johnson syndrome but without black pigment in hepatocytes. Decreased extrahepatic bile flow. Gallstone in common bile duct Carcinoma of head of pancreas</td>
</tr>
</tbody>
</table>

AD, Autosomal dominant; AIHA, autoimmune hemolytic anemia; AR, autosomal recessive; CB, conjugated bilirubin; HDN, hemolytic disease of newborn; OCP, oral contraceptive pill; UBG, urobilinogen; UCB, unconjugated bilirubin; UGT, uridine glucuronosyltransferase.
Common Causes of Jaundice

Normal bilirubin metabolism (A) shows liver uptake of lipid-soluble unconjugated bilirubin (UCB) and its conjugation with glucuronic acid by uridine glucuronyltransferase to produce water-soluble conjugated bilirubin (CB). CB is secreted into the common bile duct (CBD) and is emptied into the bowel. Intestinal bacteria convert CB to urobilinogen (UBG, stercobilinogen), which is spontaneously oxidized to the pigment urobilin. Urobilin is responsible for the color of stool. A small percentage of UBG is reabsorbed into the blood. Most of it enters the liver (larger arrow) and a small percentage (smaller arrow) enters the urine (UBG). Urobilin is responsible for the color of urine. All of the normal bilirubin in blood is UCB (CB% < 20%) primarily derived from macrophage destruction of senescent RBCs. UCB does not enter urine, because it is attached to albumin in the blood and is soluble in lipid, not water. CB is never a normal finding in urine because it does not have contact with blood in its metabolism.

In extravascular hemolysis (B) (e.g., hereditary spherocytosis), there is increased macrophage production of UCB causing an increase in serum UCB (++) (CB% <20%). There is a corresponding increase in uptake and conjugation of UCB, conjugation to CB (++), and conversion of CB in the bowel to UBG (++). This causes darkening of the stool. There is a greater percentage of UBG recycled back into the liver (wider arrow) and urine (wider arrow). The increase in urine UBG (++), darkens the color of urine. Because RBCs contain the enzyme aspartate aminotransferase (AST), hemolysis of RBCs causes an increase in serum AST. Alanine aminotransferase (ALT), alkaline phosphatase (ALP), and γ-glutamyltransferase (GGT) levels are normal.

In viral hepatitis (C), there is generalized liver dysfunction involving uptake and conjugation of UCB, secretion of CB into bile ducts, and recycling of UBG. Serum UCB is increased (++) owing to a decrease in uptake and conjugation. Serum and urine CB are increased (++) because of liver cell necrosis and disruption of bile ductules between hepatocytes. Urine UBG is increased (++) because UBG is redirected from the liver (smaller arrow) to the kidneys (larger arrow). Because there is an increase in serum UCB and CB, there is a mixed hyperbilirubinemia with a CB% of 20% to 50%. In viral hepatitis, ALT is higher (+++ than AST (++) and there is a slight increase in ALP and GGT (+). In alcoholic hepatitis, AST is greater than ALT, because alcohol damages mitochondria, which is where AST is normally located.

In obstructive liver disease (D), an increase in serum and urine CB (++) is due to obstruction of intrahepatic or extrahepatic bile flow (stone in the CBD in this case). This causes increased pressure in the intrahepatic bile ductules leading to rupture and egress of CB into sinusoidal blood. There is absence of UBG in the stool (light-colored) and urine. CB% >50% and there is a marked increase in serum ALP and GGT (+++ and only a slight increase in serum AST and ALT (+)).
TABLE 19-2 Liver Function Tests

<table>
<thead>
<tr>
<th>TEST</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver Cell Necrosis</strong></td>
<td></td>
</tr>
<tr>
<td>Serum alanine transaminase (ALT)</td>
<td>Specific enzyme for liver cell necrosis  &lt;br&gt;Present in the cytosol  &lt;br&gt;ALT &gt; AST: viral hepatitis</td>
</tr>
<tr>
<td>Serum aspartate transaminase (AST)</td>
<td>Present in mitochondria  &lt;br&gt;Alcohol damages mitochondria: AST &gt; ALT indicates alcoholic hepatitis.</td>
</tr>
<tr>
<td><strong>Cholestasis</strong></td>
<td></td>
</tr>
<tr>
<td>Serum γ-glutamyltransferase (GGT)</td>
<td>Intrahepatic or extrahepatic obstruction to bile flow  &lt;br&gt;Induction of cytochrome P450 system (e.g., alcohol): increases GGT</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (ALP)</td>
<td>Normal GGT and increased ALP: source of ALP other than liver (e.g., osteoblastic activity in bone)  &lt;br&gt;Increased GGT and ALP: liver cholestasis. GGT and ALP are synthesized by bile duct epithelium.</td>
</tr>
<tr>
<td><strong>Bilirubin Excretion</strong></td>
<td></td>
</tr>
<tr>
<td>CB &lt;20%</td>
<td>Unconjugated hyperbilirubinemia: e.g., extravascular hemolytic anemias (e.g., hereditary spherocytosis).</td>
</tr>
<tr>
<td>CB 20%–50%</td>
<td>Mixed hyperbilirubinemia (e.g., viral hepatitis)</td>
</tr>
<tr>
<td>CB &gt;50%</td>
<td>Conjugated hyperbilirubinemia (e.g., liver cholestasis)  &lt;br&gt;Bilirubinuria: viral hepatitis, intrahepatic or extrahepatic obstruction of bile ducts</td>
</tr>
<tr>
<td>Urine bilirubin</td>
<td>Increased urine UBG: extravascular hemolytic anemias, viral hepatitis  &lt;br&gt;Absent urine UBG: liver cholestasis</td>
</tr>
<tr>
<td>Urine UBG</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatocyte Function</strong></td>
<td></td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Albumin is synthesized by the liver  &lt;br&gt;Hypoalbuminemia: severe liver disease (e.g., cirrhosis)</td>
</tr>
<tr>
<td>Prothrombin time (PT)</td>
<td>Majority of coagulation factors are synthesized in the liver  &lt;br&gt;Increased PT: severe liver disease</td>
</tr>
<tr>
<td>Factor V</td>
<td>Decreased in severe liver disease</td>
</tr>
<tr>
<td>Blood urea nitrogen (BUN)</td>
<td>Urea cycle is present in the liver  &lt;br&gt;Decreased serum BUN: cirrhosis, fulminant hepatitis</td>
</tr>
<tr>
<td>Serum ammonia</td>
<td>Ammonia is metabolized in the urea cycle in the liver  &lt;br&gt;Derives from large bowel and amino acid degradation  &lt;br&gt;Increased serum ammonia: cirrhosis, Reye syndrome</td>
</tr>
<tr>
<td><strong>Immune Function</strong></td>
<td></td>
</tr>
<tr>
<td>Serum IgM</td>
<td>Increased in primary biliary cirrhosis</td>
</tr>
<tr>
<td>Antimitochondrial antibody</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Anti–smooth muscle antibody</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Antinuclear antibody (ANA)</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td><strong>Tumor Marker</strong></td>
<td></td>
</tr>
<tr>
<td>α-Fetoprotein (AFP)</td>
<td>Hepatocellular carcinoma</td>
</tr>
</tbody>
</table>

*RBCs contain AST.

TABLE 19-3 Summary of Laboratory Findings in Selected Liver Disorders

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>% CB</th>
<th>AST</th>
<th>ALT</th>
<th>ALP</th>
<th>GGT</th>
<th>UB</th>
<th>URINE UBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Absent</td>
</tr>
<tr>
<td>Viral hepatitis 20%–50%</td>
<td>↑↑↑</td>
<td>↑↑↑↑</td>
<td>↑</td>
<td>↑</td>
<td>^</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Alcoholic hepatitis 20%–50%</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑↑↑↑</td>
<td>↑↑</td>
<td>↑</td>
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</tr>
<tr>
<td>Cholestasis &gt;50%</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Extravascular hemolysis &lt;20%</td>
<td>↑↑↑RBCs*</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Absent</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

Arrows represent degree of magnitude.

ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CB, conjugated bilirubin; GGT, γ-glutamyltransferase; UB, urine bilirubin, UBG, urobilinogen.


2. Jaundice
   a. Variable finding depending on the type of hepatitis
   b. Increased urine bilirubin and urine UBG
3. Recovery
   • Jaundice resolves.
B. Microscopic findings in acute viral hepatitis

1. Lymphocytic infiltrate with destruction of hepatocytes (see Fig. 2-17)
   • Apoptosis of hepatocytes (Councilman bodies; see Fig. 2-17)
2. Persistent inflammation and fibrosis is an unfavorable sign.
   • Sign of chronic hepatitis progressing to postnecrotic cirrhosis

C. Epidemiology clinical findings of viral hepatitis (Table 19-4)

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>DISCUSSION</th>
</tr>
</thead>
</table>
| Hepatitis A (HAV) | Incubation 15–50 days (average 30 days)  
RNA virus  
Transmission: oral-fecal yes, sexual yes, blood no.  
Second most common acute hepatitis in U.S.  
Most preventable infection in travelers (immunize with vaccine).  
Increased incidence in children/employees in day care centers, prisons, travelers to developing countries, men who have sex with men (anal intercourse), parents adopting children from other countries.  
Virus replicates in the liver and is shed in high concentrations in feces from 2 weeks before to 1 week after the onset of clinical illness.  
Adults more likely to be symptomatic than children.  
Clinical: jaundice >70% of cases (most common hepatitis producing jaundice). Fever, nausea/vomiting, abdominal pain.  
Majority recover; no carrier state; no chronic hepatitis  
Serology: see text  
Passive immunization: immunoglobulin (passive transfer of antibodies) for preexposure prophylaxis and postexposure prophylaxis.  
Active immunization: protective antibodies in 1 month. Recommended for all travelers to high-risk countries and all children >1 years old |
| Hepatitis B (HBV) | Incubation 30–180 days  
DNA virus  
Transmission: oral-fecal (possible but not common), sexual yes, blood yes, vertical transmission via pregnancy and breast-feeding yes.  
Primarily spread via blood (IVDA 40%–60% of cases), accidental needlestick (1%–40% chance of developing HBV; most common mechanism for HBV in health care workers).  
Most common acute hepatitis in the U.S. Second most common cause of fulminant hepatitis.  
Clinical: variable fever, profound malaise, painful hepatomegaly (87% of cases), serum sickness prodrome (15%–20% of cases), immunocomplex disease (HBsAg + antibody), vasculitis (PAN), urticaria, polyarthritis, membranous glomerulopathy.  
Recovery in >90% of immunocompetent patients. 1–2% develop chronic hepatitis.  
Newborns and immunodeficient patients more likely to develop chronic hepatitis (>90% of cases).  
Complications: fulminant hepatitis 7% of cases. Hepatocellular carcinoma secondary to postnecrotic cirrhosis (15%–25% risk).  
Serology: see text  
Prevention: immunization with recombinant vaccine.  
Treatment of chronic hepatitis: pegylated IFN-α, nucleoside analogs that block viral replication (e.g., lamivudine, entecavir). Liver transplant. |
| Hepatitis C (HCV) | Incubation 2–26 weeks (average, 6–7 weeks)  
RNA virus  
Transmission: oral-fecal no, rare sexual (unless multiple partners are involved), blood yes; most common cause of hepatitis due to IVDA (60%–70% of cases; >90% of persons with HIV from IVDA are infected with HCV); hemophiliacs transfused before 1987, accidental needlestick (1%–6% chance of developing HCV), tattoo.  
Most common chronic blood-borne infection in the U.S.  
Third most common acute hepatitis in U.S.  
Most common main indication for liver transplantation in U.S.  
Posttransfusion hepatitis is rare because of screening.  
Maternal-fetal transmission is infrequent (estimated to be 5%).  
Clinical: mild hepatitis (70%–80% subclinical); jaundice uncommon (80% are anicteric)  
Chronic hepatitis in 85% of cases if not treated; 20% develop postnecrotic cirrhosis  
Other clinical associations: type I MPGN, alcohol excess, PCT, lichen planus, B cell lymphoma, cryoglobulinemia  
Complications: hepatocellular carcinoma (HCC) secondary to postnecrotic cirrhosis (1%–3% risk per year for developing HCC)  
Prevention: no preventive vaccine available  
Treatment: early treatment of acute infection with pegylated IFN-α + ribavirin + telaprevir decreases the viral load to below detectable levels in >50% of patients (considered a cure) depending on the virus genotype; also decreases the chance for developing chronic hepatitis; genotypes 1 and 4 do not have as good a response to therapy as genotypes 2 and 3 (~50% response in the former vs ~75% response in the latter); other genotypes are more aggressive and do not respond well to therapy; the above therapy has also been used in treating previously untreated patients with chronic HCV, depending on the genotype of the virus; liver transplant is also used. |
TABLE 19-4 Viral Hepatitis: Clinical Findings—cont’d

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis D</td>
<td>Incubation variable</td>
</tr>
<tr>
<td>(HDV)</td>
<td>Incomplete RNA virus that requires HBsAg to replicate</td>
</tr>
<tr>
<td></td>
<td>Transmission: oral-fecal no, sexual yes, blood yes</td>
</tr>
<tr>
<td></td>
<td>Accounts for &lt;1% of acute hepatitis in U.S.</td>
</tr>
<tr>
<td></td>
<td>Chronic state less likely with co-infection (HBV and HDV exposure at same time) than superinfection (HBV carrier exposed to blood containing HDV); cytolytic virus, so fulminant hepatitis may occur</td>
</tr>
<tr>
<td></td>
<td>Chronic infection develops in 60%–85% of people infected</td>
</tr>
<tr>
<td></td>
<td>Serology: see text</td>
</tr>
<tr>
<td></td>
<td>Prevention: immunization with recombinant vaccine for HBV</td>
</tr>
</tbody>
</table>

Hepatitis E

Incubation 15–45 days
RNA virus
Transmission: oral-fecal yes, sexual no, blood no.
Occurs in developing countries.
Only produces acute hepatitis.
Fulminant hepatitis may develop in pregnant women

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>Anti-HBc IgM</th>
<th>Anti-HBs IgG</th>
<th>Anti-HBs</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Earliest phase of acute HBV</td>
</tr>
<tr>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute infection</td>
</tr>
<tr>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Window phase, or serologic gap</td>
</tr>
<tr>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recovered from HBV</td>
</tr>
<tr>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“Healthy” carrier</td>
</tr>
<tr>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infective carrier</td>
</tr>
</tbody>
</table>

Anti-HBc, Core antibody; anti-HBs, surface antibody; HBeAg, e antigen; HBsAg, surface antigen.

HAV: MC viral cause jaundice
HAV: anti-HAV IgM indicates infection; anti-HAV IgG indicates recovery/vaccination
HBsAg: first antigen to arrive, last one to leave with recovery

19-2: A, Clinical course and serologic markers in hepatitis A. B, Serologic markers in hepatitis B. Anti-HBc, Anti-HBV core antigen; anti-HBe, anti-HBV e antigen; anti-HBs, anti-HBV surface antibody; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IgG, immunoglobulin G; IgM, immunoglobulin M. (A from Mandell GL, Bennett JE, Dolin R: Principles and Practice of Infectious Diseases, 7th ed, Philadelphia, Elsevier, Churchill Livingstone, 2010, p 1582, Fig. 115.4A.)

D. Serologic studies in viral hepatitis
1. Hepatitis A virus (HAV) (Fig. 19-2A)
   a. Anti-HAV IgM indicates active infection.
   b. Anti-HAV IgG indicates recovery from infection or vaccination.
      • Protective antibody
2. Hepatitis B virus (HBV) (see Fig. 19-2B and Table 19-5)
   a. Hepatitis B surface antigen (HBsAg)
      (1) Appears within 2 to 8 weeks after exposure
         • First marker of infection
      (2) Persists up to 4 months in acute hepatitis
         • HBsAg longer than 6 months defines chronic HBV.
b. Hepatitis B e antigen (HBeAg) and HBV-DNA  
   (1) Infective particles  
   (2) Appear after HBsAg and disappear before HBsAg  

c. Anti-HBV core antibody IgM (anti-HBc IgM)  
   (1) Nonprotective antibody  
      • Remains positive in acute infections  
   (2) Persists during "window phase" or "serologic gap"  
      • HBsAg, HBV DNA, and HBeAg are absent.  
   (3) Converts entirely to anti-HBc IgG by 6 months  

d. Anti-HBV surface antibody (anti-HBs)  
   (1) Protective antibody  
   (2) Marker of immunization after HBV vaccination  

e. Chronic HBV  
   (1) Persistence of HBsAg longer than 6 months  
      • All anti-HBc IgM converts to anti-HBc IgG by 6 months.  
   (2) "Healthy" chronic carrier  
      (a) Presence of HBsAg and anti-HBc IgG  
      (b) Absence of DNA and e antigen  
      (c) Still contagious but at a much lower risk  
   (3) Infective chronic carrier  
      (a) Presence of HBsAg, anti-HBc IgG, and infective particles (DNA and e antigen)  
      (b) Increased risk for postnecrotic cirrhosis and hepatocellular carcinoma

3. Hepatitis C virus (HCV)  
   a. Screen with enzyme immunoassay (EIA)  
      (1) Presence of anti-HCV IgG indicates active infection or recovery.  
         • Sensitivity >97%  
      (2) It does not differentiate among acute, chronic, or resolved infection.  
      (3) It is not a protective antibody.  
   b. Confirmatory tests  
      (1) Recombinant immunoblot assay (RIBA)  
         (a) Must be ordered if EIA is positive  
         (b) More specific but less sensitive than EIA  
      (2) HCV RNA using polymerase chain reaction detects viral load  
         (a) Gold standard test for diagnosing HCV  
         (b) Detects virus as early as 1 to 2 weeks after infection  
         (c) Used to confirm active infection and to monitor patients on antiviral therapy to  
             indicate a cure from HCV  
      (3) Positive RIBA and HCV RNA indicate active infection.  
      (4) Positive RIBA and negative HCV RNA indicate cure from treatment.  

4. Hepatitis D virus (HDV)  
   a. Presence of anti-HDV IgM or IgG indicates active infection.  
   b. IgG is not a protective antibody.  

5. Hepatitis E virus (HEV)  
   a. Presence of anti-HEV IgM indicates active infection.  
   b. Anti-HEV IgG indicates recovery (protective antibody).

E. Other laboratory test findings in viral hepatitis (see Box 19-1C)  
   1. Mixed hyperbilirubinemia (†UCB + CB)  
      a. Uptake/conjugation of UCB is decreased.  
      b. CB accesses blood via damaged bile ductules.  
   2. Increased urine UBG and urine bilirubin  
      a. CB is water soluble and is filtered in the kidneys.  
      b. UBG recycled back to inflamed liver is redirected to the kidneys.  
   3. Increased serum transaminases  
      a. Serum ALT > AST  
         • ALT more specific for liver necrosis than AST  
      b. Serum ALT is the last liver enzyme to return to normal.

III. Other Inflammatory Liver Disorders  
   A. Summary of important infectious diseases (Table 19-6; Fig. 19-3)  
   B. Autoimmune hepatitis  
      1. Epidemiology  
         a. Two types  
            (1) Type 1 is the predominant form in the United States and worldwide (80% of cases).  
            (2) Type 2 is uncommon in the United States (not discussed).
<table>
<thead>
<tr>
<th>DISEASE</th>
<th>PATHOGEN(S)</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending cholangitis</td>
<td><em>Escherichia coli</em></td>
<td>Inflammation of bile ducts (cholangitis) from concurrent biliary infection and duct obstruction (e.g., stone). Life-threatening disease. Triad of fever, jaundice, RUQ pain. Majority of cases are solitary. Depending on the cause, multiple liver abscesses. Treatment: decompression and drainage; piperacillin-tazobactam.</td>
</tr>
<tr>
<td>Liver abscess</td>
<td><em>Escherichia coli</em>, <em>Bacteroides fragilis</em>, <em>Enterococcus faecalis</em></td>
<td>Majority are in the right lobe; majority are solitary. Causes: ascending cholangitis (most common), intra-abdominal infection (e.g., spread via the portal vein, diverticulitis, bowel perforation), direct extension (e.g., empyema of gallbladder, subphrenic abscess), hematogenous spread (e.g., bacterial endocarditis). Clinical: spiking, intermittent fever; RUQ or right costovertebral angle tenderness. Jaundice is uncommon. Diagnosis: ultrasound (least expensive), CT scan. Treatment: percutaneous drainage, metronidazole + ceftriaxone.</td>
</tr>
<tr>
<td>Granulomatous hepatitis</td>
<td><em>Mycobacterium tuberculosis</em>, <em>Histoplasma capsulatum</em></td>
<td>Sign of miliary spread (refer to Chapter 17)</td>
</tr>
<tr>
<td>Spontaneous peritonitis</td>
<td><em>Escherichia coli</em> in adults, <em>Streptococcus pneumoniae</em> in children</td>
<td>Develops in ascites (e.g., cirrhosis, nephrotic syndrome). Treatment: cefotaxime.</td>
</tr>
<tr>
<td>Leptospirosis (see Fig. 19-3A)</td>
<td><em>Leptospira interrogans</em></td>
<td>Gram-negative; tightly wound spirochetes; crook at the end resembles a shepherd's staff. Reservoirs: rats, dogs (most common). Spirochetes are excreted in urine. Transmission: swimming in contaminated water (ponds in farms; rivers, particularly if they are rising after a rain because animals with the organism urinate near rivers), farmers, miners, people who work with sewage. Biphasic disease (Weil disease). Septicemic phase: fever, jaundice, hemorrhagic diathesis, renal failure (interstitial nephritis), conjunctivitis and photophobia, meningitis; phase is terminated by the appearance of antibodies (beginning of immune phase). Immune phase: presence of numerous organisms in the urine; urine is best examined by dark field microscopy. Diagnosis: serum enzyme immunoassay 90% sensitive; urine test for detecting antigen is also available. Treatment: penicillin G.</td>
</tr>
<tr>
<td>Amebiasis (see Fig. 19-3B)</td>
<td><em>Entamoeba histolytica</em></td>
<td>Protozoan (amoeba) Most common cause of a liver abscess worldwide (not in the United States). Usually produces a right lobe abscess (refer to Chapter 18). Treatment: metronidazole followed by paromomycin.</td>
</tr>
<tr>
<td>Clonorchiasis</td>
<td><em>Clonorchis sinensis</em> (Chinese liver fluke)</td>
<td>Intestinal fluke (trematode) Nonchistosomil life cycle: egg (human) → ciliated miracidial larva → infects snail (1st intermediate host) → produce fork-tailed cercarial larva → infect a 2nd intermediate host (fish in clonorchiasis) → form infective metacercariae → man ingests the 2nd intermediate host → develops disease Contracted by ingesting encysted larvae in fish; larvae enter CBD and become adults. May produce cholangiocarcinoma. Treatment: praziquantel.</td>
</tr>
<tr>
<td>Schistosomiasis (see Fig. 19-3C and D)</td>
<td><em>Schistosoma mansoni</em></td>
<td>Fluke (trematode) Schistosomil life cycle: egg (human) → ciliated miracidial larva → infects snail (1st intermediate host) → produce fork-tailed cercarial larva → penetrate skin in human → produce disease Schistosoma mansoni: larvae in the superior mesenteric vein enter into the portal vein, where they develop into adult worms that deposit eggs to which the host develops an inflammatory response marked by concentric fibrosis (“pipestem cirrhosis”) in the vessel wall; S. japonicum also produces pipestem cirrhosis, though it more commonly invades the urinary bladder vessels and produces squamous cancer of the bladder. Complications of cirrhosis: portal hypertension, ascites, esophageal varices. Treatment: praziquantel.</td>
</tr>
<tr>
<td>Echinococcosis (see Fig. 19-3E)</td>
<td><em>Echinococcus granulosus</em> (sheepherder's disease)</td>
<td>Intestinal tapeworm (cestode) Single or multiple cysts contain larval forms; cysts often present in the liver (most common site), lungs, and brain Eggs develop into a larval form only; larval form only develops into an adult, which lays eggs. The infected sheep is the intermediate host (larval form is in the liver cyst); dog eats the liver of a dead sheep and becomes the definitive host, because the larvae develop into adults, which produce eggs; the human who accidentally ingests the embryonated eggs from the dog becomes the intermediate host, because the eggs develop into larvae; the larvae in humans penetrate the bowel and they enter the liver (most common) or other sites to produce the hydatid cyst. Disease also contracted by children eating grass contaminated with dog excreta containing the eggs. Rupture of cysts can produce anaphylaxis. Treatment: percutaneous drainage + albendazole.</td>
</tr>
</tbody>
</table>
b. Occurs most often in young women

c. Range of presentations
   - Symptomatic with increased transaminases, fulminant hepatitis, cirrhosis

d. Associated with human leukocyte antigens (HLA) DR3 and DR4

e. Other autoimmune associations
   - Examples—Hashimoto thyroiditis, Graves disease

2. Clinical findings
   - Fever, jaundice, hepatosplenomegaly

3. Laboratory findings for type 1
   a. Positive serum antinuclear antibody (ANA) test (>60% of cases)
   b. Anti-smooth muscle antibodies (>85% of cases)
   c. Increased serum transaminases
   d. Decreased serum albumin in severe disease
   e. Prolonged prothrombin time in severe disease

4. Treatment
   a. Initial treatment with corticosteroids + azathioprine
   b. Liver transplantation if resistant to therapy

C. Neonatal hepatitis

1. Epidemiology
   a. Idiopathic
   b. Associated with congenital infections
      - Example—cytomegalovirus (CMV)
c. Associated with inborn errors of metabolism
   • Example—α₁-antitrypsin deficiency

2. Biopsy shows multinucleated giant cells.
   • Giant cell hepatitis

D. Reye syndrome
1. Epidemiology
   a. Postinfectious triad to define Reye syndrome includes:
      (1) Encephalopathy
      (2) Microvesicular fatty change (Fig. 19-4A)
      (3) Serum transaminase elevation
   b. Uncommon since the role of aspirin was elucidated
   c. Usually develops in children <4 years old
      • Often follows a chickenpox or influenza infection

2. Pathogenesis
   a. Mitochondrial damage (?) virus, salicylates
   b. Disruption of the urea cycle (normally used to metabolize ammonia)
      • Increase in serum ammonia
   c. Defective β-oxidation of fatty acids in damaged mitochondria
      • More fatty acids are available to synthesize triglyceride (fatty change; refer to Chapter 2)

3. Microvesicular fatty change (see above explanation)
   a. Small cytoplasmic globules without nuclear displacement
   b. No inflammatory infiltrate

4. Clinical findings
   a. Initially afebrile, quiet, lethargic, sleepy, and vomiting
      • Hepatomegaly and liver dysfunction are present
   b. Encephalopathy (cerebral edema with increased cerebral pressure) findings in progression include:
      (1) Sleepy but respond; vomiting
      (2) Stuporous, seizures, decorticate rigidity, intact papillary reflexes
      (3) Deepening coma, decerebrate rigidity, fixed pupils
      (4) Coma, loss of deep tendon reflexes, fixed dilated pupils, flaccidity/decerebrate
      (5) Death

5. Laboratory findings
   a. Increased serum transaminases (AST and ALT)
   b. Normal to slight increase in total bilirubin
   c. Increased serum ammonia and prothrombin time (PT)
      • Levels predict degree of severity
   d. Hypoglycemia (impaired glycogenesis and gluconeogenesis in liver)
   e. Cerebrospinal fluid analysis is usually normal

6. Treatment
   a. Supportive
   b. Mannitol, glycerol, or hyperventilation to reduce cerebral edema

7. Approximately 25% to 50% mortality rate

E. Acute fatty liver of pregnancy
1. Abnormality in β-oxidation of fatty acids (FAs)
2. Fatal to mother and fetus unless the baby is delivered
F. Preeclampsia (refer to Chapter 22)
   1. Hypertension, proteinuria, dependent pitting edema in third trimester
   2. Liver cell necrosis around portal triads (zone 1; see Fig. 2-7B)
      • Increased serum transaminases
   3. HELLP syndrome
      a. Hemolytic anemia with schistocytes (refer to Chapter 12)
      b. Elevated serum transaminases
      c. Low platelets
      • Due to disseminated intravascular coagulation (refer to Chapter 15)

G. Fulminant hepatic failure (FHF)
   1. Epidemiology
      a. Definition—acute liver failure with encephalopathy within 8 weeks of hepatic dysfunction
      b. Causes
         (1) Drugs (e.g., acetaminophen most common cause)
         (2) Viral hepatitis (second most common cause)
            • HBV, nonalphabetical viruses (e.g., herpes viruses, enteroviruses, parvovirus), HDV
         (3) Reye syndrome, Wilson disease, autoimmune hepatitis
   2. Gross and microscopic findings (see Fig. 19-4B)
      a. Wrinkled capsular surface due to loss of hepatic parenchyma
      b. Dull red areas of necrotic parenchyma with regenerative nodules and blotches of green (bile), in some cases
   3. Clinical findings
      • Hepatic encephalopathy (see section VII), jaundice
   4. Laboratory findings
      a. Decrease in transaminases
      b. Liver parenchyma is destroyed.
      • Progressive increase in the PT and serum ammonia
   5. Treatment (refer to section VII)

IV. Circulatory Disorders of the Liver
A. Prehepatic obstruction to blood flow
   1. Definition—obstruction of blood flow to the liver (i.e., hepatic artery, portal vein)
   2. Hepatic artery thrombosis with infarction
      a. Liver infarction (usually pale infarction) is uncommon because of a dual blood supply (Fig. 19-5A).
         • Hepatic artery and portal vein tributaries normally empty blood into the sinusoids.
      b. Causes
         (1) Liver transplant rejection
         (2) Vasculitis due to polyarteritis nodosa (PAN)
   3. Portal vein (PV) thrombosis
      a. Causes
         (1) Pylephlebitis (inflammation of portal vein)
            (a) Most often due to acute appendicitis
            (b) Air present in the portal vein from bacterial gas
         (2) Polycythemia vera (hyperviscosity of blood)

19-5: A. Liver infarctions showing multiple irregular pale areas of infarction. B. Centrilobular hemorrhagic necrosis ("nutmeg" liver). The liver has a mottled cut surface. Dark areas represent congested central venules and sinusoids. (A from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 134, Fig. 6-12; B from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 146, Fig. 8-8.)
(3) Hepatocellular carcinoma

b. Clinical findings
   (1) Portal hypertension (PH), ascites, splenomegaly
   (2) No hepatomegaly

B. Intrahepatic obstruction to blood flow

1. Definition—Intrahepatic obstruction to sinusoidal blood flow

2. Causes
   a. Cirrhosis (see section VII)
   b. Centrilobular hemorrhagic necrosis
   c. Peliosis hepatis
   d. Sickle cell disease (refer to Chapter 12)

3. Centrilobular hemorrhagic necrosis
   a. Most often due to left-sided heart failure (LHF) and right-sided heart failure (RHF)
      (1) LHF decreases cardiac output, causing hypoperfusion of the liver.
         • Leads to ischemic necrosis of hepatocytes located around the central venules (zone III; see Fig. 2-7B)
      (2) RHF causes a backup of systemic venous blood into the central venules and sinusoids, and portal vein.
   b. Enlarged liver with a mottled red appearance ("nutmeg" liver) (see Fig. 19-5B)
      (1) Congestion of central venules and sinusoids
      (2) Necrosis of hepatocytes around the central venules
   c. Clinical findings
      (1) Painful hepatomegaly with or without jaundice
      (2) Increased serum transaminases is caused by ischemic necrosis
      (3) May progress to cardiac cirrhosis
         • Fibrosis around central venules
   d. Treatment
      • Treat heart failure

4. Peliosis hepatis
   a. Definition—sinusoidal dilation due to blood
   b. Causes
      (1) Anabolic steroids
      (2) *Bartonella henselae* causing bacillary angiomatosis (refer to Chapter 10)
         • Occurs in AIDS
   c. Potential for intraperitoneal hemorrhage

C. Posthepatic obstruction to blood flow

1. Definition—Obstruction of blood flow out of the liver (e.g., hepatic vein)

2. Causes
   a. Hepatic vein thrombosis
   b. Venoocclusive disease

3. Hepatic vein thrombosis (Budd-Chiari syndrome)
   a. Causes
      (1) Polycythemia vera (due to hyperviscosity; refer to Chapter 13)
         • Most common cause (up to 40% of cases)
      (2) Hypercoagulable state (20% of cases; refer to Chapter 15)
         (a) Oral contraceptive pills
         (b) Proteins C and S deficiency
         (c) Antiphospholipid syndrome
      (3) Hepatocellular carcinoma (<5% of cases)
         • Invades hepatic vein
   b. Clinical findings
      (1) Enlarged, painful liver
      (2) Portal hypertension, ascites, splenomegaly
      (3) High mortality rate
   c. Laboratory findings
      (1) Increased serum transaminases
      (2) Increased serum PT
   d. Diagnosis
      (1) Ultrasound with pulsed Doppler is first-line test
      (2) Magnetic resonance imaging (MRI)
e. Treatment
   (1) Anticoagulation
   (2) In situ thrombolysis
   (3) Stenting, various shunts
f. Prognosis
   • Approximately 75% mortality rate in first year
4. Venocclusive disease
   a. Complication of bone marrow (BM) transplantation
   b. Collagen develops around the central venules.

D. Hematobilia
   • Blood in the bile in patients with trauma to the liver

V. Alcohol-Related and Drug- and Chemical-Induced Liver Disorders
   A. Alcohol-related disorders
      1. Risk factors for alcohol-related liver disease (refer to Chapter 7)
      2. Pathways for alcohol metabolism (refer to Chapters 2 and 7)
      3. Types of liver disease
         a. Fatty change is the most common type of disease (see Fig. 2-12A and B).
            (1) Substrates of alcohol metabolism are used to synthesize liver triglycerides.
            (2) Clinical findings
               • Tender hepatomegaly without fever or neutrophilic leukocytosis
            (3) Treatment
               • Alcohol rehabilitation
         b. Alcoholic hepatitis
            (1) Pathogenesis
               (a) Genetic predisposition is likely.
               (b) Due to acetaldehyde damage to hepatocytes
               (c) Stimulation of collagen synthesis around the central venules
                  • Perivenular fibrosis
            (2) Microscopic findings
               (a) Fatty change with neutrophil infiltration
               (b) Mallory bodies
                  • Damaged cytokeratin intermediate filaments in hepatocytes
                     (see Fig. 2-11)
            (3) Clinical findings
               (a) Painful hepatomegaly
               (b) Fever, neutrophilic leukocytosis, ascites, hepatic encephalopathy
               (c) May progress to alcoholic cirrhosis
            (4) Laboratory findings
               (a) Absolute neutrophilic leukocytosis
               (b) Serum AST > ALT
               (c) Increased serum ALP and GGT
                  • Serum GGT is disproportionately increased when compared to ALP
                     (see Table 19-2)
               (d) Thrombocytopenia in some cases
               (e) Hypoglycemia in some cases
            (5) Treatment
               (a) Mandatory to stop drinking
               (b) Corticosteroids helpful in some cases
         c. Cirrhosis (see section VII)
      4. Laboratory findings (refer to Chapter 7; see Fig. 7-1)
   B. Chemical- and drug-induced liver diseases (Table 19-7)
   VI. Obstructive (Cholestatic) Liver Disease
   A. Types of cholestatic liver disease
      1. Intrahepatic cholestasis
         a. Definition—blockage of the intrahepatic bile ducts
         b. Causes
            (1) Drugs (e.g., oral contraceptive pills [OCPs], anabolic steroids)
               • Drugs most common cause of intrahepatic cholestasis
            (2) Neonatal hepatitis
            (3) Pregnancy-induced cholestasis (estrogen)
2. Extrahepatic cholestasis
   a. Blockage of common bile duct (CBD)
   b. Causes
      (1) Stone usually originating from the gallbladder (most common cause)
      (2) Primary sclerosing cholangitis
      (3) Extrahepatic biliary atresia
      (4) Carcinoma at head of pancreas

B. Gross and microscopic findings in cholestatic liver disease
1. Enlarged, greenish liver
2. Bile ducts distended with bile (Fig. 19-6A), bile lakes, bile infarcts

C. Clinical findings in cholestatic liver disease
1. Jaundice with pruritus
   • Pruritus due to bile salts deposited in skin
2. Malabsorption
   • Bile salts do not enter the small intestine.
3. Cholesterol (CH) deposits in skin
   a. Due to CH in bile
   b. Example—xanthelasma (see Fig. 10-4B)
4. Light-colored stools
   • Due to a lack of urobilin
D. Laboratory findings (see Box 19-1D)
1. CB >50%
2. Bilirubinuria
3. Absent urine UBG
4. Increase in serum ALP and GGT
5. Increase in serum CH (present in bile)
E. Benign intrahepatic cholestasis of pregnancy
1. Due to estrogen inhibition of intrahepatic bile secretion
2. Not dangerous to the fetus or mother
F. Extrahepatic biliary atresia
1. Cause of jaundice in newborns
2. Inflammatory destruction of all or part of the extrahepatic bile ducts
3. Bile duct proliferation in the triads
4. Common indication for liver transplantation in a child
G. Primary sclerosing cholangitis (PSC)
1. Epidemiology
   a. Obliterative fibrosis of intrahepatic and extrahepatic bile ducts (see Fig. 19-6B)
   b. Primary disease
      (1) Genetic predisposition
         • Association with HLA-DR52a (100%) and HLA-Cw7 (86%)
      (2) Male dominant (70% of cases); usually <45 years old
      (3) Associations
         (a) Inflammatory bowel disease (70% of cases)
            • Ulcerative colitis (UC) > Crohn disease (CD)
         (b) Other sclerosing disorders
            • Retroperitoneal and mediastinal sclerosing fibrosis
      (4) Complications
         (a) Cirrhosis
         (b) Cholangiocarcinoma
2. Clinical findings
   a. Jaundice
   b. Pruritus
      • Deposition of bile salts/acids in skin
   c. Hepatosplenomegaly
3. Laboratory findings
   a. CB >50%
   b. Bilirubinuria
   c. Absent urine UBG
   d. Increase in serum ALP and GGT
4. Diagnosis
   a. Endoscopic retrograde cholangiopancreatography (ERCP)
   b. Dye study shows narrowing and dilation of bile ducts (“beading”; see Fig. 19-6C)
5. Treatment
   a. Immunosuppressants
      • Corticosteroids, azathioprine, methotrexate
   b. Invariably require a liver transplant
VII. Cirrhosis
A. Definition
   • Irreversible diffuse fibrosis of the liver with formation of regenerative nodules
B. Regenerative nodules in cirrhosis
1. Hepatocyte reaction to injury (Fig. 19-7A and B)
2. Lack normal liver architecture (see Fig. 3-15)
   • Lack of portal triads and sinusoids
3. Surrounded by bands of fibrosis
19-7: A, Surface of a liver with alcoholic cirrhosis showing a micronodular pattern. B, Cut section of a liver with alcoholic cirrhosis, showing micronodules representing regenerative nodules surrounded by collagen. C, Trichrome stain of a liver with alcoholic cirrhosis accentuating the regenerative nodules (red) and the fibrotic tissue (blue). D, Portal vein anatomy and anastomoses. Note that the portal vein derives from the splenic vein and the superior mesenteric veins. Portacaval anastomoses occur when there is reversed blood flow in portal hypertension. These lead to the development of esophageal varices (via anastomoses of the left gastric vein [portal] and the azygous vein [systemic]), caput medusae (via anastomoses of the paraumbilical vein [portal] with the superficial veins of the anterior abdominal wall [systemic], and hemorrhoids (via anastomoses of the superior rectal vein [portal] and inferior rectal [systemic] veins). E, Patient with alcoholic cirrhosis showing ascites (abdominal distention), caput medusae (dilates superficial abdominal wall veins), and bilateral gynecomastia. F, Spider angiomata (telangiectasia) showing a single central arteriole and numerous radiating capillaries. G, Liver biopsy stained with Prussian blue in a patient with hereditary hemochromatosis. The hepatocytes are filled with blue iron granules. This is an early stage before parenchymal damage and fibrosis develop. H, Hemochromatosis in a male patient showing the characteristic bronze appearance of the skin. The hyperpigmentation results from the combination of iron deposited in skin plus and increase in melanin synthesis. Also note clubbing of the finger nails. I, Kayser-Fleischer ring. This shows deposition of a copper-colored pigment in Descemet membrane in the cornea. J, α-1-Antitrypsin deficiency. The globules of α-1-antitrypsin accumulating in hepatocytes are periodic acid–Schiff positive. (A, C, and J from MacSween R, Burt A, Portmann B, Ishak K, Scheuer P, Anthony P: Pathology of the Liver, 4th ed, London, Churchill Livingstone, 2002, pp 596, 280, 176, respectively, Figs. 13.13, 6.9, 4.21, respectively; B from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 154, Fig. 8-42; D from Moore A, Roy W: Rapid Review Gross and Developmental Anatomy, 3rd ed, Philadelphia, Mosby Elsevier, 2010, p 95, Fig. 3.40; E from Swartz M: Textbook of Physical Diagnosis History and Examination, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 497, Fig. 17.14; F from Gitlin M, Strauss R: Atlas of Clinical Hepatology, Philadelphia, Saunders, 1995, p 3, Fig. 1.4; G from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 910, Fig. 18-28; H from Gitlin N, Strauss R: Atlas of Clinical Hepatology, Philadelphia, Saunders, 1995, p 22, Fig. 2.9; I from Perkin GD: Mosby’s Color Atlas and Text of Neurology, St. Louis, Mosby, 2002, p 151, Fig. 8-15.)
4. Compress sinusoids and central venules
   a. Intrasinusoidal hypertension
   b. Reduction in the number of functional sinusoids
   c. Increase in hydrostatic pressure in portal vein

C. Causes of cirrhosis
1. Alcoholic liver disease (most common)
2. Postnecrotic cirrhosis (HBV, HCV)
3. Autoimmune disease
   a. Primary biliary cirrhosis
   b. Autoimmune hepatitis (see section III)
4. Metabolic diseases
   a. Hemochromatosis
   b. Wilson disease
   c. α1-Antitrypsin deficiency
   d. Galactosemia

D. Complications associated with cirrhosis
1. Hepatic failure
   a. Definition—end-point of progressive damage to the liver
   b. Variable coagulation defects
      (1) Due to inability to synthesize coagulation factors, a patient can have a bleeding diathesis
      (2) Due to decreased synthesis of protein C/S, a patient can be hypercoagulable.
   c. Hypoalbuminemia from decreased synthesis of albumin
      • Produces dependent pitting edema and ascites due to a decrease in plasma oncotic pressure (refer to Chapter 5)
   d. Hepatic encephalopathy
      (1) Reversible metabolic disorder
      (2) Increase in aromatic amino acids (e.g., phenylalanine, tyrosine, tryptophan)
         • Converted into false neurotransmitters (e.g., γ-aminobutyric acid)
      (3) Increase in serum ammonia
         • Due to a defective urea cycle that cannot metabolize ammonia

Ammonia derives from metabolism of amino acids and from the release of ammonia from amino acids by bacterial ureases in the bowel. Ammonia (NH₃) is diffusible and is reabsorbed into the portal vein for delivery to the urea cycle where it is metabolized into urea. Ammonium (NH₄⁺) is not reabsorbed in the bowel and is excreted in stool. Methods for reducing ammonia in the colon include restriction of protein intake (most cost-effective) and the use of oral neomycin, which destroys the colonic bacteria that synthesize ureases. Oral administration of lactulose results in the release of hydrogen ions, causing NH₃ to be converted to NH₄⁺, which is excreted in the feces.

(4) Factors precipitating encephalopathy
   (a) Increased protein (most important)
      • Dietary sources or blood in gastrointestinal tract leads to increased bacterial conversion of urea into ammonia.
   (b) Alkalosis keeps ammonia in the NH₃ state (see earlier discussion).
      • Diuretics (loop/thiazide) produce metabolic alkalosis (↓hydrogen ions).
   (c) Sedatives
   (d) Portosystemic shunts
      • Shunt ammonia away from the liver, which normally metabolizes ammonia in the urea cycle
(5) Clinical findings
   (a) Alterations in the mental status
   (b) Somnolence and disordered sleep rhythms
   (c) Asterixis (i.e., inability to sustain posture, flapping tremor)
   (d) Coma and death in late stages
(6) Treatment (see ammonia discussion)

2. Portal hypertension (PH)
   a. Portal vein anatomy (see Fig. 19-7D)
   b. Pathogenesis
      (1) Resistance to intrahepatic blood flow due to intrasinusoidal hypertension
      (2) Anastomoses between portal vein tributaries and the arterial system

Ammonia: derives from amino acid metabolism and urease-producing bacteria in bowel
↓Ammonia: ↓protein intake; antibiotics; lactulose

Precipitating factors:
↑protein intake, alkalosis, sedatives, portosystemic shunts

Hepatic encephalopathy: alterations mental status, somnolence, asterixis (flapping tremor)
PV: splenic vein + superior mesenteric vein

PH: due to intrasinusoidal hypertension from regenerative nodule compression

Regenerative nodules: produce intrasinusoidal hypertension; no triads
Alcoholic liver disease: MCC cirrhosis
Cirrhosis: variable coagulation defects — bleeding diathesis, hypercoagulable
Hepatic encephalopathy: reversible metabolic disorder; ↑false neurotransmitters; ↑serum ammonia

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c. Complications
   (1) Ascites (see later)
   (2) Congestive splenomegaly
      (a) Increased hydrostatic pressure in splenic vein
      (b) Hypersplenism with various cytopenias may occur (refer to Chapter 14)
   (3) Esophageal varices (refer to Chapter 18; see Fig. 18-11)
   (4) Hemorrhoids (see Fig. 18-26A)
   (5) Periumbilical venous collaterals (caput medusae; see Fig. 19-7D and E)

d. Shunts used in treating PH
   (1) Portacaval shunt
      • Connects the portal vein with the vena cava
   (2) Mesocaval shunt
      • Connects the superior mesenteric vein with the vena cava
   (3) Splenorenal
      (a) Most physiologic shunt
      (b) Connects the splenic vein with the renal vein
      (c) Reduces PH and bleeding from varices without bypassing the liver
   (4) Transjugular intrahepatic portosystemic shunt (TIPS)
      (a) Metal stent connects portal vein (PV) with hepatic vein
      (b) Reduces portal vein pressure
      (c) Increases risk for encephalopathy
      (d) Used in treatment of acute esophageal bleeds (refer to Chapter 18)
      (e) Used in treating patients awaiting liver transplantation

3. Ascites (see Fig. 19-7E)
   a. Pathogenesis
      (1) Portal hypertension (PH)
      • Increase in portal vein hydrostatic pressure (HP)
      (2) Hypoalbuminemia
      • Decreases oncotic pressure (OP)
      (3) Secondary hyperaldosteronism occurs because:
         (a) Cardiac output is decreased (refer to Chapter 5)
            • Decreased renal blood flow activates the renin-angiotensin-aldosterone
              (RAA) system (retention of Na⁺ and water).
         (b) Liver is unable to metabolize aldosterone
   b. Clinical findings
      (1) Abdominal distention with a fluid wave
      (2) Increased risk for spontaneous bacterial peritonitis

**Peritoneal fluid analysis** is useful in distinguishing ascites of liver origin from ascites of
peritoneal origin. The gradient between serum albumin and ascitic fluid albumin (serum albumin
– ascitic fluid albumin) is very helpful in making this distinction. A difference >1.1 g/dL is ascsites
of liver origin, whereas a difference <1.1 g/dL is of peritoneal origin (e.g., peritonitis). Recall that
ascites of liver origin is a transudate, which is a protein-poor and cell-poor fluid; hence the
expected difference between serum albumin and ascitic albumin is increased. However, ascitic
fluid from peritonitis is an exudate, which is a protein-rich and cell-rich fluid; hence, the difference
between serum and ascitic fluid is much less. Peritoneal fluid protein concentration and cell count
are also useful. A total peritoneal fluid protein concentration <2.5 g/dL and white blood cell
(WBC) count <300 cells/mm³ + neutrophils <25% of the total count is consistent with a
transudate, whereas a concentration >2.5g/dL and a WBC count >300 cells/mm³ + neutrophils
>25% of the total count indicates an exudate.

4. Hepatorenal syndrome
   a. Definition—condition of intense renal vasoconstriction due to a loss of renal
      autoregulation occurring as a complication of severe, chronic liver disease
      (i.e., cirrhosis)
   b. Reversible renal failure **without** renal parenchymal disease
      • Creatinine clearance <40 mL/minute (refer to Chapter 20)
   c. Approximately 20% of people with hepatic failure die of this syndrome.
   d. There is absence of:
      (1) Shock
      (2) Volume depletion
(3) Infection
(4) Obstructive or parenchymal renal disease
e. Preservation of renal tubular function
   (1) Random urine Na\(^+\) <20 mEq/L (refer to Chapter 20)
   (2) Absence of significant proteinuria (<500 mg/day) or hematuria
f. Due to decreased renal blood flow
   • Serum blood urea nitrogen and creatinine are increased (refer to Chapter 20).
g. Treatment
   (1) Supportive care including dialysis
   (2) Vasopressin analogues
   (3) Vasocostrictors (e.g., norepinephrine, midodrine)
   (4) Albumin for volume expansion
   (5) Liver transplantation only curative treatment
h. Mortality rate is >80%

5. Hyperestrinism in males
   a. Pathogenesis
      (1) Liver cannot degrade estrogen and 17-ketosteroids (e.g., androstenedione).
      (2) Androstenedione is aromatized into estrogen in the adipose cells.
b. Clinical findings
   (1) Gynecomastia (see Fig. 19-7E)
   (2) Spider telangiectasia (refer to Chapter 10) (see Fig. 19-7F)
   (3) Female distribution of hair
      (a) Hair is sparse.
      (b) Hair does not extend from the pubic area to the umbilicus (see Fig. 19-7E).
   (4) Impotence and erectile dysfunction
      (a) Increased estrogen increases synthesis of sex hormone–binding protein, which increases binding of free testosterone (refer to Chapter 21).
      (b) Decreased free testosterone levels decreases libido, leading to erectile dysfunction.

E. Postnecrotic cirrhosis
1. Most often caused by chronic hepatitis due to HBV and HCV
2. Increased incidence of hepatocellular carcinoma
   • Incidence of which virus is most common varies around the world

F. Primary biliary cirrhosis (PBC)
1. Epidemiology
   a. Definition—cirrhosis due to granulomatous destruction of bile ducts in the portal triads
   b. Autoimmune disorder
      • Association with other autoimmune diseases (e.g., Sjögren syndrome)
   c. Occurs in women (>90% of cases) between 40 and 50 years of age
   d. Progresses from a chronic inflammatory reaction to cirrhosis with PH
   e. Increased risk for hepatocellular carcinoma
2. Pathogenesis
   a. Environmental insult affecting mitochondrial proteins triggers CD8 T-cell destruction of intralobular bile duct epithelium.
   b. Enzyme complex subunit in mitochondrial membrane is the autoantigen recognized by CD8 T cells.
   c. Autoantibodies (antimitochondrial antibodies) develop against the mitochondria.
      • Do not correlate with disease activity
3. Clinical findings
   a. Pruritus (20%–70% of cases)
      (1) Unknown etiology (not bile salts in skin)
      (2) Early finding well before jaundice appears
   b. Painful hepatosplenomegaly
   c. Jaundice (60% of cases)
      • Late finding after most of the bile ducts have been destroyed
   d. Inflammatory arthropathy (40%–70% of cases)
   e. Xanthelasma (40% of cases; see Fig. 10-4B)
      (1) Late finding
      (2) Due to CH in bile backing up into the blood
   f. Kayser-Fleischer ring in cornea
      • Due to retention of copper
4. Laboratory findings
   a. Antimitochondrial antibodies (AMAs; >90% of cases)
   b. Serum ANA positive (50% of cases)
   c. Increase in serum IgM
   d. Increased serum ALP and GGT
   e. Increased serum CH
      • Component of bile

5. Treatment
   a. Budesonide + ursodeoxycholic acid
   b. Cholestyramine for pruritus
   c. Liver transplantation
      • Improves survival; 70% survive 10 years

G. Secondary biliary cirrhosis
1. Complication of chronic extrahepatic bile duct obstruction
   • Example—cystic fibrosis, where bile is dehydrated (refer to Chapter 17)
2. No increase in serum AMA or IgM

H. Hereditary hemochromatosis (HHC)
1. Epidemiology
   a. Autosomal recessive (AR) disorder
      (1) Linked to short arm of chromosome 6
      (2) HLA-A3 association
   b. Most common genetic disorder in people of North European ancestry
   c. Male dominant disorder
      • Diagnosis usually made in fifth decade
   d. In women, diagnosis usually made 10 to 20 years after menopause
      • Due to menses causing loss of iron

2. Pathogenesis
   a. Unrestricted reabsorption of iron in the small intestine
   b. Mutations involving hereditary hemochromatosis gene (HFE)
      (1) Two missense mutations (C282Y and H63D) occur on chromosome 6.
      (2) There is a 1:10 carrier rate in the population.
   c. Iron stimulates the production of hydroxyl free radicals (refer to Chapter 2)
      • Free radicals (FRs) damage tissue and cause fibrosis.

   The normal function of the HFE gene protein product (refer to Chapter 12 and Fig. 12-9) is to facilitate the binding of plasma transferrin (binding protein for iron) to the mucosal cell transferrin receptors in the duodenum. In general, if there is less transferrin-bound iron that binds to the receptor (indicating decreased iron stores), the synthesis and release of the hormone hepcidin by the liver is decreased, leading to increased duodenal reabsorption of iron. If there is more transferrin-bound iron that binds to the receptor (indicating increased iron stores), then there is increased liver synthesis and release of hepcidin and less iron is reabsorbed by the duodenum. Because there is a mutated HFE gene in hemochromatosis, there is no binding of transferrin-bound iron to the transferrin receptor; therefore no hepcidin is synthesized and released by the liver. This leads to unrestricted reabsorption of iron from the duodenum. Excess iron in the blood leads to excess iron in tissue. Iron in the tissue increases the formation of hydroxyl free radicals (refer to Chapter 2) causing tissue damage.

   3. Iron deposits in multiple organs
      • Liver (target organ), pancreas, heart, joints, skin, pituitary

   Hemosiderosis (secondary hemochromatosis) is caused by multiple blood transfusions (e.g., sickle cell anemia, thalassemia major), alcohol abuse (alcohol increases iron reabsorption), and well water (iron pipes). Iron deposits are more prevalent in macrophages than in parenchymal tissue.

   4. Clinical findings
      a. Cirrhosis (60% of cases)
         (1) Iron deposits primarily in hepatocytes (see Fig. 19-7G).
         (2) Increased risk of hepatocellular carcinoma
b. “Bronze diabetes”
   (1) Type I diabetes mellitus (60% of cases)
      - Destruction of β-islet cells in the pancreas
   (2) Hyperpigmentation (75% of cases; see Fig. 19-7H)
      - Iron deposits in skin and increases melanin production

c. Malabsorption
   - Destruction of exocrine pancreas

d. Restrictive cardiomyopathy

e. Hypogonadism (destruction of the pituitary gland)
   (1) Amenorrhea in women due to hypogonadism (25% of cases)
   (2) Loss of libido in men due to decreased testosterone (50% of cases)

f. Degenerative joint disease (>40% of cases)
   - Chondrocalcinosis (refer to Chapter 24)

5. Laboratory findings
   a. Increased serum iron, percent saturation, and ferritin (refer to Chapter 12)
      (1) Transferrin saturation is the best screening test.
      (2) Values >45% indicate further evaluation is necessary.
      (3) Decreased total iron-binding capacity (TIBC)
         - Transferrin synthesis is decreased when iron stores are increased (refer to Chapter 12).
      (4) Serum ferritin is primarily used to follow therapy.
   b. Liver biopsy to confirm
   c. Decreased serum luteinizing hormone and follicle-stimulating hormone
      - Destruction of the anterior pituitary gland

6. Screening test for relatives
   - HFE gene testing for C282Y mutation

7. Treatment
   a. Phlebotomy until serum ferritin <50 µg/mL, saturation <30%
   b. Deferoxamine (iron chelator)

8. Normal life expectancy if no cirrhosis is present

I. Wilson disease (WD; hepatolenticular degeneration)

1. Epidemiology
   a. Definition—disorder of copper metabolism with inadequate biliary excretion of copper; leads to copper accumulation and damage in multiple organs
   b. Autosomal recessive disorder
   c. Affects men and women equally
   d. Onset of symptoms from 3 to 40 years of age
      - Usually late childhood
   e. Liver disease progresses from acute hepatitis to cirrhosis and portal hypertension.

2. Pathogenesis
   a. Gene mutation
      (1) Defective hepatocyte transport of copper into bile for excretion
      (2) Defective incorporation of copper into ceruloplasmin (binding protein for copper in blood)
   b. Unbound copper eventually accumulates in blood.
      (1) Copper is loosely attached to albumin.
      (2) Copper deposits in other tissues cause a toxic effect.

Ceruloplasmin is a protein that is synthesized in the liver. It contains six copper atoms in its structure. Ceruloplasmin is secreted into the plasma where it represents 90% to 95% of the total serum copper concentration. The remaining 5% to 10% of copper is free copper that is loosely bound to albumin. Ceruloplasmin is eventually taken up and degraded by the liver. The copper that was bound to ceruloplasmin is excreted into the bile. The gene defect in Wilson disease affects a copper transport system that produces a dual defect—decreased incorporation of copper into ceruloplasmin in the liver (ceruloplasmin is decreased) and decreased excretion of copper into bile (intrahepatic copper is increased). Accumulation of copper in the liver increases the formation of hydroxyl free radicals (Fenton reaction; see Chapter 2) that damage hepatocytes. Liver disease progresses from acute hepatitis to cirrhosis. In a few years, unbound copper is released from the liver into the circulation (increased in blood and urine) where it damages the brain, kidneys, cornea, and other tissues.
3. Clinical findings
   a. Kayser-Fleischer ring (~70% of cases)
      (1) Due to free copper deposits in Descemet membrane in the cornea
          (see Fig. 19-7I)
      (2) Not pathognomonic of Wilson disease
          • It is also seen in primary biliary cirrhosis.
   b. Central nervous system disease (>50% of cases; see Fig. 26-21A)
      (1) Copper deposits in the putamen
          • Produces a movement disorder resembling parkinsonism
      (2) Copper deposits in the subthalamic nucleus
          • Produces hemiballismus
      (3) Copper is toxic to neurons in the cerebral cortex
          • Produces dementia
   c. Hepatosplenomegaly (50% of cases)
      • Liver biopsy shows increased copper and fibrosis.
   d. Hemolytic anemia
   e. Renal disease
      • Proximal tubule damage produces Fanconi syndrome (refer to Chapter 5).

4. Laboratory findings
   a. Decreased total serum copper
      • Due to decreased ceruloplasmin
   b. Decreased serum ceruloplasmin (85% sensitivity)
      • Useful in diagnosing Wilson disease in its early stages
   c. Increased serum and urine free copper
      • Useful in diagnosing Wilson disease in the later stages

5. Treatment
   a. Penicillamine (copper chelator)
   b. Zinc
   c. Ammonium tetrathiomolybdate
      (1) Competes for copper reabsorption in bowel
      (2) Increases copper excretion in urine
   d. Liver transplantation

J. α₁-Antitrypsin (AAT) deficiency

1. Epidemiology
   a. Autosomal dominant (codominant)
   b. Pathogenesis
      (1) Alleles are inherited codominantly (each allele expresses itself).
      (2) Normal allele is M (95% frequency in the United States).
          • MM is normal genotype with AAT in normal range.
      (3) Deficient variant (decreased AAT) Z allele (1%–2% frequency)
      (4) Deficient variant (decreased AAT) S allele (2%–3% frequency)
      (5) Severe deficiency most commonly occurs in homozygous ZZ variant.
          (a) Decreased (<15% of normal) AAT levels in serum
          (b) Associated with panacinar emphysema (refer to Chapter 17)
          (c) Associated with cirrhosis of the liver (see later)
      (6) Risk of lung disease in heterozygotes (e.g., MZ) is uncertain.
   c. Most common cause of cirrhosis in children

2. Children with accumulation of AAT in hepatocytes
   a. In ~50% of homozygous ZZ patients, AAT is not secreted properly from hepatocytes.
   b. Pathologic accumulation of AAT in hepatocytes causes liver damage.
      • Periodic acid–Schiff stains show red cytoplasmic granules (see Fig. 19-7I).
   c. Presents as neonatal hepatitis with intrahepatic cholestasis
   d. Hepatitis progresses into cirrhosis.
      • AAT deficiency is the most common cause of cirrhosis in children.
   e. Increased risk for hepatocellular carcinoma

3. Treatment
   a. Pooled AAT given intravenously
   b. Liver and lung transplantation

K. Laboratory test abnormalities in cirrhosis

1. Decreased serum blood urea nitrogen (BUN) and increased serum ammonia
   • Due to disruption of the urea cycle
2. Fasting hypoglycemia
   • Defective gluconeogenesis and decreased glycogen stores
3. Chronic respiratory alkalosis
   • Toxic products from hepatic dysfunction overstimulate respiratory center
   (refer to Chapter 5)
4. Lactic acidosis
   • Liver dysfunction in converting lactic acid to pyruvate
5. Hyponatremia (refer to Chapter 5)
   a. Decreased cardiac output
   b. Kidneys reabsorb a slightly hypotonic solution (↑Total Body Sodium
      [TBNa]/↑↑TBW)
6. Hypokalemia
   • Secondary aldosteronism increases renal exchange of Na⁺ for K⁺ (refer to
     Chapter 5)
7. Increased PT
   • Decreased synthesis of coagulation factors
8. Hypoalbuminemia
   • Decreased synthesis of albumin
9. Hypocalcemia
   a. Hypoalbuminemia decreases the total serum calcium without affecting
      the ionized calcium level (refer to Chapter 23)
   b. Vitamin D deficiency
      • Decreased liver 25-hydroxylation of vitamin D (refer to Chapters 8 and 23).
10. Mild serum transaminasemia
    • Enzymes are not markedly increased because of the loss of parenchymal
        cells.

VIII. Liver Tumors and Tumor-like Disorders
A. Focal nodular hyperplasia (FNH)
   1. Epidemiology
      a. Tumor-like condition
      b. More common in women than men
      c. Cause is unknown
      • Probable reaction to injury
      d. Usually an incidental finding
   2. Gross findings
      a. Poorly encapsulated nodule
      b. Central depressed stellate scar
         • Contains large blood vessels
      c. Fibrous septae radiating to the periphery
   3. CT scan
      • Hypervascular mass with arteriovenous connections
   4. Treatment
      • None unless associated with pain
B. Benign tumors of the liver
   1. Cavernous hemangioma
      a. Most common benign tumor of the liver
      b. Best diagnosed with enhanced CT scan
      c. Rare cause of intraperitoneal hemorrhage
   2. Liver (hepatic) cell adenoma
      a. Benign tumor of hepatocytes
      b. Occurs in women > men
      c. Causes
         (1) OCPs (most common cause)
         (2) Anabolic steroids
         (3) Von Gierke glycogenosis
      d. Highly vascular tumors
         (1) Tendency to rupture during pregnancy
         (2) Cause intraperitoneal hemorrhage
      e. Tend to regress if stop taking OCP and anabolic steroids
   3. Treatment is surgery if symptomatic.
C. Malignant tumors of the liver

1. Metastasis
   a. Most common liver cancer (see Fig. 9-6E, Fig. 19-8A)
   b. Primary cancers of lung (most common), gastrointestinal tract, breast
   c. Multiple nodular masses

2. Hepatocellular carcinoma (HCC)
   a. Epidemiology
      (1) Most common primary liver cancer
      (2) Rapidly increasing in the United States from increase in HCV infection
      (3) Occurs in males more than females
         • Peaks around fifth and sixth decades
      (4) Causes
         (a) Postnecrotic cirrhosis due to chronic HBV and HCV
         (b) Alcoholic cirrhosis
         (c) Aflatoxins (from Aspergillus mold in grains and peanuts)
         (d) Hereditary hemochromatosis, Wilson disease
         (e) PBC, AAT deficiency, tyrosinemia
   b. Pathogenesis
      (1) Most often associated with preexisting cirrhosis
      (2) Postnecrotic cirrhosis HBV/HCV most common risk factors
   c. Gross findings
      (1) Focal, multifocal, or diffusely infiltrating cancer (see Fig. 19-8B)
         • With or without preexisting cirrhosis (usually with preexisting cirrhosis)
      (2) Portal and hepatic vein invasion is common.
   d. Microscopic findings
      • Characteristic finding is the presence of bile in neoplastic cells.
   e. Clinical findings
      (1) Over one-third are asymptomatic.
      (2) Abdominal pain is a common initial presentation.
      (3) Liver cell necrosis causes fever.
      (4) Rapid enlargement of the liver occurs in a patient with cirrhosis.
         • Increased ascites with blood in the fluid
   f. Laboratory findings
      (1) Increased α-fetoprotein (AFP; 70% of cases)
         • Sensitivity 40% to 60%, specificity 80% to 94%
      (2) Increased serum ALP and GGT
         • Sudden increase in these enzymes is a characteristic finding in HCC.
      (3) Production of ectopic hormones
         (a) Erythropoietin (EPO; secondary polycythemia)
         (b) Insulin-like factor (hypoglycemia)
         (c) Parathyroid hormone (PTH)-related protein (hypercalcemia)
g. Lung most common metastatic site
h. Diagnosis
   (1) CT scan and ultrasound localize HCC.
   (2) Angiography shows pooling and increased vascularity.
i. Treatment
   (1) Surgery (<20% of cases are surgical candidates)
   (2) Liver transplantation
   (3) Radiation and chemotherapy are usually not helpful.
j. Prognosis
   (1) If unresectable, most die within 6 months.
   (2) If resectable, 5-year survival rate is 30% to 50%.

3. Angiosarcoma
   • Exposure to vinyl chloride (most common cause), arsenic, or thorium dioxide

IX. Gallbladder and Biliary Tract Disease
A. Cystic diseases of the biliary tract
1. Choledochal cyst
   a. Most common cyst in biliary tract in children younger than 10 years old
   b. Clinical findings
      (1) Abdominal pain with persistent or intermittent jaundice
      (2) Increased incidence of cholelithiasis, cholangiocarcinoma, and cirrhosis
   c. Diagnosis
      (1) Ultrasound is the screening test of choice.
      (2) ERCP or transhepatic cholangiography may be used.
         (a) Useful in identifying intrahepatic and extrahepatic cysts
         (b) Useful in identifying sites of obstruction
   d. Treatment is surgery.
2. Caroli disease
   a. Autosomal dominant and recessive types
   b. Segmental dilatation of intrahepatic bile ducts (Fig. 19-9A)
   c. Portal tract fibrosis
   d. Clinical findings
      (1) Association with polycystic kidney disease
         • Autosomal recessive type in children or the autosomal dominant type in adults
      (2) Increased incidence of cholangiocarcinoma
      (3) Increased incidence of the following:
         • Intrahepatic cholelithiasis, cholangitis, hepatic abscesses, and PH
   e. Treatment
      (1) Surgical resection of an involved lobe
      (2) Liver transplantation

B. Cholangiocarcinoma
1. Most common malignancy of bile ducts
2. Causes of cholangiocarcinoma
   a. Primary sclerosing cholangitis (see section VI)
      • Most common cause in the United States
   b. Clonorchis sinensis (Chinese liver fluke)
   c. Thorotras (thorium dioxide)
   d. Choledochal cyst, Caroli disease
3. Locations
   a. Ampulla or common bile duct (most common sites)
   b. Junction of right/left hepatic duct (called a Klatskin tumor)
   c. Intrahepatic
4. Clinical findings
   a. Obstructive jaundice
   b. Palpable gallbladder (GB; Courvoisier sign)
      • Only if the cancer is located in the middle portion of the common bile duct (CBD) or ampulla
   c. Hepatomegaly
5. Diagnosis
   • Ultrasound, ERCP
6. Treated surgically
19-9: A, Caroli disease. Note the segmental dilatation of the intrahepatic ducts. B, Yellow cholesterol stones with centers containing entrapped bile pigments. The wall of the gallbladder is scarred. C, Black pigmented stones. This type of stones is usually a sign of a chronic extravascular hemolytic anemia (e.g., hereditary spherocytosis, sickle cell disease), where there is an increase in unconjugated bilirubin (UCB) (macrophage destruction of spherocytes/sickle cells) and a corresponding increase in the uptake and conjugation of UCB to conjugated bilirubin (CB) in the liver. Note that a gallstone (black circle) that is lodged in the distal end of the CBD forces bile into the main pancreatic duct as well as the bile ducts in the liver (arrows). This produces extrahepatic cholestasis with jaundice and acute pancreatitis. E, Ultrasound showing gallstones (arrow). F, Calcified gallbladder wall. The rim-like calcification (solid white arrow) identifies this as occurring in the wall of the gallbladder. This is a porcelain gallbladder, which occurs with chronic inflammation and stasis and is associated with gallstones and an increased incidence of carcinoma of the gallbladder. G, Grey-Turner sign. Note the purplish discoloration in the loins due to tracking of hemorrhagic necrotic pancreatic material along the retroperitoneal planes. H, Cullen sign. Note the hemorrhagic discoloration around the umbilicus. It is due to tracking of hemorrhagic necrotic pancreatic tissue around the falciform and umbilical ligaments. I, Sentinel loop from acute pancreatitis. A single, persistently dilated loop of small bowel is seen in the left upper quadrant (solid white arrow) in the prone radiograph of the abdomen. A sentinel loop or localized ileus often signals the presence of an adjacent irritative or inflammatory process. They are also seen in retrocecal acute pancreatitis. J, Pancreatic adenocarcinoma. Yellow tumor has extensively replaced the pancreas. (A from MacSween R, Burt A, Portmann B, Ishak K, Scheuer P, Anthony P: Pathology of the Liver, 4th ed, London, Churchill Livingstone, 2002, p 125, Fig. 3.29; B and C from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, pp 930, 931, respectively; Figs. 18-50, 18-51, respectively; D from Moore A, Roy W: Rapid Review Gross and Developmental Anatomy, 3rd ed, Philadelphia, Mosby Elsevier, 2010, p 82, Fig. 3.27; E, from Goldman L, Schafer AI: Cecil’s Textbook of Medicine, 24th ed, Philadelphia, Saunders Elsevier, 2012, p 1017, Fig. 158-5; F and I from Herring W: Learning Radiology Recognizing the Basics, 2nd ed, Philadelphia, Elsevier Saunders, 2012, pp 157, 140, respectively; Figs. 16.3, 14-1B, respectively; G and H from Grieg JD: Color Atlas of Surgical Diagnosis, London, Mosby-Wolfe, 1996, p 162, Figs. 22-5, 22-4, respectively; J from Klatt F: Robbins and Cotran Atlas of Pathology, Philadelphia, Saunders, 2006, p 226, Fig. 9-14.)
C. Gallstones (cholelithiasis)

1. Components of bile
   a. Bile salts/acid (~67%)
      (1) Hepatic product of CH metabolism
      (2) Water soluble
      (3) Detergent action renders CH soluble in bile.
   b. Phospholipid (22%)
      (1) Mainly lecithin
      (2) Hydrophobic
      (3) Solubilizes CH in bile
   c. Protein (4.5%), free CH (4%), conjugated bilirubin (0.3%)
      • In extravascular hemolytic anemia (EHA; e.g., hereditary spherocytosis, sickle cell disease), there is an increase in UCB (macrophage destruction of spherocytes/sickle cells) and a corresponding increase in the uptake and conjugation of UCB to conjugated bilirubin (CB) in the liver. In the gallbladder, some of the CB is converted back to UCB, which combines with calcium to form calcium bilirubinate stones.
   d. Water, electrolytes, bicarbonate

2. Types
   a. Cholesterol stones (75% of cases) (see Fig. 19-9B)
      (1) Usually stones are of mixed composition.
      (2) Stones contain CH, calcium carbonate, some bilirubin pigment.
      • Can be radiopaque if they contain calcium carbonate
      (3) Rarely are stones purely CH.
      (4) CH stones are radiolucent.
   b. Pigment stones
      (1) Black pigment stones (see Fig. 19-9C)
         (a) Sign of chronic extravascular hemolytic anemia
            • Examples—sickle cell anemia, hereditary spherocytosis
         (b) Excess CB in bile is converted into UCB, which combines with calcium to produce calcium bilirubinate stones (black pigment stones)
      (2) Brown pigment stones
         (a) Sign of infection in the CBD
         (b) Commonly seen in Asians
         (c) Infection deconjugates CB, which increases UCB in bile and causes the brown pigment stones.

3. Pathogenesis of CH stones includes one or both of the following:
   a. Supersaturation of bile with CH
   b. Decreased bile salts/acid (refer to Chapter 18) and lecithin
      • Bile salts and acids normally solubilize CH in bile.
   c. Risk factors
      (1) Female >40 years old
      (2) Use of OCPs
      (3) Obesity
      • CH is increased in bile.

   **Estrogen** increases CH stone formation by several mechanisms. Estrogen increases the synthesis of high-density lipoprotein (HDL), which transports CH from peripheral tissue to the liver for excretion in bile. Estrogen upregulates low-density lipoprotein (LDL) receptor synthesis in hepatocytes, which increases the uptake of LDL, the primary vehicle for carrying CH. Furthermore, estrogen increases 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase activity (rate-limiting enzyme in CH synthesis); therefore more CH is synthesized in the liver.

   (4) Rapid weight loss; use of lipid-lowering drugs
   (5) Native Americans (e.g., Pima and Navajo Indians)

4. Complications associated with stones
   a. Cholecystitis (most common)
   b. CBD obstruction (see Fig. 19-9D), gallbladder cancer, acute pancreatitis

D. Acute cholecystitis

1. Epidemiology
   a. More common in women than in men
   b. Occurs most often during the fifth and sixth decades
1. Acute cholecystitis: 
   - Native Americans; women > men; gallstones >95%

2. Stages of development of acute cholecystitis
   a. Stage 1
      (1) Stone lodges in the cystic duct
         (a) Stimulus of food causes gallbladder (GB) contraction.
         (b) Stone is forced into the cystic duct.
      (2) Midepigastric colicky pain.
         • Due to GB contraction against obstructed cystic duct
      (3) Nausea and vomiting without pain relief
   b. Stage 2
      (1) Stone becomes impacted in the cystic duct.
      (2) Mucus accumulates behind the obstruction.
      (3) Chemical irritation of mucosa
      (4) Bacterial overgrowth (no invasion)
         (a) Most commonly *Escherichia coli*
         (b) Less commonly—*Enterococcus, Bacteroides fragilis, Clostridium* spp.
      (5) Pain shifts to the right upper quadrant (RUQ)
         (a) Dull, continuous aching pain
         (b) Pain radiation to the right scapula/shoulder
   c. Stage 3
      (1) Bacterial invasion of the GB wall
      (2) Localized peritonitis with rebound tenderness
      (3) Positive Murphy sign (see later)
      (4) Absolute neutrophilic leukocytosis
      (5) Attack subsides if the stone falls out of the cystic duct
         (a) Approximately 90% subside over the ensuing month
         (b) If not, the GB perforates (next stage)
   d. Stage 4
      (1) Perforation
      (2) Wall tension from GB distention compresses lumens of intramural vessels →
         gangrenous necrosis

3. Other causes of cholecystitis not associated with stones
   a. AIDS
      • Infection with cytomegalovirus (CMV) or *Cryptosporidium*
   b. Severe volume depletion

4. Clinical findings
   a. Fever
   b. See stages of acute cholecystitis
   c. Vomiting (75% of cases)
   d. Radiation of pain to the right scapula/shoulder
   e. Murphy sign
      • On deep palpation of the RUQ, there is pain when the inflamed GB hits the
        examiner’s finger on patient inspiration
   f. Jaundice (25% of cases)
      (1) Usually indicates a stone in the CBD
      (2) Indication for CBD exploration
   g. Palpable gallbladder (15% of cases)

5. Laboratory findings
   a. Absolute neutrophilic leukocytosis with left shift
      • WBC counts >12,000 cells/mm³ (>70% of cases)
   b. Increased serum AST/ALP (usually indicates stone in CBD)
   c. Increased serum amylase suggests associated pancreatitis
   d. Increased serum bilirubin >4 mg/dL usually indicates a stone in CBD

6. Tests to identify stones
   a. Ultrasound (US) is the preferred initial test (see Fig. 19-9E)
      (1) Gold standard test (>98% sensitivity)
      (2) Detects stones >12 mm in diameter
      (3) Detects sludge; evaluates GB wall thickness
      (4) Not effective in identifying CBD stones (<30% sensitivity)
   b. Plain film
      • Only 20% are radiopaque
c. Hepatobiliary iminodiacetic acid (HIDA) radionuclide scan
   (1) Identifies stone(s) in the cystic duct
   • No visualization of the GB
   (2) No tracer in the duodenum
   • Indicates a CBD stone

7. Indications for CBD exploration
   a. Jaundice
   b. CBD dilatation >12 mm
   c. No stones in the GB
   d. Acute pancreatitis

8. Treatment
   a. Cholecystectomy (laparoscope preferred)
   b. ERCP with sphincterotomy to extract the stone in the CBD
   c. Meperidine for pain
      (1) Do not use morphine
      (2) It contracts the sphincter of Oddi and worsens the pain
   d. Piperacillin-tazobactam

E. Chronic cholecystitis
   1. Epidemiology
      • Most common symptomatic disorder of the GB
   2. Pathogenesis
      a. Cholelithiasis with repeated attacks of minor inflammation
      b. Chemical inflammation (infection is uncommon)
   3. Clinical findings
      a. Severe, persistent pain 12 hours postprandially in the evening
      b. Pain radiates into the right scapular area.
      c. Recurrent epigastric distress, belching, and bloating
   4. Treated by laparoscopic cholecystectomy

F. Cholesterolosis
   1. Excess CH in bile
      a. CH deposits in macrophages
      b. Produces a yellow, speckled mucosal surface
   2. No clinical significance

G. Hydrops of the gallbladder
   1. Chronic obstruction of cystic duct
   2. Distended GB with atrophy of the mucosa/muscle
   3. Clear secretions
   4. Treated surgically

H. Gallbladder adenocarcinoma
   1. Epidemiology
      a. Dominant in elderly women
      b. Poor prognosis
   2. Pathogenesis
      a. Cholelithiasis (95% of cases)
      b. Porcelain gallbladder (see Fig. 19-9F)
         (1) Gallbladder with dystrophic calcification
         (2) Mandatory removal of GB
            (a) Approximately 50% risk for progression to cancer
            (b) Requires immediate surgical removal
   3. Treatment is surgery.
      a. Majority have already locally invaded liver or porta hepatitis at discovery.
      b. Five-year survival rate <2%.

X. Pancreatic Disorders
   A. Embryologic abnormalities of the pancreas
      1. Annular pancreas
         a. Dorsal and ventral buds form a ring around the duodenum.
         b. Defect is associated with small bowel obstruction.
      2. Aberrant pancreatic tissue (i.e., heterotopic rest, choristoma)
         • Locations—wall of stomach (most common), duodenum, jejunum, or Meckel diverticulum
3. Major pancreatic duct
   a. Major pancreatic duct and CBD are confluent in their terminal part.
   b. Important in the pathogenesis of acute pancreatitis (see Fig. 19-9D)
      (1) Stone(s) obstruct the terminal part of the CBD.
      (2) Increased back pressure causes bile to reflux into the major pancreatic duct.
      (3) Bile activates the pancreatic proenzymes, causing acute pancreatitis.

B. Acute pancreatitis
1. Epidemiology and pathogenesis
   a. Alcohol abuse and gallstones are the major causes.
   b. Must be activation of pancreatic proenzymes (inactive enzymes)
      • Activation leads to autodigestion of the pancreas.
   c. Mechanisms of activation of proenzymes
      (1) Obstruction of the main pancreatic duct or terminal CBD
         (a) Gallstones (see section IX and Fig. 19-9D)
         (b) Alcohol thickens ductal secretions.
            • Also increases duct permeability to the enzymes
      (2) Chemical injury of acinar cells
         • Examples—thiazides, alcohol, triglycerides (>1000 mg/dL)
      (3) Infectious injury of acinar cells
         • Examples—CMV, mumps, coxsackievirus
      (4) Mechanical injury of acinar cells
         • Examples—seat belt trauma, posterior penetration of duodenal ulcer
      (5) Metabolic activation of proenzymes (e.g., hypercalcemia, ischemia, shock)
   d. Trypsin is important in the activation of proenzymes.
      (1) Proteases damage acinar cell structure.
      (2) Lipases and phospholipases produce enzymatic fat necrosis.
      (3) Elastases damage vessel walls and induce hemorrhage (see Fig. 2-15H).
      (4) Activated enzymes also circulate in the blood.

2. Clinical findings
   a. Fever, nausea, and vomiting
   b. Severe, boring (knife-like) midepigastric pain with radiation into the back
      • Radiation to the back is due to its retroperitoneal location.
   c. Hypovolemic shock

3. Complications
   a. Pancreatic necrosis
      (1) Systemic signs occur earlier than usual.
      (2) Higher fever than usual; sinus tachycardia
      (3) Greater degree of neutrophilic leukocytosis
      (4) Peripancreatic infections occur in 40% to 70% of cases.

**Third space fluid** is sequestered fluid that is unavailable for maintaining volume in the vascular compartment (nonfunctional extracellular fluid). In acute pancreatitis, it refers to the peripancreatic collection of fluid that commonly occurs as the pancreas autodigests itself. If conditions improve, the third space fluid gains entry back into the vascular compartment and may cause fluid overload.
b. Pancreatic pseudocyst (20% of cases)
   (1) Collection of digested pancreatic tissue around the pancreas (example of third spacing)
   (2) Abdominal mass with persistence of serum amylase >10 days
      • Amount of amylase in the fluid surpasses the renal clearance of amylase.
   (3) Treatment
      (a) If <5 cm, observe and follow with CT scan.
         • Most resolve without surgical intervention.
      (b) If >5 cm, treat with CT- or US-guided percutaneous drainage.

c. Pancreatic abscess
   (1) Clinical and laboratory findings
      (a) Abdominal pain
      (b) High fever due to sepsis
         • Usually gram-negative infections such as *E. coli* or *Pseudomonas* spp.
      (c) Neutrophilic leukocytosis
      (d) Persistent hyperamylasemia
   (2) Diagnosis
      (a) CT scan shows multiple radiolucent bubbles in the retroperitoneum.
      (b) CT-guided aspiration of abscess identifies the organisms.
   (3) Treatment
      (a) Surgical drainage
      (b) Imipenem-cilastin

d. Pancreatic ascites
   (1) Usually caused by leaking of a pseudocyst
   (2) Peritoneal fluid has high amylase level.
   (3) Usually resolves spontaneously

4. Laboratory findings in acute pancreatitis
a. Serum amylase
   (1) Not specific for pancreatitis
   (2) Also present in salivary glands
      • Increased in mumps
   (3) Amylase in acute pancreatitis
      (a) Sensitivity 85%, specificity 70%
      (b) Initial increase occurs at 2 to 12 hours; peaks over 12 to 30 hours; returns to normal in 2 to 4 days
         • Increased renal clearance
      (c) Present in urine for 1 to 14 days
      (d) Persistent increase in serum amylase >7 days
         • Suggests pancreatic pseudocyst; collection of amylase-rich fluid around pancreas
      (e) Urine amylase
         • Initial increase occurs over 4 to 8 hours; peaks at 18 to 36 hours; returns to normal over 7 to 10 days
   (4) Amylase in chronic pancreatitis
      (a) Less reliable than in acute disease
      (b) Values either normal, borderline, or slightly increased

b. Serum lipase
   (1) More specific for pancreatitis
      • It is not excreted in urine.
   (2) Lipase in acute pancreatitis
      (a) Sensitivity 80%, specificity 75%
      (b) Initial increase occurs in 3 to 6 hours; peaks in 12 to 30 hours; returns to normal over 7 to 14 days
   (3) Lipase in chronic pancreatitis
      • Not clinically useful

c. Serum immunoreactive trypsin (SIT)
   (1) Trypsin is specific for the pancreas.
   (2) Excellent newborn screen for cystic fibrosis (CF; increased)
   (3) Serum immunoreactive trypsin in acute pancreatitis
      (a) Sensitivity 95% to 100%
      (b) Increases 5 to 10 times normal
      (c) Remains increased for 4 to 5 days

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- Persistent increase in serum amylase >10 days: consider pancreatic pseudocyst
- Pancreatic abscess: higher fever from gram-negative sepsis; ↑ amylase; CT shows bubbles
- Pancreatic ascites: leaking pseudocyst
- Amylase: not specific for pancreatitis; present in saliva
- Acute pancreatitis: ↑ clearance amylase in urine; reason why serum amylase normal in 2–4 days
- Chronic pancreatitis: serum amylase variable
- Serum lipase: more specific and lasts longer than amylase in acute pancreatitis; excellent screen for acute pancreatitis
- SIT: excellent newborn screen for CF
- MN SIT: excellent screen for Dx acute pancreatitis
(4) Serum immunoreactive trypsin in chronic pancreatitis
   • Decreased concentration
d. Decreased fecal elastase
   • Very sensitive/specific test for pancreatic exocrine dysfunction
e. Neutrophilic leukocytosis
f. Hypocalcemia, hyperglycemia (destruction of β-islet cells)
5. Imaging studies
   a. CT scan is the gold standard for pancreatic imaging.
b. Plain abdominal radiograph
   (1) Sentinel loop in subjacent duodenum or transverse colon (cut-off sign; see Fig. 19-91)
      • Localized ileus, where the bowel does not demonstrate peristalsis
   (2) Left-sided pleural effusion containing amylase (10% of cases)
6. Ranson criteria are used to determine prognosis in acute pancreatitis.

7. Treatment
   a. NPO until clinically improved
   b. Crystalloid solutions
c. Meperidine or fentanyl for pain
d. Nasogastric suction if vomiting severe
e. Oxygen

C. **Chronic pancreatitis**

1. Epidemiology
   a. Occurs in men more often than women
   b. Majority idiopathic
c. Known causes
   (1) Alcohol abuse is the most common known cause.
   (2) Cystic fibrosis is the most common cause in children.
   (3) Malnutrition is the most common cause in developing countries.
   (4) Autoimmune disorder may be the cause.
2. Pathogenesis
   a. Repeated attacks of acute pancreatitis produces duct obstruction.
   b. Calcified concretions occur as well as dilation of the ducts.
      • Radiographic dyes show a “chain of lakes” appearance in the major duct.
3. Clinical findings
   a. Severe pain radiating into the back
   b. Malabsorption
      • Indicates >90% exocrine function destroyed
c. Type 1 diabetes mellitus (70% of cases)
      • Brittle diabetes due to loss of insulin and glucagon
d. Pancreatic pseudocyst
4. Laboratory and radiographic findings
   a. Increased amylase and lipase (neither are reliable)
   b. Decreased serum immunoreactive trypsin
   c. Tests for pancreatic insufficiency
   (1) CT scan/plain film of pancreas shows dystrophic calcification (see Fig. 2-13).
      • Sign of chronic pancreatitis
   (2) Functional tests
      (a) Secretin stimulation test (requires instrumentation)
         • Tests ability of pancreas to secrete fluids and electrolytes
      (b) Bentiromide test
         • Tests ability of pancreatic chymotrypsin to cleave orally administered bentiromide to para-aminobenzoic acid (measured in urine)
5. Treatment
   a. Abstain from alcohol.
   b. Addiction is common.
      • Try simple analgescics or NSAIDs
   c. Pancreatic enzymes
   d. Fat-soluble vitamins
   e. Octreotide for pain if idiopathic

6. Approximately 50% of patients die within 10 years.

D. Exocrine pancreatic cancer

1. Epidemiology
   a. Slightly more common in men than women
   b. Usually occurs in seventh and eighth decades of life
   c. Adenocarcinoma with varying degrees of differentiation
   d. Causes
      (1) Smoking (most common cause)
         • Includes smokeless tobacco
      (2) Chronic pancreatitis
      (3) Hereditary pancreatitis
      (4) Diabetes mellitus
         • Particularly in women
      (5) High saturated fat diet; obesity; cirrhosis

2. Pathogenesis
   a. High association with KRAS gene mutation
   b. Mutation of suppressor genes (p16 and p53)

3. Location
   a. Most occur in the pancreatic head (65% of cases) (see Fig. 19-9)
      • Often blocks the CBD causing jaundice
   b. Remainder occur in the body and tail.

4. Clinical and laboratory findings
   a. Epigastric pain with weight loss (>90% of cases)
   b. Signs of CBD obstruction (carcinoma of head of pancreas)
      (1) Jaundice (>90% of cases; CB >50%)
      (2) Light-colored stools (absent UBG)
      (3) Palpable gallbladder (Courvoisier sign; 30% of cases)
   c. Superficial migratory thrombophlebitis (SMT; refer to Chapter 9)
   d. Metastasis to the left supraclavicular node (Virchow node)
      • Also occurs in stomach cancer
   e. Periumbilical metastasis (Sister Mary Joseph sign)
      • Also occurs in stomach cancer
   f. Increased CA19-9
      • Gold standard tumor marker

5. Diagnosis
   a. Helical CT scan is best test.
   b. Shows C sign in cancer of head of pancreas
      • Cancer indents duodenum; looks like the letter C
   c. CT-guided percutaneous biopsy for diagnosis

6. Treatment
   • Surgery (Whipple procedure), radiation, chemotherapy

**Whipple procedure** is an en bloc resection of the pancreatic head and neck (distal pancreas remains to prevent diabetes mellitus) and resection of part of the CBD. In some cases, there is resection of the antrum with vagotomy.

7. Five-year survival rate is 20%.
CHAPTER 20

Kidney Disorders

I. Renal Function Overview

A. Excretes harmful waste products
   - Examples—urea, creatinine, uric acid

B. Maintains acid-base homeostasis (refer to Chapter 5)
   - Controls the synthesis and excretion of bicarbonate and hydrogen ions

C. Reabsorbs essential substances
   - Examples—sodium, glucose, amino acids

D. Regulates water and sodium metabolism (refer to Chapter 5)
   1. Controls water by concentrating and diluting urine
   2. Controls sodium reabsorption in the proximal and distal and collecting tubules

E. Maintains vascular tone (refer to Chapter 5)
   1. Angiotensin II (ATII)
      a. Vasoconstricts peripheral resistance arterioles and efferent arterioles
      b. Stimulates the synthesis and release of aldosterone from the zona glomerulosa of the adrenal cortex (activates 18-hydroxylase)
      c. Increases reabsorption of sodium in the proximal tubule
   2. Renal-derived prostaglandin (PGE₂)
      • Vasodilates the afferent arterioles

F. Produces erythropoietin (refer to Chapter 12)
   - Synthesized in the renal cortex by interstitial cells in the peritubular capillary bed

G. Maintains calcium homeostasis (refer to Chapters 8 and 23)
   1. Second hydroxylation of vitamin D
      a. 1-α-Hydroxylase is synthesized in the proximal renal tubule cells.
         • Parathyroid hormone (PTH) is instrumental in the synthesis of the enzyme.
      b. Enzyme converts 25-hydroxycholecalciferol (synthesized in the liver) to 1,25-dihydroxycholecalciferol.
   2. Functions of vitamin D
      a. Increases small intestine reabsorption of calcium and phosphorus and renal reabsorption of calcium in the distal tubules
      b. Promotes bone mineralization and maintains the serum calcium level

   c. Increases monocyctic stem cells to become osteoclasts

II. Important Laboratory Findings in Renal Disease

A. Hematuria
   1. Upper urinary tract (UUT; kidneys, ureter) causes of hematuria include:
      a. Renal stone (most common)
b. Glomerulonephritis
   - Characterized by dysmorphic RBCs (damaged RBCs with an irregular membrane)
c. Renal cell carcinoma (RCC) and Wilms tumor
2. Lower urinary tract (LUT; bladder, urethra, prostate) causes of hematuria include:
   a. Infection (most common)
   b. Transitional cell carcinoma (TCC)
   - Most common noninfectious cause of hematuria
c. Benign prostatic hyperplasia (BPH)
   - Most common cause of microscopic hematuria in adult males
3. Drugs associated with hematuria include:
   a. Anticoagulants (warfarin, heparin)
   b. Cyclophosphamide
      (1) Hemorrhagic cystitis
      (2) Risk factor for TCC

B. Proteinuria
   1. General
      a. Definition—protein >150 mg/24 hours or >30 mg/dL (dipstick)
      b. Persistent proteinuria usually indicates renal disease.
      c. Qualitative tests include dipsticks and sulfosalicylic acid (SSA).
         (1) Dipsticks are specific for albumin.
         (2) SSA detects albumin and globulins.
      d. Quantitative test is a 24-hour urine collection.
   2. Types of proteinuria (Table 20-1)

III. Renal Function Tests
A. Serum blood urea nitrogen (BUN)
   1. Normal serum BUN is 7 to 18 mg/dL.
   2. Definition—end-product of amino acid (AA), pyrimidine, and ammonia metabolism
      a. Produced by the liver urea cycle
      b. Filtered in the kidneys
         (1) Urea is partly reabsorbed in the proximal tubule.
         (2) Amount reabsorbed is renal blood flow dependent.
            (a) If glomerular filtration rate (GFR) is decreased, more is reabsorbed.
            (b) If GFR is increased, less is reabsorbed.
      c. Extrarenal loss (e.g., skin, bowel) may occur with very high serum concentration.
      d. Serum levels depend on the following:
         (1) GFR
         (2) Protein content in the diet
         (3) Proximal tubule reabsorption
         (4) Functional status of the urea cycle
   3. Causes of increased and decreased serum BUN (Table 20-2)

<table>
<thead>
<tr>
<th>TABLE 20-1 Types of Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYPE</strong></td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Functional</td>
</tr>
<tr>
<td>Overflow</td>
</tr>
<tr>
<td>Glomerular</td>
</tr>
<tr>
<td>Tubular</td>
</tr>
<tr>
<td>BJ, Bence Jones; GBM, glomerular basement membrane; LMW, low molecular weight.</td>
</tr>
</tbody>
</table>

**Infection MCC LUT hematuria**
**TCC bladder: MC noninfectious cause of LUT hematuria**
**BPH: MCC microscopic hematuria in adult males**
**Anticoagulants: MC drugs causing hematuria**
**Persistent proteinuria: usually indicates intrinsic renal disease**
**Urea: end-product of AA, pyrimidine, ammonia metabolism**
**Urea produced in urea cycle in liver**
**Urea: proximal tubule reabsorption is renal blood flow dependent**
**Urea: some extrarenal loss (e.g., skin) with high serum concentration**
**CHF: MCC ↑ serum BUN**
GFR; ratio ↓

Prerenal azotemia: tubules reabsorbed in proximal

Urea: filtered; partly secreted

Azotemia: serum creatinine ↑

Creatinine supplements: creatine metabolism

Creatinine: end-product

Creatinine: filtered in kidney; not reabsorbed/secreted

Azotemia: serum BUN + creatinine

Urea: filtered; partly reabsorbed in proximal tubules

Creatine: bound phosphate in muscle for ATP synthesis.

Creatine: falsely increased with creatine supplements used by body builders.

Creatinine is filtered in the kidneys and not reabsorbed or secreted.

Serum creatinine • Excellent metabolite for renal clearance testing

Serum concentration varies with age and muscle mass.

Increased with age; decreased with muscle wasting

Increase in serum BUN and creatinine is called azotemia.

Causes of increased and decreased serum creatinine

Similar to those for serum BUN

B. Serum creatinine

1. Normal serum creatinine is 0.6 to 1.2 mg/dL.

2. Definition—metabolic end product of creatine in muscle

   a. Creatine binds phosphate in muscle for ATP synthesis.

   b. Creatine is falsely increased with creatine supplements used by body builders.

3. Creatinine is filtered in the kidneys and not reabsorbed or secreted.

   • Excellent metabolite for renal clearance testing

4. Serum concentration varies with age and muscle mass.

   • Increased with age; decreased with muscle wasting

5. Increase in serum BUN and creatinine is called azotemia.

6. Causes of increased and decreased serum creatinine

   • Similar to those for serum BUN

C. Serum BUN/creatinine (Cr) ratio

1. Using normal values, the normal ratio is 15 (Fig. 20-1A).

   a. Creatinine is filtered and is neither reabsorbed nor secreted.

   b. Urea is filtered and partly reabsorbed in the proximal tubule (earlier discussion).

   c. BUN/Cr ratio depends on changes in the following locations:

      (1) Before the kidneys (prerenal)

      (2) Within the kidney parenchyma (renal)

      (3) Past the kidneys (postrenal)

2. Prerenal, renal, and postrenal azotemia

   a. Definition—azotemia refers to an increase in serum BUN and creatinine

   b. Prerenal azotemia

      (1) Definition—azotemia caused by a decrease in cardiac output (CO)

         (a) Hypoperfusion of the kidneys decreases GFR.

         (b) There is no intrinsic renal parenchymal disease.

      (2) Examples—blood loss, congestive heart failure (CHF)

      (3) Serum BUN/Cr ratio >15 (see Fig. 20-1B)

         (a) Decreased GFR causes creatinine and urea to back up in the blood.

             • Ratio remains unchanged, because of a proportionate increase in urea and creatinine.

         (b) After filtration, proportionately more urea is reabsorbed back into the blood because of the decreased flow rate (P_a > P_b; refer to Chapter 5).

             • Recall that urea reabsorption is flow dependent.

             • All of the creatinine is excreted in the urine.

TABLE 20-2 Causes of Increased and Decreased Serum BUN

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Serum BUN</td>
<td>CHF, shock (e.g., hemorrhage)</td>
</tr>
<tr>
<td>Decreased cardiac output</td>
<td>GFR, ↓ Cardiac output → ↓GFR → ↑proximal tubule reabsorption of urea → ↑serum BUN</td>
</tr>
<tr>
<td>Increased protein intake</td>
<td>High-protein diet, blood in gastrointestinal tract</td>
</tr>
<tr>
<td>Increased tissue catabolism</td>
<td>Third-degree burns, postoperative state</td>
</tr>
<tr>
<td>Acute glomerulonephritis</td>
<td>Poststreptococcal glomerulonephritis</td>
</tr>
<tr>
<td>Acute or chronic renal failure</td>
<td>Acute tubular necrosis, diabetic glomerulopathy</td>
</tr>
<tr>
<td>Postrenal disease</td>
<td>Urinary tract obstruction (e.g., urinary stone, BPH)</td>
</tr>
</tbody>
</table>

| Decreased Serum BUN | Normal pregnancy, SIADH |
| Increased plasma volume | Plasma volume → ↑GFR → ↓serum BUN (less reabsorbed) |
| Decreased urea synthesis | Cirrhosis, Reye syndrome, fulminant liver failure |
| Decreased protein intake | Kwashiorkor (↑CHO is protein sparer; refer to Chapter 8), starvation gluconeogenesis in kidneys |

BUN, blood urea nitrogen; CHF, congestive heart failure; CHO, carbohydrate; GFR, glomerular filtration rate; SIADH, syndrome of inappropriate antidiuretic hormone.

BPH, Benign prostatic hyperplasia; TABLE 20-2, Causes of Increased and Decreased Serum BUN.
(c) The addition of proportionately more urea to blood increases the ratio to >15.

(d) Example—serum BUN 80 mg/dL, serum creatinine 4 mg/dL
  - BUN/Cr ratio is 20.

c. Renal azotemia (uremia)
   (1) Definition—azotemia caused by parenchymal damage to the kidneys
   (2) Examples—acute tubular necrosis (ATN), chronic renal failure (CRF)
   (3) Serum BUN/Cr ratio ≤15 (see Fig. 20-1C)
      (a) Decreased GFR causes creatinine and urea to back up in the blood, which leads to increased extrarenal loss of urea.
         - Ratio is already <15 because of extrarenal loss of urea (e.g., skin, bowel)
      (b) After filtration, both urea and creatinine are lost in the urine.
         - Proximal tubule cells are sloughed off in renal failure.
      (c) Serum BUN/Cr ratio remains ≤15.
      (d) Example—serum BUN 80 mg/dL, serum creatinine 8 mg/dL.
         - BUN/Cr ratio is 10.

d. Postrenal azotemia
   (1) Definition—azotemia caused by urinary tract obstruction past the kidneys
      - No intrinsic parenchymal disease, unless obstruction persists
   (2) Examples—BPH; blockage of the ureters by stones/cancer
   (3) Serum BUN/Cr ratio >15 (see Fig. 20-1D)
      (a) Obstruction to urine flow decreases the GFR.
      (b) Both urea and creatinine back up in the blood because of decreased GFR.
         - Proportionate increase at this point; ratio remains unchanged
      (c) Increased tubular pressure causes urea (not creatinine) to diffuse back into the blood.
         - Disproportionate increase in urea increases ratio to >15.
   (4) Persistent obstruction damages tubular epithelium causing renal azotemia (ratio ≤15).
D. Creatinine clearance (CCr)

1. Correlates with GFR

Elderly patients normally have a decrease in CCr. Therefore it is important to calculate the dose and dose interval for drugs that are nephrotoxic (e.g., aminoglycosides) to prevent precipitating ARF due to nephrotoxic ATN.

- Annual decrease in CCr of 1 mL/minute after age 50 years
- Useful in detecting renal dysfunction

2. Creatinine clearance (CCr) formula

   a. Measured CCr = UCr (mg/dL) × V (mL/min) ÷ PCr (mg/dL)

   (1) V = volume of a 24-hour urine collection in mL/minute, and UCr and PCr are the creatinine concentration of urine and plasma, respectively.

   (2) CCr results are dependent on an accurate 24-hour urine collection.

b. Normal adult CCr is 97 to 137 mL/minute.

   (1) In general, CCr <100 mL/minute is abnormal.

   (2) CCr <10 mL/minute indicates renal failure.

   (3) ↑ CCr is normal in pregnancy and early diabetic glomerulopathy.

3. Causes of increased and decreased CCr (Table 20-3)

**TABLE 20-3 Causes of Increased and Decreased Creatinine Clearance (CCr)**

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased CCr</strong></td>
<td></td>
</tr>
<tr>
<td>Normal pregnancy</td>
<td>Normal increase in plasma volume causes an increase in the GFR leading to an increase in CCr, highest at the end of the first trimester</td>
</tr>
<tr>
<td>Early diabetic glomerulopathy</td>
<td>Efferent arteriole becomes constricted due to hyaline arteriolosclerosis causing an increase in the GFR and CCr. Increased GFR damages the glomerulus (hyperfiltration injury).</td>
</tr>
<tr>
<td><strong>Decreased CCr</strong></td>
<td></td>
</tr>
<tr>
<td>Elderly people</td>
<td>GFR normally decreases with age causing a corresponding decrease in the CCr; danger when using nephrotoxic drugs; therefore the dose amount and interval must be adjusted accordingly for the person’s age and CCr</td>
</tr>
<tr>
<td>Acute and chronic renal disease</td>
<td>ARF due to acute tubular necrosis, CRF due to diabetic glomerulopathy, chronic pyelonephritis, renal amyloidosis</td>
</tr>
</tbody>
</table>

ARF, acute renal failure; CRF, chronic renal failure; GFR, glomerular filtration rate.

**TABLE 20-4 Urinalysis**

<table>
<thead>
<tr>
<th>COMPONENTS</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Examination</td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td>Dark yellow: concentrated urine, bilirubinuria, ↑ UBG, vitamins Red or pink: hematuria, hemoglobinuria, myoglobinuria, drugs (e.g., phenazopyridine, a urinary anesthetic), porphyrin Smoky-colored urine: acid pH urine converts Hb to hematin. Common finding in nephritic type of glomerulonephritis Black urine after exposure to light: alkaptonuria (AR disease with deficiency of homogentisate oxidase) with an increase in homogentisic acid in the urine, turns black when exposed to light</td>
</tr>
<tr>
<td>Clarity</td>
<td>Cloudy urine with alkaline pH: normal finding that is most often due to phosphates Cloudy urine with acid pH: normal finding that is most often due to uric acid Other causes: bacteria, WBCs, Hb, myoglobin also decrease clarity</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>Evaluates urine concentration and dilution Specific gravity &gt;1.023 (corresponds with a UOsm of 900 mOsm/kg) indicates urine concentration and excludes intrinsic renal disease Hypotonic urine has a specific gravity &lt;1.015 (corresponds with a UOsm of 220 mOsm/kg) UOsm is the best indicator of urine concentration/dilution Fixed specific gravity (1.008–1.010): correlates with lack of concentration and dilution (e.g., chronic renal failure)</td>
</tr>
</tbody>
</table>
### TABLE 20-4 Urinalysis—cont’d

<table>
<thead>
<tr>
<th>COMPONENTS</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical Dipsticks</strong></td>
<td></td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>Determined by diet and acid-base status of the patient; pure vegan usually has alkaline pH (citrate converted into bicarbonate); meat eater usually has acid pH (organic acids in meat); Alkaline pH + smell of ammonia: urease-producing pathogen (e.g., <em>Proteus</em>)</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>Detects albumin (not globulins); SSA: detects albumin and globulins (e.g., BJ protein); Albuminuria: reagent strip and SSA have the same results; BJ protein: SSA greater than reagent strip result because SSA is detecting the light chains, whereas the reagent strip is not; always confirm BJ protein with urine immunoelectrophoresis; Microalbuminuria dipsticks: more sensitive than standard dipstick; sensitive to 1.5–8 mg/dL; microalbuminuria is the first sign of diabetic nephropathy</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>Specific for glucose; will not detect fructose or other sugars; Detects urine glucose as low as 30 mg/dL; ↑Serum glucose + glucosuria: diabetes mellitus; Normal serum glucose + glucosuria: normal pregnancy (normally have a low renal threshold for glucose); benign glucosuria (low renal threshold for glucose)</td>
</tr>
<tr>
<td><strong>Ketones</strong></td>
<td>Detects acetone, acetoacetic acid (not β-OHB); nitroprusside in the test system only reacts with AcAc and acetone, not β-OHB; Ketonuria: DKA, starvation, ketogenic diets, pregnancy (normal finding), isopropyl alcohol poisoning</td>
</tr>
<tr>
<td>Bilirubin (refer to Chapter 19)</td>
<td>Detects conjugated (water-soluble) bilirubin; unconjugated bilirubin (lipid-soluble) is never present in urine; Bilirubinuria: viral hepatitis, obstructive jaundice</td>
</tr>
<tr>
<td>Urobilinogen (refer to Chapter 19)</td>
<td>Normal to have trace amounts (normal urine color is due to urobilin); Absent urine UBG, ↑Urine bilirubin: obstructive jaundice; ↑Urine UBG, absent urine bilirubin: extravascular hemolytic anemia (e.g., hereditary spherocytosis); ↑Urine UBG, ↑Urine bilirubin: hepatitis</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td>Detects RBCs, Hb, and myoglobin; Hematuria: e.g., renal stone; Hemoglobinuria: e.g., intravascular hemolytic anemia; Myoglobinuria: e.g., crush injuries; ↑Tserum creatine kinase</td>
</tr>
<tr>
<td><strong>Nitrites</strong></td>
<td>Detects nitrates produced by nitrate reducing uropathogens (e.g., <em>Escherichia coli</em>); test sensitivity and specificity is 30% and 90%, respectively; requires ~4 hr for nitrate-reducing uropathogens to convert nitrates to nitrites, and persons with a UTI have increased frequency of urination, which explains the tests poor sensitivity</td>
</tr>
<tr>
<td><strong>Leukocyte esterase</strong></td>
<td>Detects esterase in neutrophils (pyuria; ~80% sensitivity); Infections: urethritis, cystitis, pyelonephritis; Sterile pyuria (neutrophils present but negative standard urine culture): <em>Chlamydia trachomatis</em> urethritis, tuberculosis, drug-induced interstitial nephritis</td>
</tr>
<tr>
<td><strong>Sediment</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td>Bacteria: usually a sign of a UTI; Red blood cells (hematuria): renal stone, cancer (bladder, renal), glomerulonephritis; hematuria is ≥2–3 RBCs per HPF; Dysmorphic RBCs: indicates hematuria of glomerular origin (see Fig. 20-2A); sign of nephritic type of glomerulonephritis (inflammation damages RBCs); Neutrophils (pyuria; see Fig. 20-2B): UTI, sterile pyuria; pyuria refers to ≥10 WBCs/HPF in a centrifuged specimen or ≥5 WBCs/HPF in an uncentrifuged specimen; Oval fat bodies (see Fig. 20-2C): renal tubular cells with lipid (nephrotic syndrome)</td>
</tr>
<tr>
<td><strong>Casts</strong></td>
<td>Casts are formed in tubular lumens in the kidney and are composed of a protein matrix (Tamm-Horsfall protein) within which are entrapped cells, debris, or protein leaking through the glomeruli; their presence proves a renal origin of the disease; Hyaline cast (see Fig. 20-2D): acellular, ghost-like cast containing protein; no clinical significance in the absence of proteinuria; RBC cast (see Fig. 20-2E): nephritic type of glomerulonephritis (e.g., poststreptococcal glomerulonephritis); WBC cast (see Fig. 20-2F): acute pyelonephritis, acute tubulointerstitial nephritis; Renal tubular cell cast (see Fig. 20-2G): acute tubular necrosis; Fatty cast: contains lipid (e.g., cholesterol); sign of nephrotic syndrome (e.g., lipoid nephrosis); Waxy (broad) cast (see Fig. 20-2H): refractile, acellular cast; sign of chronic renal failure with tubular atrophy</td>
</tr>
<tr>
<td><strong>Crystals</strong></td>
<td>Calcium oxalate: pure vegan diet, ethylene glycol poisoning, calcium oxalate stone; Uric acid: hyperuricemia associated with gout or massive destruction of cells after chemotherapy; Triple phosphate: may be a sign of urinary tract infection due to urease producing uropathogens (e.g., <em>Proteus</em> spp.); Cystine: hexagonal crystal seen in cystinuria (inborn error of metabolism)</td>
</tr>
</tbody>
</table>

*AcAc*, Acetooacetic acid; *AR*, autosomal recessive; *BJ*, Bence Jones; *DKA*, diabetic ketoacidosis; *Hb*, hemoglobin; *HPF*, high-powered field; *β-OHB*, hydroxybutyric acid; *SSA*, sulfosalicylic acid; *UBG*, urobilinogen; *UTI*, urinary tract infection.
IV. Clinical Anatomy of the Kidney

A. Blood supply of the kidney

1. Renal cortex receives ~90% of the blood supply to the kidneys.
2. Renal medulla is relatively ischemic because blood supply is reduced (10% of blood supply to the kidneys).
3. Renal vessels are end arteries.
   a. There is no collateral circulation.
   b. Occlusion of any branch of a renal artery produces infarction (refer to Chapter 2).
4. Afferent arterioles
   a. Contain the juxtaglomerular (JG) apparatus
      • Produces the enzyme renin
b. Blood flow controlled by renal-derived PGE₂ (vasodilator)
c. Direct blood into the glomerular capillaries

5. Efferent arterioles
   a. Drain the glomerular capillaries
   b. Blood flow controlled by ATII (vasoconstrictor).
   c. Eventually become the peritubular capillaries

Nonsteroidal antiinflammatory drugs inhibit production of PGE₂; therefore intrarenal blood flow is controlled by the efferent arterioles, whose blood flow is maintained by ATII, a vasoconstrictor. This increases the risk of ischemic damage to the medulla.

B. Structure of the glomerulus (Fig. 20-3A and B)
   1. Glomerular capillaries contain fenestrated epithelium.
      • Holes in the endothelial surface are important in the filtration process.
   2. Glomerular basement membrane (GBM)
      a. Composed of type IV collagen
      b. Size and charge are the primary determinants of protein filtration.
         (1) Heparan sulfate produces the negative charge of the GBM.
         (2) Cationic proteins of low molecular weight (LMW) are permeable.
         (3) Albumin has a strong negative charge and is not permeable.
            (a) Loss of the negative charge causes loss of albumin in the urine.
            (b) Called selective proteinuria (e.g., minimal change disease)
         (4) GBM is permeable to water and LMW (<70,000 daltons) proteins (e.g., amino acids).
      c. Causes of GBM thickening
         (1) Deposition of immunocomplexes
            • Example—membranous glomerulopathy
         (2) Increased synthesis of type IV collagen
            • Example—diabetes mellitus (DM)
   3. Visceral epithelial cells (VEC)
      a. Primarily responsible for production of the GBM
      b. Contain podocytes (foot-like processes) and slit pores between the podocytes
         • Serve as a distal barrier for preventing protein loss in the urine
      c. Fusion of the podocytes is present in any cause of the nephrotic syndrome.
   4. Mesangial cells
      a. Support the glomerular capillaries
      b. Can release inflammatory mediators and proliferate in disease
         • Example—IgA glomerulopathy has mesangial immunocomplex deposits
   5. Parietal epithelial cells
      a. Lining cells of Bowman capsule
      b. Proliferation causes “crescents” that encroach upon and destroy the glomerulus.

V. Congenital Disorders and Cystic Diseases of the Kidneys
A. Horseshoe kidney
   1. Most common congenital kidney disorder
   2. Majority (90% of cases) are fused at the lower pole (Fig. 20-4A).
      • Kidney is trapped behind the root of the inferior mesenteric artery.
   3. Clinical findings
      a. Increased incidence with Turner syndrome
      b. Danger of infection and stone formation

B. Cystic diseases of the kidney (Table 20-5)

VI. Glomerular Diseases
A. Terminology of glomerular disease (Table 20-6)
   • Normal glomerulus (Fig. 20-5A)

B. Routine studies on biopsy specimens
   1. H&E (hematoxylin-eosin stain) and other special stains
      • Used to help classify the type of glomerular disease
   2. Immunofluorescence (IF) stain
      a. Identifies patterns and types of protein deposition
      b. Linear pattern (see Fig. 20-5B)
         (1) Characteristic finding in anti-GBM disease.
            • Example—Goodpasture syndrome

Granular pattern: IC type glomerulonephritis

- Antibodies line up against evenly distributed antigens in the GBM.
  - Antibodies are *not* detected by electron microscopy.

- Granular ("lumpy-bumpy") pattern (see **Fig. 20-5C**)
  - Usually indicates immunocomplex (IC) deposition in the glomerulus

3. Electron microscopy (EM)

  a. Detects submicroscopic defects in the glomerulus; examples include:
    - Fusion of podocytes in the nephrotic syndrome (see **Fig. 20-5D**)
    - Damage to visceral epithelial cells

EM: IC deposits are electron-dense
TABLE 20-5 Cystic Diseases of the Kidneys

<table>
<thead>
<tr>
<th>CYSTIC DISEASE</th>
<th>DISCUSSION</th>
</tr>
</thead>
</table>
| Renal dysplasia (see Fig. 20-4B)                                              | Most common cystic disease in children  
No inheritance pattern  
Abnormal development of one or both kidneys; abnormal structures persist in the kidneys (e.g., cartilage, immature collecting ductules)  
Present as an enlarged, irregular, cystic, unilateral (bilateral) flank mass in a newborn  
Bilateral dysplastic kidneys may lead to renal failure; accounts for ~20% of cases of CRF in children |
| Juvenile polycystic kidney disease (see Fig. 6-29A)                            | AR inheritance; mutation of PKHD1 gene, whose protein product codes for fibrocystin (modulates renal tubular formation by regulating polycystin-2 expression and function)  
Bilateral cystic disease; cysts in the cortex and medulla  
Cysts also occur in the liver  
Association with congenital hepatic fibrosis leading to portal hypertension  
Enlarged kidneys at birth; most serious types are incompatible with life  
Maternal oligohydramnios (decreased amniotic fluid); newborns have Potter facies, a deformation due to oligohydramnios—findings include low-set ears, parrot beak nose, and lung hypoplasia  
End-stage renal disease (>50% of cases) in first decade  
Renal transplantation is the only curative treatment. |
| Adult polycystic kidney disease (see Fig. 20-4C)                              | AD inheritance; defect on chromosome 16; mutation in PKD1 gene that encodes for polycystin (important in renal tubule development)  
Bilateral cystic disease develops by 20–25 years of age; bilaterally palpable kidneys; cysts involve all parts of the nephron in the cortex and medulla  
Cysts present in the liver (50% of cases), pancreas (10% of cases), spleen (5% of cases)  
Hypertension (>80% of cases); associated with stroke due to rupture of intracranial berry aneurysms (aneurysms in 10%–30% of cases), intracerebral hemorrhage, lacunar infarcts  
CRF begins at age 40–60 years, because of destruction of kidneys by slowly expanding cysts; accounts for ~10% of cases of CRF; CRF is the most common cause of death  
Other associations: sigmoid diverticulosis, hematuria, mitral valve prolapse, slight risk for developing renal cell carcinoma  
Treatment: renal transplantation |

(A to C from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, pp 211, 213, 212, respectively; Fig. 11-3, 11-11, 11-7, respectively.)
### TABLE 20-6 Nomenclature and Description of Glomerular Disorders

<table>
<thead>
<tr>
<th>TERM</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal glomerulonephritis</td>
<td>Only a few glomeruli are abnormal</td>
</tr>
<tr>
<td>Diffuse glomerulonephritis</td>
<td>All glomeruli are abnormal</td>
</tr>
<tr>
<td>Proliferative glomerulonephritis</td>
<td>&gt;100 nuclei in affected glomeruli</td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
<td>Thick GBM, no proliferative change</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>Thick GBM, hypercellular glomeruli</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>Fibrosis involving only a segment of the involved glomerulus</td>
</tr>
<tr>
<td>Crescentic glomerulonephritis</td>
<td>Proliferation of parietal epithelial cells around glomerulus</td>
</tr>
<tr>
<td>Primary glomerular disease</td>
<td>Involves only glomeruli and no other target organs (e.g., minimal change disease)</td>
</tr>
<tr>
<td>Secondary glomerular disease</td>
<td>Involves glomeruli and other target organs (e.g., SLE)</td>
</tr>
</tbody>
</table>

GBM, Glomerular basement membrane; SLE, systemic lupus erythematosus.

---

**GOODPASTURE SYNDROME**

- Antibodies against GBM
  - Immune complexes cause GBM damage
  - Cytokines cause GBM damage
  - Compromised GBM allows ICs to deposit
  - ICs activate complement
  - C5a attracts neutrophils

**ICs: MC mechanism causing glomerulonephritis**

- ICs activate the complement system
  - C5a produced 
    - Attracts neutrophils
    - Causes GBM damage

**C. MECHANISMS PRODUCING GLOMERULAR DISEASE**

1. Immune complexes (example of type III hypersensitivity)
   - a. Circulate and deposit in glomeruli or they develop in-situ.
     - Example—DNA–anti-DNA complexes in systemic lupus erythematosus (SLE)
   - b. Activate the complement system.
     - (1) Complement 5a (C5a) is produced, which is chemotactic to neutrophils.
     - (2) Neutrophils damage the glomeruli.
       - Damage to the glomeruli by neutrophils primarily occurs in nephritic types of glomerulonephritis (below).

2. Antibodies are directed against GBM antigens.
   - Example—Goodpasture syndrome

3. T-cell production of cytokines
   - a. Cytokines cause the GBM to lose its negative charge.
   - b. Cytokines damage podocytes causing them to fuse.
   - c. Example—Minimal change disease (lipoïd nephrosis) in the nephrotic syndrome

**D. CLINICAL MANIFESTATIONS OF GLOMERULAR DISEASES**

1. Nephritic syndrome
2. Nephrotic syndrome
3. Chronic glomerulonephritis
Kidney Disorders

20-5: A, Normal glomerulus. B, Linear immunofluorescence. The uninterrupted smooth immunofluorescence along the glomerular basement membrane is caused by deposition of IgG antibodies directed against the membrane (e.g., Goodpasture syndrome). C, Granular immunofluorescence. Granular irregular deposits in the capillaries are caused by immunocomplex deposition (e.g., poststreptococcal glomerulonephritis). D, Fusion of the podocytes. Arrows show fusion of the podocytes. The finding occurs in all glomerular diseases that present with the nephrotic syndrome (e.g., minimal change disease). E, Subendothelial immunocomplex deposits viewed with electron microscopy. The band of electron-dense material extends around the glomerular basement membrane and hugs the interface of the membrane with the capillary lumen. The arrow points to immune deposits directly beneath the nucleus of the endothelial cell. A thin rim of normal basement membrane (light gray) separates the deposits from the epithelial side of the membrane. The patient had diffuse proliferative glomerulonephritis due to systemic lupus erythematosus. F, Subepithelial immunocomplex deposits viewed with electron microscopy. Arrows point to electron-dense deposits directly beneath the visceral epithelial cells in a patient with poststreptococcal glomerulonephritis. The normal basement membrane has a light gray appearance. G, Poststreptococcal diffuse proliferative glomerulonephritis. The glomerulus is hypercellular because of an increase in neutrophils and mesangial cells. H, Crescentic glomerulonephritis. Arrows point to a proliferation of parietal epithelial cells in Bowman capsule, occupying approximately 50% of the entire urinary space. The cells encase and compress the glomerular tuft. I, Diffuse membranous glomerulopathy. The H&E (hematoxylin-eosin)–stained biopsy shows glomerular basement membranes that are uniformly thickened. There is no proliferative component. J, Diabetic glomerulosclerosis. Broken arrow points to an afferent or efferent arteriole that has hyaline arteriolosclerosis, with an increase in proteinaceous material in the wall of the vessel. Solid arrow shows a mesangial nodule containing type IV collagen and trapped protein. (A, F, and G from Damjanov I: Pathology for the Health-Related Professions, 2nd ed. Philadelphia, Saunders, 2000, pp 329, 341, 329, Figs. 13-5A, 13-8C, 13-5B, respectively; B and H from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed. Philadelphia, Saunders, 2004, pp 969, 977, Figs. 20-10E, 20-17, respectively; C, E, and J from Damjanov I, Linder J: Pathology: A Color Atlas. St. Louis, Mosby, 2000, pp 224, 229, Figs. 11-54, 11-64, respectively; D from Laszik ZG, Lajoie G, Nadasky T, Silva FG: Medical diseases of the kidney in Silverberg SG, Delellis RA, Frable WJ [eds]: Principles and Practice of Surgical Pathology and Cytopathology, 3rd ed. New York, Churchill Livingstone, 1997, p 2079; I from Kern WF, Silva FG, Laszik ZG, et al [eds]: Atlas of Renal Pathology. Philadelphia, Saunders, 1999, p 53, Fig. 5-30.)
E. Nephritic syndrome
1. Definition—glomerular injury is primarily due to neutrophils.
2. Clinical and laboratory findings
   a. Hypertension due to salt retention
   b. Periorbital puffiness due to salt retention in the loose skin in that area.
      (1) In some cases, edema is more generalized and produces pitting edema (refer to Chapter 5).
      (2) Sodium retention increases plasma hydrostatic pressure.
   c. Oliguria (~400 mL urine/day), due to decreased GFR from inflamed glomeruli
      • Tubular function intact
   d. Hematuria
      (1) Dysmorphic RBCs are present with irregular membranes (see Fig. 20-2A).
      (2) Glomeruli become inflamed from IC deposition causing damage to RBC membranes (dysmorphic RBCs).
   e. Neutrophils are present in the urine sediment (see Fig. 20-2B).
      • Particularly in IC types of nephritic glomerulonephritis
   f. RBC casts are a key finding (see Fig. 20-2E).
      • Occasionally, WBC casts are also present.
   g. Proteinuria is >150 mg/day, but <3.5 g/day.
   h. Azotemia is present with a BUN/Cr ratio >15.
      • Tubular function is intact in acute glomerulonephritis.
3. Primarily nephritic types of glomerular disease (Table 20-7)

F. Nephritic syndrome
1. Definition—glomerular injury is due to cytokines not neutrophils.
   a. Cytokines damage podocytes, causing them to fuse together.
   b. Cytokines destroy the negative charge of the GBM.
2. Clinical and laboratory findings
   a. Key finding is proteinuria >3.5 g/24 hours.
   b. Generalized pitting edema and ascites due to hypoalbuminemia cause a decrease in plasma oncotic pressure.
      (1) Pitting edema in nephritic syndrome is due to sodium retention causing an increase in plasma hydrostatic pressure.
      (2) Increased risk for developing spontaneous peritonitis due to Streptococcus pneumoniae or Escherichia coli (refer to Chapter 19).
   c. Hypertension in some types due to sodium retention
   d. Hypercoagulable state due to loss of antithrombin III (refer to Chapter 15)
      • Potential for renal vein thrombosis
   e. Hypercholesterolemia
      • Hypoalbuminemia increases synthesis of cholesterol (unknown mechanism).
   f. Hypogammaglobulinemia due to the loss of γ-globulins in the urine
   g. Fatty casts with Maltese crosses and oval fat bodies (see Fig. 20-2C)
      • Key finding of the nephrotic syndrome
3. Primarily nephritic types of glomerular disease (Table 20-8)

G. Systemic diseases with nephrotic syndrome
1. Diabetic glomerulopathy (nephropathy)
   a. Nodular glomerulosclerosis (Kimmelstiel-Wilson disease)
   b. Epidemiology
      (1) Glomerulopathy occurs in types 1 and 2 DM.
         • Occurs more often in type 1 (35%–45% of cases) than type 2 DM (20% of cases)
      (2) Most common cause of chronic renal failure in United States
         • Type 1 > type 2 DM
      (3) Risk factors
         (a) Poor glycemic control
         (b) Hypertension
         (c) Diabetic retinopathy
            • High correlation with coexisting glomerulopathy
   c. Pathogenesis
      (1) Nonenzymatic glycosylation (NEG) of the GBM and tubular basement membrane
         (refer to Chapter 23)
         (a) Glycosylation refers to glucose attaching to amino acids.
         (b) This increases vessel and tubular cell basement membrane permeability to proteins.
TABLE 20-7 Primarily Nephritic Types of Glomerular Disease

<table>
<thead>
<tr>
<th>GLOMERULAR DISEASE</th>
<th>CLINICOPATHOLOGIC FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA glomerulopathy (Berger disease)</td>
<td>Most common nephropathy; majority are nephritic (5% of cases are nephrotic) Affects children and adults; most common cause of chronic glomerulonephritis in children Increased mucosal synthesis and decreased clearance of IgA; increased serum IgA (50% of cases) Focal proliferative glomerulopathy Mesangial IgA IC deposits with granular IF; ICs activate the alternative complement pathway Overlapping features with HSP may occur Episodic bouts of hematuria (microscopic or gross) usually occur following an upper respiratory infection; hypertension is common Slow progression to CRF (40%–50% of cases) Treatment: corticosteroids decrease proteinuria; treat hypertension</td>
</tr>
<tr>
<td>Poststreptococcal glomerulonephritis (see Fig. 20-5C, F, and G)</td>
<td>Most common type of postinfectious GN Usually follows group A streptococcal infection of skin (e.g., scarlet fever) or pharynx Subepithelial IC deposits with granular IF; ICs activate the alternative complement pathway Hematuria 1–3 weeks following group A streptococcal infection by a nephritogenic strain (never produces acute rheumatic fever); periorbital edema (sodium retention); edema can occasionally be more extensive and produce pitting in dependent areas (e.g., ankles); hypertension is usually transient; however, in some cases it is severe Increased anti–DNAase B titers; ASO is degraded by oil in the skin and is not increased; streptozyme test is positive because it detects anti-DNAase B antibodies Usually resolves; CRF is uncommon in children but common in adults Treatment: supportive; penicillin G or V is given if cultures are positive for Streptococcus pyogenes; treat hypertension</td>
</tr>
<tr>
<td>Diffuse proliferative glomerulonephritis (SLE) (see Fig. 20-5C and E)</td>
<td>Diffuse proliferative GN is the most common subtype of glomerular disease in SLE; one other type has a nephrotic presentation Subendothelial IC deposits with granular IF; DNA–anti-DNA ICs activate the classical complement pathway “Wire looping” of capillaries corresponds with subendothelial ICs; neutrophil infiltration with hyaline thrombi in capillary lumens Kidneys are the major target organ in SLE (~90% of cases) Serum ANA test usually has rim pattern (refer to Chapter 4), corresponding to presence of anti-dsDNA antibodies Evolves into CRF in most cases; common cause of death in SLE Treatment: corticosteroids + cyclophosphamide</td>
</tr>
<tr>
<td>Rapidly progressive crescentic glomerulonephritis (see Fig. 20-5B and H)</td>
<td>Definition—clinical syndrome that may be a primary or secondary type of glomerular disease Rapid loss of renal function progresses to ARF over days to weeks; very poor prognosis May or may not be associated with crescent formation (crescentic GN; see Fig. 20-5H). Clinical associations: Goodpasture syndrome, microscopic polyarteritis (p-ANCA), Wegener granulomatosis (c-ANCA) Goodpasture syndrome: Male dominant disease: 80% HLA-DR2 positive Anti–basement membrane antibodies against collagen in glomerular and pulmonary capillaries Linear IF (see Fig. 20-5B); EM has no electron-dense deposits; crescentic GN (Goodpasture syndrome accounts for 5% of all cases) Begins with hemoptysis and ends with renal failure Treatment: plasma exchange; immunosuppressive therapy with corticosteroids and cyclophosphamide; renal transplantation</td>
</tr>
</tbody>
</table>

ANA, Antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ARF, acute renal failure; ASO, anti–streptolysin O; CRF, chronic renal failure; ds, double-stranded; EM, electron microscopy; GN, glomerulonephritis; HSP, Henoch-Schönlein purpura; IC, immunocomplex; IF, immunofluorescence; NAD, nicotinamide adenine dinucleotide; SLE, systemic lupus erythematosus.

(2) NEG of the afferent and efferent arterioles
   (a) Produces hyaline arteriolsclerosis (refer to Chapter 10)
   (b) NEG involves the efferent arterioles before the afferent arterioles.

(3) Osmotic damage to glomerular capillary endothelial cells (refer to Chapter 23)
   (a) Glucose is converted by aldose reductase into sorbitol.
   (b) Sorbitol is osmotically active, causing water to enter the cells and damage them.

(4) Hyperfiltration damage to the mesangium
   - Due to selective hyaline arteriolsclerosis of the efferent arterioles, which increases the GFR and damages the mesangial cells

(5) Diabetic microangiopathy
   - Definition—increased deposition of type IV collagen in the GBM, tubular cell basement membranes, and mesangium

Osmotic damage: ↑sorbitol
Hyaline arteriolsclerosis
efferent arteriole: ↑GFR producing hyperfiltration injury
Table 20-8 Primarily Nephrotic Types of Glomerular Disease

<table>
<thead>
<tr>
<th>GLOMERULAR DISEASE</th>
<th>CLINICOPATHOLOGIC FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change disease (lipoid nephrosis) (see Fig. 20-5D)</td>
<td>Most common cause of nephrotic syndrome in children; more common in girls than boys; occurs in ~15% of adults with nephrotic syndrome. T-cell cytokines cause the GBM to lose its negative charge; selective proteinuria (albumin not globulins). Secondary causes: Hodgkin lymphoma. Structurally normal glomeruli; positive fat stains in glomerulus and tubules. Negative IF; EM shows fusion of podocytes and no electron-dense deposits. Often preceded by an upper respiratory infection or routine immunization. Usually normotensive (90% of cases), unlike other types of nephrotic syndrome. Treatment: children respond well to steroid therapy; CRF is rare.</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>Primary or secondary disease; secondary causes—HIV (most common glomerular disease; mainly in young black males) and intravenous heroin abuse. Most common cause of nephrotic syndrome in adults. Negative IF; EM shows focal damage of VECs. Nonselective proteinuria, microscopic hematuria (60%–80%). Hypertension early (20%). Poor prognosis; commonly progresses to CRF. Treatment: corticosteroids (only 15%–20% response).</td>
</tr>
<tr>
<td>Diffuse membranous glomerulopathy (see Fig. 20-5I)</td>
<td>Second most common cause of nephrotic syndrome in adults. Highest incidence of renal vein thrombosis and deep vein thrombosis with pulmonary embolism most likely due to loss of antithrombin III in the urine. Primary and secondary types; secondary causes: Drugs: e.g., captopril, gold therapy. Infections: HBV, Plasmodium malariae, syphilis. Malignancy: carcinomas, Hodgkin lymphoma. Autoimmune disease: SLE (nephrotic presentation). Diffuse thickening of membranes; silver stains show “spike and dome” pattern beneath VECs (subepithelial deposits). Subepithelial ICs with granular IF. Treatment: corticosteroids may slow progression.</td>
</tr>
<tr>
<td>Type I MPGN</td>
<td>Most common type of MPGN; nephrotic presentation (60% of cases); some cases have a nephritic presentation. Associations: HBV, HCV (more common), cryoglobulinemia. Subendothelial ICs with granular IF; ICs activate the classical and alternative complement pathways; EM shows tram tracks caused by splitting of the GBM by an ingrowth of mesangium. Hypertension (35% of cases); majority have hematuria. Majority progress to CRF. Treatment: response to corticosteroids not established.</td>
</tr>
<tr>
<td>Type II MPGN</td>
<td>Associated with the C₃ nephritic factor (C₃NeF), an autoantibody that binds to C₃ convertase (C₃bBb); autoantibody prevents degradation of C₃ convertase, causing sustained activation of C₃ resulting in very low C₃ levels. Diffuse intramembranous deposits (“dense deposit disease”); EM shows tram tracks. Hypertension (35% of cases); majority have hematuria. Majority progress to CRF. Treatment: response to corticosteroids not established.</td>
</tr>
</tbody>
</table>

CRF, Chronic renal failure; EM, electron microscopy; GBM, glomerular basement membrane; HBV, hepatitis B virus; HCV, hepatitis C virus; ICs, immunocomplexes; IF, immunofluorescence; MPGN, memranoproliferative glomerulonephritis; SLE, systemic lupus erythematosus; VECs, visceral epithelial cells.

**Microangiopathy:**
- deposition of type IV collagen

**Microalbuminuria:**
- first lab sign of diabetic glomerulopathy

- a. Nonspecific IF
- b. EM shows fusion of podocytes (see Fig. 20-5D)
- c. Microscopic findings (see Fig. 20-5I)
  1. Afferent and efferent hyaline arteriolosclerosis
  2. Nodular masses develop in the mesangial matrix.
  - Nodules due to increased type IV collagen synthesis and trapped proteins
- d. Clinical and laboratory findings
  1. Microalbuminuria
    - (a) Initial laboratory manifestation of diabetic glomerulopathy
    - Usually begins after ~10 years of poor glycemic control
    - (b) Microalbuminuria dipsticks detect albumin levels in the range of 1.5 to 8 mg/dL.
An **angiotensin-converting enzyme (ACE) inhibitor** is prescribed when microalbuminuria is first detected. It slows the progression of diabetic glomerulopathy and retinopathy in both types of diabetes mellitus. One possible mechanism is by reducing pressure in the glomerular capillaries by decreasing ATII vasoconstriction of the hyalinized efferent arterioles. Angiotensin receptor blockers are also useful, particularly in type 2 diabetes mellitus. These changes are independent of diabetes mellitus. One possible mechanism is by reducing pressure in the glomerular capillaries by decreasing ATII vasoconstriction of the hyalinized efferent arterioles. Angiotensin receptor blockers are also useful, particularly in type 2 diabetes mellitus. These changes are independent of the abilities of both drugs to lower blood pressure.

(2) Other renal diseases associated with DM
- Renal papillary necrosis, acute and chronic pyelonephritis

2. Renal amyloidosis (refer to Chapter 4, Fig. 4-19A to C)
- Associated with primary and secondary amyloidosis

H. **Hereditary glomerular diseases**

1. Alport syndrome
   a. X-linked recessive (most common) and autosomal dominant/recessive types
   b. EM/monoclonal antibody studies to detect GBM defects are useful in confirming the diagnosis.
   c. Hypertension, gross/microscopic hematuria, RBC casts are common.
   d. Sensorineural hearing loss and ocular findings
   e. End-stage renal disease is more common in men than women.

2. Thin basement membrane disease (“benign familial hematuria”)
   a. Autosomal dominant disorder
   b. Extremely thin GBMs
   c. Normal renal function
   d. Mild proteinuria with persistent microscopic hematuria

I. **Chronic glomerulonephritis**

1. Causes in descending order of incidence:
   a. Rapidly progressive glomerulonephritis (RPGN)
   b. Focal segmental glomerulosclerosis (FSG)
   c. Type I membranoproliferative glomerulonephritis
   d. Membranous glomerulopathy
   e. Type IV diffuse proliferative glomerulonephritis in SLE
   f. IgA glomerulopathy

2. Gross and microscopic findings
   a. Shrunken kidneys
   b. Glomerular sclerosis and tubular atrophy

VII. **Disorders Affecting Tubules and Interstitium**

A. **Acute tubular necrosis (ATN)**

1. Epidemiology
   a. Greater than 10% of intensive care unit patients develop acute renal failure (ARF).
   b. Greater than 40% of hospital ARF is iatrogenic (doctor-induced).
   c. Hemolytic uremic syndrome (HUS) is the most common cause of intrinsic ARF in the United States (refer to Chapter 15)
   d. ARF occurs in 20% of patients with sepsis.
   e. ARF develops in >50% of patients with septic shock.
   f. ARF
      (1) Definition—acute suppression of renal function developing in 24 hours
      (2) Accompanied by anuria or oliguria (~400 mL/24 hours)
      (3) ATN is the most common cause of ARF.
         • Subdivided into ischemic and nephrotoxic types
   g. Other causes of ARF
      (1) Postrenal obstruction
         • Examples—BPH, invasive cervical cancer
      (2) Vascular disease
         • Example—malignant hypertension
      (3) RPGN, drugs, disseminated intravascular coagulation (DIC), urate nephropathy

2. Ischemic ATN
   a. Most often caused by prerenal azotemia due to hypovolemia
   b. Ischemia damages endothelial cells.
      (1) Causes decrease in vasodilators (nitric oxide, PGIL₂)
      (2) Increase in vasoconstrictors (endothelin)
      (3) Net effect is vasoconstriction of afferent arterioles, which decreases GFR.
c. Ischemia damages tubule cells
   (1) Causes detachment of tubular cells into the lumen causing obstruction
      (Fig. 20-6A)
      (a) Produces pigmented renal tubular cell casts (see Fig. 20-2G)
      (b) Coagulation necrosis of renal tubular cells
   (2) Casts obstruct the lumen, causing an increase in intratubular pressure.
      (a) Decreases GFR
      (b) Pushes fluid into the interstitium
      (c) Net effect is oliguria.

d. Sites of tubular damage
   (1) Straight segment of proximal tubule
      • Part of the nephron most susceptible to hypoxia (refer to Chapter 2)
   (2) Medullary segment of the thick ascending limb (TAL; refer to Chapter 2)
      • Location of the Na⁺-K⁺-2Cl⁻ cotransporter
   (3) Tubular basement membranes are disrupted at these sites.
      • Interferes with renal tubular cell regeneration

3. Nephrotoxic type
   a. Causes
      (1) Aminoglycosides most common cause (e.g., gentamicin)
      (2) Radiocontrast agents
      (3) Heavy metals (e.g., lead, mercury)
b. Microscopic findings
   (1) Primarily damages the proximal tubule cells
   (2) Tubular basement membrane is intact.
   • This allows renal tubular cells to regenerate properly
4. Clinical and laboratory findings
   a. Oliguria, in most cases (~400 mL/24 hours)
      • Some cases have polyuria (~800 mL/24 hours).
   b. Pigmented renal tubular cell casts (see Fig. 20-2G)
   c. Hyperkalemia, increased anion gap (AG) metabolic acidosis (refer to Chapter 5)
   d. Increased serum BUN and creatinine (ratio ≤15)
   e. Hypokalemia (diuresis phase) and infection are common problems
5. Treatment
   a. Treat prerenal azotemia
      (1) Volume expansion if hypovolemic
      (2) Increase renal blood flow
   b. Low dose dopamine (increases renal blood flow)
   c. Fenoldopam (dopamine α1-receptor agonist)
   d. Dialysis
6. Differential diagnosis of oliguria (Box 20-1)

B. Tubulointerstitial nephritis (TIN)
1. Epidemiology
   a. Definition—acute or chronic inflammation of tubules and interstitium
   b. Causes
      (1) Acute pyelonephritis (APN; most common)
      (2) Drugs

**BOX 20-1 Differential Diagnosis of Oliguria**

Oliguria is defined as a urine output <400 mL/day or <20 mL/hour. The major causes of oliguria include prerenal azotemia (most common cause), acute glomerulonephritis (nephritic type), acute tubular necrosis (renal azotemia), and postrenal azotemia. Laboratory tests that are commonly used in differentiating the types of oliguria include urine osmolality (UOsm), fractional excretion of sodium (FENa\(^+\)), random urine sodium (UNa\(^+\)), and the serum BUN/Cr (blood urea nitrogen/creatinine) ratio (see section III). These tests evaluate tubular function. A UOsm >500 mOsm/kg indicates good concentrating ability and intact tubular function, but a UOsm <350 mOsm/kg indicates poor concentrating ability and tubular dysfunction. The FENa\(^+\) represents the amount of sodium excreted in the urine divided by the amount of sodium that is filtered by the kidneys. The calculation is as follows:

\[
\text{FENa}^+ = \frac{(\text{UNa}^+ \times \text{PCr}) - (\text{PNa}^+ \times \text{UCr})}{\text{Cr}} \times 100
\]

where UNa\(^+\) is a random urine sodium, PNa\(^+\) is serum sodium, UCr is random urine creatinine, and PCr is plasma creatinine. Creatinine is used in the formula, because the amount of sodium filtered is dependent on the glomerular filtration rate (GFR), which closely approximates the creatinine clearance (CCr). An FENa\(^+\) <1% good tubular function and excludes acute tubular necrosis (ATN) as a cause of oliguria. An FENa\(^+\) >2% indicates tubular dysfunction and is highly predictive of ATN as the cause of oliguria. A random UNa\(^+\) <20 mEq/L indicates intact tubular function, while a random UNa\(^+\) >40 mEq/L indicates tubular dysfunction. A serum BUN/Cr ratio >15 indicates intact tubular function, but a serum BUN/Cr ratio ≤15 indicates tubular dysfunction. In prerenal azotemia and acute glomerulonephritis (nephritic type), tubular function is preserved. In order to distinguish the two, the urine sediment examination is most useful. In prerenal azotemia, the urine sediment has no abnormal findings or may have a few hyaline casts. The sediment in acute glomerulonephritis (nephritic type) has hematuria and RBC casts. ATN and postrenal azotemia (long-standing obstruction) both have tubular dysfunction. Postrenal azotemia of short duration has normal tubular function and has laboratory findings similar to prerenal azotemia. In order to distinguish ATN from postrenal azotemia as a cause of tubular dysfunction and oliguria, the urine sediment is most useful. In ATN, the sediment has pigmented renal tubular cell casts, but in postrenal azotemia, the sediment is usually normal. In addition, the patient will likely have a history of a renal stone, benign prostatic hyperplasia, or cervical cancer, which commonly obstructs the ureters where they enter the urinary bladder.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>FENa(^+) %</th>
<th>BUN/Cr</th>
<th>UNa(^+)</th>
<th>UOsm</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal azotemia</td>
<td>&lt;1</td>
<td>&gt;15</td>
<td>&lt;20</td>
<td>&gt;500</td>
<td>Normal sediment or hyaline casts</td>
</tr>
<tr>
<td>Acute glomerulonephritis</td>
<td>&lt;1</td>
<td>&gt;15</td>
<td>&lt;20</td>
<td>&gt;500</td>
<td>RBC casts, hematuria</td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>&gt;2</td>
<td>≤15</td>
<td>&gt;40</td>
<td>&lt;350</td>
<td>Renal tubular cell casts</td>
</tr>
<tr>
<td>Postrenal azotemia (prolonged obstruction)</td>
<td>&gt;2</td>
<td>≤15</td>
<td>&gt;40</td>
<td>&lt;350</td>
<td>Normal sediment</td>
</tr>
</tbody>
</table>
2. Acute pyelonephritis
   a. Epidemiology
      (1) More common in women than men
         • Women have a short urethra (subject to ascending infection).
      (2) *Escherichia coli* most common cause
         • *Enterococcus* second in frequency
   b. Pathogenesis
      (1) Vesicoureteral reflux (VUR) with ascending infection (most common)
         (a) Intravesical portion of the ureter is normally compressed with micturition
            (see Fig. 20-6B, left).
            • This prevents reflux of urine into the ureter(s).
         (b) In VUR, the intravesical portion of the ureter is *not* compressed during micturition (see Fig. 20-6B, right).
            • Urine refluxes into the ureter(s).
         (c) VUR is corrected by reimplantation of the ureters/stents.
      (2) Ascending infection
         (a) Most common mechanism for lower and upper urinary tract infections (UTIs) in females
         (b) Distal urethra and vaginal introitus are normally colonized by *E. coli*.
         (c) Organisms ascend into the urethra and bladder.
            • Causes urethritis and cystitis
         (d) If VUR is present, infected urine ascends to the renal pelvis and renal parenchyma.
            • Causes APN
      (3) Hematogenous spread to kidneys
         (a) Uncommon cause of APN
         (b) Suspect hematogenous spread if *Staphylococcus aureus* is cultured in urine.
   c. Gross and microscopic findings
      (1) Grayish-white areas of abscess formation are in the cortex and medulla.
      (2) Microabscess formation occurs in the tubular lumens and interstitium
         (see Fig. 20-6C).
   d. Clinical findings
      (1) Spiking fever, flank pain
      (2) Increased frequency of urination
      (3) Painful urination (dysuria)
   e. Laboratory findings
      (1) WBC casts (key finding; see Fig. 20-2F)
      (2) Pyuria, bacteriuria (usually *E. coli*)
      (3) Hematuria
   f. Complications
      (1) Chronic pyelonephritis
      (2) Perinephric abscess
      (3) Renal papillary necrosis
      (4) Septicemia with endotoxic shock
   g. Treatment
      (1) Ciprofloxacin given orally if uncomplicated
      (2) Ciprofloxacin IV if hospitalized
      (3) Repair VUR
   3. Chronic pyelonephritis (CPN)
      a. Pathogenesis
         (1) VUR starting in young girls
         (2) Lower urinary tract obstruction
            (a) Produces hydronephrosis
            (b) Examples—BPH, renal stones
b. Gross and microscopic findings
   (1) Reflux type of CPN
      (a) U-shaped cortical scars (see Fig. 20-6D) overlying a blunt calyx
      (b) Visible with an intravenous pyelogram (IVP)
   (2) Obstructive type of CPN
      (a) Uniform dilation of the calyces
      (b) Diffuse thinning of cortical tissue
   (3) Microscopic findings
      (a) Chronic inflammation
      (b) Tubular atrophy
      (c) Secondary scarring of the glomeruli
      (d) Tubules contain eosinophilic material resembling thyroid tissue
      (“thyroidization”).

c. Clinical and laboratory findings
   (1) Usually a history of recurrent APN
   (2) May cause hypertension
      • Reflux nephropathy is a cause of hypertension in children.
   (3) May cause CRF

4. Acute drug-induced TIN
   a. Common drug associations
      (1) Penicillin, particularly methicillin
      (2) Rifampin, sulfonamides
      (3) Nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics
   b. Pathogenesis
      (1) Combination of type I and type IV hypersensitivity
      (2) Occurs ~2 weeks after beginning a drug
   c. Clinical and laboratory findings
      (1) Abrupt onset of fever, oliguria, and rash
         • Withdrawal of the drug reverses the disease.
      (2) Laboratory findings
         (a) BUN/Cr ratio ≤15
         (b) Eosinophilia and eosinophiluria (highly predictive)
   d. Treatment is to withdraw the drug.

5. Analgesic nephropathy
   a. Epidemiology
      (1) Common cause of chronic drug-induced TIN
      (2) More common in women than men
      (3) Usually occurs in persons with chronic pain
   b. Pathogenesis
      (1) Chronic use of acetylsalicylic acid for 3 or more years
      (2) Acetaminophen free radicals damage renal tubules in medulla (refer to Chapter 2).
      (3) Aspirin inhibits renal synthesis of PGE₂ leaving ATII unopposed.
         • This decreases blood flow to the renal medulla.
   c. Complications
      (1) Renal papillary necrosis (see Fig. 20-6E)
         (a) Sloughing of renal papillae
            • Produces gross hematuria, proteinuria, and flank pain
         (b) An IVP shows a “ring defect” where one or more papillae used to reside.
         (c) Other causes of renal papillary necrosis include:
            • Diabetes mellitus, sickle cell trait/disease, APN
      (2) Hypertension, CRF
      (3) Renal pelvic and bladder transitional cell carcinomas

6. Urate nephropathy
   a. Definition—deposition of urate crystals in the tubules and interstitium
   b. Causes
      (1) Massive release of purines (precursor of uric acid)
         • Usually occur after aggressive treatment of disseminated cancer (e.g., leukemia, lymphoma)
      (2) Lead poisoning, gout
   c. May produce ARF
Patients with disseminated cancers should receive allopurinol, a xanthine oxidase inhibitor, before being treated with chemotherapy. This prevents urate nephropathy (tumor lysis syndrome) and acute renal failure.

VIII. Chronic Renal Failure (CRF)

A. Epidemiology and pathology

1. Definition—progressive irreversible azotemia that develops over months to years

2. Culminates in end-stage renal disease
   a. Kidneys no longer function well enough to sustain life.
   b. GFR <10 mL/min

3. Causes
   a. Diabetes mellitus (most common)
   b. Hypertension
   c. Chronic glomerulonephritis
      • Particularly due to RPGN and FSG
   d. Cystic renal disease
      • Renal dysplasia in children, adult polycystic kidney disease

4. Gross appearance
   • Bilateral, small shrunken kidneys

B. Clinical findings

1. Hematologic findings
   a. Normocytic anemia with corrected reticulocyte count <3% (refer to Chapter 12)
      • Primarily due to decreased erythropoietin (EPO)
   b. Qualitative platelet defects that are corrected with dialysis (refer to Chapter 15)

2. Renal osteodystrophy
   a. Osteitis fibrosa cystica
      (1) Secondary to hypovitaminosis D (loss of 1-α-hydroxylase in proximal renal tubules; refer to Chapter 8)
      • Hypovitaminosis D produces hypocalcemia, which stimulates production of parathyroid hormone (PTH) and leads to secondary hyperparathyroidism (HPTH) (refer to Chapter 23).
      (2) Secondary HPTH increases bone resorption, causing cystic lesions in bone (e.g., jaw),
         • Hemorrhage into cysts causes a brown discoloration.
   b. Osteomalacia
      (1) Definition—decreased mineralization of the organic bone matrix (osteoid) (refer to Chapter 24)
      (2) In CRF, it is due to hypovitaminosis D producing hypocalcemia, leading to decreased bone mineralization.
      (3) Soft bone (increased osteoid) produces fractures and bone pain.
c. Osteoporosis (refer to Chapter 24)
   (1) Definition—loss of osteoid and mineralized bone
      • Causes an overall reduction in bone mass
   (2) In CRF, it is due to chronic metabolic acidosis.
      • Excess H+ ions are buffered by bone.
   (3) Soft bone causes fractures and bone pain.
3. Cardiovascular findings
   a. Hypertension (HTN) from salt retention
   b. Hemorrhagic fibrinous pericarditis
   c. Congestive heart failure, accelerated atherosclerosis
4. Miscellaneous clinical findings
   a. Hemorrhagic gastritis
   b. Uremic frost (urea crystals deposit on skin)

C. Laboratory findings
1. Acid-base and electrolyte abnormalities
   a. Hyperkalemia and increased AG metabolic acidosis (refer to Chapter 5)
   b. Sodium is usually normal except in salt-losing types of CRF
2. Hypocalcemia; causes include:
   a. Hypovitaminosis D, due to decreased synthesis of 1-α-hydroxylase in proximal tubule cells, leading to decreased reabsorption of calcium from the small intestine
   b. Hyperphosphatemia, due to decreased renal excretion of phosphorus
      • Excess phosphorus drives calcium into bone and soft tissue (metastatic calcification; refer to Chapter 2).
3. Normocytic anemia, due to decreased synthesis of EPO (refer to Chapter 12)
4. Prolonged bleeding time, due to defects in platelet aggregation (refer to Chapter 15)
5. Increased serum cystatin C
   a. It is a cysteine protease inhibitor that is produced by all nucleated cells.
   b. It is filtered by the glomerulus but is not secreted.
   c. The level is less dependent on age, sex, race, and muscle mass than creatinine.
   d. Serum value >1.3 mg/L has an 88% sensitivity and 96% specificity for detecting renal dysfunction.
6. Urinalysis findings
   a. Fixed specific gravity
      (1) Tubular dysfunction causes lack of concentration and dilution.
      (2) Free water clearance is zero (refer to Chapter 5).
   b. Waxy/broad casts (see Fig. 20-2H)

D. Treatment
1. Nonpharmacologic
   a. Restrict sodium
   b. Low-protein diet (refer to Chapter 8)
   c. Adjust drug doses to the renal clearance
   d. Kidney transplantation
2. General treatment
   a. ACE inhibitors
      • Reduce proteinuria and disease progression and also treats hypertension
   b. Dialysis
   c. Erythropoiesis-stimulating agents
   d. Calcium supplementation and vitamin D (calcitriol)
      • Treat renal osteodystrophy
   e. Phosphate binder (e.g., sevelamer)

IX. Vascular Diseases of the Kidney
A. Benign nephrosclerosis (BNS)
1. Most common renal disease in essential hypertension
2. Pathogenesis
   a. Hyaline arteriolosclerosis of arterioles in the renal cortex
   b. Causes tubular atrophy, interstitial fibrosis, and glomerular sclerosis
3. Small kidneys with a finely granular cortical surface (Fig. 20-7A)
4. Laboratory findings
   a. Mild proteinuria
   b. Hematuria (no RBC casts)
   c. Renal azotemia
B. Malignant hypertension

1. Epidemiology
   a. Sudden onset of accelerated hypertension may occur:
      (1) In normotensive individuals
      (2) In those with BNS (most common)
      (3) As a complication of various disorders (e.g., systemic sclerosis)
   b. Risk factors
      (1) Preexisting BNS (most common)
      (2) Hemolytic-uremic syndrome (refer to Chapter 15)
      (3) Thrombotic thrombocytopenic purpura (refer to Chapter 15)
      (4) Systemic sclerosis (refer to Chapter 4)

2. Pathogenesis
   a. Vascular damage to arterioles and small arteries
   b. Gross and microscopic changes
      (1) Fibrinoid necrosis and necrotizing arteriolitis and glomerulitis
         - Manifested by pinpoint hemorrhages on the cortical surface ("flea-bitten" kidneys) of both kidneys
      (2) Hyperplastic arteriolosclerosis ("onion skin" lesion; refer to Chapter 19)
         (see Fig. 20-7B)
         - Smooth muscle hyperplasia and reduplication of basement membrane

3. Clinical findings
   a. Rapid increase in blood pressure to ≥210/120 mm Hg
   b. Hypertensive encephalopathy
      (1) Cerebral edema
      (2) Papilledema
      - Loss of the normal optic nerve disk margin
      (3) Retinopathy
      - Flame hemorrhages, exudates
      (4) Potential for an intracerebral bleed
   c. Oliguric acute renal failure

4. Laboratory findings
   a. Azotemia with BUN/Cr ratios ≤15
   b. Hematuria with RBC casts
   c. Proteinuria

5. Initial treatment is intravenous sodium nitroprusside.

C. Renal infarction

1. Causes
   a. Embolization from thrombi in the left side of the heart (most common)
   b. Atheroembolic renal disease
   c. Vasculitis, particularly polyarteritis nodosa

2. Gross and microscopic appearance
   a. Irregular, wedge-shaped pale infarctions occur in the cortex.
   b. Old infarcts have a V-shaped appearance due to scar tissue.

3. Sudden onset of flank pain and hematuria
D. Sickle cell nephropathy
   1. Occurs with sickle cell trait or disease
   2. Clinical presentations
      a. Asymptomatic hematuria (most common) (refer to Chapter 12)
         • Due to infarctions in the renal medulla
      b. Loss of concentrating ability
      c. Renal papillary necrosis, pyelonephritis
E. Diffuse cortical necrosis
   1. Complication of an obstetric emergency
      • Examples—preeclampsia, abruptio placentae
   2. Due to DIC limited to the renal cortex
      a. Fibrin clots are present in arterioles and glomerular capillaries
      b. Bilateral, diffuse, pale infarct of the renal cortex
   3. Anuria (no urine) in a pregnant woman followed by ARF
X. Obstructive Disorders of the Kidney
A. Hydronephrosis
   1. Epidemiology
      a. Children usually have congenital malformation.
         • Examples—bladder neck obstruction, urethral valve
      b. Adults usually have acquired disease.
         • Examples—stone (most common), prostate hyperplasia
   2. Causes
      a. Renal stone (most common)
      b. Retroperitoneal fibrosis
      c. Cervical cancer, BPH
   3. Gross findings
      a. Dilated ureter and renal pelvis (Fig. 20-8A)
      b. Compression atrophy of the renal medulla and cortex
   4. May produce postrenal azotemia
   5. Treatment is to relieve the obstruction.
      • Catheter (most often), nephrostomy tube, cystoscopy
B. Renal stones (urolithiasis)
   1. Epidemiology of renal stones
      a. Stones occur in males more often than females.
      b. Incidence is greater during the summer.
         • Insufficient fluid intake
   2. Causes
      a. Hypercalciuria in the absence of hypercalcemia
         (1) Most common metabolic abnormality producing stones
         (2) Due to increased gastrointestinal reabsorption of calcium
         • Called absorptive hypercalciuria
      b. Decreased urine volume concentrates the urine.
         • Hydration is essential in preventing stone formation.
      c. Reduced urine citrate
         • Citrate normally chelates calcium.
      d. Urine pH alterations
         (1) Alkaline urine pH favors crystallization of calcium- and phosphate-containing stones.
         (2) Acidic urine pH favors crystallization of uric acid, cystine stones
      e. Primary HPTH (10% of cases)
      f. Diets high in dairy products (contain phosphate) or oxalates
      g. Urinary infections due to urease producers (e.g., Proteus; ammonia smell of urine)
   3. Types of renal stones
      a. Calcium stones (~80% of cases)
         (1) Calcium oxalate stone (>50% of cases) is the most common type in adults.
         • Increased incidence associated with pure vegan diet, vitamin C deficiency, and Crohn disease
         (2) Calcium phosphate stones (10%–20% of cases) are the most common type in children.
         • Associated with dairy products and distal renal tubular acidosis

Sickle cell trait/disease: hematuria; loss of concentration; renal papillary necrosis, APN
Diffuse cortical necrosis: anuria followed by ARF in pregnant woman
Hydronephrosis: MC complication upper urinary tract obstruction
Hypercalciuria: MC metabolic abnormality causing calcium stones
Renal stone: MCC upper urinary tract obstruction
Renal stone: calcium oxalate MC; calcium phosphate (dairy products)
Struvite stone: MAP; urease producers; alkaline urine pH; ammonia smell of urine

b. Magnesium ammonium phosphate (MAP)
   (1) "Staghorn calculus" or struvite stone (15% of cases; see Fig. 20-8B)
   (2) Associated with urease producers (e.g., Proteus)
   (3) Urine is alkaline and smells like ammonia.

c. Uric acid (8% of cases), cystine (3% of cases)

4. Clinical findings
   a. Sudden onset of flank tenderness
   b. Nausea and vomiting
   c. Colicky pain radiating into the ipsilateral groin
   d. Patient is constantly moving to try to relieve pain
   e. Gross hematuria may be evident.

5. Laboratory findings
   a. Hematuria
   b. Crystals may be present in the urine
   c. Hypercalcemia
      • Consider primary HPTH

6. Diagnosis
   a. Plain film (kidney-ureter-bladder [KUB])
      • Approximately 80% of stones are radiopaque.
   b. Unenhanced spiral (helical) CT
      • Sensitivity 96%, specificity 100%
   c. Ultrasound (sensitivity 15%, specificity 90%)
   d. Strain urine to collect stone
      (1) Always send for analysis.
      (2) Greater than 50% pass the stone within 48 hours.
      (3) Recurrence occurs in ~50% of patients.
7. Treatment is tailored to the type of stone.
   a. Calcium stone
      (1) Hydrochlorothiazide
         • Increases distal renal tubule reabsorption of calcium (refer to Chapter 5)
      (2) Cellulose phosphate
         • Binds calcium in the intestine
   b. Uric acid stone
      (1) Allopurinol prevents synthesis of uric acid.
      (2) Increase urinary pH
         • Alkaline pH makes uric acid soluble in urine.
   c. Struvite stone
      (1) Surgical removal because of size
      (2) Antibiotic to eliminate the urease producer
   d. Surgical removal
      (1) Extracorporeal shock wave lithotripsy
      (2) Ureteroscopic stone extraction

XI. Tumors of the Kidney and Renal Pelvis
A. Angiomyolipoma
   1. Hamartoma composed of blood vessels, smooth muscle, and adipose cells
   2. Associated with tuberous sclerosis (refer to Chapter 26)
      a. Mental retardation
      b. Multisystem hamartomas

B. Renal cell carcinoma
   1. Epidemiology
      a. Sporadic (most common) and hereditary types
      b. Occurs in men more frequently than women
         • Occurs in the sixth to seventh decades
      c. Risk factors
         (1) Smoking (most common cause)
         (2) Von Hippel–Lindau disease (VHL; refer to Chapter 10)
            (a) Autosomal dominant
            (b) Chromosome 3 relationship
            (c) Hemangioblastomas of cerebellum and retina
            (d) Bilateral renal cell carcinoma (50%–60% of cases)
      (3) Adult polycystic kidney disease
      (4) Obesity, asbestos exposure, lead exposure
      (5) Exposure to gasoline and petroleum products
   2. Pathogenesis
      a. Cytogenetic abnormalities occur in sporadic and hereditary cancers
         • Translocations with loss of von Hippel–Lindau suppressor gene
      b. Cancer derives from proximal tubule cells
   3. Gross and microscopic findings
      a. Clear cell carcinoma most common type (70%–80% of cases)
      b. Most are sporadic
         • Remainder are associated with VHL
      c. Upper pole mass with cysts and hemorrhage
         • Tumor is a bright yellow mass larger than 3 cm (75%–80% of cases; Fig. 20-9A).
      d. Composed of clear cells that contain lipid and glycogen (see Fig. 20-9B)
      e. Tendency for renal vein invasion (15%–20% of cases)
         • Yellow tumor may invade inferior vena cava and extend to the right side of heart.
      f. Metastasis
         (1) Lungs are the most common site (50%–60% of cases)
            • Often hemorrhagic, "cannonball" appearance on radiographs
         (2) Bone (lytic lesions; 30%–40% of cases)
         (3) Regional nodes (15%–30% of cases)
         (4) Hemorrhagic nodules in the skin
            • Due to increased vascularity in the tumor
   4. Clinical findings
      a. Hematuria (50%–60% of cases)
      b. Abdominal mass (25%–45% of cases)
      c. Flank pain (35%–40% of cases)
      d. Hypertension (20%–40% of cases)
e. Triad—hematuria, abdominal mass, flank pain (5%–10% of cases)

f. Weight loss (30%–35% of cases)

g. Fever (5%–15% of cases)

h. Left-sided varicocele (2%–3% of cases; refer to Chapter 21)
  • Relates to invasion of left renal vein blocking left spermatic vein drainage

5. Laboratory findings
   a. Elevated erythrocyte sedimentation rate (nonspecific finding; 50%–60% of cases)
   b. Normocytic anemia (20%–40% of cases)
   c. Ectopic secretion of hormones (refer to Chapter 9)
      (1) Erythropoietin (EPO)
          • Produces secondary polycythemia (4% of cases)
      (2) PTH-related protein
          • Produces hypercalcemia (3%–6% of cases)

6. Diagnosis
   • Ultrasound, abdominal CT, MRI

7. Treatment is nephrectomy.

8. Prognosis
   a. Characteristically has late metastases
      • May recur 1 to 20 years after the tumor has been removed
   b. Average 5-year survival rate is 45% with metastasis.
      • Up to 70% of cases do not have metastasis.
   c. Poor prognosis associated with extension into the renal vein or through the renal capsule
      • 10% to 15% 5-year survival rate

C. Renal pelvis cancer

1. Transitional cell carcinoma (TCC)
   a. Most common type
      • Approximately 50% have similar tumors elsewhere in the urinary tract.
   b. Risk factors
      (1) Smoking (most common)
      (2) Phenacetin abuse
      (3) Aromatic amines (aniline dyes)
      (4) Cyclophosphamide

2. Squamous cell carcinoma (SCC)
   • Risk factors include renal stones and chronic infection.

D. Wilms tumor

1. Epidemiology
   a. Accounts for ~5% of childhood cancer
   b. Most common primary renal tumor in children
c. Occurs between 2 and 5 years of age  
d. Sporadic type (most common)  
e. Genetic type  
  (1) Autosomal dominant inheritance (chromosome 11)  
  (2) WAGR syndrome  
      • Wilms tumor, aniridia (absent iris), genitourinary, retardation (mental)  
  (3) Beckwith-Wiedemann syndrome  
      • Wilms tumor, macroglossia, enlarged body organs (liver, adrenal, pancreas),  
        hemihypertrophy of extremities

2. Large, necrotic, gray-tan tumor  
a. Derived from mesonephric mesoderm  
b. Contains abortive glomeruli and tubules, primitive blastemal cells, and  
   rhabdomyoblasts

3. Clinical findings  
a. Unilateral palpable mass in a child with hypertension  
   • Hypertension is due to renin secretion.  
b. Lungs are the most common site of metastasis.  
c. With combined therapies 2-year survival rate is >90%. 
I. Common Ureteral Disorders
   A. Congenital megaloureter
      • May be associated with Hirschsprung disease
   B. Ureteritis cystica
      1. Disorder is a manifestation of chronic inflammation.
      2. Smooth cysts project from the mucosa into the lumen.
         • Similar findings may be present in the bladder.
      3. Cysts may undergo glandular metaplasia and predispose to adenocarcinoma.
   C. Ureteral stones
      • Ureters are the most common site for stones to cause obstruction.
   D. Retroperitoneal fibrosis
      1. Causes
         a. Most cases are idiopathic.
         b. Known causes/associations include:
            (1) Ergot derivatives used in the treatment of migraines
            (2) Retroperitoneal malignant lymphoma
            (3) Association with other sclerosing conditions
               (a) Primary sclerosing cholangitis (PSC)
               (b) Sclerosing mediastinitis, Reidel fibrosing thyroiditis
      2. Complications
         a. Hydronephrosis is the most common complication.
         b. It may cause a right scrotal varicocele (see section V).
            • Blocks the drainage of the right spermatic vein into the vena cava
   E. Ureteral cancers
      • Transitional cell carcinoma (TCC) is the most common cancer.

II. Urinary Bladder Diseases
   A. Congenital diseases of the urinary bladder
      1. Exstrophy of the bladder (Fig. 21-1A)
         a. Developmental failure of the anterior abdominal wall and bladder
            (1) Bladder mucosa is exposed to the body surface.
            (2) It is often associated with epispadias (see section IV).
         b. Complications
            (1) Inflammation predisposes to glandular metaplasia.
            (2) The likelihood of developing adenocarcinoma of the bladder is high.
      2. Urachal cyst remnants
         a. Usually the embryonic allantois (part of the yolk sac) is obliterated to form the fibrous
            urachus connecting the apex of the bladder with the umbilicus (called the median
            umbilical ligament in adults).
            • If the lumen remains patent in the newborn, fistulas may develop between
              the bladder and the umbilicus; midline cysts may persist that may drain
              urine.
b. Cyst remnants predispose to adenocarcinoma of the bladder
   - Most common cause of bladder adenocarcinoma

B. Acute and chronic cystitis

1. Risk factors for lower urinary tract (LUT) infection
   a. Female sex
      (1) Short urethra
      (2) Ascending infection (refer to Chapter 20)
   b. Indwelling urinary catheter
      (1) Most common cause of sepsis in hospitalized patients
      (2) Account for 50% of nosocomial urinary tract infections (UTIs)
   c. Sexual intercourse
      (1) “Honeymoon cystitis” occurs from trauma to the urethra.
      (2) Voiding after intercourse reduces the risk for infection by washing out bacteria in the urethra.
   d. Diabetes mellitus, neurogenic bladder
   e. Cyclophosphamide
      (1) Produces hemorrhagic cystitis
      (2) Prevented with mesna
f. Schistosoma haematobium
   (1) Transmission
      (a) The fork-tailed cercariae penetrate the skin.
      (b) Larvae enter veins in the adult urinary bladder wall.
      (c) Larvae develop into adult worms that deposit eggs.
      (d) Host develops an intense inflammatory response consisting of
eosinophils that surround the eggs.
      (e) Inflammation causes squamous metaplasia of the bladder
epithelium.
   (2) Eggs have a large terminal spine (see Fig. 21-1B).
   (3) Treatment is praziquantel.

2. Causes of acute cystitis
   a. Escherichia coli
      (1) Most common uropathogen (80%–90% of cases)
      (2) Gram-negative rod (see Fig. 21-1C)
      (3) UTIs account for 40% of hospital-acquired (nosocomial) infections.
      (4) Most common cause of sepsis in a hospitalized patient
      (5) Treatment is double-strength trimethoprim-sulfamethoxazole.
   b. Adenovirus
      • Causes hemorrhagic cystitis
   c. Staphylococcus saprophyticus
      (1) Causes acute cystitis in young, sexually active women
         • Accounts for ~10% to 20% of LUT infections
      (2) Coagulase negative
      (3) Treatment is oral cephalosporin or amoxicillin-clavulanate.
   d. Acute urethral syndrome in women
      (1) Female counterpart to nonspecific urethritis (NSU) in men
      (2) Chlamydia trachomatis is the most common cause of acute urethral syndrome.
      (3) Identification of Chlamydia
         • Polymerase chain reaction (PCR) testing of voided urine
      (4) Treatment is azithromycin
   e. Other uropathogens
      • Mycoplasma hominis, Ureaplasma urealyticum, Neisseria gonorrhoeae

3. Clinical findings in LUT infections
   a. Dysuria (painful urination)
   b. Increased frequency, urgency, nocturia
   c. Suprapubic discomfort
   d. Gross hematuria

4. Laboratory findings in LUT infections
   a. Pyuria ≥10 white blood cells (WBCs) per high-power field (HPF) in a
centrifuged specimen
      • More than 2 WBCs/HPF in an uncentrifuged specimen
   b. Bacteriuria, hematuria
   c. Positive dipstick for leukocyte esterase and nitrite (refer to Chapter 20)
   d. Culture showing at or above 10⁵ colony-forming units (CFUs)/mL
      • Gold standard criterion of infection

5. Asymptomatic bacteriuria in women
   a. Two successive cultures with 10⁵ or more CFUs/mL in an asymptomatic
      patient
   b. Causes
      (1) Pregnancy
         • Acute pyelonephritis may occur in 1% to 2% of cases.
      (2) Elderly women in nursing homes
   c. Treatment
      (1) Pregnant women
         • Amoxicillin
      (2) Asymptomatic, healthy elderly women
         • No treatment necessary

6. Sterile pyuria
   a. Neutrophils in the urine and negative standard culture after 24 hours
      • Positive leukocyte esterase, negative nitrite
   b. Causes
(1) \textit{C. trachomatis}
(2) Renal tuberculosis (TB)
(3) Acute tubulointerstitial nephritis (TIN; refer to Chapter 20)

7. Malacoplakia
   a. Associated with a chronic \textit{E. coli} infection of the bladder
   b. Microscopic findings
   (1) Yellow, raised mucosal plaques
   (2) Foamy macrophages filled with laminated mineralized concretions
      • Called Michaelis-Gutmann bodies, which are defective phagosomes that cannot
        degrade bacterial products

C. Miscellaneous diseases of the urinary bladder
   1. Acquired diverticula
      a. Most are due to benign prostatic hyperplasia (BPH)
      b. BPH causes obstruction of urine outflow and increased intravesical pressure,
         predisposing to diverticula formation through areas of weakness.
      c. Diverticulitis and stone formation are common complications.
   2. Cystocele
      a. Common in middle-aged to elderly women
      b. Mechanism
         (1) Relaxation of pelvic support causes descent of the uterus
         (2) Bladder wall protrudes into the vagina
            • Creates a pouch that collects residual urine
   3. Cystitis cystica and glandularis
      a. Bladder analog of urethritis cystica
      b. Increased risk for developing bladder adenocarcinoma

\begin{boxed_text}
\textbf{Urinary bladder control and incontinence disorders}: Relaxation of the detrusor muscle is involved in the storage of urine, whereas contraction of the muscle is important in emptying the bladder. The sympathetic nervous system relaxes the detrusor muscle and contracts the internal sphincter; hence it is important in the retention of urine in the bladder. In contradistinction, the parasympathetic nervous system is involved in emptying the bladder. It accomplishes this function by contracting the detrusor muscle and relaxing the internal sphincter muscle. There are four types of urinary incontinence: urge incontinence (40%–70% of cases), overflow incontinence, stress incontinence, and functional incontinence. \textbf{Urge incontinence} is caused by overactivity of the detrusor muscle resulting in the production of low volumes of urine. Symptoms include increased urinary frequency, urgency, small volume voids, and nocturia. The most common causes are bladder irritation due to BPH, atrophic urethritis, and infection. Treatment is with anticholinergics, which inhibit parasympathetic stimulation of detrusor contraction. The mechanisms for \textbf{overflow incontinence} are outflow obstruction (e.g., BPH) or detrusor underactivity related to autonomic neuropathy (e.g., diabetes mellitus). Symptoms include dribbling and low urine flow. Treatment involves the use of cholinergic drugs to enhance muscle tone (i.e., increase detrusor contraction) or, if obstruction is the cause (e.g., BPH), \(\alpha\)-adrenergic blockers to relax smooth muscles in the bladder neck. The mechanism for \textbf{stress incontinence} is laxity of pelvic floor muscles with a concomitant lack of bladder support. This may be the result of not maintaining the posterior urethrovesical angle of 90 to 100 degrees or a lack of estrogen; hence this type of incontinence primarily occurs in women. Symptoms relate to the loss of urine when there is an increase in intra-abdominal pressure (e.g., laughing, coughing, sneezing). Treatment is to increase internal sphincter tone with \(\alpha\)-adrenergic agonists (contract smooth muscle cells at the bladder neck), use topical estrogen therapy, and encourage the patient to do Kegel pelvic floor muscle exercises. If these treatments do not control the incontinence, then surgery is the final option. The mechanism for \textbf{functional incontinence} is inability to reach toilet facilities in time. Patients are normally continent; however, if they are taking diuretics or drinking too many caffeinated beverages, incontinence may occur.
\end{boxed_text}
TCC: MCC smoking cigarettes; cyclophosphamide

SCC bladder: S. haematobium infection

TCC: multifocal tumor; recurrences are the rule

TCC: painless hematuria MC sign

Bladder SCC due to S. haematobium; common in Egypt

Killing helminth eggs: type II HSR involving eosinophils

(3) Increased incidence with aging

(4) Causes
(a) Smoking cigarettes (most common cause)
• Less risk for other tobacco products
(b) Workers in dye, rubber, or leather industries
(c) Cyclophosphamide
(d) Arsenic exposure
(e) Beer consumption
• Due to nitrosamines in beer
(f) S. haematobium
• 70% produce squamous cell carcinoma (SCC), 30% TCC

b. Pathogenesis
(1) Genetic factors
(a) Numerous chromosomes implicated
(b) Genes implicated: p53 and RB suppressor genes; HRAS proto-oncogene
(c) Alteration in epidermal growth factor receptor
(2) Environmental factors (see earlier discussion)
(3) Multifocality (“field effect”) and recurrence are the rule, due to:
(a) A common malignant stem cell abnormality
(b) Reimplantation of the tumor from another site

c. Gross and microscopic findings
(1) Low-grade cancers
• Usually papillary and not usually invasive (see Fig. 21-1D)
(2) High-grade cancers
• Papillary or flat and usually invasive
(3) Most common sites
• Lateral or posterior walls at the base of the bladder
(4) Significance of blood group antigens (A, B, or H)
• Better prognosis if the tumor has these antigens

d. Clinical findings
(1) Painless gross/microscopic hematuria
• Most common sign (70%–90% of cases)
(2) Dysuria, increased frequency of urination

e. Treatment
(1) Surgical resection
(2) Intravesical chemotherapy
(3) Radiotherapy

f. Prognosis
• Five-year survival rate for all stages combined is 80%.

3. Squamous cell carcinoma (SCC) of the bladder

a. Epidemiology
(1) Association with S. haematobium (see Fig. 21-1B)
• Eggs are located in the urinary bladder venous plexus.
(2) Common cancer in Egypt
(3) 70% of cancers are SCC, 30% are TCC

b. Pathogenesis
(1) Eggs are surrounded by eosinophils.
(2) IgE antibodies are attached to the eggs.
(3) Eosinophils have Fc receptors for IgE.
(4) Eosinophils attach to receptors and release major basic protein, which destroys the egg.
• Type II hypersensitivity reaction (HSR)
(5) Chronic bladder irritation/infection causes squamous metaplasia.
• Metaplasia can progress to dysplasia and SCC.

4. Causes of adenocarcinoma of the bladder
a. Urachal remnants (most common cause)
b. Cystitis glandularis
c. Exstrophy of the bladder

5. Embryonal rhabdomyosarcoma (sarcoma botryoides)
a. Most common sarcoma in children
• Accounts for ~3% of childhood cancer
b. Most common site for boys is the urinary system.
   - Presents as grape-like masses protruding from the urethral orifice
   c. Most common site in girls is the vagina.

6. Cancers invading the bladder
   a. Invasive cervical cancer and prostate cancer
   b. Obstruct the urethra and the ureters
   c. Produce hydronephrosis, postrenal azotemia, and death by renal failure

III. Urethral Diseases

A. Infections of the urethra
   1. Chlamydial and gonococcal infections in men and women
      • Urethra is the most common site for these sexually transmitted diseases (STDs).
   2. Nonvenereal diseases causing urethritis
      a. Most commonly due to *E. coli*
      b. Complications
         (1) Cystitis in women
         (2) Prostatitis in men
   3. Chlamydial urethritis is a common component of Reiter syndrome in men.
      a. Urethritis
      b. Sterile conjunctivitis
      c. Human leukocyte antigen (HLA)-B27–associated arthritis (refer to Chapter 24)

B. Urethral caruncle
   1. Female dominant disease
   2. Friable, red, painful mass is present at the urethral orifice.
   3. Chronically inflamed granulation tissue causes bleeding.

C. Squamous cell carcinoma of the urethra
   • Most common cancer of the urethra

IV. Penis Diseases

A. Malformations of the urethral groove of the penis
   1. Hypospadias
      a. Abnormal opening on the ventral surface of the penis (Fig. 21-2A)
      b. Most common malformation of urethral groove
      c. Risk factors
         (1) Father or previous male sibling with defect
         (2) Monozygotic twins
            • Insufficient production of human chorionic gonadotropin by single placenta
      d. Frequently associated with ventral curvature of penis
         • Called chordee
      e. Pathogenesis
         (1) Due to faulty closure of the urethral folds
         (2) Possibly related to abnormal androgen production
   2. Epispadias
      a. Abnormal opening on the dorsal surface of the penis
      b. Due to a defect in the genital tubercle

21-2: A, Hypospadias. The arrow shows the urethral opening on the ventral surface of the penis. B, Phimosis. Note the long foreskin with non-retractile prepuce. (A from Kliegman, R: Nelson Textbook of Pediatrics, 19th ed, Philadelphia, Elsevier Saunders, 2011, p 1853, Fig. 538.1B; B from Taylor S, Raffles A: Diagnosis in Color Pediatrics, London, Mosby-Wolfe, 1997, p 182, Fig. 6.18.)
B. Phimosis of the penis
1. Orifice of the prepuce is too small to retract over the head of the penis (see Fig. 21-2B)
2. Commonly associated with infections

C. Balanoposthitis of the penis
1. Infection of the glans and prepuce
   a. It usually occurs in uncircumcised males with poor hygiene.
   b. Accumulation of smegma leads to infection.
      • *Candida*, pyogenic bacteria, and anaerobes
2. Inflammatory scarring may produce an acquired phimosis.

D. Miscellaneous disorders of the penis
1. Peyronie disease
   a. Type of fibromatosis (refer to Chapter 24)
   b. Painful contractures of the penis
      • Causes lateral curvature of the penis
   c. May cause infertility
2. Priapism
   a. Persistent and painful erection
   b. Causes include sickle cell disease, penile trauma

E. Carcinoma in situ (CIS) of the penis
1. Bowen disease
   a. Leukoplakia involving the shaft of the penis and scrotum
      (1) Patients are usually >35 years old
      (2) Association with human papillomavirus (HPV) type 16
   b. Precursor for invasive SCC (~10% of cases)
   c. Association with other types of visceral cancer
2. Erythroplasia of Queyrat
   a. Erythroplakia located on the mucosal surface of the glans and prepuce
   b. HPV type 16 association
   c. Precursor for invasive SCC
3. Bowenoid papulosis
   a. Multiple pigmented reddish brown papules on the external genitalia
   b. Association with HPV type 16
   c. Does not develop into invasive SCC
      • Only CIS with no predisposition for invasion

F. SCC of the penis
1. Epidemiology
   a. Circumcision protects against developing SCC of penis.
   b. SCC is the most common cancer of the penis.
      (1) Usually affects men 40 to 70 years old
      (2) Most common sites
         • Glans or mucosal surface of prepuce
   c. Two-thirds of cases associated with HPV types 16 and 18
      • Products from smoking tobacco may act as cocarcinogens with HPV.
   d. Risk factors
      (1) Lack of circumcision
         • Greatest risk factor
      (2) Bowen disease, erythroplasia of Queyrat
2. Metastasizes to inguinal and iliac nodes

V. Testis, Scrotal Sac, and Epididymis Diseases
A. Embryology (see Fig. 6-26A)
B. Cryptorchidism of the testes
1. Normal descent of testes
   a. Transabdominal phase
      (1) Testes descend to lower abdomen or pelvic brim
      (2) Müllerian inhibitory substance (MIS) is responsible for this phase.
   b. Inguinoscrotal phase
      (1) Descent through the inguinal canal into the scrotum
      (2) Androgen- and human chorionic gonadotropin (hCG)-dependent
2. Cryptorchidism
   a. Epidemiology
      (1) Incomplete or improper descent of the testis into the scrotal sac
      (2) Most common genitourinary (GU) disorder in male children
(3) Occurs in 30% of premature males and 5% of full-term males

(4) Associations
   • Androgen insensitivity syndrome, Kallmann syndrome, cystic fibrosis

(5) Locations
   (a) Inguinal canal is the most common site (80% of cases)
      • Palpable mass; majority are unilateral (90% of cases)
   (b) Intra-abdominal (5%–10% of cases)

(6) Many will spontaneously descend by 3 months of age
   (a) Due to combination of androgens and hCG
   (b) Spontaneous descent is uncommon after 3 months.

b. Complications if uncorrected
   (1) Potential for infertility
      (a) Arrest in germ cell maturation
      (b) Testicular atrophy
      (c) Similar changes occur in the normally descended contralateral testis.
      (d) Greatest risk if intra-abdominal or long duration in the inguinal canal

   (2) Increased risk for developing a seminoma
      (a) Risk for cancer in the cryptorchid testis increases by fivefold to tenfold.
      (b) Risk also applies to the normally descended testicle.

   (3) Increased risk for the undescended testis to undergo torsion (see later)

c. Treatment
   (1) Orchiopexy may be done as early as 6 months; it should be performed by 2 years of age.
   (2) Hormonal therapy with hCG produces variable results.
   (3) Administration of gonadotropin-releasing hormone (GnRH) before orchiopexy may improve fertility in adult.

C. Orchitis
   1. Mumps
      a. Infertility is uncommon.
      b. Most cases are unilateral.
      c. Orchitis is more likely to occur in an older child or adult.

   2. Congenital or acquired syphilis

   3. HIV

   4. Extension of acute epididymitis

D. Epididymitis
   1. Causes
      a. Common pathogens in persons <35 years old
         (1) *N. gonorrhoeae*
         (2) *C. trachomatis*

      b. Common pathogens in persons >35 years old
         (1) *E. coli*
         (2) *Pseudomonas aeruginosa*

      c. Tuberculosis
         (1) Begins in the epididymis
            • Spreads to the seminal vesicles, prostate, and testicles
         (2) Caseating granulomatous inflammation

      d. AIDS
         • Association with cytomegalovirus, *Toxoplasma, Salmonella*

   2. Clinical findings in acute epididymitis
      a. Usually unilateral scrotal pain with radiation into spermatic cord or flank
      b. Scrotal swelling, epididymal tenderness
      c. Urethral discharge
         • If it is sexually transmitted
      d. Prehn sign
         • Elevation of the scrotum decreases pain.

   3. Treatment
      a. If <35 years old, ceftriaxone + doxycycline (STD treatment)
      b. If >35 years old, ciprofloxacin extended release

E. Varicocele
   1. Epidemiology
      a. Occurs in 15% to 20% of all males
         (1) Usually occurs between 15 and 25 years of age
         (2) Rarely occurs after 40 years old

   ```
   ```
Infertility controversial

**Testicular cancer:**
- Most common tumor of males
- 5% of solid tumors in males
- Most occur in young adults
- Average age is early 20s
- Type: Seminoma & Non-Seminoma
- Most have germ cell origin
- **Seminoma:**
  - Most common testicular tumor
  - Occurs in 40% of infertile males
  - Testicular cancer more often in whites than blacks
- **Non-Seminoma:**
  - Seminomas: MC have germ cell origin
  - 95% of testicular cancers are of germ cell origin
  - The most common type
- Testicular cancers more common in blacks
- **Torsion of the testicle:**
  - Occurs in 40% of infertile males
  - Testicular cancer more often in whites than blacks
- **Varicocele:**
  - More common in infertile males
  - Bag of worms appearance
  - Testicular cancer more often in whites than blacks
  - Inguinal hernia also
  - Hydrocele:
    - Persistent scrotal enlargement
    - Inguinal canal, testis high
    - Absent cremasteric reflex
  - Torsion of testicle:
    - Trauma
    - Occurs in 40% of infertile males
  - Varicocele:
    - Blockage of left renal vein can also produce a varicocele
    - Examples—renal cell carcinoma invading renal vein; superior mesenteric artery compressing the left renal vein
  - Right spermatic vein drains into the vena cava
    - Examples—retroperitoneal fibrosis; thrombosis of the inferior vena cava
  - Incompetent valves in the left spermatic vein from increased pressure
- **Clinical findings:**
- Dragging sensation in testicle
- Visible "bag of worms" (Fig. 21-3A)
- Infertility (controversial)
  - Heat decreases spermatogenesis
- Diagnosis by ultrasound
- Embolization by an intervention radiologist
- **Treatment:**
  - Varicocelectomy
  - Surgery
  - One-third spontaneously remit.
  - Surgery is imperative within 12 hours for those that do not remit

**Torsion of the testicle:**
- Epidemiology
  - Majority occur between 12 and 18 years old.
  - Predisposing factors
    - Violent movement or physical trauma
    - Most common causes
    - Cryptorchid testis
    - Atrophy of testis
  - Twisting of spermatic cord cuts off the venous/arterial blood supply
  - Danger for hemorrhagic infarction of the testicle (see Fig. 21-3B)
- Clinical findings
  - Sudden onset of testicular pain
  - Absent cremasteric reflex (key diagnostic finding)
  - Stroking the inner thigh with a tongue blade normally causes the scrotum to retract
- Testicle is drawn up into the inguinal canal (see Fig. 21-3C)
- Diagnosis
  - Ultrasound distinguishes fluid versus a testicular mass causing scrotal enlargement
- Other fluid accumulations
  - Hematocele contains blood.
  - Spermatocele contains sperm
- Treatment is surgery

**Testicular tumors:**
- Epidemiology
  - Most common malignancy among those 15 and 35 years
  - Occurs more often in whites than blacks
- Types of testicular tumors
  - Malignant testicular tumors most often have germ cell origin (95% of cases)
  - Benign testicular tumors are usually sex cord–stromal tumors (5% of cases)
  - Classification of germ cell tumors
    - 40% are of one cell type.
    - Seminoma is the most common type (40% of cases).
21-3: A, Varicocele in the left scrotal sac. Note the “bag of worms” appearance. B, Left testicular torsion in an adolescent. The testis is enlarged, discolored, and necrotic (hemorrhagic infarction). C, “Late phase torsion” in an adolescent with severe testicular pain 1 month previously. Note the absence of inflammation and the high position of the testis in the scrotum. D, Hydrocele in the right scrotal sac. E, Seminoma of the testicle showing the scrotal mass. F, Seminoma that has been surgically removed. Note that the tumor replaces most of the testicle. G, Microscopic section of a seminoma. Note the large tumor cells with fibrous septa infiltrated by numerous lymphocytes. (A from Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 545, Fig. 18-27; B, C, and D from Kliegman R: Nelson Textbook of Pediatrics, 19th ed, Philadelphia, Elsevier Saunders, 2011, pp 1861, 1863, respectively, Fig. 539.2A and B, 539.6 respectively; E and F from Grieg JD: Color Atlas of Surgical Diagnosis. London, Mosby-Wolfe, 1996, p 307, Fig. 38-8; G from Rosai J, Ackerman LV: Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 1421, Fig. 18-57.)
(2) 60% of cases are mixtures of two or more patterns.

- Most common mixture is embryonal carcinoma, teratoma, choriocarcinoma, and yolk sac tumor.

(3) They are best classified as seminomas or nonseminomas.

3. Risk factors
   a. Cryptorchid testicle
      (1) Overall most common risk factor
      (2) Greatest risk is an intra-abdominal cryptorchid testis.
   b. Androgen insensitivity syndrome (refer to Chapter 6)
   c. Klinefelter syndrome (XXY) (refer to Chapter 6)
   d. Peutz-Jeghers syndrome (Sertoli-Leydig cell tumor)
   e. Inguinal hernia, mumps orchitis

4. Clinical finding
   • Unilateral, painless enlargement of the testis

5. Tumor markers
   a. α-Fetoprotein (AFP)
      • Yolk sac (endodermal sinus) tumor origin
   b. Human chorionic gonadotropin (hCG)
      • Choriocarcinoma
   c. Lactate dehydrogenase
      (1) Nonspecific cancer enzyme
      (2) Degree of elevation correlates with tumor mass

6. Summary of testicular tumors (Table 21-1)
7. Diagnosis
   a. Ultrasound
   b. CT scan or MRI of pelvis and abdomen

- Testicular cancer most often involves para-aortic lymph nodes.

## Table 21-1 Testicular Tumors*

<table>
<thead>
<tr>
<th>TUMOR (see Fig. 21-3E to G)</th>
<th>AGE (YEARS)</th>
<th>MORPHOLOGIC/ CLINICAL FINDINGS</th>
<th>TUMOR MARKER(S)</th>
<th>PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma (see Fig. 21-3E to G)</td>
<td>30–35; &gt;65</td>
<td>Most common germ cell tumor (40% of cases). Yellow tumor usually without significant hemorrhage or necrosis. Neoplastic cells are large and have a centrally located nucleus containing prominent nucleoli. Stroma has a prominent lymphocytic infiltrate. Metastasis: lymphatic (para-aortic lymph nodes) metastasis before hematogenous (lungs) Spermatocytic variant occurs in older individuals and rarely metastasizes.</td>
<td>↑hCG in 10% of cases</td>
<td>Excellent Extremely radiosensitive</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>20–25</td>
<td>Bulky tumor with hemorrhage and necrosis. Other tumor types are often present. Metastasis: hematogenous before lymphatic</td>
<td>↑AFP and/or hCG in 90% of cases</td>
<td>Intermediate Less radiosensitive than seminomas</td>
</tr>
<tr>
<td>Yolk sac (endodermal sinus) tumor</td>
<td>Most common testicular tumor in children &lt;4 years old</td>
<td>Characteristic Schiller-Duval bodies resemble primitive glomeruli.</td>
<td>↑AFP in all cases</td>
<td>Good</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>20–30</td>
<td>Most commonly mixed with other tumor types. Contains trophoblastic tissue (syncytiotrophoblast and cytotrophoblast). May produce gynecomastia (hCG is an LH analogue)</td>
<td>↑hCG in all cases</td>
<td>Poor Most aggressive testicular tumor; hematogenous spread to lungs</td>
</tr>
<tr>
<td>Teratoma</td>
<td>Affects males of all ages</td>
<td>Contains derivatives from ectoderm, endoderm, mesoderm. If mixed with embryonal carcinoma, it is called a teratocarcinoma.</td>
<td>↑AFP and/or hCG in 50%</td>
<td>Good Usually benign in children and malignant in adults (usually SCC)</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>Most common testicular cancer in men &gt;60 years of age</td>
<td>Secondary involvement of both testes by diffuse large cell lymphoma</td>
<td>None</td>
<td>Poor</td>
</tr>
</tbody>
</table>

*Listed in order of prognosis.

AFP, α-Fetoprotein; hCG, human chorionic gonadotropin; LH, luteinizing hormone; SCC, squamous cell carcinoma.
8. Treatment
   a. Inguinal orchietomy
   b. Adjunct chemotherapy

VI. Prostate Diseases
A. Clinical anatomy of the prostate
   1. Dihydrotestosterone (DHT) is responsible for developing the prostate.
   2. Zones of the prostate
      a. Peripheral zone
         (1) Palpated during a digital rectal examination (DRE)
         (2) Primary site for prostate cancer
      b. Transitional zone
         • Primary site for the glandular component of BPH
      c. Periurethral zone
         • Primary site for the fibromuscular (stromal) component of BPH

B. Acute and chronic prostatitis
   1. Epidemiology
      a. Approximately 50% of males develop prostatitis in their lifetime.
      b. Chronic prostatitis is more common than acute prostatitis.
      c. Causes
         (1) Acute prostatitis
            (a) Intraprostate reflux of urine from the posterior urethra or urinary bladder
            (b) Often associated with acute cystitis
            (c) Young to middle-aged adult males
            (d) Pathogens in persons <35 years old
               • Consider C. trachomatis, N. gonorrhoeae
            (e) Pathogens in persons >35 years old
               • E. coli, P. aeruginosa, Klebsiella pneumoniae
         (2) Chronic prostatitis
            (a) Majority are abacterial
            (b) Common in bicycle riders (seat compression on the prostate)
            (c) Chronic bacterial infection
               • Due to recurrent acute prostatitis
   2. Clinical findings
      a. Dysuria, urgency, increased frequency
      b. Fever occurs in acute prostatitis (not chronic prostatitis).
      c. Lower back, perineal, or suprapubic pain
      d. Painful/swollen gland on rectal examination
      e. Hematuria may occur.
   3. Fractionated urine culture and examination for WBCs
      a. Specimen collections
         • Some consider this cumbersome and impractical.
            (1) First 10 mL is the urethral component.
            (2) Second midstream sample is the bladder component.
            (3) Third specimen at the end of micturition is the prostate component.
            (4) Fourth specimen is secretions milked out after prostate massage.
               • Contraindicated in acute prostatitis
      b. Diagnosis of prostatitis
         (1) More than 20 WBCs/HPF in the third and fourth samples suggests acute prostatitis.
         (2) Increased bacterial count in third and fourth specimens is confirmatory.
   4. Treatment
      a. If acute prostatitis in men <35 years old, ceftriaxone + doxycycline (STD treatment)
      b. If acute prostatitis in men >35 years old, ciprofloxacin, extended release, or trimethoprim-sulfamethoxazole
      c. If chronic bacterial prostatitis, ciprofloxacin

C. Benign prostatic hyperplasia (BPH)
   1. Epidemiology
      a. Age-dependent change
         (1) Majority of men develop BPH as they age.
         (2) Approximately 80% have BPH at 80 years of age.
      b. More common in blacks than whites
      c. Develops in the transitional and periurethral zones
2. Pathogenesis
   a. Increased sensitivity of prostate tissue to DHT is the primary cause.
      • Causes hyperplasia of glandular and stromal cells (see Fig. 2-14E)
   b. Stromal cells contain 5α-reductase and are the site of DHT synthesis.

3. Gross and microscopic findings
   a. Hyperplasia of glandular and stromal cells
      (1) Leads to nodule formation (Fig. 21-4A and B)
      (2) Nodules are yellow-pink and are soft.
   b. Glandular hyperplasia develops nodules in the transitional zone.
   c. Stromal hyperplasia develops nodules in the periurethral zone.
      • Most responsible for obstruction of the urethra

4. Clinical and laboratory findings
   a. Signs of obstruction
      (1) Trouble initiating and stopping the urinary stream
      (2) Dribbling, incomplete emptying
      (3) Nocturia, dysuria
   b. Hematuria
   c. Prostate-specific antigen (PSA)
      (1) Proteolytic enzyme
         (a) Increases sperm motility
         (b) Maintains seminal secretions in the liquid state

d. DRE has a sensitivity of 50% in detecting BPH.
e. Approximately 30% of men with BPH have occult prostate cancer.
PSA is usually normal (0–4 ng/mL) or between 4 and 10 ng/mL (30%–50% of cases).
- Rarely >10 ng/mL.

Complications
1. Obstructive uropathy
   - Most common complication
   - Postrenal azotemia
     - Potential for progressing to acute renal failure if left untreated
   - Bilateral hydronephrosis
   - Bladder diverticula from increased pressure
   - Bladder wall smooth muscle hypertrophy/hyperplasia
2. Bladder infections due to residual urine
3. Prostatic infarcts (see Fig. 21-1D)
   - Pain on DRE
   - Enlarged, indurated gland
   - Increased PSA values due to infarction

No risk for progression into carcinoma

Diagnosis
a. DRE is an insensitive test.
b. Transrectal ultrasound if nodules palpated or increased PSA (see later discussion)

Treatment
a. Nonpharmacologic
   - Avoid caffeine or any other foods that exacerbate symptoms
b. General
   - Medications
     - α-Adrenergic blockers
       - Relax smooth muscle tone in capsule/bladder neck
     - 5α-Reductase inhibitors
       - Block conversion of testosterone to DHT
     - Saw palmetto is a 5α-reductase inhibitor
   - Surgery
     - Transurethral resection of the prostate (TURP) is most commonly done.

Prostate cancer

Pathogenesis
- DHT-dependent

Gross and microscopic findings
a. Develops in the peripheral zone
   - Palpable by DRE
   - Obstructive uropathy is not an early finding.
b. Prostate intraepithelial neoplasia (PIN)
   - Foci of atypia/dysplasia
   - May be a precursor lesion for prostate cancer
   - Invasive cancer has a firm, gritty, yellow appearance (see Fig. 21-4C).
d. Hallmarks of malignancy
   - Invasion of the capsule around the prostate
   - Blood vessel/lymphatic invasion

Epidemiology
a. Most common cancer in adult males
   - Second most common cancer-related death in adult males
b. Approximately 65% of all prostate cancers are diagnosed in men ≥65 years old.
   - Average age of diagnosis is 72 years old.
c. More common in blacks than whites
   - Rare in Asians
   - Usually asymptomatic until advanced
   - Peripheral in location
f. Risk factors
   - Advancing age
     - Most important risk factor
   - First-degree relatives (father and brothers)
   - Black men
   - Smoking cigarettes, diet high in saturated fat

Pathogenesis
- DHT-dependent

Gross and microscopic findings
a. Develops in the peripheral zone
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d. Hallmarks of malignancy
   - Invasion of the capsule around the prostate
   - Blood vessel/lymphatic invasion
improved treatment

4. Clinical findings in symptomatic prostate cancer
   a. Generally silent until advanced stage
   b. Obstructive uropathy implies extension into the bladder base
   c. Low back/pelvic pain
      (1) Portends bony metastases to vertebrae and pelvic bones
          • Due to spread via the Batson venous plexus (refer to Chapter 9)
      (2) Alkaline phosphatase (ALP) is increased.
          • Due to osteoblastic metastases (see Fig. 21-4D)
   d. Compression of the spinal cord

5. Diagnosis
   a. DRE is negative in 10% of cases.
   b. Screening
      (1) DRE/PSA annually beginning at 50 years of age
      (2) PSA is sensitive but not specific for cancer.
          (a) BPH and prostatic infarcts can increase PSA, lowering its specificity by
              increasing false positive results.
          (b) Controversy exists in the literature on the value of PSA as a screening test for
              prostate cancer.
      (3) PSA >10 ng/mL is highly predictive of cancer.
          • 70% positive predictive value
      (4) PSA between 4 and 10 ng/mL is a gray zone.
          • Overlap between early cancer and BPH
      (5) Other more sensitive methods of reporting PSA
          (a) Measurement of free versus bound forms of circulating PSA
              • Increased free levels are seen in BPH, whereas increased bound levels are
                seen in prostate cancer.
          (b) PSA doubling time
              • The shorter the doubling time, the more aggressive the tumor
          (c) Rate of change of PSA values with time (PSA velocity)
              • Yearly PSA velocity >0.75 ng/mL increases likelihood of developing
                prostate cancer if total serum PSA is normal.
          (d) Age-adjustment of total serum PSA (controversial)
          (e) Ratio between serum PSA and volume of the prostate gland (prostate
density)

6. Spread of prostate cancer
   a. Perineural invasion
   b. Lymphatic spread to regional lymph nodes (internal iliac)
   c. Hematogenous spread
      (1) Bone is the most common extranodal site (see Fig. 21-4D).
          • In descending order—lumbar spine, proximal femur, and pelvis
      (2) Lungs and liver

7. Diagnosis with transrectal needle core biopsies of prostate; indications:
   a. Abnormal PSA value (see earlier)
   b. Abnormal DRE
   c. Previous diagnosis of atypia or carcinoma in situ

8. Imaging
   a. Radionuclide bone scan
      • Evaluate bone metastasis
   b. CT scan, MRI, transrectal ultrasound
      • Evaluate extent of disease

9. Treatment
   a. Early disease
      • Surgery, external beam radiation, radioactive seed implants
   b. Advanced disease
      • Hormonal therapy, chemotherapy, radiation, or combination

10. Prognosis
    a. The dramatic increase in survival is due to early detection and improved therapy.
    b. Five-year survival rate for all stages is almost 99%.
    c. Ten-year relative survival rate is 91%.
    d. Fifteen-year relative survival rate is 76%.
VII. Male Hypogonadism

A. Normal male reproductive physiology
1. Follicle-stimulating hormone (FSH)
   a. Stimulates spermatogenesis in the seminiferous tubules of the testes.
   b. Negative feedback relationship with inhibin
      (1) Inhibin is synthesized in Sertoli cells in the seminiferous tubules.
      (2) Decreased inhibin causes an increase in FSH.
2. Luteinizing hormone (LH)
   a. LH stimulates testosterone synthesis in the Leydig cells in the testes.
   b. Testosterone has a negative feedback with LH.
      • Decreased testosterone causes an increase in LH.
3. Testosterone
   a. Maintains male secondary sex characteristics
   b. Enhances spermatogenesis in the seminiferous tubules
   c. Increases libido (sexual desire)
   d. Decreased testosterone causes male hypogonadism, infertility, and decreased libido (impotence).
4. Sex hormone–binding globulin (SHBG or androgen-binding globulin)
   a. Binding protein for testosterone and estrogen
      (1) In both men and women, SHBG is mainly synthesized in the liver.
      (2) In men, the Sertoli cells also synthesize SHBG.
      (3) Estrogen increases synthesis of SHBG in the liver.
      (4) Androgens, insulin, obesity, and hypothyroidism all cause decreased synthesis of SHBG.
   b. SHBG has a higher binding affinity for testosterone than estrogen.
      (1) Increased SHBG decreases free testosterone levels.
      (2) Decreased SHBG increases free testosterone levels.

B. Overview of pathogenesis of male hypogonadism
1. Decreased production of testosterone
   • Examples—hypopituitarism, Leydig cell dysfunction
2. Resistance to testosterone
   • Example—androgen receptor deficiency in the androgen insensitivity syndrome
     (testicular feminization; refer to Chapter 6)

C. Causes of male hypogonadism
1. Primary hypogonadism due to Leydig cell dysfunction
   a. Causes include:
      (1) Chronic alcoholic liver disease
      • Inhibits binding of LH to Leydig cells (? mechanism)
      (2) Chronic renal failure
      • Toxins have a direct toxic effect on Leydig cells
      (3) Irradiation, orchitis, trauma of the testes
   b. Laboratory findings include:
      (1) Decreased testosterone
      • Due to destruction of Leydig cells or lack of binding of LH to Leydig cells
      (2) Increased LH
         (a) Due to decreased testosterone
         (b) This type of primary hypogonadism is called hypergonadotropin (↑LH) hypogonadism
      (3) Decreased sperm count
      • Due to decreased testosterone, which normally enhances spermatogenesis
      (4) Normal FSH
      • Inhibin is present in Sertoli cells, therefore it is unaffected by Leydig cell dysfunction.
2. Primary hypogonadism due to Leydig cell and seminiferous tubule dysfunction
   a. Causes are the same as listed for Leydig cell dysfunction
   b. Laboratory findings
      (1) Decreased testosterone
      • Due to destruction of Leydig cells or lack of binding of LH to Leydig cells
      (2) Increased LH
      • Due to decreased testosterone
      (3) Decreased sperm count
      • Due to testosterone deficiency and seminiferous tubule dysfunction
(4) Increased FSH
   (a) Due to decrease in inhibin from Sertoli cell dysfunction
   (b) Note that in Leydig cell dysfunction alone, FSH is normal

3. Secondary hypogonadism due to hypothalamic/pituitary dysfunction; causes include:
   a. Constitutional delay in puberty most common cause
      • Normal laboratory test findings
   b. Hypopituitarism (refer to Chapter 23)
      (1) Causes
         (a) Craniopharyngiomy in children, nonfunctioning pituitary, adenoma in adults
         (b) Prolactinoma (prolactin inhibits gonadotropin releasing hormone [GnRH] production in the hypothalamus); therefore both FSH and LH are decreased.
      (2) Laboratory findings
         (a) Decreased FSH, LH, testosterone, and sperm count
         (b) Because LH is decreased, this type of hypogonadism is called hypogonadotropic hypogonadism
   c. Hypothalamic dysfunction: Kallmann syndrome
      (1) Causes
         (a) Autosomal dominant disorder
         (2) Maldevelopment of the olfactory bulbs and GnRH-producing cells in the hypothalamus
            • GnRH normally stimulates the release of LH and FSH from the anterior pituitary; hence, laboratory findings are the same as those listed above for hypopituitarism.

D. Clinical presentations for hypogonadism

1. Impotence
   a. Most common manifestation
   b. Definition—failure to sustain an erection during attempted intercourse or during intercourse

Testosterone, per se, does not have any role in producing an erection (parasympathetic response) or ejaculation (sympathetic response). However, decreased testosterone decreases libido, which decreases psychic desire and leads to impotence.

2. Loss of male secondary sex characteristics
   a. Estrogen activity is unopposed if testosterone is decreased or unable to bind to receptors.
   b. Findings include female hair distribution, gynecomastia, soft skin.

3. Osteoporosis
   a. Testosterone normally inhibits osteoclastic activity and increases osteoblastic activity.
   b. Decreased testosterone increases osteoclastic activity and decreases osteoblastic activity.

4. Infertility
   • Due to decreased spermatogenesis

E. Summary of causes of male hypogonadism (Table 21-2)

VIII. Male Infertility

A. Epidemiology and pathogenesis

1. Decreased sperm count
   a. Primary testicular dysfunction
      (1) Leydig cell dysfunction (refer to section VII)
      (2) Seminiferous tubule dysfunction

Table 21-2 Summary of Causes of Male Hypogonadism

<table>
<thead>
<tr>
<th>DYSFUNCTION</th>
<th>TESTOSTERONE</th>
<th>SPERM COUNT</th>
<th>LH</th>
<th>FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leydig dysfunction</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Seminiferous tubule dysfunction</td>
<td>N</td>
<td>↓</td>
<td>N</td>
<td>↑</td>
</tr>
<tr>
<td>Leydig cell and seminiferous tubule dysfunction</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

FSH, Follicle-stimulating hormone; LH, luteinizing hormone; N, normal.
IX. Erectile Dysfunction

A. Causes of erectile dysfunction (ED)

1. Psychogenic
   a. Most common cause of impotence in young men
   b. Stress at work, marital conflicts, performance anxiety
   c. Nocturnal penile tumescence (NPT)
      (1) The average male has ~5 erections while asleep.
      (2) NPT is preserved in impotence that is due to psychogenic causes.
      (3) All other causes of impotence have a loss of NPT.

2. Decreased testosterone
   • Decreased libido (sexual desire; see section VII)

3. Vascular insufficiency
   a. Most common cause of impotence in men >50 years old
   b. Example—Leriche syndrome; findings include:
      (1) Impotence due to vascular insufficiency related to aortoiliac atherosclerosis with decreased penile blood flow
      (2) Calf claudication at atrophy (refer to Chapter 10)
      (3) Diminished femoral artery pulse with bruits (refer to Chapter 10)

4. Neurologic disease
   a. Parasympathetic system (S2–S4) is necessary for erection.
   b. Sympathetic system (T12–L1) is necessary for ejaculation.
   c. Neurogenic causes of impotence
      (1) Multiple sclerosis
      (2) Autonomic neuropathy due to diabetes mellitus
      (3) Radical prostatectomy

5. Drug effects; examples:
   a. Leuprolide (GnRH agonist)
   b. Methyldopa, psychotropics

B. Laboratory tests for infertility

1. Semen analysis
   a. Gold standard test for infertility
   b. Components of semen
      (1) Spermatozoa derive from the seminiferous tubules.
      (2) Coagulant derives from the seminal vesicles.
      (3) Enzymes to liquefy semen derive from the prostate gland.
   c. Components evaluated in a standard semen analysis
      (1) Volume
         • Volume is not positively correlated with the number of sperm.
      (2) Sperm count
         • Normal count is 20 to 150 million sperm/mL.
      (3) Sperm morphology
         • Morphology is very abnormal in reconnections of a vasectomy.
      (4) Sperm motility

2. Serum gonadotropins, testosterone, prolactin

Semen analysis: gold standard test for infertility

Impotence + preserved NPT: psychogenic cause of impotence

ED due to ↓testosterone is due to ↓libido

Vascular insufficiency: MCC impotence men >50 years old

Leriche syndrome: aortoiliac atherosclerosis → ↓penal blood flow; calf claudication; ↓femoral artery pulse

Parasympathetic for erection: S2–S4

Sympathetic for ejaculation: T12–L1

Neurologic causes of ED: multiple sclerosis, DM, radical prostatectomy

Drugs causing ED: leuprolide, methyldopa, psychotropics
6. Endocrine disease
   a. Diabetes mellitus
      • Autonomic neuropathy + vascular insufficiency
   b. Primary hypothyroidism
      • Increased prolactin inhibits GnRH release
   c. Prolactinoma
      • Prolactin inhibits GnRH release

7. Penis disorders (refer to IV.D.)
   a. Peyronie disease (fibromatosis)
   b. Priapism (permanent erection)

B. Treatment
   1. Sildenafil (Viagra)
      a. Most common drug used to treat ED
      b. Mechanism
         (1) Sildenafil inhibits the breakdown of cyclic guanosine monophosphate (cGMP) by type 5 phosphodiesterase.
         (2) Increased levels of cGMP cause vasodilation in the corpus cavernosum and the penis.
   2. Yohimbe
      • Herb that induces vasodilatation of vessels in the penis
I. Sexually Transmitted Diseases and Other Genital Infections
   • Summary of infections (Table 22-1; Fig. 22-1)

II. Vulva Disorders
   A. Bartholin gland abscess
      • Most often caused by Neisseria gonorrhoeae
   B. Nonneoplastic dermatoses
      1. Lichen sclerosus (Fig. 22-2A)
         a. Usually occurs in postmenopausal women
         b. Thinning of the epidermis
            • Parchment-like appearance of the skin
         c. Small risk for developing squamous cell carcinoma (SCC)
      2. Lichen simplex chronicus
         a. White plaque-like lesion (leukoplakia)
            • Due to squamous cell hyperplasia
         b. Small risk for developing SCC
      C. Benign and malignant tumors
         1. Papillary hidradenoma
            a. Benign tumor of the apocrine sweat gland
            b. Painful nodule on the labia majora
         2. Vulvar intraepithelial neoplasia (VIN)
            a. Dysplasia ranges from mild to carcinoma in-situ (CIS)
            b. Strong association with human papillomavirus (HPV) type 16
            c. Precursor for developing SCC
         3. Squamous cell carcinoma (see Fig. 22-2B and C)
            a. Most common cancer
            b. Risk factors
               (1) HPV type 16
               (2) Smoking cigarettes
               (3) Immunodeficiency (e.g., AIDS)
            c. Metastasize first to the inguinal nodes
         4. Extramammary Paget disease
            a. Red, crusted vulvar lesion (see Fig. 22-2D)
            b. Intraepithelial adenocarcinoma
               (1) Tumor derives from primitive epithelial progenitor cells.
               (2) Malignant Paget cells contain mucin (see Fig. 22-2E).
                  • Mucin is periodic acid–Schiff (PAS) positive.
               (3) Spreads along the epithelium
                  • Rarely invades the dermis
<table>
<thead>
<tr>
<th>PATHogen</th>
<th>DESCRIPTION AND TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida albicans</em> (Fig. 22-1A)</td>
<td>Yeasts and pseudohyphae (elongated yeasts; indicate infection); part of normal vaginal flora. Symptomatic vaginitis: burning and itching; symptoms may be more severe in pregnancy. Risk factors: diabetes, antibiotics, pregnancy, OCs. Treatment: single oral dose of fluconazole or itraconazole.</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em> (Fig. 22-1B)</td>
<td>Third most common STD; often coexists with <em>Neisseria gonorrhoeae</em> (45% of cases). Incubation period 7–12 days after exposure; noninfective intracellular inclusions (reticulate bodies) present in phagosomes of metaplastic endocervical squamous cells in the cervix; reticulate bodies divide to form extracellular elementary bodies, which are the infective bodies producing infection; elementary bodies enter metaplastic endocervical squamous cells and become noninfective reticulate bodies. Infections in males: NSU (sterile pyuria), epididymitis, proctitis. Infections in females: urethritis (sterile pyuria), cervicitis, PID, perihepatitis (FHC syndrome—scar tissue between peritoneum and surface of liver from pus from PID), proctitis, Bartholin gland abscess. Infections in newborns: conjunctivitis (ophthalmia neonatorum), pneumonia. (refer to Chapter 17). Treatment: azithromycin or doxycycline.</td>
</tr>
<tr>
<td><em>Gardnerella vaginalis</em> (Fig. 22-1C)</td>
<td>Gram-negative rod that causes bacterial vaginosis. Most common vaginitis. Douching alters the microenvironment by decreasing lactobacilli (gram-positive rods that produce lactic acid and the normal vaginal pH of 3.8–4.5); new or multiple sex partners also predisposes to this vaginitis, because the pH of semen is alkaline (7.2–7.8), which allows the bacteria to proliferate and produce a malodorous vaginal discharge with a vaginal pH &gt; 4.5. Organisms adhere to (they do not invade) squamous cells producing “clue cells.” Increased incidence of preterm delivery and low-birth-weight newborns. Treatment: metronidazole (400–500 mg by mouth 3 times/day for 7 days) in pregnant women.</td>
</tr>
<tr>
<td><em>Haemophilus ducreyi</em> (Fig. 22-1D)</td>
<td>STD; lymphogranuloma venereum Papules and/or ulcerations; inguinal lymphadenitis with granulomatous micro-abscesses and draining sinuses; Lymphedema of scrotum or vulva; Women also may develop rectal strictures. Treatment: doxycycline.</td>
</tr>
<tr>
<td>HSV-2 (Fig. 22-1E and F)</td>
<td>STD; virus remains latent in the sensory ganglia. Characterized by recurrent vesicles that ulcerate; locations—penis, vulva, cervix, perianal area. Tzanck preparation: scrapings removed from the base of an ulcer show multilevel squamous cells with eosinophilic intranuclear inclusions. Pregnancy: if the virus is shedding, the baby is delivered by cesarean section. Treatment: acyclovir (decreases recurrences).</td>
</tr>
<tr>
<td>HPV (Fig. 22-1G)</td>
<td>Second most common overall STD (a few studies still consider it the most common STD); types 6 and 11 (90% of cases; low risk types) produce condyloma acuminata (venereal warts); they are fern-like or flat lesions located in the genital area (e.g., penis, vulva, cervix, perianal); approximately 80% of sexually active women will have acquired HPV by age 50 years. Virus produces koilocytic change in the squamous epithelium (see Fig. 22-4B); cells have wrinkled pyknotic nuclei surrounded by a clear halo. Approximately 90% of the warts spontaneously clear within 2 years (most within 8 months); older women more often have persistent disease, because of a decrease in cellular immunity. HPV vaccine decreases the risk for developing venereal warts. Treatment: topical podophyllin, sinecatechin (botanical drug) ointment, α-IFN injection, imiquimod cream, laser phototherapy.</td>
</tr>
<tr>
<td><em>Klebsiella granulomatis</em></td>
<td>STD; gram-negative coccobacillus that causes granuloma inguinale. Organism is phagocytized by macrophages (Donovan bodies). Creeping, raised sore that heals by scarring; no lymphadenopathy. Treatment: doxycycline.</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em> (Fig. 22-1H and I)</td>
<td>Fourth most common STD; gram-negative diplococcus that infects glandular or transitional epithelium; symptoms appear 2–7 days after sexual exposure. Infection sites are similar to <em>C. trachomatis</em>. Complications: ectopic pregnancy, male sterility, disseminated gonococccemia (C6–C9 deficiency is a risk factor), septic arthritis, FHC syndrome, disseminated gonococccemia (septic arthritis [knee], tenosynovitis [hands, feet], pustules [hands, feet], women &gt; men). Nucelic acid amplification test has the highest sensitivity and specificity; other tests: urethral swab in symptomatic males with Gram stain; endocervical swab for culture. Treatment: ceftriaxone.</td>
</tr>
<tr>
<td><em>Treponema pallidum</em> (Fig. 22-1J to L)</td>
<td>Fifth most common STD; gram-negative spirochete that causes syphilis. Primary syphilis: solitary painless, indurated chancre; locations—penis, labia, anus, mouth. Secondary syphilis: maculopapular rash on trunk, palms, soles; generalized lymphadenopathy; condylomata lata, which are flat lesions in the same area as condylomata acuminata; alopecia (hair loss). Tertiary syphilis: neurosyphilis, aortitis, gummas. Congential syphilis (refer to Chapter 6). Confirmatory treponemal test: FTA-ABS; positive (with or without treatment) Jarisch-Herxheimer reaction: intensification of the rash in secondary syphilis may occur because of proteins released from dead organisms after treatment with penicillin. Treatment: penicillin.</td>
</tr>
</tbody>
</table>
TABLE 22-1 Sexually Transmitted Diseases and Other Genital Infections—cont’d

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>DESCRIPTION AND TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Trichomonas vaginalis</em></td>
<td>Most current studies consider it to be the most common STD; flagellated protozoan with jerky motility in a wet prep of discharge.</td>
</tr>
<tr>
<td></td>
<td>Most women are asymptomatic or have a vaginal discharge; men are asymptomatic carriers who serve as a reservoir for infection in women; increased susceptibility for HIV and increased HIV shedding.</td>
</tr>
<tr>
<td></td>
<td>Produces vaginitis, cervicitis, and urethritis, PID, preterm delivery, low-birth-weight babies; strawberry-colored cervix and fiery red vaginal mucosa; greenish, frothy discharge.</td>
</tr>
<tr>
<td></td>
<td>Diagnosis: nucleic acid amplification test has the highest sensitivity and specificity; other tests: culture, monoclonal fluorescent antibody staining; oral and rectal tests not recommended.</td>
</tr>
<tr>
<td></td>
<td>Treatment: metronidazole (both partners)</td>
</tr>
</tbody>
</table>

*FHC,* Fitz-Hugh–Curtis; *FTA-ABS,* fluorescent treponeme antibody-absorption test; *HPV,* human papillomavirus; *HSV,* herpes simplex virus; *IFN,* interferon; *NSU,* nonspecific urethritis; *OCP,* oral contraceptive pill; *PCR,* polymerase chain reaction; *PID,* pelvic inflammatory disease; *RPR,* rapid plasma reagin; *STD,* sexually transmitted disease; *VDRL,* Venereal Disease Research Laboratory.

22-1: Genital infections. **A,** *Candida.* Bottom arrow shows elongated yeasts (pseudohyphae); top arrow shows yeasts. **B,** *Chlamydia trachomatis* life cycle. See Table 22-1 for discussion. **C,** Lymphogranuloma venereum (*Chlamydia trachomatis* subspecies). The patient has unilateral vulvar lymphedema and inguinal ulcerations (four white areas). **D,** *Gardnerella vaginalis.* Superficial squamous cells are covered by granular material representing bacterial organisms attached to (not invading) the surface. **E,** Herpes type 2. Arrows show ulcerated, red lesions on the shaft of the penis. **F,** Herpes type 2. Biopsy showing a multinucleated squamous cell with smudged, “ground glass” nuclei with intranuclear inclusions (arrow). **G,** *Human papillomavirus.* Numerous keratotic papillary (fern-like) processes are present on the surface of the labia. These are called venereal warts or condylomata acuminata. **H,** *Neisseria gonorrhoeae* purulent penile discharge.

5. Malignant melanoma
   a. Melanoma cells are histologically similar to Paget cells.
   b. Unlike Paget cells, melanoma cells are PAS negative.

III. Vagina Disorders

A. Rokitansky–Küster–Hauser (RKH) syndrome
   1. Definition—condition where the vagina and uterus are underdeveloped or absent
      • Ovaries are usually present and functional.
   2. Most likely results from a combination of genetic and environmental factors
      • Some cases appear to have an autosomal dominant inheritance pattern.
   3. Anatomic cause of primary amenorrhea

B. Gartner duct cyst
   1. Remnant of the Wolffian (mesonephric) duct
   2. Presents as a cyst on the lateral wall of the vagina

C. Benign and malignant tumors
   1. Rhabdomyoma
      a. Benign tumor (? hamartoma) of skeletal muscle
      b. Other locations are the tongue and heart (associated with tuberous sclerosis).
   2. Embryonal rhabdomyosarcoma
      a. Most common sarcoma in girls
      • Malignancy of skeletal muscle (rhabdomyoblasts with striations)
      b. Occurs in common sarcoma in girls
      c. Necrotic, grape-like mass protrudes from the vagina (Fig. 22-3A).
   3. Clear cell adenocarcinoma of the vagina (see Fig. 22-3B)
      a. Epidemiology
         (1) Occurs in women with intrauterine exposure to diethylstilbestrol (DES)
            • DES was used to prevent a threatened abortion (refer to Chapter 6).
22-2: A, Lichen sclerosis. The vulva shows a parchment-like appearance (arrow). B, Gross appearance of invasive squamous cell carcinoma of vulva. Note the huge tumor mass involving all vulvar structures. C, Microscopic appearance of invasive squamous cell carcinoma of the vulva. It is a well-differentiated tumor. Note the keratin squamous pearls (arrows), a very characteristic finding in squamous cancers. D, Clinical and gross appearance of vulvar Paget disease. Note the extensive red, crusted lesion. E, Extramammary Paget disease. Large, pink-staining, malignant Paget cells (arrows) are disposed singly and in clusters within the epidermis. In Paget disease of the nipple, the same kinds of cells are present in the epidermis. (A from Savin JAA, Hunter JAA, Hepburn NC: Diagnosis in Color: Skin Signs in Clinical Medicine. London, Mosby-Wolfe, 1997, p 124, Fig. 4.81; B to E from Rosai J: Rosai and Ackerman’s Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, pp 1489, 1490, 1492, respectively, Figs. 19.11D, 19.12A, 19.16A, 19.17B, respectively.)

22-3: A, Embryonal rhabdomyosarcoma of vagina. Note the bloody, necrotic mass protruding out of the vagina. B, Clear cell carcinoma of the vagina. Note the clear, vacuolated cells with ill-defined glandular spaces. (A from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 266, Fig. 13-29; B from Klatt E: Robbins and Cotran Atlas of Pathology, Philadelphia, Saunders, 2006, p 295, Fig. 13-12.)
(2) DES inhibits müllerian differentiation.
   - Müllerian structures include fallopian tubes, uterus, cervix, upper one third of vagina
(3) Vaginal adenosis
   (a) Benign remnants of müllerian glands
   - Produces red, superficial ulcerations in the upper portion of the vagina
   (b) Precursor lesion for clear cell adenocarcinoma
(4) The risk for developing the cancer is small (1:1000).
(5) Cancer involves the upper vagina.

b. Other DES abnormalities
   (1) Abnormally shaped uterus that thwarts implantation
   (2) Cervical incompetence
      - Common cause of recurrent abortions

4. Vaginal squamous cell carcinoma
   a. Primary SCC is associated with HPV type 16.
   b. Most cancers are an extension of a cervical SCC into the vagina.
   c. Primary cancers metastasize to the inguinal lymph nodes.

IV. Cervix Disorders

A. Clinical anatomy and histology

1. Cervix includes the endocervix + exocervix.
   - Exocervix begins at the cervical os.
2. Exocervix is normally lined by squamous epithelium.
3. Endocervical glands are normally lined by mucus-secreting columnar cells.
4. Endocervical epithelium normally migrates down to the exocervix
   (Fig. 22-4A).
   a. Exposure to the acid pH of the vagina causes benign squamous metaplasia.
      - Lactobacilli (gram + rod) produce lactic acid, which maintains the acid pH in the vagina.
   b. Area undergoing metaplasia is called the transformation zone (TZ).
      (1) TZ is where squamous dysplasia and cancer develop.
      (2) TZ must be sampled when performing a cervical Papanicolaou (Pap) smear.
   c. Metaplastic squamous cells block endocervical gland orifices.
      (1) Obstruction of outflow of mucus produces nabothian cysts.
      (2) Nabothian cysts are a normal finding in adult women.

B. Acute and chronic cervicitis

1. Epidemiology
   a. Accounts for 20% to 25% of patients presenting with vaginal discharge
   b. Can be found in any sexually active woman
   c. Subdivided into acute and chronic cervicitis
2. Acute cervicitis
   a. Acute inflammation is normally present in the TZ.
   b. Pathologic acute cervicitis; causative agents include:
      - Chlamydia trachomatis, N. gonorrhoeae, Trichomonas vaginalis, Candida, human herpesvirus 2 (HSV-2), HPV
   c. Clinical findings
      (1) Vaginal discharge (most common)
      (2) Pelvic pain, dyspareunia (painful intercourse)
      (3) Painful on palpation, bleeds easily when obtaining cultures
      (4) Cervical os is erythematous and may be covered by an exudate
   d. Diagnosis
      (1) DNA probe for C. trachomatis and N. gonorrhoeae
      - These organisms account for >50% of cases of acute cervicitis.
      (2) Wet mount for T. vaginalis (jerky movements)
      (3) Obtain a cervical Pap smear
   e. Treatment
      (1) Culture or DNA probe positive for C. trachomatis, N. gonorrhoeae, treat with appropriate antibiotic
      (2) Culture negative, cryosurgery is an option
      (3) Advise safe sex with the use of condoms
3. Chronic cervicitis
   - Occurs when acute cervicitis persists
4. Follicular cervicitis
   a. Caused by *C. trachomatis*
   b. Pronounced lymphoid infiltrate with germinal centers
   c. *C. trachomatis* infects metaplastic squamous cells.
      (1) Cells contain vacuoles (phagosomes) with inclusions (reticulate bodies).
      (2) Reticulate bodies divide into elementary bodies, which are infective particles.
   d. Cervicitis is the primary source for *C. trachomatis*, *N. gonorrhoeae* conjunctivitis
      (ophthalmia neonatorum), and pneumonia in newborns.
     - Example of vertical transmission of an infection to a newborn (contact with infected
cervix during delivery)
C. Cervical Pap smear

1. Purpose
   a. Screening test to rule out (R/O) squamous dysplasia and cancer
   b. To evaluate the hormone status of the woman

2. Sample sites
   a. Vagina, exocervix, TZ

Because the transformation zone (TZ) is the site for squamous dysplasia and squamous cancer, it must be adequately sampled. The presence of metaplastic squamous cells or mucus-secreting columnar cells indicates proper sampling. Absence of these cells means that the Pap smear must be repeated.

3. Interpretation
   a. Superficial squamous cells indicate adequate estrogen.
   b. Intermediate squamous cells indicate adequate progesterone.
   c. Parabasal cells indicate a lack of estrogen and progesterone.
   d. Normal nonpregnant adult woman
      • 70% superficial squamous cells, 30% intermediate squamous cells
   e. Pregnant woman
      • 100% intermediate squamous cells from progesterone effect
   f. Elderly woman with lack of estrogen and progesterone
      • Atrophic smear with parabasal cells and inflammation
   g. Woman with continuous exposure to estrogen without progesterone
      (1) 100% superficial squamous cells
      (2) Woman may be taking estrogen without progesterone or she has a tumor secreting estrogen (e.g., granulosa cell tumor of ovary)

D. Cervical (endocervical) polyp

1. Epidemiology
   a. Nonneoplastic polyp that protrudes from the cervical os
   b. Arises from the endocervix, not the cervix
   c. Most commonly present in perimenopausal women and multigravida women
   d. Most commonly occurs between 30 and 50 years of age
   e. Not precancerous

2. Pathogenesis
   • Inflammation, trauma, pregnancy have been implicated.

3. Clinical findings
   • Postcoital bleeding, vaginal discharge

4. Treatment is surgical excision.

E. Cervical intraepithelial neoplasia (CIN)

1. Epidemiology
   a. Majority of cases are associated with HPV.
      (1) Types 6 and 11 carry a low risk.
      (2) Types 16 and 18 carry a high risk.
      (3) HPV produces koilocytosis in squamous cells (see Fig. 2-4B and C).
         • Clear halo containing a wrinkled, pyknotic nucleus
   b. Peak incidence is 35 years of age.
   c. False negative rate for detecting dysplasia on a cervical Pap smear is ~40%.
   d. Risk factors
      (1) Early age of onset of sexual intercourse
      (2) Multiple, high-risk partners
      (3) High-risk types of HPV in a biopsy
      (4) Smoking, oral contraceptive pills (OCPs), immunodeficiency

2. Classification
   a. CIN I
      • Mild dysplasia involving the lower one third of the epithelium
   b. CIN II
      • Moderate dysplasia involving the lower two thirds of the epithelium
   c. CIN III (see Fig. 2-14H)
      • Severe dysplasia to CIS involving the full thickness of the epithelium

3. Progression from CIN I to CIN III is not inevitable.
   a. Reversal to normal is more likely in CIN I.
   b. Requires ~10 years to progress from CIN I to CIN III
Female Reproductive Disorders and Breast Disorders

V. Reproductive Physiology and Selected Hormone Disorders

A. Sequence to menarche
1. Breast budding (thelarche)
2. Growth spurt
3. Pubic hair
4. Axillary hair
5. Menarche
   a. Mean age of menarche is 12.8 years.
   b. Anovulatory cycles last for 1 to 1.5 years.

B. Summary of the normal menstrual cycle
1. Synthesis of sex hormones in the ovary (Fig. 22-5)
2. Proliferative (follicular) phase (Fig. 22-6)
   a. Estrogen-mediated proliferation of glands
      • Most variable phase of the cycle
   b. Estrogen surge (dark hashed curve) occurs 24 to 36 hours before ovulation.
      (1) Stimulates luteinizing hormone (LH) release (dark solid blue line)
         a. Positive feedback
         b. Called the LH surge

4. Clinical findings
   a. Dysplasia is not usually visible to the naked eye and requires colposcopy (direct visualization with a scope).
      • Occasionally, flat to warty condyloma acuminata are visible.
   b. Colposcopy findings, after application of acetic acid include:
      • White areas with punctuation, mosaic pattern, or abnormal vascularity

5. Treatment
   • Electrocoagulation, cryotherapy, laser ablation, local surgery (conization)

F. Cervical cancer
1. Epidemiology
   a. Least common gynecologic cancer and least common gynecologic cancer producing mortality
   b. Higher incidence in developing countries (no easy access to health care)
   c. In the U.S. population, the incidence of cervical cancer in descending order is:
      • Hispanic, black, white
   d. Majority are SCC (75%–80% of cases)
      • Small cell cancer and adenocarcinoma are less common types.
   e. Cause and risk factors
      • Same as those listed for CIN
   f. Cervical Pap smears have markedly reduced the incidence and mortality from cervical cancer.
      (1) Pap smear detection of low-grade cervical dysplasia has a sensitivity of ~70% and specificity of 75%.
      (2) Pap smear detection of high-grade cervical dysplasia has a sensitivity of 75% and specificity of 95%.

2. Clinical findings (see Fig. 22-4D and E)
   a. Abnormal vaginal bleeding (most common)
      • Usually postcoital
   b. Malodorous discharge
   c. Postcoital bleeding

3. Cancer characteristics
   a. Extends down into the vagina
   b. Extends out into the lateral wall of the cervix and vagina
   c. Frequently infiltrates the bladder wall and obstructs the ureters
      • Postrenal azotemia leading to renal failure is a common cause of death.
   d. Distant metastasis (e.g., lungs)

4. Treatment of invasive cancer
   a. Surgery, radiation, or both
   b. Chemotherapy in selected cases

5. Prognosis
   • The 1- and 5-year relative survival rates are 88% and 72%, respectively.

Average age for cervical SCC is ~45 years

Cervical cancer: least common gynecologic cancer; cancer with lowest mortality

Cervical Pap smear most responsible for decreased incidence/mortality

Cervical cancer: renal failure common cause of death

Sequence to menarche: breast budding, growth spurt, pubic hair, axillary hair, menarche

Proliferative phase: estrogen-mediated; most variable phase

Estrogen causes gland proliferation

---
22-5: Synthesis of sex hormones in the ovaries. Luteinizing hormone is responsible for stimulation of hormone synthesis in the theca interna surrounding the developing follicle. Follicle-stimulating hormone increases the synthesis of aromatase in granulosa cells. Aromatase converts testosterone to estradiol. (From Goljan EF: Star Series: Pathology; Philadelphia, Saunders, 1998, Fig. 18-1.)

22-6: Menstrual cycle. Estrogen is most important in the proliferative phase and progesterone the secretory phase of the cycle. Estrogen surge causes LH surge, which initiates ovulation. Note the positive feedback of estrogen on LH is greater than FSH. *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone. (From Brown TA: Rapid Review Physiology, Philadelphia, Mosby, 2007, p 99, Fig. 3-15.)
3. Secretory phase (see Fig. 22-6)
   a. Progesterone-mediated
      - Least variable phase of the cycle
   b. Increased gland tortuosity and secretion
   c. Edema of stromal cells
   d. Other functions of progesterone
      - Important in maintaining pregnancy

   e. Changes that occur after fertilization
      1. Fertilization usually takes place in the ampullary portion of the fallopian tube.
      2. Fertilized egg spends 3 days in the fallopian tube and 2 days in the uterine cavity.
         • Implants in the endometrial mucosa on day 21
      3. An exaggerated secretory phase occurs in pregnancy.
         • Called the Arias-Stella phenomenon

4. Menses
   a. Initiated by drop-off in serum levels of estrogen and progesterone
      1. This is a signal for the endometrial cells to undergo apoptosis.
      2. Newborn baby girls commonly have vaginal bleeding.
         • Due to sudden drop of maternal hormones with delivery
   b. Plasmin prevents menstrual blood from clotting.
      • Excess clotting is a sign of menorrhagia, because it implies that plasmin did not have enough time to lyse fibrinogen in the clot.

5. Functions of FSH
   a. Prepares the follicle of the month
      1. Unstimulated follicles in the ovary are arrested in meiosis I prophase.
      2. FSH causes the follicle to get larger.
   b. Increases aromatase synthesis in the granulosa cells in the follicle
   c. Increases the synthesis of LH receptors
      • LH is important in stimulating sex hormone synthesis in the theca interna around the follicle.

6. Functions of LH
   a. LH in the proliferative phase
      1. LH increases the synthesis of 17-ketosteroids (17-KSs) in the theca interna of the developing follicle (see Fig. 22-5).
         • 17-KSs are dehydroepiandrosterone (DHEA) and androstenedione.

   b. Takes 5 days for egg to implant
   c. Arias-Stella phenomenon: exaggerated secretory phase that occurs in pregnancy
   d. Menses: drop in hormones initiates apoptosis
   e. Newborn girls: vaginal bleeding; mother’s estrogen causes endometrial hyperplasia
   f. FSH: prepares follicle, aromatase synthesis, LH receptor synthesis
   g. Unstimulated follicles are in meiosis I prophase
   h. LH proliferative phase: synthesis of testosterone for conversion by aromatase into estradiol in granulosa cells
2. DHEA is converted to androstenedione.
3. Oxidoreductase converts androstenedione to testosterone.
4. Testosterone enters granulosa cells in the developing follicle and aromatase converts it to estradiol (called aromatization).

b. LH surge is induced by a sudden increase in estrogen (earlier discussion).
   (1) Ovulation occurs when LH > FSH.
   (2) The LH-stimulated follicle moves from meiosis I prophase into meiosis II metaphase.
   (3) Fertilization of the stimulated follicle by a sperm causes the follicle to develop into a mature oocyte with 23 chromosomes.

c. LH in the secretory phase (see Fig. 22-5)
   • Theca interna primarily synthesizes 17-hydroxyprogesterone (17-OH-progesterone).

7. Hormone changes in pregnancy
   a. Human chorionic gonadotropin (hCG)
      (1) Synthesized in the syncytiotrophoblast lining the chorionic villus in the placenta
      (2) Acts as an LH analogue by maintaining the corpus luteum of pregnancy.
      (3) Corpus luteum synthesizes progesterone for ~8 to 10 weeks.
   b. Corpus luteum involutes after ~8 to 10 weeks.
      (1) Placenta synthesizes progesterone for the remainder of the pregnancy.
      • Important in maintaining pregnancy
      (2) Spontaneous abortion may occur at this time if placental production of progesterone is inadequate.

C. Oral contraceptive pills (OCPs)
   1. Mixture of estrogen + progesterins (progesterone)
      a. Baseline levels of estrogen in OCPs prevent the midcycle estrogen surge; hence, preventing the LH surge and ovulation.
      b. Progestins arrest the proliferative phase and cause gland atrophy.
      c. Progestins inhibit LH, which also prevents the LH surge.
   2. OCPs alter fallopian tube motility.

D. Sources and types of estrogen
   1. Estradiol
      a. Primary estrogen in nonpregnant women
      b. Principally derived from the ovaries
      c. Primary hormone responsible for the proliferative (follicular) phase of the menstrual cycle (earlier discussion)
      d. Stimulates growth of the stroma in the endometrium
      e. Stimulates elongation of the spiral arteries, which supply the endometrium
      f. Causes cervical mucus to become copious and watery
         (1) In the proliferative phase, it is responsible for "ferning" when cervical mucus is spread on a glass slide
         (2) Watery mucous allows sperm to move through the cervix
      g. Stimulates growth and development of the female reproductive system
      h. Important in normal breast development, prolactin secretion, and maintaining pregnancy
   2. Estrone
      a. Weak estrogen produced during menopause
      b. Derived from adipose cell aromatization of androstenedione
         • Androstenedione is synthesized in the adrenal cortex, because the ovaries undergo atrophy in the menopause.
   3. Estriol
      a. Primary estrogen of pregnancy
      b. Derives from fetal adrenal/liver, placenta, and maternal liver (refer to section IX)

E. Sources and types of androgens
   1. Androstenedione
      • Equal derivation from ovaries and adrenal cortex
   2. DHEA
      a. Most is synthesized in the adrenal cortex (80%).
      b. Remainder is synthesized in the ovaries.
   3. DHEA-sulfate (DHEA-S)
      • Almost exclusively synthesized in the adrenal cortex
4. Testosterone  
   a. Derived from conversion of androstenedione to testosterone  
   b. Testosterone is synthesized in the ovaries and adrenal glands.  
      • Testosterone is peripherally converted to 5-α-dihydrotestosterone (DHT) by  
        5-α-reductase, located in the ovaries, adrenal glands, and liver.  

F. Sex hormone-binding globulin (SHBG) (Fig. 22-8)  
1. Binding protein for testosterone and estrogen (refer to Chapter 21)  
   a. In both men and women, SHBG is primarily synthesized in the liver.  
   b. Estrogen increases synthesis of SHBG in the liver.  
   c. Androgens, obesity, hypothyroidism all decrease the synthesis of SHBG.  
2. SHBG has a greater binding affinity for testosterone than for estrogen.  
   a. Increased SHBG decreases free testosterone (FT) levels.  
   b. Decreased SHBG increases FT levels.  
      • Common cause of hirsutism in women (see later discussion)  

G. Normal changes in pregnancy (refer to Chapter 1)  
1. Plasma volume and RBC mass  
   a. Both are increased  
      • Increase in plasma volume > increase in RBC mass  
   b. Causes a 1 g/dL drop in hemoglobin (Hb) (dilutional effect)  
   c. Increases glomerular filtration rate (GFR)  
      (1) Creatinine clearance (CCr) is increased.  
      (2) Clearance of urea and creatinine is increased.  
         • Serum levels are at the lower limit of normal.  
      (3) Increases pressure to pump blood into the maternal lake in the placenta  
2. Respiratory alkalosis  
   a. Effect of estrogen and progesterone stimulating respiratory center  
   b. Decrease in PaCO₂ causes a corresponding increase in PaO₂ (more O₂ for fetus)  
3. Increased serum thyroxine (T₄) and cortisol  
   a. Estrogen stimulates synthesis of thyroid-binding globulin and transcortin.  
   b. Increased binding proteins increases total T₄ and cortisol.  
   c. Metabolically active free hormone levels are normal (refer to Chapter 23).  
      • No clinical signs of overactivity  

H. Menopause  
1. Epidemiology  
   a. Definition—no menses for 1 year after age 40 years  
   b. Causes  
      (1) Physiologic  
         (a) Waxing and waning of estrogen levels  
            • Due to decreased ovarian function  
         (b) Depletion of granulosa and thecal cells  
         (c) Lack of ovarian response to gonadotropins  
         (d) Increased LH stimulates androgen production in stromal cells  
      (2) Surgical removal/radiation of ovaries  
      (3) Turner syndrome (refer to Chapter 6)  
      (4) Family history of early menopause  
      (5) Left-handedness  
   c. Average age of menopause is 51 years old.  
      (1) Age at which menopause occurs is genetically determined.  
      (2) Smokers reach menopause earlier than nonsmokers.  
      (3) Onset of perimenopause is mid to late 40s.  
2. Clinical findings  
   a. Secondary amenorrhea  
   b. Hot flushes, night sweats
Hirsutism: PCOS MCC

Testosterone ↑ in menopause: ↑ Libido in some women

Menopause: ↑ FSH best marker; ↓ estradiol, progesterone

Menopause: hot flushes, night sweats, mood swings

c. Atrophic vaginitis
   - Pruritus, burning, bleeding, dyspareunia
d. Mood swings, anxiety, depression, insomnia
e. Increased libido (sexual desire) may occur
   1. Testosterone is thought to be the key hormone that determines libido in a woman.
   2. Testosterone normally increases before ovulation in the normal menstrual cycle.
   3. Because estradiol decreases in menopause, a decrease in SHBG synthesis leads to higher free testosterone levels and increased libido.
f. Urinary incontinence (refer to Chapter 21)
g. Headaches, tiredness, lethargy
h. Osteoporosis (refer to Chapter 24)
   • Increased risk for vertebral and Colles fractures

3. Laboratory findings
a. Increase in FSH and LH
   1. Due to drop in estrogen and progesterone, respectively
   2. Serum FSH is the best marker.
b. Decrease in serum estradiol

4. Treatment
a. Estrogen replacement if symptomatic
b. Progestin is added if uterus is still present
   - Prevents endometrial adenocarcinoma
c. Risks of long-term combined therapy (refer to Chapter 7)
   1. Thromboembolism
   2. Coronary heart disease, stroke
   3. Slight risk for breast cancer
   4. Increased risk for dementia in women ≥65 years old
      • Applies also if only taking estrogen

I. Hirsutism and virilization
1. Epidemiology and pathogenesis
a. Hirsutism is excess hair in normal hair-bearing areas (Fig. 22-9A).
   • Virilization is hirsutism + male secondary sex characteristics.
b. Male secondary sex characteristics
   1. Increased muscle mass
   2. Male hair distribution from mons pubis to umbilicus (see Fig. 22-9B)
   3. Acne
   4. Enlarged clitoris (clitoromegaly) (see Fig. 22-9C)
      • Most important finding
c. Both conditions are due to increased androgens of ovarian or adrenal origin
   1. Ovarian origin—testosterone (free testosterone; sometimes total) is primarily increased
   2. Adrenal origin—DHEA-S and testosterone increased
d. Causes
   1. Polycystic ovary syndrome (PCOS; see later discussion; 75% of cases)
   2. Idiopathic (5%–15% of cases)
   3. Adrenogenital syndrome (congenital adrenal hyperplasia; 1%–8% of cases; refer to Chapter 23)
   4. Insulin resistance syndrome (3%–4% of cases; see section VIII)
   5. Drugs (<1% of cases)
      • Examples—androgenic progestins, phenytoin, cyclosporin, minoxidil
   6. Ovarian tumor (<1% of cases; see section VIII)
      • Leydig cell tumor, Sertoli-Leydig cell tumor
   7. Adrenal tumor (<1% of cases)
      • Adenoma/carcinoma producing Cushing syndrome
   8. Obesity
      • Decreased SHBG causes an increase in free testosterone.
   9. Hypothyroidism
2. Polycystic ovary syndrome (PCOS)
a. Epidemiology and pathophysiology
   1. Occurs in 3% of adolescents and adults
   2. Symptoms begin around menarche.
Female Reproductive Disorders and Breast Disorders

22-9: **A**, Hirsutism. This woman has excess hair above the lip and on the chin. **B**, Virilization. This woman has a male distribution of hair from the mons pubis to the umbilicus. **C**, Clitoromegaly. Note the elongation of the clitoris, which is the gold standard sign of virilization. **D**, Polycystic ovary syndrome showing an enlarged ovary with multiple subcortical cysts. **E**, Polycystic ovary syndrome showing an ultrasound with an enlarged ovary demonstrating multiple subcortical cysts (arrows). (A from Goljan EF, Sloka KI: Rapid Review Laboratory Testing in Clinical Medicine, Philadelphia, Mosby Elsevier, 2008, p 369, Fig. 10-12; B and C from Bouloux P: Self-Assessment Picture Tests: Medicine, Vol. 1. London, Mosby-Wolfe, 1997, pp 47, 4, respectively, Figs. 93, 7, respectively; D from Damjanov I, Linder J: Pathology: A Color Atlas. St. Louis, Mosby, 2000, p 262, Fig. 13-17A; E from Pretorius ES, Solomon JA: Radiology Secrets, 2nd ed. Philadelphia, Mosby, 2006, p 204, Fig. 24-7.)

(3) Associated with an increase in the incidence of obesity (40%-50% of cases), insulin resistance (metabolic syndrome; refer to Chapter 23), and acanthosis nigricans (refer to Chapter 25)

(4) Key to the pathogenesis of PCOS is increased secretion of LH by the anterior pituitary gland relative to secretion of FSH (LH/FSH ratio >3)
   (a) May result from either increased gonadotropin–releasing hormone hypothalamic secretion or, less likely, from a primary anterior pituitary abnormality
   (b) Increased LH produces hyperplasia of ovarian theca cells around ovarian follicles (called follicular hyperthecosis) and an increase in the production of testosterone and androstenedione (hyperandrogenicity, earlier discussion).

(5) Pituitary secretion of FSH is decreased relative to LH secretion
   (a) The effect of this imbalance leads to decreased ovarian granulosa cell aromatization of androgens to estrogens (normally a function of FSH).
      • Clinical problems related to this imbalance are hyperandrogenicity and chronic anovulation (due to decreased estrogen).
   (b) Another clinical effect is follicular arrest (lack of further maturation of the follicle) and the formation of subcortical cysts that enlarge the ovaries (see Fig. 22-9D and E).
Menstrual dysfunction

1. Menorrhagia
   a. Definition—loss of blood >80 mL per period
   b. Menorrhagia is likely if there is:
      (1) Staining of sheets at night with heavy protection.
      (2) Excessive passage of clots.
         • Indicates plasmin does not have enough time to dissolve clot

2. Dysmenorrhea
   a. Epidemiology
      (1) Definition—painful menses
      (2) Approximately 50% of women have dysmenorrhea.
         • Approximately 10% are incapacitated for 1 to 3 days.
      (3) Primary type
         (a) Only occurs in ovulatory cycles
         (b) Due to increased prostaglandin $F_{2\alpha}$ (PGF$_{2\alpha}$)
            • Increases uterine contractions
      (4) Secondary type
         • Associated with other disorders
            (a) Endometriosis (most common)
            (b) Adenomyosis
            (c) Leiomyomas, cervical stenosis
   b. Treatment
      (1) Primary type
         • Nonsteroidal antiinflammatory drugs, OCPs, nifedipine, magnesium sulfate
      (2) Secondary type
         • Treat the underlying disease

3. Dysfunctional uterine bleeding (DUB)
   a. Epidemiology
      (1) Definition—abnormal uterine bleeding with no anatomic cause
      (2) Hormone imbalances are frequently present.
      (3) Types of abnormal bleeding
         (a) Menorrhagia (most common)
            • Regular normal intervals with excessive flow and duration
         (b) Hypomenorrhoea
            • Definition—regular normal intervals with decreased amount of bleeding
         (c) Menorrhagia
            • Definition—irregular intervals with excessive flow and duration
         (d) Menometrorrhagia
            • Definition—irregular or excessive bleeding during menstruation and between periods

(6) Excess androstenedione is converted to estrone
   • Although a weak estrogen, increased levels of estrone may produce endometrial gland hyperplasia/cancer and breast cancer (discussed below).

b. Clinical findings
   (1) Oligomenorrhea (infrequent menses)
   (2) Hirsutism (more common than virilization), infertility, obesity, diabetes mellitus (insulin-resistance)
   (3) Problems related to endometrial gland hyperplasia/cancer (e.g., vaginal bleeding)

c. Laboratory findings
   (1) LH/FSH ratio >3
   (2) Increased serum free testosterone and androstenedione
   (3) Decreased serum SHBG
   (4) Serum FSH levels normal to decreased

d. Treatment
   (1) Weight reduction in obese women
   (2) Reduce ovarian production of androgens with an oral contraceptive (first line treatment)
      • Induce regular menses, inhibits ovarian androgen production, increases sex hormone-binding globulin (SHBG) production.
   (3) LH-releasing hormone analogues
      • Inhibit ovarian androgen production

DUB: abnormal bleeding unrelated to an anatomic cause
(e) Oligomenorrhea  
- Definition—menses at intervals >35 days  
(f) Polymenorrhea  
- Definition—menses at interval <21 days  
(4) Most cases occur postmenarchal and perimenopausal (most common).  
- Majority of these are anovulatory types of DUB  
(5) Overall, ~90% of cases of DUB are anovulatory and the remaining 10% are ovulatory types of DUB  
(6) During the reproductive age, 80% are ovulatory types of DUB.  

b. Anovulatory DUB  
(1) Occurs at the extremes of reproductive life  
   (a) Menarche to age 20 years  
   (b) Perimenopausal period  
(2) Pathogenesis—excessive estrogen stimulation relative to progesterone stimulation  
   (a) Absent secretory phase of the cycle  
   (b) Produces endometrial hyperplasia and excessive bleeding  
(3) Treatment  
- OCPs, progestational agents  

c. Ovulatory DUB  
(1) Inadequate luteal phase  
   (a) Pathogenesis—inadequate maturation of the corpus luteum leading to inadequate synthesis of progesterone  
   (b) Delay in development of the secretory phase  
   (c) Implicated in infertility, recurrent pregnancy loss, irregular cycles (<26 days)  
   (d) Document by showing decreased serum 17-hydroxyprogesterone levels drawn after ovulation  
(2) Irregular shedding of the endometrium  
   (a) Pathogenesis—persistent luteal phase with continued secretion of progesterone  
   (b) Mixture of proliferative and secretory glands in the menstrual effluent  
   (c) Menorrhagia, break-through bleeding  

4. Causes of abnormal bleeding by age (Table 22-2)  

K. Amenorrhea  
1. Epidemiology  
   a. Primary amenorrhea  
      (1) Definition—absence of menses by 16 years of age  
      (2) Most cases are due to constitutional delay.  
         - Family history of delayed onset of menses  
   b. Secondary amenorrhea  
      (1) Definition—absence of menses for >6 months in a patient who has had normal menstrual cycles  
      (2) Most cases are due to pregnancy.  
2. Pathogenesis  
   a. Hypothalamic or pituitary disorder  
      (1) Decreased synthesis of FSH and LH  
         (a) Decreased synthesis of estrogen and progesterone  
         (b) Hypogonadotropic (↓FSH and LH) hypogonadism  
      (2) No withdrawal bleeding after receiving progesterone  
         - Endometrial mucosa is not estrogen stimulated.  

**Table 22-2 Causes of Abnormal Bleeding by Age**  

<table>
<thead>
<tr>
<th>AGE BRACKET</th>
<th>CAUSES OF BLEEDING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal</td>
<td>Vulvovaginitis: poor hygiene, infection (e.g., gonorrhea), sexual abuse, foreign bodies Embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>Menarche to 20 years</td>
<td>Anovulatory DUB (most common cause) von Willebrand disease (refer to Chapter 15)</td>
</tr>
<tr>
<td>20–40 years</td>
<td>Pregnancy and its complications (most common cause) Ovulatory types of DUB PID, hypothyroidism, submucosal leiomyomas, adenomyosis, endometrial polyp, endometriosis</td>
</tr>
<tr>
<td>≥40 years</td>
<td>Anovulatory DUB (most common cause in perimenopausal period) Endometrial hyperplasia/cancer (most common cause in menopause)</td>
</tr>
</tbody>
</table>

*Oligomenorrhea: menses at intervals >35 days  
Polymenorrhea: menses at interval <21 days  
DUB: menarche, perimenopausal period; most are anovulatory  
Anovulatory DUB: MC type DUB; excessive estrogen stimulation; extremes of reproductive life  
Ovulatory types DUB: inadequate luteal phase; irregular shedding of the endometrium  
Ovulatory DUB (inadequate luteal phase); inadequate maturation of corpus luteum; delayed secretory phase due to ↓17-OH progesterone synthesis  
Ovulatory DUB (irregular shedding of endometrium); persistent luteal phase with continued secretion progesterone; mixture proliferative/secretory glands  
1° amenorrhea: no menses by 16 years of age; MCC constitutional delay  
Secondary amenorrhea: no menses for >6 months; MCC pregnancy.*
**TABLE 22-3 Differential Diagnosis of Amenorrhea**

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>FSH/LH</th>
<th>ESTROGEN</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamic/pituitary disorder</td>
<td>↓</td>
<td>↓</td>
<td>Hypopituitarism, anorexia nervosa, prolactinoma</td>
</tr>
<tr>
<td>Ovarian disorder</td>
<td>↑</td>
<td>↓</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>End-organ defect</td>
<td>N</td>
<td>N</td>
<td>Imperforate hymen, Asherman syndrome</td>
</tr>
<tr>
<td>Constitutional delay</td>
<td>N</td>
<td>N</td>
<td>Family history of delayed onset of menses</td>
</tr>
</tbody>
</table>

FSH, Follicle-stimulating hormone; LH, luteinizing hormone; N, normal.

Hypothalamic/pituitary cause: ↓FSH, LH, estrogen

Hypothalamic/pituitary causes: anorexia nervosa, prolactinoma, hypopituitarism

Ovarian cause: ↑FSH, LH; ↓estrogen

1° amenorrhea + poor female secondary sex characteristics: probable Turner syndrome

End-organ defect: normal FSH, LH, estrogen

End-organ defect causes: imperforate hymen, RKH syndrome

Asherman syndrome: removal of stratum basalis by excessive curettage

Acute endometritis: uterine infection following delivery or abortion

Acute endometritis: group B streptococcus is common pathogen

Acute endometritis: fever, uterine pain, discharge

Intrauterine device: *Actinomyces* infection

Chronic endometritis: plasma cells in biopsy

IUD: *Actinomyces* infection

Chronic endometritis: plasma cells in biopsy

Adenomyosis: functioning glands/stroma in myometrium

(3) Examples
(a) Hypopituitarism, prolactinoma (refer to Chapter 23)
(b) Anorexia nervosa (refer to Chapter 8)

b. Ovarian disorder
(1) Decreased synthesis of estrogen and progesterone
(a) Increase in serum FSH and LH, respectively
(b) Hypergonadotropic (↑FSH and LH) hypogonadism
(2) No withdrawal bleeding after receiving progesterone
• Endometrial mucosa is not estrogen-stimulated.
(3) Examples
(a) Turner syndrome (refer to Chapter 6)
(b) Surgical removal of ovaries

c. End-organ defect
(1) Prevents the normal egress of blood
• More likely to be a cause of primary amenorrhea
(2) Normal levels of FSH, LH, estrogen, and progesterone
(3) No withdrawal bleeding after receiving progesterone
(4) Examples
(a) Imperforate hymen, Rokitansky-Küster-Hauser (RKH) syndrome
(b) Asherman syndrome
• Definition—removal of stratum basalis owing to repeated curettage
d. Summary of amenorrhea (Table 22-3)

VI. Uterine Disorders

A. Endometritis
1. Epidemiology
   a. Definition—uterine infection following delivery (vaginal/cesarean section) or abortion
   b. Rate of postpartum endometritis is 1% to 8%.
   c. Most common genital tract infection following delivery
   d. More common in preterm deliveries
2. Acute endometritis
   a. Most often due to bacterial infection following delivery or miscarriage
   b. Group B streptococcus (*Streptococcus agalactiae*) is a common pathogen.
   c. Other pathogens: group A streptococcus, *Staphylococcus aureus*, *Bacteroides fragilis*, *C. trachomatis*, *N. gonorrhoeae*, *Escherichia coli*
   d. Clinical findings
      (1) Fever
      (2) Uterine tenderness
      (3) Purulent or foul vaginal discharge (lochia)
      (4) Abdominal pain
   e. Treatment
      • Cefoxitin, ticarcillin-clavulanate, ampicillin-sulbactam
3. Chronic endometritis
   a. Causes
      (1) Retained placenta
      (2) Gonorrhea, intrauterine device (IUD, *Actinomyces israelii*)
   b. Key histologic finding is the presence of plasma cells.
   c. Treatment (see earlier discussion)

B. Adenomyosis
1. Epidemiology
   a. Definition—invasion of the stratum basalis into the myometrium (Fig. 22-10A)
      (1) Glands and stroma thicken myometrial tissue.
      (2) The uterus becomes enlarged.
**22-10**: A, Adenomyosis. The solid arrow shows an area of hemorrhage surrounded by irregularly thickened endometrial stroma. The interrupted arrow shows a nabothian cyst in the endocervical canal. B, Endometriosis implants on a loop of intestine. Note the serosal surface has multiple areas of hemorrhage with a “powder burn” appearance. C, Endometrial polyp. Note hemorrhagic polyp arising from the endometrial mucosa. It is a common cause of uterine bleeding. D, Simple hyperplasia of endometrial glands showing cystic dilation and focal areas of glandular outpouching. There is no gland crowding or stratification of the epithelial lining. E, Endometrial carcinoma showing necrotic tumor filling the uterine cavity and extending completely through the uterine wall and into the endocervical canal. F, Leiomyomas. In sagittal section, multiple well-circumscribed, gray-white nodules (leiomyomas) are dispersed throughout the myometrium. Submucosal leiomyomas are a common cause of uterine bleeding. (A and E from Rosai J, Ackerman LV: Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, pp 1578, 1586, respectively, Figs. 19-123, 19-136B, respectively; B and F from Damjanov I, Linder J: Pathology: A Color Atlas. St. Louis, Mosby, 2000, pp 126, 277, respectively, Figs. 7-77, 13-49, respectively; C and D from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, pp 1082, 1086, respectively, Figs. 22-27C, 22-31A, respectively.)

b. Highest incidence occurs in women in mid to late 40s.
c. Common finding in hysterectomy specimens
2. Clinical findings
   - Menorrhagia, dysmenorrhea, pelvic pain
3. Definitive diagnosis with myometrial biopsy
4. Treatment is hysterectomy.
C. **Endometriosis**

1. **Epidemiology**
   a. Definition—functioning glands and stroma are located outside the uterus
   b. Prevalence is highest in women with dysmenorrhea (40%–60% of cases)
   c. Average age at time of diagnosis is 25 to 29 years old.
   d. Multifactorial inheritance has been implicated.
      • Approximately 7% occurrence rate in first-degree female relatives

2. **Pathogenesis**
   a. Reverse menses through fallopian tubes (most common)
   b. Implantation of viable endometrial cells
   c. Vascular or lymphatic spread

3. **Common sites**
   - Ovaries (most common), rectal pouch, fallopian tubes, intestine

---

4. **Clinical findings**
   a. Dysmenorrhea (most common)
   b. Abnormal bleeding
      • Premenstrual spotting, menorrhagia
   c. Painful stooling during menses
      • Bleeding implants on the rectal serosa in the pouch of Douglas are stretched with stooling
   d. Intestinal obstruction and intestinal bleeding during menses
   e. Increased risk for ectopic pregnancy
   f. Infertility, dyspareunia
   g. Enlargement of ovaries
      • Due to blood-filled cysts

5. **Diagnosis**
   a. Laparoscopy useful for diagnosis and treatment
      • Implants have a “powder burn” appearance (see Fig. 22-10B)
   b. Increased serum cancer antigen 125 (CA125)
      1. Excellent sensitivity but poor specificity (increased false positive results)
      • It is a cancer antigen that is also increased in surface-derived ovarian cancers and other gynecologic disorders.
      2. More useful in excluding endometriosis when it returns negative

6. **Treatment**
   a. Combination oral contraceptives
   b. Progestins (e.g., medroxyprogesterone acetate)
   c. Gonadotropin-releasing hormone agonists
   d. Laparoscopic removal of implants

---

D. **Endometrial polyp** (see Fig. 22-10C)

1. **Epidemiology**
   a. Benign polyp that enlarges with estrogen stimulation
   b. Does not progress to endometrial carcinoma
   c. Can protrude through the cervix into the vagina

2. **Clinical findings**
   a. Common cause of menorrhagia in 20- to 40-year-old age bracket
   b. Spotting occurs between menstrual periods or after menopause

3. **Diagnosis**
   a. Vaginal ultrasound
   b. Dilation and curettage (D&C)

4. **Treatment**
   a. Dilation and curettage
   b. Hysteroscopy
Endometrial hyperplasia:
1. Epidemiology and pathogenesis
   a. Definition—endometrial gland hyperplasia due to prolonged, unopposed estrogen stimulation
   b. Risk factors
      (1) Early menarche or late menopause
      (2) Nulliparity
      (3) Obesity
         • Increased aromatization of androgens to estrogen in adipose
      (4) Polycystic ovary syndrome (PCOS)
      (5) Taking estrogen without progesterone
      (6) Anovulatory menstrual cycles
      (7) Hereditary nonpolyposis colorectal cancer (Lynch syndrome; refer to Chapter 9)
   c. Classification
      (1) Simple hyperplasia (see Fig. 22-10D)
         (a) Increased number of cystically dilated glands
         (b) No glandular crowding
      (2) Complex hyperplasia
         (a) Increased number of dilated glands with branching
         (b) Glandular crowding
      (3) Atypical hyperplasia
         (a) Glandular crowding and dysplastic epithelium
         (b) Greatest risk for endometrial cancer

2. Clinical findings
   a. Menorrhagia, metrorrhagia, menometrorrhagia
   b. Postmenopausal bleeding

3. Diagnosis
   • Endometrial biopsy

4. Treatment
   a. OCPs
   b. Medroxyprogesterone acetate
   c. Hysterectomy if atypia is present

F. Endometrial carcinoma
1. Epidemiology and pathogenesis
   a. Most common gynecologic tumor
   b. Median age at onset, 60 years old
   c. Pathogenesis: prolonged estrogen stimulation
      • Same risk factors as endometrial hyperplasia
   d. OCPs decrease risk.
      • Due to antiestrogen effect of progestins
   e. Slightly increased risk for breast cancer
   f. Types of endometrial cancer
      (1) Well-differentiated adenocarcinoma
         (a) Most common type
         (b) Adenoacanthoma
            • Contains foci of benign squamous tissue (no prognostic significance)
         (c) Adenosquamous carcinoma
            • Contain foci of malignant squamous cancer (worse prognosis)
      (2) Papillary adenocarcinoma
         • Highly aggressive cancer

2. Cancer characteristics
   a. Spreads down into the endocervix
   b. Spreads out into the uterine wall (see Fig. 22-10E)
   c. Lungs are the most common site of metastasis.

3. Clinical findings
   • Postmenopausal bleeding (90% of cases)

4. Diagnosis
   • Endometrial biopsy

5. Treatment
   • Surgery, radiation, hormones (tamoxifen), or chemotherapy depending on stage
G. Leiomyoma (fibroids)

1. Epidemiology
   a. Benign smooth muscle tumor (see Fig. 22-10F)
   b. Most frequently diagnosed gynecologic tumor
   c. Occurs in 20% to 50% of women >30 years old
   d. More common in blacks than whites
   e. Estrogen-sensitive tumors
      • May become larger during pregnancy

2. Tumor characteristics
   a. Commonly undergo the following:
      (1) Degeneration
      (2) Dystrophic calcification
      (3) Hyalinization
      • Reason for the term “fibroids”
   b. Rarely transform into leiomyosarcomas (<1% of cases)

3. Clinical findings
   a. Menorrhagia (when located in submucosa)
   b. Obstructive delivery
   c. Cramping during menses
   d. Pressure on colon (constipation)
   e. Pressure on bladder
      • Increased frequency, urgency, incontinence

4. Diagnosis
   a. Transabdominal or transvaginal ultrasound
   b. MRI

5. Treatment
   a. Myotomy for women who want to preserve fertility
   b. Hysterectomy

H. Leiomyosarcoma

1. Most common sarcoma of the uterus
2. Tumor characteristics
   • Numerous atypical mitoses and foci of necrosis
3. Treatment is surgery.

I. Malignant mixed müllerian tumors (carcinosarcomas)

1. Endometrial adenocarcinoma + malignant mesenchymal (stromal) tumor
   a. Primarily occur in postmenopausal women
   b. Bulky, necrotic tumors that often protrude through the cervical os
2. Mesenchymal component may include muscle, cartilage, and bone.
3. Strong association with previous irradiation
4. Poor prognosis
5. Treatment is surgery.

VII. Fallopian Tube Disorders

A. Hydatid cysts of Morgagni

1. Cystic müllerian remnants
2. Most often located around the fimbriated end of the tube
3. May undergo torsion (>25% of cases), causing abdominal pain
4. Treatment is surgical removal (laparoscope).

B. Pelvic inflammatory disease (PID)

1. Epidemiology
   a. Diagnosed in 2% to 5% of women in STD clinics
   b. Most common cause of female infertility and ectopic pregnancy
   c. Risk factors
      (1) Multiple sexual partners
      (2) Vaginal douching
      (3) Previous episodes of PID
      (4) Unprotected sex
   d. Most but not all cases of PID are STDs.
   e. Causes of PID
      (1) Most often due to N. gonorrhoeae or C. trachomatis
         • Coexisting infection in 45% of cases
      (2) Other non-STD pathogens include:
         • B. fragilis, streptococci, Clostridium perfringens, Mycobacterium tuberculosis, cytomegalovirus (CMV)
2. Gross findings
   a. Fallopian tubes are filled with pus (Fig. 22-11A).
   b. Most common cause of a hydrosalpinx
      • Definition—pus resorbs, leaving a clear fluid distending the tube

3. Clinical findings
   a. Fever usually >38.3°C (101°F)
   b. Lower abdominal pain
   c. Pain with cervical motion, palpation of adnexa and uterus during pelvic examination
   d. Abnormal uterine bleeding, vaginal discharge
   e. Mucopurulent discharge in cervical os
   f. Right upper quadrant pain (5% of cases)
      • Perihepatitis (Fitz-Hughes–Curtis syndrome; see Table 22-1)

4. Diagnosis
   a. Finding of cervical motion tenderness and adnexal tenderness
   b. Culture of cervical discharge
   c. Laparoscopy
   d. Transvaginal ultrasound, MRI (best sensitivity and specificity)

5. Treatment
   a. Empirical treatment with uterine, adnexal, and cervical motion tenderness
   b. Ceftriaxone + doxycycline (covers both N. gonorrhoeae and C. trachomatis)

C. Salpingitis isthmica nodosa (SIN)
   1. Definition—invagination of the mucosa into the muscle ("tubal diverticulosis")
      a. Produces nodules in the tube that narrow the lumen
      b. Probably a postinfectious reaction (e.g., previous C. trachomatis infection)

2. Complications
   • Infertility, ectopic pregnancy

3. Diagnose with hysterosalpingography
   • Beading appearance in areas of constriction

D. Ectopic pregnancy (EP)
   1. Epidemiology and pathogenesis
      a. Definition—implantation of a fetus outside the normal uterine location
      b. Occurs in 1% to 2% of pregnancies
      c. Accounts for 13% of maternal deaths
      d. Risk factors
         (1) Scarring from previous PID (most common cause)
         (2) Endometriosis
         (3) Altered tubal motility, SIN
         (4) Progestin-only pill, previous tubal ligation
      e. Sites of implantation
         (1) Majority occur within the tubes (see Fig. 22-11B)
            • Most are in the broad ampullary portion below the fimbriae.
         (2) Ovaries, abdominal cavity

2. Clinical findings
   a. Sudden onset of lower abdominal pain and tenderness (95% of cases)
      • Usually ~6 weeks after a previous normal menstrual period
b. Adnexal tenderness (87%–99% of cases)
c. Peritoneal signs (rebound tenderness; >70% of cases)
d. Abnormal uterine bleeding (75% of cases)
e. Hypovolemic shock (intraperitoneal bleeding; 2%–17% of cases)

3. Complications
a. Rupture with intra-abdominal bleed
   • Most common cause of death in early pregnancy
b. Most common cause of hematosalpinx
   • Definition—blood in the tube

c. Laparoscopy is used in equivocal cases.

d. Treatment
a. Methotrexate if stable and no hemorrhage
b. Conservative surgery, salpingectomy

VIII. Ovarian Disorders

A. Follicular cyst
1. Most common ovarian mass
2. Nonneoplastic cyst
   • Definition—accumulation of fluid in a follicle or previously ruptured follicle
3. Rupture produces sterile peritonitis with pain.
4. Most regress spontaneously.
5. US is best screening test.
6. Surgical removal if symptomatic

B. Corpus luteum cyst
1. Most common ovarian mass in pregnancy
2. Nonneoplastic cyst
   a. Definition—accumulation of fluid in the corpus luteum during pregnancy
   b. May be confused with an amniotic sac
   c. Most regress spontaneously.
3. Surgical removal if symptomatic

C. Oophoritis
   • May be a complication of mumps or PID

D. Stromal hyperthecosis
1. Epidemiology
   a. Occurs primarily in obese postmenopausal women
   • Causes bilateral ovarian enlargement
   b. Definition—hypercellular ovarian stroma
      (1) Vacuolated (luteinized) stromal hilar cells are present
   • Synthesize excess androgens
      (2) May cause hirsutism or virilization
2. Clinical findings
   a. Hirsutism or virilization
   b. Association with acanthosis nigricans, insulin resistance, PCOS
   c. Hypertension
3. Treatment is oophorectomy.

E. Ovarian tumors
1. Epidemiology and pathogenesis
   a. Tumors are more likely benign in women <45 years of age.
      (1) Risk increases with age.
      (2) Median age of presentation is 61 years of age.
      (3) Incidence peaks in women in their late 70s.
      (4) Approximately 60% present with advanced disease.
   b. Risk factors
      (1) Nulliparity
      (a) A greater number of ovulatory cycles increases risk.
      (b) Risk for surface-derived ovarian tumors is increased.
22-12: Schematic showing the derivation of primary ovarian tumors. (From Kumar V, Abbas AK, Fausto N, Mitchell RN: Robbins Basic Pathology, 8th ed. Philadelphia, Saunders Elsevier, 2007, p 729, Fig. 19-16.)

(2) Genetic factors
   (a) Mutations of BRCA1 and BRCA2 suppressor genes
   (b) Lynch syndrome (refer to Chapter 9)
   (c) Turner syndrome (refer to Chapter 6)
   - Increased risk for dysgerminoma
   (d) Peutz-Jeghers syndrome (refer to Chapter 18)
   - Increased incidence of ovarian sex cord tumors

(3) History of breast cancer
(4) Postmenopausal estrogen therapy, obesity (increased estrogen)
(5) OCPs/pregnancy decrease risk for surface-derived ovarian cancers.
   - Decreased number of ovulatory cycles

2. Classification of ovarian tumors (Table 22-4; Fig. 22-12)
   a. Surface-derived tumors
      (1) Account for 65% to 70% of ovarian tumors
      (2) Derive from coelomic epithelium
      (3) Account for the greatest number of malignant ovarian tumors
      (4) Malignant tumors commonly seed the omentum (refer to Chapter 9).
   b. Germ cell tumors
      (1) They account for 15% to 20% of ovarian tumors.
      (2) Cancers are similar to those seen in the testicle (refer to Chapter 21).
      (3) A relatively small number of germ cell tumors are malignant.
   c. Sex cord–stromal tumors
      (1) Account for 3% to 5% of ovarian tumors
      (2) Derive from stromal cells
      (3) Some of them are hormone-producing (e.g., granulosa cell tumor produces estrogen)
      (4) Majority of these tumors are benign.
   d. Metastasis
      (1) Accounts for 5% of ovarian tumors
      (2) Majority are hematogenous metastasis; seeding is less common.
      (3) Common primary cancers metastasizing to ovaries
         (a) Müllerian origin from uterus, fallopian tubes, contralateral ovary
         (b) Extramüllerian origin from breast, gastrointestinal tract
         (c) Krukenberg tumor is unique in that signet ring cells are present and implicate diffuse cancer of the stomach or breast cancer as the primary site (Fig. 22-13D; refer to Chapter 18).

3. Clinical findings
   a. Abdominal enlargement due to fluid (most common sign)
      (1) Malignant ascites is most often due to seeding.
      (2) Signs of malignant ascites due to seeding include:
         (a) Induration in the rectal pouch on digital rectal examination
         (b) Intestinal obstruction with colicky pain
   b. Palpable ovarian mass in a postmenopausal woman
      - Ovaries should not be palpable in menopausal women because they are atrophic.
   c. Malignant pleural effusion
      - Pleural cavity is a common site for ovarian cancer metastasis.

Ovarian cancer: genetic factors; excess estrogen exposure; nulliparity (surface-derived tumors)

Turner syndrome: risk for dysgerminoma

OCPs/pregnancy: ↓ risk surface-derived ovarian cancers

Surface-derived tumors: MC group of ovarian tumors

Serous cystadenocarcinoma: MC ovarian cancer; bilaterality; psammoma bodies

Malignant surface-derived cancers: commonly seed the abdominal cavity

Germ cell tumors: teratoma/dysgerminoma
MC benign/malignant, respectively

Sex cord–stromal tumors: hormone-producing tumors (estrogen/testosterone); most are benign

Krukenberg tumors: metastasis to ovaries with signet ring cells; diffuse cancer of stomach or breast

Ovarian cancer: abdominal enlargement due to fluid MC sign

Malignant ascites: seeding MCC

Malignant ascites: induration in rectal pouch; intestinal obstruction

Ovarian cancer: palpable ovaries in postmenopausal women is cancer until proved otherwise

Pleural cavity: common site for ovarian metastasis
### TABLE 22-4 Classification of Ovarian Tumors

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>CHARACTERISTICS</th>
</tr>
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<tbody>
<tr>
<td><strong>Surface-Derived Tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Serous tumors (see Fig. 22-13A and B)</td>
<td>Most common group of primary benign and malignant tumors</td>
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<td></td>
<td>Most common group of tumors that can be bilateral</td>
</tr>
<tr>
<td></td>
<td>Cysts are lined by ciliated cells (similar to the fallopian tube)</td>
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<tr>
<td></td>
<td>Serous cystadenoma: benign; most common benign ovarian tumor</td>
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<tr>
<td></td>
<td>Serous cystadenocarcinoma: malignant; has psammoma bodies (dystrophically calcified tumor cells); most common malignant tumor that is bilateral</td>
</tr>
<tr>
<td>Mucinous tumors</td>
<td>Cysts are lined by mucus-secreting cells (similar to the endocervix)</td>
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<tr>
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<td>Large, multiloculated tumors</td>
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<td></td>
<td>Seeding may produce pseudomyxoma peritonei (most common primary site for psammoma peritonei is not mucinous tumors of the ovary but mucinous tumors of the appendix)</td>
</tr>
<tr>
<td></td>
<td>Mucinous cystadenoma: benign; may be associated with Brenner tumors</td>
</tr>
<tr>
<td></td>
<td>Mucinous cystadenocarcinoma: malignant</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>Malignant tumors that are commonly associated with endometrial carcinoma (15%–30% of cases); tumor resembles endometrial carcinoma</td>
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<tr>
<td></td>
<td>Commonly bilateral</td>
</tr>
<tr>
<td>Brenner tumor</td>
<td>Usually benign</td>
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<tr>
<td></td>
<td>Contain Walthard cell rests (transitional-like epithelium)</td>
</tr>
<tr>
<td><strong>Germ Cell Tumors</strong></td>
<td></td>
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<tr>
<td>Cystic teratoma (see Figs. 9-1C; 22-13C)</td>
<td>Most are benign; &lt;1% become malignant (usually squamous cancer)</td>
</tr>
<tr>
<td></td>
<td>Most common benign germ cell tumor; contain ectodermal (e.g., hair), mesodermal (e.g., muscle), and endodermal tissues (e.g., thyroid); ectodermal differentiation (hair, sebaceous glands, teeth) is the most prominent component</td>
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<tr>
<td></td>
<td>Most of these derivatives are found in a nipple-like structure in the cyst wall called Rokitansky tubercle</td>
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<tr>
<td></td>
<td>Immature malignant types contain mature and immature components (e.g., muscle, neuroepithelium)</td>
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<tr>
<td></td>
<td>Struma ovarii type has functioning thyroid tissue and will take up radioactive iodine-123</td>
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<tr>
<td>Dysgerminoma</td>
<td>Most common malignant germ cell tumor; same histologic appearance as a seminoma of the testis</td>
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<tr>
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<td>Characteristic increase in serum LDH</td>
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<td></td>
<td>Associated with the streak gonads of Turner syndrome</td>
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<tr>
<td>Yolk sac tumor</td>
<td>Malignant tumor (similar to yolk sac tumor in males)</td>
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<tr>
<td></td>
<td>Most common ovarian cancer in girls &lt;4 years old; however, the average age of occurrence of the tumor is 23 years old</td>
</tr>
<tr>
<td></td>
<td>Contain Schiller-Duval bodies (resemble yolk sac)</td>
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<tr>
<td></td>
<td>Increased serum α-fetoprotein</td>
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<tr>
<td><strong>Sex Cord–Stromal Tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Thecoma-fibroma</td>
<td>Benign tumor associated with Meigs syndrome (ascites, right-sided pleural effusion); regression of effusions follows removal of the tumor</td>
</tr>
<tr>
<td></td>
<td>Commonly calcify</td>
</tr>
<tr>
<td>Granulosa-theca cell tumor</td>
<td>Low-grade malignant tumor</td>
</tr>
<tr>
<td></td>
<td>Feminizing tumor (produces estrogen) that contains Call-Exner bodies</td>
</tr>
<tr>
<td>Sertoli-Leydig cell tumor</td>
<td>Benign masculinizing tumor (produces androgens)</td>
</tr>
<tr>
<td></td>
<td>Pure Leydig cell tumors contain cells with crystals of Reinke</td>
</tr>
<tr>
<td></td>
<td>Association with Peutz-Jeghers syndrome</td>
</tr>
<tr>
<td>Gonadoblastoma</td>
<td>Malignant tumor with mixture of a germ cell tumor (dysgerminoma) and sex cord–stromal tumor</td>
</tr>
<tr>
<td></td>
<td>Associated with abnormal sexual development in 80% of cases</td>
</tr>
<tr>
<td></td>
<td>Commonly calcify</td>
</tr>
<tr>
<td><strong>Tumors Metastatic to Ovary</strong></td>
<td></td>
</tr>
<tr>
<td>Metastasis from müllerian tumors or extramüllerian tumors</td>
<td>May effect one or both ovaries; usually hematogenous spread; less commonly due to seeding</td>
</tr>
<tr>
<td></td>
<td>Müllерian origin—uterus, fallopian tubes, contralateral ovary</td>
</tr>
<tr>
<td></td>
<td>Extramüllerian origin—breast, gastrointestinal tract</td>
</tr>
<tr>
<td>Krukenberg tumor (see Figs. 18-15C and 22-13D)</td>
<td>May affect one or both ovaries</td>
</tr>
<tr>
<td></td>
<td>Contains signet-ring cells from hematogenous spread of a gastric cancer (diffuse carcinoma [linitis plastica]); breast cancer also metastases to the ovaries (some breast cancer variants have signet ring cells)</td>
</tr>
</tbody>
</table>

LDH, Lactate dehydrogenase.
d. Cystic teratomas undergo torsion leading to infarction.
   • Radiographs show calcification from bone and/or teeth (see Fig. 9-1C).

e. Signs of hyperestrinism from estrogen-secreting tumors
   (1) Bleeding occurs from endometrial hyperplasia/cancer
   (2) 100% superficial squamous cells are present in a cervical Pap smear.

f. Hirsutism or virilization is associated with androgen-secreting tumors (e.g., Sertoli-Leydig cell tumor).

4. Tumor markers
   a. Increased serum cancer antigen 125 (CA125)
   b. Only increased in surface-derived malignant tumors

5. Treatment
   • Surgery, chemotherapy, occasionally radiation

6. Prognosis
   a. Better prognosis if <65 years old
   b. Overall 1- and 5-year relative survival rates for ovarian cancer are 75% and 45%, respectively.

IX. Gestational Disorders
A. Placental anatomy
1. Fetal surface (Fig. 22-14A)
   a. Surface is entirely covered by the chorionic plate.
   b. Chorionic villi vessels converge with the umbilical cord.
   c. Chorion is covered by the amnion.

2. Maternal surface (see Fig. 22-14B)
   a. Surface contains cotyledons covered by a layer of decidua basalis.
   b. Cotyledons contain fetal vessels, chorionic villi, and the intervillous space.
   c. Chorionic villi project into the intervillous space.
      (1) Intervillous space contains maternal blood from which O₂ is extracted.
      (2) Spiral arteries from the uterus empty into the space.
22-14: A, Normal placenta, showing the fetal side. Covered by the chorionic plate. Chorionic villi vessels converge with the umbilical cord. The chorion is covered by the amnion. B, Normal placenta the maternal side. Note the cotyledons covered by a layer of decidua basalis. C, Chorionic villi. The outer layer of the villus is covered by two layers of cells called the trophoblast (arrowheads). The outer layer of the trophoblast is lined by syncytiotrophoblast, whereas the inner layer is lined by cytotrophoblast. The vessels in the chorionic villus converge to become the umbilical vein, which is the vessel with the highest O₂ content. D, Schematic of placenta previa. Note how the placenta is implanted over the cervical os. E, Abruptio placentae. Note the retroplacental blood clot that separated the placenta from its implantation site. (A, B, C, and E from Klatt F. Robbins and Cotran Atlas of Pathology. Philadelphia, Saunders, 2006, p 326 for A, B, and C, p 327 for E, respectively; Figs. 13-108A, B, 13-109, 13-112, respectively. D from Greer I, Cameron IT, Kitchener HC, Prentice A: Mosby’s Color Atlas and Text of Obstetrics and Gynecology. St. Louis, Mosby, 2000, p 184, Fig. 7-28.)
d. Chorionic villi are lined by trophoblastic tissue (see Fig. 22-14C).
   (1) Outside layer is composed of syncytiotrophoblast.
      (a) Synthesizes hCG (see earlier discussion)
      (b) Synthesizes human placental lactogen (HPL)
         • Amount of HPL directly correlates with placental mass.
         • It has anti-insulin activity and is similar to human growth hormone.
   (2) Inside layer is composed of cytotrophoblast.

c. Placental infections

1. Epidemiology
   a. Most are due to ascending bacterial infections from the vagina
      (1) Complication of premature rupture of membranes
      (2) Group B streptococcus is a common pathogen in the vagina.
      (3) Other pathogens: B. fragilis, Prevotella bivia, group A streptococcus
   b. Congenital infections (e.g., cytomegalovirus, syphilis)

2. Funisitis and placentitis
   • Definitions—infected of the umbilical cord and placenta, respectively

3. Chorioamnionitis
   a. Definition—infected of the fetal membranes
   b. Danger of neonatal sepsis and meningitis

C. Selected placental abnormalities

1. Placenta previa (see Fig. 22-14D)
   a. Epidemiology
      (1) Implantation over cervical os
      (2) Previous cesarean section (C-section) is a risk factor (approaches 10%).
   b. Clinical findings
      (1) Presents with painless vaginal bleeding
         • Usually presents in the second or third trimester
      (2) Uterus is soft and nontender
      (3) Fetal distress not usually present.
   c. Diagnosis
      (1) Transabdominal US localizes the placenta.
      (2) Transvaginal US confirms placenta previa.
   d. Treatment
      (1) Careful observation of fetus and mother
      (2) Delivery by C-section

2. Abruptio placentae (see Fig. 22-14E)
   a. Epidemiology
      (1) Premature separation of placenta due to formation of a retroplacental clot
         (a) Separates the placenta from the implantation site
         (b) Most common cause of late pregnancy bleeding
         (c) Occurs in 1:830 pregnancies
      (2) Fetal mortality rate is 20% to 40%.
      (3) Risk factors
         (a) Hypertension (greatest risk factor; 40%–50% of cases)
         (b) Smoking cigarettes
         (c) Cocaine addiction, advanced maternal age
         (d) Trauma, chorioamnionitis
         (e) Premature rupture of membranes, previous abruptio placentae
   b. Clinical findings
      (1) Painful uterine bleeding
         • Concealed (20% of cases) or vaginal bleeding (80% of cases)
      (2) Forceful uterine contractions (~15% of cases) or signs of preterm labor
      (3) Evidence of fetal distress is usually present.
c. Diagnosis
   • Ultrasound should be used.

d. Treatment
   (1) Fetal heart monitoring
   (2) Monitor maternal hemodynamic status
   (3) Deliver baby

3. Placenta increta/percreta
   a. Definition—direct implantation of placenta into muscle (varying depths) without intervening decidua
   b. Great risk for hemorrhage during delivery
   c. Commonly requires surgery to control bleeding
      • Hysterectomy is often necessary.

4. Velamentous insertion
   a. Definition—umbilical cord inserts away from the placental edge
      • Vessels pass to the placenta through the membranes between the amnion and the chorion.
   b. Increased risk for hemorrhage if vessels are torn
   c. Can be diagnosed by US
   d. Often delivered by C-section to prevent vessel tear

5. Accessory lobes
   • Increased risk for hemorrhage if they are detached

6. Enlarged placenta; causes include:
   a. Diabetes mellitus (DM)
   b. Rh hemolytic disease of newborn (HDN)
   c. Congenital syphilis

7. Twin placentas (Fig. 22-15)
   a. Monochorionic types are associated with identical twins.
      (1) Identical twins derive from a single fertilized egg.
      (2) Monoamniotic with a single amniotic sac (see Fig. 22-15A)
         • Type of placenta for Siamese twins or tangling of umbilical cords
      (3) Diamniotic with separate amniotic sacs (see Fig. 22-15B)
      (4) Fetal-to-fetal transfusion can occur in either type (A or B).
   b. Dichorionic placentas
      (1) Can be identical or fraternal twins
         • Fraternal twins occur when separate eggs are fertilized.
      (2) Placentas can be diamniotic (see Fig. 22-15C) or separated (see Fig. 22-15D).

D. Preeclampsia/eclampsia (toxemia of pregnancy)

1. Epidemiology
   a. Usually occurs after the 20th week of pregnancy
   b. Occurs in 0% to 14% of primigravidas and 5.7% to 7.3% of multigravidas

22-15: Twin placentas. See text for description. (Redrawn from Goljan EF: Star Series: Pathology. Philadelphia, Saunders, 1998, Fig. 18-2.)
c. Risk factors
   (1) More common in women <20 years of age and >35 years of age
   (2) History of previous preeclampsia
   (3) Positive family history
   (4) Multiple gestations
   (5) Blacks
   (6) Thrombocytosis, obesity, renal or collagen vascular diseases

2. Pathogenesis
   a. Abnormal placentation
      (1) Causes mechanical or functional obstruction of the spiral arteries
      (2) Abnormal trophoblastic tissue invades the spiral arteries.
   b. Imbalance favoring vasoconstrictors over vasodilators
      (1) Normal vasodilators are decreased.
          • Example—PGE₂
      (2) Vasoconstrictors are increased.
          (a) Example—thromboxane A₂
          (b) Increased sensitivity to angiotensin II by the muscular walls of the arteries
      (3) Increase in various growth factors (e.g., vascular endothelial growth factor, placental growth factor)
   c. Net effect is placental hypoperfusion.
3. Pathologic findings
   a. Premature aging of the placenta
   b. Multiple placental infarctions
   c. Spiral arteries show intimal atherosclerosis.

4. Clinical and laboratory findings
   a. Hypertension (increased vasoconstrictors)
      •Ranges from just below 140/90 mm Hg (mild) to >160/110 mm Hg (severe)
   b. Proteinuria in nephrotic range (>3.5 g/24 hours)
      • Usually >5 g/24 hour urine collection
   c. Dependent pitting edema
      • Due to loss of albumin in the urine
   d. Weight gain >4 pounds/week
      • Due to retention of sodium
   e. Generalized seizures
      (1) Preeclampsia + seizures is called eclampsia.
      (2) Magnesium sulfate is used for treatment.
   f. Renal disease
      (1) Swollen endothelial cells in the glomerular capillaries
      (2) Produces oliguria (<400 mL/24 hr)
   g. Liver disease
      (1) Right upper quadrant pain and hepatomegaly
      (2) Periportal necrosis with increased transaminases
   h. HELLP syndrome (refer to Chapter 19)
      • Hemolytic anemia and disseminated intravascular coagulation

5. Treatment
   a. Delivery is the treatment of choice and only cure for the disease.
   b. Methyldopa is the best drug for Rx of hypertension.
   c. Magnesium sulfate is also used.

E. Gestational trophoblastic neoplasms
1. Hydatidiform moles
   a. Benign tumors of the chorionic villus
      • Complete and partial moles
   b. More common at the extremes of age
   c. Occurs in 1:1200 pregnancies in the United States
      • Occurs in 1:200 pregnancies in Indonesia
   d. Complete mole is the most common type.
      (1) All of the chorionic villi are neoplastic.
      (2) Dilated, swollen villi without fetal blood vessels or parts (Fig. 22-16A)
      (3) Ovum 46, XX (90% of cases)
22-16: A. Complete hydatidiform mole. The enlarged and edematous villi are interconnected by thin cord-like structures. No fetus is present. B. Ultrasound of a complete hydatidiform mole showing the classic “snowstorm” appearance. (A from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 290, Fig. 13-111A; B from Greer I, Cameron IT, Kitchener HC, Prentice A: Mosby’s Color Atlas and Text of Obstetrics and Gynecology, St. Louis, Mosby, 2000, p 94, Fig. 4-22.)

Complete mole: all villi are neoplastic; diluted neoplastic villi with no fetal parts

Complete mole: empty ovum; fertilization by 23X sperm that has duplication of its chromosomes (46XX; most common)

Complete mole: empty ovum; fertilization by 2 separate sperm (23X or Y; dispermy); 46XX or 46XY

Complete mole: US with “snowstorm” appearance; too large for gestational age

Partial mole: normal villi intermixed with neoplastic villi; fetal parts intermixed with neoplastic villi

Partial mole: fertilization of 23X ovum by 2 sperm either X or Y (69XXY most common)

Partial mole: incomplete/missed abortion; vaginal bleeding; very high β-hCG for gestational age

Choriocarcinoma: malignancy of trophoblastic tissue; no chorionic villi

(a) Ovum lacks maternal chromosomes (empty ovum).
(b) Chromosomes are paternally derived.
   • Duplication of 23X sperm in ovum (46XX; most common), or—
   • Two separate 23X or Y sperm enter ovum (called dispermy; 46XX or 46XY)

(4) Increased risk for developing choriocarcinoma (15%–20%)

(5) Clinical findings
(a) Vaginal bleeding at 6 to 16th week gestational age (80%–90%)
(b) Severe vomiting (hyperemesis gravidarum; 8%)
(c) Preeclampsia is present in 1% of patients.
(d) Uterus is too large for gestational age (~30%).
(e) Increased β-hCG for gestational age (>100,000; 15%)s
(f) Bilateral theca lutein cysts (15%)
   • Develop in response to high levels of β-hCG
(g) “Snowstorm appearance” with ultrasound (Fig. 22-16B)

(6) Treatment
(a) Dilation and curettage
   • Must remove all the material
(b) Follow patient with β-hCG levels
   • Should go down to zero

e. Partial mole
(1) Normal villi are intermixed with neoplastic villi.
(2) Fetal parts are intermixed with neoplastic villi.
   • Amnion and fetal vessels with fetal erythrocytes are present within the mesenchyme of the villi.
      (a) Ovum triploid (69 XXY in 70% of cases; XXX in 27% of cases)
      (b) Most commonly due to fertilization of a paternally-derived 23X ovum by 2 sperm that are either 23X or Y producing an ovum with 69XXY (most common) or XXX.
(3) Preeclampsia in 5% of patients
(4) No risk for developing a choriocarcinoma
(5) Clinical findings
(a) Incomplete or missed abortion (90%)
(b) Vaginal bleeding (75%)
(c) Uterine enlargement 5% of patients
(d) Theca lutein cysts and hyperemesis gravidarum extremely rare
(e) Majority have β-hCG <100,000 for gestational age

(6) Treatment: similar to complete mole

2. Choriocarcinoma
   a. Malignant tumor composed of syncytiotrophoblast and cytotrophoblast
      • Chorionic villi are not present.
   b. Risk factors
      (1) Complete mole (50% of cases)
      (2) Spontaneous abortion (25% of cases)
(3) Full term pregnancy (22% of cases)
(4) Ectopic pregnancy (3% of cases)

c. Common sites of metastasis
   (1) Lungs, vagina, liver, brain
   (2) Lesions are hemorrhagic.

d. Excellent response to chemotherapy (methotrexate)
   (1) Low mortality rate
   (2) Good response does not apply to non–gestationally derived choriocarcinomas
      (e.g., those that occur in the male testis).

F. Amniotic fluid (AF)

1. Composition
   a. Predominantly fetal urine
   b. High salt content causes “fernng” when dried on a slide.
      • Do not confuse this ferning with the type seen in watery cervical mucus (earlier discussion)
      • Excellent sign of premature rupture of the amniotic sac
   c. Swallowed and recycled by the fetus
   d. Polyhydramnios
      (1) Definition—excessive AF
      (2) Causes
         (a) Tracheoesophageal (TE) fistula (refer to Chapter 18)
         (b) Duodenal atresia (refer to Chapter 18)
         (c) Maternal diabetes (20% of cases)
            • Maternal hyperglycemia → fetal hyperglycemia → fetal polyuria
   e. Oligohydramnios
      (1) Definition—decreased amount of AF
      (2) Causes
         (a) Juvenile polycystic kidney disease (refer to Chapter 20)
         (b) Fetal genitourinary obstruction
         (c) Uteroplacental insufficiency
         (d) Premature rupture of membranes

2. α-Fetoprotein (AFP) in pregnancy
   a. Increased maternal AFP
      (1) Open neural tube defect
      (2) Related to folic acid deficiency
      (3) Folic acid stores should be adequate before pregnancy.
         • Neural tube is already developed by the end of the first month of gestation.
   b. Decreased maternal AFP
      • Down syndrome

3. Lecithin/sphingomyelin (L/S) ratio
   a. Lecithin
      (1) Synthesized by type II pneumocytes
      (2) Decreases alveolar surface tension to prevent atelectasis
   b. L/S ratio >2 in AF indicates adequate surfactant.
   c. Cortisol and thyroxine increase surfactant synthesis.
      • Maternal administration of glucocorticoids increases surfactant synthesis if babies
         must be delivered before term.
   d. Insulin inhibits surfactant synthesis.

G. Urine estriol in pregnancy

1. Derived from the fetal adrenal gland, placenta, and maternal liver
   a. Fetal zone of the adrenal cortex
      (1) Converts pregnenolone synthesized in the placenta to DHEA-S
      (2) Fetal zone is absent in anencephaly (absent brain; refer to Chapter 26).
   b. Fetal liver
      • DHEA-S is 16-hydroxylated to 16-OH-DHEA-S.
   c. Placenta
      (1) Placental sulfatase cleaves off the sulfate from 16-OH-DHEA-S.
      (2) 16-OH-DHEA is converted by aromatase to free unbound estriol.
   d. Maternal liver
      (1) Free estriol is conjugated to estriol sulfate and estriol glucosiduronate.
      (2) Both compounds are excreted in maternal urine and bile.

Choriocarcinoma risk:
- complete mole > spontaneous abortion > normal pregnancy > partial mole

Choriocarcinoma:
- hemorrhagic; lungs/ vagina metastasis; excellent prognosis

AF predominantly fetal urine

Oligohydramnios:
- juvenile polycystic kidney disease

↑AFP in pregnancy:
- open neural tube defect; inadequate folic acid before pregnancy

↓AFP: Down syndrome

L/S ratio >2: adequate surfactant; ↓alveolar surface tension; prevent atelectasis

Surfactant: ↑with glucocorticoids; thyroxine; ↓with insulin

Estriol: derived from fetal adrenal gland/liver; placenta, maternal liver

↓Estriol: fetal-maternal-placental dysfunction
2. Decreased levels of estriol
   • Sign of fetal-maternal-placental dysfunction
3. Down syndrome triad
   a. Decreased urine estriol
   b. Decreased serum AFP
   c. Increased serum β-hCG

X. Breast Disorders

A. Clinical anatomy
1. High-density locations of breast tissue
   a. Upper outer quadrant
   • Underscores why cancer is most commonly located in this quadrant
   b. Beneath the nipple
2. Hormone effects during menstrual cycle
   a. Estrogen
   • Stimulates ductal and alveolar cell growth, fat, and stroma
   b. Progesterone
   • Stimulates alveolar cell proliferation and lobule differentiation for milk production (does not stimulate secretion), breast swelling in secretory phase
3. Hormone effects in lactation
   a. Prolactin
   • Stimulates and maintains lactogenesis and secretion
   b. Oxytocin
   (1) Released by suckling reflex
   (2) Expulsion of milk into ducts
4. Lymph nodes
   a. Outer quadrant cancers
   • Drain to the axillary lymph nodes
   b. Inner quadrant cancers
   • Drain to the internal mammary nodes

B. Locations for breast lesions (Fig. 22-17)

C. Nipple discharges
1. Galactorrhea; causes other than lactation:
   a. Mechanical stimulation of the nipple (physiologic causes)
      (1) Prolonged sucking of nipple
      (2) Sexual intercourse
   b. Prolactinoma (refer to Chapter 23)
      • Most common pathologic cause of galactorrhea (Fig. 22-18A)
   c. Primary hypothyroidism (refer to Chapter 23)
      (1) Most common nonpituitary endocrine disease causing galactorrhea
      (2) Decreased serum thyroxine increases thyrotropin-releasing factor (TRF).
       • TRF stimulates prolactin.
   d. Drugs
      • Examples—OCPs, phenothiazines, methyl dopa, H2-receptor blockers, anxiolytics, tricyclic antidepressants (TCAs)
2. Bloody nipple discharge
   • Intraductal papilloma, ductal cancer
22-18: A, Galactorrhea in a patient with a prolactinoma. B, Mammogram with benign “popcorn” calcifications. C, Mammogram with benign round calcifications. D, Fibrocystic change. The microscopic section shows cystic spaces surrounded by a dense fibrous stroma. The large cyst at the top has eosinophilic staining cells exhibiting apocrine metaplasia. The smaller cysts (arrows) show extensive ductal hyperplasia with a sieve-like pattern. E, Fibroadenoma. Note the bulging gray-white surface of this benign stromal tumor. F, Fibroadenoma. A microscopic section shows compressed, elongated benign ducts surrounded by neoplastic stromal tissue. (A from Mansel R, Bundred N: Color Atlas of Breast Disease, St. Louis, Mosby, 1995; B and C from Pretorius ES, Solomon JA: Radiology Secrets Plus, 3rd ed, Philadelphia, Mosby Elsevier, 2011, p 40, Figs. 6.8, 6.7, respectively; D from Rosai J, Ackerman LV: Surgical Pathology, 9th ed. St. Louis, Mosby, 2004, p 1780, Fig. 20-30; E from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 298, Fig. 14-3; F from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 405, Fig. 16-5B.)
3. Purulent nipple discharge
   a. Acute mastitis due to *S. aureus*
   b. Usually occurs during lactation or breast-feeding
   c. Treatment
      (1) If not methicillin resistant, dicloxacillin or cephalaxin
      (2) If methicillin resistant, trimethoprim-sulfamethoxazole double strength

4. Greenish brown nipple discharge
   • Mammary duct ectasia (plasma cell mastitis)

D. Breast pain
   1. Most common cause is fibrocystic change (FCC)
   2. Mondor disease
      a. Superficial thrombophlebitis of veins overlying the breast
      b. Presents as a palpable, painful cord

E. Examples of benign types of microcalcifications in mammograms
   • Popcorn calcifications (see Fig. 22-18B), round calcifications (see Fig. 22-18C)

F. Fibrocystic change (FCC)
   1. Epidemiology and pathogenesis
      a. Most common painful breast mass in women <50 years old
      b. Occurs in >50% of women in the reproductive period of life
      c. Distortion of normal cyclic breast changes
   2. Small and large cysts (see Fig. 22-18D)
      a. Some cysts hemorrhage into the cyst fluid.
         • Called “blue-domed” cysts
      b. Vary in size with the menstrual cycle
      c. No malignant potential
      d. May have to surgically remove if recurrent
   3. Fibrosis
      • No malignant potential
   4. Sclerosing adenosis
      a. Proliferation of small ductules/acini in the lobule
         • Pattern is often confused with infiltrating ductal cancer.
      b. Often contain microcalcifications
   5. Ductal hyperplasia
      a. Ducts are estrogen sensitive.
      b. Pathologic findings
         (1) Papillary proliferation is called papillomatosis.
         (2) Apocrine metaplasia refers to the presence of large, pink-staining cells.
         (3) Atypical ductal hyperplasia
            • Increased risk for developing cancer, because it is due to excess estrogen stimulation

G. Inflammation
   1. Acute mastitis (see earlier discussion)
   2. Mammary duct ectasia (plasma cell mastitis)
      a. Epidemiology
         (1) Affects 25% of women in menopause
         (2) Main ducts fill up with debris.
            • Causes dilation, rupture, and inflammation
            • Greenish brown nipple discharge
         (3) May produce skin and nipple retraction simulating cancer
         (4) No increased risk for breast cancer
      b. Treatment
         (1) Antibiotics if infection is present
         (2) Surgical removal of blocked duct
   3. Traumatic fat necrosis
      a. Trauma to breast tissue
      b. Microscopic findings
         (1) Lipid-laden macrophages with foreign body giant cells
         (2) Fibrosis, dystrophic calcification
      c. Painless, indurated mass
         • Painful in acute stage
      d. May produce skin retraction simulating cancer
   4. Silicone breast implant
      a. Polymer of silica, oxygen, and hydrogen
      b. Silicone gel can leak, or the implant can rupture
(1) Silicone produces foreign body giant cells and chronic inflammation.
(2) Association with autoimmune disease has not been proved.

H. Benign breast tumors

1. Fibroadenoma
   a. Epidemiology
      (1) Most common breast tumor in women <35 years old
      (2) Most commonly diagnosed breast tumor
      (3) Develop in 50% of women who receive cyclosporine after renal transplantation
      (4) Discrete movable, painless or painful mass (see Fig. 22-18E).
         • Multiple lesions may be present (10%–15% of cases).
      (5) Benign tumor derived from the stroma
         (a) Stroma proliferates and compresses the ducts (see Fig. 22-18F).
         (b) Duct epithelium is not neoplastic.
      (6) Increases in size during pregnancy
         • Estrogen sensitive
      (7) May spontaneously disappear or involute during menopause
      (8) Do not progress into cancer; however, breast cancer may secondarily develop within duct epithelial cells as a separate event (3% of cases)
   b. Diagnosis
      • Fine needle or core needle biopsy
   c. Treatment
      (1) Surgical removal
      (2) Cryoablation

2. Phyllodes tumor
   a. Bulky tumor derived from stromal cells
   b. Most often benign but can be malignant in some cases
      • Hypercellular stroma with mitoses are signs of malignancy.
   c. Lobulated tumor with cystic spaces containing leaf-like extensions
      • Often reach a massive size
   d. Treat by wide excision.

3. Intraductal papilloma
   a. Most common cause of a bloody nipple discharge in women <50 years old
   b. Develop in the lactiferous ducts or sinuses
   c. No increased risk for cancer
   d. Surgically remove the duct or sinus.

I. Breast cancer

1. Epidemiology
   a. Most common cancer in adult women (1:8 lifetime risk)
      (1) Mean age is 64 years old.
      (2) Risk increases with age.
   b. Most common breast mass in women >50 years old
   c. Slightly decreasing in incidence because of early detection and treatment
   d. Second most common cancer-producing death in women
      • It is also the second most common cancer-producing death in adults (includes men and women as a group).

2. Factors that increase the risk for breast cancer
   a. Common denominators for increased risk of cancer
      (1) Prolonged estrogen stimulation
      (2) Genetically susceptible background
   b. Family history and genetics
      (1) Increased risk if breast cancer involves first-generation relatives
         • Mother, sister
      (2) Genetic basis is involved in <10% of cases (refer to Chapter 9)
         (a) Autosomal dominant BRCA1 and BRCA2 association
            • Breasts or ovaries are frequently prophylactically removed.
         (b) Li-Fraumeni multicancer syndrome
            • Inactivation of p53 suppressor gene (refer to Chapter 9)
      (3) Other gene relationships
         • RAS oncogene, ERBB2, RB1 suppressor gene
   c. Prolonged estrogen stimulation
      (1) Early menarche/late menopause
      (2) Nulliparity

Breast cancer: MC breast tumor in women <35 years old

Fibroadenoma: commonly develop in women taking cyclosporine

Phyllodes tumor: benign, borderline, or malignant stromal tumor; depends on stromal cellularity

Intraductal papilloma: MCC of bloody nipple discharge in women <50 years old

Breast cancer: MC breast cancer in women

Breast cancer risk: prolonged estrogen stimulation, genetically susceptible background

Breast cancer risk: genetic basis <10% of cases

Breast cancer: MC breast mass in women >50 years old

Breast cancer: MC breast cancer-production death in adults (includes men and women as a group).
(3) Postmenopausal obesity
   - Aromatization of androstenedione to estrone
(4) Hormone replacement therapy
(5) Ductal carcinoma in-situ (DCIS), lobular carcinoma in-situ (LCIS)
d. Atypical ductal hyperplasia
e. Endometrial cancer, ionizing radiation, smoking cigarettes
f. High breast density (determined by mammogram)
g. Recent use of OCPs, obesity after menopause

3. Factors that decrease the risk for breast cancer
   a. Breast-feeding
   b. Moderate or vigorous physical training
   c. Healthy body weight

4. Clinical findings
   a. Painless mass in the breast
      - Usually in the upper outer quadrant
   b. Skin or nipple retraction
   c. Painless axillary lymphadenopathy
d. Hepatomegaly, bone pain if metastasis has occurred

5. Mammography
   a. Primarily a screening test
      - Detects nonpalpable breast masses (detects 80%–90% of nonpalpable masses)
   b. Does not distinguish benign from malignant lesions
   c. Screening usually starts annually at age 40 years, but earlier if patient is high risk.
   d. Identifies microcalcifications and spiculated masses with or without microcalcifications
      (30%–50% of cases)
         (1) Most often occur in DCIS and sclerosing adenosis (FCC)
         (2) Microcalcification pattern suggesting malignancy
            - Five or more tightly clustered microcalcifications that are punctate, microlinear, or branching (Fig. 22-19)

6. Types of breast cancer (Table 22-5; Fig. 22-20)

7. Natural history, treatment, and prognosis
   a. Spread first by lymphatics and then a hematogenous route
      (1) Outer quadrant cancer spreads to axillary nodes.
      (2) Inner quadrant cancers spread to internal mammary nodes.
   b. Extranodal metastasis
      (1) Common sites of metastasis
         - Lungs, bone, liver, brain, ovaries
      (2) May metastasize 10 to 15 years after treatment
      (3) Pain in bone metastasis is relieved with radiation.
   c. Staging
      (1) Extranodal metastasis has greater significance than nodal metastasis (refer to Chapter 9)
      (2) Sentinel node biopsy
         - The initial node that drains the tumor is sampled.

22-19: Mammogram showing breast cancer with microlinear, branching malignant microcalcifications. (From Pretorius ES, Solomon JA: Radiology Secrets Plus, 3rd ed, Philadelphia, Mosby Elsevier, 2011; p 39, Fig. 6-5.)
22-20: A, Ductal carcinoma in situ (DCIS) showing dilated ducts lined by layers of neoplastic cells. Central areas of necrosis (comedo pattern) are present, some of which contain microcalcifications (white arrow). B, Lobular carcinoma in situ showing complete replacement and expansion of a lobule by a monomorphic population of cells. C, Infiltrating ductal carcinoma showing a stellate-shaped scar (arrow) in the fat tissue of the breast. D, Mammogram showing a large irregular spicular mass lesion, which on biopsy showed an infiltrating ductal carcinoma. E, Paget disease of the breast showing an erythematous rash around the nipple. F, Inflammatory carcinoma of the right breast. Note the dimpled appearance of the breast (peau d’orange). (A and B from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, pp 1139, 1142, Figs. 23-16B, 23-20, respectively; C from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 304, Fig. 14-14A; D and F from Grieg JD: Color Atlas of Surgical Diagnosis. London, Mosby-Wolfe, 1996, p 33, Figs. 6-22, 6-23, respectively; E from Swartz MH: Textbook of Physical Diagnosis, 5th ed. Philadelphia, Saunders Elsevier, 2006, p 464, Fig. 16-7.)
## TABLE 22-5 Types of Breast Cancer

<table>
<thead>
<tr>
<th>TYPE</th>
<th>COMMENTS</th>
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</thead>
<tbody>
<tr>
<td><strong>Noninvasive</strong></td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma in-situ (DCIS) (see Fig. 22-20A)</td>
<td>Nonpalpable; Patterns: cribriform (sieve-like), comedo (necrotic center) Commonly contain microcalcifications; cannot be detected by mammogram unless microcalcifications are present One-third eventually invade Treated with lumpectomy</td>
</tr>
<tr>
<td>Lobular carcinoma in-situ (LCIS, see Fig. 22-19B)</td>
<td>Nonpalpable; virtually always an incidental finding in a breast biopsy for other reasons; cannot be identified by mammography (no calcifications) Lobules are distended with bland neoplastic cells; one-third eventually invade; usually positive for estrogen and progesterone receptors Increased incidence of cancer in the opposite breast (20%–40% of cases)</td>
</tr>
<tr>
<td><strong>Invasive</strong></td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal carcinoma (see Fig. 22-19C and D)</td>
<td>Stellate morphology (noted in the gross specimen and mammogram), indurated, gray-white tumor One third have amplification of the ERBB2 oncogene Gritty on cut section; induration is caused by reactive fibroplasia (desmoplastia) of the stroma to the tumor</td>
</tr>
<tr>
<td>Paget disease of nipple (see Fig. 22-19E)</td>
<td>Extension of DCIS into the lactiferous ducts and skin of the nipple producing a rash, with or without nipple retraction Paget cells are present (see Fig. 22-2E) Palpable mass is present in 50%–60% of cases</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>Associated with BRCA1 mutations Bulky, soft tumor with large cells and a lymphoid infiltrate Majority are negative for estrogen and progesterone receptors</td>
</tr>
<tr>
<td>Inflammatory carcinoma (see Fig. 22-19F)</td>
<td>Erythematous breast with dimpling like an orange (peau d’orange) due to fixed opening of the sweat glands, which cannot expand with lymphedema Plugs of tumor blocking the lumen of dermal lymphatics cause localized lymphedema Very poor prognosis Combination chemotherapy followed by surgery and irradiation</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>Neoplastic cells are arranged linearly or in concentric circles (bull’s-eye appearance) in the stroma; invasive carcinoma develops in contralateral breast in 5%–10% of cases.</td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>Develops in terminal ductules Increased incidence of cancer in opposite breast (10% of cases)</td>
</tr>
<tr>
<td>Colloid (mucinous) carcinoma</td>
<td>Usually occurs in elderly women Neoplastic cells are surrounded by extracellular mucin</td>
</tr>
</tbody>
</table>

**ERA-PRA receptor assays:** positive assay confers better prognosis

(b) If negative for metastasis, the other nodes in that group are usually negative.

(c) If positive for metastasis, there is a one-third chance that other nodes in that group have metastases.

d. Estrogen and progesterone receptor assays (ERA and PRA, respectively)
   (1) Most often positive in postmenopausal women
   (2) Clinical significance
      (a) Confers an overall better prognosis; however, this improvement decreases as the follow-up interval increases
      (b) Candidate for antiestrogen therapy (e.g., tamoxifen, oophorectomy)

**ERBB2 (HER-2NEU) oncogene:** if positive in breast tissue, poor prognosis

e. Other tests performed on tissue
   (1) S phase fraction
      • Above 5% is poor prognosis.
   (2) DNA ploidy
      • Diploid tumor is better than an aneuploid tumor.
   (3) ERBB2 (HER-2NEU) oncogene status
      • Poor prognosis if amplification or overexpression are present (refer to Chapter 9).

f. Treatment for high-risk patients without breast cancer
   • Treatment with tamoxifen or raloxifene reduces risk.

g. Surgical procedures
   (1) Modified radical mastectomy
      (a) Nipple/areolar complex
      (b) All breast tissue
      (c) Pectoralis minor
      (d) Axillary node dissection

**Winged scapula:** damage to long thoracic nerve

A **winged scapula** may occur from damage to the long thoracic nerve. There is also a danger for developing lymphedema.
(2) Breast conservation therapy
   (a) Lumpectomy with microscopically free margins
   (b) Sentinel node biopsy
   (c) Breast irradiation

h. Prognosis
   (1) Prognosis after curative therapy is dependent on tumor size, extent of nodal metastasis, pathologic grade of the tumor, and systemic adjuvant chemotherapy.
   (2) Patient with 1-cm tumor with no axillary node involvement has a 10-year disease-free survival rate of 90%.
   (3) Patient with 3-cm tumor with metastasis in 4 nodes has a 10-year disease-free survival rate of 15% if no adjuvant therapy is given.
   (4) Outlook for most other patients is somewhere in between these extremes.

J. Gynecomastia
   1. Definition—benign subareolar glandular proliferation in the male breast due to estrogen
      a. More often unilateral than bilateral
      b. Due to increased estrogen stimulation related to:
         (1) An increase in estrogen
         (2) A decrease in androgens (leaves estrogen unopposed)
         (3) A defect in androgen receptors (leaves estrogen unopposed)
   c. Sources of estrogen
      (1) Peripheral aromatization (85% of cases)
         (a) Testosterone is converted to estradiol by aromatase.
         (b) Androstenedione is converted to estrone by aromatase.
      (2) Leydig cells (15% of cases)
   2. Physiologic gynecomastia
      a. Gynecomastia is normal in:
         (1) Newborns (present in 60%–90% of cases).
         (2) Puberty (peaks at ages 13–14 years).
         (3) Elderly persons (occurs between 50 and 80 years of age)
      b. In general, surgery is not indicated.
   3. Pathologic gynecomastia
      a. Cirrhosis (most common pathologic cause)
         (1) Liver cannot metabolize estrogen
         (2) Liver cannot metabolize 17-ketosteroids (17-KS)
            • 17-KS peripherally aromatized to estrone
      b. Genetic diseases
         (1) Klinefelter syndrome (refer to Chapter 6)
            • Increased aromatization of androgens to estrogens in Leydig cells and decreased responsiveness of testosterone to androgen receptors
         (2) Androgen insensitivity syndrome (testicular feminization; refer to Chapter 6)
            • Decreased androgen receptor synthesis
      c. Drugs
         (1) Drug displacement of estrogen from SHBG
            • Spironolactone, ketoconazole
         (2) Drugs with estrogen activity
            • DES, digoxin (activates estrogen receptors)
         (3) Drugs that block androgen receptors
            • Spironolactone, flutamide
         (4) Drugs that decrease androgen production
            • Leuprolide
      d. Cancer
         • Choriocarcinoma of testis produces hCG (LH analogue)
      e. Disorders with decreased androgen production
         (1) Primary hypogonadism
            • Leydig cell dysfunction (refer to Chapter 21)
         (2) Secondary hypogonadism
            • Pituitary/hypothalamic dysfunction (refer to Chapter 21)

K. Breast cancer in men
   1. Risk factors
      a. Inactivation of **BRCA2** suppressor gene
      b. Klinefelter syndrome
   2. Usually have a poor prognosis
I. Overview of Endocrine Disease

A. Negative feedback loops

1. Control an increase or a decrease in hormone production (inverse relationship)
2. Example—increased calcium decreases parathyroid hormone (PTH) synthesis and release
d3. Example—increased plasma adrenocorticotropic hormone (ACTH) decreases serum
cortisol production and release by the adrenal cortex

B. Positive feedback loops

1. Positive relationship
2. Example—in the proliferative phase of the menstrual cycle, estradiol surges and causes
luteinizing hormone (LH) to increase greater than follicle-stimulating hormone (FSH),
which is the stimulus for ovulation (see Fig. 22-6)

C. Stimulation tests

1. Evaluate hypofunctioning disorders
   a. Example—ACTH stimulation test is used in the workup of hypocortisolism to see if
      hypocortisolism is due to adrenal hypofunction or pituitary/hypothalamic hypofunction
         (1) If ACTH does not cause an increase in serum cortisol, the problem is with adrenal
            hypofunction.
         (2) If ACTH causes an increase in serum cortisol, the problem is with hypopituitarism
             or hypothalamic dysfunction.
   b. Example—gonadotropin-releasing hormone (GnRH) stimulation test to distinguish
      hypothalamic dysfunction causing amenorrhea (lack of menses) or hypopituitarism
         (1) If GnRH does not cause an increase in serum luteinizing hormone (LH) and follicle
            stimulating hormone (FSH), the problem is hypopituitarism.
         (2) If GnRH causes an increase in serum luteinizing hormone (LH) and follicle
            stimulating hormone (FSH), the problem is hypothalamic dysfunction.

2. Causes of endocrine hypofunction
   a. Autoimmune destruction (most common cause of hypofunction)
      • Examples—Addison disease, Hashimoto thyroiditis
   b. Infarction
      • Example—Sheehan postpartum necrosis, Waterhouse-Friderichsen syndrome in
        meningococcemia
   c. Decreased gland stimulation
      • Example—decreased thyroid-stimulating hormone in hypopituitarism causes a
        decrease in thyroid production of thyroxine
d. Enzyme deficiency, infection, metastasis, congenital disorder

D. Suppression tests

1. Evaluate hyperfunctioning endocrine disorders
   a. Example—low-dose dexamethasone (DXM; cortisol analogue) suppression test
      evaluates hypercortisolism due to pituitary, adrenal, or ectopic Cushing syndrome
   b. Cortisol is not suppressed in Cushing syndrome with a low dose of dexamethasone.
II. Hypothalamus

A. Tumors or tumor-like conditions altering hypothalamic function
1. Pituitary adenoma (see section IV)
   • Most common tumor affecting hypothalamic function
2. Craniopharyngioma (see section IV)
3. Midline hamartoma
   a. Not a neoplasm
   b. Produces precocious puberty in boys
4. Langerhans histiocytosis (refer to Chapter 14)
   • Metastasis of malignant histiocytes to the hypothalamus

B. Inflammatory disorders altering hypothalamic function
1. Sarcoidosis (refer to Chapter 17)
   • Produces granulomatous inflammation in the hypothalamus
2. Meningitis (refer to Chapter 26)

C. Clinical findings of hypothalamic dysfunction
1. Secondary hypopituitarism
   a. No releasing hormones from the hypothalamus to stimulate the anterior pituitary
   b. Example—deficiency of GnRH causes a decrease in FSH/LH
   c. Example—deficiency of corticotropin-releasing hormone (CRH) causes a decrease in ACTH
2. Central diabetes insipidus (CDI; discussed fully in Chapter 5)
   a. Antidiuretic hormone (ADH) is synthesized in the hypothalamus, primarily in the supraoptic and paraventricular nuclei.
   b. It travels down the nerve fibers through the pituitary stalk and is stored in the nerve endings in the posterior pituitary.
   c. Therefore dysfunction of the hypothalamus (e.g., metastasis in malignant histiocytoses; granulomatous destruction in sarcoidosis), transection of the pituitary stalk (e.g., trauma), or destruction of the posterior pituitary (e.g., metastasis) leads to lack of ADH, which is called CDI.
3. Hyperprolactinemia
   • Loss of dopamine inhibition of prolactin causes an increase in prolactin leading to milk production in females (galactorrhea).
4. Precocious puberty
   • Midline hamartoma in a boy causes precocious puberty.

“True” precocious puberty implies a central nervous system (CNS) origin for the disorder, but pseudoprecocious puberty implies a peripheral cause (e.g., adrenogenital syndrome). True precocious puberty in boys is the onset of puberty before 9 years of age. A common cause is a midline hamartoma in the hypothalamus. True precocious puberty in girls is the onset of puberty before 8 years of age. In most cases, it is idiopathic and less likely to be caused by a midline hamartoma.
Dysfunction: 1° due to Kallmann syndrome

Pineal gland: midline above quadrigeminal plate

Melatonin: sleep/moods, circadian rhythms

Pineal gland: commonly undergoes dystrophic calcification

Tumors: germ cell tumors/teratomas

Pineal gland tumors: paralysis upward gaze ("setting sun" sign)

Infarction: panhypopituitarism

1° hypopituitarism (pituitary dysfunction); 2° hypopituitarism (hypothalamic dysfunction)

Hypopituitarism in adults: MCC is nonfunctioning adenoma

MEN I: pituitary adenoma, HPTH, pancreatic tumor

Hypopituitarism in children: MCC is craniopharyngioma

Rathke pouch is derived from the oral ectoderm. It develops into the anterior lobe of the pituitary gland.

Rathke pouch: develops into anterior pituitary

Sheehan postpartum necrosis: lactation ends suddenly; pituitary infarction secondary to shock

III. Pineal Gland Disorders

A. Clinical anatomy

1. Pineal gland has a midline location above the quadrigeminal plate in the midbrain.
2. Site for melatonin production
   a. Superior cervical sympathetic ganglia stimulates receptors on pinealocytes.
   b. Causes release of melatonin into spinal fluid and blood
5. Melatonin functions
   (1) Important in sleep/moods and circadian rhythms
   (2) Used in the treatment of sleep and mood disorders

B. Disorders

1. Dystrophic calcification of the pineal gland begins in childhood.
   a. Calcification is useful in radiology to show shifts due to mass lesions in the brain.
   b. Approximately 80% are calcified between 70 and 80 years of age.
2. Pineal tumors
   a. Majority are germ cell tumors resembling seminomas in the testis (refer to Chapter 21).
   b. Minority of tumors are teratomas with ectodermal, endodermal, and mesodermal components (refer to Chapter 9).

C. Clinical findings

1. Visual disturbances
   a. Paralysis of upward conjugate gaze (Parinaud syndrome; see Fig. 26-3B)
   b. Due to compression of the aqueduct of Sylvius in the third ventricle

IV. Pituitary Gland Disorders

A. Anterior pituitary hypofunction

1. Epidemiology
   a. Partial or complete loss of secretion of one or more hormones
   b. Infarctions of the pituitary invariably lead to panhypopituitarism
   c. Types of pituitary dysfunction
      (1) Primary hypopituitarism (pituitary dysfunction)
      (2) Secondary hypopituitarism (hypothalamic dysfunction)
   2. Causes of hypopituitarism
      a. Nonfunctioning (null) pituitary adenoma (Fig. 23-1)
      (1) Most common cause of hypopituitarism in adults
      (2) Microadenoma <10 mm; macroadenoma >10 mm
      (3) Association with multiple endocrine neoplasia (MEN) I syndrome, which includes:
      • Pituitary adenoma, hyperparathyroidism (HPTH), pancreatic tumor (Zollinger-Ellison syndrome or insulinoma).
      b. Craniopharyngioma
      (1) Most common cause of hypopituitarism in children
      (2) Benign pituitary tumor derived from Rathke pouch remnants

8. Primary amenorrhea due to Kallmann syndrome (refer to Chapter 21)
   • Decreased synthesis of GnRH

Rathke pouch: develops into anterior pituitary

Sheehan postpartum necrosis: lactation ends suddenly; pituitary infarction secondary to shock

(3) Located above the sella turcica
   - Extends into the sella turcica and destroys the gland
(4) Cystic tumor with hemorrhage and calcification
(5) Commonly causes bitemporal hemianopia (compresses optic chiasm)
(6) May cause central diabetes insipidus (CDI)

C. Sheehan postpartum necrosis
   (1) Hypovolemic shock (e.g., blood loss) causes infarction.
   (2) Sudden cessation of lactation is due to loss of prolactin.
   • Eventual development of hypopituitarism
Endocrine Disorders

23-1: Pituitary adenoma. The interrupted arrow shows a well-circumscribed mass that has almost completely replaced the pituitary gland. A thin rim of sella turcica is present at the base of the tumor. The solid arrow shows the optic nerve and its proximity to the sella turcica. (From Burger PC, Scheithauer BW, Vogel KS: Surgical Pathology of the Nervous System, 4th ed, London, Churchill Livingstone, 2002, p 444, Fig. 9-20.)

The pituitary gland doubles in size during pregnancy because of prolactin synthesis. Prolactin release is inhibited by the high levels of progesterone during pregnancy.

d. Pituitary apoplexy
   (1) Definition—“apoplexy” refers to a sudden onset of neurologic dysfunction
   (2) Most often due to hemorrhage/infarction of a preexisting pituitary adenoma
   (3) Predisposing factors
      • Trauma, pregnancy (Sheehan postpartum necrosis, a nontumorous cause), treatment of a prolactinoma with bromocriptine
   (4) Clinical findings; sudden onset of:
      (a) Headache, mental status dysfunction, visual disturbances
      (b) Hormone dysfunction

e. Sickle cell anemia (HbSS)
   • Pituitary infarction from vascular occlusion by sickled cells

f. Lymphocytic hypophysitis
   (1) Female dominant autoimmune destruction of the pituitary gland
   (2) Occurs during or after pregnancy

gh. Empty sella syndrome
   (1) Epidemiology
      (a) Radiologic studies show an empty sella turcica.
      (b) Primary and secondary types
   (2) Primary type
      (a) Anatomic defect is present above the pituitary.
      (b) Subarachnoid space extends into the sella turcica and fills up with cerebrospinal fluid (CSF).
      (c) Increase in pressure on the pituitary gland causes it to flatten out and undergo atrophy.
      (d) This type is often associated with women who are obese and have high blood pressure.
   (3) Secondary type
      • Regression in size due to radiation, trauma, or surgery
   h. Hypothalamic dysfunction (see section II)

3. Clinical and laboratory findings (Table 23-1; Fig. 23-2)
4. Diagnosis
   a. CT scan or MRI (better test) of the sella turcica
      • Sella turcica is in the sphenoid bone
   b. Stimulation tests for the various deficiencies
### Table 23-1 Clinical Findings in Hypopituitarism

<table>
<thead>
<tr>
<th><strong>TROPHIC HORMONE DEFICIENCY</strong></th>
<th><strong>DISCUSSION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonadotropins (FSH, LH)</td>
<td>Children have delayed puberty; adult females have secondary amenorrhea, hot flashes (lack of estrogen), decreased libido (sexual desire); males have impotence, due to decreased libido from decreased testosterone (refer to Chapter 21). GnRH stimulation test: no significant increase of FSH/LH in hypopituitarism; eventual increase of FSH/LH in hypothalamic disease.</td>
</tr>
<tr>
<td>Growth hormone (GH)</td>
<td>Decreased GH decreases synthesis and release of IGF-1. Children have growth delay: delayed fusion of epiphyses; bone growth does not match the age of the child. Adults have hypoglycemia: decreased gluconeogenesis; loss of muscle mass; increased adipose around the waist. Arginine and sleep stimulation tests: no increase in GH or IGF-1.</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Secondary hypothyroidism: decreased serum T4 and TSH. Cold intolerance, constipation, weakness. No increase in TSH after TRF stimulation.</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone (ACTH) (see Fig. 23-2A and B)</td>
<td>Metyrapone test: stimulation test of pituitary ACTH and adrenal gland reserve; metyrapone inhibits adrenal 11-hydroxylase, which causes a decrease in cortisol and a corresponding increase in plasma ACTH (pituitary) and 11-deoxycortisol (adrenal), which is proximal to the enzyme block; in hypopituitarism, neither ACTH or 11-deoxycortisol are increased; in adrenal disease, ACTH is increased, but 11-deoxycortisol is decreased.</td>
</tr>
</tbody>
</table>

ADH, Antidiuretic hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; SIADH, syndrome of inappropriate antidiuretic hormone; T4, thyroxine; TRF, thyrotropin-releasing factor.

#### Figure 23-2: Schematic of the metyrapone test: a normal response (A) and the response expected in hypopituitarism (B). A, Metyrapone blocks 11-hydroxylase in the adrenal cortex. This decreases cortisol leading to an increase in ACTH and 11-deoxycortisol. B, A decrease in cortisol does not increase pituitary ACTH indicating hypopituitarism as the cause of hypocortisolism. Because ACTH is not increased, there is no increase in 11-deoxycortisol proximal to the enzyme block. ACTH, Adrenocorticotropic hormone.

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5. Treatment
   a. Surgery for tumors (usually transsphenoidal)
   b. Hormone replacement for deficiencies

B. **Posterior pituitary hypofunction**
   1. Normal function of posterior pituitary
      a. Stores antidiuretic hormone (ADH)
         (1) ADH controls total body water.
         (2) Presence of ADH induces concentration of urine.
         (3) Absence of ADH produces dilution of urine.
      b. Releases oxytocin after suckling
         (1) Primarily produced in the paraventricular nucleus in the hypothalamus.
         (2) Causes milk ejection and uterine contractions
   2. Refer to Chapter 5 for complete discussion of diabetes insipidus

C. **Pituitary hyperfunction disorders**
   1. Prolactinoma
      a. Epidemiology
         (1) Benign adenoma
         (2) Overall most common pituitary tumor (35% of all tumors)
         (3) Also secretes growth hormone in 7% of cases
b. Clinical and laboratory findings

(1) Women
   (a) Secondary amenorrhea (loss of menses)
      - Prolactin inhibits GnRH.
      - Decrease in FSH/LH causes decrease in estrogen synthesis in the ovaries.
   (b) Galactorrhea (see Fig. 22-18A)

(2) Men
   (a) Impotence
      - Loss of libido (sexual desire) is due to decrease in testosterone from decrease in serum LH.
   (b) Headache
      - Tumors tend to be larger in men than in women.
   (c) Not enough estrogen-dependent breast tissue to produce galactorrhea

(3) Serum prolactin level is usually >200 ng/mL.

(4) Decreased serum FSH and LH
   (a) Due to decreased GnRH
   (b) Decreased estrogen and progesterone due to decrease in FSH/LH, respectively

c. Other causes of galactorrhea (refer to Chapter 22)

d. Treatment

(1) Dopamine analogues (e.g., cabergoline)
   (a) Tumor does respond to suppression.
      - Shrinks in <50% of cases
   (b) Gonadal function is restored in 70% to 90% of cases.

(2) Surgery if macroadenomas

2. Growth hormone (GH) adenoma

a. Epidemiology

(1) Accounts for 20% of all pituitary adenomas

(2) Functions of GH
   (a) Stimulates liver synthesis/release of insulin-like growth factor (IGF)-1
   (b) Stimulates gluconeogenesis and amino acid (AA) uptake in muscle
   (c) Negative feedback relationship with glucose and IGF-1
      - Hyperglycemia inhibits GH, whereas hypoglycemia stimulates GH.
   (d) Antinatriuretic action (retains sodium)

(3) Functions of IGF-1
      - Stimulates growth of bone (linear and lateral), cartilage, and soft tissue

b. Clinical and laboratory findings

(1) Children develop gigantism.
   (a) Condition is due to increased linear bone growth (epiphyses have not fused).
   (b) Lateral bone growth is also increased.

(2) Adults develop acromegaly (Fig. 23-3).
   (a) Increased lateral bone growth (e.g., hands, feet, jaw)
      - No linear growth because the epiphyses are fused.
   (b) Prominent jaw
      - Spacing between the teeth
   (c) Frontal bossing
      - Enlarged frontal sinus increases hat size.

23-3: Acromegaly showing the patient before development of the tumor (left) and after development of the tumor (right). Note the coarse facial features and enlargement of the jaw and lips. Looking at previous photographs is very useful in suspecting acromegaly. (From Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 407.)
Acromegaly: heart failure from dilated cardiomyopathy MCC of death

Acromegaly: DM, hypertension, macroglossia, enlarged hat size

Laboratory: ↑GH, IGF-1 (most sensitive), glucose (secondary DM)

V. Thyroid Gland Disorders

A. Steps in thyroid hormone synthesis

1. Trapping of iodide is mediated by thyroid-stimulating hormone (TSH).
   - If TSH is not stimulating the thyroid gland (e.g., hypopituitarism, person taking excess thyroid hormone suppresses TSH release), the thyroid gland atrophies.

2. Oxidation of iodides to iodine is peroxidase mediated.

3. Organification
   a. Iodine is incorporated into tyrosine to form MIT (monoiiodotyrosine) and DIT (diiodotyrosine).
   b. Organification is TSH mediated.

4. Coupling of MIT with DIT produces triiodothyronine (T₃).

5. Coupling of DIT with DIT produces thyroxine (T₄).

6. Hormones are stored as colloid.

7. Proteolysis of colloid by lysosomal proteases is TSH mediated.

8. T₄ and T₃ bind to thyroid-binding globulin (TBG).
   - One-third of TBG binding sites are normally occupied.

9. Free T₄ (FT₄) is peripherally converted to free T₃ (FT₃) by an outer ring deiodinase.
   a. FT₃ is the metabolically active hormone.
   b. FT₄ is considered a prohormone.
   c. FT₄ and FT₃ have a negative feedback relationship with TSH and thyrotropin-releasing hormone (TRH).
      - An increase in FT₄/FT₃ should decrease serum TSH.
      - A decrease in FT₄/FT₃ should increase TSH.

B. Functions of thyroid hormone

1. Controls basal metabolic rate (BMR; refer to Chapter 8)

2. Growth and maturation of tissue (e.g., brain)

3. Turnover of hormones and vitamins

4. Cell regeneration

5. Synthesis of low-density lipoprotein (LDL) receptors for LDL (main vehicle for transporting cholesterol)

6. Synthesis of β-adrenergic receptors for catecholamines

C. Thyroid function tests

1. Total serum T₄ (Fig. 23-4A)
   a. Represents T₄ bound to TBG and free (unbound) T₄ (FT₄)
      - Note: the values used in the schematic do not represent true values for each of the components.
      - Figure 23-4A shows one third of TBG binding sites on two TBGs occupied by T₄.
         - Six molecules of T₄ are bound to TBG.
(3) FT₄ is 4.
(4) Total serum T₄ is 10 (6 bound to TBG and 4 FT₄ = 10).
(5) TSH is normal because FT₄ is normal.
b. Increase in TBG synthesis by the liver automatically increases total serum T₄
(see Fig. 23-4B).
(1) Estrogen increases the synthesis of TBG.
   • Causes of increased estrogen include pregnancy, taking oral contraceptive pills
     (OCPs), hormone replacement in menopause
(2) The extra TBG in the schematic has one-third of its binding sites occupied by T₄.
   • This increases the total amount of T₄ bound to TBG from 6 to 9.
(3) The 3 FT₄ used to bind to the extra TBG are immediately replaced by 3 T₄ released
    from the thyroid gland; therefore the FT₄ remains normal (4).
(4) Total serum T₄ is increased (9 + 4 = 13), because of T₄ bound to the extra TBG.
(5) TSH is normal because FT₄ is normal.
(6) No signs of thyrotoxicosis are present, because the FT₄ is normal.
c. Decrease in TBG synthesis decreases the total serum T₄.
(1) Causes of a decreased TBG include:
   • Anabolic steroids, nephrotic syndrome (urinary loss)
(2) Total serum T₄ is decreased, because the amount of TBG is decreased.
(3) FT₄ and TSH remain normal.
(4) No signs of hypothyroidism are present.
d. Clinical situations where TBG is altered
(1) TBG is normal and FT₄/FT₃ is increased—Graves disease or thyroiditis (release of
    FT₄ from colloid in the damaged thyroid).
(2) TBG is normal and FT₄/FT₃ is decreased—hypothyroidism.
(3) TBG is decreased and FT₄/FT₃ is normal—anabolic steroids, or nephrotic syndrome
    with loss of TBG.
(4) TBG is increased and FT₄/FT₃ is normal—woman taking estrogen or during
    pregnancy.
2. Serum thyroid-stimulating hormone (TSH)
a. Excellent screening test for thyroid dysfunction
b. Examples of serum TSH alterations
(1) Increased serum TSH
   • Primary hypothyroidism—decrease in synthesis of FT₄/FT₃ by thyroid gland →
     increase in serum TSH by negative feedback
(2) Decreased TSH; possibilities include:
   (a) Thyrotoxicosis (e.g., Graves disease)
      • Increased synthesis of FT₄/FT₃ → decrease in serum TSH by negative
        feedback
(b) Hypopituitarism
- Decrease in serum TSH → decrease in synthesis of FT₄/FT₃ by the thyroid gland (called secondary hypothyroidism)
(c) Hypothalamic dysfunction
- Decrease in TRH → decreases TSH release from the anterior pituitary → decrease in synthesis of FT₄/FT₃ by the thyroid gland (called tertiary hypothyroidism)

3. ¹²³I (radioactive) uptake
   a. ¹²³I uptake is used to measure synthetic activity of the thyroid gland.
      - Iodide is used to synthesize thyroid hormone (see V.A.).
   b. Increased uptake indicates increased synthesis of T₄.
      - Examples—Graves disease, toxic nodular goiter
   c. Decreased uptake of ¹²³I
      1. Inactivity of the gland
         - Example—patient taking thyroid hormone → decreases TSH → decreases uptake of ¹²³I
      2. Inflammation of the gland
         - Example—acute/subacute/chronic thyroiditis → inflammation interferes with normal functions of the gland
   d. Evaluates functional status of thyroid nodules
      1. Decreased ¹²³I uptake in a nodule
         - “Cold” nodule—cyst, adenoma, cancer (Fig. 23-5)
      2. Increased ¹²³I uptake in a nodule
         - “Hot” nodule—toxic nodular goiter

4. Thyroglobulin
- Marker for thyroid cancer

D. Lingual thyroid
1. Failed descent of thyroid anlage from the base of the tongue (Fig. 23-6A and B)
   - Usually represents all of the thyroid tissue
2. Clinical findings
   a. Dysphagia for solids
   b. Mass lesion
3. ¹²³I scan locates the lesion
   - Also identifies any other thyroid tissue that is present (e.g., functioning thyroid in a cystic teratoma of the ovary)
4. Treatment
   a. Suppression with thyroxine
   - Lingual thyroids are usually hypofunctional.
   b. Ablation with radioactive iodine
   c. Surgery if obstructive

E. Thyroglossal duct cyst
1. Cystic midline mass that is close to or within the hyoid bone (see Fig. 23-6A and C)
2. Surgery with removal of the proximal duct and a portion of the hyoid bone.

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**23-5:** Nuclear scan of thyroid showing “cold” nodules (lack of uptake or radioactive iodine) in both lobes of the thyroid (arrows). (From Katz D, Math K, Groskin S: Radiology Secrets, Philadelphia, Hanley & Belfus, 1998, p 531, Fig. 2.)
F. Thyroiditis

1. Acute thyroiditis
   a. Bacterial infection (e.g., *Staphylococcus aureus*)
   b. Clinical findings
      (1) Fever
      (2) Tender gland with painful cervical adenopathy
      (3) Initial thyrotoxicosis from gland destruction
         • Increased serum T4, decreased serum TSH
      (4) Permanent hypothyroidism is uncommon.
   c. Decreased 123I uptake
   d. Treatment
      • Penicillin or ampicillin

2. Subacute granulomatous thyroiditis
   a. Viral infection (e.g., coxsackievirus, mumps)
   b. Occurs most often in women 40 to 50 years old
   c. Granulomatous inflammation with multinucleated giant cells
   d. Clinical findings
      (1) Most common cause of a painful thyroid gland
      (2) Often preceded by an upper respiratory infection
      (3) Cervical adenopathy is not prominent.
      (4) Initial thyrotoxicosis from gland destruction
         • Increased serum T4, decreased serum TSH
      (5) Permanent hypothyroidism is uncommon.
   e. Decreased 123I uptake
   f. Self-limited; does not require treatment

3. Hashimoto thyroiditis
   a. Epidemiology
      (1) Autoimmune thyroiditis
      (2) Incidence increases with age
      (3) More common in women than men
      (4) Human leukocyte antigen (HLA)-Dr3 and HLA-Dr5 associations

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**23-6:** A. The broken blue line shows the course of the thyroglossal duct. Blue circles indicate possible sites of ectopic thyroid tissue and thyroglossal duct remnants. The arrow shows the direction of thyroid migration. B. Lingual thyroid. Note the mass lesion at the base of the tongue (white arrow). An 123I uptake study will show uptake by the thyroid tissue and identifies any other thyroid tissue that is present. C. Person with a midline thyroglossal duct cyst. (A from Moore A, Roy W: Rapid Review Gross and Developmental Anatomy, 3rd ed, Mosby-Elsevier, 2010, p 221, Fig. 7-18; B and C from Bouloux P: Self-Assessment Picture Tests: Medicine, Vol. 1, London, Mosby-Wolfe, 1997, pp 7, 52, respectively, Figs. 14, 103, respectively.)
increased incidence in:
- Turner syndrome, Down syndrome, Klinefelter syndrome

b. Pathogenesis (multifactorial)
(1) Cytotoxic T cells destroy parenchyma (type IV hypersensitivity reaction [HSR])
- Initial thyrotoxicosis, eventual hypothyroidism
(2) Blocking antibodies against TSH receptor (type II HSR)
- Decrease hormone synthesis; type II hypersensitivity
(3) Helper T cells release cytokines attracting macrophages that damage tissue (type IV HSR)
(4) Antimicrosomal and antithyroglobulin antibodies destroy parenchyma (type II HSR)
c. Gross and microscopic
(1) Enlarged, gray gland
(2) Lymphocytic infiltrate with prominent germinal follicles (Fig. 23-7A)
d. Clinical findings
(1) Most common cause of primary hypothyroidism
(2) Initial thyrotoxicosis from gland destruction
- Known as hasithoxicosis
(3) Signs of hypothyroidism (see later discussion)
(4) Risk factor for primary B-cell malignant lymphoma of the thyroid

4. Riedel thyroiditis
a. Fibrous tissue replacement of the gland
b. Extension of fibrosis into surrounding tissue
- Can obstruct the trachea
c. Associated with other sclerosing conditions
- Example—sclerosing mediastinitis
d. Hypothyroidism may occur.
e. Treatment
(1) Initially treated with corticosteroids
(2) Tamoxifen
- First-line therapy or if corticosteroids are unsuccessful
(3) Surgery
5. Subacute painless lymphocytic thyroiditis
   a. Autoimmune disease that develops postpartum
   b. Gland lacks germinal follicles.
   c. Clinical findings
      (1) Abrupt onset of thyrotoxicosis due to gland destruction
      (2) Slightly enlarged and painless gland
      (3) Progresses to primary hypothyroidism in 40% to 50% of cases
      (4) Antimicrosomal antibodies (50%–80% of cases)
   d. Treatment
      • Levothyroxine in the hypothyroid stage

G. Hypothyroidism
1. Definition—reduced secretion of thyroid hormone
   a. Patients are hypometabolic.
   b. Basal metabolic rate (BMR) is decreased.
   c. β-Receptor/LDL receptor synthesis is decreased.
2. Causes
   a. Hashimoto thyroiditis (90% of cases)
   b. Subacute painless lymphocytic thyroiditis
   c. Hypopituitarism, iodine deficiency, enzyme deficiency
   d. Drugs
      • Amiodarone, lithium, sulfonamides, phenylbutazone
   e. Hypothalamic dysfunction/hypopituitarism (see sections II and IV, respectively)
   f. Congenital (see later)
3. Cretinism
   a. Definition—hypothyroidism in infancy or early childhood
   b. Fetal thyroid starts developing during the seventh week and produces hormone by the twelfth week of gestation.
   c. Brain requires thyroxine for its maturation during the first year of life.
   d. Causes
      (1) Maternal hypothyroidism
         • Must be present before the fetal thyroid is developed
      (2) Enzyme or iodine deficiency
   e. Clinical findings
      (1) Severe mental retardation
      (2) Increased weight and short stature
         • Pituitary dwarfism—decreased weight and short stature
   f. Treatment is thyroid hormone replacement.
4. Clinical findings in adult hypothyroidism
   a. Proximal muscle myopathy
      (1) Very common finding
      (2) Increased serum creatine kinase
   b. Weight gain
      • Due to hypometabolic state with retention of water and salt
   c. Dry and brittle hair, loss of the outer one third of eyebrow
   d. Bradycardia (slow heart rate)
      • Fewer β-adrenergic receptors
   e. Coarse yellow skin
      • Less conversion of β-carotenes into retinoic acid produce carotenemia
   f. Periorbital puffiness, hoarse voice (only in Hashimoto thyroiditis)
      (1) Due to myxedema (see Fig. 23-7B)
      (2) Increased hyaluronic acid in interstitial tissue
      (3) Nonpitting edema
   g. Fatigue, cold intolerance, constipation
   h. Menstrual irregularities
      • Most often menorrhagia
   i. Diastolic hypertension
      • Due to retention of sodium and water
   j. Dilated cardiomyopathy with biventricular heart failure
   k. Atherosclerotic coronary artery disease (CAD)
   l. Delayed recovery of Achilles deep tendon reflex (DTR), mental slowness, dementia

Subacute painless lymphocytic thyroiditis: develops postpartum; progression to hypothyroidism
Hypothyroidism: hypometabolic; ↓ BMR
Brain: requires thyroxine for maturation
Cretinism: maternal hypothyroidism present before fetal thyroid is developed
Cretinism: severe mental retardation; ↑ weight/short stature
Pituitary dwarfism: ↓ weight/short stature
Adult hypothyroidism: muscle weakness, common complaint; weight gain; dry, brittle hair
Adult hypothyroidism: bradycardia, yellow skin (carotenemia)
Hashimoto thyroiditis: periorbital puffiness, hoarse voice; signs of myxedema
Adult hypothyroidism: cold intolerance, constipation, menorrhagia
Adult hypothyroidism: HTN from sodium retention; delayed reflexes
Adult hypothyroidism: dilated cardiomyopathy, CAD, delayed DTRs, dementia
5. Laboratory findings
   a. Decreased serum $T_3$, increased serum TSH
   b. Increased antimicrosomal, antiperoxidase, and antithyroglobulin antibodies
      - Hashimoto thyroiditis, subacute painless lymphocytic thyroiditis
   c. Hypercholesterolemia
      - Due to decreased synthesis of low-density lipoprotein (LDL) receptors (type II hyperlipoproteinemia; refer to Chapter 10)

6. Treatment
   a. Levothyroxine in small increments every 6 to 8 weeks
   b. Bring serum TSH into the normal range (euthyroid state)

7. Myxedema coma
   a. Causes
      (1) Idiopathic; cold exposure
      (2) Use of sedatives/opiates
      (3) Acute illness
   b. Clinical findings
      (1) Progressive stupor, hypothermia
      (2) Bradycardia, hypoventilation
      (3) Hypoglycemia, hypocortisolism, SIADH
   c. Treatment
      (1) Ventilatory support
      (2) Treat hypothermia
      (3) IV levothyroxine
      (4) High doses of corticosteroids
   d. Mortality rate is 20% to 50%.

H. Thyroid hormone excess
1. Classification
   a. Thyrotoxicosis
      - Definition—describes hormone excess regardless of cause (e.g., Graves disease, thyroiditis, increased intake of thyroid hormone)
   b. Hyperthyroidism
      (1) Definition—describes hormone excess due to increased synthesis
      (2) Examples—Graves disease, toxic nodular goiter

2. Patients are hypermetabolic.
   - Increase in the basal metabolic rate

3. Graves disease
   a. Epidemiology
      (1) Most common cause of hyperthyroidism and thyrotoxicosis (80% of cases)
      (2) Female dominant autoimmune disease
      (3) HLA-B8 and HLA-Dr3 association with Graves disease in whites
   b. Pathogenesis
      (1) T cells induce specific B cells to produce IgG antibodies against the TSH receptor
      (a) Stimulating type of antibody as opposed to a blocking antibody
      (b) Type II HSR (refer to Chapter 4)
      (2) Antimicrosomal and antithyroglobulin antibodies are present.
      (3) Inciting events that may initiate onset of the disease
         - Infection, withdrawal of steroids, iodide excess, postpartum state
   c. Symmetrical, nontender thyromegaly
      (1) Scant colloid
      (2) Papillary inolding of the glands
   d. Clinical features unique to Graves disease
      (1) Infiltrative ophthalmopathy (exophtalmos; 50% of cases)
      (a) Proptosis and muscle weakness of the eye (Fig. 23-8A and B)
      (b) Caused by increased swelling of orbital tissue (adipose and muscle, due to water retention from hydrophilic mucopolysaccharides and lymphocytic infiltrate) and increased fibroblast growth in orbital tissue, which may cause fibrosis of orbital muscles
      (2) IgG-TSH receptor antibodies cross placenta and produce transient hyperthyroidism in fetus
      (3) Pretibial myxedema (1%–2% of cases; see Fig. 23-8C)
         - Due to excess glycosaminoglycans (hyaluronic acid) in the dermis
(4) Thyroid acropachy
   (a) Digital swelling and clubbing of fingers
   (b) Nails separate from nail bed (lifted up)
   (c) Exophthalmos and pretibial myxedema are usually present

4. Graves disease in the elderly (apathetic hyperthyroidism)
   a. Cardiac abnormalities
      • Atrial fibrillation, congestive heart failure
   b. Muscle weakness, apathy
   c. Thyromegaly

5. Toxic multinodular goiter (Plummer disease)
   a. One or more nodules in a multinodular goiter become TSH-independent.
   b. See "hot" nodules with $^{123}$I scan
   c. Distinctions from Graves disease
      • Lack exophthalmos and pretibial myxedema
   d. Treated surgically

6. Clinical findings in all causes of thyrotoxicosis
   a. Constitutional signs
      (1) Weight loss (good appetite)
      (2) Fine tremor of the hands
      (3) Heat intolerance, diarrhea, anxiety
      (4) Menstrual irregularities
         • Usually oligomenorrhea
      (5) Lid stare
         • Due to increased sympathetic stimulation of eyelid muscles (e.g., levator palpebrae superioris)
   b. Cardiac findings
      (1) Sinus tachycardia (>90 beats/min)
      (2) Increased risk for atrial fibrillation

23-B: A, Graves disease. The patient has exophthalmos and a diffuse enlargement of the thyroid gland (goiter). B, Severe exophthalmos in Graves disease. Note the proptosis of the eye, increased vascularity of the conjunctiva, and the enlarged lacrimal gland. C, Pretibial myxedema in Graves disease. Note the thickened area of erythema involving the pretibial area and dorsum of the foot. D, Schematic of euthyroid sick syndrome (ESS). In ESS, the outer ring deiodinase is blocked and the inner ring deiodinase converts T$_4$ to reverse T$_3$, which is inactive. (A from Forbes C, Jackson W: Color Atlas and Text of Clinical Medicine, 2nd ed, London, Mosby, 2002, p 323, Fig. 7-61; B from Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 232, Fig. 10-35; C courtesy R.A. Marsden, MD, St. George's Hospital, London; D courtesy Edward Goljan, MD.)
Thyrotoxicosis: atrial fibrillation, sinus tachycardia, systolic HTN, high output failure

Thyrotoxicosis: brisk reflexes, osteoporosis

Graves hyperthyroidism:
\[ \text{↑ serum } T_4/T_3, \text{↑ } 123^\text{I} \text{ uptake, ↓ serum TSH} \]

Thyrotoxicosis:
T-glucose, calcium, lymphocytes; \( \downarrow \) cholesterol

Rx Graves disease:
\( \beta \)-blockers, thionamides

Thyroid storm:
tachyarrhythmias, hyperpyrexia, coma, shock

Thyrotoxicosis:
(3) Systolic hypertension, high-output heart failure
   (a) Thyroid hormone increases \( \beta \)-receptor synthesis in the heart.
   (b) Excess hormone increases inotropic and chronotropic effect on the heart.

Thyrotoxicosis: brisk reflexes, osteoporosis (increased bone turnover)

7. Laboratory findings
   a. Increased serum \( T_4 \), decreased serum TSH
   b. Increased \( 123^\text{I} \) uptake
      • Graves disease and toxic multinodular goiter
   c. Decreased \( 123^\text{I} \) uptake
      • Thyroiditis, patient taking excess thyroid hormone
   d. Hyperglycemia
      • Increased glycogenolysis, increased incidence type I diabetes mellitus
   e. Hypocholesterolemia
      • Increased LDL receptor synthesis
   f. Hypercalcemia
      • Increased bone turnover
   g. Absolute lymphocytosis

8. Treatment of Graves disease
   a. \( \beta \)-Blockers decrease adrenergic effects.
   b. Thionamides decrease hormone synthesis.
   c. Ablative \( 131^\text{I} \) therapy is used in 1 year if \( \beta \)-blockers and thionamides do not work.

9. Thyroid storm
   a. Causes
      (1) Inadequately treated patients with Graves disease undergo surgery.
      (2) Infection, trauma
      (3) Iodine, pregnancy
   b. Clinical findings
      (1) Tachyarrhythmias
      (2) Hyperpyrexia
      (3) Shock
         • Volume depletion from vomiting
      (4) Coma
   c. Treatment
      (1) Inhibit hormone synthesis
         (a) Propylthiouracil
         (b) Iodide
      (2) Sympathetic blockade with \( \beta \)-blockers
      (3) Hydrocortisone
      (4) Cooling blanket

10. Euthyroid sick syndrome (ESS)
   a. Epidemiology
      (1) Definition—serum levels of \( T_3 \) and \( T_4 \) are abnormal but gland function appears normal
      (2) Associated with:
         • Malignancy, heart failure, anorexia nervosa, chronic renal failure, sepsis, myocardial infarction, and others
      (3) Laboratory test alterations usually return to normal with resolution of the illness.
   b. Pathogenesis
      (1) In the normal condition, a peripheral tissue outer ring deiodinase converts \( FT_4 \) into metabolically active \( FT_3 \).
      (2) In ESS, the outer ring deiodinase is blocked and inner ring deiodinase converts \( FT_4 \) into inactive reverse \( T_3 \).
         • There are also abnormalities in TBG.
      (3) Most common variant of ESS (see Fig. 23-8D)
         (a) Normal/decreased serum \( FT_4 \)
         (b) Decreased serum \( FT_3 \)
         (c) Normal/decreased serum TSH
         (d) Increased serum reverse \( T_3 \)
   c. Treatment
      • Varies from no treatment to levothyroxine during the time of the illness
I. Summary of laboratory findings in thyroid disorders (Table 23-2)

J. Nontoxic goiter
   1. Definition—thyroid enlargement from excess colloid (Fig. 23-9A)
   2. Types of goiter
      a. Endemic type
         - Due to iodide deficiency (most common)
      b. Sporadic type; causes include:
         - Goitrogens (e.g., cabbage), enzyme deficiency, puberty, pregnancy
   3. Pathogenesis
      a. Absolute or relative deficiency of thyroid hormone
      b. Combination of hyperplasia and hypertrophy growth alterations
         - Thyroid gland is attempting to increase hormone synthesis.
      c. Bouts of hyperplasia/hypertrophy are followed by gland involution.
         - Involution is due to failure of the gland to sustain hormone synthesis.
      d. Initial diffuse thyromegaly is followed by multinodular goiter (see Fig. 23-9B).
   4. Complications
      a. Hemorrhage into cysts
         - Produces sudden, painful, gland enlargement
      b. Compression of the jugular vein causing neck congestion
         - Called Pemberton sign
      c. Primary hypothyroidism
      d. Toxic nodular goiter
         - One or more nodules become TSH independent and develop “hot” nodules.
      e. Hoarseness (compression of the laryngeal nerve)
      f. Dyspnea (compression of the trachea)
   5. Treatment
      a. Levothyroxine reduces gland size and achieves the euthyroid state.
      b. Surgery is indicated if compressive symptoms persist.

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**Table 23-2: Laboratory Findings in Thyroid Disease**

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>SERUM T₄</th>
<th>FREE T₄</th>
<th>SERUM TSH</th>
<th>¹²³I UPTAKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves disease</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>Patient taking excess hormone</td>
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<tr>
<td>Initial phase of thyroiditis</td>
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<tr>
<td>Primary hypothyroidism</td>
<td>↓</td>
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<td>↔</td>
</tr>
<tr>
<td>Secondary hypothyroidism (hypopituitarism)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Increased TGB (e.g., excess estrogen)</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>↔</td>
</tr>
<tr>
<td>Decreased TGB (e.g., anabolic steroids)</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>↔</td>
</tr>
</tbody>
</table>

N, Normal; T₄, thyroxine; TGB, thyroid-binding globulin; TSH, thyroid-stimulating hormone; ↔, not indicated.

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23-9: A, Patient with a multinodular goiter. Note the diffuse enlargement of the lower anterior neck. B, Thyroid gland with multinodular goiter. Note the diffusely enlarged gland with numerous cystic nodules filled with excess colloid. Hemorrhage has occurred into many of the cysts. (A from Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 799, Fig. 9-7; B from Grieg JD: Color Atlas of Surgical Diagnosis, London, Mosby-Wolfe, 1996, p 268, Fig. 33-3.)

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Goiter: thyroid enlargement from excess colloid

Nontoxic goiter: absolute/relative thyroid hormone deficiency due to iodide deficiency

Nontoxic goiter: combination of hyperplasia and hypertrophy

Nontoxic goiter: initially diffuse enlargement and then nodular

Sudden enlargement: hemorrhage into cysts

Toxic nodular goiter: one/more nodules become TSH independent
K. Solitary thyroid nodule

1. Epidemiology
   a. Majority are cold (nonfunctioning) nodules (95% of cases).
   b. Causes in adult women
      (1) Majority are cysts in a goiter (60% of cases) or a follicular adenoma (25% of cases).
      (2) Approximately 15% are malignant.
      (3) Approximately 85% to 90% of solitary nodules are euthyroid.
   c. Causes in adult men and children
      • Similar to women; however, there is a greater chance of malignancy
   d. Prior history of radiation to head and neck
      • Nodule is more likely to be malignant (40% of cases).

2. Diagnosis
   a. Fine needle aspiration (FNA) is the most important initial step.
   b. Thyroid hormone studies

3. Treatment
   a. Depends on the FNA result
   b. If malignant, surgical removal
   c. If benign and asymptomatic, periodic follow-up

L. Benign and malignant tumors

1. Follicular adenoma
   a. Most common benign tumor
      • Surrounded by a complete capsule
   b. Presents as a solitary “cold” nodule (see Fig. 23-5)
   c. Approximately 10% progress into a follicular carcinoma.

2. Papillary adenocarcinoma
   a. Epidemiology
      (1) Most common endocrine cancer
      (2) Papillary adenocarcinoma most common thyroid cancer (>75% of cases)
      (3) More common in women than men (3:1)
      • Usually occur in the second and third decades
      (4) Associated with radiation exposure
   b. Gross and microscopic findings
      (1) Usually multifocal
      (2) Papillary fronds intermixed with follicles
      (3) Psammoma bodies (35%–45% of cases)
      • Dystrophically calcified cancer cells (Fig. 23-10)
      (4) Nuclei that appear empty
      • Called Orphan Annie nuclei
      (5) Lymphatic invasion
   c. Metastasize to cervical nodes, lung
   d. Diagnose with FNA
   e. Treatment
      (1) Usually subtotal or near total thyroidectomy with sampling of cervical nodes
      (2) Followed in a few weeks by radiotherapy with ¹³¹I
      (3) Suppressive therapy with thyroid hormone
      • Tumor is TSH dependent.
   f. Five-year survival rate is >95%.

23-10: Papillary carcinoma of thyroid showing branching papillae and blue concretions (arrows) representing psammoma bodies. (From Rosai J, Ackerman LV: Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 534, Fig. 9-37A.)
3. Follicular carcinoma
   a. Epidemiology
      (1) Most common thyroid cancer presenting as a solitary cold nodule
      (2) Female dominant cancer
   b. Gross and microscopic findings
      (1) Cancer can be encapsulated or invasive
      (2) Neoplastic follicles invade blood vessels.
      (3) Lymph node metastasis is uncommon.
   c. Metastasize to lung and bone
   d. Treatment
      • Similar to papillary cancer
   e. Five-year survival rate is ~80%.

4. Medullary carcinoma
   a. Epidemiology
      (1) Types
         (a) Sporadic (80% of cases)
         (b) Familial (20% of cases)
      (2) Familial type
         (a) Associated with autosomal dominant MEN IIa/IIb
         (b) MEN IIa syndrome includes:
            • Medullary carcinoma, primary hyperparathyroidism (HPTH), and 
              pheochromocytoma
         (c) MEN IIb (III) syndrome includes:
            • Medullary carcinoma, mucosal neuromas (lips/tongue), pheochromocytoma, 
              Marfan like habitus
      (3) Familial type has a better prognosis than the sporadic type.
      (4) Ectopic hormones
         • ACTH, which can produce Cushing syndrome
   b. Pathogenesis
      (1) Tumors derive from parafollicular C cells.
      (2) C cells synthesize calcitonin.
         (a) Tumor marker
         (b) May produce hypocalcemia (uncommon)
         (c) Converted into amyloid (refer to Chapter 4)
      (3) C-cell hyperplasia is a precursor lesion for medullary carcinoma.
         • Calcitonin levels increase with infusion of pentagastrin.
   c. Diagnosis
      (1) FNA
      (2) Serum calcitonin
   d. Treatment
      (1) Total thyroidectomy
      (2) Genetic screening for familial cases
         (a) Detection of mutation of RET proto-oncogene
         (b) Thyroidectomy is performed if the patient is a gene carrier.
   e. Five-year survival rate is 5%.

5. Primary B-cell malignant lymphoma
   • Most often develop from Hashimoto thyroiditis

6. Anaplastic thyroid cancer
   a. Most often occurs in elderly women
   b. Risk factors
      • Multinodular goiter, history of follicular cancer
   c. Rapidly aggressive and uniformly fatal
   d. Treatment
      (1) Palliative surgery because it often compresses the trachea
      (2) Irradiation or chemotherapy
   e. Five-year survival rate is 5%.

VI. Parathyroid Gland Disorders
A. Clinical anatomy and physiology
   1. Superior and inferior parathyroid glands (Fig. 23-11)
      a. The glands derive from fourth pharyngeal pouch and third pharyngeal pouch, 
         respectively.
      b. Thymus also develops from the third pharyngeal pouch.
**23-11:** Developmental origins of thyroid, parathyroid, and thymus glands. Arrows show pathways of migration. Note how pouch III develops into the inferior parathyroid gland and the thymus (synthesizes T cells), whereas pouch IV develops into the superior parathyroid glands. (From Moore A, Roy W: Rapid Review Gross and Developmental Anatomy, 3rd ed, Philadelphia, Mosby Elsevier, 2010, p 221, Fig. 7-17.)

c. In DiGeorge syndrome, the third and fourth pharyngeal pouches fail to develop; hence patients have hypoparathyroidism and a pure T cell deficiency with no thymic shadow (absent thymus; refer to Chapter 5).

2. Parathyroid hormone (PTH)
   a. Increases calcium reabsorption in the early distal tubule
   b. Decreases phosphorus reabsorption in the proximal tubule
   c. Increases intestinal reabsorption of calcium and phosphorus
   d. Decreases bicarbonate reclamation in the proximal tubule
   e. Maintains the ionized calcium level in blood
      • Increases bone resorption and renal reabsorption of calcium
   f. Increases the synthesis of 1-α-hydroxylase in the proximal renal tubule
   • Increases the synthesis of 1,25-(OH)₂D (dihydroxycholecalciferol; calcitriol)
   g. PTH is stimulated by hypocalcemia and hyperphosphatemia.
   h. PTH is suppressed by hypercalcemia and hypophosphatemia.

3. Role of vitamin D in calcium metabolism (see Fig. 8-5; refer to Chapter 8)
   a. Preformed vitamin D in the diet consists of cholecalciferol (fish) and ergocalciferol (plants).
   b. Endogenous synthesis of vitamin D in the skin occurs by solar photoconversion of 7-dehydrocholesterol to vitamin D₃ (cholecalciferol).
   c. Reabsorption of vitamin D occurs in the small intestine.
   d. Hydroxylation of precursor vitamin D to 25-hydroxyvitamin D (25-[OH]D; calcidiol) occurs in the liver.
      • Occurs in the cytochrome P-450 system
   e. 25-(OH)D is secreted into the blood and bound to a protein for delivery to the proximal tubules of the kidneys.
   f. Kidney hydroxylation of 25-(OH)D by 1-α-hydroxylase produces 1,25-(OH)₂D (active form of vitamin D; calcitriol).
      • If PTH is decreased, 1-α-hydroxylase is decreased, and calcitriol is decreased
   g. Calcitriol attaches to nuclear receptors in target tissues.
   h. Functions of calcitriol (refer also to Chapter 8) include the following:
      (1) Increases calcium reabsorption in duodenum
      (2) Increases phosphorus reabsorption in the jejunum and ileum
      (3) Increases calcium reabsorption in the distal tubule of the kidney
      (4) Increases bone resorption (minor role) to help maintain serum ionized calcium level
         • Induces monocytic stem cells to become osteoclasts
      (5) Increases bone mineralization (major role)
   i. Feedback control of calcitriol is calcium mediated.
      (1) Decreased serum calcium: ↑PTH → ↑synthesis of 1-α-hydroxylase → ↑synthesis 1,25-(OH)₂D
      (2) Increased serum calcium: ↓PTH → ↓synthesis of 1-α-hydroxylase → ↓synthesis 1,25-(OH)₂D
4. Total serum calcium
   a. Components of the total serum calcium (Fig. 23-12A)
      (1) Calcium bound to albumin (40%) and phosphorus and citrate (13%)
         (a) Albumin has the most acidic amino acids (e.g., aspartate, glutamate) that have carboxyl groups (COOH, COO−).
         (b) At a normal pH of 7.4, ~40% of the acidic groups are COO− and bind to positively charged calcium.
      (2) Free, ionized calcium (47%)
         • Metabolically active fraction that has a negative feedback with PTH.
   b. Hypoalbuminemia (see Fig. 23-12B)
      (1) Decreased total serum calcium
         • Due to a decrease in calcium bound to albumin
      (2) Normal free ionized level, normal PTH
      (3) No evidence of tetany
      (4) Formula that corrects total serum calcium when hypoalbuminemia is present
         • Corrected serum calcium = serum calcium – serum albumin + 4.
   c. Effect of respiratory alkalosis (see Fig. 23-12C)
      (1) Respiratory alkalosis increases negative charges on albumin
         (a) Due to fewer H+ ions on the COOH groups of acidic amino acids
            • Change of COOH groups to COO−, because there are fewer H+ ions in alkalosis.
         (b) Extra negative charges bind some of the ionized calcium (arrows in Fig. 12C).
      (2) Total serum calcium remains normal.
      (3) Decreased ionized calcium, increased PTH (normal negative feedback relationship)
      (4) Patient develops tetany,
         • Although serum PTH is in equilibrium with ionized calcium, it cannot keep pace with the binding of ionized calcium to the negative charges on albumin; hence tetany occurs.
   d. Tetany is due to a decreased ionized calcium level.
      (1) Causes partial depolarization of nerves and muscle
         (a) Lowers the threshold potential (Ei)
            • Comes closer to the resting membrane potential (Em)
         (b) An action potential can be initiated with a smaller stimulus.
      (2) Clinical findings of tetany
         (a) Carpopedal spasm
            • The thumb flexes into the palm (Fig. 23-13A).
         (b) Chvostek sign
            • Facial twitch after tapping the facial nerve

B. Hypoparathyroidism
1. Epidemiology
   a. Definition—hypofunction of the parathyroid glands leading to hypocalcemia
Carpal spasm (Trousseau sign; thumb adducts into the palm) is a manifestation of tetany, which is due to a decrease in the ionized calcium level in blood. Its onset can be provoked by inflating a sphygmomanometer cuff to just above the systolic pressure for at least 2 minutes. Pseudohypoparathyroidism. Note the short fourth and fifth digits, producing the classic “knuckle-knuckle-dimple-dimple” sign. Parathyroid adenoma in primary hyperparathyroidism. Subperiosteal resorption in primary hyperparathyroidism. The radiologic hallmark of hyperparathyroidism is subperiosteal bone resorption, seen especially well on the radial aspect of the middle phalanges of the index and middle fingers. Here the cortex appears shaggy and irregular, compared to the cortex on the opposite side of the same bone, which is well defined. This patient also displays two other findings of hyperparathyroidism: a small brown tumor and resorption of the terminal phalanges (acro-osteolysis) (dotted white arrows). Hypoparathyroidism: MCC is autoimmune hypoparathyroidism. Hypomagnesemia: MC pathologic cause of hypocalcemia in hospital. Hypomagnesemia: diarrhea, aminoglycosides, diuretics, alcohol.

b. Causes

1. Autoimmune hypoparathyroidism (most common cause)
2. Previous thyroid surgery
   - Not common in current day surgery
3. DiGeorge syndrome (see earlier; refer to Chapter 4)
4. Hypomagnesemia
   a. Magnesium is a cofactor for adenylate cyclase.
      - Cyclic adenosine monophosphate (cAMP) is required for PTH activation and secretion.
(b) Causes of hypomagnesemia
- Diarrhea, aminoglycosides, diuretics, alcoholism

2. Clinical findings
   a. Tetany
   b. Calcification of basal ganglia
      (1) Due to metastatic calcification
      (2) Increased phosphorus drives calcium into the brain tissue.
   c. Cataracts, Candida infections (? cause)

3. Laboratory findings
   - Hypocalcemia, hyperphosphatemia, ↓PTH

4. Other causes of hypocalcemia (Table 23-3)

5. Treatment
   a. Calcium and vitamin D₃ ( calcitriol )
   b. Teriparatide (recombinant PTH) may be used in near future.

C. Primary Hyperparathyroidism (HPTH)

1. Epidemiology
   a. Most common nonmalignant cause of hypercalcemia
   b. Occurs most frequently in postmenopausal women
   c. Asymptomatic in >50% of patients
   d. Association with MEN I and MEN IIa
   e. Causes
      (1) Adenoma (~80% of cases; see Fig. 23-13C)
         (a) Usually a single adenoma
         (b) Sheets of chief cells with no intervening adipose
         (c) Remainder of the gland plus all other glands show atrophy.
            - Hypercalcemia suppresses PTH produced from normal tissue.
         (d) Right inferior parathyroid gland is most often involved.
      (2) Primary hyperplasia (~20% of cases)
         (a) All four glands are involved.
         (b) Usually a chief cell hyperplasia
         (c) Clear cell hyperplasia ( wasserhelle cell hyperplasia )
            - Associated with markedly increased serum calcium levels
      (3) Carcinoma (uncommon)

2. Clinical findings
   a. Renal
      (1) Calcium stones
         - Most common presentation

---

**Table 23-3  Other Causes of Hypocalcemia**

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>Calcium is bound to fatty acids in enzymatic fat necrosis Poor prognostic sign</td>
</tr>
</tbody>
</table>
| Hypovitaminosis D      | Lack of sunlight: decreased photoconversion of cholesterol to (nonrenal) vitamin D₃ (cholecalciferol) in the skin  
                          | Malabsorption (e.g., celiac disease): ↓reabsorption of fat-soluble vitamin D; ↓25-(OH)D → 1,25-(OH)₂D; ↓serum calcium, ↓serum phosphorus, ↓serum PTH (2° HPTH)  
                          | Cirrhosis: decreased synthesis of 25-(OH)D → ↓1,25-(OH)₂D; ↓serum calcium, ↓serum phosphorus, ↓serum PTH  
                          | Drugs enhancing cytochrome system (e.g., alcohol, phenytoin): increased metabolism of 25-(OH)D into an inactive metabolite; decreased 25-(OH)D → ↓1,25-(OH)₂D; ↓serum calcium, ↓serum phosphorus, ↓serum PTH (2° HPTH)  
                          | Chronic renal failure (most common cause): ↓synthesis of 1,25-(OH)₂D (↓1-α-hydroxylation); ↓serum calcium, ↓serum phosphorus, ↑serum PTH (2° HPTH) |
| Pseudohypoparathyroidism (see Fig. 23-13B) | Autosomal dominant disease  
                          | End-organ resistance to PTH (includes its ability to synthesize 1-α-hydroxylase in the proximal tubule)  
                          | Mental retardation, basal ganglia calcification, short fourth and fifth metacarpals (“knuckle-knuckle-dimple-dimple” sign)  
                          | Hypocalcemia, normal to ↑PTH, normal 25-(OH)D, ↓1,25-(OH)₂D; ↓serum calcium, ↓serum phosphorus |

2° HPTH: Secondary hypoparathyroidism; 25-(OH)D, calcidiol; 1,25-(OH)₂D, calcitriol; PTH, parathyroid hormone.
1° HPTH: nephrocalcinosis; metastatic calcification

b. Gastrointestinal
   (1) Peptic ulcer disease (PUD)
      • Calcium stimulates gastrin, which increases gastric acid.
   (2) Acute pancreatitis
      • Calcium activates phospholipase.
   (3) Constipation
   c. Bone and joints
      (1) Osteitis fibrosa cystica
         • Cystic and hemorrhagic bone lesion
         • Caused by increased osteoclastic activity
         • Commonly involves the jaw
      (2) Radiographic findings
         (a) Subperiosteal bone resorption of phalanges (see Fig. 23-13D) and tooth sockets
         (b) “Salt and pepper” appearance of the skull
         (c) Resorption of the distal phalanges (acro-osteolysis; see Fig. 23-13D)
      (3) Osteoporosis
      (4) Chondrocalcinosis (pseudogout)

1° HPTH: PUD, acute pancreatitis

d. Diastolic HTN
   • Due to hypercalcemia increasing smooth muscle contraction of peripheral resistance arterioles (refer to Chapter 10)

e. Eyes
   (1) Band keratopathy in the limbus of the eye
   (2) Due to metastatic calcification

f. Central nervous system
   • myriad of different findings—psychosis, confusion, anxiety, coma

3. Laboratory findings

a. Increased serum PTH, increased calcium, decreased phosphorus
   • Intact serum PTH is the best initial screening test.

b. Normal anion gap metabolic acidosis
   (1) Due to decreased proximal tubule reclamation of bicarbonate
   (2) Type II renal tubular acidosis (refer to Chapter 5)

c. Chloride/phosphorus ratio >33
   (1) Recall than in a normal anion gap metabolic acidosis, serum chloride is increased to counterbalance the loss of negative charges related to the decrease in bicarbonate.
   • Therefore, it makes sense that in 1° HPTH, the increase in serum chloride from the normal anion gap metabolic acidosis plus the decrease in serum phosphorus leads to an increase in the chloride/phosphorus ratio.
   (2) Ratio <29 excludes primary HPTH.

d. Decreased serum 1,25-(OH)₂D
   (1) Hypercalcemia decreases synthesis of 1-α-hydroxylase in the proximal renal tubule.
   (2) Protective effect so that serum calcium is not too high.

e. Electrocardiogram shows shortening of QT interval.

4. Localization of adenoma
   • Technetium-99m-sestamibi radionuclide scan

5. Treatment
   a. Surgical removal of the adenoma
   b. Treatment of hypercalcemia
      (1) IV hydration with normal saline followed by IV furosemide
         • Most common therapy
      (2) Bisphosphonates
      (3) Cinacalcet directly lowers PTH levels
         • Increases the calcium-sensing receptor to extracellular calcium

6. Other causes of hypercalcemia (Table 23-4)
   a. Primary HPTH and the hypercalcemia of malignancy (refer to Chapter 9) account for ~80% of all cases of hypercalcemia.
   b. Primary differentiating feature between these two diagnoses is serum PTH.
      (1) Serum PTH is increased in primary HPTH.
      (2) Serum PTH is decreased in hypercalcemia of malignancy, whether it is due to lytic lesions (most common) or PTH-related peptide.
c. Hypercalcemia in pregnancy can produce hypocalcemia in fetus.
   - Suppression of PTH in the fetus

D. Secondary hyperparathyroidism
   1. Hyperplasia of all four parathyroid glands
      a. It is a physiologic compensation for hypercalcemia.
      b. Example—hypovitaminosis D due to renal failure and malabsorption
   2. Decreased calcium, increased PTH
   3. May develop tertiary hyperparathyroidism
      a. Glands become autonomous regardless of the calcium level.
      b. This may bring the serum calcium into a normal or increased range.

E. Schematic summarizing serum PTH and calcium relationships (Fig. 23-14)

F. Phosphorus disorders
   1. Causes of hypophosphatemia (Table 23-5)
   2. Clinical findings in hypophosphatemia
a. Muscle weakness
   (1) Decreased synthesis of adenosine triphosphate (ATP) causes muscle weakness.
   (2) Muscle paralysis and rhabdomyolysis may occur.

b. RBC hemolysis
   • RBCs require ATP to maintain ion pumps and membrane integrity.
   • Osteomalacia (soft bones)
   • Phosphorus is required to mineralize bone (refer to Chapter 8).

3. Causes of hyperphosphatemia (Table 23-6)
4. Clinical findings in hyperphosphatemia
   a. Metastatic calcification: excess phosphorus drives calcium into normal tissue.

G. Summary table integrating calcium, phosphorus, and PTH in calcium and phosphorus disorders (Table 23-7)

VII. Adrenal Gland Disorders

A. Overview of adrenal cortex hormones (Fig. 23-15)
1. Zona glomerulosa produces mineralocorticoids (e.g., aldosterone).
   • Angiotensin II activates 18-hydroxylase, which converts corticosterone to aldosterone.
2. Zona fasciculata produces glucocorticoids.
   • 11-Deoxycortisol and cortisol are 17-hydroxycorticoids (17-OH).
   a. 17-Ketosteroids (17-KS)
      • Dehydroepiandrosterone (DHEA) and androstenedione
   b. Testosterone
      (1) Converted to dihydrotestosterone (DHT) by 5α-reductase in peripheral tissue sites
      (2) Peripheral tissue sites that produce DHT: skin, testis, prostate, seminal vesicles, epididymis, liver, ovaries

B. Overview of adrenal medulla hormones
1. Neural crest origin
2. Produces catecholamines
   • Epinephrine (EPI) and norepinephrine (NOR)
3. Metabolic products of EPI and NOR
   • Metanephrine and vanillylmandelic acid (VMA)
4. Metabolic product of dopamine is homovanillic acid (HVA).
C. Adrenocortical hypofunction (primary hypocortisolism)

1. Acute adrenocortical insufficiency
   a. Causes
      (1) Abrupt withdrawal of corticosteroids (most common cause)
      (2) Waterhouse-Friderichsen syndrome
      (3) Anticoagulation therapy
   b. Waterhouse-Friderichsen syndrome (WFS)
      (1) WFS is usually associated with septicemia from Neisseria meningitidis.
      (2) Patients develop endotoxic shock.
      - Release of tissue thromboplastin and damage to endothelial cells causes disseminated intravascular coagulation (DIC; refer to Chapter 15).
      (3) Bilateral adrenal hemorrhage
         - Fibrin clots in vessels cause hemorrhagic infarction.

2. Chronic adrenal insufficiency (Addison disease)
   a. Epidemiology; causes:
      (1) Autoimmune destruction
         - Most common cause (80% of cases)
      (2) Miliary tuberculosis (15% of cases/histoplasmosis)
      (3) Adrenogenital syndrome (see later discussion)
      (4) Metastasis
         - Most often from a primary lung cancer
      (5) AIDS (30% of patients)
   b. Clinical findings
      (1) Weakness and hypotension
         - Due to sodium loss from mineralocorticoid and glucocorticoid deficiency
      (2) Diffuse hyperpigmentation (Fig. 23-16A)
         (a) Increased plasma ACTH stimulates melanocytes.
         (b) Buccal mucosa, skin, skin creases
   c. Laboratory findings
      (1) Short and prolonged ACTH stimulation test
         - No increase in cortisol or 17-OH

23-15: Adrenocortical hormone synthesis. The zona glomerulosa produces mineralocorticoids (e.g., aldosterone), the zona fasciculata produces glucocorticoids (e.g., cortisol), and the zona reticularis produces sex hormones (e.g., testosterone). The 17-hydroxycorticoids (17-OH) are 11-deoxycortisol and cortisol. The 17-ketosteroids (17-KSs; weak androgens) are dehydroepiandrosterone and androstenedione. Testosterone is converted to dihydrotestosterone (DHT) by 5α-reductase in extra-adrenal tissue.
(2) Metyrapone test (see Fig. 23-16B)
- Increased ACTH but no increase in 11-deoxycortisol

(3) Increased plasma ACTH

(4) Electrolyte findings (refer to Chapter 5 for a fuller discussion)
- Hyponatremia, hyperkalemia, and normal anion gap metabolic acidosis

**Aldosterone** enhances the exchange of sodium for potassium in the kidneys (see Fig. 5-7). Hence its deficiency leads to a hypertonic loss of sodium in the urine (hyponatremia), retention of potassium (hyperkalemia), and retention of hydrogen ions (metabolic acidosis). Aldosterone also enhances the proton pump (see Fig. 5-8). Deficiency leads to retention of protons and metabolic acidosis (normal anion gap type).

(5) Fasting hypoglycemia
- Due to decrease in cortisol (cortisol is gluconeogenic)

(6) Eosinophilia, lymphocytosis, and neutropenia
- Due to decrease in cortisol (refer to Chapter 13)

d. Treatment
- Glucocorticoid and mineralocorticoid replacement
3. Adrenogenital syndrome (congenital adrenal hyperplasia)
   a. Autosomal recessive disorder
   b. Enzyme deficiency causes hypocortisolism and a corresponding increase in ACTH.
      (1) Increase in ACTH
         • Causes adrenocortical hyperplasia and diffuse skin pigmentation
      (2) Increase in 17-KS, testosterone, and DHT; causes:
         (a) Ambiguous genitalia in females (see Fig. 23-16C and D)
            • Primarily due to the increase in DHT and its effect on the external genitalia
            • First step when identifying ambiguous genitalia is to check the genetic sex of
              the newborn with a chromosome analysis.
         (b) Precocious puberty may develop in males and females.
            • In girls, excess androgens are aromatized in peripheral tissue to estrogen.
         (c) Girls experience irregular menses and infertility as adults.
         (d) Both sexes have rapid growth in childhood, but early fusion of epiphyses.
            • Majority have short stature as adults.
      (3) Decrease in 17-KS, testosterone, and DHT causes hypogonadism in both sexes.
         (a) Females have a delay in menarche and development of secondary sex
             characteristics.
            • Recall that female hormones derive from androgens.
         (b) Males develop pseudohermaphroditism.
            • Male external genitalia development requires DHT (refer to Chapter 6).
      (4) Increase in mineralocorticoids
         • Causes sodium retention leading to hypertension
      (5) Decrease in mineralocorticoids; causes:
         (a) Sodium loss (hyponatremia), hyperkalemia
         (b) Hypotension and possible hypovolemic shock
   c. Substrates proximal to the enzyme block increase.
   d. Substrates distal to the enzyme block decrease.
   e. Classic 21-hydroxylase (21-OHase) deficiency (Fig. 23-17)
      (1) Most common enzyme deficiency (90%–95% of cases)
      (2) Increase in 17-KS, testosterone, and DHT
         • All proximal to the enzyme block

Newborn with ambiguous genitalia:
first step is to determine genetic sex with
chromosome analysis

↑ 17-KS, testosterone, DHT; ambiguous
   genitalia in females;
precocious puberty in
   males and females

↓ 17-KS, testosterone, DHT: delayed menarche/
   secondary sex
   characteristics;
   males develop
   pseudohermaphroditism

↑ Mineralocorticoids:
   sodium retention with
   hypertension

↓ Mineralocorticoids:
sodium losers with
   hypertension

↑ Substrates proximal
to enzyme block;
↓ substrates distal to
   enzyme block

Classic 21-OHase
deficiency: MCC of
adrenogenital syndrome

23-17: Schematic for adrenogenital syndrome: 21-hydroxylase deficiency (salt loser) See text for discussion.
(3) Decrease in mineralocorticoids (salt losers)
   (a) All distal to the enzyme block
   (b) Sodium losers similar to Addison disease (danger of hypovolemic shock)
(4) Decrease in 17-OH
   • All distal to the enzyme block
(5) Increase in 17-hydroxyprogesterone
   • Proximal to the enzyme block
f. Nonclassic 21-OHase deficiency
(1) Cortisol and mineralocorticoid activity are normal (no loss of sodium).
(2) Ambiguous genitalia in females and virilization; precocious puberty in boys
g. 11-Hydroxylase deficiency (Fig. 23-18)
(1) Increase in 17-KS, testosterone, and DHT
   • All proximal to the enzyme block
(2) Increase in mineralocorticoids (11-deoxycorticosterone; salt retainer)
   (a) 11-Deoxycorticosterone is proximal to the enzyme block
   (b) Salt retention produces hypertension.
(3) Increase in 17-OH
   • 11-Deoxycortisol is proximal to the enzyme block.
(4) Increase in 17-hydroxyprogesterone
   • Proximal to the enzyme block
h. 17-Hydroxylase deficiency (rare)
(1) Decrease in 17-KS, 17-OH, 17-hydroxyprogesterone, testosterone, and DHT
   • All distal to the enzyme block.
(2) Increase in mineralocorticoids (salt retainers)
   • Zona glomerulosa mineralocorticoid pathway is wide open.

---

**23-18:** Schematic for adrenogenital syndrome: 11-hydroxylase deficiency (salt retainer). See text for discussion.
i. Diagnosis of adrenogenital syndrome
   (1) Serum 17-OH progesterone is an excellent screening test
      (a) Increased in 21- and 11-OHase deficiency
      (b) Decreased in 17-OHase deficiency
      (c) Can measure prenatally with chorionic villous sampling
      (d) Screening test in most but not all states on newborns
   (2) Urine for 17-hydroxycorticoids and 17-ketosteroids
j. Treatment
   (1) Glucocorticoids
   (2) Mineralocorticoids (21-OHase deficiency)
   (3) Estrogen or testosterone at time of puberty
k. Summary of adrenogenital syndrome (Table 23-8)

D. Adrenocortical hyperfunction
1. Cushing syndrome
   a. Causes
      (1) Prolonged corticosteroid therapy
         • Most common cause
      (2) Pituitary Cushing syndrome (Cushing disease)
         (a) 60% of cases
         (b) Due to a pituitary adenoma
         (c) Increased ACTH and cortisol
      (3) Adrenal Cushing syndrome
         (a) 25% of cases
         (b) Most often due to an adenoma
         (c) Decreased ACTH and increased cortisol
      (4) Ectopic Cushing syndrome
         (a) 15% of cases
         (b) Usually small cell carcinoma of lung; less commonly thymus, thyroid
            • Ectopic ACTH production
         (c) Markedly increased ACTH and cortisol
   b. Clinical findings
      (1) Weight gain
         (a) Due to hyperinsulinism from hyperglycemia
            • Insulin increases storage of fat (triglyceride) in adipose.
            • Insulin also has mineralocorticoid effects and retains sodium.
         (b) Fat deposition in face (moon facies), upper back (“buffalo hump”), and trunk
            (truncal obesity) (Fig. 23-19A)
      (2) Muscle weakness
         (a) Cortisol breaks down muscles in the extremities (thin extremities).
         (b) Muscles supply amino acids (e.g., alanine) for gluconeogenesis (produces
            hyperglycemia).
      (3) Diastolic hypertension
         (a) Due to increased weak mineralocorticoids (e.g., corticosterone,
            11-deoxycorticosterone), glucocorticoids, and insulin (↑mineralocorticoid
            activity)
         (b) Aldosterone is not increased (requires angiotensin II)
      (4) Hirsutism/virilization
         • Due to increased androgens (17-KS, testosterone, insulin [↑androgen synthesis in
            ovaries])
      (5) Purple abdominal stria
         • Cortisol weakens collagen, causing rupture of blood vessels in the stretch marks.
      (6) Osteoporosis
         • Hypercortisolism causes increased breakdown of bone.

---

**TABLE 23-8 Summary of Adrenogenital Syndromes**

<table>
<thead>
<tr>
<th>LABORATORY MEASUREMENT</th>
<th>21-OHase DEFICIENCY</th>
<th>11-OHase DEFICIENCY</th>
<th>17-OHase DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-Ketosteroids</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>17-Hydroxyprogesterone</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>17-Hydroxycorticoids</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Mineralocorticoids</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

OHase, Hydroxylase.
c. Laboratory findings
   (1) Increased free cortisol in urine
      • Very high positive and negative predictive value
   (2) Low-dose dexamethasone (DXM; cortisol analogue) suppression test
      • Cannot suppress cortisol in all types
   (3) High-dose dexamethasone suppression test
      • Can suppress cortisol in pituitary Cushing syndrome but not the other types
   (4) Hyperglycemia
      (a) Cortisol enhances gluconeogenesis.
      (b) Stimulates the release of insulin, which increases centrally located adipose and
          also contributes to producing hypertension (mineralocorticoid effect)
   (5) Hypokalemia metabolic alkalosis
      • Due to increased weak mineralocorticoids (refer to Chapter 5)

d. Nelson syndrome
   (1) Bilateral adrenocortical causes enlargement of a preexisting pituitary adenoma.
   (2) Clinical findings
      • Sudden drop in cortisol causes an increase in synthesis of ACTH.

e. Summary of Cushing syndrome (Table 23-9)

2. Hyperaldosteronism
   a. Primary aldosteronism (Conn syndrome; refer to Chapter 5 for full discussion)
      (1) Most often due to a benign adenoma in the zona glomerulosa (see Fig. 23-19B)
      (2) Clinical findings
         (a) Diastolic hypertension
         (b) Muscle weakness (hypokalemia), tetany (from metabolic alkalosis)
      (3) Laboratory findings (refer to Chapter 5; see Fig. 5-7)
         (a) High normal or mild hypernatremia, hypokalemia, metabolic alkalosis
         (b) Decreased plasma renin activity (PRA)
            • Increases plasma volume from sodium retention, increases renal blood flow,
            and decreases activation of the juxtaglomerular apparatus
   b. Secondary aldosteronism (refer to Chapter 5)
      (1) Compensatory reaction is related to a decrease in cardiac output.
      (2) Decreased renal blood flow activates the renin-angiotensin-aldosterone (RAA)
          system.
      (3) Plasma renin activity (PRA) is increased.
E. Adrenal medulla hyperfunction
1. Definition—increased production of catecholamines causes hypertension
2. Pheochromocytoma
   a. Epidemiology
      (1) Unilateral (~90% of cases)
      (2) Benign adenoma (~90% of cases)
      (3) Arises in the adrenal medulla (~90% of cases)
         • Other sites—bladder, organ of Zuckerndl near the bifurcation of the aorta, posterior mediastinum
      (4) N'-Methyltransferase converts NOR to EPI (Fig. 23-20A).
         (a) Adrenal medulla and the organ of Zuckerndl contain the enzyme.
         • Pheochromocytoma in these sites produce NOR and EPI.
         (b) Other sites lack the enzyme.
         • Pheochromocytoma in these sites only produce NOR.
   b. Tumor characteristics
      • Brown, hemorrhagic, and often necrotic
c. Clinical findings
   (1) Diastolic hypertension
      (a) Sustained (55% of cases)
      (b) Paroxysmal bursts (45% of cases)
         • Not present in essential hypertension
   (2) Pounding headache (80% of cases)
   (3) Palpitations (70% of cases)
      (a) With or without tachycardia
      (b) Palpitations are not present in essential hypertension.
   (4) Drenching sweats (hyperhidrosis; 70% of cases)
      (a) Correlates with paroxysms of hypertension
      (b) Hyperhidrosis is not present in essential hypertension.
      (c) Sweat glands receive sympathetic innervation but have muscarinic
          acetylcholine receptors, which are normally stimulated by the
          parasympathetic nervous system.
   (5) Anxiety
      (a) Correlates with paroxysms of hypertension
      (b) Anxiety is not present in essential hypertension.
   (6) Chest pain from subendocardial ischemia
   (7) Orthostatic hypotension
      • Plasma volume is reduced owing to vasoconstriction of arterioles/
        venules.
   (8) Ileus
      • Catecholamines inhibit peristalsis.

d. Laboratory findings
   (1) Increased plasma free metanephrines
      • Best test to screen and confirm pheochromocytoma
   (2) Increased plasma normetanephrine
   (3) Increased 24-hour urine level of metanephrine (100% sensitivity)
   (4) Increased 24-hour urine level of VMA
   (5) Lack of suppression of plasma norepinephrine with clonidine
   (6) Hyperglycemia
      • Increased glycogenolysis and gluconeogenesis
   (7) Neutrophilic leukocytosis
      • Inhibition of neutrophil adhesion molecules (refer to Chapter 3)

e. Treatment is surgery.
   (1) Preoperative stabilization
      (a) Phenoxybenzamine
      (b) β-Blocker
      (c) Metyrosine (catecholamine synthesis inhibitor)
      (d) Liberal fluid and salt intake
   (2) Preoperative or intraoperative hypertensive crisis
      • Phentolamine or nitroprusside in concert with a β-adrenergic
        blocker

3. Neuroblastoma
   a. Malignant tumor
      (1) Neoplasm of postganglionic sympathetic neurons
      (2) Most often occurs in children <5 years old
         (a) Third most common cancer in children
         (b) Mean age of onset is 18 months
      (3) Primarily located in the adrenal medulla
         • Occasionally located in the posterior mediastinum
           (paraspinal)
      (4) Amplification of N-MYC oncogene (nuclear transcriber)
      (5) Opsoclonus-myoclonus syndrome
         (a) Paraneoplastic syndrome
         (b) Myoclonic jerks of extremities
         (c) Chaotic eye movements in all directions
         (d) Associated with neuroblastoma in 20% to 50% of cases
   b. Commonly metastasize to skin and bones
      • Approximately 70% have metastases at the time of diagnosis.
   c. Prognosis depends on age.
      • Children <1 year old have a good prognosis.
d. “Small cell” tumor
   (1) Tumor is composed of malignant neuroblasts.
   (2) Homer-Wright rosettes are present.
     - Neuroblasts are located around a central space (see Fig. 23-20B).
   (3) Electron microscopy shows neurosecretory granules.

e. Clinical and laboratory findings
   (1) Palpable abdominal mass
   (2) Diastolic hypertension
   (3) Increased urine VMA and HVA (90%–95% sensitivity)

f. Diagnosis
   (1) Urine collections for VMA and HVA
   (2) Imaging studies
     (a) Body scan with ¹³¹I-MIBG (metaiodobenzylguanidine)
       - Malignant cells pick up the radioactive material.
     (b) Bone scans to detect lytic lesions

g. Treatment
   (1) Depends on age, stage of disease
   (2) Surgery, irradiation, multiagent chemotherapy

h. Prognosis
   (1) Overall survival is 40%.
   (2) Children <1 year old have a 90% cure rate.

VIII. Islet Cell Tumors (Table 23-10)

IX. Diabetes Mellitus (DM)

A. Epidemiology
   1. Affects 5% to 7% of population in the United States
      - Increased in Native Americans (35% of Pima Indians)
   2. Leading cause in the United States for:
      a. Legal blindness
      b. Peripheral neuropathy
      c. Chronic renal failure (CRF)
      d. Below-the-knee amputation
   3. Incidence increases with age.
### Table 23-11 Comparison Between Type 1 and Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>TYPE 1</th>
<th>TYPE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>5%–10%</td>
<td>90%–95%</td>
</tr>
<tr>
<td>Age at onset</td>
<td>&lt;30 years</td>
<td>&gt;40 years</td>
</tr>
<tr>
<td>Speed of onset</td>
<td>Rapid</td>
<td>Insidious</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Usually thin</td>
<td>Usually obese (80% of cases)</td>
</tr>
<tr>
<td>Genetics</td>
<td>Family history uncommon</td>
<td>Family history common</td>
</tr>
<tr>
<td></td>
<td>Environmental factors required for expression (HLA-DR3 and HLA-DR4)</td>
<td>No HLA association</td>
</tr>
<tr>
<td>Associations</td>
<td>Other autoimmune diseases: Graves disease, Hashimoto thyroiditis, pernicious anemia, Addison disease</td>
<td>No autoimmune associations</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Lack of insulin</td>
<td>Relative deficiency of insulin. Early stages have hyperinsulinemia</td>
</tr>
<tr>
<td></td>
<td>Pancreas devoid of β-islet cells</td>
<td>Insulin resistance related to receptor and postreceptor problems</td>
</tr>
<tr>
<td></td>
<td>Insulitis: T-cell cytokine destruction (type IV HSR) and autoantibodies against β-islet cells (&gt;80%) and insulin (&gt;50%) (type II HSR)</td>
<td>Decreased insulin receptors: downregulation by increased adipose.</td>
</tr>
<tr>
<td></td>
<td>Triggers for destruction—e.g., viruses</td>
<td>Postreceptor defects: most important factor; examples—tyrosine kinase defects (normally is activated when insulin attaches to its receptor (muscle, adipose), GLUT-4 abnormalities (normally moves from the cytosol to the cell membrane to attach to glucose and bring glucose into the cytosol).</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Polyuria (osmotic diuresis from glucosuria), polydipsia (TPOSM), polyphagia, weight loss</td>
<td>Insidious onset of symptoms</td>
</tr>
<tr>
<td></td>
<td>Ketoacidosis (hyperglycemia, coma; production of ketone bodies); lactic acidosis from shock (losing sodium by osmotic diuresis from glucosuria)</td>
<td>Recurrent blurry vision: alteration in lens refraction from sorbitol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent infections: bacterial, Candida</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Target organ disease: nephropathy, retinopathy, neuropathy, coronary artery disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reactive hypoglycemia: too much insulin is released for a glucose load (early finding)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased risk for Alzheimer disease (refer to Chapter 26)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin</td>
<td>Weight loss: upregulates insulin receptor synthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral hypoglycemic agents; may require insulin</td>
</tr>
</tbody>
</table>

GLUT, Glucose transport unit; HLA, human leukocyte antigen; HNK C, hyperosmolar nonketotic coma; HSR, hypersensitivity reaction.

### B. Classification

1. Type 1 and type 2 diabetes mellitus (DM; Table 23-11)
2. Secondary causes
   a. Pancreatic disease
   b. Drugs
   c. Endocrine disease
   d. Genetic disease
   e. Insulin-receptor deficiency
   f. Infections
3. Impaired glucose tolerance (IGT)
4. Gestational diabetes mellitus (GDM)
5. Maturity onset diabetes of the young (MODY)
   a. Autosomal dominant (AD) inheritance
      (1) Various subtypes
      (2) Mutations of transcription factor genes (e.g., glucokinase gene)
   b. Patients <25 years old and are not obese.
   c. Mild to severe hyperglycemia
      • Impaired glucose-induced secretion of insulin release
   d. Resistance to ketosis
   e. May progress into type 2 DM
   f. Treatment varies with regard to oral hypoglycemic agents or insulin.

6. Metabolic syndrome
   a. May affect as much as 25% of the U.S. population
   b. Insulin resistance syndrome
      (1) Genetic defect causes insulin resistance that is exacerbated by obesity.
      (2) Commonly associated with polycystic ovary syndrome in women
      (3) May be associated with acanthosis nigricans (refer to Chapter 24)
      (4) Increased risk for developing Alzheimer disease (refer to Chapter 26)
   c. Clinical and laboratory findings
      (1) Hyperinsulinemia leads to:
         (a) Increased synthesis of very-low-density lipoprotein (VLDL; hypertriglyceridemia).
            • Serum triglyceride ≥150 mg/dL
         (b) Hypertension (≥130/85 mm Hg).
            • Increased insulin increases sodium retention by the renal tubules.
         (c) Coronary artery disease (CAD).
            • Increased insulin damages endothelial cells.
      (2) Obesity exacerbates insulin resistance.
         • Increased adipose downregulates insulin receptor synthesis
           (type 2 DM).
      (3) Definition for obesity in metabolic syndrome
         (a) Abdominal waistline girth in men >40 inches (102 cm)
         (b) Abdominal waistline girth in women >35 inches (88 cm)
      (4) Serum high-density lipoprotein cholesterol (HDL-CH) <40 mg/dL in
           men and <50 mg/dL in women
      (5) Fasting serum glucose ≥110 mg/dL
   d. Treatment
      (1) Statin drugs to lower lipids
      (2) Treat hypertension
         • Angiotensin-converting enzyme (ACE) inhibitors or diuretics
      (3) Correct insulin resistance with weight loss.
      (4) Correct insulin resistance with drugs.
         • Metformin, thiazolidinediones

C. Pathologic processes and complications in diabetes mellitus (Table 23-12)
1. Poor glycemic control
   a. Hyperglycemia is the key factor that produces organ damage.
   b. Glucose control reduces onset and severity of complications.
      • Complications are related to retinopathy, neuropathy, and nephropathy, in
descending order.
2. Nonenzymatic glycosylation (NEG)
   a. Glucose combines with amino groups in proteins.
   b. Advanced glycosylation products are synthesized.
      (1) Increase vessel permeability to protein
      (2) Increase atherogenesis
   c. Role in diabetes mellitus
      (1) Production of glycosylated HbA1c
      (2) Hyaline arteriolosclerosis (refer to Chapter 10)
      (3) Diabetic glomerulopathy (refer to Chapter 20)
      (4) Ischemic heart disease, strokes (lacunar strokes), peripheral vascular disease
3. Osmotic damage
   a. Aldose reductase
      (1) Converts glucose to sorbitol.
      (2) Sorbitol draws water into tissue causing damage.

MODY: AD inheritance; not obese; impaired glucose-induced secretion of insulin

Metabolic syndrome: insulin resistance exacerbated by obesity

Associations: acanthosis nigricans; Alzheimer disease

Hyperinsulinemia: ↑VLDL, hypertension, CAD; ↓HDL-CH

Good glycemic control prevents complications of diabetes.

NEG: HbA1c, hyaline arteriolosclerosis, glomerulopathy

Aldose reductase: converts glucose to sorbitol; osmotic damage
TABLE 23-12 Complications of Diabetes Mellitus

<table>
<thead>
<tr>
<th>COMPLICATION CATEGORY</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic disease (see Fig. 2-15D and F)</td>
<td>Increased incidence of strokes, CAD, and peripheral vascular disease. Acute MI is the most common cause of death. Gangrene of the lower extremities; diabetes is the most common cause of nontraumatic amputation of the lower extremity.</td>
</tr>
<tr>
<td>Renal disorders (see Fig. 20-5J)</td>
<td>Renal failure due to nodular glomerulosclerosis (refer to Chapter 20). Renal papillary necrosis.</td>
</tr>
<tr>
<td>Ocular disorders (see Fig. 23-21B)</td>
<td>Increased risk for cataracts and glaucoma. Retinopathy (15%): Nonproliferative: microaneurysm formation, flame hemorrhages, exudates. Proliferative: formation of new vessels (neovascularization), increased risk for retinal detachment and blindness, annual ophthalmologic examination is mandatory (photocoagulate microaneurysms).</td>
</tr>
<tr>
<td>Peripheral nerve disorders (see Fig. 23-21A)</td>
<td>Diabetes mellitus is the most common cause of peripheral neuropathy in the United States; occurs in 70%–80% of cases. Sensory: paresthesias, patients complain of burning feet, ↓ pinprick sensation, ↓ proprioception (ataxia). Motor dysfunction: muscle weakness, ↓ deep tendon reflexes. Neurophysiology is the most important risk factor for neuropathic ulcers on the bottom of the feet (patient cannot feel pain). Treatment for neuropathy: duloxetine (selective serotonin and norepinephrine reuptake inhibitor), topical capsaicin, amitriptyline.</td>
</tr>
<tr>
<td>Autonomic nervous system disorders</td>
<td>Autonomic neuropathy: gastroparesis (delayed emptying of stomach), impotence, neurogenic bladder, orthostatic hypotension. Treatment for gastroparesis: prokinetic agents (e.g., metoclopramide).</td>
</tr>
<tr>
<td>Cranial nerve (CN) disorders</td>
<td>Diabetes is the most common cause of multiple cranial nerve palsies. Cranial nerves most often involved: CN III, IV, and VI.</td>
</tr>
<tr>
<td>Infectious disorders</td>
<td>Urinary tract infections. <em>Candida</em> infections: e.g., vulvovaginitis. Malignant external otitis due to <em>Pseudomonas aeruginosa</em>. Rhinocerebral mucormycosis: <em>Mucor</em> extends from the frontal sinuses to the frontal lobes, producing infarction (vessel invader) and abscesses. Cutaneous infections: usually <em>Staphylococcus aureus</em> abscesses.</td>
</tr>
<tr>
<td>Skin disorders</td>
<td>Necrobiosis lipoidica diabeticorum: well-demarcated yellow plaques over the anterior surface of the legs/dorsum of ankles. Lipoatrophy: atrophy at insulin injection sites due to impure insulin. Lipohypertrophy: increased fat synthesis at insulin injection sites.</td>
</tr>
<tr>
<td>Joint disorders</td>
<td>Neuropathic joint: related to lack of sensation; bone or joint deformity from repeated trauma (refer to Chapter 24).</td>
</tr>
</tbody>
</table>

**CAD**, Coronary artery disease; **MI**, myocardial infarction.

b. Role in diabetes mellitus
   1. Formation of cataracts
   2. Peripheral neuropathy
      a. Osmotic damage of Schwann cells causes demyelination and sensorimotor peripheral neuropathy.
      b. Peripheral neuropathy leads to neuropathic ulcers (Fig. 23-21A).
         - Patient cannot feel pain.
   3. Retinopathy
      - Osmotic damage to pericytes produces microaneurysms of retinal vessels (see Fig. 23-21B).

4. Diabetic microangiopathy
   a. Increased synthesis of type IV collagen in basement membranes and mesangium (see Fig. 20-5J)
   b. Important in diabetic glomerulopathy (refer to Chapter 20)

**D. Clinical findings**

1. Insulin-induced hypoglycemia
   a. Most common complication
   b. Produces irreversible brain damage by destroying neurons
   c. Clinical findings
      1. Sympathetic nervous system signs
         - Sweating, tachycardia, palpitations, and tremulousness
(2) Parasympathetic nervous system signs
- Nausea and hunger
(3) Focal neurologic deficits, mental confusion, coma

2. Diabetic ketoacidosis (DKA; Fig. 23-22)
a. Complication of type 1 DM
b. Precipitated by medical illness or omission of insulin
c. Produces severe volume depletion and coma
   - Volume depletion due to loss of sodium and water with osmotic diuresis
d. Mechanisms for hyperglycemia
   (1) Increased gluconeogenesis
      (a) Due to increase in glucagon and epinephrine
      (b) Most important mechanism of hyperglycemia
   (2) Increased glycogenolysis in the liver (short-lived)
e. Mechanism for ketone bodies
   (1) Increased lipolysis with release of fatty acids
      (a) No inhibition of hormone-sensitive lipase
      (b) Insulin normally inhibits hormone-sensitive lipase

DKA: complication of type 1 DM
Gluconeogenesis: most important mechanism for hyperglycemia
(2) Increased β-oxidation of fatty acids increases production of acetyl CoA.
   a. No malonyl CoA to inhibit carnitine acyltransferase, the rate-limiting enzyme of β-oxidation
   b. Insulin normally enhances fatty acid (FA) synthesis.
      i. Malonyl CoA is produced in FA synthesis and inhibits carnitine acyltransferase, which prevents β-oxidation of FAs.
   c. Acetyl CoA is converted by the liver to ketone bodies.
      i. Acetone (fruity odor), acetooacetic acid, and β-hydroxybutyric acid
f. Mechanism for hypertriglyceridemia
   1. Lack of insulin decreases capillary lipoprotein lipase (CLL) synthesis in the peripheral blood.
      i. Insulin normally increases the synthesis of CLL (refer to Chapter 10)
   2. Chylomicrons and VLDL accumulate in the blood, because they cannot be hydrolyzed by CLL to fatty acids and glycerol.
      i. Type V hyperlipoproteinemia (refer to Chapter 10)
   3. Hypertriglyceridemia may precipitate acute pancreatitis and eruptive xanthomas in the skin.
      i. Called hyperchylomicronemia syndrome (refer to Chapter 10)
g. Laboratory findings
   1. Hyperglycemia
      i. Glucose ranges from 250 to 1000 mg/dL.
   2. Increased HbA1c, ≥6%
   3. Dilutional hyponatremia (refer to Chapter 5)
      a. Glucose overrides sodium in controlling the osmotic gradient.
      b. Water shifts out of the intracellular fluid compartment into the extracellular fluid compartment and dilutes the serum sodium.
   4. Hyperkalemia (refer to Chapter 4)
      i. Transcellular shift as excess H+ ions enter cells in exchange of potassium.
   5. Increased anion gap metabolic acidosis (refer to Chapter 5)
      i. Due to ketoacidosis and lactic acidosis
   6. Prerenal azotemia (refer to Chapter 20)
      i. Due to volume depletion from osmotic diuresis, which decreases cardiac output and renal blood flow
h. Mortality rate in DKA is 5% to 10%.
3. Hyperosmolar nonketotic coma (HNKC; see Table 23-11)
   a. Complication of type 2 DM
   b. Increased mortality rate (20%–50%)
      i. Patients are older and usually have underlying cardiac and renal problems.
General principles in treatment of type 2 diabetes mellitus. Oral hypoglycemic agents are most often used in treatment, because most patients are not insulin deficient. The primary mechanism of action (MOA) of metformin is to decrease hepatic output of glucose. Because metformin, a biguanide, does not induce hypoglycemia, it is a preferred drug for most patients. Side effects include diarrhea and lactic acidosis. Sulfonylureas (e.g., glyburide, glipizide) increase pancreatic secretion of insulin. They are a common cause of hypoglycemia in a type 2 diabetic.

Akarbose and miglitol inhibit α-glucosidase. In this regard, they work by competitively inhibiting pancreatic amylase and small intestinal glucosidases from breaking down glucose in the bowel, hence decreasing glucose reabsorption after eating. Side effects include flatulence and diarrhea.

Pioglitazone and rosiglitazone (thiazolidinediones) increase insulin sensitivity. They accomplish this by decreasing peripheral insulin resistance, increasing glucose disposal, and decreasing hepatic glucose production. Side effects include hepatotoxicity with an increase in serum transaminases.

Repaglinide and nateglinide (meglitinides) acutely increase pancreatic insulin secretion as their MOA. Hypoglycemia may occur as a side effect. Exenatide is a synthetic peptide that stimulates release of insulin from pancreatic β-islet cells. Combinations of oral hypoglycemic drugs are commonly used if one drug does not produce adequate glycemic control. If oral hypoglycemic agents alone or in combination are still ineffective in glycemic control, then insulin is used.

E. Laboratory diagnosis

1. Criteria
   a. Random (nonfasting) plasma glucose ≥200 mg/dL plus classic symptoms
   b. Fasting plasma glucose ≥126 mg/dL (normal <110 mg/dL)
      • Set for high sensitivity
   c. Two-hour glucose level after 75-g glucose challenge is >200 mg/dL (normal is <140 mg/dL)
   d. One of the preceding three criteria must be present on a subsequent day to confirm the diagnosis of diabetes.
   e. Glycosylated hemoglobin (HbA1c) can also be used to diagnose diabetes mellitus (see later)

2. Glycosylated hemoglobin (HbA1c)
   a. Evaluates long-term glycemic control
   b. Represents the mean glucose value for the preceding 8 to 12 weeks
   c. Normal range is between 4% and 5.6%
      (1) HbA1c levels between 5.7% and 6.4% indicate increased risk of diabetes.
      (2) HbA1c levels of 6.5% or higher indicate diabetes.
   d. Goal in therapy is <7%.

3. Fructosamine
   • Reflects glycemic control for the preceding 2 weeks

F. Impaired glucose tolerance (IGT)

1. Patient has hyperglycemia that is nondiagnostic of diabetes.
   a. Fasting glucose >110 mg/dL, but <126 mg/dL
   b. Two-hour glucose >140 mg/dL, but <200 mg/dL after 75-g oral glucose tolerance test

2. Pathogenesis
   • Prediabetic state with insulin resistance
   • Increased risk for macrovascular disease and neuropathy
   3. Approximately 30% develop type 2 DM within 10 years.
   4. Treatment is to exercise regularly and to reduce sugar intake.

G. Gestational diabetes mellitus (GDM)

   a. Antiinsulin effect of human placental lactogen (HPL), cortisol, and progesterone
   b. Increased risk for GDM in future pregnancies

2. Screening
   a. Pregnant women are screened between 24 and 28 weeks gestation.
   b. 50-g glucose challenge followed by 1-hour glucose level
      • A value above 140 mg/dL is a positive screen.
   c. Positive screen is confirmed with a 3-hour oral glucose tolerance test.

3. Newborn risks
   a. Macrosomia (Fig. 23-23)
      (1) Hyperglycemia in the fetus causes release of insulin.
      (2) Insulin increases fat stored in adipose tissue.
      (3) Insulin increases muscle mass by increasing amino acid uptake in muscle (growth hormone effect of insulin).
Rapid Review Pathology

23-23: Hyperglycemia in the fetus causes release of insulin. Insulin increases fat stored in adipose tissue. Insulin increases muscle mass by increasing amino acid uptake in muscle (growth hormone effect of insulin). (From Taylor S, Raffles A: Diagnosis in Color Pediatrics, London, Mosby-Wolfe, 1997, p 36, Fig. 1-71.)

RDS: ↑Insulin inhibits fetal surfactant production

Neonatal hypoglycemia: ↑Insulin drives glucose into hypoglycemic range; give newborn glucose at birth

- Respiratory distress syndrome (RDS; refer to Chapter 17; Fig. 17-3B)
  - Insulin inhibits fetal surfactant production.
- Increased risk for open neural tube defects
- Neonatal hypoglycemia
  - High insulin level at birth drives glucose into the hypoglycemic range (give newborn glucose after birth to prevent this complication).

4. Maternal risk
   - Diabetes may develop at a later date (>50% of cases).
5. If patients cannot keep their blood glucose in control by diet alone, then insulin is recommended.

X. Polyglandular Deficiency Syndromes

A. Type I polyglandular syndrome
   1. Autosomal recessive
   2. Mean age of onset is 12 years old.
   3. No HLA relationship
   4. Clinical findings
      a. Addison disease
      b. Primary hypoparathyroidism
      c. Mucocutaneous candidiasis

B. Type II polyglandular syndrome
   1. Autosomal dominant
   2. Mean age of onset is 24 years old.
   3. HLA-DR3 and HLA-DR4
   4. Clinical findings
      a. Addison disease
      b. Hashimoto thyroiditis
      c. Type 1 DM

XI. Hypoglycemia

A. Definition
   1. Difficult to arrive at a consensus for a cutoff point
   2. Ranges have been anywhere from 40 to 70 mg/dL (normal fasting 70–110 mg/dL)
   3. Reasonable cutoff point is <50 mg/dL.

B. Fed state hypoglycemia
   1. Reactive type of hypoglycemia
   2. Causes
      a. Insulin treatment in type 1 DM
         (1) Most common cause
      b. Sulfonylurea-related hypoglycemia is less common.
      c. IGT or type 2 DM
         (1) Excessive amount of insulin is released for the glucose absorbed.
   3. Develop adrenergic symptoms ~1 to 5 hours after eating:
      a. Sweating, trembling, anxiety
      b. Palpitations, tachycardia, mydriasis
      c. Numbness and tingling.
4. Treatment  
a. Carbohydrate intake (grape juice, candy)  
b. Glucagon IM injection

**Idiopathic postprandial syndrome (IPS):** This syndrome is characterized by the presence of adrenergic symptoms without demonstrable evidence of hypoglycemia. Patients also complain of lack of energy, mental dullness, and inability to concentrate. Symptoms usually disappear if mixed carbohydrate-protein meals are eaten at frequent intervals.

C. **Fasting type of hypoglycemia**

1. Fasting state hypoglycemia
2. Causes
   a. Alcohol (most common cause; refer to Chapter 7)  
      (1) Increased nicotinamide adenine dinucleotide (NADH) converts pyruvate to lactate.  
          • Less pyruvate is available for gluconeogenesis.  
      (2) Decreased glycogen stores in severe liver disease  
   b. Renal failure  
      • Kidney is a site of gluconeogenesis.  
   c. Malnutrition  
   d. Chronic liver disease  
      • Decreased gluconeogenesis, glycogen depletion  
   e. Insulinoma, hypopituitarism (decreased GH and cortisol)  
   f. Ketotic hypoglycemia in childhood  
      (1) Most common cause of hypoglycemia from 18 months to mid-childhood  
      (2) Multiple etiologies  
         (a) Maple syrup urine disease, galactosemia, hereditary fructose intolerance, von Gierke glycogen storage disease (refer to Chapter 6)  
         (b) Carnitine deficiency

**Carnitine** is required for the synthesis of carnitine acyltransferase (CAT). CAT is the rate-limiting reaction of β-oxidation of fatty acids, which are an important source of energy in the fasting and starvation states for muscle tissue. Any excess of acetyl CoA, the end-product of β-oxidation, is used by the liver to synthesize ketone bodies. Ketone bodies are used for energy by muscle in the fasting state and by the brain in starvation. Therefore, in carnitine deficiency, a decrease in CAT significantly reduces the amount of ketone bodies as a source of energy. This leaves glucose as the only fuel available for all tissues to use for energy, which results in hypoglycemia.

3. Neuroglycopenic symptoms  
   a. Dizziness, confusion, headache, inability to concentrate  
   b. Motor disturbances, seizures, visual disturbances, coma

4. Diagnosis  
   a. Prolonged fast  
   b. Must satisfy the Whipple triad:  
      (1) Symptoms occur.  
      (2) Hypoglycemia is demonstrated.  
      (3) Symptoms are relieved by glucose.
I. Bone Disorders
   A. Osteogenesis imperfecta (brittle bone disease)
      1. Autosomal dominant (AD)
      2. Definition—defective synthesis of type I collagen
      3. Clinical findings
         a. Pathologic fractures at birth
         b. Blue sclera (Fig. 24-1A)
            • Reflection of the underlying choroidal veins through the thin sclera
         c. Deafness in some patients
      4. Treatment
         • Bisphosphonates to increase bone mineralization

   B. Achondroplasia
      1. Autosomal dominant
      2. Pathogenesis
         a. Mutation in fibroblast growth factor receptor 3 (FGFR3) gene
         • Gene mutations increase with paternal age
         b. Impaired proliferation of cartilage at the growth plate
      3. Clinical findings (see Fig. 24-1B)
         a. Normal-sized head and vertebral column
         b. Shortened arms and legs
         c. Normal growth hormone and insulin-like growth factor 1 levels
      4. No treatment

   C. Osteopetrosis (marble bone disease)
      1. Autosomal recessive (severe)
      • Autosomal dominant (less severe)
      2. Pathogenesis
         a. Deficiency osteoclasts
         b. Normal balance of osteoblasts making bone and osteoclasts breaking down bone is disrupted favoring increased bone formation.
         c. Overgrowth and sclerosis of cortical bone ("too much bone")
      3. Clinical findings
         a. Pathologic fractures
         b. Anemia
            • Replacement of marrow cavity
         c. Cranial nerve compression
            • Visual and hearing loss
      4. No treatment

   D. Osteomyelitis
      1. Osteomyelitis in children and adults
         a. Sepsis is the most likely cause with subsequent spread to bone.
         b. Metaphysis is the most common site of infection.
            (1) Vascular supply is best in the metaphysis, which favors hematogenous spread of the infection to bone.
            (2) The tibia and fibula are the most common sites in children.
24-1: A, Osteogenesis imperfecta. Note the faint blue tint of the sclera representing the reflection of the underlying choroidal veins. B, Child with achondroplasia. The head is a normal size; however, the lower extremities show tibial bowing. (A from Mir MA: Atlas of Clinical Diagnosis, London, Saunders, 1995; B from Kliegman R: Nelson Textbook of Pediatrics, 19th ed, Philadelphia, Elsevier Saunders, 2011, p 2429, Fig. 687-3C.)

c. Infection is most often due to Staphylococcus aureus (90% of cases).
   • Other pathogens include Streptococcus pyogenes and Haemophilus influenzae

2. Osteomyelitis in sickle cell disease (refer to Chapter 12)
   a. Salmonella paratyphi is the usual causative agent.
   b. Dysfunctional spleen (related to numerous splenic infarctions) cannot remove Salmonella from the bloodstream

3. Tuberculous osteomyelitis
   a. Hematogenous spread from a primary lung focus
   b. Targets the vertebral column (Pott disease)

4. Pseudomonas aeruginosa osteomyelitis
   • Most often due to puncture of foot through rubber footwear

5. Neutrophils enzymatically destroy bone (Fig. 24-2).
   a. Devitalized bone is called sequestra.
   b. Chronic disease produces reactive bone formation in the periosteum.
      • Called involucrum
   c. Draining sinus tracts to the skin surface often occur.
      • Danger of squamous cell carcinoma (SCC) developing at the orifice of sinus tracts

6. Clinical findings
   • Fever, bone pain
24-2: Chronic osteomyelitis. The solid arrow points to necrotic bone in the center of a draining abscess (sequestrum). The interrupted arrow is a rim of new bone formation (involucrum). (From Kumar V, Abbas AK, Fausto N, Mitchell RN: Robbins Basic Pathology, 8th ed, Philadelphia, Saunders Elsevier, 2007, p 810, Fig. 21-7.)

7. Diagnosis
   a. Bone biopsy for culture
   b. Imaging studies—CT scan or MRI

8. Treatment
   a. Surgical débridement
   b. Antibiotics

E. Osteoporosis
   1. Epidemiology
      a. Most common metabolic abnormality of bone
      b. Definition—loss of both organic bone matrix (osteoid) and mineralized bone
         (1) Decreased bone mass and density
            • Radiograph shows osteopenia (washed-out appearance).
         (2) Decreased thickness of cortical and trabecular bone
      c. More common in women than men
         • Men have greater bone mass to begin with; therefore it takes longer to develop osteoporosis.
      d. Primary osteoporosis
         (1) Idiopathic type
            (a) Unknown pathogenesis
            (b) Primarily occurs in children and young adults
         (2) Osteoporosis in postmenopausal women (ages 51–75 years) (type 1; discussed later)
         (3) Type II osteoporosis (senile type)
            (a) Occurs in women and men >70 years old
            (b) Progressive decline in osteoblasts and increased activity of osteoclasts (bone resorption exceeds bone formation)
            (c) Decreased physical activity (less stress on bone)
            (d) Wrist, hip, and vertebral fractures commonly occur
      e. Secondary osteoporosis
         (1) Underlying disease (e.g., hypercortisolism-inhibition of osteoblasts, enhanced osteoclast activity)
         (2) Drugs (e.g., heparin-decreased bone formation and increased bone resorption)
         (3) Hypogonadism (e.g., hypopituitarism)
         (4) Malnutrition (e.g., anorexia nervosa)
         (5) Space travel
            • Lack of gravity reduces bone stress.

2. Pathogenesis of postmenopausal osteoporosis
   a. Role of estrogen (EGN) on maintaining bone mass
      (1) Estrogen normally enhances osteoblastic activity and inhibits osteoclastic activity in bone
      (2) This effect on bone mass is mediated by inhibiting secretion of cytokines (e.g., interleukin [IL]-1, IL-6, tumor necrosis factor [TNF]) that modulate osteoclastogenesis (osteoclast differentiation, activation, life span, and function)
   b. In EGN deficiency, there is an increase in secretion of the previously mentioned cytokines by monocytes and cells in the bone marrow.
      (1) These cytokines have the following effects:
         (a) They enhance expression of RANKL (receptor activator of nuclear factor κB ligand) and RANK genes (receptor activator of nuclear factor κB), which increases osteoclastogenesis (increase in recruitment and activity).
(b) They inhibit expression of osteoprotegerin (OPG), a receptor produced by osteoblasts that inhibits RANKL/RANK interaction.

(2) In postmenopausal osteoporosis, osteoclastic activity is greater than osteoblastic activity, which leads to loss of bone mass.

c. Clinical findings
(1) Compression fractures of vertebral bodies (Fig. 24-3A)
   (a) Most common fracture
   (b) Patients lose stature
(2) Dowager's hump (see Fig. 24-3B)
   • Kyphosis (forward bending of the spine) is due to advanced osteoporosis.
(3) Increased risk for Colles fracture of the distal radius

d. Diagnosis
(1) Dual photon absorptiometry
(2) Noninvasive test that evaluates bone marrow density (BMD)

e. The World Health Organization uses a T-score to define osteoporosis.
(1) It is calculated by subtracting the mean BMD (in g/cm^2) of a young adult reference population from the patient's BMD and dividing this by the standard deviation (SD) of the young adult reference population.
(2) Using the T-score, osteoporosis is defined as −2.5 SD and below.

f. Prevention
(1) Take calcium and vitamin D supplements
(2) Stop smoking (inhibits osteoblast activity)
(3) Perform weight-bearing exercise that stresses bones
   (a) Weight lifting, vigorous walking
   (b) Note: swimming provides excellent cardiovascular health, but does not stress bones and prevent osteoporosis.

g. Treatment
(1) Bisphosphonates inhibit bone resorption.
   • First-line treatment
(2) Calcitonin inhibits osteoclasts.
(3) Estrogen replacement is prescribed alone or in combination with bisphosphonates.

F. **Avascular (aseptic) necrosis (AVN)**

1. Definition—cellular death of bone components due to interruption of the blood supply
   a. Causes
      (1) Corticosteroids (35% of cases)
         - Associated with fat embolism, which occludes microcirculation in bone
      (2) Alcohol (22% of cases)
      (3) Other causes (43% of cases)
         (a) Idiopathic
         (b) Fractures
   b. Sites
      (1) Femoral head and condyle (most common site)
      (2) Humeral head
      (3) Scaphoid (navicular) and lunate bones in the wrist
      (4) Talus bone
         - Located between the calcaneus and the tibia and fibula
   c. Femoral head
      (1) Fracture in elderly persons
         (a) Peritrochanteric fracture is extracapsular and does not compromise the blood supply to the femoral head; therefore no aseptic necrosis occurs (Fig. 24-4A, left).
         (b) Subcapsular fracture disrupts the blood supply to the retinacular arteries from the femoral artery; therefore aseptic necrosis occurs (see Fig. 24-4A, right; and Fig. 24-4B).
      (2) Sickle cell disease (due to vasoocclusive disease; refer to Chapter 12)
      (3) Long-term use of corticosteroids
   d. Scaphoid bone (see Fig. 24-4C)
      (1) Located on the thumb side of the wrist
      (2) Most common bone in the wrist that is fractured
   e. Digits
      - Dactylitis in sickle cell anemia (see Fig. 12-27B; refer to Chapter 12)

2. Clinical findings
   a. Asymptomatic in some cases
   b. Localized pain is exacerbated by movement
   c. Functional limitation of activity

3. Imaging studies
   a. Magnetic resonance imaging (MRI)
      - Most sensitive test (75%–100%) for early detection of aseptic (avascular) necrosis
   b. CT scan
      - Shows central necrosis and area of collapse before a standard x-ray
   c. Bone scan
      (1) Early—shows no uptake (cold area; sensitivity 70%)
      (2) Later—increased uptake (result of bone remodeling)
   d. X-ray study
      (1) Most insensitive test in the early phases
      (2) Later—radiolucency (resorption of dead bone) with a sclerotic (increased density) border due to reactive bone formation.

4. Treatment
   - Core decompression, bone graft, joint replacement, bisphosphonates

5. Osteochondrosis
   a. Definition—AVN of ossification centers (epiphyses) in children
   b. Legg-Calve-Perthes (LCP) disease
      (1) Definition—AVN involving the femoral head ossification center
      (2) Occurs most often in boys 3 to 10 years of age
      (3) Presents with pain in the knee or a limp
      (4) Secondary osteoarthritis is common.
G. Osteochondritis dissecans (OCD)

1. Definition—variant of osteochondrosis limited to the articular epiphysis (see Fig. 24-4D)
   a. Trauma is the primary insult.
   b. Ischemia is a secondary injury.
   c. Portion of articular cartilage and underlying subchondral bone separates.

2. Occurs between 10 and 50 years of age

3. No sex predilection

4. Most common joint is knee.
   a. Lateral surface of the medial femoral condyle is the most frequent site.
   b. Piece of cartilage along with a thin layer of bone become detached

5. Clinical findings
   a. Localized pain, stiffness, swelling
   b. Locking of joint by loose body
   c. Tenderness at site of lesion

OCD: variant of osteochondrosis limited to articular epiphysis

OCD: trauma is primary insult; ischemia is secondary injury

OCD: lateral surface of medial femoral condyle

MC site

OCD: piece of cartilage along with a thin layer of bone detaches
Fibrous dysplasia: defect in osteoblastic differentiation/maturation

OSD: painful swelling of tibial tuberosity at patellar tendon insertion; boys

Paget: primarily occurs in men >50 years old; ? paramyxovirus

Paget: pelvis, skull, femur

Paget: osteoclastic phase followed by an osteoblastic phase

Paget: ↑ALP in osteoblastic phase; weak, thick, vascular bone

Paget: pain, ↑hat size

Complications: fractures, osteogenic sarcoma, high-output heart failure

Fibrous dysplasia: defect in osteoblastic differentiation/maturation

Fibrous dysplasia: medullary bone replaced by fibrous tissue with cyst formation

6. Complication
   - Osteoarthritis (OA)
7. Diagnosis
   a. Imaging studies used depend on the site involved.
   b. X-ray; spiral (helical CT), MRI
8. Treatment
   a. Ice after exercise
   b. Nonsteroidal antiinflammatory drugs (NSAIDs) for pain, immobilization, arthroscopic surgery

H. **Osgood-Schlatter disease (OSD)**
1. Affects physically active boys 11 to 15 years of age
2. Painful swelling of the tibial tuberosity
   - Inflammation of proximal tibial apophysis at insertion of the patellar tendon
3. Clinical findings
   a. Pain aggravated by
      1. Squatting
      2. Walking upstairs
      3. Extending knee with resistance
   b. Permanent knobby-appearing knees
4. No effect on bone growth
5. Treatment
   a. Ice after exercise
   b. NSAIDs for pain
   c. Knee splint 2 to 4 weeks in resistant cases

I. **Paget disease (osteitis deformans)**
1. Epidemiology
   a. Primarily occurs in men >50 years of age
   b. Possible paramyxovirus infection of osteoclasts
   c. Targets the pelvis, skull (enlarged), and femur
2. Pathogenesis
   a. Early phase of osteoclastic resorption of bone
      - Causes shaggy-appearing lytic lesions
   b. Late phase of increased osteoblastic bone formation
      1. Markedly increased serum alkaline phosphatase (ALP)
      2. Production of thick, weak bone (mosaic bone)
3. Clinical findings
   a. Bone pain is the most common complaint.
   b. Headaches and hearing loss occur if it affects skull.
   c. Hat size is increased with skull involvement.
4. Complications
   a. Pathologic fractures
   b. Risk for developing osteogenic sarcomas
   c. Risk for developing high-output heart failure (refer to Chapter 11)
      - Due to arteriovenous connections in vascular bone
5. Diagnosis
   a. Radiographs show thickened bone with shaggy areas of radiolucency (Fig. 24-5A).
   b. Bone scans show “hot spots” (see Fig. 24-5B).
   c. Serum alkaline phosphatase is markedly increased, but serum calcium and phosphorus are normal.
6. Treatment
   a. Bisphosphonates
   b. Calcitonin

J. **Fibrous dysplasia**
1. Skeletal developmental anomaly
   a. Definition—defect in bone-forming mesenchyme with replacement of medullary bone by fibrous tissue
   - Defect in osteoblastic differentiation and maturation
   b. Cysts may develop in the fibrous tissue matrix that manifests as a defect in osteoblastic differentiation and maturation.
2. May involve single (monostotic; 70%–80% of cases) or multiple bones (polyostotic)
3. No sex predilection
4. Occurs between 10 and 30 years of age
5. Most common locations
a. Ribs (28% of cases)
b. Femur (24% of cases)
c. Tibia or craniofacial bones (10%–25% of cases)
   - In the craniofacial bone, it produces cherubism.
d. Humerus, vertebrae

6. Polyostotic bone involvement is associated with Albright syndrome; additional findings include:
   - Café au lait spots on skin, precocious sexual development

7. Clinical findings
   - Pain and swelling overlying the bone

8. Complications
   a. Risk for a pathologic fracture
   b. Malignant degeneration in <1% of cases
      - Osteogenic sarcoma, fibrosarcoma

9. Diagnose with imaging studies.

10. Treatment is surgery.

K. Neoplastic disorders of bone
1. Metastasis is the most common malignancy of bone (Fig. 9-6A to D).
   - Breast cancer is the most common primary site.
2. Primary malignant tumors of bone, in descending order of frequency include:
   - Multiple myeloma, osteogenic sarcoma, chondrosarcoma, and Ewing sarcoma
3. Treatment for primary bone tumors is surgery.
4. Summary of bone tumors (Table 24-1)

II. Joint Disorders

A. Synovial fluid (SF) analysis
1. Routine studies
   - White blood cell count and differential, crystal analysis, mucin clot, culture, Gram stain
2. Crystal identification
   a. Monosodium urate (MSU)
      (1) Needle-shaped (monoclinic) crystal
      (2) Special polarization shows negative birefringence.
         - Crystal is yellow when parallel to the slow ray (Fig. 24-6).
   b. Calcium pyrophosphate
      (1) Monoclinic-like or triclinic (rhomboid) crystals
      (2) Special polarization shows positive birefringence.
         - Crystal is blue when parallel to the slow ray.
Mucin clot: joint viscosity; hyaluronic acid key lubricant

Group I: noninflammatory; OA, neuropathic joint

Group II: inflammatory; rheumatoid arthritis, gout

**24-6:** Synovial fluid with special polarization. Special red filter causes the background to be red. Crystals are aligned parallel to the slow ray (axis) of the compensator (arrow). If the crystal is yellow when parallel to the slow ray, as in this figure, the crystal demonstrates negative birefringence. If the crystal is blue when parallel to the slow ray, the crystal demonstrates positive birefringence. (From Henry JB: Clinical Diagnosis and Management by Laboratory Methods, 20th ed, Philadelphia, Saunders, 2001, Plate 19-7.)

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>EPIDEMIOLOGY</th>
<th>PRIMARY LOCATION</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteochondroma</td>
<td>Males, 10–30 yr Solitary or multiple</td>
<td>Metaphysis of distal femur</td>
<td>Outgrowth of bone (exostosis) capped by benign cartilage Most common benign tumor</td>
</tr>
<tr>
<td>Enchondroma</td>
<td>Equal distribution, 20–50 yr Solitary or multiple</td>
<td>Medullary location Small tubular bones in hands and feet</td>
<td>Multiple enchondromas Risk for chondrosarcoma</td>
</tr>
<tr>
<td>Osteoma</td>
<td>Males, any age Facial bones</td>
<td>Associated with Gardner polyposis syndrome</td>
<td></td>
</tr>
<tr>
<td>Osteoid osteoma</td>
<td>Males, 10–20 yr</td>
<td>Cortex of proximal femur Radiographic finding: radiolucent focus surrounded by sclerotic bone Nocturnal pain relieved by aspirin</td>
<td></td>
</tr>
<tr>
<td>Osteoblastoma</td>
<td>Males, 10–20 yr</td>
<td>Vertebra</td>
<td>Similar to osteoid osteoma</td>
</tr>
<tr>
<td>Giant cell tumor</td>
<td>Females, 20–40 yr</td>
<td>Epiphysis of distal femur or proximal tibia</td>
<td>Reactive multinucleated giant cells resemble osteoclasts Neoplastic mononuclear cells</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>Males, 30–60 yr</td>
<td>Pelvic bones, proximal femur</td>
<td>Grade determines biological behavior Metastasizes to lungs</td>
</tr>
<tr>
<td>Osteogenic sarcoma (see Fig. 9-1H)</td>
<td>Males, 10–25 yr Risk factors: Paget disease, familial retinoblastoma, irradiation, fibrous dysplasia</td>
<td>Metaphysis of distal femur, proximal tibia</td>
<td>Malignant osteoid Metastasizes to lungs</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>Males, 10–20 yr</td>
<td>Pelvic girdle, diaphysis and metaphysis of proximal femur or rib</td>
<td>Small, round cell tumor Radiographic finding: “onion skin” appearance around bone (periosteal reaction) Possible fever and anemia</td>
</tr>
</tbody>
</table>

**B. Classification of joint disorders**

1. **Group I**
   a. Noninflammatory
   b. Examples—osteoarthritis (OA), neuropathic joint

2. **Group II**
   a. Inflammatory
   b. Examples—rheumatoid arthritis (RA), gout
3. Group III
   a. Septic
   b. Examples—Lyme disease, disseminated gonococcemia
4. Group IV
   a. Hemorrhagic
   b. Examples—trauma, hemophilia

C. Signs and symptoms of joint disease
1. Arthralgia is a general term for joint pain.
2. Arthritis connotes pain associated with joint swelling, tenderness, and warmth.
3. Morning stiffness
   a. Definition—pain in the joints that lasts >30 minutes
   b. Characteristic finding in:
      (1) Rheumatoid arthritis (RA)
      (2) Polymyalgia rheumatica
      (3) Systemic lupus erythematosus (SLE)
4. Abnormal joint mobility
   a. Caused by damage to ligaments/joint capsule
   b. Example—tear of the anterior cruciate ligament
5. Swelling of the joint (effusion)
   a. Due to increased joint fluid
   b. Examples—exudate, blood
6. Redness and warmth of the joint
   a. Sign of acute inflammation
   b. Examples—septic arthritis, rheumatoid arthritis
7. Joint crepitus with motion
   a. Crackling feeling when moving a joint
   b. Example—osteoarthritis

D. Osteoarthritis (OA)
1. Epidemiology
   a. Definition—progressive degeneration of articular cartilage
      • Targets weight-bearing joints
   b. Most common disabling joint disease
   c. Noninflammatory joint disease
   d. No sex predilection
   e. Almost universal >65 years of age
   f. Secondary causes
      (1) Legg-Calvé-Perthes disease
      (2) Osteochondritis dissecans
      (3) Obesity, trauma, neuropathic joint
      (4) Meniscus injuries, hemochromatosis

   g. Common sites
      (1) Femoral head, knee
      (2) Cervical and lumbar vertebrae
      (3) Hands (usually genetic)
   h. Less common sites
      (1) Shoulder
      (2) Elbow
      (3) Feet with the exception of the first metatarsophalangeal joint
         • Site for bunion formation
2. Pathogenesis
   a. Components of normal articular cartilage
      (1) Proteoglycans that provide elasticity
      (2) Type II collagen that provides tensile strength
   b. In OA, cytokines activate metalloproteinases
      • Causes degradation of proteoglycans and collagen

Ochronosis (alkaptonuria) is an autosomal recessive (AR) disease caused by deficiency of homogentisic acid oxidase and subsequent accumulation of homogentisic acid (urine turns black when oxidized; refer to Fig. 6-5). Homogentisic acid deposits in the intervertebral disks, causing osteoarthritis and other systemic findings.

OA: femoral head, knee, cervical/lumbar vertebrae, hands
Ochronosis: AR; deficiency homogentisic acid; OA
Articular cartilage: proteoglycans, type II collagen
OA: cytokine activate metalloproteinases → degrade proteoglycans/collagen
24-7: A, Schematic of osteoarthritis in a joint. The blue color represents articular cartilage. Note that the cartilage is thin and disrupted causing narrowing of the joint space. Subchondral cysts are noted, which would appear as lucencies in a radiograph. Reactive bone formation (osteophytes) is present at the margins of the joint. The osteophytes project into the synovial tissue. B, Erosion of the femoral head and acetabular surfaces. Note that the joint space is narrow. Radiolucent subchondral cysts are present as well as dense sclerotic bone. C, Osteoarthritis of the hands. Both the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints in both hands show protuberances along their lateral margins representing osteophyte formation in the joints. The DIP protuberances are called Heberden nodes, and the PIP protuberances are called Bouchard nodes. (A from Kumar V, Abbas AK, Fausto N, Mitchell RN: Robbins Basic Pathology, 8th ed, Philadelphia, Saunders Elsevier, 2007, p 820, Fig. 7-18 on the right; B from Marx J: Rosen's Emergency Medicine Concepts and Clinical Practice, 7th ed, Philadelphia, Mosby Elsevier, 2010, p 622, Fig. 53.5; C from Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 636, Fig. 20-59.)

OA: osteophytes at joint margins
OA: clefs, subchondral cysts
OA: no joint fusion

OA: pain MC complaint; aggravated by movement
OA: joint stiffness after inactivity
OA fingers: Heberden nodes; DIP joint enlargement/pain
OA fingers: Bouchard nodes; PIP joint enlargement/pain

3. Clinical findings

a. Pain is the most common complaint
   (1) Osteophytes irritate the synovial lining.
   (2) Bone is rubbing on bone.
   (3) Hip OA may refer pain to the groin.
   (4) Pain is aggravated with movement of the joint.
       • Due to secondary synovitis from osteophytes
b. Joint stiffness occurs after inactivity.
   (1) Waking up in the morning
   (2) After sitting

   c. Crepitus of the joint with movement, decreased range of motion

   d. Hand involvement (see Fig. 24-7C)
   (1) Enlargement of the distal interphalangeal (DIP) joints
       • Called Heberden nodes (osteophytes)
   (2) Enlargement of the proximal interphalangeal (PIP) joints (PIP)
       • Called Bouchard nodes (osteophytes)
Musculoskeletal and Soft Tissue Disorders

4. Diagnosis
   a. Imaging studies

5. Treatment
   a. Heat, decrease weight bearing, range of motion exercises
   b. Use of a cane
   c. Analgesics (NSAIDs, acetaminophen; do not use at the same time [refer to Chapter 20])
   d. Viscosupplementation (questionable usefulness)
      • Oral chondroitin sulfate, glucosamine
   e. Joint replacement

E. Neuropathic arthropathy (Charcot joint)

1. Definition—noninflammatory joint disease secondary to a neurologic disease
   • Loss of proprioception and deep pain sensation leading to recurrent trauma

2. Causes
   a. Diabetes mellitus (15% of cases)
      • Primarily affects the tarsometatarsal joint
   b. Syringomyelia (20%–25% of cases)
      • Primarily affects the shoulder, elbow, wrist joints
   c. Tabes dorsalis (10%–20% of cases)
      • Primarily affects the hip, knee, and ankle joints

3. Treatment
   a. Immobilization
   b. Pneumatic walking braces

F. Rheumatoid arthritis (RA)

1. Epidemiology
   a. Definition—systemic disorder associated with chronic joint inflammation that most commonly affects peripheral joints
   b. Occurs more often in women 30 to 50 years of age
   c. HLA-DR4 association
   d. ? Initial inciting agents
      • Epstein-Barr virus, parvovirus, human herpesvirus 6, *Mycoplasma*
   e. Risk factor for septic arthritis
      • Medications may suppress the immune system, making infections more likely to occur.

2. Pathogenesis of joint disease involves both type III and type IV reactions.
   a. One proposed mechanism is CD4 + helper T cells (cell-mediated type IV) are activated leading to release of proinflammatory agents (e.g., tumor necrosis factor).
   b. Inflamed synovial cells express an antigen that triggers B cells to produce rheumatoid factor (RF).
      • RF is an IgM autoantibody that has specificity for the Fc portion of IgG.
   c. RF and IgG join to form immunocomplexes (ICs; type III hypersensitivity).
   d. ICs activate the complement system to produce C5a, a chemotactic agent for neutrophils and other leukocytes to enter the joint space.
   e. Chronic synovitis and pannus formation eventually occur (Fig. 24-8A).
      • Pannus is granulation tissue formed within the synovial tissue by fibroblasts and inflammatory cells (refer to Chapter 3).
   f. Pannus proliferates and releases cytokines (e.g., ILs, TNF) that eventually destroy the articular cartilage leading to fusion of the joint by scar tissue (called ankylosis).

3. Clinical findings
   a. Symmetric involvement of second/third metacarpophalangeal (MCP) and PIP joints
      (1) Causes ulnar deviation, morning stiffness (see Fig. 24-8B)
      (2) Swan neck deformity (see Fig. 24-8C)
         • Flexion of the DIP joint
         • Extension of the PIP joint
      (3) Boutonnière deformity (see Fig. 24-8D)
         • Extension of the DIP joint
         • Flexion of the PIP joint
   b. Other joints commonly involved
      (a) Knees, cervical spine, hips
      (b) Shoulders, elbows

• Loss

• Pannus

• RF

• RA: activated CD4 + T cells release proinflammatory agents

• RA: women > men; HLA-DR4

• RA: B cells produce RF; IgM antibody against Fc portion of IgG

• RA: RF forms ICs with IgG → activate complement system

• Pannus (granulation tissue): releases cytokines that destroy articular cartilage

• Repair by fibrosis causes fusion of the joint (ankylosis)

• RA hand: MCP and PIP joints; bilateral ulnar deviation

• Swan neck: DIP flexed, PIP extended

• Boutonnière: DIP extended, PIP flexed
b. Lung disease
   - Chronic pleuritis with effusions, interstitial fibrosis

c. Hematologic disease
   (1) Anemia of chronic disease (ACD)
   (2) Felty syndrome
      - Autoimmune neutropenia and splenomegaly
   (3) Autoimmune hemolytic anemia (AIHA)

d. Carpal tunnel syndrome (see section V)
   - Entrapment of the median nerve under the transverse carpal ligament

e. Cervical spine
   (1) Entire cervical spine is frequently involved.
   (2) Subluxation of the atlantoaxial joint is particularly dangerous.
      (a) Possible compression of spinal cord
      (b) Possible compression of the vertebral artery causing stroke
f. Rheumatoid nodules
   (1) Occur on the extensor surface of the forearm and in the lungs
      • Caplan syndrome—rheumatoid nodules in lung plus pneumoconiosis
   (2) Fibrinoid necrosis is present in the center of the nodules (refer to Chapter 2)
   (3) Correlates with very high titer of RF

g. Cardiovascular disease
   (1) Fibrinous pericarditis
   (2) Aortitis
   (3) Immunocomplex small vessel vasculitis
      (a) Usually located around the ankles
      (b) Correlates with high RF titer

h. Popliteal (Baker) cyst behind the knee joint (see Fig. 24-8E)
   (1) Extension of the semimembranous bursa into the posterior joint space because of increased intra-articular pressure
   (2) Sometimes ruptures and dissects into the calf
      • Frequently misdiagnosed as deep venous thrombosis (DVT)
   (3) Sometimes confused with popliteal artery aneurysm (pulsatile)
      • Diagnosis easily clarified with ultrasound

4. Laboratory findings
   a. Positive serum antinuclear antibody (ANA) test (30% of cases)
   b. Positive serum RF (70%–90% of cases)
   c. Normal to increased serum C3, decreased synovial C3
   d. Increased serum total protein
      (1) Due to increase in γ-globulins (IgG) in chronic inflammation
      (2) Polyclonal gammopathy on serum protein electrophoresis (see Fig. 3-2B)

5. Treatment
   a. Physical therapy emphasizing movement of joints
      • Swimming pool exercises are very useful.
   b. Initial treatment with NSAIDs (aspirin) to relieve inflammation
   c. Early treatment with disease-modifying drugs
      (1) Minimizes long-term joint damage
      (2) Methotrexate (most commonly used agent)
      (3) Cyclosporine, corticosteroids, hydroxychloroquine, gold compounds
      (4) Tumor necrosis factor (TNF)-α blockers are effective if disease-modifying drugs are ineffective

G. Sjögren syndrome (SS)
   1. Epidemiology and pathogenesis
      a. Definition—autoimmune destruction of minor salivary glands and lacrimal glands
      b. Female dominant autoimmune disease
   2. Clinical findings
      a. Rheumatoid arthritis
      b. Keratoconjunctivitis sicca
         (1) Dry eyes described as "sand in my eyes"
         (2) Due to autoimmune destruction of the lacrimal glands
      c. Xerostomia or dry mouth
         (1) Autoimmune destruction of the minor salivary glands
         • "Doctor, I can't swallow dry crackers."
         (2) Dental caries
   3. Laboratory findings
      a. Positive serum ANA in most cases
      b. Positive serum RF (90% of cases)
      c. Anti–SS-A antibodies (anti-Ro; 70%–95% of cases)
      d. Anti–SS-B antibodies (anti-La; 60%–90% of cases)
   4. Confirm with a lip biopsy
      • Must demonstrate lymphoid destruction of the minor salivary glands
   5. Treatment
      a. Artificial tears
      b. Pilocarpine or cyclosporine eye drops
      c. Cevimeline (cholinergic agent with muscarinic agonist activity)
         • Used for dry mouth

Rheumatoid nodules: extensor surface forearms/lungs
RA cardiovascular: pericarditis, aortitis, vasculitis
Baker cyst: outpouching semimembranous bursa into posterior joint space
RA lab: positive serum RF, ANA, polyclonal gammopathy
SS: destruction of minor salivary glands/lacrimal glands; female dominant
SS: RA, dry eyes, dry mouth
Lab: positive serum ANA, RF, anti–SS-A/anti–SS-B; lip biopsy confirms
H. Juvenile rheumatoid arthritis (JRA)

1. Epidemiology
   a. Occurs in children <16 years of age
   b. More common in girls than boys
   c. RF is usually absent.
2. Still disease (20% of cases)
   a. Commonly presents as an “infectious disease”
   b. Fever, rash, polyarthritis
   c. Generalized painful lymphadenopathy
   d. Neutrophilic leukocytosis
3. Polyarticular JRA (40% of cases)
   - Disabling arthritis predominates.
4. Pauciarticular JRA (40% of cases)
   a. Arthritis limited to a few joints.
   b. Uveitis with the potential for blindness

I. Gouty arthritis

1. Epidemiology
   a. Definition—tissue deposition of monosodium urate (MSU) due to prolonged hyperuricemia
   b. Occurs more often in men >30 years of age (95% of cases)
   c. Uncommon in women before menopause (5% of cases)
   d. Primary gout arises from inborn errors of metabolism involving purine metabolism.
      - Example—deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) in Lesch-Nyhan syndrome (refer to Chapter 6)
   e. Secondary causes are more common causes of gout.
      (1) Underexcretion of uric acid (UA) in kidneys (80%–90% of cases)
          - Examples—lead (Pb) poisoning, alcoholism, diets rich in red meat, seafood, beer, thiazides
      (2) Overproduction of uric acid (increased nucleated cell turnover; 10%–20% of cases)
          - Examples—treating leukemia, psoriasis
   f. Clinical conditions commonly associated with gout
      (1) Urate nephropathy, renal stones (refer to Chapter 20)
      (2) Hypertension (HTN), coronary artery disease (CAD)
      (3) Lead poisoning
          - Produces interstitial nephritis, which interferes with uric acid excretion
2. Recurrent acute attacks of gout are the rule.
   a. Most commonly involve the first metatarsophalangeal joint (MTP; called podagra; joint in the foot with the most trauma)
      - Polyarticular involvement occurs in 10% to 15% of cases.
   b. Often precipitated by dietary indiscretions, illness, exercise, emotional stress
   c. Free UA crystals in the synovial fluid are proinflammatory.
      (1) Activate synovial cells, leukocytes, and the complement cascade; the latter releases C5a, which attracts neutrophils into the joint producing acute inflammation
         - Neutrophils also phagocytose uric acid crystals.
      (2) Another common site for acute gout is the extensor tenosynovium on the dorsum of the midfoot.
   d. Clinical findings acute gout
      (1) Sudden onset of severe pain in the big toe
      (2) Hot, red, and swollen joint (Fig. 24-9A)
      (3) Fever, tachycardia, and other constitutional signs
   e. Laboratory findings
      (1) Hyperuricemia
         (a) Increased serum uric acid >7 mg/dL in men
         (b) Increased serum uric acid >6 mg/dL in women
      (2) Absolute neutrophilic leukocytosis
      (3) Joint aspiration is confirmatory.
         - Negatively birefringent MSU crystals
3. Chronic gout
   a. Chronic gout is likely to occur if gout is poorly controlled.
   b. UA crystals accumulate in the joint and produce a tophus.
      (1) MSU crystals leak into the soft tissue around the joint (see Fig. 24-9B and C).
      (2) Distal joints are preferential sites.
24-9: A, Acute gouty arthritis involving the left big toe. Note the erythema and swelling of the joint. B, Digit with white, tophaceous crystals beneath the skin. C, Tophus over the proximal interphalangeal joint. Note white discoloration beneath the skin. This may be confused with Bouchard nodes in osteoarthritis. D, Gout. Metatarsal-phalangeal joint of the great toe shows an erosive arthritis. The hallmark of gout is the sharply margined, juxta-articular erosion, which may have a sclerotic border (solid white arrows) and overhanging edges, as in this case. E, Chondrocalcinosis. Chondrocalcinosis refers only to calcification of the articular cartilage (solid white arrows) or fibrocartilage. If this patient had acute pain, redness, swelling, and limitation of motion, the combination would be called pseudogout. (A from Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 634, Fig. 20-55; B from Bouloux, P: Self-Assessment Picture Tests Medicine, Vol. 3, London, Mosby-Wolfe, 1997, p 13, Fig. 25; C from Goldman L, Schafer AI: Cecil's Medicine, 24th ed, Philadelphia, Saunders Elsevier, 2012, p 1740, Fig. 281-4D; D from Herring W: Learning Radiology Recognizing the Basics, 2nd ed, Philadelphia, Elsevier Saunders, 2012, p 257, Fig. 23-16; E, from Marx J: Rosen’s Emergency Medicine Concepts and Clinical Practice, 7th ed, Philadelphia, Mosby Elsevier, 2010, p 1482, Fig. 114.8.)

(3) MSU excites a brisk granulomatous reaction in the periarticular tissue.
   - Microscopic sections reveal numerous multinucleated giant cells within which are MSU crystals that polarize.
   c. Tophi destroy subjacent bone, causing erosive arthritis that breaks down bone and leaves overhanging edges (sometimes called rat bites; see Fig. 24-9D).

4. Treatment
a. Modify diet to eliminate foods high in purine
b. Moderate alcohol intake (refer to Chapter 7)
c. Drugs
   (1) Treatment for acute gouty arthritis
      a. NSAIDs (e.g., indomethacin, ibuprofen) or colchicine
      b. Intra-articular corticosteroids or systemic corticosteroids if intolerant to the drugs just mentioned
   (2) Chronic treatment to prevent acute gout
      a. Goal is to normalize serum uric acid.
      b. Uricosuric agents for underexcretors (e.g., sulfinpyrazone)
         • If 24-hour urine collection of uric acid <700 mg
      c. Allopurinol or febuxostat (xanthine oxidase inhibitors) for overproducers
         • If 24-hour urine collection of uric acid >900 mg
      d. Pegloticase (pegylated uricase) for refractory tophaceous gout

J. Calcium pyrophosphate dihydrate deposition (CPPD) disease
1. Epidemiology
   a. Deposition of calcium pyrophosphate in tissues
      (1) Deposition in cartilage (called chondrocalcinosis)
      (2) Less commonly in tendons, ligaments, synovial tissue, bursa

Tophus: erosive arthritis; bone disintegrates, leaving overhanging edges

Nonpharmacologic Rx: eliminate high-purine diet; moderate alcohol intake

Pharmacologic Rx for acute gout: NSAIDs or colchicine

Drugs to prevent gout: uricosuric agents for underexcretors; allopurinol for overproducers

CPPD disease: calcium pyrophosphate deposited in tissues
b. Incidence of CPPD increases in the presence of:
   (1) Hemochromatosis, hemosiderosis
      (a) Pyrophosphate inhibitor is increased in these diseases.
      (b) Causes an increase in inorganic pyrophosphate concentration
   (2) Primary hyperparathyroidism (HPTH)
      • Increase in calcium is responsible.

c. Four variants are associated with the disease.

d. Most common variant is osteoarthritis (OA).
   (1) It is most common in the elderly.
      • Present in 50% of patients who are over the age of 85 years old
   (2) It is a degenerative arthritis with symptoms similar to OA.
   (3) Most common joint involved is the knee.
   (4) Calcium pyrophosphate crystals deposit in articular cartilage (usually knee).
      (a) Crystals produce linear deposits in articular cartilage (see Fig. 24-9E).
      (b) It is called chondrocalcinosis when it deposits in articular cartilage.
         • If the patient has acute pain, redness, swelling, and limitation of motion in the joint, the combination is called pseudogout.
   (5) Crystals phagocytosed by neutrophils show positive birefringence.
   (6) Treatment
      • NSAIDs, colchicine, arthroscopic surgery

K. Seronegative spondyloarthropathies (spondyloarthritis)

1. Definition—family of overlapping syndromes that are linked in disease manifestations and genetic susceptibility.

2. Characteristics
   a. Rheumatoid factor (RF) negative (meaning of seronegative)
   b. Involve the axial skeleton (spondylitis)
   c. Individuals HLA-B27 positive
   d. Male dominant with reactive arthritis (10:1) and ankylosing spondylitis (3:1)
   e. Sacroiliitis with or without peripheral arthritis

3. Types of spondyloarthritis
   a. Ankylosing spondylitis (AS)
   b. Reactive arthritis
      (1) Reiter syndrome associated with Chlamydia trachomatis urethritis
      (2) Arthritis associated with gastroenteritis due to Shigella flexneri, Salmonella typhimurium, Campylobacter jejuni, Yersinia enterocolitica
   c. Psoriatic arthritis
   d. Enteropathic arthritis
      • Associated with ulcerative colitis, Crohn disease

4. Ankylosing spondylitis (AS)
   a. Initially targets the sacroiliac joint in young men
      • Bilateral sacroiliitis with morning stiffness
   b. Eventually involves the vertebral column
      (1) Fusion of vertebrae (bamboo spine) causes forward curvature of the spine (kyphosis; Fig. 24-10A and B).
      (2) Kyphosis interferes with chest wall movement.
         (a) Nonpulmonary restrictive lung disease
         (b) Schober test evaluates degree of restriction to forward bending.
   c. Aortitis with aortic regurgitation
   d. Anterior uveitis (20% of cases)
      (1) Blurry vision
      (2) Potential for blindness
   e. Treatment
      (1) NSAIDs
      (2) Disease-modifying agents
         • Methotrexate, cyclosporine, corticosteroids
      (3) TNF-α inhibitors
         • Extremely effective in slowing down progression of the disease

5. Reiter syndrome
   a. Urethritis due to Chlamydia trachomatis
   b. Arthritis and Achilles tendon periostitis
      • Bone formation at the junction of the Achilles tendon with the plantar fascia is a confirmatory radiologic sign (see Fig. 24-10C).
   c. Conjunctivitis (noninfectious; Fig. 24-11D)
24-10: A, Man with ankylosing spondylitis. The patient cannot bend forward owing to fusion of the vertebrae. B, Radiograph showing fused vertebrae (bamboo spine) in ankylosing spondylitis. C, New bone formation at the junction of the Achilles tendon with the plantar fascia in a patient with Reiter syndrome. D, Sterile conjunctivitis (note redness of the conjunctiva) in a patient with Reiter syndrome. E, Circinate balanitis in Reiter syndrome. Shallow ulcerations are noted on the distal shaft and glans penis. F, Psoriatic arthritis of the hand. Psoriatic arthritis typically involves the small joints of the hands, especially the distal interphalangeal (DIP) joints (solid white arrows) leading to telescoping of one phalanx into another (pencil-in-cup deformity).

24-11: A, Erythema chronicum migrans in a patient with Lyme disease. Raised central area is the site of the tick bite. Concentric area of erythema surrounds the bite site. B, Babesia microti. RBCs in the peripheral blood show a predominance of ring forms. Clusters of extraerythrocytic parasites (arrows) are also seen free in the plasma.
d. Circinate balanitis
  • Rash on the distal shaft and glans penis that appears as vesicles, shallow ulcerations, or both (see Fig. 24-10E)

6. Psoriatic arthritis
   a. Sausage-shaped DIP joints (finger or toe)
   b. Radiographs show erosive joint disease.
      • “Pencil-in-cup” deformity (see Fig. 24-10F)
   c. Extensive nail pitting (see Fig. 25-9)

I. Septic arthritis
1. Staphylococcus aureus
   a. Most common nongonococcal cause of septic arthritis
   b. Treatment
      • Nafcillin + cephalosporin (third generation)

2. Neisseria gonorrhoeae
   a. Most common cause of septic arthritis in urban populations
   b. May produce disseminated gonococemia
      (1) More common in young women
         (a) Deficiency of C6–C9 predisposes to dissemination
         (b) These complement components are required to kill the bacteria.
      (2) Septic arthritis (knee)
      (3) Tenosynovitis (wrists and ankles)
      (4) Dermatitis (pustules on wrists or ankles)
      (5) Treated with ceftriaxone

3. Lyme disease (LD)
   a. Epidemiology and pathophysiology
      (1) *Borrelia burgdorferi* (spirochete) is transmitted by the bite of an *Ixodes* tick.
         • Different ticks produce the disease in North America, Europe, and Asia.
      (2) Adult ticks acquire the spirochete by feeding on an infected white-tailed deer (reservoir for the disease).
      (3) Nymphs acquire the spirochete by feeding on an infected white-footed mouse.
         • Nymphs are responsible for the majority of human cases (90%), particularly in the summer months.
      (4) Most cases in the United States occur in the Northeast and the Upper Midwest.
      (5) LD is the fastest growing vector-borne disease in the United States.
      (6) The organism has a strong tropism for the skin, central nervous system (CNS), joints, heart, and eyes.
      (7) Affects all ages and sexes, but has a predilection for the white population (higher exposure rate to ticks than other races).
      (8) Inflammation related to the organism itself, cross-reacting antibodies to spirochetal proteins against human tissue (type II hypersensitivity reaction [HSR]), and immunocomplexes (type III HSR) have been implicated.

   b. Clinical presentation
      (1) Early localized infection (first month)
         (a) Erythema migrans (EM) develops on the skin 1 to 2 weeks after tick removal (see Fig. 24-11A).
            • Vesicular red center (site of tick bite) with a red, expanding lesion with concentric circles (“bull’s-eye” lesion)
            • Single (most common) or multiple lesions (not from multiple bites)
            • Only phase of Lyme disease where empirical therapy is recommended based on a clinical diagnosis without laboratory confirmation.
            • Pathognomonic skin lesion of LD
         (b) Common complaints include fever, flu-like symptoms (e.g., fever, chills, headache, arthralgia), and neck stiffness.
         (c) One third of patients with EM do not develop further symptoms, whereas two thirds progress to further stages.
      (2) Early disseminated disease (weeks to months post–tick bite)
         (a) Further spread to skin, lymphatics (lymphadenopathy)
         (b) Migratory polyarticular arthritis (involving bursa, tendons, joints) evolving into monoarticular (e.g., knee [MC], wrist)
         (c) Neuroborreliosis with cranial neuropathy (particularly facial nerve palsy bilaterally), meningeal irritation (nuchal rigidity)
(3) Chronic disease (months to years after infection)
   (a) Disabling arthritis (e.g., knee)
   (b) Subacute encephalopathy, encephalomyelitis, peripheral neuropathies
   (c) Other findings include myocarditis, pericarditis, iritis, keratitis, optic neuritis

c. Diagnosis for other stages of Lyme disease (excluding EM)
   (1) ELISA (enzyme-linked immunosorbent assay) testing first as screen (highly sensitive)
   (2) Western blot assay for equivocal or positive ELISA test
      • High specificity (94%–96%)
   (3) PCR (polymerase chain reaction) test is also available

d. Treatment
   (1) Adults—doxycycline (most often used), amoxicillin, ceftriaxone
      • Use of doxycycline also covers the potential for coinfection with Ehrlichia chaffeensis (Chapter 25)
   (2) Children—amoxicillin

e. Babesiosis
   (1) Intraerythrocytic (sometimes extrerythrocytic) protozoal disease due to Babesia microti
   (2) Secondary infection transmitted by Ixodes
      • Often presents concurrently with Lyme disease
   (3) Fever, headache, hemolytic anemia
   (4) Diagnosis
      (a) Wright- or Giemsa-stained peripheral smear to look for organisms in RBCs or free in plasma (see Fig. 24-11B)
      (b) Serologic testing
   (5) Treatment
      • Atovaquone + azithromycin

4. Septic arthritis and tendinitis due to cat/dog bite
   a. Causal agent is Pasteurella multocida, a gram-negative coccobacillus with bipolar staining.
   b. Most common infection is secondary to animal injury.
      (1) Cat bites are more common than dog bites.
      (2) Approximately 60% to 90% of cats normally have the organism in their mouth.
      (3) Only 5% to 15% of dogs get infected.
   c. Types of infection
      (1) Cellulitis (most common)
      (2) Septic arthritis/tendinitis
      (3) Osteomyelitis
      (4) Endocarditis, meningitis
d. Rapid onset of infection at the bite site (usually within 24 hours)
e. Treatment
   • Penicillin G, ampicillin, amoxicillin-clavulanate

III. Muscle Disorders

A. Muscle fibers
   1. Innervation of the muscle determines fiber type.
   2. Type I fibers
      a. Slow twitch (red) fibers
         (1) Slow contraction but repetitive
         (2) Do not fatigue easily (good for aerobic activities)
         (3) Example—long muscles in the back
      b. Rich in mitochondria, myoglobin, and oxidative enzymes
      c. Weak in ATPase enzymes
   3. Type II fibers
      a. Fast twitch (white) fibers
         (1) Fast contraction, but fatigue easily
         (2) Specialized for fine, skilled movement
         (3) Examples—extraocular muscles, some muscles in the hand
      b. Poor in mitochondria, myoglobin, oxidative enzymes
      c. Rich in ATPase enzymes

B. Muscle disorders
   1. Pathogenesis of muscle weakness
      a. Abnormality in the motor neuron pathways
         • Example—poliomyelitis

Chronic disease: disabling arthritis (knee), encephalopathy, neuropathy, myocarditis
Babesiosis: tick-transmitted hemolytic anemia; may accompany Lyme disease
P. multocida: septic arthritis/tendinitis due to cat > dog bite
Type I: slow twitch (red); rich in mitochondria, oxidative enzymes; poor in ATPase enzymes
Type II: fast twitch (white); poor in mitochondria, oxidative enzymes; rich in ATPase enzymes
Muscle weakness: motor neuron, neuromuscular synapse, muscle dysfunction
b. Abnormality in the neuromuscular synapse
   • Example—myasthenia gravis

2. Neurogenic atrophy
   a. Motor neuron or its axon degenerates.
   b. Produces atrophy of type I and II fibers

3. *Trichinella spiralis* infection
   a. Epidemiology
      (1) Causative agent *T. spiralis* (nematode)
      (2) Transmission
         (a) Eating raw or poorly cooked pork containing the encysted larvae in muscle
         (b) Common on pig farms where pigs are fed uncooked garbage
         (c) Bear and seal meat are other sources
         (d) Often mixed in with deer meat to make sausage
         (e) Larva excyst and develop into adult worms within small intestine mucosa.
            • Eggs hatch within the adult female worm.
            • Larvae are released into the bloodstream.
            • Larvae encyst in striated muscle (Fig. 24-12A).
            • Commonly undergo dystrophic calcification, which is visible on x-ray
            (f) Larvae die if deposited in other sites.
   b. Trichinosis
      (1) Muscle pain
      (2) Periorbital edema (larva)
      (3) Splinter hemorrhages in nails
      (4) Complications
         • Myocarditis, encephalitis
      (5) Diagnosis
         • Pronounced eosinophilia, muscle biopsy
      (6) Treatment is albendazole.

4. Invasive infections due to group A streptococcus
   a. Types of invasive infections
      (1) Necrotizing fasciitis
      (2) Myositis
      (3) Streptococcal toxic shock syndrome (STSS)
   b. Related to various toxins produced by the streptococcus
      (1) Pyrogenic exotoxin A
         • Superantigen associated with STSS
      (2) Exotoxin B
         • Protease that destroys tissue associated with necrotizing fasciitis
   c. Treatment
      • Intravenous penicillin G + clindamycin
   d. Death rates range from 20% to 100%.

5. *Clostridium tetani*: tetanus
   a. Gram-positive anaerobic rod that lives in the soil
   b. Transmission: spores in soil enter via:
      (1) Closed wounds
      (2) Skin-popping among intravenous drug abusers (IVDA)
      (3) Umbilical cord/circumcision site in newborns
   c. Germination of spores is enhanced if necrosis co-occurs with a poor blood supply.
   d. Organisms are rarely isolated in the wound.
   e. Bacterial proliferation in the wound releases a neurotoxin called tetanospasmin
      (virulence factor).
      (1) *No* inflammatory exudate
      (2) Toxin is carried intra-axonally (retrograde) to the CNS.
      (3) Toxin binds to ganglioside receptors of spinal afferent fibers.
         • Inhibits release of inhibitory neurotransmitters glycine and γ-aminobutyric acid (GABA) in the spinal cord
      (4) Causes sustained motor stimulation of all voluntary muscles
   f. Clinical findings
      (1) Incubation period
         • Few days to 2 months
24-12: A, *Trichinella spiralis*, cross-section of a larva in gastrocnemius muscle. B, Risus sardonicus in a person with tetanus due to *Clostridium tetani*. C, Gram stain of *Clostridium perfringens* in a wound specimen. Note the rectangular shape of the rods, the presence of many decolorized rods appearing gram-negative, and the absence of blood cells. D, Duchenne muscular dystrophy showing pseudohypertrophy of the calf. E, Duchenne muscular dystrophy showing a child performing the Gower maneuver in order to stand up. F, Myotonic dystrophy. The patient shows frontal balding, drooping of the eyelids, sagging of the facial muscles, and atrophy of the sternocleidomastoid muscles. G, Patient with myasthenia gravis showing ptosis of the left eye (left) followed by opening of the eye (right) after intravenous injection of Tensilon. (A from McPherson R, Pincus M. *Henry's Clinical Diagnosis and Management by Laboratory Methods*, 22nd ed, Philadelphia, Saunders, 2011, p 1221, Fig. 62-18E; B and C from Murray PR, Rosenthal KS, Pfaller MA. *Medical Microbiology*, 6th ed, Philadelphia, Mosby Elsevier, 2009, pp 383, 379, respectively, Figs. 39.4, 39.1, respectively; D to G from Perkin GD. *Mosby's Color Atlas and Text of Neurology*, St. Louis, Mosby, 2002, pp 269, 269, 272, 263, respectively, Figs. 14-10, 14-12, 14-16, 14-5A, B, respectively.)
(2) It begins with muscle stiffness in the jaw.
   (a) Lockjaw (inability to open the mouth)
   (b) Risus sardonicus (perpetual, sardonic smile on the face; see Fig. 24-12B)
(3) Slightest stimulus causes generalized, painful muscle contractions.
(4) Contractions of back muscles produce opisthotonus (painful arching of the back).
(5) Patients are mentally alert.

6. *Clostridium perfringens*
   a. Gram-positive anaerobic rod (see Fig. 24-12C)
      (1) Virulence factor
         (a) Produces α-toxin (lecithinase)
         (b) Damages cell membranes (produces RBC hemolysis)
      (2) Normal flora in the vagina and colon
   b. Gas gangrene (myonecrosis)
      (1) Formation of gas bubbles in tissue (crepitus)
         (a) Gas produced by organism’s anaerobic metabolism
         (b) Gas is noted on radiographs (e.g., wet gangrene in a diabetic foot; see Fig. 2-15F)
      (2) Pain, edema, cellulitis, foul smelling exudate in the wound
      (3) Hemolytic anemia, jaundice, shock, disseminated intravascular coagulation, and renal failure are common
      (4) Treatment
         (a) Wound tissue is débrided.
         (b) Drug therapy includes penicillin G ± clindamycin.
         (c) Hyperbaric oxygen therapy is extremely useful.
   c. Other infections
      (1) Food poisoning
         (a) Heat-resistant spores survive cooking and germinate in food.
         (b) Organisms proliferate rapidly in reheated foods.
            • Meat dishes like beef and turkey
         (c) Enterotoxin (superantigen similar to *Staphylococcus aureus*) is the virulence factor.
            • Produced during spore formation in the gut
         (d) Self-limited
      (2) Septicemia
      (3) Intra-abdominal infections—peritonitis, gangrenous cholecystitis
      (4) Pelvic inflammatory disease (PID)
      (5) “Backroom abortion” septic endometritis

7. Duchenne muscular dystrophy (DMD)
   a. Epidemiology
      (1) X-linked recessive (XR)
      (2) Incidence 1:3500 male births
   b. Pathogenesis
      (1) Absence of dystrophin due to frameshift mutation of the dystrophin gene on the X chromosome
         (a) Dystrophin normally anchors actin to membrane glycoprotein.
         (b) Becker type has deficiency/defective dystrophin.
      (2) Most common childhood muscular dystrophy
      (3) Progressive degeneration of type I and II fibers
      (4) Fibrosis and infiltration of muscle tissue by fatty tissue
         • Produces pseudohypertrophy of calf muscles (see Fig. 24-12D)
c. Clinical findings
   (1) Symptoms occur between 2 and 5 years of age.
   (2) Weakness and wasting of pelvic muscles
      (a) Child places hands on the knees for help in standing (Gower maneuver; see Fig. 24-12E).
      (b) Waddling gait (duck-like)
   (3) Cardiac involvement is present and causes a cardiomyopathy leading to heart failure and arrhythmias.
   (4) Respiratory muscle weakness eventually leads to respiratory failure.
   (5) Death usually occurs by 20 years of age.

d. Laboratory findings
   (1) Serum creatine kinase (CK) is increased at birth (20 to 100 times greater).
      • It progressively declines as the muscle degenerates over time.
   (2) Female carriers have increased levels of serum CK.

e. Diagnosis
   (1) Muscle biopsy, electromyography (EMG)
   (2) DNA testing is available (Western blot)
      • Diagnosed prenatally via chorionic villous sampling

f. Treatment
   • Mainly supportive

8. Myotonic dystrophy (MD)
   a. Epidemiology and pathogenesis
      (1) Autosomal dominant
      (2) Most common adult muscular dystrophy
      (3) Trinucleotide repeat disorder (refer to Chapter 6)
         (a) Genetic disorder encoded on chromosome 19
         (b) Expanded CTG repeat within the noncoding 3’ untranslated region of the myotonic dystrophy protein kinase gene
      (4) Selective atrophy of type I fibers
   b. Clinical findings
      (1) Facial muscle weakness (see Fig. 24-12F)
         • Sagging face, problem in closing the mouth
      (2) Percussion and grip myotonia
         • Inability to relax muscles (sustained grip)
      (3) Frontal balding (see Fig. 24-12F), cataracts
      (4) Testicular atrophy, glucose intolerance
      (5) Cardiac involvement (conduction defects)
   c. Increased serum CK
   d. Diagnosis
      • EMG, muscle biopsy
   e. No specific treatment
   f. Muscle wasting and defects in cardiac function are the most common causes of death.

9. Myasthenia gravis (MG)
   a. Epidemiology
      (1) Afflicts men in sixth and seventh decades of life
      (2) Afflicts women in second and third decades of life
   b. Pathogenesis
      (1) Definition—autonomic disorder of postsynaptic neuromuscular transmission
      (2) Autoantibody against acetylcholine (ACh) receptors
         (a) Type II hypersensitivity reaction
         (b) Antibodies inhibit and/or destroy the receptors.
         (c) Decrease in functional ACh receptors
      (3) Antibody is synthesized in the thymus.
         • Thymic hyperplasia with germinal follicles (85% of cases)
   c. Clinical findings
      (1) Fluctuating muscle weakness
         • Worsened with exercise, improved with rest
      (2) Ptosis most common initial finding (see Fig. 24-12G, left).
         • Diplopia is also common and is due to eye muscle weakness.
      (3) Weakness in proximal muscles, diaphragm, neck extension and flexion (85% of cases)
      (4) Dysphagia for solids and liquids
         • Occurs in the upper esophagus (striated muscle)
IV. Soft Tissue Disorders

A. Fibromatosis
1. Non-neoplastic, proliferative connective tissue disorder
2. Fibrous infiltrations in tissue (usually muscle).
3. Dupuytren contracture (Fig. 24-13)

Dupuytren contracture: fibromatosis of palmar fascia

Table 24-2: Soft Tissue Tumors

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>LOCATION</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoma (see Fig. 9-1B)</td>
<td>Trunk, neck, proximal extremities</td>
<td>Most common benign soft tissue tumor Arises in subcutaneous tissue (? after trauma to tissue) No clinical significance</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>Thigh, retroperitoneum</td>
<td>Most common adult sarcoma Lipoblasts identified with fat stains</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>Thigh, upper limb</td>
<td>May arise after irradiation</td>
</tr>
<tr>
<td>Dermatofibroma</td>
<td>Lower extremities</td>
<td>Benign, nonencapsulated proliferation of spindle cells confined to dermis Red nodule that umbilicates (has a central dimple) when squeezed</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>Retroperitoneum, thigh</td>
<td>Associated with radiation therapy and scarring</td>
</tr>
<tr>
<td>Rhabdomyoma</td>
<td>Heart, also tongue and vagina</td>
<td>Benign heart tumor associated with tuberous sclerosis</td>
</tr>
<tr>
<td>Embryonal rhabdomyosarcoma</td>
<td>Penis and vagina</td>
<td>Most common sarcoma in children Grape-like, necrotic mass protrudes from penis or vagina</td>
</tr>
<tr>
<td>Leiomyoma (see Fig. 22-10F)</td>
<td>Uterus, stomach</td>
<td>Most commonly located in uterus Most common benign tumor in gastrointestinal tract</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Gastrointestinal tract, uterus</td>
<td>Most common sarcoma of gastrointestinal tract and uterus</td>
</tr>
<tr>
<td>Neurofibrosarcoma</td>
<td>Major nerve trunks</td>
<td>Associated with neurofibromatosis</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>Around joints</td>
<td>Does not arise from synovial cells in joints but from mesenchymal cells around joints Biphasic pattern: epithelial cells forming glands + intervening spindle cells</td>
</tr>
</tbody>
</table>
### TABLE 24-3 Selected Orthopedic Disorders

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>DISCUSSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colles fracture (see Fig. 24-14A)</td>
<td>Common fracture when falling on outstretched hand Fracture of distal radius with or without fracture of ulnar styloid</td>
</tr>
<tr>
<td>Rotator cuff tear (see Fig. 24-14B)</td>
<td>Components: tendon insertions of supraspinatus, infraspinatus, teres minor, subscapularis muscles Pain/weakness with active shoulder abduction Diagnosis: arthrography, MRI Treatment: physical therapy, arthroscopic surgery</td>
</tr>
<tr>
<td>Tennis elbow</td>
<td>Causes: racquet sports, repetitive use of a hammer or screwdriver, arm wrestling (top roll; pronation of forearm; palm faces down) Pain where extensor muscle tendons insert near the lateral epicondyle (lateral epicondylosis) of the distal radius; pain when gripping something or pronating the forearm Treatment: NSAIDs, rest, local injection with corticosteroids, localized pressure</td>
</tr>
<tr>
<td>Golfer’s elbow</td>
<td>Pain where the flexor muscle tendons insert near the medial epicondyle (medial epicondylosis) of the distal radius Pain duplicated by flexing hand muscles and supinating the arm (hook in arm wrestling movement; palm faces up) Treatment: NSAIDs, rest, local injection with corticosteroids, localized pressure</td>
</tr>
<tr>
<td>De Quervain tenosynovitis (see Fig. 24-14C)</td>
<td>Chronic stenosing tenosynovitis of the first dorsal compartment of the wrist; overuse of the hands and wrist; first dorsal compartment has abductor pollicis longus and extensor pollicis brevis Excessive friction thickens tendon sheath causing stenosis of the osseofibrous tunnel Pain on the radial aspect of the wrist is aggravated by moving the thumb Finkelstein test: patient puts thumb in the palm, closes fist, tilts hand toward little finger (ulnar deviation) causes pain in the first dorsal compartment Treatment: corticosteroid injection, spica splint</td>
</tr>
<tr>
<td>Ganglion (synovial) cyst (see Fig. 24-14D)</td>
<td>Bulge on the dorsum of the wrist when the wrist is flexed More common in women than in men Cyst communicates with synovial sheaths on the dorsum of the wrist Treatment: aspiration, excision by arthroscopy</td>
</tr>
<tr>
<td>Compartment syndrome (see Fig. 24-14E)</td>
<td>Increase of pressure in a confined space (fascial compartment). Pressure reduces perfusion, which may cause ischemic contractures of the muscle(s) Most common locations are anterior and posterior compartments in the leg and the forearm muscle compartment 5 Ps: pain, paresthesias, pallor, paralysis, pulselessness Risk factors: fractures, injuries to arteries/soft tissue, excessive use of the muscles (cyclists, arm wrestlers) Volkman ischemic contracture: displaced supracondylar fracture of the distal humerus causing compression of the brachial artery and median nerve; forearm muscles (superficial and deep flexor muscles) may undergo contracture; although most of the muscles are innervated by the median nerve, the flexor carpi ulnaris is innervated by the ulnar nerve Diagnosis: measure pressures Treatment: fasciotomy if pressure cannot be relieved with supportive therapy (ice packs)</td>
</tr>
<tr>
<td>Carpal tunnel syndrome (Fig. 24-14F and G)</td>
<td>Entrapment syndrome of the median nerve in the transverse carpal ligament of the wrist Causes: rheumatoid arthritis and pregnancy most common causes. Other causes: obesity, excessive use of hands, acromegaly, amyloidosis Pain, numbness, or paresthesias in the thumb, index finger, 2nd finger, 3rd finger, and the radial side of 4th finger; thenar atrophy produces “ape hand” appearance Diagnosis: nerve conduction; electromyography Phalen maneuver: gently flexing of the wrist as far as possible and holding this position reproduces the findings within 1 minute Tinel sign: light tapping over the transverse carpal ligament produces numbness and tingling in the median nerve Treatment: wrist splint at night, corticosteroid injection, surgery</td>
</tr>
<tr>
<td>Intervertebral disk disease (see Fig. 24-14H)</td>
<td>Degeneration of fibrocartilage/nucleus pulposus; ruptured disk material may herniate posteriorly and compress the nerve root and/or spinal cord Radicular pain; leg pain aggravated by straight leg raising Herniation of L3–L4 disk: loss of knee jerk (femoral nerve L2–L4) Herniation of L4–L5 disk: no loss of reflexes (ankle and knee reflexes intact) Herniation of L5–S1 disk: loss of ankle reflex (tibial nerve L4–S3) Treatment: physical therapy, traction, surgery</td>
</tr>
</tbody>
</table>
### Knee joint injuries (see Fig. 24-14i and j)
- **Valgus injury**: angulation away from the midline
- Lateral originating force is applied to the knee (e.g., clipping injury in football)
- McMurray test: meniscus injuries
- Anterior and posterior draw test: cruciate injuries
  - "Unhappy triad": most common internal derangement of the knee joint; valgus injury (acute): damage to the lateral meniscus, medial collateral ligament, anterior cruciate ligament; if chronic, the medial meniscus is more commonly injured than the lateral meniscus

**Treatment**: physical therapy, arthroscopic surgery

### Scoliosis (see Fig. 24-14K)
- Lateral curvature of the spine (S- or C-shaped on x-ray)
- Congenital, idiopathic, related to another disease (e.g., cerebral palsy)
- Idiopathic type: usually affects adolescent girls between 10 and 16 years of age; usually a right thoracic curve; forward bending causes a paraspinous prominence on the right from a hump in the ribs due to a rotational component of the vertebra

**Treatment**: bracing, surgery

### Talipes equinovarus (clubfoot) (see Fig. 24-14L)
- Malalignment of the calcaneo-talar-navicular complex; entire foot is deviated toward the midline; there is forefoot adduction, fixed inversion of the hindfoot, and fixed plantar flexion; the Achilles tendon is foreshortened; hence the foot assumes the position of a horse's hoof
- Occurs in 1:1000 births; multifactorial; more common in males than females; bilateral in 50% of cases; increased risk if either parent has the condition; increased risk with smoking during pregnancy
- Associations: deformation in oligohydramnios associated with juvenile polycystic kidney disease (refer to Chapter 6), breech presentation, spina bifida, neuromuscular disorders

**Treatment**: manipulation, serial casting, surgery

### Table 24-3 Selected Orthopedic Disorders—cont’d

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>DISCUSSION</th>
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<tbody>
<tr>
<td>Knee joint injuries (see Fig. 24-14i and j)</td>
<td>Valgus injury: angulation away from the midline&lt;br&gt;Laterally originating force is applied to the knee (e.g., clipping injury in football)&lt;br&gt;Varus injury: angulation toward the midline&lt;br&gt;Medially originating force is applied to the knee&lt;br&gt;McMurray test: meniscus injuries&lt;br&gt;Anterior and posterior draw test: cruciate injuries&lt;br&gt;&quot;Unhappy triad&quot;: most common internal derangement of the knee joint; valgus injury (acute): damage to the lateral meniscus, medial collateral ligament, anterior cruciate ligament; if chronic, the medial meniscus is more commonly injured than the lateral meniscus&lt;br&gt;<strong>Treatment</strong>: physical therapy, arthroscopic surgery</td>
</tr>
<tr>
<td>Scoliosis (see Fig. 24-14K)</td>
<td>Lateral curvature of the spine (S- or C-shaped on x-ray)&lt;br&gt;Congenital, idiopathic, related to another disease (e.g., cerebral palsy)&lt;br&gt;Idiopathic type: usually affects adolescent girls between 10 and 16 years of age; usually a right thoracic curve; forward bending causes a paraspinous prominence on the right from a hump in the ribs due to a rotational component of the vertebra&lt;br&gt;<strong>Treatment</strong>: bracing, surgery</td>
</tr>
<tr>
<td>Talipes equinovarus (clubfoot) (see Fig. 24-14L)</td>
<td>Malalignment of the calcaneo-talar-navicular complex; entire foot is deviated toward the midline; there is forefoot adduction, fixed inversion of the hindfoot, and fixed plantar flexion; the Achilles tendon is foreshortened; hence the foot assumes the position of a horse's hoof&lt;br&gt;Occurs in 1:1000 births; multifactorial; more common in males than females; bilateral in 50% of cases; increased risk if either parent has the condition; increased risk with smoking during pregnancy&lt;br&gt;Associations: deformation in oligohydramnios associated with juvenile polycystic kidney disease (refer to Chapter 6), breech presentation, spina bifida, neuromuscular disorders&lt;br&gt;<strong>Treatment</strong>: manipulation, serial casting, surgery</td>
</tr>
</tbody>
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**24-14**: A, Radiograph showing a Colles fracture. Note the fracture lines (arrows) in the distal radius and the styloid process of the ulna. B, Rotator cuff muscles (supraspinatus, infraspinatus, teres minor, subscapularis). C, De Quervain tenosynovitis. First dorsal compartment has the abductor pollicis longus and extensor pollicis brevis. Excessive friction thickens tendon sheath causing stenosis of the osseofibrous tunnel. D, Ganglion cyst on the dorsum of the wrist.
Desmoid tumor: fibromatosis of anterior abdominal wall, associated with polyposis syndromes

Liposarcoma: MC adult sarcoma


Desmoid tumor:
- Definition—fibromatosis involving palmar fascia
- Causes contraction of single or multiple fingers
- Associated with alcoholism, diabetes mellitus, epilepsy

Liposarcoma: MC adult sarcoma

4. Desmoid tumor
- Definition—fibromatosis of the anterior abdominal wall in women
- Associated with previous trauma
- Associated with familial adenomatous polyposis syndrome and Gardner syndrome

B. Selected soft tissue tumors (Table 24-2)

V. Selected Orthopedic Disorders (Table 24-3; Fig. 24-14)
I. Skin Histology and Terminology
   A. Normal skin histology
      1. Epidermis (Fig. 25-1)
         a. Stratum basalis
            (1) Actively dividing stem cells along the basement membrane
            (2) Mitoses should be limited to this area.
         b. Stratum spinosum
            • Contains prominent desmosome attachments
         c. Stratum granulosum
            • Granular layer with keratohyaline granules
         d. Stratum corneum
            (1) Anucleate cells with keratin
            (2) Site for superficial dermatophyte infections
      2. Dermis (see Fig. 25-1)
         a. Papillary
            • Loose connective tissue beneath the epidermis
         b. Reticular
            • Dense dermal collagen
      3. Melanocytes
         a. Derived from neural crest cells
         b. Located in the stratum basalis
            • Dendritic processes extend between keratinocytes.
         c. Melanin is synthesized in membrane-bound melanosomes.
            (1) Tyrosinase converts tyrosine to 3,4-dihydroxyphenylalanine (DOPA).
            (2) DOPA is converted to melanin.
            (3) Melanosomes are transferred by dendritic processes to keratinocytes.
         d. Skin color
            (1) Number of melanocytes is essentially the same in all races.
            (2) Melanin is degraded more rapidly in whites than in blacks.
            (3) In whites, melanosomes are concentrated in the basal layer.
            (4) In blacks, melanosomes are present throughout all layers.
               • Melanocytes are larger and have more dendritic processes.
         e. Sunlight and adrenocorticotropic hormone stimulate melanin synthesis.
   B. Common terms used in dermatology (Table 25-1)

II. Selected Viral Disorders
   A. Common warts
      1. Caused by human papillomavirus (HPV; DNA virus)
      2. Common sites are the fingers and soles.
      3. Verrucous papular lesions covered by scales (Fig. 25-2A)
25-1: Epidermal layers and papillary dermis. (From Fitzpatrick JE, Morelli JG: Dermatology Secrets Plus, 4th ed, Philadelphia, Elsevier Mosby, 2011, p 7, Fig. 1.2.)

**Table 25-1 Common Terms in Dermatology**

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
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<tbody>
<tr>
<td>Macroscopic</td>
<td></td>
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</tr>
<tr>
<td>Macule</td>
<td>Pigmented or erythematous flat lesion on epidermis</td>
<td>Tinea versicolor</td>
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<tr>
<td>Papule</td>
<td>Peaked or dome-shaped surface elevation &lt;5 mm in diameter</td>
<td>Acne vulgaris</td>
</tr>
<tr>
<td>Nodule</td>
<td>Elevated, dome-shaped lesion &gt;5 mm in diameter</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>Plaque</td>
<td>Flattened, elevated area on epidermis &gt;5 mm in diameter</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Fluid-filled blister &lt;5 mm in diameter</td>
<td>Varicella (chickenpox)</td>
</tr>
<tr>
<td>Bulla</td>
<td>Fluid-filled blister &gt;5 mm in diameter</td>
<td>Bullous pemphigoid</td>
</tr>
<tr>
<td>Pustule</td>
<td>Fluid-filled blister with inflammatory cells</td>
<td>Impetigo</td>
</tr>
<tr>
<td>Wheal (hive)</td>
<td>Edematous, transient papule or plaque caused by infiltration of dermis by fluid</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Scales</td>
<td>Excessive number of dead keratinocytes produced by abnormal keratinization</td>
<td>Seborrheic dermatitis</td>
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<tr>
<td>Microscopic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>Increased thickness of stratum corneum produces scaly appearance of skin</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Parakeratosis</td>
<td>Persistence of nuclei in stratum corneum layer</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Papillomatosis</td>
<td>Spire-like projections from surface of skin or downward into papillary dermis</td>
<td>Verruca vulgaris</td>
</tr>
<tr>
<td>Acantholysis</td>
<td>Loss of cohesion between keratinocytes</td>
<td>Pemphigus vulgaris</td>
</tr>
</tbody>
</table>

4. Treatment
   a. Cryotherapy with liquid nitrogen
   b. Chemotherapy—e.g., salicylic acid, trichloroacetic acid
   c. Biological therapeutic agent—imiquimod (induces cytokines)

**B. Molluscum contagiosum**

1. Caused by a poxvirus (DNA virus)
2. Bowl-shaped lesions with central depression filled with keratin (see Fig. 25-2B)
   - Depression contains viral particles called molluscum bodies.
4. Usually disseminated in HIV infections
5. Transmission
   a. Can be sexually transmitted in adults (common in AIDS)
   b. Self-inoculation by scratching the infective viral particles out of the crater
6. Treatment
   a. Spontaneous remission occurs in 6 to 9 months if the person is immunocompetent.
      - Cell-mediated immunity must be intact.
   b. Cryotherapy
Viral infections. A, Verruca vulgaris (common wart) on the fingers, showing scaling, verrucous papules with interrupted skin lines. B, Molluscum contagiosum, showing small bowl-shaped lesions with central areas of depression (umbilication). C, Rubeola (regular measles). Note the white Koplik spots on the erythematous surface of the buccal mucosa. D, Rubeola. A macular rash begins on the face and neck and then becomes maculopapular (this patient) and spreads to the trunk and extremities in irregular confluent patches. E, Rubella. Note the red Forchheimer spots on the soft and hard palate. F, Rubella. Note the fine pinkish red maculopapular rash that usually begins on the hairline and then extends cephalocaudally. G, Erythema infectiosum. Note the “slapped face” appearance.

Continued
H. Roseola infantum. Note the maculopapular rash, which normally blanches with pressure. There are subtle peripheral halos due to vasoconstriction around some of the lesions. I. Varicella. Note the vesicles and pustules surrounded by an erythematous base. The lesions are at different stages of development. J. Herpes zoster (shingles). Note the erythematous vesicular rash with the characteristic “band” distribution, which starts from the midline and extends to the lateral trunk. K. Hand-foot-and-mouth disease due to coxsackievirus. Note the vesicles on the hands, feet, and in the mouth. (A from Lookingbill D, Marks J: Principles of Dermatology, 3rd ed, Philadelphia, Saunders, 2000, p 68, Fig. 6-1A; B and G from Savin JA, Hunter IAA, Hepburn NC: Diagnosis in Color: Skin Signs in Clinical Medicine, London, Mosby-Wolfe, 1997, pp 79, 6, respectively, Figs. 2-47, 1-10, respectively; C from Goldman L, Schafer AI: Cecil’s Medicine, 24th ed, Philadelphia, Saunders Elsevier, 2012, p 2105, Fig. 390.2; D from Goldman L, Ausiello D: Cecil’s Medicine, 23rd ed, Philadelphia, Saunders Elsevier, 2008, p 2476, Fig. 375-1; E from Eisen D, Lynch DP: The Mouth: Diagnosis and Treatment. St. Louis, Mosby, 1998; F and K from Kliegman, R: Nelson Textbook of Pediatrics, 19th ed, Philadelphia, Elsevier Saunders, 2011, pp 1076, 1090, respectively, Figs.239-3, 242-1, respectively; H from Paller AS, Mancinin AJ [eds]: Hurwitz Clinical Pediatric Dermatology, 3rd ed, Philadelphia, Elsevier, 2006, p 434; I from Bouloux P: Self-assessment picture tests Medicine, Vol. 2, London, Mosby-Wolfe, 1997, p 99, Fig. 198; J from Forbes C, Jackson W: Color Atlas and Text of Clinical Medicine, 2nd ed, London, Mosby, 2002, p 29, Fig. 1-85.)

25-2, cont’d: C. Rubeola (measles)
1. RNA paramyxovirus
2. Vaccination has reduced the incidence of rubeola.
3. Prodrome
   • Fever, cough, coryza (runny nose), conjunctivitis
4. Koplik spots develop on the buccal mucosa.
   • Koplik spots are white spots overlying an erythematous base (see Fig. 25-2C).
5. Maculopapular rash develops after Koplik spots disappear (see Fig. 25-2D).
   a. Cytotoxic T cell damage of endothelial cells containing the virus
   b. Typically begins on the head and then spreads to the trunk and extremities
   c. Tends to become confluent on face and trunk but discrete on extremities
6. Complications
   a. Giant cell pneumonia
   • Warthin-Finkeldey multinucleated giant cells
   b. Acute appendicitis in children
   • Virus stimulates lymphoid hyperplasia in the appendix causing ischemia to the tissue.
   c. Otitis media
d. Encephalitis
   • Before immunization, encephalitis was a common cause of death in measles.
e. Not teratogenic
7. Prevented through vaccinations
D. Rubella (German measles)
   1. RNA togavirus
      • Produces three-day measles
   2. Vaccination has reduced the incidence of rubella.
   3. Forchheimer spots (see Fig. 25-2E)
      a. Dusky red spots that develop on posterior soft/hard palate
      b. Develop at beginning of the rash
   4. Maculopapular rash lasts 3 days (see Fig. 25-2F).
      a. Pinkish, red maculopapular eruption
      b. Begins first at hairline and rapidly spreads cephalocaudally
      c. Unlike rubeola, the macules and papules are discrete and do not become confluent.
      d. Fades in 3 days
   5. Painful postauricular lymphadenopathy (characteristic)
   6. Polyarthritis is common in adults.
   7. Infection during first trimester may produce congenital anomalies (refer to Chapter 6).
   8. Infection is prevented through vaccination.

E. Erythema infectiosum (fifth disease)
   1. Caused by parvovirus B19 (DNA virus)
   2. Most often occurs in school-age children
      • Often occurs in epidemics
   3. Confluent net-like erythema type of rash
      a. Begins on cheeks ("slapped face" appearance; see Fig. 25-2G)
      b. Extends to the trunk and proximal extremities
   4. Polyarthritis is common in adults.

Other disorders caused by parvovirus B19 include pure red cell aplasia and aplastic anemia in chronic hemolytic diseases (e.g., hereditary spherocytosis) and chronic arthritis. Pregnant mothers exposed to a child with the infection may abort the fetus.

F. Roseola infantum (exanthem subitum)
   1. Human herpesvirus 6 (DNA virus) is the cause.
   2. It is the most common viral exanthem in children <2 years old.
   3. Erythematous macules develop on soft palate 48 hours before rash.
   4. Maculopapular rash occurs abruptly after 3 to 7 days of high fever (see Fig. 25-2H).
   5. Tender cervical and/or posterior occipital lymphadenopathy is a key feature in distinguishing roseola from rubella (postauricular lymphadenopathy).
   6. High fever may precipitate a febrile convulsion.
   7. Infection is treated with ganciclovir.

G. Disorders caused by varicella-zoster virus
   1. DNA herpesvirus
      • Remains latent in cranial and thoracic sensory ganglia
   2. Varicella (chickenpox)
      a. Predominantly a childhood disease
         (1) Approximately 90% of cases occur in those <10 years of age.
         (2) Incidence peaks in spring months.
      b. Incubation 2 to 3 weeks
      c. Patient is infectious 1 week before the rash appears.
         • Infectious an additional 4 to 5 days until vesicles become crusted
      d. Pruritic rash progresses from macules, to vesicles, to pustules (see Fig. 25-2I).
         (1) All stages of development are simultaneously present.
         (2) Lesions are most prominent on the trunk.
            (a) Also involves extremities (including palms and soles), mucous membranes in mouth, conjunctiva
            (b) Vesicles are often umbilicated (depressed center) and hemorrhagic.
      e. Positive Tzanck test similar to herpes simplex virus (refer to Chapter 22)
      f. Complications
         (1) Association with Reye syndrome if child takes aspirin
         (2) Pneumonia, self-limited cerebellitis
         (3) In adults—hepatitis, pneumonia, encephalitis

Rubella: three-day measles
Rubella: maculopapular rash with discrete lesions; not confluent; fades in 3 days
Rubella: painful postauricular lymphadenopathy
Rubella: teratogenic
Erythema infectiosum: parovirus; slapped face appearance
Polyarthritis in adults: rubella and parovirus
Roseola: HHV-6; MC viral exanthem children <2 years old
Roseola: rash appears abruptly after high fever
Roseola: common cause of febrile convulsions
Varicella: predominantly a childhood disease; latent virus
Infectious: week before rash; week after rash until vesicles become crusted
Varicella: macules, vesicles, pustules present at same time
Complications: children—Reye syndrome (aspirin), cerebellitis; adult—pneumonia, encephalitis, hepatitis
Herpes zoster:
- Incidence with age: cancer; immunocompromised state
- Radicular pain before rash
- Herpes zoster: painful vesicles/pustules follow sensory dermatomes

3. Herpes zoster (shingles)
   a. Occurs in 10% to 20% of people in their lifetime.
   b. Incidence increases with age.
   c. Incidence increased in patients with cancer and AIDS
   d. Prodrome of radicular pain and itching before rash occurs
   e. Eruption characterized by groups of vesicles on an erythematous base
      (1) Rash follows sensory dermatomes in the distribution of cranial nerves or spinal nerves (see Fig. 25-2J).
      (2) Like varicella, pustules form that rupture, causing crusting and weeping.
   f. Treatment
      (1) Prevention with previous immunization for varicella
      (2) Prevention with zoster vaccine
      - Greater than 50% reduction in infection
      (3) Analgesics commensurate with amount of pain
      (4) Immunocompromised patients are often treated with valacyclovir or famciclovir.
         - Best started before the rash has erupted

H. Hand-foot-and-mouth (HFM) disease
   1. Caused by coxsackievirus
   2. Febrile disease that primarily occurs in young children
   3. Vesicular rash occurs on the hands, feet, and in the mouth (see Fig. 25-2K).

III. Selected Bacterial Disorders
A. *Staphylococcus aureus* skin infections
   1. Gram-positive coccus in clusters (Fig. 25-3A)
   2. Toxic shock syndrome
      a. Production of toxic shock syndrome toxin (TSST)
         - Superantigen that stimulates release of cytokines
      b. Usually occurs in menstruating women who use tampons
      c. Clinical findings
         (1) Fever, hypotension
         (2) Desquamating, sunburn-like rash
   3. Other infections
      a. Skin abscess (see Fig. 3-8A)
         - Treatment: trimethoprim-sulfamethoxazole (TMP-SMX; community acquired)
      b. Hidradenitis suppurativa
         (1) Chronic condition characterized by:
            (a) Apocrine glands, usually in the axillae and groin, are swollen, painful, and inflamed.
            (b) Infection can also involve adjacent subcutaneous tissue and fascia.
            (c) Hallmark is the presence of sinus tracts.
         (2) Must aspirate and culture pus
         (3) Difficult to treat and may require surgery
      c. Postsurgical wound infection (most common pathogen, refer to Chapter 3 for discussion on methicillin-sensitive and methicillin-resistant strains)
         (1) If not septic, treat with trimethoprim-sulfamethoxazole (TMP-SMX) double strength.
         (2) If septic, treat with IV vancomycin.
      d. Impetigo
         (1) Most common cause is *Staphylococcus aureus*.
            - *Streptococcus pyogenes* second most common cause
         (2) Rash usually begins on the face (see Fig. 25-3B).
            (a) Vesicles and pustules rupture to form honey-colored, crusted lesions.
            (b) The infection is highly contagious.
         (3) Bullae commonly occur.
         (4) Treatment
            - Mupirocin ointment + dicloxacillin
      e. Scalded skin syndrome
         (1) Toxin-induced epidermolysis damage to skin in young children
            - Exfoliatin toxin is produced
25-3: Bacterial infections. 

A, Gram stain of Staphylococcus aureus. Note the gram-positive cocci, some of which are forming clusters. 

B, Impetigo of the face showing honey-colored crusts overlying an erythematous base. 

C, Infant with scalded child syndrome due to Staphylococcus aureus. 

D, Gram stain of Streptococcus pyogenes. Note the gram-positive cocci in chains. 

E, Tuberculoid leprosy. Note the hypopigmented macule, an early finding in tuberculoid leprosy. 

F, Lepromatous leprosy. Note the nodular lesions on the face giving the patient a leonine facies. 

G, Acne vulgaris. Note the severe facial acne with inflamed papules and cystic lesions. 


(2) Fever, large bullae, erythematous rash
(3) Skin sloughs off with loss of electrolytes (see Fig. 25-3C)
(4) Treatment with nafcillin

B. Streptococcus pyogenes skin infections
1. Gram-positive coccus in chains (see Fig. 25-3D)
2. Scarlet fever
   a. Particular strains of S. pyogenes produce an erythrogenic toxin.
   b. Patients are febrile and have a sore throat due to streptococcal pharyngitis.
An erythematous rash develops that involves the skin and tongue.

1. Initially it occurs on the face and neck before spreading to other parts of the body.
2. The mouth is spared, which produces a conspicuous circumoral pallor.
3. The rash feels like sandpaper.
4. The tongue is covered by a white exudate studded with prominent red papillae.
5. Rash begins to fade after 6 days, and desquamation (peeling) begins, which may last up to 10 days.
6. White exudate on the tongue disappears and the tongue is beefy red (strawberry tongue).

d. Increased risk for developing poststreptococcal glomerulonephritis (GN; refer to Chapter 20)
e. Treatment is penicillin V.

3. Erysipelas
   a. Type of cellulitis
      1. Border is raised and surface appears like an orange peel (see Fig. 3-1).
      2. Skin surface is hot and bright red (rubor of acute inflammation).
   b. Commonly occurs on the face and lower extremities
   c. Patient feels ill and is febrile.
   d. Treatment is IV penicillin G if on extremities, vancomycin if on the face.

C. Leprosy
1. Caused by *Mycobacterium leprae*
   a. Grows in footpads of mice and armadillos
   b. Cannot be cultured
2. Tuberculoid type
   a. Granulomas present
      • Very few acid-fast bacteria are present in the granulomas.
   b. Positive lepromin skin test
      • Indicates intact cellular immunity
   c. Localized skin lesions with nerve involvement
      1. Autoamputation of digits
      2. Anesthetic macules with hypopigmentation (see Fig. 25-3E)
   d. Treatment
      • Dapsone + rifampin
3. Lepromatous type
   a. Absence of granulomas
      1. Numerous bacteria are present in foamy macrophages.
      2. Macrophages are located under a subepidermal zone free of organisms.
         • Called the Grenz zone
   b. Negative lepromin skin test
      • Indicates a lack of cellular immunity
   c. Nodular lesions produce the classic leonine facies (see Fig. 25-3F).
   d. Treatment
      • Dapsone + rifampin + clofazimine

D. *Acne vulgaris*
1. Definition—chronic inflammation of the pilosebaceous unit
2. Most common disease seen by dermatologists
3. Begins at an early age (9–11 years old)
   a. Male dominant
   b. Sebaceous glands have androgen receptors
4. Increases in severity in the teenage years
5. Clinical lesions
   • Inflammatory papules, pustules, nodules, cysts
6. Noninflamed comedones
   a. Plugging of the outlet of a hair follicle by keratin debris
   b. Open comedone is called a blackhead.
   c. Closed comedone is called a whitehead.
7. Inflammatory type
   a. Abnormal keratinization of the follicular epithelium
   b. Increased sebum production (androgen-dependent)
      1. Androgen receptors are located in the hair follicle.
      2. Testosterone increases sebum formation in the hair follicle.
c. Bacterial lipase (*Propionibacterium acnes*) converts the sebum into irritating fatty acids (FAs), which produces the inflammatory reaction (see Fig. 25-3G).

8. Treatment
   a. Topical agents—e.g., topical retinoid + benzoyl peroxide
   b. Systemic antibiotics—e.g., tetracycline (first choice); erythromycin
   c. Systemic retinoids—isotretinoin (decreases follicular keratinization, sebum production, bacterial count)
   d. Hormonal therapy
      (1) Oral contraceptives (women; reduce free testosterone levels by increasing the synthesis of sex hormone–binding globulin)
      (2) Antiandrogens (spironolactone blocks the androgen receptor)

IV. Selected Fungal Disorders

A. Superficial mycoses (dermatophytes)
   1. Fungi are confined to the stratum corneum or its adnexal structures (Fig. 25-4A).
      a. Incidence increases in warm, humid climates.
      b. Most infections present with a scaling rash.
      c. Tinea means "worm" in Latin, but it is used to describe superficial fungal infections.
         (1) Tinea is followed by a word that qualifies its location (e.g., capitis [head], pedis [feet], corporis [body])
         (2) Most common infections in decreasing order: tinea pedis (foot), tinea unguim (nail), tinea versicolor (describes color variation rather than location), tinea cruris (groin)

**Wood lamp and potassium hydroxide (KOH)-treated skin scrapings** from lesions are commonly used for diagnosis of the dermatophytes. Wood lamp (ultraviolet A light) detects fluorescent metabolites produced by organisms (e.g., fungi, some bacteria). KOH preparations identify yeasts and hyphae in the stratum corneum or hair shafts (see Fig. 25-4B).

2. Tinea capitis
   a. Superficial fungal infection of the scalp
   b. Pathogens
      (1) Most often caused by *Trichophyton tonsurans*
         (a) Infects the inner hair shaft
         (b) Negative Wood lamp test
         (c) Predominant type present in blacks
      (2) *Microsporum canis* and *Microsporum audouinii*
         (a) Former type is associated with exposure to dogs.
         (b) Both infect the outer hair shaft.
         (c) Wood lamp test is positive.
         (d) These two species are the predominant pathogens in whites.
   c. Circular or ring-shaped patches of hair loss (alopecia)
      • Black dot is present where hair breaks off (see Fig. 25-4C).
   d. Treatment is oral terbinafine.

3. Other infections are most often caused by *Trichophyton rubrum*.
   a. Tinea corporis (body surface) (see Fig. 25-4D)
      (1) Sometimes called ringworm (misnomer)
      (2) May have history of exposure to a cat or dog
      (3) One or more lesions present
      (4) Typically annular with an elevated red, scaly border
         • Tendency for central clearing
      (5) Treated with topical agents (e.g., miconazole, clotrimazole)
         • Oral terbinafine is an alternative treatment.
   b. Tinea pedis (athlete’s foot)
      (1) Most common site for superficial dermatophyte infections
      (2) Most common in a person with sweaty feet
      (3) Macerated scaling rash between the toes
      (4) Elderly people have diffuse plantar scaling
         • "Moccasin" appearance
      (5) Treated with topical agents (e.g., miconazole, clotrimazole)
         • Oral terbinafine is an alternative treatment.

Acne vulgaris: *P. acnes* produces lipase; FAs cause inflammation

Superficial dermatophytes: live in stratum corneum; adnexal structures

*T. tonsurans*: MCC in blacks; negative Wood lamp

*M. canis/audouinii*: MCC in whites; positive Wood lamp

*Tinea capitis*: oral terbinafine; topical imidazoles do not work

*T. rubrum*: MCC all other tineas (except versicolor)

*Tinea corporis*: annular; outer border raised/scaly; central clearing

*Tinea pedis*: sweating is important cause
25-4: A, Dermatophytosis due to *Trichophyton*, demonstrated by periodic acid Schiff (PAS) stain. B, Potassium hydroxide (KOH) preparation of skin scrapings showing hyphae and yeasts. C, Tinea capitis due to *Trichophyton tonsurans*. Note the area of alopecia (hair loss) with black dots representing broken off hairs and scaling of the skin. D, Tinea corporis showing annular lesions with erythematous margins and clear centers. E, Tinea cruris. Note the scaly, erythematous rash in the groin. F, Tinea versicolor due to *Malassezia furfur* showing skin with pink-tan patches (hyperpigmentation) intermixed with normal skin. The hyperpigmented lesions should be scraped for a KOH preparation. G, *Malassezia furfur*. Note the classic spaghetti (hyphae) and meatball (yeasts) morphologic appearance.
Tinea cruris: sweat is important in pathogenesis

Onychomycosis: raised, discolored nail; nail plate is white, thick, crumbly

Rx onychomycosis: oral terbinafine

Tinea versicolor: alteration in skin pigmentation; hypopigmentation or hyperpigmentation

Tinea versicolor caused by M. furfur

KOH: spaghetti and meatballs

Candida skin infections: intertrigo; diaper rash; onychomycosis

Sporotrichosis: subcutaneous mycosis; S. schenckii

B. Sporotrichosis
1. Caused by Sporothrix schenckii
   a. Subcutaneous mycotic infection
   b. Dimorphic fungus
      • Mold in soil, yeast in tissue
2. Traumatic implantation of fungus
   a. Rose gardening
   b. Sphagnum peat moss for packing material
   c. Splinters from carpentry work
   d. Landscapers, berry pickers
3. Lymphocutaneous disease
   • Chain of suppurating lymphocutaneous nodules (see Fig. 25-4K)
4. Treatment
   a. Oral itraconazole
   b. Saturated solution of potassium iodide (SSKI)
      (1) Poorly tolerated
      (2) Not the treatment of choice

V. Selected Parasitic and Arthropod Disorders
A. Cutaneous larva migrans
1. Caused by *Ancylostoma braziliense* (nematode)
   a. Dog and cat hookworm
   b. Transmission
      (1) Dogs and cats are the definitive host.
      • Definitive host has the sexually mature hookworm that can mate and lay eggs.
      (2) Larvae evolve in sand/soil from eggs passed in the feces of dogs or cats.
      (3) Larvae penetrate the skin in children/adults (intermediate hosts).
2. Cutaneous larva migrans (creeping eruption)
   a. Larvae penetrate the skin.
      (1) It is commonly contracted by children while playing in sand boxes.
      (2) Cover sandboxes so dogs/cats do not use them as litter boxes.
   b. Larvae create serpiginous tunnels in the skin (Fig. 25-5A).
      • Causes intense pruritus, scratching, and eosinophilia
   c. Treatment is albendazole.

B. Arthropod disorders: mites
1. Chiggers
   a. Small, red to orange mite
   b. Induces a pruritic dermatitis
      (1) Bright red papular, urticarial, or vesicular rash
      (2) Favor the legs and areas of tight-fitting clothing
   c. Treatment
      • Topical antipruritic agents (crotamiton and calamine lotion)
2. Human itch mite (*Sarcoptes scabiei* var. *hominis*)
   a. Adult females bore into the stratum corneum.
      (1) Burrows are visible as dark lines between the fingers, at the wrists, on the nipples, or on the scrotum.
      (2) Females lay eggs at the end of the tunnel.
      • Eggs are responsible for the intensely pruritic lesion.
   b. Adults
      (1) Disease is limited to the webs between the fingers (see Fig. 25-5B), intertriginous areas
      (2) It spares the soles, palms, face, and head.
   c. Infants
      (1) No burrows are present.
      (2) Pruritic rash occurs on the palms, soles, face, or head.
   d. Treatment is permethrin cream.

C. Arthropod disorders: lice
1. *Pediculus humanus capitis* (head louse)
   a. Adults lay eggs (nits) on hair shafts (see Fig. 25-5C).
   b. Itching of the scalp
   c. Treatment
      (1) Permethrin (kills newly hatched lice)
      (2) Followed by lindane (Kwell), if the initial treatment is unsuccessful
2. *Pediculus humanus corporis* (body louse)
   a. Adults live on the surface of the skin and breed in the clothing (see Fig. 25-5D).
   b. Skin lesions are papular and produce intense itching (see Fig. 25-5E).
   c. To eradicate the disease, treat the clothing, *not* the patient.
      • Treat clothing with malathion or DDT powder or discard clothes.
25-5: A, Cutaneous larva migrans. Note irregular, erythematous tracts beneath the skin surface. B, Scabies. Note the erythematous area in the web between the fingers. The arrows show raised burrows. C, Pediculus capitis. Note the white nits (eggs) attached to the hair shafts. D, Pediculus corporis feeding. E, Pediculus corporis. Note the numerous erythematous papules over the back of this homeless person. F, Pthirus pubis. Note the crab-like appearance of the louse. G, Bedbug bites. Note the red papules and wheals. H, Morula (arrow) of Anaplasma in a granulocyte. (A and B courtesy R.A. Marsden, MD, St. George’s Hospital, London; C and H from Kliegman RM, Jenson HB, Behrman RE, Stanton BF: Nelson’s Textbook of Pediatrics, 18th ed, Philadelphia, Saunders Elsevier, 2007, pp 2758, 1050, respectively, Figs. 667-6, 228-1B, respectively; D from Cohen J, Opal SM, Powderly WG: Infectious Diseases, 3rd ed, St. Louis, Mosby Elsevier, 2007, pp 2758, 1050, respectively; F from Klatt E: Robbins and Cotran Atlas of Pathology, Philadelphia, Saunders, 2006, p 399, Fig. 16-90, right; G from Swartz M: Textbook of Physical Diagnosis History and Examination, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 176, Fig. 8-90.)
3. *Pthirus pubis* (pubic louse, crabs)
   a. Adults live in the pubic hairs (see Fig. 25-5F).
     • Looks like a crab
   b. Treatment is permethrin or malathion.

D. **Arthropod disorders: bedbug**
1. Common bedbug is *Cimex lectularius*.
2. Dwellings (houses, motels) are usually completely infested.
3. They feed on human blood.
   a. Active just before dawn
   b. Attracted by warmth and CO₂
4. Skin lesions
   a. Intensely pruritic red papules/wheals (see Fig. 25-5G)
   b. Allergic reaction to anesthetic in saliva of bedbug
5. Treatment
   • Exterminators use permethrin.

E. **Arthropod: tick**
1. Rocky Mountain spotted fever (RMSF; see Fig. 10-14G and Table 10-3)
2. Ehrlichiosis (*Ehrlichia chaffeensis*): human monocyte ehrlichiosis (HME)
   a. Obligate intraleukocytic (monocyte) bacteria
   b. Locations—southeastern, south central, and mid-Atlantic United States (same areas as RMSF)
   c. Reservoir for the bacteria is the white-tailed deer.
   d. Produces a mulberry-like inclusion called a morula in the cytoplasm of a monocyte
      • *Anaplasma*, a closely related species that is tick transmitted, infects granulocytes
        (Ixodes deer tick; see Fig. 25-5H)
   e. Transmission
      • Bite of a tick, *Amblyomma* (lone star tick)
   f. Clinical findings
      (1) Fever, headache (meningoencephalitis; lymphocyte predominant)
      (2) Myalgia, rash (macular, maculopapular, or petechial; ~30% of cases)
      (3) Hepatosplenomegaly in children (50% of cases)
      (4) Edema in face, hands, and feet more common in children than adults
   g. Diagnosis—serologic tests, demonstration of the organism in tissue
   h. Doxycycline
   i. Case mortality 3%

VI. **Melanocytic Disorders**
A. **Solar lentigo**
1. Common finding in elderly individuals
2. Brown, macules located on sun-exposed areas (liver spots) (Fig. 25-6A)
   a. Increased number of melanocytes
   b. In contradistinction, freckles (ephelides) have a normal number of melanocytes but an increase in melanosomes.
3. *Not* precancerous
4. No treatment

B. **Vitiligo**
1. Common in blacks
2. Autoimmune destruction of melanocytes
   a. Causes localized to extensive areas of skin depigmentation (see Fig. 25-6B).
   b. In contrast, albinism is due to a deficiency of tyrosinase leading to absence of melanin in melanocytes.
3. Often associated with other autoimmune conditions
   • Examples—Hashimoto thyroiditis, hypoparathyroidism

C. **Melasma**
1. Definition—macular, hyperpigmented lesions on the forehead and cheeks in women (see Fig. 25-6C)
2. Female predominance
3. Exacerbated (melanocytes produce more melanin) by:
   a. Oral contraceptive pills (OCPs)
   b. Pregnancy (mask of pregnancy)
   c. Sunlight
4. Treatment
   • Application of hydroquinone (bleaching agent) to skin
25-6: A, Solar lentigo. Note the numerous brown macules on the dorsum of the hand. B, Vitiligo. Note the patchy depigmentation of the skin. C, Melasma. Note the facial hyperpigmentation in this pregnant woman. D, Junctional nevus. Note the oval, uniformly pigmented macular lesion. E, Compound nevus. Note the pigmented lesion with the slightly papillomatous appearing surface. F, Intradermal nevus. Note the raised, pigmented lesion with the papillomatous appearing surface. G, Dysplastic nevus syndrome. Note the numerous pigmented lesions over the back and neck. The inset shows a dysplastic nevus that is >6 mm in diameter and shows variable pigmentation. H, Superficial spreading malignant melanoma. The lesion on the patient’s forearm is black, is multinodular, and has an irregular border with areas of pale gray discoloration. I, Lentigo maligna melanoma. Note that the facial lesion shows asymmetry, border irregularity, color variation, and a diameter >6 mm.

D. Nevocellular nevus (mole)

1. Neoplasmic melanocytic disorder
   • Definition—benign tumor of neural crest–derived nevus cells (modified melanocytes)
2. Whites have an average of 15 to 40 nevi on their skin.
3. Frequently contain hair
4. Begins in early childhood as a junctional nevus (see Fig. 25-6D)
   a. Pigmented macular (flat) lesion
   b. Nests of nevus cells along the basal cell layer
5. Junctional nevus develops into a compound nevus.
   a. Usually occurs in children and adolescents
   b. Nevus cells extend into the superficial dermis.
      • Junctional and intradermal components are present.
   c. Pigmented lesion with a papillomatous surface (see Fig. 25-6E)
6. Intradermal nevus
   • Develop when a compound nevus loses its junctional component (see Fig. 25-6F)
7. Dysplastic nevus (atypical mole)
   a. May arise sporadically
**Malignant melanoma**

1. **Epidemiology**
   a. Malignant tumor of melanocytes
   b. Most rapidly increasing cancer worldwide
      - More common in whites than blacks

2. **Leading cause of death due to skin cancer**

3. **Median age at diagnosis is 53 years.**

4. **Risk factors**
   a. Exposure to excessive sunlight (UVA and UVB) at an early age
      - Single most important risk factor
   b. History of a family member with melanoma
   c. Use of tanning booths
   d. Dysplastic nevus syndrome
   e. History of melanoma in first- or second-degree relative
   f. Xeroderma pigmentosum (refer to Chapter 9)

5. **Radial growth phase**
   a. Initial phase of invasion
   b. Melanocytes proliferate:
      1. Laterally within the epidermis
      2. Along the dermoeidermal junction
      3. Within the papillary dermis
   c. No metastatic potential in this phase

---

**25-6, cont’d**:

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<tr>
<th>J</th>
<th>Asymmetry</th>
<th>Border</th>
<th>Color</th>
<th>Diameter</th>
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J. **Nodular melanoma.** Note the dark, red nodular mass in the center of the lesion and the irregular border. A biopsy would show absence of a radial growth phase and distinguish this melanoma from a superficial malignant melanoma. **K. Acral lentiginous malignant melanoma.** Note the pigmented lesion under the nail that has spread to involve the proximal nail bed. **L. Subungual hematoma.** The easiest way of differentiating this from a subungual hematoma is that the hematoma would have a history of trauma to the nail. **M. ABCD changes in malignant melanoma.** See text for discussion. (A and I from Lookingbill D, Marks J: Principles of Dermatology, 3rd ed, Philadelphia, Saunders, 2000, p 94, Figs. 7-2, 7-4B, respectively; B courtesy The Honickman Collection of Medical Images in memory of Elaine Garfinkel and The Jefferson Clinical Images Collection [through the generosity of JMB, AKR, LKB, and DA]; C to F from Habif T: Clinical Dermatology, 4th ed, St. Louis, Mosby, 2004; G from Kumar V, Abbas AK, Fausto N, Mitchell RN: Robbins Basic Pathology, 8th ed, Philadelphia, Saunders Elsevier, 2007, p 854, Fig. 22-20C; H from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 327, Fig. 15-57A; J from Townsend, C: Sabiston Textbook of Surgery, 18th ed, Philadelphia, Saunders Elsevier, 2008, p 771, Fig. 30-5; K from Savin JA, Hunter JAA, Hepburn NC: Diagnosis in Color: Skin Signs in Clinical Medicine, London, Mosby-Wolfe, 1997, p 119, Fig. 4.63; L from Seidel H, Ball J, Dains, J, Benedict G: Mosby’s Guide to Physical Examination, 6th ed, St. Louis, Mosby Elsevier, 2006, p 218, Fig. 8-63; M reproduced with permission from the American Academy of Dermatology, Copyright © 2012. All rights reserved.)

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(1) Controversy about whether they may develop into a malignant melanoma

(2) **Characteristics:**
   a. Usually >6 mm
   b. Variegated color with an erythematous background
   c. Irregular borders

b. May be associated with the dysplastic nevus syndrome (see Fig. 25-6G)
   1. Autosomal dominant syndrome with >100 nevi on the skin
   2. In this syndrome, dysplastic nevi often develop into malignant melanomas.
   3. All persons with this syndrome should have a yearly exam by a dermatologist.

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**E. Malignant melanoma**

1. **Epidemiology**
   a. Malignant tumor of melanocytes
   b. Most rapidly increasing cancer worldwide
      - More common in whites than blacks

2. **Leading cause of death due to skin cancer**

3. **Median age at diagnosis is 53 years.**

4. **Risk factors**
   a. Exposure to excessive sunlight (UVA and UVB) at an early age
      - Single most important risk factor
   b. History of a family member with melanoma
   c. Use of tanning booths
   d. Dysplastic nevus syndrome
   e. History of melanoma in first- or second-degree relative
   f. Xeroderma pigmentosum (refer to Chapter 9)

5. **Radial growth phase**
   a. Initial phase of invasion
   b. Melanocytes proliferate:
      1. Laterally within the epidermis
      2. Along the dermoeidermal junction
      3. Within the papillary dermis
   c. No metastatic potential in this phase
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<th>6. Vertical growth phase</th>
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<tr>
<td>a. Final phase of invasion</td>
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<td>b. Penetration of malignant cells into the underlying reticular dermis</td>
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<td>c. Potential for metastasis</td>
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<th>7. Types of malignant melanoma</th>
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<tbody>
<tr>
<td>a. Superficial spreading melanoma (SSM; see Fig. 25-6H)</td>
</tr>
<tr>
<td>(1) Most common type (70% of cases)</td>
</tr>
<tr>
<td>(2) Common sites—lower extremities, arms, upper back</td>
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<td>b. Lentigo maligna melanoma (LMM; 4% to 10% of cases)</td>
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<tr>
<td>(1) Common in the elderly population</td>
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<td>(2) Extension of lentigo maligna (intraepidermal lesion) into the dermis</td>
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<td>(3) Long radial growth phase</td>
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<td>(4) Occurs on parts of the face most exposed to the sun (see Fig. 25-6I)</td>
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<td>(5) Least likely of all melanomas to have a vertical phase</td>
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<td>(6) Good prognosis</td>
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<td>c. Nodular melanoma (15%–30% of cases; see Fig. 25-6J)</td>
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<tr>
<td>(1) No radial growth phase</td>
</tr>
<tr>
<td>(2) Can be found in any sun-exposed area</td>
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<tr>
<td>• Most often located on the trunk</td>
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<td>(3) No radial phase, only a vertical phase</td>
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<td>(4) Poor prognosis</td>
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<td>d. Acral lentiginous melanoma (ALM; 2%–8% of cases)</td>
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<td>(1) Not related to sun exposure</td>
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<td>(2) Located on the palm, sole, or beneath the nail (see Fig. 25-6K)</td>
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<td>• Often confused with a subungual hematoma (see Fig. 25-6L)</td>
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<td>(3) Most often occurs in Asians and blacks</td>
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<td>(4) Poor prognosis</td>
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<th>8. Biological behavior best determined by depth of invasion</th>
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<tr>
<td>a. If &lt;0.76 mm invasion—99% 5-year survival</td>
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<td>b. If &gt;4 mm invasion—44% 5-year survival</td>
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<th>9. ABCD criteria for malignancy (see Fig. 25-6M)</th>
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<tbody>
<tr>
<td>a. Asymmetry of shape</td>
</tr>
<tr>
<td>b. Border irregularity</td>
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<td>c. Color variation</td>
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<td>d. Diameter &gt;6 mm</td>
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<th>10. Prevention</th>
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<tr>
<td>a. Sunscreen &gt;15 SPF (controversial)</td>
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<td>• Prevention for UVA and UVB light</td>
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<td>b. Protective clothing</td>
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<th>11. Treatment</th>
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<tr>
<td>a. Excision of the entire lesion and surrounding normal tissue</td>
</tr>
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<td>• Sentinel lymph node biopsy to determine stage</td>
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<td>b. More extensive disease</td>
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<tr>
<td>• Immunotherapy, irradiation</td>
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### VII. Benign Epithelial Tumors

#### A. Seborrheic keratosis

1. Epidemiology
   a. Most common benign tumor in older people
   b. Occurs in individuals >50 years of age

2. Benign pigmented epidermal tumor
   a. Coin-like, macular to raised verrucoid lesion with "stuck-on" appearance
   b. Extremities and shoulders are the most common sites
   c. Occur commonly on the face in elderly patients

3. Leser-Trélat sign (refer to Chapter 9)
   a. Rapid increase in number of keratoses (Fig. 25-7A)
   b. Phenotypic marker for stomach adenocarcinoma

4. Treatment
   • Cryotherapy, curettage, shave biopsy/excision

#### B. Acanthosis nigricans (AN)

1. Velvety, pigmented skin lesion

2. Commonly located in the axilla (see Fig. 25-7B)
   • Other sites—neck, axilla, groin, under breasts
25-7: A, Seborrheic keratosis. Note the numerous raised, pigmented lesions with a verrucoid surface. These lesions appeared suddenly (Leser-Trélat sign) in this patient indicating a possible underlying gastric adenocarcinoma. In most cases, they are a common lesion in the elderly population where they frequently occur on the face and axilla. B, Acanthosis nigricans. Note the pigmented verrucoid lesion in the axilla. Like the Leser-Trélat sign, these lesions may be associated with an underlying gastric adenocarcinoma or other disorders. C, Keratoacanthoma. Note the crateriform tumor with a central keratin plug. This looks very similar to a basal cell carcinoma; however, it appears rapidly and spontaneously resolves, unlike a basal cell carcinoma. A biopsy settles the issue. D, Epidermal inclusion cyst. Note the dome-shaped lesion near the hairline on the neck. In this case, it has two openings on the surface. E, Pilar cyst. Note the dome-shaped swelling on the scalp. F, Fibroepithelial tag. Note the flesh-colored pedunculated lesion attached to the body by a narrow stalk. These are common lesions in the elderly. (A from Kumar V, Cotran RS, Robbins SL: Robbins Basic Pathology, 7th ed. Philadelphia, Saunders, 2003, p 799, Fig. 22-13A; B from Lookingbill D, Marks J: Principles of Dermatology, 3rd ed. Philadelphia, Saunders, 2000, pp 350, 83, respectively, Figs. 25-5, 6-12, respectively; C from Rosai J: Rosai and Ackerman’s Surgical Pathology, 9th ed, St. Louis, Mosby, 2004, p 150, Fig. 4-88; D courtesy R.A. Marsden, MD, St. George’s Hospital, London; E courtesy A. du Vivier, MD, King’s College Hospital, London; F from Habif T: Clinical Dermatology, 4th ed. St. Louis, Mosby, 2004.)

3. Pathogenesis
   - Excess insulin is noted in many cases

4. Associations
   a. Metabolic syndrome (refer to Chapter 23)
     - Obesity association is important because of insulin resistance (downregulation of insulin receptors), which produces hyperinsulinemia.
B. Insulin receptor deficiency
C. Polycystic ovary syndrome (PCOS; refer to Chapter 22)
D. Phenotypic marker for gastric cancer (refer to Chapters 9 and 18)
E. Multiple endocrine neoplasia type IIb (refer to Chapter 23)
5. Treatment
a. Treating underlying condition causes some regression
b. Topical tretinoin

C. Keratoacanthoma (KA)
1. Male predominance
2. Rapidly growing, crateriform tumor with a central keratin plug (see Fig. 25-7C)
   a. Grows within 4 to 6 weeks
   b. Develops in sun-exposed areas
   c. ? Well-differentiated squamous cell carcinoma (SCC)
3. May regress spontaneously with scarring within 6 months
4. Excision recommended

D. Benign epidermal cysts
1. Epidermal inclusion cysts (follicular cyst)
   a. Derived from the epidermis of the hair follicle (see Fig. 25-7D)
   b. Locations
      • Face, base of ears, trunk
      • Cyst wall is composed of normal epidermis that produces keratin.
      • Keratin is intermixed with lipid-rich debris.
   c. Spontaneous inflammation and rupture may occur.
   d. Treatment
      • Surgical excision if necessary
2. Pilar cyst (wen)
   a. Derived from hair root sheaths
   b. Located on the scalp and face (see Fig. 25-7E)
   c. Cyst wall lacks stratum granulosum.
      • Keratin has a laminated appearance.
   d. Spontaneous inflammation and rupture may occur.
   e. Treatment
      • Surgical excision if necessary

E. Fibroepithelial polyp (tag)
1. Flesh-colored soft tag of skin attached to the body by a narrow stalk (see Fig. 25-7F)
2. Common finding in the elderly
3. Locations
   • Neck, upper chest, upper back
4. Treatment
   • Excise if necessary

VIII. Premalignant and Malignant Epithelial Tumors
A. Actinic (solar) keratosis (refer to Chapter 9)
1. Associated with prolonged ultraviolet light exposure
2. Precursor (squamous dysplasia) of squamous cell carcinoma
   • Squamous cancer occurs in 2% to 5% of cases.
3. Hyperkeratotic, pearly gray-white appearance
   a. Occurs on face, back of neck, dorsum of hands/forearms (Fig. 25-8A)
   b. Commonly recurs when scraped off
4. Treatment
   a. Protection of skin with sunscreen
   b. Topical therapy—5-fluorouracil
   c. Cryotherapy

B. Basal cell carcinoma (BCC)
1. Most common malignant skin tumor
2. Caused by chronic exposure to ultraviolet light
3. Occurs in sun-exposed areas
   a. Raised papule or nodule with a central crater (see Fig. 25-8B)
      • Sides of the crater are surfaced by telangiectatic vessels.
   b. Common locations—inner canthus of the eye, upper lip
   c. Very general rule of thumb is that BCCs favor upper lip and higher.
25-8: A, Actinic (solar) keratosis. Note the pearly gray-white hyperkeratotic lesion (arrow) on the hand. The other lesions (circles) are good examples of solar lentigo. Both of these lesions are common in the elderly population and are located in sun-exposed areas. B, Basal cell carcinoma. Note the ulcerated nodular mass on the inner aspect of the nose. This is a particularly common site for this cancer that invades but does not metastasize. C, Basal cell carcinoma. This microscopic section shows multifocal nests of basophilic staining cells with peripheral palisading. This section does not show a connection with the basal cell layer of skin; however, these tumors arise from multifocal locations and extend into the dermis. D, Squamous cell carcinoma. Note the nodular, hyperkeratotic lesion occurring on the ear. This is a common site for this cancer in the elderly population. The arrow shows metastasis to a lymph node. (A courtesy R.A. Marsden, MD, St. George’s Hospital, London; B from Savin JA, Hunter JAA, Hepburn NC. Diagnosis in Color: Skin Signs in Clinical Medicine, London, Mosby-Wolfe, 1997, p 104, Fig. 4-27; C from Rosai J, Ackerman LV. Surgical Pathology, 9th ed. St. Louis, Mosby, 2004, p 137, Fig. 4-60; D from Kumar V, Abbas AK, Fausto N, Mitchell RN: Robbins Basic Pathology, 8th ed, Philadelphia, Saunders Elsevier, 2007, p 851, Fig. 22-17.)

4. Locally aggressive, infiltrating cancer that does not metastasize
   a. Arises from the basal cell layer of the epidermis
   b. Multifocal in origin
      • This makes it difficult to get free margins after surgery
   c. Cords of basophilic-staining basal cells infiltrate the underlying dermis (see Fig. 25-8C).
5. Diagnosis
   • Punch biopsy or shave biopsy
6. Treatment
   a. Varies with location and size of the cancer
   b. Options include topical 5-fluorouracil, cryotherapy, curettage and electrodesiccation, surgical excision, radiation (usually in elderly).

C. Squamous cell carcinoma (SCC)
1. Risk factors
   a. Excessive exposure to ultraviolet light (most common)
   b. Actinic (solar) keratosis
   c. Arsenic exposure
   d. Scar tissue in a third-degree burn
   e. Orifice of chronically draining sinus tract
   f. Immunosuppressive therapy
2. Scaly to nodular lesions
   a. Nodules are often ulcerated.
   b. Majority occur in sun-exposed areas of the body.
IX. Selected Skin Disorders

A. Ichthyosis vulgaris
1. Autosomal dominant
   • Most common inherited skin disorder
2. Defect in keratinization
   a. Causes increased thickness of the stratum corneum
   b. Absent stratum granulosum
3. Hyperkeratotic, dry skin
   • Involves palms, soles, and extensor areas

B. Xerosis
1. Most common cause of dry skin and pruritus in the elderly
   • Due to a decrease in skin lipids
2. Other age-related changes in elderly
   a. Decreased number of hair follicles, sweat glands
   b. Decreased thickness of epidermis
   c. Decreased dermal collagen/elastic tissue
   d. Decreased subcutaneous fat
      • Example—over dorsum of hands
   e. Increased cross-linking of collagen and elastic tissue

C. Polymorphous light eruption (PLE)
1. Most common photodermatitis
2. Affects ~10% of the population
3. Positive family history
   • Very common in Native Americans
4. More common in women than men
5. More common in blacks than whites
6. Rapid onset after sun exposure (Fig. 25-9A)
   a. Erythematous macules, papules, plaques, or vesicles/bullae
   b. Pruritic rash that is sometimes painful
   c. Not related to drugs
7. Treatment
   a. Broad-spectrum high-potency sunscreen against UVA and UVB
      • Often vitamin E is added to the mixture or given as an oral supplement.
   b. Topical corticosteroids

D. Eczema
1. Definition—group of inflammatory dermatoses
   • Characterized by pruritus
2. Acute eczema
   • Weeping, erythematos rash with vesicles
3. Chronic eczema
   • Dry, thickened skin (hyperkeratosis) caused by continual scratching
4. Atopic dermatitis
   a. Type I IgE-mediated hypersensitivity reaction (HSR)
   b. Dermatitis in children
      • Dry skin and eczema on cheeks and extensor and flexural surfaces (see Fig. 25-9B and C)
   c. Dermatitis in adults
      • Dry skin and eczema on hands, eyelids, elbows, and knees
5. Contact dermatitis
   a. Allergic contact dermatitis (refer to Chapter 4)
      (1) Type IV HSR
      (2) Examples—poison ivy (see later), nickel in jewelry
   b. Irritant contact dermatitis
      • Skin reaction to an irritant (e.g., laundry detergent)

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c. Contact photodermatitis
   (1) UV light reacts with drugs that have a photosensitizing effect.
   (2) Example—tetracycline
d. Poison ivy (rhus dermatitis) (see Fig. 25-9D)
   (1) The sensitizing agent in poison ivy is urushiol, which is in the sap of the plant.
   (2) Sensitivity to poison ivy results in sensitivity to poison oak and sumac as well.
   (3) Contact with the smoke of burning plants often results in widespread, severe dermatitis of the skin that may even extend into the respiratory tract.

6. General treatment
   a. Avoid drugs and irritants that produce a rash
   b. Apply moistening agents (emollients) to skin
c. Topical corticosteroids
   (1) Only low-potency hydrocortisone for the face
   (2) Higher potency corticosteroids for other sites
      (a) High potency—clobetasol propionate, fluocinonide
      (b) Medium potency—clobetasone butyrate, triamcinolone

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Contact photodermatitis: e.g., tetracycline, a drug with photosensitizing effect
Poison ivy: sensitizing agent is urushiol in the sap
Sensitivity to poison ivy also extends to poison oak/sumac
25-9, cont’d: M, Erythema nodosum. Note the raised, erythematous nodular lesions on the anterior shins. This is commonly associated with coccidioidomycosis. N, Granuloma annulare. Note the erythematous, annular plaque on the dorsum of the hands. There is an increased association of this skin lesion with diabetes mellitus. O, Porphyria cutanea tarda. Wood light examination of the urine in a patient with porphyria cutanea tarda demonstrating classic coral red fluorescence with normal urine specimen exhibited for comparison. P, Urticaria. One of the manifestations of urticaria is dermatographism. In this case, there is swelling with the word HIVE.


E. Autoimmune skin disorders

1. Chronic cutaneous lupus erythematous (refer to Chapter 4)
   a. Associated with atrophy of the epidermis
   b. DNA–anti-DNA immunocomplex (IC) deposition in the basement membrane
      (1) Degeneration of basal cells and hair shafts (alopecia)
      (2) Positive immunofluorescent (IF) band test
         • IF shows immunocomplexes deposited along the basement membrane.
   c. Clinical findings
      (1) Erythematous maculopapular eruption
         • Usually over malar eminences and bridge of nose (butterfly rash) (see Fig. 4-11A)
      (2) Skin lesions are exacerbated by UV light.
   d. Antimalarials remain cornerstone of treatment.

2. Pemphigus vulgaris (PV)
   a. IgG antibodies against intercellular attachment sites (desmosomes) between keratinocytes
      • Type II HSR
   b. Vesicles and bullae develop on the skin and oral mucosa.
   c. Intraepithelial vesicles are located above the basal layer (suprabasal; see Fig. 25-9E).
      (1) Basal cells resemble a row of tombstones.
      (2) Acantholysis of keratinocytes is present in the vesicle fluid.
      (3) Nikolsky sign is positive.
         • Outer epidermis separates from the basal layer with minimal pressure
   d. Treatment
      • Corticosteroids and other immunosuppressive agents (e.g., methotrexate, azathioprine)

3. Bullous pemphigoid
   a. IgG antibodies form against the basement membrane.
      • Type II HSR
b. Vesicles are subepidermal (see Fig. 25-9F).
   (1) Develop on the skin and oral mucosa (see Fig. 25-9G)
   (2) No acantholytic cells in the vesicle fluid
   (3) Negative Nikolsky sign
c. Disease usually subsides after months or years.
d. Resistant cases may require systemic corticosteroids.

4. Dermatitis herpetiformis (DH; see Fig. 18-17C)
a. IgA–anti-IgA complexes (type III HSR) deposit at the tips of the dermal papillae.
   • Produces subepidermal vesicles with neutrophils.
b. DH has a strong correlation with celiac disease.
   • Increase in antireticulin and antiendomysial antibodies
c. Treatment
   (1) Gluten-free diet
   (2) Dapsone or sulfapyridine

F. Lichen planus (LP)
1. Intensely pruritic, scaly, violaceous, flat-topped papules (see Fig. 25-9H)
a. Fine white reticular pattern on the surface (called Wickham striae)
b. Commonly located on the wrists, ankles
c. Nails are commonly dystrophic.
d. Lesions develop in areas of scratching (Koebner phenomenon).
2. Women are more commonly affected than men.
3. Oral mucosa is often involved (50% of cases; see Fig. 18-5C).
a. Produces a fine, white, net-like lesion (Wickham striae)
b. Slight risk of developing SCC
4. Association with hepatitis C virus (HCV)
5. Treatment
a. Topical high-potency corticosteroids
b. Antihistamines (for pruritus)
c. Systemic corticosteroids, retinoids, and cyclosporine in resistant cases

G. Psoriasis
1. Epidemiology
   a. Afflicts 1% to 3% of the world population
   b. Strong human leukocyte antigen (HLA) relationship
   c. Peak age at onset is bimodal.
      • Adolescents and 60 years of age
   d. No gender difference
2. Pathogenesis
   a. Unregulated proliferation (hyperplasia) of keratinocytes
      (1) Genetic factors involved (30% of cases)
      (2) Aggravating factors
         (a) Streptococcal pharyngitis
         (b) HIV
            • Sudden onset of psoriasis is highly suspicious for HIV
         (c) Drugs: lithium, β-blockers, nonsteroidal antiinflammatory drugs (NSAIDs)
            (d) Scratching the skin produces lesions (Koebner phenomenon)
b. Microcirculatory changes in the superficial papillary dermis
3. Well-demarcated, flat, elevated, salmon-colored plaques (see Fig. 25-9J)
a. Covered by adherent white to silver-colored scales
   • Pinpoint areas of bleeding occur when scales are scraped off.
b. Rash commonly develops in areas of trauma (elbows, lower back).
   • Koebner phenomenon
4. Pitting of the nails (see Fig. 25-9J)
5. Microscopic findings
   a. Hyperkeratosis and parakeratosis
   b. Elongation of the rete pegs
      • Downward extensions of the basal layer
   c. Extension of the papillary dermis close to the surface epithelium
      • Blood vessels in the dermis rupture when scales are picked off (Auspitz sign).
d. Neutrophils collect in the stratum corneum.
   • Called Munro microabscesses

Bullous pemphigoid: subepidermal vesicles; negative Nikolsky sign; no acantholytic cells
PV and bullous pemphigoid: type II HSRs
DH: associated with celiac disease; subepidermal vesicles with neutrophils; type III HSR
LP: pruritic, violaceous, flat-topped papules, wrists, ankles
LP: oral mucosa commonly involved; Wickham striae
LP: associated with HCV, slight risk SCC
Psoriasis: strong HLA relationship
Psoriasis: unregulated proliferation of keratinocytes
Psoriasis: commonly preceded by streptococcal pharyngitis
Psoriasis: erythematous plaques with silver scales
Psoriasis: rash in areas of trauma (e.g., elbows); pitting of nails
Psoriasis: Munro microabscesses in stratum corneum; Auspitz sign
6. Treatment modalities
   a. Topical high-potency corticosteroids
   b. Topical calcipotriene (vitamin D analogue)
   c. Ultraviolet light A plus psoralen applied to plaques
   d. Ultraviolet light B plus coal tar applied to plaques
   e. Retinoids
   f. Systemic treatment
      • Methotrexate, cyclosporine

H. Pityriasis rosea
1. Initially presents as a single, large, oval, scaly, rose-colored plaque on the trunk
   a. Called the herald patch (see Fig. 25-9K)
   b. Frequently misdiagnosed as tinea corporis (ringworm)
2. Days or weeks later, a papular eruption develops on the trunk.
   a. Rash follows the lines of cleavage ("Christmas tree" distribution).
   b. Lesions tend to be pruritic.
   c. Rash remits spontaneously in 2 to 10 weeks.
3. Antihistamines control pruritus; UV light therapy hastens resolution.

I. Erythema multiforme (EM)
1. Type IV immunologic HSR of skin that is triggered by:
   a. Infection
      • *Mycoplasma pneumoniae*, herpes simplex virus (HSV; primary agent if recurrent EM occurs)
   b. Drugs
      • Sulfonamides, penicillin, barbiturates, phenytoin
2. Vesicles and bullae have a "targetoid" appearance (see Fig. 25-9L).
   • Located on the palms, soles, and extensor surfaces
3. Stevens-Johnson syndrome (SJS)
   a. SJS was recently separated from EM as a distinct entity.
   b. It is a type IV HSR that primarily involves the skin and mucous membranes
      (e.g., mouth, genitals).
      • Infections (e.g., HIV, group A streptococcus), drugs (antibiotics most common
        [penicillin, sulfa drugs]), and malignancies have been implicated; however, most cases
        are idiopathic.
   c. Erosions develop on the mucous membranes, and small blisters develop on
      purpuric or erythematous macules on the skin (different from target lesions
      of EM).
   d. It can be fatal.
4. Toxic epidermal necrolysis syndrome (TENS)
   a. Idiosyncratic reaction, most commonly drug-induced (e.g., sulfonamides, NSAIDs,
      anticonvulsants)
   b. May occur alone or overlap with SJS
   c. Characterized by extensive areas of erythema, necrosis, and bullous detachment of
      the epidermis and mucous membranes → exfoliation of skin
   d. Mucous membrane involvement can result in gastrointestinal bleeding, respiratory
      failure, and genitourinary complications.
   e. It can be fatal.
5. Treatment of EM
   a. Treat with systemic corticosteroids
   b. Treat triggering infection
   c. Discontinue drug

J. Erythema nodosum (EN)
1. Definition—inflammatory lesion of subcutaneous fat (panniculitis)
2. More common in women than men
3. Raised, erythematous, painful nodules
   • Usually located on the anterior portion of the shins (see Fig. 25-9M)
4. Common associations
   a. Coccidioidomycosis, histoplasmosis
   b. Tuberculosis (TB), leprosy
   c. Streptococcal pharyngitis
   d. *Yersinia enterocolitica* infections
   e. Sarcoïdosis, ulcerative colitis
   f. Pregnancy, OCPs
5. Treatment
   a. Identify and treat precipitating causes.
   b. NSAIDs
   c. Systemic corticosteroids if severe

K. **Granuloma annulare**
   1. Chronic inflammatory dermal disorder
      • Unknown etiology
   2. Occurs in children and adults
      • Female predominance
   3. Begin as erythematous papules
      • Papules evolve into annular plaques (see Fig. 25-9N).
   4. Occurs on the dorsum of the hands and feet
      • Disseminated type may be associated with diabetes mellitus (DM).
   5. Spontaneously resolves within 2 years
      • Recurrence in 40% of cases
   6. Treatment
      a. High-potency topical corticosteroids
      b. Intralional injection of corticosteroids

L. **Porphyria cutanea tarda (PCT)**
   1. Genetic or acquired disease involving porphyrin metabolism
   2. Deficiency of uroporphyrinogen decarboxylase
      a. Urine is wine-red color on voiding and is coral red when viewed with a Wood lamp.
      (see Fig. 25-9O).
      b. Uroporphyrin I is increased in urine.
   3. Precipitating factors
      a. Sunlight, HCV
      b. Excessive alcohol intake, OCPs, iron
   4. Clinical findings
      a. Photosensitive bullous skin lesions
         (1) Lesions are caused by porphyrin metabolites deposited in the skin.
         (2) Patients avoid light.
      b. Hyperpigmentation, fragile skin, hypertrichosis
   5. Treatment
      a. Avoid alcohol, OCPs
      b. Phlebotomy (decrease iron)
      c. Chloroquine

M. **Urticaria**
   1. Pruritic elevations of the skin
      a. Most often due to mast cell release of histamine
      b. Type I IgE-mediated reactions associated with certain exposures:
         (1) Certain foods (e.g., peanuts)
         (2) Insect bites (e.g., fire ant)
         (3) Drugs (e.g., penicillin, morphine, aspirin, laxative)
         (4) Emotional stress
         (5) Hepatitis B virus (HBV; part of serum sickness prodrome)
            • This is a type III HSR.
   2. Dermatographism (see Fig. 25-9P)
      • Urticaria develops in areas of mechanical pressure on skin.
   3. Treatment
      a. Discontinue offending drug.
      b. Avoid taking aspirin and other NSAIDs.
      c. Antihistamines, tricyclic drugs (e.g., doxepin), systemic steroids

N. **Cherry angiomas**
   1. Tiny, bright red papules (see Fig. 25-9Q)
      • Turn brown with time
   2. Invariably occur in all individuals >30 years old.
   3. No treatment is required.

O. **Acne rosacea**
   1. Definition—Inflammatory reaction of the pilosebaceous units of facial skin
      • Causal relationship with a mite (*Demodex folliculorum*)
   2. Pustules and flushing of the cheeks (see Fig. 25-9R)
      • Exacerbated by drinking alcohol, stress, eating spicy foods
3. **Sebaceous gland hyperplasia (see Fig. 25-9R)**
   - Causes enlargement of the nose (rhinophyma)

4. **Treatment**
   a. Topical metronidazole gel
   b. Systemic treatment
      1. Isotretinoin
      2. Tetracycline

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**P. Pyoderma gangrenosum (PG)**

1. **Epidemiology**
   a. Definition—ulcerative cutaneous condition often associated with systemic disease (>50% of cases)
   b. Systemic disease associations
      1. Ulcerative colitis/Crohn disease
      2. Myeloproliferative disease (MPD); monoclonal gammopathy
      3. Seronegative spondyloarthritis
      4. Rheumatoid arthritis (RA)

2. **Pathogenesis**
   a. Probable dysregulation of immune system
   b. Neutrophil dysfunction often present
   c. May be initiated by trauma (called pathergy)

3. **Clinical findings**
   a. Small red pustule/papule that ulcerates and enlarges (see Fig. 25-9S)
      1. Reminiscent of a brown recluse spider bite
      2. Single or multiple ulcers
   b. Violaceous border overhangs ulcer crater.

4. **Diagnosis**
   a. Culture to rule out secondary infection
   b. Biopsy

5. **Treatment**
   a. Topical—high-potency corticosteroids
   b. Systemic—corticosteroids; tumor necrosis factor-α inhibitors, cyclosporine

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**X. Selected Skin Disorders in Newborns**

**A. Erythema toxicum**

1. **Definition**—self-limited benign eruption of unknown cause
   a. Occurs in 30% to 70% of full-term newborns *(not premature newborns)*
   b. Lasts 2 to 3 weeks

2. **Erythematous papules, macules, and pustules** *(Fig. 25-10A)*

3. **Locations**
   - All sites except the palms and soles

**B. Sebaceous hyperplasia**

1. **Definition**
   - Profuse yellow-white papules
   a. Hyperplastic sebaceous glands
   b. Disappear in the first weeks of life

2. **Locations**
   - Forehead, nose (see Fig. 25-10B), upper lip, cheeks

**C. Milia**

1. **Definition**—superficial epidermal inclusion cysts
   - Pearly white papules contain laminated keratin material.

2. **Location in neonates**
   - Face (see Fig. 25-10C), gingiva, midline of palate and gingiva *(called Epstein pearls)*

3. **Exfoliate spontaneously or can be unroofed with a fine needle**

**D. Miliaria**

1. **Miliaria crystallina**
   a. Definition—retention of sweat in occluded eccrine sweat glands
   b. Pinpoint clear vesicles on the skin
   c. May suddenly erupt in profusion over large areas of the body *(see Fig. 25-10D)*
   d. Often associated in warm, humid conditions or fever
   e. Responds dramatically to cooling the patient and removal of excess clothing

2. **Miliaria rubra** *(“prickly heat”)*
   a. Definition—retention of sweat in occluded eccrine glands
   b. Erythematous, minute papulovesicles *(see Fig. 25-10E)*
   c. Like miliaria crystallina, it responds dramatically to cooling.
E. Mongolian spot
1. Definition—bluish black to slate gray spots that are present at birth
2. Usually occur in dark-skinned babies
3. Locations
   • Buttocks (see Fig. 25-10F), back, shoulders, legs
4. Disappears in the preschool years

XI. Selected Hair and Nail Disorders
A. Phases of hair growth in succession
1. Anagen phase
   a. Development of a new shaft of hair comes from the hair bulb.
   b. Hair length is determined in this stage.
   c. Growth stops at the end of this phase.
2. Telogen phase
   a. Resting phase
   b. Matrix portion shrivels and hair within the follicle is shed.
   c. New matrix is formed at the bottom of the follicle.
   d. Cycle repeats itself.
3. Length of each phase varies in the body.
   • Scalp hair—anagen phase lasts 6 years; telogen phase lasts 4 months
4. Hair growth is usually asynchronous; for scalp hair:
   a. At any one time, ~80% is in the anagen phase and ~10% to 20% is in the telogen phase.
   b. Only a small percentage of hair is lost at any point in time.
5. Estrogen effect on hair growth  
   a. Estrogen causes synchronous hair growth.  
   b. All hairs enter the resting phase at once.

**B. Massive hair loss**

1. Postpartum  
   - Most common cause
2. Oral contraceptive pills  
3. Stress  
4. Radiation/chemotherapy  
   - Inhibition of the anagen phase when cells in the hair bulb are dividing

**C. Alopecia areata**

1. Condition affects both sexes equally.
2. Onset most commonly occurs in young adults.
3. Cause is unknown.
   a. In some cases, it may have an autoimmune association.  
      - Hashimoto thyroiditis, pernicious anemia
   b. Family history is present in 20% to 25% of cases.
4. Clinical findings
   a. Hair is lost in well-circumscribed, round to oval patches.  
      - Hair loss may occur on the scalp, beard, eyebrows, and eyelashes.
   b. Hairs have the appearance of exclamation marks (Fig. 25-11A).
   c. Hair loss occurs over a period of weeks.
   d. Regrowth of hair occurs over several months.
   e. It may recur in up to one-third of cases.
5. Treatment
   a. Topical—clobetasol  
   b. Intralesional triamcinolone  
   c. Systemic corticosteroids  
   d. Psoralen + UVA, immunotherapy

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**25-11:** A, Alopecia areata. Note the area of baldness and the short hairs that have the appearance of exclamation marks. B, Nail anatomy. See text for discussion. C, Mees bands. Note the transverse white lines in the nail plate that extend proximally until they are pared off. D, Beau lines. Note the transverse grooves or depressions that are oriented parallel to the lunula. (A from Savin JA, Hunter JAA, Hepburn NC: Diagnosis in Color: Skin Signs in Clinical Medicine. London, Mosby-Wolfe, 1997, p 96, Fig. 4.5; B and C from Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, pp 140, 146, respectively, Figs. 8-3, 8-7, respectively; D from Callen JP, Paller AS, Greer KE, Swinyer LJ: Color Atlas of Dermatology, 2nd ed. Philadelphia, Saunders, 2000.)
D. Nail disorders

1. Nail anatomy (see Fig. 25-11B)
   a. Lunula
      (1) White half-moon–shaped area proximal to the cuticle
      (2) Underlying nail bed is partially keratinized, which produces the white color.
   b. Nail plate
      - Attached to the nail bed except distally where it separates from the hyponychium
   c. Nail matrix
      (1) Underneath the cuticle (eponychium)
      (2) Germinative zone where the nail plate originates

2. Nail disorders
   a. Psoriasis (see Fig. 25-9J)
      - Greater than 80% of patients have nail pitting.
   b. Chronic iron deficiency
      - Koilonychia (spoon nails; see Fig. 12-10C)
   c. Subacute infective endocarditis and trichinosis
      - Splinter hemorrhages in nails (see Fig. 11-20C)
   d. Mees lines
      (1) Sign of arsenic poisoning and systemic illness of any kind
      (2) Transverse white lines present in the nail plate (see Fig. 25-11C)
         - Extend proximally until they are pared off
   e. Beau lines
      (1) Transverse grooves or depressions parallel to lunula (see Fig. 25-11D)
      (2) Caused by conditions that cause the nail to grow slowly
         - Examples—infections, nutritional disorders, hypothyroidism
   f. Subungual hematoma
      (1) Blood clot under the nail plate due to trauma (see Fig. 25-6L)
      (2) Often confused with acral lentiginous melanoma
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I. Cerebral Edema, Pseudotumor Cerebri (Idiopathic Intracranial Hypertension), Herniation and Hydrocephalus

A. Cerebral edema

1. Subdivided into intracellular and extracellular types (Fig. 26-1A)
2. Intracellular edema
   a. Water moves into cells.
   b. Causes of intracellular edema include:
      (1) Dysfunctional Na⁺/K⁺-ATPase pump (e.g., global hypoxia)
      (2) Hyponatremia causing osmotic shift (e.g., syndrome of inappropriate antidiuretic hormone, SIADH)
3. Extracellular edema
   a. Due to increased vessel permeability (vasogenic)
   b. Causes of extracellular edema include:
      (1) Acute inflammation (e.g., meningitis, encephalitis)
      (2) Metastasis, trauma, lead poisoning

A patient with head trauma is purposely hyperventilated to produce respiratory alkalosis, which causes cerebral vessel constriction. This decreases the risk of increased vessel permeability and cerebral edema. Respiratory acidosis and hypoxemia cause vasodilation of cerebral vessels, which increases cerebral vessel permeability, resulting in cerebral edema. Both conditions cause increased activity of the K⁺ channels in smooth muscle cells → produces hyperpolarization → relaxes smooth muscle cells (↓ intracellular calcium) producing vasodilation with increased vessel permeability.

4. Produces signs of increased intracranial pressure (intracranial hypertension)
   a. Papilledema
      • Swelling of the optic disk (see Fig. 26-1B)
   b. Headache, projectile vomiting without nausea
   c. Sinus bradycardia, hypertension
   d. Potential for herniation (see later)

B. Pseudotumor cerebri (idiopathic intracranial hypertension)

1. Epidemiology
   a. Increased intracranial pressure
      • Papilledema is present (see Fig. 26-1B)
   b. Absence of tumor and obstruction to cerebrospinal fluid (CSF) flow
   c. No mental status alterations as one would see with cerebral edema
   d. No focal neurologic signs
   e. Most commonly seen in obese women of childbearing age
   f. Other risk factors include:
      (1) All-trans-retinoic acid used in treating acute promyelocytic leukemia (refer to Chapter 13)
(2) Hypothyroidism, Cushing disease, oral contraceptive pills
(3) Isotretinoin in treating acne, tamoxifen

2. Pathogenesis
   a. CSF reabsorption is decreased in the arachnoid villi.
   b. Eventual equilibration occurs with inflow and outflow.

3. Clinical findings
   a. Headache
   b. Rhythmic sound heard in one or both ears
   c. Diplopia, blurry vision (danger of complete visual loss)

4. Diagnosis
   a. MRI shows flattening of the posterior globe (100% positive predictive value).
   b. CSF pressure is increased.
      • Usually >300 mm H₂O (normal, 70–180 mm H₂O)
   c. Decreased CSF protein

5. Treatment
   a. Medical
      • Carbonic anhydrase inhibitor or systemic corticosteroids if visual disturbances present (lowers CSF pressure)
   b. Surgery
      (1) Lumboperitoneal shunt
      (2) Optic nerve sheath fenestration (regresses papilledema in the eye)

C. Cerebral herniation
1. Pathogenesis
   a. Complication of increased intracranial pressure
   b. Portions of the brain become displaced through (Fig. 26-2A):
      (1) Openings of dural partitions
      (2) Openings of the skull

2. Subfalcine herniation
   a. Cingulate gyrus herniates under the falx cerebri.
   b. Herniation causes compression of the anterior cerebral artery (ACA).

3. Uncal herniation
   a. Medial portion of the temporal lobe herniates through the tentorium cerebelli.

b. Complications include:
   (1) Compression of the midbrain
       - Produces Duret hemorrhages
   (2) Compression of the oculomotor nerve (cranial nerve [CN] III)
       (a) Eye is deviated down and out.
       (b) Pupil is mydriatic (dilated).
       - Compression of the parasympathetic postganglionic fibers
   (3) Compression of the posterior cerebral artery (PCA)
       - Causes hemorrhagic infarction of the occipital lobe

4. Tonsillar herniation
   a. Cerebellar tonsils herniate into the foramen magnum.
   b. Causes "coning" of the cerebellar tonsils (see Fig. 26-2B)
   c. Produces cardiorespiratory arrest

D. Hydrocephalus
1. Definition—increase in the CSF volume causes enlargement of the ventricles.
2. Production and movement of CSF (Fig. 26-3A)
   a. Produced by the choroid plexus in the ventricles
   b. Exits fourth ventricle through foramina of Luschka and Magendie and enters the subarachnoid space
   c. Reabsorbed by the arachnoid villus into the dural venous sinuses
   d. CSF analysis (Box 26-1)
3. Communicating (nonobstructive) hydrocephalus
   a. Open communication between ventricles and subarachnoid space
   b. Causes include:
      (1) Increased CSF production
          - Example—choroid plexus papilloma
      (2) Obstruction in reabsorption of CSF by the arachnoid villi
          - Examples—postmeningitic scarring, tumor, subarachnoid hemorrhage
4. Noncommunicating (obstructive) hydrocephalus
   a. Obstruction of CSF flow out of the ventricles
Nervous System and Special Sensory Disorders

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26-3: A, Schematic of the ventricles. Cerebrospinal fluid (CSF) is synthesized by the choroid plexus in the ventricles. The aqueduct of Sylvius (arrow) is a narrow communication between the third and fourth ventricles. CSF exits the fourth ventricle via the foramina of Luschka and Magendie (not shown in the schematic) where it enters the subarachnoid space. CSF is reabsorbed in the arachnoid villus (parasagittal location), which empties into the dural venous sinuses. B, Hydrocephalus and Parinaud syndrome. Note the increased head circumference and paralysis of upward gaze in this newborn with stenosis of the aqueduct of Sylvius. (A from Weyhenmeyer J, Gallman E: Neuroscience, Rapid Review Series, 1st ed, 2007, Philadelphia, Mosby, p 20, Fig. 2.3; B courtesy Dr. Albert Biglan, Children’s Hospital of Pittsburgh.)

b. Causes include:
   (1) Stricture of the aqueduct of Sylvius
      (a) This is the most common cause in newborns.
         • Causes paralysis of upward gaze (Parinaud syndrome; see Fig. 26-3B)
      (b) A pineal gland tumor can also obstruct the aqueduct of Sylvius and cause Parinaud syndrome (refer to Chapter 23).
   (2) Tumor in the fourth ventricle
      • Examples—ependymoma, medulloblastoma
   (3) Scarring at the base of the brain
      • Example—tuberculous meningitis
   (4) Colloid cyst in the third ventricle
   (5) Developmental disorders (see section II)

5. Clinical findings
a. Newborns
   • Ventricles dilate and enlarge the head circumference (see Fig. 26-3B).

b. Adults
   • Ventricles enlarge; however, there is no increase in head circumference.

6. Hydrocephalus ex vacuo
a. Dilated appearance of the ventricles when the brain mass is decreased from cerebral atrophy
b. Example—cerebral atrophy in Alzheimer disease

7. Normal pressure hydrocephalus
a. Epidemiology
   (1) Dilated ventricles + symptom complex of:
      (a) Wide-based gait
      (b) Urinary incontinence
      (c) Dementia
   (2) Dilated ventricles; normal CSF pressure
   (3) Accounts for 5% of dementia cases
   (4) Potentially reversible cause of dementia
b. Causes include:
   (1) Idiopathic (50% of cases)
   (2) Secondary causes
      (a) Prior subarachnoid hemorrhage
      (b) Prior intracranial surgery
      (c) Prior trauma

b. Causes include:
   (1) Stricture of the aqueduct of Sylvius
      (a) This is the most common cause in newborns.
      • Causes paralysis of upward gaze (Parinaud syndrome; see Fig. 26-3B)
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BOX 26-1 Cerebrospinal Fluid (CSF) Analysis

CSF derives from the choroid plexus in the ventricles and enters the subarachnoid space. It cushions the brain and spinal cord and transmits chemicals to other parts of the brain. CSF is reabsorbed by the arachnoid villi and drained into dural venous sinuses, which eventually drain into the jugular vein.

CSF normally is clear and colorless. Turbidity is caused by an increase in protein, cells, microbial pathogens, or a combination of all three elements. Bloody CSF from spinal taps is most commonly iatrogenic but can also represent a pathologic hemorrhage into the subarachnoid space (e.g., ruptured berry aneurysm, intracerebral bleed near the surface of the brain or ventricles). If the bloody tap is iatrogenic, the supranate should be clear after centrifugation, particularly in the last tube collected in the spinal tap. In pathologic bleeds, sequential color changes occur. CSF colors after centrifugation may be pink- or orange-tinted. A pink color is due to oxyhemoglobin (oxyHb) from ruptured red blood cells. It first occurs 2–4 hours post-bleed, peaks in 24–36 hours, and subsides in 4–8 days. A yellow to orange color (xanthochromia) is due to oxyHb breakdown into bilirubin. It first appears 12 hours post-bleed, peaks in 2–4 days, and subsides in 2–4 weeks.

CSF protein normally is 15–45 mg/dL. CSF prealbumin and albumin derive from plasma; therefore increased levels of these proteins must be due to increased capillary permeability (e.g., acute inflammation). **CSF gamma (γ) globulins** derive from the synthesis of IgG by plasma cells within the central nervous system (CNS). In a CSF electrophoresis, CSF γ-globulins account for <12% of the total protein. An increase in CSF IgG is due to either increased synthesis of IgG in the CNS (e.g., multiple sclerosis) or an increase in capillary vessel permeability in acute inflammation (e.g., meningitis). It is clinically important to make this distinction. A **CSF IgG index** (calculated with a formula) is useful in distinguishing acute inflammation from demyelinating diseases, the most common CNS disease producing an increase in IgG. An increase in the CSF IgG index correlates with a CNS origin of the IgG, and a decreased index indicates acute inflammation. **Routine CSF electrophoresis** quantitates the amount of γ-globulins that are present when CSF protein is increased. **High-resolution CSF electrophoresis**, however, is most useful in detecting demyelinating disease, of which multiple sclerosis is the most common cause. Other demyelinating diseases include neurosyphilis and Guillain-Barré syndrome. High-resolution detects **oligoclonal bands** in the γ-globulin region (Fig. 26-17D). These are discrete, discontinuous bands originating from single clones of immunocompetent B cells. Another test for demyelinating disease is myelin basic protein (MBP), a protein that is normally present in myelin. An increased CSF MBP occurs with active demyelinating disease. CSF MBP is decreased when a demyelinating disease is in remission.

**CSF glucose** does not have the same concentration as serum glucose. A normal value for CSF glucose is 50–75 mg/dL, but a normal value in serum glucose is 70–110 mg/dL. A rough estimate of what the CSF glucose should be is to multiply a serum sample value obtained 30–90 minutes before the lumbar puncture by 0.66. For example, if the serum glucose is 100 mg/dL, then the CSF glucose should be ~66 mg/dL. A decreased CSF glucose (hypoglycorrhachia) is defined as a glucose level <40 mg/dL. It implies that there has been increased uptake of glucose by cellular elements in the CSF (e.g., neutrophils in acute bacterial/fungal meningitis, malignant cells) or a defect in the glucose carrier system (frequently occurs in bacterial/fungal meningitis). CSF glucose is usually normal in viral meningitis, neurosyphilis, demyelinating disease, and a cerebral abscess. Exceptions in which viral infections of the CNS produce a decreased CSF glucose include infections associated with mumps, herpes simplex, and the lymphocytic chorimeningitis virus.

- The **CSF white blood cell count** normally is 0–5 mononuclear cells/mm³. Neutrophils are never normal in the CSF. An increased CSF WBC count is most often due to meningitis caused by microbial pathogens. Bacterial meningitis usually has a predominance of neutrophils, whereas viral meningitis initially has a neutrophil response in the first 24 hours that changes to a predominantly lymphocytic response in 2–3 days. Fungal meningitis is characterized by a predominance of lymphocytes. A parasitic meningitis usually has a mixed inflammatory infiltrate (eosinophils suggest a helminth infection).

- A **Gram stain** is useful for detecting bacteria (75%–80% sensitivity) in the sediment after ultracentrifugation of the CSF. Other tests include culture, India ink for Cryptococcus neoformans (sensitivity is 50%), antigen detection (sensitivity depends on the pathogen; specificity is 96%–100%), enzyme immunoassay (96%–100% sensitivity/specificity), and polymerase chain reaction studies that detect DNA (sensitivity 94%, specificity 96%).

**c. Pathogenesis**

1. Subarachnoid space volume is increased.
2. Ventricular dilation is out of proportion to sulcal atrophy (ventriculomegaly).
3. Wide-based gait and urinary incontinence are due to stretching of sacral motor fibers near the dilated ventricle.
4. Dementia is due to stretching of limbic fibers near the dilated ventricle.

**d. Diagnosis**

1. MRI documents ventriculomegaly and sulcal atrophy.
2. Large volume of CSF is removed at lumbar puncture.
   - Symptoms improve with removal of the fluid.
e. Treatment
   • Ventriculoperitoneal or ventriculoatrial shunting

II. Developmental Disorders
A. Neural tube defects
1. Pathogenesis
   a. Failure of fusion of the lateral folds of the neural plate
   b. Rupture of a previously closed neural tube
   c. Maternal folic acid levels must be adequate before pregnancy to prevent open neural tube defects (refer to Chapter 8).
2. Maternal findings
   • Increased maternal α-fetoprotein (AFP) in serum and/or amniotic fluid in anencephaly, meningocele, or myelomeningocele but not spina bifida occulta
3. Anencephaly (Fig. 26-4A and B)
   a. Complete absence of the brain
   b. Frog-like appearance
   c. Open spinal canal
   d. Maternal polyhydramnios (refer to Chapter 22)

26-4: A, Anencephaly frontal view. The entire cranium is missing and the foreshortened face appears frog-like. B, Anencephaly, posterior view. The brain is missing and the spinal canal is open. C, Spina bifida occulta. See text for discussion. D, Meningocele. See text for discussion. E, Meningomyelocele. See text for discussion. F, Syringomyelia. Note the collapsed cystic cavity (syrinx) in the center of the cervical spinal cord. The oval dashed circle encompasses the area where the crossed spinothalamic tracts and anterior horn cells would have been located. (A and B from Damjanov I: Pathology for the Health-Related Professions, 2nd ed, Philadelphia, Saunders, 2000, p 117, Fig. 5-23A and B; C to E from Moore NA, Roy WA: Rapid Review Gross and Developmental Anatomy, 2nd ed, Philadelphia, Mosby Elsevier, 2007, p 12, Fig. 1-13; F from Burger PC, Scheithauer BW, Vogel KS: Surgical Pathology of the Nervous System, 4th ed, London, Churchill Livingstone, 2002, p 554, Fig. 11-70.)
4. Spina bifida occulta (see Fig. 26-4C)
   a. Defect in closure of the posterior vertebral arch
   b. Dimple or tuft of hair in the skin overlying L5–S1
5. Meningocele (see Fig. 26-4D)
   a. Spina bifida with cystic mass containing meninges
   b. Most common in the lumbosacral region
6. Meningomyelocele (see Fig. 26-4E)
   a. Spina bifida with cystic mass containing meninges and spinal cord
   b. Most common in the lumbosacral region

B. Arnold-Chiari malformation
1. Definition—caudal extension of the medulla and cerebellar vermis through foramen magnum
2. Noncommunicating hydrocephalus
3. Platybasia (flattening of the base of the skull)
4. Associations:
   • Meningomyelocele, syringomyelia
5. Treatment
   • Decompression surgery

C. Dandy-Walker malformation
1. Definition—partial or complete absence of the cerebellar vermis
2. Cystic dilation of the fourth ventricle
3. Noncommunicating hydrocephalus
4. Treatment
   • Shunt to treat the hydrocephalus

D. Syringomyelia
1. Definition—degenerative disease of spinal cord
   a. Symptoms appear in the third and fourth decades.
   b. Fluid-filled cavity (syrinx) within the cervical spinal cord (see Fig. 26-4F)
   c. Produces cervical cord enlargement
   d. Cavity expands and causes degeneration of spinal tracts.
2. Associated with Arnold-Chiari malformation
3. Pathogenesis
   a. Obstruction of outflow from fourth ventricle
   b. Birth injury
4. Clinical findings
   a. Disruption of the crossed lateral spinothalamic tracts (see Fig. 26-4F)
      (1) Pain and temperature sensation is lost in the hands.
       • Tactile sense is preserved.
      (2) Person can burn the hands without being aware of the burn.
   b. Destruction of anterior horn cells (see Fig. 26-4F)
      (1) Atrophy of the intrinsic muscles of the hands
      (2) Often confused with amyotrophic lateral sclerosis (ALS)
       • No sensory changes in ALS
   c. Charcot joint in the shoulder, elbow, or wrist (refer to Chapter 24)
5. Diagnosis
   • MRI shows an enlarged cervical cord and a cystic cavity.
6. Treatment
   • Drainage of the syrinx slows progression.

E. Phakomatoses (neurocutaneous syndromes)
1. Epidemiology
   a. Definition—neurocutaneous syndromes include:
      (1) Disordered growth of ectodermal tissue
      (2) Malformations or tumors of the CNS
   b. Disorders include the following in descending order of incidence:
       • Neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome
2. Neurofibromatosis (NF)
   a. Autosomal dominant (AD) disorder with incomplete penetrance
   b. No gender predominance
   c. Neurofibromatosis type 1 (NF1; most common) and type 2 (NF2) variants
III. Head Trauma

A. Cerebral contusion
1. Permanent damage to small blood vessels and the surface of the brain
2. Most often secondary to an acceleration-deceleration injury
3. Coup injuries occur at the site of impact (Fig. 26-6).
4. Contrecoup injuries occur opposite the site of impact.
   • Common sites are at the tips of the frontal and temporal lobes.

d. NF1 (peripheral type) is associated with:
   (1) Café au lait–colored macules (Fig. 26-5A)
       (a) Occur in both types
   (2) Optic gliomas (2%–5% of cases), astrocytomas
   (3) Lisch nodules (>90% of cases; see Fig. 26-5B)
       • Pigmented hamartoma of the iris
   (4) Axillary and inguinal freckling (70% of cases; see Fig. 26-5C)
   (5) Mild scoliosis
   (6) Pigmented plexiform neurofibromas (not in NF2)
       • May progress into neurofibrosarcoma involving large nerves
   (7) Pigmented cutaneous/subcutaneous neurofibromas (see Fig. 26-5A)
       (a) Occur in both types
       (b) Occur anywhere on the body except the palms and soles
       (c) Appear in late adolescence and increase in size with age
       (d) Focal or diffuse
   (8) Tumor associations
       (a) Pheochromocytoma, Wilms tumor
           • Both produce hypertension.
       (b) Juvenile chronic myelogenous leukemia (CML)
   (9) Neurodevelopment problems (30%–40% of cases)

NF1—mutation on chromosome 17 coding for neurofibromin
NF2—mutation on chromosome 22 coding for merlin
Both proteins act as tumor suppressors.

NF1: optic gliomas; Lisch nodules; axillary/inguinal freckling
NF2: bilateral acoustic neuromas; juvenile cataracts; meningiomas
Tuberous sclerosis: AD; mental retardation
Key findings: seizures, mental retardation, angiofibromas, ash leaf spots
Hamartomas: subependymal proliferations, angiomyolipomas in kidneys, rhabdomyoma
Rhabdomyoma heart: highly predictive of tuberous sclerosis
SWS: vascular malformation on face; ipsilateral arteriovenous malformation in meninges in some patients
Coup injuries: site of impact
Contrecoup injuries: opposite site of impact; tips of frontal/temporal lobes
B. **Acute epidural hematoma**

1. Epidemiology
   a. Occurs in 1% to 2% of head injuries
   b. Definition—arterial bleed creates a blood-filled space between the bone and dura (Fig. 26-7A [left] and B)
   c. Caused by a fracture of the temporoparietal bone
      (1) Causes: hammer, baseball bat, any focused blow to head
      (2) Severance of the middle meningeal artery
      (3) Vessel lies between the dura and inner table of bone.
2. Some patients have a lucid interval after trauma followed later by neurologic deterioration.
3. Intracranial pressure increases, leading to herniation and death.
4. Diagnosis
   a. Head CT scan is the imaging test of choice (see Fig. 26-7C).
   b. Hematoma rarely crosses the suture line because the dura is firmly attached at these sites.
5. Treatment consists of creating burr holes to relieve pressure.

C. **Subdural hematoma**

1. Epidemiology
   a. Definition—venous bleeding between the dura and arachnoid membranes
   b. Causes
      (1) Most often the result of blunt trauma
         • Examples—car accident, baseball bat
      (2) Other causes include:
         (a) Medical anticoagulation, hemophilia
         (b) Child abuse, shaken baby syndrome
         (c) Spontaneous
      (3) Risk factors
         (a) Elderly persons and alcoholics with atrophy of the brain have increased risk.
         (b) Loss of brain mass leads to excess traction on the inflexible bridging veins.
2. Pathogenesis
   a. The bridging veins between brain and dural sinuses (Fig. 26-7A [right] and D) are torn.
   b. Slowly enlarging blood clot covers the convexity of the brain.
3. Clinical findings
   a. Consciousness level fluctuates.
   b. Herniation and death may occur.
   c. Chronic subdural hematomas may produce dementia.
4. CT scan is best imaging study (see Fig. 26-7E).
5. Treatment consists of creating burr holes to relieve pressure.

IV. Cerebrovascular Diseases

A. **Overview of cerebrovascular diseases (CVD)**

1. CVDs are subdivided into three major categories that include:
   a. Thrombosis (refer to Chapter 5)
   b. Infarction (refer to Chapter 2)
   c. Hemorrhage
2. Pathophysiologic processes that produce CVDs include:
   a. Reduced blood supply and oxygenation of tissue due to hypoxia, ischemia, and infarction (complication of ischemia; refer to Chapter 2)
   b. CNS hemorrhage (parenchyma, subarachnoid space) from rupture of cerebral vessels
26-7: A, Schematic of epidural hematoma (left side) and subdural hematoma (right side). B, Epidural hematoma. Note the blood is located on top of the dura (arrow). C, Non–contrast-enhanced CT scan of an acute epidural hematoma at the level of the right mid-convexity. There is an associated mass effect and moderate midline shift. D, Subdural hematoma. The reflected dura shows the outer membrane of an organized venous clot covering the convexity of the brain. E, Non–contrast-enhanced CT scan of an acute right temporal subdural hematoma. There is acute bleeding as well as delayed bleeding, which explains the mixed density. Mass effect is large, with a massive midline shift right to left. The right lateral ventricle has been obliterated. (A from Kumar V, Abbas AK, Fausto N, Mitchell RN: Robbins Basic Pathology, 8th ed. Philadelphia, Saunders Elsevier, 2007, p 871, Fig. 23-13A; B courtesy Dr. Raymond D. Adams, Massachusetts General Hospital, Boston; C and E from Marx J: Rosen’s Emergency Medicine Concepts and Clinical Practice, 7th ed, Philadelphia, Mosby Elsevier, 2010, pp 306, 320, respectively; Figs. 38-7, 38-9, respectively; D from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 405, Fig. 19-20.)

B. Global hypoxic injury

1. Causes of global hypoxic injury (refer to Chapter 2)
   a. Cardiac arrest
   b. Hypovolemic shock, septic shock
   c. Chronic carbon monoxide (CO) poisoning

Hypoglycemia: similar effect on brain as global hypoxia

Repeated episodes of hypoglycemia have the same effects on the brain as does global hypoxic injury. Hypoglycemia most commonly occurs in type 1 diabetes mellitus.
26-8: A, Red neurons. Note the brightly eosinophilic staining cells with the pyknotic nuclei within spaces representing apoptotic neurons. B, Distribution of the middle cerebral artery. C, Atherosclerotic stroke showing necrotic areas at the periphery of the cerebral cortex (pale infarction) in the distribution of the middle cerebral artery. Arrows are located at the line of demarcation between normal and infarcted tissue. D, Cholesterol embolus to retinal artery. Note the yellow embolus trapped at the bifurcation of the retinal artery (arrow). This produces a sudden, painless loss of vision (“curtain coming down”) followed in a variable period of time by restoration of vision (“curtain coming up”) as the embolus dislodges. This is called amaurosis fugax. (A from Burger PC, Scheithauer BW, Vogel KS: Surgical Pathology of the Nervous System, 4th ed. London, Churchill Livingstone, 2002, p 415, Fig. 7-34; B from Weyhenmeyer J, Gallman E: Neuroscience, Rapid Review Series, 1st ed, 2007, Philadelphia, Mosby, p 34, Fig. 3-5; C from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 408, Fig. 19-25A; D from Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 271, Fig. 10-113.)

2. Complications
   a. Cerebral atrophy (see Fig. 2-14A)
      (1) Atrophy is caused by apoptosis of neurons in layers 3, 5, and 6 of the cerebral cortex.
         • Produces laminar necrosis
      (2) Neurons are the most susceptible cell to hypoxic injury.
      (3) Neurons undergo apoptosis (“red” neurons; Fig. 26-8A).
   b. Watershed infarcts (refer to Chapter 2; Fig. 2-7A)
      (1) Occur at the junctions of arterial territories
      (2) Example—junction between the anterior and middle cerebral arteries
   c. Stroke

Red neurons: apoptotic neuron

Complications: cerebral atrophy; watershed infarcts; stroke
C. Strokes

1. Epidemiology
   a. Definition: sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function
   b. Increased incidence with age
   c. Peak incidence: 80 to 84 years of age
   d. More common in men than women
   e. Types of strokes
      (1) Ischemic (70%-80% of cases)
         (a) Atherosclerotic (thrombotic)
             • Most common type
         (b) Embolic
      (2) Intracerebral hemorrhage
      (3) Subarachnoid hemorrhage
      (4) Lacunar stroke

2. Atherosclerotic (thrombotic) stroke
   a. Pathophysiology
      (1) Most common overall type of stroke
      (2) Ischemic type of stroke caused by a platelet thrombosis that develops over a disrupted atherosclerotic plaque (refer to Chapter 10)
      (3) Common locations include:
         (a) Middle cerebral artery (MCA; most common location; see Fig. 26-8B)
         (b) Internal carotid artery near the bifurcation
         (c) Basilar artery
   b. Gross and microscopic findings
      (1) Develops at the periphery of the cerebral cortex (see Fig. 26-8C)
         • Reperfusion does not usually occur (becomes hemorrhagic if reperfusion occurs); hence, the majority are pale infarctions
      (2) Swelling of the brain
         (a) Loss of demarcation between gray and white matter
         (b) Breakdown of myelin
      (3) Gliosis is the reaction to injury (refer to Chapter 3).
         (a) Astrocytes proliferate at the margins of the infarct.
         (b) Microglial cells (macrophages) remove lipid debris.
      (4) Cystic area develops after 10 days to 3 weeks due to liquefactive necrosis.
   c. Clinical findings
      (1) Most atherosclerotic strokes are preceded by transient ischemic attacks (TIAs).
         (a) Definition: transient episode of neurologic dysfunction caused by focal brain/spinal cord/retinal ischemia without infarction
         (b) An example of a retinal TIA is amaurosis fugax.
            • Caused by microembolization of atherosclerotic material to a bifurcation of retinal arteries (called Hollenhorst plaque [see Fig. 26-8D])
         (c) Treatment of TIA
            • Antithrombotic therapy as soon as intracranial hemorrhage has been ruled out
            • Antiplatelet therapy: aspirin, clopidogrel, or ticlopidine
            • Possible carotid endarterectomy/stenting
      (2) Strokes involving the MCA (Fig. 26-9)
         (a) Contralateral hemiparesis and sensory loss in the face and upper extremity
         (b) Expressive aphasia
            • If Broca area is involved in the dominant (left) hemisphere
         (c) Visual field defects
         (d) Head and eyes deviate toward the side of the lesion.
      (3) Strokes involving anterior cerebral artery (ACA; Fig. 26-10)
         • Contralateral hemiparesis and sensory loss in the lower extremity
      (4) Strokes involving verteobasilar arterial system
         (a) Vertigo, ataxia
         (b) Ipsilateral sensory loss in the face
         (c) Contralateral hemiparesis and sensory loss in the trunk and limbs
   d. Prevention of atherosclerotic strokes
      • Aspirin, clopidogrel if allergic to aspirin
### Clinical features of a stroke involving the middle cerebral artery


<table>
<thead>
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<th>Site of Occlusion</th>
<th>Regions Affected</th>
<th>Signs and Symptoms</th>
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<tbody>
<tr>
<td>Motor area for upper body</td>
<td>Paresis or paralysis of contralateral face, hand, and arm</td>
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<tr>
<td>Somatosensory cortex for upper body</td>
<td>Sensory deficits involving contralateral face, hand, and arm</td>
<td></td>
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<tr>
<td>Axons of coronal radiata projecting from somatic motor area for lower limb (<em>left arrow</em>)</td>
<td>Paresis of contralateral leg</td>
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<tr>
<td>Axons from thalamic ventroposterolateral nucleus to somatosensory cortex for lower limb (<em>right arrow</em>)</td>
<td>Sensory deficit involving contralateral leg</td>
<td></td>
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<tr>
<td>Frontal lobe of <strong>dominant</strong> hemisphere (usually left hemisphere) related to speech production (Broca area)</td>
<td>Expressive aphasia (nonfluent or motor aphasia)</td>
<td></td>
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<tr>
<td>Superior temporal lobe areas of <strong>dominant</strong> hemisphere related to interpretation of speech</td>
<td>Receptive aphasia, fluent aphasia</td>
<td></td>
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<tr>
<td>Angular gyrus and parieto-occipital cortex of <strong>dominant</strong> hemisphere</td>
<td>Acalculia, agraphia, finger agnosia, right-left disorientation (collectively referred to as Gerstmann syndrome)</td>
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<tr>
<td>Supramarginal or angular gyrus</td>
<td>Loss or impairment of optokinetic reflex</td>
<td></td>
</tr>
<tr>
<td>Parietal lobe of <strong>nondominant</strong> hemisphere</td>
<td>Contralateral neglect (hemi-neglect), anosognosia</td>
<td></td>
</tr>
<tr>
<td>Frontal eye fields in frontal lobe</td>
<td>Transient loss of voluntary saccadic eye movement to contralateral side</td>
<td></td>
</tr>
<tr>
<td>Optic radiation within temporal lobes (Meyer loop)</td>
<td>Superior quadrantanopsia</td>
<td></td>
</tr>
<tr>
<td>Optic radiation within parietal and temporal lobes</td>
<td>Homonymous hemianopia</td>
<td></td>
</tr>
<tr>
<td>Upper portion of posterior limb of internal capsule and adjacent corona radiata</td>
<td>Capsular (pure motor) hemiplegia</td>
<td></td>
</tr>
</tbody>
</table>

3. Embolic (hemorrhagic) stroke
   a. Ischemic type of stroke due to embolization
   b. Source of emboli
      (1) Most often originate from the left side of the heart (refer to Chapter 5)
      (2) Examples include:
         (a) Mural thrombi in the left ventricle (LV) after an acute myocardial infarction (AMI; refer to Chapter 11), aortic and/or mitral valve vegetations, and the left atrium in atrial fibrillation
         (b) Atrial fibrillation (AF) is particularly notable as a progenitor of embolic strokes due to thrombus formation in the left atrium (LA) from stasis of blood.

---

**ACA stroke:**
contralateral paresis/sensory loss in lower extremity

**Vertebralbasilar artery stroke:** vertigo/ataxia, ipsilateral sensory loss in face, contralateral hemiparesis/sensory loss in trunks/limbs

**Embolic stroke:** ischemic stroke due to embolization
(c) “Shower” embolization refers to emboli blocking numerous small vessels (e.g., fat embolism, amniotic fluid embolism; refer to Chapter 5).

4. Intracerebral hemorrhage
   a. Most often due to stress imposed on vessels by hypertension
      (1) Branches of the lenticulostriate vessels develop Charcot-Bouchard microaneurysms (see Fig. 26-8B).
      (2) Rupture of aneurysms produces intracerebral hemorrhage (hematoma).
         • Intracerebral hematoma pushes the brain parenchyma aside (see Fig. 26-11B).
   b. Common sites of hemorrhage
      (1) Basal ganglia (35%–50% of cases occur in the putamen)
      (2) Thalamus (10% of cases)
      (3) Pons and cerebellar hemispheres (10% of cases)
   c. Slit hemorrhages associated with hypertension
      • Rupture of small caliber penetrating vessels producing hemorrhages that resorb blood, leaving slit-like spaces with a brownish-red pigment (hemosiderin from breakdown of red blood cells)

5. Subarachnoid hemorrhage
   a. Causes
      (1) Majority are secondary to rupture of a saccular (berry) aneurysm.
      (2) Bleeding from an arteriovenous malformation is a less common cause.
b. Saccular (berry) aneurysm (refer to Chapter 10)
   - Some use the term congenital berry aneurysm, with the understanding that they are not present at birth.
   
   (1) Risk factors
   (a) Normal hemodynamic stress
   (b) Presence of hypertension of any cause
   (c) Coarctation of aorta
   (d) Atherosclerosis
   (e) Cigarette smoking

   (2) Most develop at the junctions of communicating branches with the main cerebral artery (Fig. 26-12A).
   (a) Junctions lack internal elastic lamina and smooth muscle.
   (b) Most common site for berry aneurysm is the junction of the anterior communicating branch with the ACA.

   (3) Rupture releases blood into the subarachnoid space.
   - Blood covers the surface of the brain (see Fig. 26-12B).
   - Imparts a yellow color to CSF called xanthochromia (see Box 26-1)

   c. Clinical findings
   (1) Sudden onset of a severe occipital headache
   (a) Described as the “worst headache ever”
   (b) Nuchal rigidity is present from blood irritating the meningeal membranes.
   (2) About 50% of patients die soon after the hemorrhage.
   (3) Complications include:
   (a) Further hemorrhage
   (b) Hydrocephalus
      • Blockage of arachnoid villi
      • Blocks egress of CSF from the foramina of Luschka and Magendie
   (c) Permanent neurologic deficits

6. Lacunar infarcts
   a. Cystic areas of microinfarction <1 cm in diameter (see Fig. 26-12C)
   b. Caused by hyaline arteriolosclerosis (see Fig. 10-6)
   - Secondary to either hypertension (most common) or diabetes mellitus
c. Stroke syndromes
   (1) Pure motor strokes with or without dysarthria
      • Occur if the posterior limb of the internal capsule is involved
   (2) Pure sensory strokes
      • Occur if the thalamus is involved

7. Diagnosis of strokes
   a. CT scan without contrast is best for diagnosis.
      (1) Overall best imaging technique
   (2) Distinguishes hemorrhage from nonhemorrhagic strokes
   b. MRI is most useful for identification of posterior fossa infarcts.

8. Treatment of strokes
   a. Acute treatment
      (1) Depends on the type of stroke and the elapsed time to arrival at a hospital
      (2) Thrombolytic therapy in thromboembolic strokes
         a. Depends on the time interval of symptoms (<3 hours is ideal)
         b. Usually not implemented if stroke is hemorrhagic
      (3) In some cases, intracerebral hemorrhages can be surgically evacuated.
   b. Chronic treatment in strokes
      (1) Antiplatelet treatment (e.g., aspirin, clopidogrel)
      (2) Warfarin for embolic types of strokes
      (3) Treat risk factors for strokes (e.g., hypertension, diabetes)

V. CNS Infections
A. Pathogenesis
   1. Hematogenous spread (most common)
   2. Traumatic implantation
   3. Local extension from a nearby infection (e.g., frontal sinus, mastoid)
   4. Ascent via peripheral nerve (e.g., rabies)

B. Meningitis
   1. Definition— inflammation of pia mater covering the brain (Fig. 26-13A)
   2. Usually due to hematogenous spread
   3. Mechanism for bacterial meningitis
      a. Adherence of bacteria to the mucosa of the nasopharynx
      b. Bacteremia

Nervous System and Special Sensory Disorders

26-13: A, Bacterial meningitis showing engorged blood vessels and a creamy exudate covering the surface of the pia mater. B, Cerebral abscess showing a cystic mass lined by necrotic, purulent material. (A from Perkin GD: Mosby's Color Atlas and Text of Neurology. St. Louis, Mosby, 2002, p 196, Fig. 11-1; B from Burger PC, Scheithauer BW, Vogel KS: Surgical Pathology of the Nervous System, 4th ed, London, Churchill Livingstone, 2002, p 121, Fig. 3-17.)

Table 26-1 Cerebrospinal Fluid (CSF) Findings in Viral, Bacterial, and Fungal Meningitis

<table>
<thead>
<tr>
<th>CSF FEATURE</th>
<th>BACTERIAL</th>
<th>VIRAL</th>
<th>FUNGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cell count</td>
<td>Increased</td>
<td>Usually normal or slightly</td>
<td>Usually normal or slightly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>increased</td>
<td>increased</td>
</tr>
<tr>
<td>Differential count</td>
<td>Predominantly neutrophils;</td>
<td>First 24–48 hours, neutrophils,</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td></td>
<td>tuberculosis usually lymphocytes</td>
<td>then switches to lymphocytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>after 48 hours</td>
<td></td>
</tr>
<tr>
<td>CSF glucose</td>
<td>Decreased</td>
<td>Normal: exceptions—mumps,</td>
<td>Decreased</td>
</tr>
<tr>
<td>CSF protein</td>
<td>Increased</td>
<td>herpes, LCM</td>
<td></td>
</tr>
<tr>
<td>Gram stain</td>
<td>Frequently positive (60%–90%)</td>
<td>Culture positive (65%–90%)</td>
<td>Frequently positive</td>
</tr>
<tr>
<td></td>
<td>Culture (65%–90%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LCM, Lymphocytic choriomeningitis.

4. Risk factors in children
   a. Undernutrition, otitis media
   b. Pneumonia, immunodeficiency
   c. Viral infection, sickle cell disease
   d. Craniofacial abnormality

5. Viral meningitis
   a. Most are transmitted by the fecal-oral route.
   b. Respiratory route is less common.

6. Clinical findings in meningitis
   a. Fever, nuchal rigidity, headache

7. Complications of meningitis
   a. Seizures, focal neurologic deficits
   b. Cranial nerve palsies, sensorineural hearing loss
   c. Communicating and noncommunicating hydrocephalus

8. Laboratory findings in viral meningitis (Table 26-1; see Box 26-1)
   a. Increased CSF protein
      • Due to increased vessel permeability (refer to Chapter 3)
   b. Increased total CSF leukocyte count
      • Initially neutrophils, but converts to lymphocytes in 24–48 hours
VI. Demyelinating Disorders

A. Pathogenesis
1. Destruction of normal myelin
   • Example—multiple sclerosis
2. Production of abnormal myelin
   • Example—leukodystrophy
3. Destruction of oligodendrocytes
   • Examples—multiple sclerosis, slow virus infections

B. Acquired disorders
1. Multiple sclerosis (MS)
   a. Epidemiology
      (1) Most common demyelinating disease
      (2) Most common debilitating disease among young adults
      (3) Female predominance
         • Occurs most often in women 20 to 40 years of age
   b. Many subtypes
   c. Pathogenesis
      (1) Autoimmune disease initiated by:
         (a) Genetic factors (e.g., HLA-DR2)
         (b) Environmental factors
            • Microbial pathogens (e.g., Epstein-Barr virus, human herpesvirus 6, Chlamydia pneumoniae), vitamin D, sun exposure
      (2) CD4 TH1 cells and TH17 cells react against self myelin antigens (e.g., myelin basic protein [MBP] and other antigens; type IV hypersensitivity reaction; refer to Chapter 4).
      (3) CD4 TH1 cells secrete interferon-γ (γ-IFN), which activates macrophages (produce tumor necrosis factor-α; TNF-α) and TH17 cells release cytokines that recruit neutrophils and monocytes.
      (4) Both leukocytes and TNF-α attack the myelin sheath and oligodendrocytes, causing demyelination.
      (5) Antibodies produced by autoreactive B cells are directed against the myelin sheath and oligodendrocytes as well (type II hypersensitivity reaction).
### Table 26-2: Viral Infections of the Central Nervous System

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>DISEASE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arboviruses</td>
<td>Encephalitis</td>
<td>Mosquitoes are the vector&lt;br&gt;Wild birds are the reservoir for the virus&lt;br&gt;West Nile virus: crows and other birds have spread the disease from New York to the West Coast&lt;br&gt;Encephalitis can be fatal</td>
</tr>
<tr>
<td>Coxsackievirus</td>
<td>Meningitis</td>
<td>Enterovirus: most common cause of viral meningitis&lt;br&gt;Viral meningitis peaks in late summer and early autumn</td>
</tr>
<tr>
<td>Cytomegalovirus (see Fig. 26-14A)</td>
<td>Encephalitis</td>
<td>Most common viral CNS infection in AIDS&lt;br&gt;Primarily intranuclear eosinophilic inclusions&lt;br&gt;Periventricular calcification in newborns&lt;br&gt;Treatment: ganciclovir; valganciclovir; foscarnet (nephrotoxic, electrolyte abnormalities)</td>
</tr>
<tr>
<td>Herpes simplex virus type 1 (see Fig. 26-14B)</td>
<td>Meningitis and encephalitis</td>
<td>Causes hemorrhagic necrosis of the temporal lobes&lt;br&gt;Treatment: IV acyclovir</td>
</tr>
<tr>
<td>HIV (see Fig. 26-14C)</td>
<td>Encephalitis</td>
<td>Most common cause of AIDS dementia&lt;br&gt;Microglial cells fuse to form multinucleated cells</td>
</tr>
<tr>
<td>Lymphocytic choriomeningitis</td>
<td>Meningitis and encephalitis</td>
<td>Endemic in the mouse population&lt;br&gt;Transmission: food or water contaminated with mouse urine/feces&lt;br&gt;Meningoencephalitis: combination of nuchal rigidity and mental status abnormalities (encephalitis)&lt;br&gt;CSF findings: increased protein, lymphocyte infiltrate, normal to decreased glucose</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>Encephalitis and myelitis–spinal cord</td>
<td>Destroys upper and lower motor neurons&lt;br&gt;Causes muscle paralysis&lt;br&gt;Postpolio syndrome: occurs in ~50% of people with previous poliomyelitis; usually occurs 15–30 years after original infection; increased muscular weakness/pain in muscle groups already affected; excessive fatigue</td>
</tr>
<tr>
<td>Rabies virus (see Fig. 26-14D)</td>
<td>Encephalitis</td>
<td>Most often transmitted by raccoon bite (40% of cases)&lt;br&gt;Other vectors are dog, skunk, bat, and coyote&lt;br&gt;Viral receptor is acetylcholine receptor&lt;br&gt;Initially replicates at site of the bite; moves by axonal transport to the CNS; after CNS replication, it migrates to the saliva&lt;br&gt;Animal transmits virus when in the agitated state (encephalitis stage)&lt;br&gt;Incubation period 10–90 days&lt;br&gt;Prodrome: fever, paresthesias in and around the wound site&lt;br&gt;Hydrophobia: due to spasms of throat muscles when swallowing; followed by flaccid paralysis&lt;br&gt;Encephalitis: death of neurons; eosinophilic intracytoplasmic inclusions called Negri bodies&lt;br&gt;Seizures, coma, death&lt;br&gt;Treatment: wash wound site (quaternary ammonium compound); give passive immunization (immune globulin) mostly into wound site (where virus initially replicates); give active immunization (human diploid vaccine)&lt;br&gt;Universally fatal if not treated</td>
</tr>
</tbody>
</table>

### Table 26-3: Slow Viruses and Spongiform Encephalopathy of the Central Nervous System

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creutzfeldt-Jakob disease (CJD) (see Fig. 26-15)</td>
<td>Due to prions (contain infectious proteins devoid of RNA or DNA)&lt;br&gt;Infected prions have misfolded proteins; prion protein (PrP) becomes resistant to proteases; protease-resistant PrP promotes conversion of normal PrP to protease-resistant PrP; explaining the infectious nature of the disease; cannot be killed with standard sterilization techniques&lt;br&gt;Kill neurons (? apoptosis); brains have “bubble and holes” spongiform change in the cerebral cortex&lt;br&gt;Transmission: corneal transplantation, contact with human brains (neurosurgeons, neuropathologists), use of improperly sterilized cortical electrodes, ingestion of tissues from cattle with bovine spongiform encephalopathy (mad cow disease)&lt;br&gt;Death occurs within 1 year</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Conventional slow virus encephalitis due to papovavirus&lt;br&gt;Intranuclear inclusion in oligodendrocytes&lt;br&gt;Occurs in AIDS when CD4 T+ count &lt;50 cells/mm³</td>
</tr>
<tr>
<td>Subacute sclerosing panencephalitis</td>
<td>Conventional slow virus encephalitis associated with rubeola (measles) virus&lt;br&gt;Intranuclear inclusions in neurons and oligodendrocytes&lt;br&gt;Death usually occurs within 1–2 years</td>
</tr>
</tbody>
</table>
26-14: A, Congenital cytomegalovirus encephalitis. The arrows show many chalky periventricular calcifications (dystrophic calcification). B, Herpes simplex encephalitis. The basal view shows hemorrhagic necrosis of the right temporal lobe. Cerebral edema is also present. C, HIV encephalitis. Note the numerous multinucleated microglial cells, which is a characteristic finding in HIV encephalitis, the cause of AIDS dementia. D, Rabies. The Purkinje cells have intracytoplasmic, eosinophilic inclusions (arrows) called Negri bodies. (A and C from Klatt E: Robbins and Cotran Atlas of Pathology, Philadelphia, Saunders, 2006, pp 476, 477, respectively, Figs. 19-94, 19-97, respectively; B from Perkin GD: Mosby’s Color Atlas and Text of Neurology, St. Louis, Mosby, 2002, p 208, Fig. 11-15; D from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 1375, Fig. 28-25.)

26-15: Spongiform encephalopathy in Creutzfeldt-Jakob disease showing classic “bubbles and holes” of the neuropil cell bodies. (From Damjanov I, Linder J: Pathology: A Color Atlas. St. Louis, Mosby, 2000, p 412, Fig. 19-41.)

d. Gross and microscopic findings
(1) Demyelinating plaques occur in white matter of brain/spinal cord (Fig. 26-17A and B),
   - White matter looks like gray matter in areas of demyelination.
(2) Inflammatory infiltrate in plaques is composed predominantly of CD4 T cells, monocytes, and microglial cells with phagocytosed lipid.
e. Clinical findings
(1) Episodic course punctuated by acute relapses and remissions (80%–90% of cases)
(2) Sensory dysfunction
   (a) Paresthesias
   (b) Loss of pain/temperature sensation
   (c) Loss of vibratory sensation
(3) Upper motor neuron (UMN) dysfunction
   (a) Spasticity
   (b) Increased deep tendon reflexes (DTRs)
   (c) Muscle spasms
### TABLE 26-4 Bacterial Infections of the Central Nervous System

<table>
<thead>
<tr>
<th>BACTERIUM</th>
<th>DISEASE</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| **Group B streptococcus** *(Streptococcus agalactiae)* | Neonatal meningitis | Gram-positive coccus  
Most common cause of neonatal meningitis  
Spreads from a focus of infection in the maternal vagina  
*Treatment*: penicillin G or ampicillin |
| *Escherichia coli* | Neonatal meningitis | Gram-negative rod  
Second most common cause of neonatal meningitis (18%)  
*Treatment*: cefazidime + gentamicin |
| *Listeria monocytogenes* | Neonatal meningitis | Gram-positive rod with tumbling motility; actin rockets help organism to move from cell to cell  
Pathogen found in soft cheese, hot dogs  
*Treatment*: ampicillin + gentamicin |
| *Neisseria meningitidis* | Meningitis | Gram-negative diplococcus; found in posterior nasopharynx  
Most common cause of meningitis in those between 1 month and 18 years of age  
*Treatment*: ceftriaxone  
Prophylaxis for people in close contact: ciprofloxacin or rifampin or ceftriaxone |
| *Streptococcus pneumoniae* | Meningitis | Gram-positive diplococcus  
Most common cause of meningitis in patients >18 years of age (some authors say *N. meningitidis* is the most common and *S. pneumoniae* the 2nd most common)  
*Treatment*: ceftriaxone + vancomycin + dexamethasone |
| *Mycoplasma tuberculosis* | Meningitis | Complication of primary tuberculosis  
Involves base of brain  
Vasculitis (infarction) and scarring (hydrocephalus)  
*Treatment*: isoniazid, rifampin, ethambutol, pyrazinamide, dexamethasone |
| *Treponema pallidum* | Meningitis, encephalitis, myelitis | Spirochete (gram-negative)  
Types of neurosyphilis:  
Meningovascular: vasculitis causing strokes  
General paresis: dementia  
Tabes dorsalis: involves posterior root ganglia and posterior column; causes ataxia, loss of vibration sensation, absent deep tendon reflexes, Argyll Robertson pupil (pupils accommodate [constrict with near object] but do not react to light)  
*Treatment*: penicillin G (difficult to treat) |

### TABLE 26-5 Fungal and Parasitic Infections of the Central Nervous System

<table>
<thead>
<tr>
<th>FUNGUS/PARASITE</th>
<th>DISEASE</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| *Cryptococcus neoformans* *(see Fig. 26-16A)* | Meningitis and encephalitis | Occurs in an immunocompromised host  
Most common fungal CNS infection in AIDS  
Budding yeasts visible with India ink  
*Treatment*: fluconazole non-AIDS, amphotericin + flucytosine |
| *Mucor species* *(see Fig. 26-16B)* | Frontal lobe abscess | Occurs in diabetic ketoacidosis; spreads from frontal sinuses  
*Treatment*: amphotericin B |
| *Naegleria fowleri* | Meningoencephalitis | Protozoa (amoeba)  
Involves frontal lobes  
Contracted by swimming in freshwater lakes  
*Treatment*: amphotericin B |
| *Trypanosoma brucei gambiense*  
*Trypanosoma brucei rhodesiense* | Encephalitis | Protozoa (hemoflagellate).  
Transmission: bite of an infected tsetse fly *(Glossina)*  
Trypanosomes invade the blood and lymphatics early in the disease; initial drainage into the posterior cervical nodes produces lymphadenopathy *(Winterbottom sign)*; encephalitis occurs in later stages  
Diffuse encephalitis: somnolence (sleeping sickness) due to the release of sleep mediators by the organisms  
Trypanosomes are capable of antigen variation (cyclical fever spike)  
Starvation is the most common cause of death  
Diagnosis: trypanosomes in blood, CSF; serologic tests with characteristic increase in IgM early in the disease  
*Treatment*: pentamidine early in the disease; melarsoprol in encephalitis stage |
| *Taenia solium* *(see Fig. 26-16C)* | Cysticercosis | Helminth (tapeworm; cestode); transmitted by pigs  
Patient (intermediate host) ingests food or water containing eggs; eggs develop into larval forms *(cysticerci)* that invade the brain, producing calcified cysts causing seizures and hydrocephalus  
*Treatment*: albendazole + dexamethasone |
| *Toxoplasma gondii* *(see Fig. 26-16D, E)* | Encephalitis | Protozoa (sporozoan)  
Most common CNS space-occupying lesion in AIDS; ring-enhancing lesions on CT  
Congenital toxoplasmosis produces basal ganglia calcification  
*Treatment*: pyrimethamine + sulfadiazine + folinic acid (leucovorin) |

*AIDS*, Acquired immunodeficiency syndrome; *CNS*, central nervous system; *CT*, computed tomography.
26-16: A, Cryptococcus. India ink preparation showing large capsules surrounding budding yeast cells. B, Mucor species (zygomycosis). Note the broad, aseptate hyphae that have wide-angled branching. C, Neurocysticercosis. Note the multiple cysts located between the gray and white matter. D, Toxoplasmosis. Note the cyst (arrow) filled with bradyzoites. E, Toxoplasmosis. The computed tomographic scan shows multiple enhancing lesions. Toxoplasmosis is the most common space-occupying lesion in the brain in AIDS. It can be confused with primary central nervous system lymphoma. (A and B from Murray PR, Shea YR: Medical Microbiology, 2nd ed, St. Louis, Mosby, 2002, pp 787, 794, Figs. 75-8, 75-18, respectively; C from Damjanov I, Linder J: Pathology: A Color Atlas. St. Louis, Mosby, 2000, p 411, Fig. 19-38; D from Burger PC, Scheithauer BW, Vogel KS: Surgical Pathology of the Nervous System, 4th ed, London, Churchill Livingstone, 2002, p 143, Fig. 3-78; E from Perkin GD: Mosby's Color Atlas and Text of Neurology, St. Louis, Mosby, 2002, p 216, Fig. 11-23.)

UMN dysfunction:
- spasticity; ↑DTRs;
- muscle spasm; Babinski;
- weakness

Autonomic dysfunction:
- urge incontinence;
- sexual dysfunction;
- bowel motility dysfunction

MS: blurry vision due to optic neuritis; MS MCC

SIN: scanning speech, intention tremor, nystagmus

(d) Extensor plantar response (Babinski)
(e) Weakness
- Shoulder abduction, finger extension, foot dorsiflexion, hip/knee flexion

(4) Autonomic dysfunction
(a) Urge incontinence
- Hyperactive detrusor muscle (refer to Chapter 21)
(b) Sexual dysfunction
(c) Bowel motility problems

(5) Optic neuritis
(a) Inflammation of the optic nerve
- MS is the most common cause of optic neuritis.
(b) Blurry vision or sudden loss of vision

(6) Cerebellar ataxia
(7) Scanning speech (sound drunk)
(8) Intention tremor, nystagmus
**26-17:** A, Multiple sclerosis, gross appearance. The brain shows multiple areas of demyelinated white matter (arrows pointing to gray-brown plaques). B, Multiple sclerosis, gross appearance. Note the periventricular location for the demyelinating plaques. C, Bilateral internuclear ophthalmoplegia in multiple sclerosis. When the patient is asked to look right, the right eye moves to the right and exhibits jerk nystagmus, while the left eye remains stationary. When the patient is asked to look left, the left eye moves to the left and shows jerk nystagmus, while the right eye remains stationary. These findings are due to bilateral demyelination of the medial longitudinal fasciculus. D, High-resolution electrophoresis of spinal fluid (CSF) showing four oligoclonal bands which indicate the presence of demyelination. E, Magnetic resonance image showing extensive demyelination (white areas). (A from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 1383, Fig. 28-32; B from Klatt E: Robbins and Cotran Atlas of Pathology, Philadelphia, Saunders, 2006, p 480, Fig. 19-105; C, E from Perkin GD: Mosby's Color Atlas and Text of Neurology, St. Louis, Mosby, 2002, pp 183, 188, respectively. D, from McPherson R, Pincus M: Henry's Clinical Diagnosis and Management by Laboratory Methods, 22nd ed, Saunders, 2011, p 911, Fig. 46-8A)

<table>
<thead>
<tr>
<th>Bilateral internuclear ophthalmoplegia (INO; see Fig. 26-17C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Demyelination of medial longitudinal fasciculus (MLF)</td>
</tr>
<tr>
<td>(10) Flexion of the neck produces an electrical sensation down the spine.</td>
</tr>
<tr>
<td>f. Laboratory findings (see Box 26-1)</td>
</tr>
<tr>
<td>(1) Increased CSF leukocyte count</td>
</tr>
<tr>
<td>• Primarily CD4 T lymphocytes/monocytes</td>
</tr>
<tr>
<td>(2) Increased CSF protein</td>
</tr>
<tr>
<td>• Primarily an increase in γ-globulins</td>
</tr>
</tbody>
</table>

Bilateral INO: pathognomonic for MS; demyelinated MLF
26-18: Central pontine myelinolysis. Note the central area of demyelination in the pons. (From Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 413, Fig. 19-45.)

Lab: ↑CSF lymphocytes/monocytes, CSF protein, CSF MBP; normal CSF glucose

Oligoclonal bands in high-resolution electrophoresis: sign of demyelination

- Increased CSF MBP
  - Indicates active disease
- Normal CSF glucose
- High-resolution electrophoresis shows oligoclonal bands.
  - Discrete bands of protein in the γ-globulin region (see Fig. 26-17D)
  - Sign of demyelination
- MRI is extremely sensitive in detecting demyelinating plaques (see Fig. 26-17E).

g. Diagnosis
   - (1) Spinal tap (see earlier text and Box 26-1)
   - (2) MRI with gadolinium (most sensitive test)
h. Treatment
   - (1) Acute relapse
     - High dose methylprednisolone
   - (2) Chronic
     - (a) Disease modifying drugs—e.g., interferon-β
     - (b) Monoclonal antibody—natalizumab
     - (c) Cytotoxic drugs—cyclophosphamide, methotrexate, azathioprine
i. Prognosis
   - (1) Varies with the type of disease
   - (2) On average, ~70% of patients with MS are alive 25 years after their diagnosis.

2. Central pontine myelinolysis (CPM; Fig. 26-18)
   - (a) Most often occurs in alcoholics who have hyponatremia
   - (b) Rapid intravenous correction causes demyelination in the basis pontis.
     - Rapid change in osmolality initiates demyelination.
   - (c) Treatment is supportive.

3. Viral infections with direct infection of oligodendrocytes
   - Examples—subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy

C. Hereditary disorders

1. Leukodystrophies are inborn errors of metabolism.

2. Adrenoleukodystrophy
   - (a) X-linked recessive (XR) disorder
   - (b) Enzyme deficiency in β-oxidation of fatty acids (FAs) in peroxisomes
     - Results in accumulation of long-chain fatty acids
   - (c) Causes generalized loss of myelin in the brain and adrenal insufficiency

3. Metachromatic leukodystrophy
   - (a) Autosomal recessive disorder
     - Lysosomal storage disease (LSD)
   - (b) Deficiency of arylsulfatase A
     - Results in accumulation of sulfatides

4. Krabbe disease
   - (a) Autosomal recessive disorder
     - LSD
   - (b) Galactocerebroside β-galactocerebrosidase deficiency
     - Leads to accumulation of galactocerebroside
   - (c) Brain shows large, multinucleated, histiocytic cells (globoid cells).
VII. Degenerative Disorders

A. Definition
- Degenerative diseases involve neurons in the brain or spinal cord.

B. Alzheimer disease (AD)

1. Epidemiology
   - Most common cause of dementia (50%–75% of all cases)
     - Sporadic late-onset type of AD (most common)
     - Sporadic early-onset type of AD (before age 65 years)
   - Related to apolipoprotein gene E, allele ε4
   - Familial early-onset type of AD (<1% of cases)
     - Mutations of amyloid precursor protein (APP) on chromosome 21
     - Mutations in presenilin 1 on chromosome 14
     - Mutations in presenilin 2 on chromosome 1
   - Prevalence increases with age.
     - Prevalence is <1% in the 60- to 64-year-old age group.
     - Prevalence is 40% to 50% by the age of 95 years.
   - Trisomy 21 (Down syndrome) has a strong association with AD.
     - By 40 years of age, most Down syndrome patients have AD.

2. Role of β-amyloid (Aβ) protein in causing AD
   - Aβ is neurotoxic and damages neurons in the following sites:
     - Medial temporal lobe structures
     - Frontal cortex, especially the entorhinal cortex and hippocampus
     - Occipital lobes usually spared
   - Pivotal role of activated glycogen synthase kinase-3β (GSK) in neurotoxicity of Aβ
     - Activation of GSK causes phosphorylation of Aβ, which in turn, causes:
       - Neuronal and synaptic dysfunction
       - Signaling for neuronal apoptosis
     - Phosphorylated Aβ also has a positive feedback on GSK, which maintains the cycle of neurotoxicity
     - Initial activation of GSK has been traced to dysfunction within the Wnt (wingless integration pathway), which is a family of genes normally involved in:
       - Neuronal development during embryogenesis
       - Normal neuronal function
     - Normally, the Wnt signaling pathway inactivates GSK, which prevents phosphorylation of Aβ and its harmful effect on neurons.
     - However, if the Wnt signaling pathway is dysfunctional, GSK remains activated leading to phosphorylation of Aβ and its neurotoxic effects (e.g., apoptosis of neurons).
   - Aβ also deposits in the wall of cerebral vessels.
     - Important in producing amyloid angiopathy (see later text)
   - Aβ stains positive with Congo red and has apple-green birefringence with polarization (refer to Chapter 4).
   - Aβ is a metabolic product of APP.
     - APP is normally coded for on chromosome 21.
     - Defects in metabolism of APP by secretases cause an increase in Aβ.
     - α-Secretases cleave APP into fragments that cannot produce Aβ.
     - β-Secretases followed by γ-secretases (presenilin is catalytic unit) cleave APP into fragments that are converted to Aβ.
     - In the sporadic early-onset type of AD, allele ε4 of apolipoprotein gene E codes for a product that cannot eliminate Aβ from the brain leading to early onset of neurotoxicity.
   - Insulin degrading enzyme
     - Involved in the clearance of Aβ
     - Insulin resistance syndromes (type 2 diabetes, metabolic syndrome) have increased risk for AD, because increased insulin lowers insulin degrading enzyme, which increases Aβ.

3. Role of tau protein in AD
   - Normal function is to maintain microtubules in neurons.
     - Assembles and supports scaffolding important in neuron structure and function
   - Activated GSK enhances hyperphosphorylation of tau protein.
NF tangle: hyperphosphorylated tau protein in neuron
PIN1 enzyme: dephosphorylates hyperphosphorylated tau protein; deficient in some cases of AD

AD: (density NF tangles/senile (neuritic) plaques in brain; occipital lobe usually spared
Senile (neuritic) plaques: core Aβ surrounded by neuronal cell processes with tau protein

Amyloid angiopathy: risk for cerebral hemorrhage
Confirmation of AD: must be made at autopsy

4. Gross and microscopic findings
   a. Cerebral atrophy with dilation of ventricles (hydrocephalus ex vacuo)
      (1) Atrophy is due to loss of neurons in the temporal, frontal, and parietal lobes.
      (2) Occipital lobe is usually spared.
   b. Presence of NF tangles in the cytoplasm of neurons
      (1) Best visualized with silver stains (see Fig. 26-19A)
      (2) They may occur in other disorders.
         - Elderly patients without dementia, Huntington disease, Niemann-Pick disease
   c. Senile (neuritic) plaques
      (1) Core of Aβ surrounded by neuronal cell processes containing tau protein,
         microglial cells, and astrocytes (see Fig. 26-19B)
         • Located in the gray matter.
      (2) Aβ stains with Congo red (refer to Chapter 4).
      (3) Best visualized with silver stains
      (4) Also normally present in the brains of elderly people
   d. Amyloid angiopathy
      (1) Aβ is present in cerebral vessels.
      (2) Causes weakening of the vessels with an increased risk for hemorrhage
   e. Confirmation of AD
      (1) Requires postmortem examination of the brain
      (2) Must be widespread presence of NF tangles and senile plaques

5. Clinical findings
   a. Prominent early sign is the decline in short-term memory.
   b. Another early sign is loss of smell.
      • Dysfunction in the entorhinal cortex
   c. Patients with mild to moderate disease have only cognitive defects.
   d. Additional deficits accumulate, including changes in behavior, judgment, language, and abstract thought.
   e. Eventually, functional deficits manifest as a reduced ability for self-care.
   f. No focal neurologic deficits are present early in the disease.
   g. Patients usually die of an infection.
      • Example—intercurrent bronchopneumonia

6. Presumptive diagnosis is made with mental status testing; tests for:
   • Orientation, attention, verbal recall, language, visual-spatial skills

26-19: A, Neurofibrillary tangle. The stain shows a neuron with neurofilaments (arrow) composed of hyperphosphorylated tau protein. These are present in Alzheimer disease. B, Senile plaque (arrow) shows an eosinophilic center with peripherally located distended neuronal processes (neurites). Like neurofibrillary tangles, these are present in Alzheimer disease. (A from Klatt E: Robbins and Cotran Atlas of Pathology, Philadelphia, Saunders, 2006, p 481, Fig. 19-110; B from Burger PC, Scheithauer BW, Vogel KS: Surgical Pathology of the Nervous System, 4th ed, London, Churchill Livingstone, 2002, p 428, Fig. 8-9.)
7. Positron emission tomography (PET) is useful for the differential diagnosis of dementia.
8. Treatment
   a. Cholinesterase inhibitors
      • Increase synaptic transmission
   b. Memantine (blocks glutamate receptors)
C. Parkinsonism
1. Epidemiology
   a. Definition—group of disorders that alter dopaminergic pathways involved in voluntary muscle movement
      (1) Striatal system is involved in voluntary muscle movement; includes:
         • Substantia nigra, caudate, putamen, globus pallidus, subthalamus, and thalamus
      (2) Dopamine is the principal neurotransmitter in the nigrostriatal tract.
         • Connects the substantia nigra with the caudate and putamen
   b. Incidence increases with age.
   c. Idiopathic Parkinson disease is the most common type (see later).
   d. Other causes of parkinsonism
      (1) Encephalitis, ischemia
      (2) Chronic carbon monoxide (CO) poisoning
         • Causes necrosis of globus pallidus
      (3) Wilson disease
      (4) Addiction to MPTP, a derivative of meperidine
         • 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
      (5) Antipsychotic drugs (e.g., phenothiazines)
2. Idiopathic Parkinson disease
   a. Epidemiology
      (1) Onset occurs between 45 and 65 years of age.
      (2) Distribution is equal in men and women.
      (3) Most cases are sporadic.
   b. Pathophysiology
      (1) Degeneration/depigmentation of neurons in substantia nigra (Fig. 26-20A)
      (2) Causes deficiency of dopamine
      (3) Neurons contain intracytoplasmic, eosinophilic bodies called Lewy bodies.
         • Ubiquitinated damaged neurofilaments (refer to Chapter 2)
   c. Clinical findings
      (1) Muscle rigidity
         a. Slowness of voluntary muscle movement (bradykinesia)
         b. Cogwheel rigidity on physical examination
      (2) Resting tremor
         a. “Pill rolling” between the thumb and index fingers
         b. Illegible handwriting
      (3) Expressionless face (“poker face”), stooped posture
      (4) Difficulty in initiating the first step, shuffling gait
      (5) Blepharospasm, postural instability
      (6) Commonly have severe seborrheic dermatitis (refer to Chapter 25)
      (7) Dementia, in some cases

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**26-20**: A, Substantia nigra in Parkinson disease. The normal amount of pigmentation in the substantia nigra is shown in the midbrain on the left. The midbrain on the right shows markedly diminished pigmentation in the substantia nigra. B, Huntington disease with atrophy of caudate nuclei (white arrows) on their lateral sides. (A and B from Damjanov I, Linder J: Pathology: A Color Atlas. St. Louis, Mosby, 2000, p 419, Figs. 19-67, 19-65, respectively.)
3. Treatment
   a. Avoid drugs that worsen parkinsonism: neuroleptics, antiemetics, monoamine oxidase (MAO) inhibitors
   b. Levodopa—transformed into dopamine
   c. Carbidopa, benserazide—dopa decarboxylase inhibitors
   d. Bromocriptine, pergolide—dopamine agonists
   e. Selegiline, rasagiline—inhibit monoamine oxidase B, which inhibits breakdown of dopamine
   f. Specialized surgical procedures

D. Huntington disease (HD)
1. Epidemiology
   a. Autosomal dominant disease
   b. Trinucleotide repeat disorder (CAG) involving chromosome 4 (refer to Chapter 6)
   c. Delayed appearance of symptoms until 30 to 40 years of age
   d. No gender dominance
2. Atrophy/loss of striatal neurons
   • Caudate, putamen, globus pallidus (see Fig. 26-20B)
3. Clinical findings
   a. Chorea
      (1) Irregular, rapid, nonstereotyped involuntary movements
      (2) Called choreoathetosis if it has a writhing quality
   b. Oculomotor abnormalities
   c. Parkinsonism in later stages
   d. Depression
4. Diagnosis
   a. Genetic testing is available
   b. Imaging studies (CT, MRI)
      • Atrophy of caudate and putamen
5. Treatment is supportive.

E. Friedreich ataxia
1. Epidemiology
   a. Autosomal recessive (AR) disease
      (1) Trinucleotide repeat disorder (GAA)
      (2) Frataxin deficiency
         (a) Deficiency leads to impaired mitochondrial iron homeostasis.
         (b) Cells are more prone to apoptosis.
   b. Most common neurodegenerative hereditary ataxic disorder
   c. Sites of degeneration
      (1) Dorsal root ganglia
      (2) Posterior columns
      (3) Spinocerebellar tract
      (4) Lateral corticospinal tracts
      (5) Large sensory peripheral neurons
   d. Hypertrophic cardiomyopathy
   e. Type 1 diabetes mellitus (10% of cases)
2. Clinical findings
   a. Progressive gait ataxia
   b. Loss of deep tendon reflexes
      • Initially at the ankles
   c. Loss of vibratory sensation and proprioception
   d. Muscle weakness in the legs
3. Diagnosis
   a. Gene testing is available.
   b. Imaging (MRI) shows spinal cord atrophy.
4. Treatment is supportive.

F. Lou Gehrig disease (amyotrophic lateral sclerosis [ALS])
1. Epidemiology
   a. ALS is a degenerative disease involving loss of upper and lower motor neurons.
   b. Symptoms usually appear between 40 and 60 years of age.
   c. Most cases are sporadic (90%–95% of cases).
2. Pathogenesis
   • Possibly due to mutated superoxide dismutase (SOD) 1 (neuron destruction by superoxide free radicals) or misfolded SOD 1 leading to apoptosis of neurons (most likely mechanism)

3. Clinical findings
   a. Upper motor neuron (UMN) signs
      • Spasticity, Babinski sign
   b. Lower motor neuron (LMN) signs
      (1) Muscle weakness
         • Begins with atrophy of intrinsic muscles of the hands
      (2) Eventual paralysis of respiratory muscles
   c. No sensory changes
   d. Preservation of bowel and bladder function

4. Diagnosis
   • Electromyography and nerve conduction studies

5. Treatment
   • Riluzole (glutamate antagonist)

6. Average survival time is 3 to 5 years.

G. Werdnig-Hoffmann disease
   • Lower motor neuron disease that occurs in children

VIII. Toxic and Metabolic Disorders

A. Wilson disease (refer to Chapter 19)
   1. Autosomal recessive disease
      a. Defect in copper excretion in bile
      b. Defect in the incorporation of copper into ceruloplasmin (decreased)
      c. Leads to liver cirrhosis and excess free copper in the blood
   2. CNS findings
      a. Atrophy and cavitation of the basal ganglia, particularly the globus pallidus and putamen (Fig. 26-21A)
      b. Signs of parkinsonism, chorea, and dementia

B. Acute intermittent porphyria (AIP)
   1. Epidemiology
      a. Autosomal dominant disorder
      b. Defect in porphyrin metabolism
         (1) Deficiency of uroporphyrinogen synthase (porphobilinogen deaminase)
         (2) Proximal increase in porphobilinogen (PBG) and δ-aminolevulinic acid (ALA)
         (3) Urine is colorless when first voided.
            (a) Exposure to light oxidizes PBG to porphobilin producing port-wine color.
            (b) Classic “window sill test”
         (4) Heme has a negative feedback relationship with ALA synthase.
            • ALA synthase is the rate-limiting enzyme of porphyrin metabolism.

ALS: mutated SOD 1 or misfolded SOD 1
ALS: usually begins in intrinsic muscles of the hands
ALS: no sensory changes; bowel/bladder function intact
Werdnig-Hoffmann disease: LMN disease in children
Wilson disease: cystic degeneration of basal ganglia; ↓ serum free copper, ↓ serum ceruloplasmin
Lenticular nucleus—putamen/globus pallidus in basal ganglia
AIP: urine colorless when first voided; exposure to light produces color (window sill test)

(5) Decreasing heme precipitates porphyric attacks by increasing porphyrin synthesis.
   • Example—drugs enhancing liver cytochrome P450 system (e.g., alcohol)

2. Clinical findings
   a. Neurologic dysfunction
      (1) Recurrent bouts of severe abdominal pain simulating an acute abdomen
      (2) Often mistaken for a surgical abdomen
         • Patient has "bellyful of scars."
   b. Psychosis, peripheral neuropathy, dementia

3. Diagnosis
   • Enzyme assay in RBCs

4. Treatment
   a. Avoid drugs that precipitate attacks
   b. Carbohydrate loading with glucose
      • Inhibits ALA synthase

C. Vitamin B₁ deficiency (refer to Chapter 12)
   1. Subacute combined degeneration of the spinal cord (see Fig. 12-18C)
      • Posterior column and lateral corticospinal tract demyelination
   2. Dementia, peripheral neuropathy

D. CNS findings associated with alcohol abuse
   1. Cortical and cerebellar atrophy
   2. Central pontine myelinolysis (see Fig. 26-18)
   3. Wernicke-Korsakoff syndrome (WKS)
      a. Most often due to thiamine deficiency (refer to Chapter 8)
      b. Gross and microscopic findings
         (1) Hemorrhages of small vessels with hemosiderin deposits
            • Mammillary bodies, wall of the third and fourth ventricles (see Fig. 26-21B)
         (2) Neuronal loss, gliosis, vessel hemorrhage
      c. Wernicke encephalopathy; reversible findings:
         • Confusion, ataxia, nystagmus, ophthalmoplegia (eye muscle weakness)
      d. Korsakoff psychosis
         (1) Advanced irreversible stage of Wernicke encephalopathy
            • Targets the limbic system
         (2) Anterograde amnesia (inability to form new memories)
         (3) Retrograde amnesia (inability to recall old memories)
         (4) Confabulation, hallucinations

4. Treatment
   • Thiamine supplementation

IX. CNS Tumors

A. Epidemiology
   1. Primary brain tumors in adults
      a. Approximately 70% occur above the tentorium cerebelli.
      b. In order of decreasing frequency:
         • Glioblastoma multiforme (GBM), meningioma, ependymoma
   2. Primary brain tumors in children
      a. Second most common cancer in children
      b. Approximately 70% occur below the tentorium cerebelli.
      c. In order of decreasing frequency:
         • Cystic cerebellar astrocytoma, medulloblastoma, brainstem glioma
   3. Risk factors
      • Turcot syndrome, neurofibromatosis, cigarette smoking
   4. General clinical findings
      a. Headache (20% initially, 60% later)
         (1) Tend to be worse during the night and often wakes the person up
         (2) Accompanied by nausea and vomiting
      b. Seizures (>30% of cases)
      c. Symptoms/signs of intracranial hypertension (see section I)
   5. Imaging studies
      a. MRI with gadolinium enhancement
      b. CT scan useful if calcium or hemorrhage is present
c. Functional MRI for lesions in vital areas
d. Positron emission tomography (PET)
6. Treatment modalities
  • Surgery, irradiation, chemotherapy

B. Astrocytoma
1. Accounts for about 70% of all neuroglial tumors
   a. The tumor usually involves the frontal lobe in adults.
   b. The tumor usually involves the cerebellum in children.
   c. Grades I and II are low-grade cancers.
   d. Grades III and IV are high-grade cancers.
2. Glioblastoma multiforme (GBM)
   a. High-grade astrocytoma
      (1) May arise de novo
      (2) May arise from dedifferentiation of a low-grade astrocytoma
   b. Hemorrhagic tumor (Fig. 26-22A)
      (1) Multifocal areas of necrosis and cystic degeneration
      (2) Commonly cross the corpus callosum

26-22: A, Glioblastoma multiforme showing hemorrhage and necrosis in the brain parenchyma and spreading into the adjacent hemisphere via the corpus callosum. B, Meningioma. Note the parasagittal multilobular tumor that is attached to the overlying dura. The tumor compresses the underlying surface of the brain. C, Meningioma. Note the swirling meningothelial cells and numerous basophilic staining psammoma bodies. D, Ependymoma of fourth ventricle. Note the hemorrhagic mass filling and expanding the fourth ventricle. E, Medulloblastoma. In the cerebellum there is a centrally located hemorrhagic tumor with necrosis that has almost compressed the fourth ventricle. F, Brain metastasis. The magnetic resonance image shows multiple nodular enhancing masses of varying sizes representing metastases from a breast cancer. (A from Damjanov I, Linder J: Anderson’s Pathology, 10th ed, St. Louis, Mosby, 1996, p 2750, Fig. 77-120; B and C from Kumar V, Fausto N, Abbas A: Robbins and Cotran Pathologic Basis of Disease, 7th ed, Philadelphia, Saunders, 2004, p 1409, Figs. 28-48A and B, respectively; D from Klatt E: Robbins and Cotran Atlas of Pathology. Philadelphia, Saunders, 2006, p 487, Fig. 19-127; E from Damjanov I, Linder J: Pathology: A Color Atlas, St. Louis, Mosby, 2000, p 424, Fig. 19-82; F from Katz D, Math K, Groskin S: Radiology Secrets, Philadelphia, Hanley & Belfus, 1998, p 349, Fig. 1.)
Meningioma: MC benign brain tumor in adults

Meningioma: derived from meningotheial cell of arachnoid membrane; parasagittal location

Meningioma: association with NF-2, history of radiation

Meningioma: female predominance; psammoma bodies

Meningioma: new-onset focal seizures

Ependymoma: fourth ventricle in children; cauda equina in adults

Medulloblastoma: malignant small cell tumor in cerebellum

Oligodendroglioma: frontal lobe calcifications in adult

Primary CNS lymphoma: occurs in AIDS; EBV-mediated cancer

Metastasis MC brain malignancy; lung MC primary site

Sensory changes: demyelination—paresthesias; glove and stocking distribution

Motor changes: axon degeneration—muscle fasciculations, atrophy

CMT: MC hereditary neuropathy

CMT: lower legs have inverted bottle appearance

c. May seed the neuraxis via the CSF
   • Rarely metastasize outside the CNS
d. Generally poor prognosis

C. Meningioma
1. Most common benign brain tumor in adults
   a. Female predominance (tumors have estrogen and progesterone receptors)
   b. Some tumors have androgen receptors.
2. Derived from the meningotheial cell within the arachnoid membrane that lines but is not adherent to the dura
   a. Most commonly has a parasagittal location
   b. Other common sites are the olfactory groove and lesser wing of the sphenoid
3. Associated with neurofibromatosis (NF) 2, history of radiation
4. Gross and microscopic findings (see Fig. 26-22B and C)
   a. Firm tumors
      (1) May indent (not invade) the surface of brain
      (2) Often infiltrate the overlying bone
         • Causes increased bone density
   b. Swirling masses of meningotheial cells encompass psammoma bodies (calcified bodies).
5. Common cause of new-onset focal seizures

D. Ependymoma
1. Benign tumor derived from ependymal cells (see Fig. 26-22D)
2. Arises in the cauda equina in adults
3. Arises in the fourth ventricle in children
   • Can produce a noncommunicating hydrocephalus

E. Medulloblastoma
1. Malignant small cell tumor
   • Primarily occurs in children
2. Arises from the external granular cell layer of the cerebellum (see Fig. 26-22E)
3. Often seeds the neuraxis and invades the fourth ventricle

F. Oligodendroglioma
1. Benign tumor derived from oligodendrocytes
   • Primarily occurs in adults
2. Frontal lobe tumor that frequently calcifies

G. CNS lymphoma
1. Majority are metastatic high-grade B-cell non-Hodgkin lymphomas.
2. Primary CNS lymphomas
   a. Most often associated with AIDS
   b. Epstein-Barr virus (EBV)-mediated B-cell lymphomas
   c. Rapidly increasing due to the increase in AIDS

H. Metastasis
1. Most common brain malignancy is metastasis (see Fig. 26-22F)
2. In order of decreasing frequency:
   a. Lung, breast, skin (melanoma), kidney, gastrointestinal tract
   b. Prostate cancer can metastasize to brain and dura but rarely to the brain

X. Peripheral Nervous System Disorders
A. Peripheral neuropathies
1. Associated with demyelination and axonal degeneration
   a. Demyelination is often segmental.
      • Sensory changes (e.g., paresthesias), often in a “glove and stocking” distribution
   b. Axonal degeneration
      • Muscle fasciculations lead to muscle atrophy
2. Charcot-Marie-Tooth (CMT) disease
   a. Most common hereditary neuropathy
      • Autosomal dominant disease
   b. Peroneal nerve neuropathy
      (1) Causes atrophy of muscles of the lower legs
      (2) Legs have an “inverted bottle” appearance.
   c. Treatment is supportive.
3. Guillain-Barré syndrome (GBS)
   a. Epidemiology
      (1) Most common acute peripheral neuropathy
      (2) Most common cause of acute flaccid paralysis
      (3) Predominantly motor involvement
      (4) Variants can be motor and sensory
      (5) Autoimmune demyelination syndrome
         (a) Involves nerve roots and peripheral nerves
         (b) Common preceding infections
            • Mycoplasma pneumoniae pneumonia, Campylobacter jejuni enteritis, viral
              infection (HIV, EBV, cytomegalovirus, influenza)
   b. Rapidly progressive ascending motor weakness
      (1) Less commonly descending motor weakness
      (2) Usually starts in the proximal muscles and eventually includes the distal
           muscles
      (3) Danger of respiratory muscle paralysis and death
   c. Depressed or absent deep tendon reflexes in the arms and legs
   d. Glove and stocking paresthesias/numbness
   e. Laboratory findings (see Box 26-1)
      (1) Increased CSF protein
         • Oligoclonal bands present on high-resolution electrophoresis
      (2) CSF glucose, cell count normal
   f. Diagnosis
      (1) Spinal tap with increased CSF protein
      (2) Electromyography and nerve conduction studies
   g. Treatment
      (1) Infusion IV immunoglobulin or plasma exchange
      (2) Mechanical ventilation if required
   h. Prognosis
      (1) Mortality 5% to 10% of cases
      (2) Full motor recovery 60% of cases
      (3) Residual weakness 15% of cases

4. Diabetes mellitus (DM)
   a. Most common cause of peripheral neuropathy
   b. Due to osmotic damage of Schwann cells (refer to Chapter 23)

5. Toxin-associated neuropathies
   • Alcohol, heavy metals, diphtheria

6. Idiopathic Bell palsy
   a. LMN palsy causing unilateral facial paralysis
   b. Inflammatory reaction of the facial nerve (CN VII)
      • Inflammation near the stylomastoid foramen or in the bony facial canal
   c. May be associated with herpes simplex virus (HSV; most common), HIV, sarcoidosis,
      Lyme disease, pregnancy
      • Often bilateral in Lyme disease
   d. Clinical findings in LMN disease (Fig. 26-23A and B, at point B in the schematic)
      (1) Ipsilateral upper and lower face involvement
      (2) Drooping of the corner of the mouth
      (3) Difficulty speaking
      (4) Inability to close the eye
      (5) Inability to wrinkle the forehead muscles
      (6) Hyperacusis in some cases
   e. Clinical findings in UMN disease (see Fig. 26-23B, at point A in the schematic)
      (1) Contralateral lower face involved
      (2) Contralateral upper face spared

7. Drugs producing peripheral neuropathy
   • Examples—vincristine, hydralazine, phenytoin

8. Vitamin deficiencies producing peripheral neuropathy
   • Examples—deficiency of thiamine, vitamin B₁₂, pyridoxine

9. Treatment of peripheral neuropathies; reduce nerve pain:
   a. Antiseizure medications—gabapentin, carbamazepine
   b. Lidocaine patch
   c. Tricyclic antidepressants—amitriptyline, nortriptyline
26-23: A, Right-sided Bell palsy showing inability to fully close the right eye (A) and drooping of the right corner of the mouth (B). B, Schematic of lower and upper motor neuron Bell palsy. Lower motor neuron (point B) is ipsilateral and involves the upper and lower face. Upper motor neuron (point A) involves the contralateral lower face and there is contralateral sparing of the upper face. (A from Perkin GD: Mosby's Color Atlas and Text of Neurology. St Louis, Mosby, 2002, p 77, Fig. 4-24A and B; B from Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, p 677, Fig. 21-16.)

26-24: Acoustic neuroma showing spindle-shaped cells with alternating dark and light areas (similar to a zebra). (From Damjanov I, Linder J: Pathology: A Color Atlas. St. Louis, Mosby, 2000, p 432, Fig. 19-107.)

B. Schwannoma (neurilemoma)
1. Definition—benign tumor derived from Schwann cells
   a. CN V (trigeminal) and CN VIII (acoustic) may be involved.
   b. Spinal nerve roots, peripheral nerves may be involved.
2. Acoustic neuroma
   a. Schwannoma of CN VIII
   b. Majority are located in the cerebellopontine angle.
      (1) Encapsulated tumors
      (2) Usually unilateral
      (3) Microscopic view shows alternating dark and light areas (Fig. 26-24).
   c. Clinical findings
      (1) Associated with neurofibromatosis (NF2)
         ▪ Usually bilateral tumors
      (2) Tinnitus (ruling in the ears)
### TABLE 26-6 Selected Nerve Injuries

<table>
<thead>
<tr>
<th>INJURY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulnar nerve (C8–T1) (see Fig. 26-25A)</td>
<td>Fracture of medial epicondyle of the humerus. Injury produces a “claw hand” (loss of interosseous muscles).</td>
</tr>
<tr>
<td>Radial nerve (C5–T1) (see Fig. 26-25B)</td>
<td>Midshaft fractures of humerus. Draping the arm over a park bench (called “Saturday night palsy”). Injury produces wrist drop.</td>
</tr>
<tr>
<td>Axillary nerve (C5–C6)</td>
<td>Fracture of surgical neck of humerus; anterior dislocation of the shoulder joint (may also injure the axillary artery). Cannot abduct the arm to horizontal position or hold the horizontal position when a downward force is applied to the arm (paralysis of deltoid muscle).</td>
</tr>
<tr>
<td>Median nerve (C6–T1) (see Fig. 26-25C and D; Fig. 24-14F and G)</td>
<td>Most commonly due to entrapment of the median nerve in the transverse carpal ligament of the wrist (carpal tunnel syndrome) or between the bellies of the pronator teres muscle (refer to Chapter 24). Rheumatoid arthritis and pregnancy are the two most common causes; also caused by overuse of the hands and wrist (e.g., in barbers), amyloidosis, hypothyroidism, and a supracondylar fracture of the humerus. Clinical: nocturnal pain; pain, numbness, or paresthesias in the thumb, index finger, third finger, and radial side of fourth finger; thenar atrophy produces an “ape hand” appearance and difficulty in opposing the thumb with the 5th finger. Tinel sign: pain reproduced by tapping over the median nerve. Phalen sign: pain reproduced with forced flexion of the wrist for 1 minute. Diagnosis: nerve conduction studies; electromyography to rule out muscle degeneration related to nerve compression.</td>
</tr>
<tr>
<td>Common peroneal nerve (L4–S2) (see Fig. 26-25E)</td>
<td>Common peripheral neuropathy. Causes: lead poisoning, fractured neck of the fibula, cast tightness. Motor deficits: Loss of foot eversion due to weakening of the peroneus longus and brevis muscles. Loss of foot dorsiflexion due to weakening of the tibialis anterior muscle; produces “slapping gait” or “high-stepping gait” like a horse. Loss of toe extension due to weakening of the extensor digitorum longus and hallucis longus muscles. Combined effect of all the above produces an equinovarus deformity, where there is plantar flexion with foot drop and inversion of the foot. Sensory deficits involve the anterolateral aspect of the leg and dorsum of the foot. Loss of the ankle jerk reflex.</td>
</tr>
<tr>
<td>Erb-Duchenne palsy (see Fig. 26-25F)</td>
<td>Brachial plexus lesion involving C5 and C6. “Waiter’s tip deformity.”</td>
</tr>
</tbody>
</table>

3. Sensorineural deafness
4. Sensory changes in CN V distribution
   - Due to tumor impingement on CN V

d. Treatment is surgery.

C. Selected peripheral nerve injuries (Table 26-6; Fig. 26-25)

XI. Selected Eye Disorders (Table 26-7; Fig. 26-26)

XII. Selected Ear Disorders (Table 26-8; Fig. 26-27)
26-25: A, Ulnar nerve injury. Note the claw hand due to an opposed action of the long flexors and extensors of the fingers. The ink markings show the distribution of impaired sensation. B, Radial nerve injury. Note the wrist drop. The ink markings show the distribution of impaired sensation. C, Effect of carpal tunnel syndrome on the median nerve. See text for discussion. D, Arrows show atrophy of thenar eminence. E, Common peroneal nerve injury. Note the foot drop. The ink markings show the distribution of impaired sensation. F, Erb-Duchenne palsy. Note how the arm is internally rotated and the forearm pronated producing a “waiter’s tip” deformity. The ink markings show the distribution of impaired sensation of the outer side of the upper arm. (A, B, E, and F from Grieg JD: Color Atlas of Surgical Diagnosis. London, Mosby-Wolfe, 1996, pp 337, 334, 338, 332, respectively, Figs. 42.8, 42.4, 42.9, 42.2, respectively; C from Goldman L, Ausiello D: Cecil’s Textbook of Medicine, 23rd ed, Philadelphia, Saunders Elsevier, 2008, p 2008, Fig. 285-5; D from Perkin GD: Mosby’s Color Atlas and Text of Neurology. St. Louis, Mosby, 2002, p 224, Fig. 12.10A.)
### TABLE 26-7 Selected Eye Disorders

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<th>DISCUSSION</th>
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<tr>
<td>Arcus senilis (see Fig. 26-26A)</td>
<td>Most often occurs in elderly Gray-opaque ring at the corneal margin (periphery of cornea) Cholesterol deposits in corneal stroma; may indicate hypercholesterolemia if the patient is &lt;50 years old and a smoker</td>
</tr>
<tr>
<td>Ophthalmia neonatorum</td>
<td>Conjunctivitis in newborn Pathogens: <em>Neisseria gonorrhoeae</em> (first week; 2–4 days), <em>Chlamydia trachomatis</em> (second week; 3–10 days) Treatment: <em>N. gonorrhoeae</em>: ceftriaxone <em>C. trachomatis</em>: erythromycin Erythromycin eye drops (chemical irritation)</td>
</tr>
<tr>
<td>Bacterial conjunctivitis (see Fig. 26-26B)</td>
<td>Purulent conjunctivitis; pain but no blurry vision Pathogens: <em>Staphylococcus aureus</em> (most common), <em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em> (<em>Haemophilus aegyptius</em>, pinkeye) Treatment: gatifloxacin ophthalmic solution</td>
</tr>
<tr>
<td>Viral conjunctivitis (see Fig. 26-26C)</td>
<td>Watery exudates Adenovirus: viral cause of pinkeye, painful preauricular lymphadenopathy No treatment HSV-1: keratoconjunctivitis with dendritic ulcers noted with fluorescein staining Treatment: trifluridine ophthalmic</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>Seasonal itching of eyes Treatment: antihistamine ophthalmic solutions; olopatadine (mast cell stabilizer)</td>
</tr>
<tr>
<td>Acanthamoeba infection</td>
<td>Severe keratoconjunctivitis in patients who do not clean their contact lenses properly Treatment: propamidine + polymyxin/neomycin/gramicidin ophthalmic</td>
</tr>
<tr>
<td>Stye (see Fig. 26-26D)</td>
<td>Infection of the eyelid most commonly due to <em>S. aureus</em> Treatment: hot packs + dicloxacillin</td>
</tr>
<tr>
<td>Chalazion (see Fig. 26-26E)</td>
<td>Granulomatous inflammation involving the meibomian gland in the eyelid; usually disappear on their own within 2 months Treatment: if they do not disappear, use an intralesional corticosteroid injection or remove it surgically</td>
</tr>
<tr>
<td>Orbital cellulitis</td>
<td>Periorbital redness and swelling that is often secondary to sinusitis (e.g., ethmoiditis in children) Pathogens: <em>S. pneumoniae</em>, <em>H. influenzae</em> Fever, proptosis (eye bulges out), periorbital swelling, ophthalmoplegia (eye movement impaired), normal retinal examination Treatment: nafcillin + ceftriaxone + metronidazole</td>
</tr>
<tr>
<td>Orbital fracture (see Fig. 26-26F)</td>
<td>Most often associated with blunt trauma to the eye that produces an orbital floor fracture Often associated with edema and ecchymoses of the eyelids and periorbital region (“raccoon” eyes) Vertical diplopia, prolapse of orbital contents into the maxillary sinus (sunken eye), damage to infraorbital nerve may occur in severe fractures Treatment: varies according to degree of severity</td>
</tr>
<tr>
<td>Pterygium</td>
<td>Raised, triangular encroachment of thickened conjunctiva on the nasal side of the conjunctiva; may grow onto the cornea Due to excessive exposure to wind, sun, and sand Treatment: surgical removal</td>
</tr>
<tr>
<td>Pinguecula (see Fig. 26-26G)</td>
<td>Yellow-white conjunctival degeneration at the junction of cornea and sclera on the temporal side of the conjunctiva Does not grow onto the cornea like a pterygium does Usually requires no treatment</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Inflammation of optic nerve Causes: multiple sclerosis (most common), methanol poisoning Blurry vision or loss of vision, may cause optic atrophy Treatment: corticosteroids</td>
</tr>
</tbody>
</table>

Continued
EYE DISORDER DISCUSSION

Central retinal artery occlusion (see Fig. 26-26H)
Causes: embolization of plaque material from ipsilateral carotid or ophthalmic artery; giant cell temporal arteritis involving the ophthalmic artery
Sudden, painless, complete loss of vision in one eye, pallor of optic disk due to narrowed arteries; "boxcar" segmentation of blood in retinal veins, and cherry red macula
Treatment: acetazolamide to lower intraocular pressure; carbogen (CO₂ dilates + O₂); hyperbaric O₂ therapy

Central retinal vein occlusion (see Fig. 26-26I)
Causes: hypercoagulable state (e.g., polycythemia vera)
Sudden, painless, unilateral loss of vision, swelling of optic disk, and engorged retinal veins with hemorrhage ("blood and thunder" appearance)
Treatment: intravitreal injections, laser photocoagulation

Glaucoma (see Fig. 26-26J)
Increased intraocular pressure
Chronic open-angle type:
Decreased rate of aqueous outflow into the canal of Schlemm
Common in persons with severe near-sightedness; bilateral aching eyes; pathologic cupping of the optic disks; night blindness and gradual loss of peripheral vision leading to tunnel vision and blindness
Treatment: 1st: β-blockers (e.g., timolol; decrease rate of flow into eye); 2nd: prostaglandins, α-adrenergic agonists, pilocarpine, carbonic anhydrase inhibitors; if drugs fail, laser trabeculoplasty
Acute angle-closure type:
Narrowing of anterior chamber angle; medical emergency; precipitated by mydriatic agent, uveitis, lens dislocation; severe pain associated with photophobia and blurry vision; red eye with a steamy cornea; pupil fixed and nonreactive to light
Treatment: pilocarpine + systemic carbonic anhydrase inhibitor to lower pressure to allow for laser surgery

Optic nerve atrophy (see Fig. 26-26K)
Pale optic disk
Most commonly due to optic neuritis or glaucoma
No effective treatment

Uveitis
Inflammation of the uveal tract (iris, ciliary body, choroid)
Causes: sarcoidosis, ulcerative colitis, ankylosing spondylitis
Pain with blurry vision, miotic pupil, circumcorneal ciliary body vascular congestion, normal intraocular pressure, adhesions between iris and anterior lens capsule
Treatment: corticosteroids (oral or topical), atropine

Macular degeneration (see Fig. 26-26L)
Most common cause of permanent visual loss in the elderly
Disruption of Bruch membrane in the retina
Dry type: thinning of the retina and formation of yellowish white deposits called drusen
Wet type: extension of the dry type; vessels under the retina hemorrhage causing retinal cells to die, creating blind spots or distorted central vision
Antioxidants may decrease risk
Treatment: antiangiogenics (drugs that block vascular growth factors), insertion of special intraocular lens

CMV retinitis (see Fig. 26-26M)
Most common cause of blindness in AIDS; usually occurs when the CD4 T helper cell count is <50 cells/µL; usually painless; varicella/zoster virus retinitis is usually painful
Cotton-wool exudates and retinal hemorrhages
Treatment: oral, IV, intraocular ganciclovir or foscarnet

Cataracts (see Fig. 26-26N)
Opacity in the lens
Causes: advanced age (most common), diabetes mellitus (osmotic damage), infection (e.g., rubella), corticosteroids
Common in congenital infections (e.g., CMV, rubella)
Treatment: cataract extraction

Malignant tumors (see Fig. 26-26O)
Retinoblastoma in children ("white eye reflex")
Malignant melanoma in adults
Treatment: enucleation

CMV, Cytomegalovirus; HSV, herpes simplex virus.

TABLE 26-7 Selected Eye Disorders—cont’d
26-26: A, Arcus senilis. Note the gray-white ring around the perimeter of the cornea. B, Bacterial conjunctivitis. Note the conjunctival hemorrhage and pus. C, Herpes simplex virus keratoconjunctivitis. The special stain highlights the dendritic ulcers associated with this infection. D, Stye. Note the swelling, erythema, and pus from this infection of the lower eyelid. E, Chalazion. Note the swelling of the eyelid and absence of pus and conjunctival irritation, which distinguishes a chalazion from a stye. F, Orbital fractures. Note the periorbital swelling and ecchymoses giving the appearance of “raccoon” eyes. G, Pinguecula. Note the yellow-white conjunctival tissue on the temporal side of the conjunctiva. It extends to the junction of the cornea and sclera but it does not extend onto the cornea, unlike a pterygium. H, Central retinal artery occlusion. Note the generalized pallor of the optic disk and narrowed arteries. There is a cherry red spot on the macula, which is to the right of the optic disk. There is no boxcar segmentation in the retinal veins. I, Central retinal vein occlusion. Note the numerous flame hemorrhages in the retina as well as swelling of the optic disk. J, Schematic of the eye. Aqueous humor is produced by the ciliary body from which it flows into the anterior chamber and then out through a spongy tissue at the front of the eye called the trabecular meshwork into a drainage canal (circle). Glaucoma is an increase in aqueous pressure. In open-angle glaucoma, fluid cannot flow effectively through the trabecular meshwork. In acute angle-closure glaucoma there is narrowing of the anterior chamber caused by forward displacement of the ciliary body (arrow).

### TABLE 26-8 Selected Ear Disorders

<table>
<thead>
<tr>
<th>EAR DISORDER</th>
<th>DESCRIPTION AND COMMENTS</th>
</tr>
</thead>
</table>
| Meniere disease | Increased endolymph in inner ear and loss of cochlear hairs  
Dizziness, vertigo, tinnitus, sensorineural hearing loss  
*Treatment:* hydrochlorothiazide + triamterene; surgery in resistant cases |
| Sensorineural defect (see Fig. 26-27A) | Weber test: lateralizes to normal ear (contralateral ear is affected) |
| Conduction defect (see Fig. 26-27A) | Weber test: lateralizes to affected ear  
Due to degeneration of cochlear hairs  
*Treatment:* amplification devices, cochlear implants |
| Otosclerosis | Most common cause of conduction deafness in elderly  
Due to fusion of middle ear ossicles  
Other causes of conduction defects: impacted cerumen in outer ear canal, otitis media  
*Treatment:* amplification devices; surgery |
| Otitis media (see Fig. 26-27B) | Most common cause of conduction deafness in children  
Usually due to *Streptococcus pneumoniae*  
Other causes: *Haemophilus influenzae, Moraxella catarrhalis*  
*Treatment:* antipyrine and benzocaine ear drops for pain; controversy regarding antibiotics; those that use antibiotics most frequently use amoxicillin-clavulanate |
| External otitis (see Fig. 26-27C) | Inflammation of outer ear canal  
“Swimmer’s ear”: due to *Pseudomonas aeruginosa, Staphylococcus aureus, Aspergillus species*  
*Treatment:* ear drops—polymyxin B + neomycin + hydrocortisone + selenium sulfide shampoo  
Malignant external otitis: severe infection of outer ear canal in patients with diabetes mellitus; *Pseudomonas aeruginosa* most common cause  
*Treatment:* imipenem-clavulanate |
26-27: A, Weber test (affected ear is marked with an X). When a vibrating tuning fork is placed on the center of the forehead, the normal response is for the sound to be heard in the center, without lateralization to either side. A, In the presence of a conductive hearing loss, the sound is heard on the side of the conductive loss. B, In the presence of a sensorineural loss, the sound is heard better on the opposite (unaffected) side. B, Otitis media. Note the bulging, erythematous tympanic membrane. C, Otitis externa. Note the inflammatory exudate in the external canal. (A to C from Swartz MH: Textbook of Physical Diagnosis, 5th ed, Philadelphia, Saunders Elsevier, 2006, pp 305, 314, 314, respectively, Figs. 11-13, 11-29, 11-26, respectively.)
Formulas for Calculations of Acid-Base Disorders

A. Note: Other authors use different formulas; however, they should roughly approximate each other and correctly distinguish single versus mixed acid-base disorders.

B. Calculation of expected compensation in acute respiratory acidosis
1. Sometimes calculations help in identifying whether there is more than one primary acid-base disorder in a patient (called a mixed disorder; see later).
2. If the calculated expected compensation closely approximates the measured compensation, a single primary disorder is present.
3. If there is an obvious disparity between calculated expected compensation and measured compensation, another primary disorder is also present.
4. In acute respiratory acidosis, expected HCO₃⁻ compensation = 0.10 \times \Delta Pco₂ (difference from normal of 40 mm Hg)
   • Recall (refer to Chapter 5) that the expected compensation in respiratory acidosis is metabolic alkalosis (↑HCO₃⁻)
5. Example: pH 7.20, Pco₂ 74 mm Hg, HCO₃⁻ 27 mEq/L
   a. Expected HCO₃⁻ compensation = 0.10 \times (74 - 40) = 3.4 mEq/L increase above normal
   b. Expected HCO₃⁻ compensation = 24 mEq/L (mean HCO₃⁻) + 3.4 = 27.4 mEq/L
      • Note that measured and expected calculated HCO₃⁻ are similar; therefore a single disorder is present.

C. Calculation of expected compensation in chronic respiratory acidosis
1. Expected HCO₃⁻ compensation = 0.40 \times \Delta Pco₂
2. Example: pH 7.34, Pco₂ 60 mm Hg, HCO₃⁻ 32 mEq/L
   a. Expected HCO₃⁻ compensation = 0.40 \times (60 - 40) = 8 mEq/L increase above normal
   b. Expected HCO₃⁻ compensation = 24 + 8 = 32 mEq/L
      • Note that measured and expected calculated HCO₃⁻ are similar; therefore a single disorder is present.

D. Calculation of expected compensation in acute respiratory alkalosis
1. Expected HCO₃⁻ compensation = 0.20 \times \Delta Pco₂ (difference from normal of 40 mm Hg)
   • Recall that the expected compensation in respiratory alkalosis is metabolic acidosis (↓HCO₃⁻)
2. Example: pH 7.56, Pco₂ 24 mm Hg, HCO₃⁻ 21 mEq/L
   a. Expected HCO₃⁻ compensation = 0.20 \times (40 - 24) = 3.2 mEq/L less than the normal
   b. Expected HCO₃⁻ compensation = 24 mEq/L (mean HCO₃⁻) - 3.2 = 20.8 mEq/L
      • Note that measured and expected calculated HCO₃⁻ are similar; therefore a single disorder is present.

E. Calculation of expected compensation in chronic respiratory alkalosis
1. Expected HCO₃⁻ = 0.50 \times \Delta Pco₂
2. Example: pH 7.47, Pco₂ 18 mm Hg, HCO₃⁻ 13 mEq/L
   a. Expected HCO₃⁻ compensation = 0.50 \times (40 - 18) = 11 mEq/L less than the normal
   b. Expected HCO₃⁻ compensation = 24 - 11 = 13 mEq/L
      • Note that measured and expected calculated HCO₃⁻ are similar; therefore a single disorder is present.

F. Calculation of expected compensation in metabolic acidosis (either type)
1. Expected Pco₂ = 1.2 \times \Delta HCO₃⁻ ± 2
   a. \Delta HCO₃⁻ is measured HCO₃⁻ subtracted from the mean HCO₃⁻ of 24 mEq/L.
   b. Recall that the expected compensation in metabolic acidosis is respiratory alkalosis (↓Paco₂).
2. Example: pH 7.27, \( \text{Paco}_2 \) 27 mm Hg, \( \text{HCO}_3^- \) 12 mEq/L
   a. Expected \( \text{Paco}_2 \) compensation = \( 1.2 \times (24 - 12) \) = 14.4 mm Hg less than the normal
   b. Expected \( \text{Paco}_2 \) = 40 (mean \( \text{Paco}_2 \) - 14.4 = 25.6 mm Hg (23.6–27.6)
      - Note that measured \( \text{Paco}_2 \) is within the calculated range; therefore only a single disorder is present.

G. Calculation of expected compensation in metabolic alkalosis
   1. Expected \( \text{Paco}_2 \) = 0.7 \times \Delta \text{HCO}_3^- \pm 2
      - Recall that the expected compensation in metabolic alkalosis is respiratory acidosis
        (\( \uparrow \text{Paco}_2 \)).
   2. Example: pH 7.58, \( \text{Paco}_2 \) 49 mm Hg, \( \text{HCO}_3^- \) 39 mEq/L
      a. Expected \( \text{Paco}_2 \) compensation = 0.7 \times (39 - 24) = 10.5 greater than the normal
      b. Expected \( \text{Paco}_2 \) compensation = 40 + 10.5 = 50.5 mm Hg (48.5–52.5)
         - Note that measured \( \text{Paco}_2 \) is within the calculated range; therefore only a single disorder is present.

H. Examples of how formulas help to identify a mixed disorder
   1. pH 7.26, \( \text{Paco}_2 \) 38 mm Hg, \( \text{HCO}_3^- \) 17 mEq/L
      a. Presumptive diagnosis: metabolic acidosis (\( \text{HCO}_3^- <22 \text{ mEq/L} \)) without compensation (\( \text{Paco}_2 \) in normal range)
      b. Formula for calculating expected compensation in metabolic acidosis:
         1) Expected \( \text{Paco}_2 \) = \( 1.2 \times \Delta \text{HCO}_3^- \pm 2 \)
         2) Expected \( \text{Paco}_2 \) = \( 1.2 \times (24 - 17) \) = 8.4 mm Hg less than the normal value
         3) Expected \( \text{Paco}_2 \) = 40 (mean \( \text{Paco}_2 \) - 8.4 = 31.6 (29.6–33.6)
         4) The measured \( \text{Paco}_2 \) is 38 mm Hg, which is higher than it should be, indicating that a
            respiratory acidosis (retention of \( \text{CO}_2 \)) must also be present as a primary disorder.
   2. pH 7.38, \( \text{Paco}_2 \) 70 mm Hg, \( \text{HCO}_3^- \) 41 mEq/L
      a. Presumptive diagnosis: mixed disorder (because the pH is normal) with chronic respiratory
         acidosis (\( \text{Paco}_2 >45 \text{ mm Hg, HCO}_3^- >30 \text{ mEq/L} \)) and primary metabolic alkalosis
         (\( \text{HCO}_3^- >28 \text{ mEq/L} \))
      b. Using either the formula for metabolic alkalosis or chronic respiratory acidosis will prove the
         presence of a mixed disorder.
      c. Using the chronic respiratory acidosis formula (expected \( \text{HCO}_3^- = 0.40 \times \Delta \text{Paco}_2 \))
         1) Expected \( \text{HCO}_3^- \) compensation = \( 0.40 \times (70 - 40) \) = 12 mEq/L increase above normal
         2) Expected \( \text{HCO}_3^- \) compensation = 24 + 12 = 36 mEq/L
         3) Measured \( \text{HCO}_3^- \) is 41 mEq/L, which is higher than the expected compensation
            indicating the presence of an additional primary metabolic alkalosis (more \( \text{HCO}_3^- \) than
            there should be for compensation).
      d. Using the metabolic alkalosis formula (expected \( \text{Paco}_2 = 0.7 \times \Delta \text{HCO}_3^- \pm 2 \))
         1) Expected \( \text{Paco}_2 \) = \( 0.7 \times (41 - 24) \) = 11.9 mm Hg increase from the normal
         2) Expected \( \text{Paco}_2 \) = 40 + 11.9 = 51.9 mm Hg (49.9–53.9)
         3) The measured \( \text{Paco}_2 \) is 70 mm Hg, which is much higher than it should be indicating the
            presence of an additional primary respiratory acidosis.
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