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To my precious girls, Maya and Anjali, who bring joy to my life, and to their mother, who remains my best friend

—TAB
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SERIES PREFACE

The first and second editions of the Rapid Review Series have received high critical acclaim from students studying for the United States Medical Licensing Examination (USMLE) Step 1 and consistently high ratings in First Aid for the USMLE Step 1. The new editions will continue to be invaluable resources for time-pressed students. As a result of reader feedback, we have improved upon an already successful formula. We have created a learning system, including a print and electronic package, that is easier to use and more concise than other review products on the market.

SPECIAL FEATURES

Book

• **Outline format**: Concise, high-yield subject matter is presented in a study-friendly format.
• **High-yield margin notes**: Key content that is most likely to appear on the exam is reinforced in the margin notes.
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- **Free content**: An interactive community center with a wealth of additional valuable resources is available.
Rapid Review Physiology, Second Edition, is intended for medical students preparing for Step 1 of the United States Medical Licensing Examination. I believe this new edition represents a significant improvement from the first edition for a variety of reasons. The first edition was written by me while I was a resident in internal medicine, with tremendous input from contributing authors. Although their input was extremely helpful, because of their varying styles I thought that the first edition did not read as smoothly as I would have liked. In contrast, this edition was authored solely by me, now a relatively seasoned clinician and physiologist, and therefore “speaks” with a single voice.

As with the first edition, my strategy was to teach the core physiological principles in an integrated fashion with respect to the basic sciences as well as in a clinical context wherever possible. The second edition also includes hundreds of margin notes containing what I think is high-yield information for the boards. Some students may peruse a particular chapter simply by reviewing the margin notes to see if they have a good grasp of the underlying material. This is what is meant by rapid review!

- **Text:** Clear and concise and in an outline format with an emphasis on imparting a conceptual understanding rather than focusing on “low-yield” minutiae.
- **Clinical notes:** Dispersed throughout the book. Stress the clinical significance of the underlying physiology, which facilitates comprehension and makes the material more enjoyable.
- **Basic science notes:** Dispersed throughout the book. Act as a “bridge” between physiology and closely related concepts in anatomy, pathology, and pharmacology, which is essential for a deeper understanding of the underlying physiology and is invaluable preparation for the boards.
- **Tables and illustrations:** Facilitate understanding and act as quick reference sources.
- **Access to questions via Internet (with password provided):** Allows students to practice questions online in a realistic USMLE format. Questions can be accessed in a subject-specific manner to review a given “system,” or in a random manner to review all of physiology.

—Thomas A. Brown, MD
The publisher expresses sincere thanks to the medical students and physicians who provided many useful comments and suggestions for improving the text in the second edition. Our publishing program will continue to benefit from the combined insight and experience provided by your reviews. For always encouraging us to focus on our target, the USMLE Step 1, we thank the following:

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Review books and textbooks are often revised every 4 to 5 years as new technologies and information become available. Occasionally, revisions involve a cursory review of the original material with relatively minor changes to the content. In my naivety, I imagined revising the first edition would be a matter of a few weeks of intense work. Instead, over the course of more than a year, I found myself overhauling the entire book, rewriting chapters, and adding two entirely new chapters to the book, which was quite a departure from the typical revision but a departure that I hope students will recognize was well worth the effort.

There are numerous people I want to thank. For starters, the high quality of the first edition was due largely to the many contributing authors and reviewers. Although these authors were not involved in the second edition, they helped lay the groundwork from which I was able to build the second edition. I am therefore tremendously grateful to the following physicians: Drs. Dave Brown, Jennie Hauschka, Jason Harris, Courtney Cuppett, Karen MacKay, John Parker, and Ronald Mudry.

As the series editor I found Dr. Goljan’s input in terms of content and style extremely helpful; thank you, Ed. As the primary driving force behind the Rapid Review Series, Jim Merritt, a senior acquisitions editor at Elsevier, deserves enormous recognition for his tenacity and perpetual faith in this series. In no small part due to his efforts, the Rapid Review Series is becoming recognized as the premiere review series for the USMLE Step 1 examination.

As the developmental editor, Christine Abshire was instrumental in editing, assisting with artwork, and perhaps most importantly, keeping me on schedule; thank you, Christine.

I am particularly proud of the quality of the artwork in this edition, and here much of the credit goes to the talented artist Matt Chansky, who drew the diagrams for the first edition; thank you, Matt.

Intellectual curiosity is critical for writing an academic book as well as for lifelong learning. I have my patients, students, residents, and colleagues to thank for keeping my intellectual curiosity alive. Finally, I would like to thank the following clinicians whose knowledge of physiology has both impressed and motivated me: Dr. Jonathan Ross at Dartmouth-Hitchcock Medical Center, Dr. Thomas Lane at the Hospital of Central Connecticut, and Dr. Gregory Buller at Saint Mary’s Hospital.
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I. Cell Structure and Function (Fig. 1-1)

A. Overview
1. Cells are the basic structural and functional unit of the body.
2. Most cells contain a nucleus, surrounded by cytoplasm.
3. The cytoplasm contains cytosol, within which sit various types of organelles.
4. The cytoplasm is enveloped by a cell membrane (plasma membrane).

B. The cell membrane
1. Structure (Fig. 1-2)
   - The cell membrane is a lipid bilayer that separates the internal cellular environment from the extracellular fluid.
   - The lipid bilayer is composed of phospholipids, arranged as a hydrophilic glycerol backbone and two hydrophobic fatty acid tails.
     a. Fat-soluble (hydrophobic) substances such as steroid hormones can dissolve in the hydrophobic bilayer and therefore can freely cross the membrane.
     b. In contrast, water-soluble (hydrophilic) substances such as Na\(^+\) and glucose cannot dissolve in this bilayer and must pass through pores or use carrier proteins.
   - Embedded in the lipid bilayer are proteins (Table 1-1), carbohydrates, and cholesterol.
The cell membrane is commonly described as a **fluid mosaic** because proteins can freely move within the phospholipid bilayer.

### Morphology
- The cellular surface may be **smooth** or **folded**.
- **Folding** of the membrane increases the **surface area** available for transport of substances in and out of the cell.
- For example, the cells of the brush border of the small intestine have microvilli along their luminal surface.
- This provides the markedly increased surface area necessary for adequate absorption of ingested nutrients.

### The nucleus (Fig. 1-3)
1. The **nucleus** is centrally located within the cell and is surrounded by a two-layer **nuclear envelope**, which separates the cytoplasm from the **nucleoplasm**.
2. Each layer of the envelope is a lipid bilayer.
3. The nucleus contains almost all the DNA of the cell, complexed with proteins (histones) in a form called **chromatin**.
4. The nucleus has several functions, including **messenger RNA synthesis** (**transcription**) and the regulation of cell division.
5. It also contains the **nucleolus**, a prominent, RNA-containing dense body that synthesizes **ribosomal RNA** (**rRNA**).

### The cytoplasm
1. The **cytosol**
   - The cytosol consists of the intracellular fluid, which contains many soluble proteins, ions, metabolites, and cytoskeletal elements.
   - It also contains nonmembranous organelles, such as ribosomes, cytoskeletal elements, and centrioles.
   - Membranous organelles sit within the cytosol, but their membranes separate them from the cytosolic compartment, so the term *cytosol* does not encompass them.
   - Cytosol composition differs greatly from that of the extracellular fluid, as shown in Table 1-2.
2. Membrane-enclosed organelles

- **Endoplasmic reticulum (ER)**
  a. This vesicular network is continuous with the nuclear envelope.
  b. It is classified according to whether ribosomes are present (rough ER) or absent (smooth ER) on the membrane.
  c. **Rough ER (rER)** is responsible for the **synthesis of proteins**, both secreted and intracellular.
  d. **Smooth ER (sER)** functions in the **detoxification of drugs** and in the synthesis of **lipids and carbohydrates**.
  e. Transport vesicles deliver the synthetic products of the ER to the Golgi apparatus.

- **Golgi apparatus**
  a. This vesicular network has the appearance of flattened membranous disks and is located between the nucleus and the cell membrane.
  b. Functions of the Golgi apparatus include the following:
    - **Post-translational modification of proteins**, such as addition of mannose-6-phosphate (M6P) “tags” to lysosomal enzyme precursors, which targets them for lysosomes
    - **Packaging of substances** destined for secretion and/or intracellular organelles (e.g., lysosomes)
    - **Maintenance of the plasma membrane** by the fusion of vesicles consisting of a phospholipid bilayer to the cell surface

**Clinical note:** In I-cell disease, the process of post-translational modification is impaired. The Golgi apparatus is unable to tag proteins with M6P because of a deficiency of a phosphorylating enzyme. Lysosomal enzyme precursors are therefore secreted from the cell instead of being taken up by lysosomes, resulting in impaired lysosomal function. The characteristic pathologic finding is the presence of inclusions within the cytoplasm. Death commonly results from cardiopulmonary complications (as a result of inclusions in heart valves) during childhood.

- **Lysosomes**
  a. Cytoplasmic, membrane-bound vesicles that contain hydrolytic digestive enzymes (see Fig. 1-7, later)
  b. Functions include the digestion of extracellular substances (**endocytosis** and **phagocytosis**) and intracellular substances (**autophagy**).
  c. The interior of the lysosome is maintained at a pH of approximately 4.8 by a hydrogen ion pump.
  d. This low pH removes the M6P tags attached to lysosomal enzyme precursors in the Golgi apparatus.

**Clinical note:** There are more than 45 **lysosomal storage diseases**, caused by impairment of lysosomal function, usually secondary to an inherited deficiency in a hydrolytic enzyme (Table 1-3). The resulting **lipid accumulation** within lysosomes eventually hinders the activity of cells in many organs, including the liver, heart, and brain. As with I-cell disease, clinical symptoms are severe, and average life expectancy across the entire group of diseases is approximately 15 years, reflecting the importance of normal lysosomal function.

- **Mitochondria**
  a. These membranous organelles are composed of outer and inner membranes, intermembranous space, and inner matrix; they contain their own genetic material, mitochondrial DNA, which codes for mitochondrial proteins and transfer RNA.
b. Responsible for energy production through aerobic metabolism and ketogenesis
c. Mitochondria and their DNA are inherited maternally (i.e., mitochondria are received only from the egg, not from sperm).

Clinical note: When mitochondrial dysfunction is inherited through mitochondrial DNA, all offspring are equally affected, but only female offspring pass on the disorder. However, other types of mitochondrial dysfunction result from defects in specific proteins that are coded by nuclear DNA but function in the mitochondria, such as Leber hereditary optic neuropathy (LHON), which is characterized by loss of vision in the center of the visual field. LHON is believed to be a result of decreased mitochondrial function and resulting lack of energy in the optic nerve and retina. Disorders resulting from mutations in nuclear genes encoding mitochondrial proteins can be passed on from both male and female offspring.

3. Cytoskeleton (Table 1-4)

- This network of filaments provides mechanical support, cell flexibility, and cell motility and aids in cell division.

- Microfilaments
  a. Small-diameter, flexible, helical polymers composed of G actin and located just beneath the plasma membrane
  b. Function in cell motility, organelle transport, cytokinesis, and muscle contraction

- Microtubules
  a. Large-diameter, rigid cylinders composed of polymers of the protein tubulin

<table>
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<th>TABLE 1-3. Lysosomal Storage Diseases</th>
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<tr>
<td><strong>DISEASE</strong></td>
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<tr>
<td>Niemann-Pick disease</td>
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<td>Tay-Sachs disease</td>
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<th>TABLE 1-4. Overview of Cytoskeletal Proteins</th>
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<td><strong>COMPONENTS</strong></td>
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<tr>
<td>Microfilaments</td>
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<tr>
<td>Intermediate filaments</td>
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<tr>
<td>Microtubules</td>
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b. One end of the microtubule is attached to the **centrosome**, a densely filamentous region of cytoplasm at the center of the cell and the major microtubule-organizing center of the cell; the other end is free in the cytoplasm.

c. Serve as **scaffolding** for the movement of particles and structures within the cell (e.g., chromosomes during mitosis)

d. Are components of **cilia** and **flagella**

- **Intermediate filaments**
  
a. Comprise a large, heterogeneous family of proteins and are the most abundant of the cytoskeletal elements
  
b. Important in the stability of cells, especially epithelial cells
  
c. Form **desmosomes**, structures that attach one epithelial cell to another, and **hemidesmosomes**, structures that anchor the cells to the extracellular matrix
  
d. An example of a constituent of a membrane-bound intermediate filament is the protein **ankyrin**.

**Clinical note:** In **hereditary spherocytosis**, a form of **hemolytic anemia**, most patients have mutations in the **ankyrin gene**, which causes impaired function of the membrane protein spectrin in red blood cells (RBCs). The characteristically spherical, mechanically unstable, and relatively inflexible RBCs tend to rupture within blood vessels and, because of their inflexibility, become lodged and subsequently scavenged within the splenic cords, resulting in a decrease in the number of circulating RBCs. The classic presentation is jaundice, splenomegaly, and anemia that typically resolves after splenectomy.

4. **Non–membrane-enclosed organelles**

- **Microvilli**
  
a. Small, fingerlike projections of the plasma membrane
  
b. Function to increase the **surface area** for absorption of extracellular substances
  
c. Examples of cell types with microvilli are the brush borders of the intestinal epithelium and the proximal convoluted tubule (PCT) of the nephron.

- **Centrioles**
  
a. Bundles of **microtubules** linked by other proteins
  
b. At least two are present in the **centrosome** of each cell capable of cellular division.
  
c. Function in **cell division** by forming spindle fibers that separate homologous chromosomes.

- **Cilia**
  
a. Long, fingerlike projections of plasma membrane, differing from microvilli in that they are supported by **microtubules**
  
b. Two types: motile and nonmotile (primary) cilia
  
c. Motile cilia function to **move fluid and/or secretions** along the cell surface, whereas primary ciliary typically play a sensory role.

**Clinical note:** In **Kartagener syndrome (immotile cilia syndrome)**, ciliary dysmotility results in the clinical triad of bronchiectasis, chronic sinusitis, and situs inversus. Respiratory tract infections occur as a result of impaired mucociliary clearance. The reason for situs inversus is unknown, although normal ciliary function is postulated to be a requirement for visceral rotation during embryogenesis. Deafness and male infertility may also result from the impaired ciliary function.

- **Flagella**
  
a. Similar in shape to cilia, but longer
  
b. Like cilia, they are supported by **microtubules**
  
c. Function in the **movement of cells** through a medium
  
d. The **sperm cell** is the only human cell with a flagellum.

- **Ribosomes**
  
a. Consist of ribosomal RNA and protein
  
b. Function in protein synthesis (translation)
  
c. Fixed ribosomes are bound to the ER, whereas free ribosomes are scattered throughout the cytoplasm.

E. **Junctions between cells**

1. **Tight junctions (zona occludens)**

   - They seal adjacent epithelial membranes to prevent most movement from one side of an epithelial layer to the other.
They also function to prevent membrane proteins from diffusing to other sections of membrane (i.e., they maintain membrane polarity between the apical and basolateral membranes).

“Tightness” of these tight junctions frequently varies: they are leaky in the proximal convoluted tubule and nonleaky in the distal convoluted tubule of the nephron.

2. Gap junctions
- Two lipid bilayers are joined by transmembrane channels (connexons) that permit passage of small molecules such as Na\(^+\), Ca\(^{2+}\), and K\(^+\); various second messenger molecules; and a number of metabolites.
- Cells interconnected through gap junctions are electrically coupled and generally act in a coordinated fashion (i.e., as a syncytium).

3. Desmosomes (macula adherens)
- They are plaquelike areas of intermediate filaments that create strong contacts between cells, typically present on the lateral membrane of cells.
- Help resist shearing forces and therefore often found in squamous epithelium.

4. Hemidesmosomes
- Resembling desmosomes, they anchor cells to the extracellular matrix (ECM).
- Composed of integrin cell adhesion proteins, which play important roles in cellular attachment and in signal transduction.

Clinical note: The integrin \(\text{GPIIb/IIIa}\) is present on the surfaces of platelets and plays an important role in binding of platelets to fibrinogen. The drug eptifibatide (Integrilin) inhibits the \(\text{GPIIb/IIIa}\) receptor on platelets, thereby preventing platelet aggregation and thrombus formation. Integrilin is commonly used during angioplasty in high-risk cardiac patients.

F. Transport across membranes
1. Simple diffusion
   - **Overview**
     a. The process whereby a **substance moves down its concentration gradient** across a semipermeable membrane.
     b. This tends to equalize the concentration of the substance on both sides of the membrane.
     c. No metabolic energy or carrier protein is required.
   - **Diffusion of uncharged substances**
     a. The **rate of diffusion** \(J\) is dependent on the **concentration gradient** \(\Delta C\), the **surface area** available for diffusion \(A\), and the **membrane permeability** \(P\):

\[
J = PA(\Delta C)
\]
   b. **Permeability** \(P\) is directly proportional to lipid solubility of the substance and inversely proportional to the size of the molecule and the thickness of the membrane.
   c. **Small hydrophobic** molecules have the **highest permeability** in the lipid bilayer.

   - **Diffusion of charged substances**
     a. If the diffusing substance is charged (e.g., ions), the net rate of diffusion \(J\) depends on the electrical potential difference across the membrane as well as the concentration gradient (i.e., charged molecules will not necessarily flow down their concentration gradient).
     b. Positively charged ions (cations) tend to diffuse into the cell, whereas negatively charged ions (anions) tend to diffuse out of the cell, because the inside of the cell (at rest) is negatively charged.

   - **Diffusion of nonpolar and polar substances**
     a. Diffusion of nonpolar substances such as oxygen and carbon dioxide gases across a membrane is **more rapid** than the diffusion of polar substances such as water.
     b. This is due to their relative solubility in lipids: nonpolar gases easily dissolve into the lipid bilayer, but water is insoluble because of its polarity.

   - **Diffusion of gases**
     a. Gases have a greater surface area available for diffusion: gases can diffuse across the entire surface area of the cell, whereas water must enter the cell through pores.
b. The diffusion rate of a gas ($V_g$) depends on the pressure difference across the membrane ($\Delta P$), the surface area of the cell ($A$), the diffusivity coefficient ($d$), and the thickness of the membrane ($T$):

$$V_g = \frac{\Delta P \times A \times d}{T}$$

Clinical note: Gas exchange in the lungs normally occurs very efficiently across the thin, lipid-rich pulmonary capillary and alveolar walls. However, in pathologic states such as pneumonia, gas exchange becomes less efficient because the accumulation of fluid increases the distance over which oxygen must diffuse.

2. Osmosis

- Osmosis is the movement of water, not dissolved solutes, across a semipermeable membrane.
- A difference in solute concentration across the membrane generates osmotic pressure, which causes the movement of water from the area of low solute concentration (hypotonic solution) to that of high solute concentration (hypertonic solution) (Fig. 1-4).
- Osmotic pressure depends on the following:
  a. The concentration of osmotically active particles
  b. The ability of these particles to cross the membrane, which depends on particle size and charge
- If the solutions on either side of the membrane have equal osmotic pressure, they are said to be isotonic.

van’t Hoff’s law

a. Osmotic force (pressure) of a solution ($\pi$) depends on the number of particles per mole in solution ($g$), the concentration of the dissolved substance ($C$), the reflection coefficient of the solute across the membrane ($\sigma$; varies from 0 to 1), the gas constant ($R$), and the absolute temperature ($T$).

$$\pi = gC\sigma RT$$

- If $\sigma = 0$, the solute is freely permeable across the membrane.
- If $\sigma = 1$, the solute is impermeable, so osmotic pressure is indirectly proportional to solute permeability.

3. Carrier-mediated transport (Table 1-5)

- Characteristics of carrier-mediated transport
  a. Stereospecificity of carrier proteins
  - Only one isomer of a substance is recognized by the carrier protein; for example, $\alpha$-glucose but not $\beta$-glucose is transported by the GLUT4 transporters in muscle and the liver.
  b. Competition for carrier binding sites
  - Substances with similar structure can compete for binding to the carrier protein; for example, $\alpha$-galactose binds to and is transported by the same GLUT4 transporter as $\alpha$-glucose, thereby inhibiting the transport of glucose.
  c. Saturation of carrier proteins
  - When all of the transport binding sites for a particular substance are occupied, the transport maximum ($T_{max}$) has been reached; the substance can no longer bind to its carrier and therefore cannot pass through the membrane (Fig. 1-5).
**Facilitated transport (diffusion)**

a. Occurs down an **electrochemical gradient** and therefore **does not require metabolic energy**

b. Stops if the concentration of the substance inside the cell reaches the extracellular concentration or if carrier molecules become saturated

c. For example, the GLUT4 transporter carries glucose into skeletal muscle and the liver; this proceeds for as long as a concentration gradient for glucose is present.

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**TABLE 1-5. Examples of Transmembrane Transport Molecules**

<table>
<thead>
<tr>
<th>MECHANISM AND ENERGY SOURCE</th>
<th>TRANSPORTER</th>
<th>FUNCTION</th>
<th>CLINICAL AND THERAPEUTIC RELEVANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facilitated diffusion:</strong> No additional energy required</td>
<td>Glucose-facilitated transporter 4 (GLUT4)</td>
<td>Transport glucose into cells</td>
<td>Deficient expression in diabetes results in impaired glucose metabolism.</td>
</tr>
<tr>
<td>Voltage-gated Na(^+) channel</td>
<td>Generation and propagation of action potentials</td>
<td>Inhibited by tetrodotoxin (puffer fish) and saxitoxin (contaminated shellfish)</td>
<td></td>
</tr>
<tr>
<td>Na(^+),K(^+)-ATPase (sodium) pump</td>
<td>Electrogenic pump that contributes to maintenance of resting membrane potential</td>
<td>Inhibited by digitalis (naturally occurring toxin); derivative, digoxin, used in treatment of congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Ca(^{2+})-ATPase</td>
<td>Maintains low cytoplasmic concentration of calcium</td>
<td>Inhibited by dantrolene (used in treatment of malignant hyperthermia)</td>
<td></td>
</tr>
<tr>
<td>H(^+),K(^+)-ATPase (sodium) pump</td>
<td>Contributes to low pH of gastric secretions and acid secretion of distal convoluted tubule of the nephron</td>
<td>Inhibited by omeprazole (used to treat GERD and peptic ulcer disease)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary active transport:</strong> ATP hydrolysis</td>
<td>Na(^+)-glucose cotransporter</td>
<td>Actively transports glucose into cells against concentration gradient, along with 2 Na(^+) Located in gastrointestinal mucosa and PCT of the nephron</td>
<td>Oral rehydration therapy exploits ideal Na(^+)/glucose ratio — uptake of salts, fluids, and glucose into intestinal epithelium. High-glucose, low-Na(^+) solutions do not provide optimal rehydration, because cotransporter does not function without Na(^+).</td>
</tr>
<tr>
<td>Na(^+)-K(^+)-2Cl(^-) cotransporter</td>
<td>Pumps 1 Na(^+), 1 K(^+), and 2 Cl(^-) into cells Has important role in thick ascending limb of loop of Henle</td>
<td>Inhibited by loop diuretics (e.g., furosemide). The nephron becomes unable to concentrate urine, resulting in loss of NaCl, K(^+), and fluid.</td>
<td></td>
</tr>
</tbody>
</table>

**ATP,** Adenosine triphosphate; **GERD,** gastroesophageal reflux disease; **PCT,** proximal convoluted tubule.

---

1-5: A comparison of simple diffusion and carrier-mediated transport. \(T_m\), Transport maximum.
• Active transport
  a. “Uphill” transport of a substance against its electrochemical gradient
  b. Energy from hydrolysis of adenosine triphosphate (ATP) is required.
  c. Primary active transport
     • The transport of a substance across the plasma membrane directly coupled to ATP hydrolysis
     • Examples include the Na⁺,K⁺-ATPase (sodium) pump in the plasma membrane of all cells, the H⁺,K⁺-ATPase (proton) pump of gastric parietal cells, and the Ca²⁺-ATPase pump in muscle cells.

Pharmacology note: Proton pump inhibitors such as omeprazole are used to treat peptic ulcer disease. These drugs directly inhibit the H⁺,K⁺-ATPase (proton) pump in gastric parietal cells. This reduces the acidic content of the stomach and allows for healing of the damaged mucosa.

   a. Secondary active transport
      • The simultaneous movement of two substances across the cell membrane indirectly coupled to ATP hydrolysis
        (1) One substance moves down its concentration gradient, and this drives the “uphill” transport of the other substance against its concentration gradient.
        • In cotransport (symport), both substances move in the same direction (e.g., Na⁺-glucose cotransport in the epithelial cells of the brush border of the small intestine).
        • In countertransport (antiport), the substances move in opposite directions (e.g., the Na⁺-Ca²⁺ countertransporter of heart muscle cells moves Ca²⁺ against its concentration gradient as Na⁺ moves down its concentration gradient) (Fig. 1-6).

Pharmacology note: Cardiac glycosides such as ouabain and digitalis inhibit the Na⁺,K⁺-ATPase (sodium) pump in the myocardium (see Fig. 1-6). This increases the amount of sodium inside the cell, triggering the Ca²⁺-Na⁺ countertransporter. More calcium is brought into the cell, which increases the contraction of atrial and ventricular myocardium and increases cardiac output.

4. Vesicular transport (Fig. 1-7)
   • Endocytosis (membrane invagination)
     a. The cell membrane forms a new membrane-bound vesicle, enclosing extracellular material, which is then internalized.
     • Most eukaryotic cells use this type of transport.
     b. In pinocytosis, the cell randomly samples the external environment by nonspecifically taking up droplets of extracellular fluid and transporting them into the cell in endocytotic vesicles.
     c. In receptor-mediated endocytosis, specific receptor-ligand interactions trigger endocytosis.
       • The receptors sit on a pitlike area of the membrane that is lined on its inner surface with the protein clathrin.

1-6: Examples of active transport in the myocardium. A, Primary active transport: the Na⁺,K⁺ transporter can be inhibited by cardiac glycosides. B, Secondary active transport: the Na⁺,Ca²⁺ countertransporter.

Active transport: transport against electrochemical gradient; energy provided by ATP hydrolysis
Primary active transport: transport of substance across membrane directly coupled to ATP hydrolysis
Examples of primary active transport: Na⁺, K⁺-ATPase pump in all cells, Ca²⁺-ATPase pump in muscle cells
Secondary active transport: diffusion of substance down its concentration gradient drives the transport of other substance against its concentration gradient
Cotransport: both substances transported in same direction
Countertransport: substances move in opposite directions
Endocytosis: internalization of a membrane-bound vesicle containing extracellular material
Pinocytosis: random sampling of extracellular fluid through endocytotic vesicles
When a ligand binds to its receptor, this clathrin-coated pit invaginates and forms an endocytic vesicle in which the entire receptor-ligand complex is included. As the vesicle buds from the membrane, it is stabilized by clathrin. After the vesicle has been internalized, it fuses with an early endosome, which lowers the pH of the vesicle. This causes clathrin and the receptor molecule to be released and recycled to the cell surface. Two medically important particles transported into the cell by receptor-mediated endocytosis are low-density lipoprotein (LDL; the “bad” cholesterol) and transferrin (which delivers iron to cells).

Clinical note: Familial hypercholesterolemia is caused by a variety of mutations in the LDL receptor protein. The result is that plasma LDL particles cannot be effectively taken up by cells and therefore accumulate in the blood at high levels. Patients who are homozygous for these mutations typically die at an early age from atherosclerosis-induced myocardial infarction.

Phagocytosis (engulfing)

a. Actin-mediated process in which cytoplasmic fingerlike extensions (pseudopodia) are extended into the extracellular fluid and surround solid particles, which are then internalized.

b. The internalized vesicle (phagosome) fuses with a lysosome that contains digestive enzymes, causing it to become a phagolysosome.

• The phagosome contents are degraded (“oxidative burst”), and the waste products are released from the cell by exocytosis.

c. Phagocytosis is carried out by a select group of cells, including neutrophils and macrophages, and is an important component of innate immunity.

Clinical note: Chronic granulomatous disease (CGD) is an X-linked recessive disorder (65% of cases) or autosomal recessive disorder (35% of cases). In chronic granulomatous disease, mutations in proteins of the NADPH oxidase system result in a reduced ability of phagocytic cells to produce the superoxide radical (O$_2^-$) and its products, the hydroxyl radical (OH$^-$) and hydrogen peroxide (H$_2$O$_2$). The enzyme catalase breaks down the hydrogen peroxide produced by the phagocytic cell and further decreases the cell’s ability to destroy the offending microbe. Microbial killing is severely impaired in these patients, and phagocytic cells accumulate (forming granulomas) in areas of infection, commonly in the skin, lungs, gastrointestinal tract, liver, spleen, and lymph nodes. The immune system often attempts to contain and wall off the clusters of phagocytic cells by creating a fibrous capsule around the affected area, forming abscesses. Macrophages fuse together to form multinucleated giant cells. Patients have severe infections involving the lungs, skin, visceral organs, and bones.

Exocytosis

a. Intracellular vesicles fuse with the plasma membrane, and vesicular contents are released into the extracellular space.
b. This process is often triggered by an increase in intracellular calcium.
   • For example, in the terminal bouton of the neuron, action potentials cause a calcium influx that triggers the fusion of neurotransmitter-laden vesicles with the cell membrane.
   • The neurotransmitters are then exocytosed into the synaptic cleft.

5. Other types of transport
   • **Paracellular** (Fig. 1-8)
     a. The transport of substances **between cells**
     b. For example, substances transported through **tight junctions** (such as those in the PCTs of the nephron) are transported through paracellular transport.

   • **Transcellular** (transcytosis) (see Fig. 1-8)
     a. The transport of substances **across cells**.
     b. Occurs because of membrane polarity; the presence of different proteins on the apical versus the basal side of the cell is responsible for this polarity.
     • For example, the polarized nature of the membrane surfaces of epithelial and endothelial cells enables the transcytotic transport of substances from the lumen of the intestine to the bloodstream.

   • **Convection**
     a. The transport of substances by the **movement of a medium**
     b. For example, the circulatory system uses the blood as a medium for transport of numerous substances (e.g., hormones), providing long-distance communication between organs.

II. Membrane Potentials, Action Potentials, and Nerve Transmission

A. **Resting membrane potential (RMP)**
   1. Overview
      • RMP is determined by the concentration difference of **permeant ions** (ions able to pass through a particular semipermeable membrane) across the cell membrane, which depends on **membrane permeability** to the ions and the **equilibrium potential** of the ions.
      • It is a **negative value**, approximately $-60$ to $-90$ mV in most cells.
      • This polarized RMP is important for numerous cellular functions, including **cotransport** processes and **generation of action potentials**.

   2. **Selective membrane permeability and equilibrium potential**
      • The term **selective permeability** expresses the differential permeability of membranes for different ions in different circumstances; this is a **dynamic** property of membranes.
      • Each ion tends to drive the membrane potential toward that ion’s **equilibrium potential**.
      • The **equilibrium potential** for an ion is the membrane potential that would counter the tendency of the ion to move down its concentration gradient (i.e., the membrane potential at which there will no longer be net diffusion of the ion across the membrane).
      • The equilibrium potential for ion X ($E_x$) can be calculated from its concentration in extracellular fluid ([X$_{out}$]) and in the cytoplasm ([X$_{in}$]) using the **Nernst equation**:
        \[
        E_x = \frac{-61 \log([X_{in}])}{[X_{out}]} \]
      • For example, given the intracellular concentration of K$^+$ of approximately 150 mmol/L and the extracellular concentration of approximately 5 mmol/L, the equilibrium potential for K$^+$ is:

\[
E_{K^+} = -61 \log\left(\frac{5}{150}\right) = -90 \text{ mV}
\]
Thus, it is the concentration gradient of K\(^+\), coupled with the relatively high membrane permeability to K\(^+\), which determines the negative RMP of most cells.

When the membrane potential is at \(-90\) mV, there will be no net potassium flux.

3. Calculating RMP: the Gibbs-Donnan equation
- RMP (Em) is determined by the **permeability** (P) and equilibrium potential (E) for each of the **major permeant ions** (Na\(^+\), K\(^+\), and Cl\(^-\)):

\[
Em = P_{Na}(E_{Na}) + P_{K}(E_{K}) + P_{Cl}(E_{Cl})
\]

- Thus, RMP reflects the equilibrium potential of the ions with the highest permeability and equilibrium potential (and concentration gradient across the membrane).
- For example, in the resting state of the neuron, the membrane is **primarily permeable to potassium**, so K\(^+\) makes the largest contribution to RMP; this explains why the RMP (roughly \(-70\) mV) of a cell approximates the equilibrium potential for K\(^+\) (\(-90\) mV).

4. Intracellular fixed anions
- The cytoplasm of the cell contains negatively charged organic ions (**anions**) that cannot leave the cell (i.e., they are “fixed”).
- These anions attract extracellular positively charged ions (**cations**), particularly K\(^+\) because of the high membrane permeability to K\(^+\) in the resting state of excitable cells.
- This results in a higher concentration of intracellular K\(^+\) than extracellular K\(^+\) and contributes to the negative RMP of cells (because there are more fixed anions than intracellular K\(^+\) at the equilibrium potential for K\(^+\)).

5. Na\(^+\),K\(^+\)-ATPase (sodium) pump
- This pump maintains the concentration gradient for Na\(^+\) and K\(^+\) across cell membranes.
- Without it, Na\(^+\) and K\(^+\) have a tendency to leak through channels in the membrane, resulting in a net influx of extracellular sodium and efflux of intracellular potassium down their respective concentration gradients.
- The constantly active electrogenic Na\(^+\),K\(^+\)-ATPase (sodium) pump removes 3 Na\(^+\) ions for every 2 K\(^+\) ions pumped into the cell to counteract leakages, thereby maintaining the concentration gradients across the membrane and preserving the RMP.

**B. Action potentials (Fig. 1-9)**

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1. Overview
   - A rapid change in membrane potential in response to a variety of stimuli
   - Occurs in excitable tissue (e.g., neurons, muscle cells) and is the “language” of the nervous system (i.e., the electrical signals that encode all information in the nervous system)

2. Generation of an action potential in skeletal muscle cells
   - The membrane potential reaches a threshold value (approximately −55 mV), which is required for activation of fast, voltage-gated sodium channels.
   - Rapid influx of sodium occurs, causing depolarization of the cell; corresponding to the sharp upstroke of the action potential.
   - The membrane potential becomes increasingly less negative as it depolarizes and approaches the equilibrium potential for Na⁺.
   - The overshoot potential is at the apex of the action potential spike and corresponds to the period during which the membrane potential becomes positive (+).
   - Next, the membrane becomes more permeable to K⁺, causing efflux of potassium down its concentration gradient.
   - This causes repolarization of the membrane potential.
   - The final phase of the action potential is characterized by a slight hyperpolarization phase, during which the Na⁺,K⁺-ATPase (sodium) pump reestablishes the original sodium and potassium electrochemical gradients across the plasma membrane.

3. Properties of action potentials
   - “All or none”
     - a. Generation of an action potential is determined solely by the ability of the stimulus to cause the cell to reach threshold (i.e., it is “all or none”).
     - b. If the threshold potential is reached, an action potential is generated; if it is not reached, no action potential is generated.
     - c. Regardless of stimulus intensity or energy content, the action potential will have the same amplitude.
   - Frequency
     - a. Increasing stimulus intensity increases the frequency of action potential generation.
     - b. For example, in a mechanoreceptor of the skin, the more the receptor is deformed (i.e., the greater the mechanical energy applied), the higher the frequency of action potential generation (action potential amplitude remains unchanged).
   - Refractory periods (Fig. 1-10)
     - a. During refractory periods, the cell is unable to generate an action potential.
     - b. This is an important property of excitable tissue because it prevents overly rapid generation of action potentials, which might cause continual contraction (tetany).
     - c. Absolute refractory period
       - An action potential cannot be generated, regardless of stimulus intensity.
       - This occurs during the depolarization phase of the action potential and is due to closure of the sodium channel inactivation gates.
     - d. Relative refractory period
       - Only a stimulus with intensity much greater than threshold can stimulate another action potential.

"All or none" phenomenon: if threshold is reached, action potential is generated; if threshold is not reached, no action potential is generated

<table>
<thead>
<tr>
<th>Stimulus intensity</th>
<th>Frequency of action potential generation, although action potential amplitude will remain unchanged.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute refractory period: action potential cannot be generated regardless of stimulus intensity; occurs during depolarization phase</td>
<td></td>
</tr>
</tbody>
</table>
This occurs during the repolarization phase and is due to the inactivated conformation of the voltage-gated sodium channels.

The conductance of $K^+$ is higher than in the resting state, so the membrane potential becomes more negative.

d. **Accommodation**

- When cells are held in the depolarization phase or are depolarized very slowly, the inactivation gates on sodium channels automatically close, and there is no sodium current.
- Even if the cell has reached its normal threshold potential, it is impossible for the cell to generate another action potential because too few sodium channels are open.

**Clinical note:** In hyperkalemia, the extracellular potassium concentration is higher than normal, so there is less of a driving force for $K^+$ to leave the cell and keep the membrane potential at $-70$ mV. The cell depolarizes enough to trigger the closure of sodium inactivation gates. This depolarization brings the membrane closer to threshold, but no action potential is generated.

**Conductance without decrement**

a. Action potentials travel along a neuron with no decrease in signal strength because of the presence of the protein myelin, which acts as an electrical insulator (Fig. 1-11).

b. At sites along the axon where myelin is absent, the nodes of Ranvier, the action potential must “jump” from one node to another, a process referred to as saltatory conduction.

**Clinical note:** Multiple sclerosis is an autoimmune disease characterized by inflammation and destruction of the protein myelin resulting in demyelination of nerves in the central nervous system. It manifests in many different forms; some patients have cognitive changes, whereas others have paresis, optic neuritis, or depression.

**C. Transmission of action potentials between cells**

- Action potentials can be transmitted between cells by either electrical or chemical transmission.

1. **Electrical transmission**

- This is a relatively rare form of action potential transmission in which current travels through openings between the cells, termed gap junctions.
- Occurs mainly in cardiac and smooth muscle, tissues in which there is cytoplasmic continuity between constituent cells (i.e., the cells function as a syncytium).

2. **Chemical transmission** (see Fig. 1-11)

- Primary form by which action potentials are transmitted

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**Fig. 1-11:** Chemical transmission at a synapse. The basic structure of a myelinated neuron synapsing with another neuron is shown. Neurotransmitter is released from vesicles in the terminal bouton of the presynaptic neuron and taken up by receptors in the postsynaptic neuron.
• Binding of the neurotransmitter (secreted from the presynaptic cell) to a ligand-gated receptor on the postsynaptic membrane results in localized depolarization and generation of an action potential in the postsynaptic cell.
  a. An action potential travels down the axon to the terminal bouton of the presynaptic neuron, causing opening of voltage-gated calcium channels.
  b. The resulting Ca\(^{2+}\) influx into the presynaptic nerve terminal causes fusion of neurotransmitter-containing vesicles with the presynaptic membrane and subsequent release of neurotransmitter into the synaptic cleft.
  c. The neurotransmitter diffuses across the synaptic cleft.
  d. The neurotransmitter binds to ligand-gated receptors located on the postsynaptic cell.
  e. This causes either an excitatory postsynaptic potential (EPSP) or an inhibitory postsynaptic potential (IPSP).
  f. EPSPs are a result of localized depolarization caused by increased conductance to (and influx of) Na\(^+\), whereas IPSPs are a result of localized hyperpolarization caused by increased conductance to Cl\(^-\) or K\(^+\).
  g. If summation of EPSPs and IPSPs at the axon hillock brings the membrane potential to threshold, generation of an action potential occurs by opening of voltage-gated sodium channels.
  h. The action potential travels toward the terminal bouton (anterograde transport).
  i. The action potential arrives at the terminal bouton, and the process repeats.
  j. To prevent repetitive stimulation of the postsynaptic cell, neurotransmitters are either degraded in the synaptic cleft or taken up by endocytosis into the presynaptic cell.

Clinical note: In Lambert-Eaton syndrome, antibodies are made against the voltage-gated calcium channels on the terminal bouton of the presynaptic motor neuron. Binding of these antibodies to the calcium channels impairs neurotransmitter (acetylcholine) release by inhibiting calcium influx, resulting in generalized muscle weakness. Proximal muscles are affected more than distal muscles.

D. Conduction velocity
1. Conduction velocity is primarily dependent on the presence or absence of myelin and the diameter of the axon.
2. Large-diameter, myelinated axons conduct impulses much more rapidly (1 to 100 m/second) than small-diameter, unmyelinated axons (<1 m/second).
3. Not having nodes of Ranvier, unmyelinated axons have to continually regenerate action potentials along the entire length of the axon, resulting in a much slower conduction velocity.
4. If the distance between the nodes of Ranvier is decreased along the length of an axon (i.e., there are more nodes of Ranvier), the conduction velocity will be reduced because more action potentials need to be produced.

Clinical note: In Guillain-Barré syndrome, segmental demyelination of peripheral nerves, nerve roots, and their associated ganglia occurs. It typically manifests as ascending weakness and paralysis, starting in the distal extremities and rapidly traveling proximally. Paralysis may occur because of immunologic destruction of the myelin sheath, effectively decreasing nerve conduction velocity. The disease can cause fatal respiratory paralysis, so prompt respiratory care and support are crucial; once the inflammation has subsided, the nerves can remyelinate, and normal function can be recovered.

E. Types of neurotransmitters
1. Acetylcholine: cholinergic transmission
   - Acetylcholine (ACh) is used by all motor axons, autonomic preganglionic neurons, and postganglionic parasympathetic nerves and by some cells of the motor cortex and basal ganglia.
   - Depending on the postsynaptic receptor, ACh can be either stimulatory (e.g., at the neuromuscular junction by motor neurons) or inhibitory (e.g., in parasympathetic postganglionic fibers to cardiac muscle).
Clinical note: In the autoimmune disease myasthenia gravis, antibodies are made against ACh receptors of the neuromuscular junction in skeletal muscle. These antibodies bind to the ACh receptor on the postsynaptic membrane and block ACh binding, resulting in muscle weakness and easy fatigability. Treatment includes administration of acetylcholinesterase inhibitors such as neostigmine to increase the amount of ACh in the synaptic cleft.

- Enzymes (synaptic cholinesterase and plasma cholinesterase) rapidly degrade ACh.
  a. ACh also functions extensively in the brain to maintain cognitive function.

Clinical note: In Alzheimer disease, there is degeneration of the basal forebrain nuclei that normally have extensive cholinergic projections throughout the brain. There is also evidence of a cortical deficiency of choline acetyltransferase, the enzyme that combines choline and acetyl coenzyme A to produce ACh. The resulting lack of acetylcholine appears to play a primary pathologic role in the learning and memory deficits.

2. Amino acids
   - Glutamate: glutamatergic transmission
     a. Glutamate is the primary stimulatory neurotransmitter of the brain.
     b. It binds to both inotropic (stimulatory) and metabotropic (modulator) receptors.
     c. Excess glutamatergic activity is associated with excitotoxicity and seizures.
   - Gamma aminobutyric acid (GABA)
     a. GABA is the primary inhibitory neurotransmitter in the brain.
     b. It is abundant within the basal ganglia and cerebellum.
     c. It is derived from the amino acid glutamate by action of the enzyme glutamate decarboxylase.
     d. Deficient GABA activity may result in movement abnormalities, anxiety disorders, seizures, and muscle spasms.

Pharmacology note: Because GABA is an inhibitory neurotransmitter, GABA agonists such as benzodiazepines, alcohol, and barbiturates are frequently used (prescribed or not) as antianxiety agents (anxiolytics), suppressing cortical function.

Clinical note: In Huntington disease, there is progressive deterioration of the caudate nucleus, putamen, and frontal cortex, but clinical symptoms do not appear until the fourth or fifth decade, by which time many patients have already passed on the mutated autosomal dominant gene to their children. Deterioration starts with hyperkinetic (choreiform) movements, progressing to hypertonicity, incontinence, anorexia, dementia, and death. Loss of GABA-secreting neurons between the striatum and globus pallidus is one of the factors responsible for the abnormal movements.

- Glycine
  a. Glycine is the primary inhibitory neurotransmitter of the spinal cord.
  b. It increases chloride conductance in the postsynaptic membrane.
  c. This results in hyperpolarization of the postsynaptic membrane and inhibition of action potential generation.

Clinical note: Glycine secretion in the spinal cord is inhibited by the tetanus toxin, exposure to which results in excessive stimulation (disinhibition) of the lower motor neurons, producing spasmodic muscle contraction (i.e., spastic paralysis). The nerves must sprout new terminals before the patient can regain normal function.

3. Monoamines
   - Overview
     a. These neurotransmitters contain a single amine group in their chemical structure and include norepinephrine, serotonin, and dopamine.
     b. Monoamines are degraded by intracellular (presynaptic) monoamine oxidase (MAO) and postsynaptic catechol-O-methyl transferase (COMT).
Clinical note: The monoamine deficiency theory of depression links depression to a deficiency in at least one of the three monoamine neurotransmitters: norepinephrine, serotonin, and dopamine. Extensive pharmacologic support for this theory has been obtained over the years, as evidenced by the efficacy of monoamine oxidase inhibitors and tricyclic antidepressants, which increase levels of monoamine neurotransmitters in the brain. However, these drugs affect levels of other neurotransmitters and have numerous side effects. More recently, serotonin-specific reuptake inhibitors (SSRIs) and non-serotonin-specific reuptake inhibitors (NSRIs) have been shown to be extremely effective in the treatment of depression with minimal side effects.

- **Norepinephrine: adrenergic transmission** *(Fig. 1-12)*
  a. Derived from the amino acid tyrosine
  b. Synthesized and released by the sympathetic nervous system, adrenal medulla, and locus ceruleus of the central nervous system

Clinical note: Cocaine is a centrally acting norepinephrine reuptake inhibitor.

- **Serotonin (5-HT)**
  a. Serotonin is derived from the amino acid tryptophan *(Fig. 1-13)*.
  b. Most of the body’s serotonin is found in the enteric nervous system of the gut.
  c. The serotonin in the brain plays an important role in control of mood.

- **Dopamine: dopaminergic transmission**
  a. Dopamine is derived from the amino acid tyrosine *(Fig. 1-14)*.
  b. Dopamine is an important neurotransmitter in the brain.

1-12: Adrenergic transmission: the norepinephrine pathway. COMT, Catecholamine-O-methyl transferase; DOPA, L-dihydroxyphenylalanine; MAO, monoamine oxidase; NE, norepinephrine.

c. There are three primary dopaminergic pathways.
   • The **nigrostriatal** pathway: transmits dopamine from the substantia nigra of the midbrain to the striatum and is important in the control of voluntary movement.
   • The **mesolimbic** pathway: dopaminergic transmission between the midbrain and the limbic system. This is important in the control of emotions and also in voluntary control of movements associated with emotion (e.g., smiling, frowning).
   • The **tuberoinfundibular** pathway: dopaminergic transmission from the hypothalamus to the pituitary, where dopamine inhibits prolactin secretion.

**Pharmacology note**: Dopamine agonists such as bromocriptine are used clinically to treat prolactinomas, the most common type of secreting pituitary tumor; they are also the mainstay of treatment of Parkinson disease. Conversely, the dopamine system may become overly active, as in schizophrenia; dopamine antagonists such as risperidone (Risperdal) and clozapine are widely used to reduce symptoms of schizophrenia such as hallucinations and delusions.

4. **Neuropeptides**
   - These have a **longer duration of action** than the smaller molecular neurotransmitters mentioned earlier, partly because neuropeptides act by altering gene expression, so their effects may continue after they are degraded.
   - Neuropeptides may be secreted at the same time as a small-molecule neurotransmitter such as norepinephrine (cotransmission).
   - This results in an immediate, rapid response (because of the smaller neurotransmitter) and a delayed but prolonged response caused by the neuropeptide.
   - For example, glutamate and the neuropeptide **substance P** are cotransmitted in the pain pathway; glutamate causes immediate inhibition of neurotransmission of pain, whereas substance P causes changes in gene expression to produce a lasting effect.
   a. Other examples of neuropeptides include neuropeptide Y, enkephalins, endorphins, and nitric oxide.

III. Neuromuscular Junction

A. **Structure of the neuromuscular junction (NMJ)**
   1. The NMJ is composed of a presynaptic motor neuron, the synaptic cleft, and the postsynaptic membrane (i.e., the plasma membrane of the muscle cell, termed the sarcolemma).
   2. The NMJ is also called the motor end plate.

B. **Mechanism of neuromuscular transmission** (Table 1-6)
   1. An action potential triggers the fusion of ACh storage vesicles and corresponding release of acetylcholine from the presynaptic neuron.
   2. ACh then diffuses across the synaptic cleft and binds to nicotinic receptors on the sarcolemma; the time required for this diffusion is termed synaptic delay.
   3. Nicotinic receptors are slow, ligand-gated sodium channels; opening them produces a local depolarization along the sarcolemma, termed the end-plate potential.
   4. If the end-plate potential reaches threshold, it triggers the opening of voltage-gated sodium channels, and an action potential is produced.
   5. A number of drugs and toxins block transmission at the NMJ (Table 1-7).
IV. Skeletal Muscle

A. Structure

1. Skeletal muscle joins bone to bone.
2. The cells are large in diameter and multinucleated.
3. Cells contain a network of membrane invaginations called the transverse tubules (T tubules); these tubules interconnect the plasma membrane (sarcolemma) and ER (called sarcoplasmic reticulum in muscle cells), which is filled with calcium at rest.
4. Actin-myosin myofilaments are arranged into sarcomeres (Fig. 1-15).
   • Sarcomeres are the functional unit of skeletal muscle (see Fig. 1-15).

### TABLE 1-6. Comparison of the Steps Involved in Synaptic Transmission at Neuron-to-Neuron Junctions and the Neuromuscular Junction

<table>
<thead>
<tr>
<th>NEURON TO NEURON ACTION</th>
<th>NEUROMUSCULAR JUNCTION ACTION</th>
<th>CLINICAL EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>An action potential in presynaptic neuron causes release of neurotransmitter from vesicles stored in terminal bouton.</td>
<td>An action potential in presynaptic neuron causes release of acetylcholine (ACh) from vesicles stored in terminal bouton.</td>
<td>Weakness and paralysis until new nerve terminals have sprouted</td>
</tr>
<tr>
<td>Diffusion of neurotransmitter across synaptic cleft</td>
<td>Diffusion of ACh across synaptic cleft</td>
<td></td>
</tr>
<tr>
<td>Neurotransmitter binds to postsynaptic ligand-gated receptor, resulting in EPSP or IPSP. If summation of EPSPs or IPSPs exceeds threshold potential at the axon hillock, an axon potential is generated.</td>
<td>ACh binds to postsynaptic nicotinic receptor, a ligand-gated receptor that when activated allows facilitated diffusion of Na⁺ and K⁺ ions, having a net depolarizing effect referred to as end-plate potential (EPP).</td>
<td></td>
</tr>
<tr>
<td>To prevent repetitive stimulation, neurotransmitters are either degraded in the presynaptic cleft or taken up by endocytosis in presynaptic cell.</td>
<td>Acetylcholinesterase breaks down ACh into acetyl coenzyme A and choline, which are taken up into the presynaptic cell.</td>
<td></td>
</tr>
</tbody>
</table>

EPSP, Excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential.

### TABLE 1-7. Drugs and Toxins Acting at the Neuromuscular Junction

<table>
<thead>
<tr>
<th>TOXIN/DRUG</th>
<th>ACTION</th>
<th>CLINICAL EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum toxin</td>
<td>Blocks release of acetylcholine (ACh) from presynaptic nerve terminal.</td>
<td>Weakness and paralysis until new nerve terminals have sprouted</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>Inhibit ACh, leading to persistently elevated ACh and tonic activation of ACh receptors</td>
<td>Diarrhea, urination, miosis, bronchoconstriction, excitation (muscle paralysis), lacrimation, and salivation</td>
</tr>
<tr>
<td>Curare (toxin)</td>
<td>Competitively antagonizing binding of ACh to the postsynaptic nicotinic receptor</td>
<td>Skeletal muscle paralysis</td>
</tr>
<tr>
<td>Nondepolarizing neuromuscular blocking drugs similar to curare (e.g., atracurium)</td>
<td>Competitively antagonizing binding of ACh to the postsynaptic nicotinic receptor</td>
<td>Skeletal muscle paralysis; used to cause paralysis in preparation for intubation</td>
</tr>
<tr>
<td>Depolarizing neuromuscular blocking drugs (e.g., succinylcholine)</td>
<td>Competitive agonist of the postsynaptic nicotinic receptor</td>
<td>Binds so strongly to nicotinic receptor that prolonged depolarization occurs, initially causing generalized skeletal muscle contraction that is short-lived, and flaccid paralysis follows</td>
</tr>
</tbody>
</table>

1-15: Structure of the sarcomere.
Sarcomeres: functional unit of skeletal muscle; overlapping of myosin and actin filaments; striated appearance

- They are composed of overlapping thick filaments (myosin) and thin filaments (actin), which gives skeletal muscle its striated appearance under the light microscope.
  a. Z disks are platelike protein structures into which actin filaments are inserted; two Z plates form the outer boundaries of one sarcomere.
  b. A bands, located in the center of the sarcomere, contain myosin filaments and appear dark under the light microscope.
  c. I bands are composed entirely of actin; they lie between A bands and are transected by the Z disks.
  d. Actin and myosin filaments overlap to form cross-bridges. However, the H zone (or bare zone), located in the center of the sarcomere, is composed entirely of myosin filaments; there is no overlap of actin and myosin filaments in this region.
  e. The M line lies in the center of the H zone and is therefore composed only of myosin filaments.

B. Contraction

1. Mechanism of contraction: the sliding-filament theory
   - Conduction of an action potential along the sarcolemma and throughout the T tubules results in release of calcium by the sarcoplasmic reticulum.
   - Ca\(^{2+}\) binds to troponin, causing a conformational change of troponin, which in turn causes tropomyosin to be displaced.
   - The displacement of tropomyosin exposes myosin-binding sites on the actin, which allows temporary covalent bonds to form between actin and myosin (cross-bridging).
   - Repetitive cycles of cross-bridging, pivoting, and detachment of actin and myosin result in the sliding of the filaments with respect to each other.
     a. ATP is required for the detachment phase of the cycle.
        - It causes a conformational change in myosin that decreases its affinity for actin.
     b. Cross-bridge cycling occurs for as long as Ca\(^{2+}\) is bound to troponin.
     c. When filaments slide over each other during cross-bridge cycling, the Z disks are pulled toward one another, the sarcomere shortens, and the muscle contracts.
     d. Each sliding cycle shortens the sarcomere, and thus the entire muscle fiber, by about 1%; many cycles are required to produce significant muscle contraction.
   - Relaxation occurs when Ca\(^{2+}\) has been pumped back into the sarcoplasmic reticulum through a Ca\(^{2+}\)-ATPase pump in its membrane.
   - Ca\(^{2+}\) no longer binds to troponin, and tropomyosin returns to its original conformation, blocking the interaction between actin and myosin.

Clinical note: The importance of ATP in skeletal muscle relaxation, or the detachment phase of contraction, is evidenced by rigor mortis, which occurs as a result of the absence of ATP after death has occurred. The actin-myosin myofilaments remain locked together because ATP had been depleted.

2. Types of contraction
   - Graded
     a. The strength of contraction depends primarily on the number of muscle fibers recruited rather than the strength of the muscle fibers.
   - Twitch
     a. Electrical stimulation of myocytes above the threshold potential results in a limited efflux of Ca\(^{2+}\) from the sarcoplasmic reticulum into the cytoplasm, stimulating a single contraction.
   - Summation and tetanus
     a. If muscle is stimulated at a high enough frequency, individual muscle twitches combine (summate) to produce sustained contraction (tetanus) (Fig. 1-16).
   - Isotonic muscle contraction
     a. A constant force is produced while the muscle length is changing.
     b. As muscle tension increases, the muscle shortens and lifts the load (e.g., biceps curls in weight lifting).
   - Isometric muscle contraction
     a. A constant force is produced while the muscle is held so that it does not change in length and can only exert tension.
     b. Active tension is produced by cross-bridge cycling, but muscle length does not change (e.g., pushing against an immovable object such as a wall).
3. Regulation of contraction
- Muscle contraction is regulated by the somatic nervous system (i.e., it is under voluntary control).
- The motor neuron (with cell body in the spinal cord or brainstem nuclei) and the muscle fiber or fibers it innervates are called the motor unit, the functional unit of skeletal muscle.
- The fewer muscle fibers innervated by a given motor neuron, the greater the precision of control of contraction.
  a. For example, motor neurons that innervate laryngeal muscles supply only a few muscle fibers, whereas motor units that innervate the gluteus maximus supply thousands of muscle fibers.
- The strength of skeletal muscle contraction is determined by four factors: metabolic condition (e.g., fatigue), amount of load, recruitment of motor units, and initial length of muscle fibers.
- The amount of tension that can be generated is determined by the extent of actin-myosin myofilament overlap.
  a. This is termed the length-tension relationship (Fig. 1-17).
  b. If the sarcomere is shortened, the actin and myosin have less room to overlap and develop tension.
  c. If the muscle is stretched to a point at which actin and myosin no longer overlap, no cross-bridges can be formed, and no tension can develop.

4. Types of skeletal muscle fiber (Table 1-8)
- Fast-twitch
  a. Fibers that are stimulated by large, fast-conducting nerves
  b. Mainly use stored glycogen and thus anaerobic respiration for energy; therefore, they fatigue easily because of lactic acid buildup
  c. Whitish in color because they contain only small amounts of myoglobin
  d. Have relatively few mitochondria and therefore are used for explosive high-intensity activity (e.g., sprinting), drawing on stored glycogen
- Slow-twitch
  a. Fibers that are innervated by small-diameter, slow-conducting nerves
  b. Use both fats and carbohydrates as an energy source and are resistant to fatigue

![Image 1-16: Types of muscle contraction.](image)

![Image 1-17: Length-tension relationship in skeletal muscle.](image)
c. Rich in myoglobin, which gives them a red appearance
d. Muscles controlling posture are mainly composed of slow-twitch fibers.
   • These muscle fibers are adapted for continual low-intensity activity (e.g., walking).

Clinical note: Strength training causes an increase in the number of myofilaments in each muscle fiber. This increases the force that the muscle is able to generate and increases the mass of the muscle even though the number of muscle fibers is unchanged. Endurance training usually does not increase the mass of muscle but instead increases the number of blood vessels (for delivery of more oxygen and glucose) and mitochondria (for delivery of ATP) in the muscle.

V. Smooth Muscle

A. Structure
1. Smooth muscle is arranged in circular layers around hollow organs (e.g., esophagus, respiratory airways) and blood vessels (including the aorta but not the heart); contraction reduces the size of these structures.
2. The cells are spindle shaped.
3. The actin-myosin myofilaments are not arranged into sarcomeres, so cells are nonstriated in appearance.
4. The absence of sarcomeres enables smooth muscle to contract even when the cells are enormously stretched (i.e., smooth muscle contraction is not limited by the length-tension relationship).
5. The sarcoplasmic reticulum is loosely arranged within the cells, and there are no T tubules.
6. Cells do contain dense bodies, structures analogous to the Z disks found in skeletal muscle.

B. Types
1. Single-unit (unitary or visceral) smooth muscle
   • The predominant type of smooth muscle in the body, located in the gastrointestinal tract, bladder, uterus, and ureters
   • Functions as a syncytium
   • Low-resistance channels between cells (gap junctions) transmit nerve impulses, causing the contraction of many cells at once.
   • A unique quality of gastrointestinal smooth muscle is the rhythmic fluctuation of membrane potential (slow waves) that gives rise to spike potentials, which can cause muscle contraction (i.e., they function as a pacemaker) (see Chapter 7, Gastrointestinal Physiology).
   • Although slow waves are the primary regulator of single-unit smooth muscle, activity can be modified substantially through the autonomic nervous system.

2. Multiunit smooth muscle
   • Located in the iris, ciliary muscle of the lens, arrector pili of the skin, and vas deferens
   • Similar to skeletal muscle in that each muscle fiber is innervated, and therefore functions, separately
   • Gap junctions are absent.
   • Because there is no pacemaker activity, regulation of multiunit smooth muscle is dependent on the autonomic nervous system.

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>SLOW-TWITCH</th>
<th>FAST-TWITCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>“Red” muscle</td>
<td>“White” muscle</td>
</tr>
<tr>
<td>Example</td>
<td>Soleus</td>
<td>Stapedius</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Primarily aerobic</td>
<td>Primarily anaerobic</td>
</tr>
<tr>
<td>Diameter of fiber</td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>More</td>
<td>Fewer</td>
</tr>
<tr>
<td>Capillary supply</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Sensitivity to hypoxia</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Resistance to fatigue</td>
<td>Higher</td>
<td>Lower</td>
</tr>
</tbody>
</table>
C. Mechanism of contraction
   1. Slow waves give rise to spike potentials, which stimulate cell contraction.
   2. The initial phase of contraction is triggered by an increase in cytoplasmic calcium, released from the sarcoplasmic reticulum, as occurs in skeletal muscle.
   3. Sustained contraction is mediated by continued influx of Ca\(^{2+}\) into the cytoplasm from the interstitial, through voltage-gated calcium channels on the cell membrane.
   4. Calcium combines with the protein calmodulin to form the calcium-calmodulin (Ca\(^{2+}\)-CaM) complex and activates myosin light-chain kinase (MLCK).
   5. MLCK in turn phosphorylates the myosin cross-bridges, exposing binding sites for actin.
   6. Actin and myosin then form cross-bridges that contract the muscle cell.
   7. Relaxation occurs when Ca\(^{2+}\) has been pumped back into the sarcoplasmic reticulum such that the Ca\(^{2+}\)-CaM complex can no longer be formed.

D. Regulation of contraction
   1. Most smooth muscle has intrinsic pacemaker activity, but smooth muscle activity can be modulated by the autonomic nervous system (i.e., it is generally not under voluntary control).
   2. Sympathetic and parasympathetic nerves are distributed to all organ systems in the body and stimulate smooth muscle activity in many organs at once.
   3. For example, in the fight-or-flight response, sympathetic stimulation causes a myriad of responses such as pupillary dilation, dilation of coronary arteries, decreased intestinal motility, and bronchial dilation.
   4. In general, parasympathetic stimulation has the opposite effects.

Clinical note: In Chagas disease, infection with the protozoan parasite Trypanosoma cruzi (found in South America) can cause destruction of the myenteric plexus of the enteric nervous system, resulting in severely impaired regulation of intestinal smooth muscle contraction, particularly in the esophagus. Clinical manifestations may include difficulty swallowing (dysphagia), chest pain from esophageal distention, and frequent bouts of pneumonia caused by aspiration of esophageal contents. The myenteric plexus of the colon may also be destroyed, causing toxic megacolon.

VI. Cardiac Muscle
A. Structure
   1. Similar to smooth muscle, the cells are interconnected through gap junctions and function as a syncytium (Table 1-9).
   2. Similar to skeletal muscle, they contain sarcomeres and are striated in appearance.

B. Mechanism of contraction
   1. Similar to skeletal muscle, contraction occurs through a sliding filament mechanism.
   2. In contrast to skeletal muscle, extracellular Ca\(^{2+}\) plays a substantial role in triggering contraction.
   3. Similar to smooth muscle, contraction occurs in an “all or none” manner.

Pharmacology note: The fact that extracellular calcium plays such an important role in stimulating cardiac muscle contraction is exploited by calcium channel blocking drugs such as diltiazem and verapamil. Calcium channel blockers reduce heart rate and contractility without adversely affecting skeletal muscle functioning and are therefore useful for treating hypertension and a myriad of cardiac conditions.

C. Regulation of contraction
   1. Similar to smooth muscle, cardiac cells have an unstable RMP that allows them to generate their own electrical pacemaker activity.
   2. Rate of contraction (chronotropy), strength of contraction (inotropy), rate of conduction (dromotropy), and rate of relaxation (lusitropy) are further regulated by the autonomic nervous system.
   3. Sympathetic stimulation has positive chronotropic, inotropic, dromotropic, and lusitropic effects through the binding of norepinephrine and epinephrine to adrenergic receptors.
   4. Parasympathetic stimulation has negative chronotropic, inotropic, dromotropic, and lusitropic effects through the binding of ACh to muscarinic receptors.
Clinical note: The most common-onset muscular dystrophy, Duchenne muscular dystrophy, is an X-linked trait and is caused by a defect in the gene for dystrophin, a protein necessary for sarcolemma stability in striated muscle. Breakdown of sarcolemma results in calcium influx, enzyme activation, and muscle necrosis; fatty tissue and connective tissue fill the spaces once occupied by muscle, giving muscle a pseudohypertrophic appearance. Muscle weakness starts in the legs, with wide-based gait, hyperlordosis, and what appears to be hypertrophy of muscle. Patients are usually wheelchair-bound by 12 years of age. Lack of dystrophin in the brain leads to mental retardation. The mortality rate is 100%, and death is caused not by skeletal muscle defects but mostly by the absence of dystrophin in cardiac muscle, which results in fibrosis of the myocardium and subsequent heart failure, pulmonary congestion, and arrhythmias.

TABLE 1-9. Comparison of Skeletal, Cardiac, and Smooth Muscle

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>SKELETAL MUSCLE</th>
<th>CARDIAC MUSCLE</th>
<th>SMOOTH MUSCLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Bone to bone</td>
<td>Heart</td>
<td>Around hollow organs (gastrointestinal tract, airways, ureters)</td>
</tr>
<tr>
<td>Cell morphology</td>
<td>Large-diameter, multinucleated cells</td>
<td>Uninuclear and/or binucleated, branched cells</td>
<td>Small diameter</td>
</tr>
<tr>
<td>Striated</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gap junctions</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sarcomeres</td>
<td>Yes</td>
<td>Yes</td>
<td>No, actin inserts into dense bodies instead of Z disks</td>
</tr>
<tr>
<td>Innervation</td>
<td>Somatic nervous system</td>
<td>Autonomic nervous system</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>Type of contraction</td>
<td>Graded</td>
<td>All or none</td>
<td>All or none</td>
</tr>
<tr>
<td>Mechanism of contraction</td>
<td>Sliding filament mechanism</td>
<td>Sliding filament mechanism</td>
<td>Calcium-calcmodulin–induced activation of myosin light-chain kinase</td>
</tr>
<tr>
<td>Origin of calcium</td>
<td>Sarcoplasmic reticulum</td>
<td>Sarcoplasmic reticulum and extracellular fluid</td>
<td>Sarcoplasmic reticulum and extracellular fluid</td>
</tr>
<tr>
<td>Troponin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Postsynaptic receptor</td>
<td>Nicotinic receptor at neuromuscular junction</td>
<td>Adrenergic and muscarinic receptors throughout the heart</td>
<td>Muscarinic receptors widely distributed along the cell surface</td>
</tr>
<tr>
<td>Action potential</td>
<td>Short duration</td>
<td>Long duration</td>
<td>Long duration</td>
</tr>
<tr>
<td>Resting membrane potential</td>
<td>Stable</td>
<td>Unstable</td>
<td>Rhythmic fluctuations (slow waves), which give rise to spike potentials</td>
</tr>
<tr>
<td>Conduction of action potentials</td>
<td>Restricted to that particular muscle fiber, action potential travels bidirectionally along fiber</td>
<td>Functional syncytium, conducted through gap junctions</td>
<td>Functional syncytium, conducted through gap junctions</td>
</tr>
<tr>
<td>Pacemaker activity</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Effect of denervation</td>
<td>Atrophy</td>
<td>Will function adequately (e.g., heart transplant), but ability to exercise will be dependent on circulating catecholamines only</td>
<td>Still able to maintain tone</td>
</tr>
<tr>
<td>Examples of pathology</td>
<td>Muscular dystrophy, myositis</td>
<td>Congestive heart failure</td>
<td>CREST syndrome, achalasia, Chagas disease</td>
</tr>
</tbody>
</table>

CREST, Calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia.
I. Overview
A. The nervous system is unique in that it affects every other system of the body.
B. It consists of several complex components that function in an organized fashion at extremely high speeds.
C. The human brain is a network of more than 100 billion nerve cells that, through specific pathways, communicate with each other and with various motor and sensory systems.
D. Ultimately, these networks allow one to think, move, feel, experience, and manipulate one's environment.
E. Injury to or deficit in any part of the nervous system can lead to devastating and debilitating effects.

II. Organization and Functional Anatomy of the Nervous System
• The nervous system is anatomically subdivided into the central nervous system (CNS) and peripheral nervous system (PNS).
A. Central nervous system (CNS)
• Comprises the brain and the spinal cord (Fig. 2-1)
B. Peripheral nervous system (PNS)
1. Comprises the peripheral nerves originating from the brainstem and spinal cord (cranial and spinal nerves, respectively), as well as specialized clusters of neurons referred to as ganglia
2. The PNS is divided into two functional components, the somatic and autonomic divisions.
C. The somatic nervous system
1. This controls all voluntary actions (i.e., intentional movements but not reflexive ones).
2. All “processing” occurs in the brain and therefore at a conscious level.
3. Anatomically consists of an afferent loop, comprising the sensory nerves leading to the brain, and an efferent loop, comprising motor nerves from the brain to the muscles
D. The autonomic nervous system (ANS)
1. This controls all involuntary actions (e.g., reflexes, respiration) by regulating functioning of viscera, smooth muscle, and exocrine and endocrine glands.
2. It comprises sensory and motor neurons running between the brain and various internal organs such as the heart, lungs, viscera, and endocrine and exocrine glands.
3. It is further divided into the parasympathetic, sympathetic, and enteric nervous systems.
E. Protection of the brain
• This is ensured by two separate systems, the blood-brain and blood-CSF barriers.
  1. Blood-brain barrier (BBB) (Fig. 2-2)
    • Composed of endothelial cells packed tightly together to form tight junctions that prevent passage of most molecules
    • An underlying basement membrane and specialized glial cells (astrocytes), which project processes (pedicels) that attach to the walls of the capillary, reinforce this barrier.
    • Very few substances can cross the BBB into brain tissue:
      a. Water is able to freely diffuse.
      b. Glucose (the primary energy source of the brain) and amino acids require carrier-mediated transport.
c. **Nonpolar lipid-soluble substances** (e.g., free unconjugated bilirubin) cross more readily than polar water-soluble ones.

d. Other **active transport systems** are present to pump weak organic acids, halides, and extracellular $K^+$ ions across the BBB.

- Certain parts of the brain are not protected by the BBB: for example, the **pineal gland**, which secretes melatonin directly into the systemic circulation, and the **chemoreceptor trigger zone**, stimulation of which promotes vomiting.
Clinical note: In vasogenic edema (typically secondary to a brain tumor), the blood vessels are poorly developed, are leaky, and lack the transport properties of a normal BBB. This abnormal vessel permeability results in accumulation of interstitial fluid in the brain. Permeability of the BBB can also be altered in infections such as bacterial meningitis; although this accounts for some of the adverse neurologic effects of infection, it also permits improved delivery of antibiotics to the CNS.

2. Blood-CSF barrier
   - Cerebrospinal fluid (CSF) is a clear, colorless fluid that normally contains none or few cells, a small amount of protein, and a moderate amount of glucose.
   - The blood-CSF barrier is composed of epithelial cells of the highly vascular choroid plexus located within the ventricles. These cells are connected through tight junctions.
   - The choroid plexus produces CSF. The tight junctions between the cells serve to selectively allow substances access to the CSF.
   - Transport mechanisms across the barrier are similar to those of the BBB.

Clinical note: The composition of CSF may be altered in various disease states. Leukocytes or excess protein makes it appear cloudy; blood may make it appear red. In some diseases, the CSF has a characteristic composition. For instance, in viral meningitis, it shows increased numbers of lymphocytes, normal to slightly elevated protein concentration, normal glucose concentration, and a normal to mildly elevated “opening pressure.” In bacterial meningitis, there are increased numbers of polymorphonuclear leukocytes, an increased protein concentration, a decreased glucose concentration, and an increased opening pressure. In multiple sclerosis, the protein content, or γ-globulin content, is increased, and there is an increase in T cells.

III. The Autonomic Nervous System

A. Overview
   1. The primary function of the autonomic nervous system (ANS) is to control and regulate the visceral functions of the body (e.g., heart rate, glandular secretions).
   2. These functions are regulated by brain “centers” in the hypothalamus and brainstem.
   3. For example, vasomotor, respiratory, and vomiting centers are located in the medulla.
   4. Temperature, thirst, and appetite-regulating centers are located in the hypothalamus.

B. Organization
   1. The ANS operates primarily through visceral reflexes.
   2. Sensory signals from visceral organs enter the autonomic ganglia, brainstem, or hypothalamus.
   3. These entities interpret the signal and reflexively send signals back to the visceral organ to control its activity.
   4. The efferent autonomic signals are transmitted to the various organs of the body through two major subdivisions, the sympathetic nervous system and the parasympathetic nervous system.
   5. A third subdivision, the enteric nervous system (ENS), controls activity of the gastrointestinal tract; however, activity of the ENS can be greatly influenced by both arms of the autonomic nervous system.
   6. An example of a visceral reflex is the response to cold.
      - Cold receptors on the skin transmit signals to the hypothalamus, which in turn causes several reflexive adjustments through autonomic efferents, including:
         a. Stimulating muscle contraction (shivering), which increases the rate of body heat production, and
         b. Promoting peripheral vasoconstriction to diminish loss of body heat from the skin
   a. The sympathetic division: “fight or flight” system
      - The sympathetic nervous system is called the fight-or-flight system because it is most active in times of stress, fear, or excitement.
      - For example, at the exact moment a sudden fear is made conscious, the sympathetic nervous system takes over.
      - Bodily changes include a racing heart, dilated pupils, sweating, and skeletal muscle prepared for running.
While the body is poising itself for escape, it recruits additional energy from systems that are not vital to surviving the encounter.

For instance, sympathetic output shuts down gut and genitourinary function, to allow all efforts to be put into the escape (or “fight”).

See Table 2-1 for a summary of the actions of the sympathetic division of the nervous system.

b. Functional anatomy (Fig. 2-3)

- Sympathetic nerves are different from skeletal motor nerves in that each sympathetic pathway is composed of two neurons, a preganglionic neuron and a postganglionic neuron (Table 2-2).
- The preganglionic nerve fibers originate in the intermediolateral horn of the spinal cord (between cord segments T1 and L2).
- They pass through the anterior roots of the cord and do one of three things:
  1. Synapse in the paravertebral sympathetic chains of ganglia that lie to the two sides of the vertebral column or in the two prevertebral ganglia (the celiac and hypogastric ganglia)
  2. Pass upward or downward in the chain and synapse in one of the other ganglia
  3. Pass through one of the sympathetic nerves radiating outward from the chain and finally synapse in a peripheral sympathetic ganglion
- The postganglionic fiber then exits the ganglion and projects to the effector organ.
- The adrenal medulla is a specialized ganglion of the sympathetic division that synthesizes and secretes epinephrine and norepinephrine.
- Preganglionic sympathetic fibers pass, without synapsing, from the intermediolateral horn cells of the spinal cord, through the sympathetic chains and the splanchnic nerves, and finally to the adrenal medulla, where they synapse on the chromaffin cells.
- Chromaffin cells are modified neuronal cells that secrete epinephrine (80%) and norepinephrine (20%) into the bloodstream.
- These circulating hormones have almost the same effects on various organs as direct sympathetic stimulation, except that the effects last five to ten times as long because of their slow removal from the bloodstream.

Table 2-1. Autonomic Nervous System Effects on Target Organs

<table>
<thead>
<tr>
<th>TARGET ORGAN</th>
<th>SYMPATHETIC PHYSIOLOGIC MECHANISM</th>
<th>PARASYMPATHETIC PHYSIOLOGIC MECHANISM</th>
<th>SYMPATHETIC PHYSIOLOGIC MECHANISM</th>
<th>PARASYMPATHETIC PHYSIOLOGIC MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Pupil dilation (mydriasis)</td>
<td>Pupil dilation from contraction of dilator pupillae (radial fibers of iris)</td>
<td>Pupil constriction (miosis)</td>
<td>Contraction of sphincter pupillae (circular fibers of iris)</td>
</tr>
<tr>
<td>Bronchioles</td>
<td>Bronchodilation</td>
<td>β2-Mediated smooth muscle relaxation</td>
<td>Bronchoconstriction</td>
<td>M3-mediated smooth muscle contraction</td>
</tr>
<tr>
<td>Kidney</td>
<td>Renal perfusion, β1-mediated vasoconstriction and β2-mediated renin secretion</td>
<td>Very limited innervation</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Heart rate, stroke volume, cardiac output</td>
<td>Permeability nodal tissue to Na+ ions, sensitivity of cardiomyocytes to calcium ions</td>
<td>Heart rate, stroke volume, cardiac output</td>
<td>Increased permeability of nodal tissue to potassium ions</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Digestion and motility</td>
<td>Stimulates sphincter muscle contraction and splanchnic vasoconstriction</td>
<td>Promotes digestion</td>
<td>Stimulates intestinal secretions and peristalsis, inhibits sphincter muscle contraction</td>
</tr>
<tr>
<td>Bladder</td>
<td>Urinary retention</td>
<td>Constricts sphincter, relaxes detrusor muscle</td>
<td>Stimulates urination</td>
<td>Relaxes sphincter, contracts detrusor muscle</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>Sweating</td>
<td>Postganglionic sympathetic cholinergic transmission</td>
<td>Sweating</td>
<td>Postganglionic parasympathetic cholinergic transmission</td>
</tr>
<tr>
<td>Penis</td>
<td>Ejaculation</td>
<td>Erection</td>
<td>Vasoconstriction</td>
<td></td>
</tr>
</tbody>
</table>

While the body is poising itself for escape, it recruits additional energy from systems that are not vital to surviving the encounter.

For instance, sympathetic output shuts down gut and genitourinary function, to allow all efforts to be put into the escape (“fight”).

See Table 2-1 for a summary of the actions of the sympathetic division of the nervous system.

b. Functional anatomy (Fig. 2-3)

- Sympathetic nerves are different from skeletal motor nerves in that each sympathetic pathway is composed of two neurons, a preganglionic neuron and a postganglionic neuron (Table 2-2).
- The preganglionic nerve fibers originate in the intermediolateral horn of the spinal cord (between cord segments T1 and L2).
- They pass through the anterior roots of the cord and do one of three things:
  1. Synapse in the paravertebral sympathetic chains of ganglia that lie to the two sides of the vertebral column or in the two prevertebral ganglia (the celiac and hypogastric ganglia)
  2. Pass upward or downward in the chain and synapse in one of the other ganglia
  3. Pass through one of the sympathetic nerves radiating outward from the chain and finally synapse in a peripheral sympathetic ganglion
- The postganglionic fiber then exits the ganglion and projects to the effector organ.
- The adrenal medulla is a specialized ganglion of the sympathetic division that synthesizes and secretes epinephrine and norepinephrine.
- Preganglionic sympathetic fibers pass, without synapsing, from the intermediolateral horn cells of the spinal cord, through the sympathetic chains and the splanchnic nerves, and finally to the adrenal medulla, where they synapse on the chromaffin cells.
- Chromaffin cells are modified neuronal cells that secrete epinephrine (80%) and norepinephrine (20%) into the bloodstream.
- These circulating hormones have almost the same effects on various organs as direct sympathetic stimulation, except that the effects last five to ten times as long because of their slow removal from the bloodstream.

Table 2-1. Autonomic Nervous System Effects on Target Organs

<table>
<thead>
<tr>
<th>TARGET ORGAN</th>
<th>SYMPATHETIC PHYSIOLOGIC MECHANISM</th>
<th>PARASYMPATHETIC PHYSIOLOGIC MECHANISM</th>
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<td>Renal perfusion, β1-mediated vasoconstriction and β2-mediated renin secretion</td>
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<tr>
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<td>Ejaculation</td>
<td>Erection</td>
<td>Vasoconstriction</td>
<td></td>
</tr>
</tbody>
</table>
Simultaneously, those organs activated in times of stress, such as skeletal and cardiac muscle, are relaxed. See Table 2-1 for a summary of the actions of the parasympathetic division of the nervous system.

d. Functional anatomy (Fig. 2-4)

- As in the sympathetic nervous system, parasympathetic pathways are composed of preganglionic and postganglionic neurons.
- The preganglionic nerve fibers originate in cranial nerve nuclei in the brainstem and in the intermediolateral horn of the spinal cord between cord segments S2 and S4 (craniosacral origin).
- These fibers pass uninterrupted all the way to the effector organ.
In the wall of the effector organ, the preganglionic fibers synapse with very short postganglionic fibers, which in turn affect the function of the organ.

e. The enteric nervous system

- This is contained entirely within the gut wall and is composed of the submucosal (Meissner) plexus and the myenteric (Auerbach) plexus.
- Stimulation of the submucosal plexus promotes digestion, largely by stimulating secretions from the mucosal epithelium.
- Stimulation of the myenteric plexus increases intestinal motility by stimulating peristalsis and inhibiting contraction of sphincter muscles throughout the intestinal tract.
- The ANS can powerfully influence functioning of the enteric nervous system:
  1. The sympathetic nervous system
     - The sympathetic nervous system inhibits peristalsis and increases sphincter tone, thereby inhibiting digestion.
  2. The parasympathetic system promotes peristalsis and relaxes the sphincters, thereby enhancing digestion.

Clinical note: In Hirschsprung disease (congenital aganglionic megacolon), the neural crest (ganglion) cells that form the myenteric plexus fail to migrate to the colon. The absence of these cells results in intestinal obstruction because of narrowing of the affected “ganglionic” segment, causing delayed passage of meconium in the neonate, abdominal distention, and vomiting. The proximal portion of the bowel is dilated (megacolon). Treatment involves resection of the narrow, aganglionic segment (samples are sent for pathologic analysis until ganglion cells are found in the bowel sections).

C. Neurotransmitters of the ANS

1. Acetylcholine (ACh)
   - Neurotransmitter used in the peripheral nervous system, central nervous system, and autonomic nervous system
   - It is also the only neurotransmitter of the motor division of the somatic nervous system, which supplies muscle cells.

2. Norepinephrine (NE)
   - Is an adrenergic neurotransmitter
   - Is released from all postganglionic neurons of the sympathetic division except neurons that control the sweat glands and some blood vessels (which release ACh)

3. Vasoactive inhibitory peptide (VIP) and substance P
   - Peptidergic neurotransmitters that are colocalized with ACh in some postganglionic parasympathetic fibers

4. Dopamine
   - Neurotransmitter in the CNS as well as the interneurons of the sympathetic ganglia
   - Produced in the substantia nigra, ventral tegmental area, and hypothalamus

### TABLE 2-2. Comparison of Neurons of the Autonomic and Somatic Nervous Systems

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>AUTONOMIC</th>
<th>SOMATIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preganglionic neuron origin of</td>
<td>Sympathetic: Spinal cord segments T1-12, L1-3</td>
<td>Sensory: Dorsal root ganglia</td>
</tr>
<tr>
<td>ANS or location of cell body of</td>
<td>Parasympathetic: Cranial nerve nuclei III, VII, IX, and X; spinal cord segments S2-4</td>
<td>Motor: Anterior horn of spinal cord</td>
</tr>
<tr>
<td>first-order neuron in somatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preganglionic neuron length</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>Preganglionic neurotransmitter</td>
<td>ACh</td>
<td>ACh</td>
</tr>
<tr>
<td>Ganglia location</td>
<td>Paravertebral chain</td>
<td>Near effector organ</td>
</tr>
<tr>
<td>Postganglionic receptor</td>
<td>Nicotinic</td>
<td>Nicotinic</td>
</tr>
<tr>
<td>Postganglionic neuron length</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Postganglionic neurotransmitter</td>
<td>Norepinephrine (except sweat glands, which are ACh)</td>
<td>ACh (at synapses in spinal cord)</td>
</tr>
<tr>
<td>Effector organs</td>
<td>Cardiac and smooth muscle, glands</td>
<td>Cardiac and smooth muscle, glands</td>
</tr>
<tr>
<td>Effector organ receptors</td>
<td>(\alpha_1, \alpha_2, \beta_1, \beta_2)</td>
<td>Muscarinic</td>
</tr>
</tbody>
</table>

**Note that in the somatic nervous system, there is a single neuron (rather than a preganglionic and postganglionic neuron) that transmits data either from the spinal cord to the effector or from the periphery/environment to the spinal cord.**
Clinical note: Patients with Parkinson disease have impaired dopamine production by the substantia nigra. Because dopamine cannot cross the blood-brain barrier, it must be supplied to these patients in the form of its precursor, levodopa (L-DOPA). L-DOPA crosses the blood-brain barrier and is converted into dopamine in the brain.

5. Nitric oxide (NO)
   - Released by vascular endothelial cells (endothelium-derived relaxation factor [EDRF]); plays an important role in blood pressure regulation by promoting vascular smooth muscle relaxation.
By promoting vascular smooth muscle relaxation and increasing blood flow, NO stimulates penile erection in patients with erectile dysfunction (ED).

**Pharmacology note:** Sildenafil (Viagra) works by the release of nitric oxide (NO), endothelial-derived relaxing factor. This occurs in part through increasing levels of cyclic guanosine monophosphate (cGMP). Sildenafil is used for the treatment of pulmonary arterial hypertension and erectile dysfunction. Nebivolol, which is very selective for the β₁ adrenergic receptor, is effective as an antihypertensive agent primarily through promoting NO release by vascular endothelial cells, which causes vasodilation and decreases peripheral vascular resistance.

**Pharmacology note:** Agents that mimic the actions of ACh (e.g., pilocarpine for contraction of ciliary muscle in glaucoma) are termed cholinomimetics (or parasympathomimetics). Agents that mimic the actions of epinephrine and norepinephrine (e.g., albuterol for bronchodilation in asthma) are termed sympathomimetics.

### D. Neurotransmitter receptor types

1. **Adrenergic receptors** (Table 2-3)

   - Located at sympathetic effector organs
   - NE released from sympathetic neurons binds to these receptors, as do adrenal catecholamines; this is why the sympathetic nervous system is referred to as the sympathoadrenal system.
   - NE has preferential affinity for α-receptors, whereas epinephrine binds to both α- and β-receptors with relatively equal affinity.

2. **Cholinergic receptors** (Table 2-4; Fig. 2-5)

   - Location
     a. Parasympathetic effector organs as well as a few sympathetic effector organs such as sweat glands
     b. Preganglionic junctions innervated by both arms of the ANS
     c. Muscle cells in the somatic nervous system
   - Types: muscarinic and nicotinic
     a. There are three well-characterized types of muscarinic receptors: M₁ (gastric, CNS), M₂ (cardiac), and M₃ (smooth muscle).
     b. There are two well-characterized types of nicotinic receptors: N₄ (preganglionic-postganglionic junction) and N₅ (neuromuscular junction).

---

**TABLE 2-3. Adrenergic Receptors**

<table>
<thead>
<tr>
<th>RECEPTOR SUBTYPE</th>
<th>PRIMARY LOCATIONS</th>
<th>NORMAL PHYSIOLOGY ASSOCIATED WITH RECEPTOR ACTIVATION</th>
<th>CLINICAL PHARMACOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁</td>
<td>Vascular smooth muscle cells</td>
<td>Binding of catecholamines stimulates contraction, usually through Gq subunit, causing vasoconstriction and increased blood pressure</td>
<td>α-Blockers (e.g., prazosin) lower blood pressure by reducing total peripheral resistance</td>
</tr>
<tr>
<td>α₂</td>
<td>Presynaptic</td>
<td>Binding of synaptic norepinephrine results in feedback inhibition through Gi subunit to regulate release of neurotransmitter</td>
<td>Centrally acting α₂-agonists (e.g., clonidine) inhibit sympathetic outflow. This lowers blood pressure by reducing cardiac output (by reducing heart rate and contractility) and lowering peripheral vascular resistance (by stimulating vasodilation).</td>
</tr>
<tr>
<td>β₁</td>
<td>Heart</td>
<td>Binding of catecholamines is generally stimulatory in nature, increasing cardiac contractility (positive inotropy) and heart rate (positive chronotropy)</td>
<td>Dopamine indicated for hypovolemic shock (e.g., arterial hemorrhage); increases cardiac output but simultaneously stimulates renal vasoconstriction, thereby preserving renal perfusion. β₁-blockers such as metoprolol lower blood pressure by reducing cardiac stroke volume and heart rate, both of which lower cardiac output.</td>
</tr>
<tr>
<td>β₂</td>
<td>Vascular and nonvascular smooth muscle cells</td>
<td>Binding of catecholamines causes relaxation of muscle cells; bronchodilation and vasodilation in blood vessels of skeletal muscle during exercise (via regulation of myosin light chain kinase and myosin light chain phosphate activities)</td>
<td>β₂-blockers (e.g., propranolol) useful antihypertensives; β₂-agonists (e.g., albuterol) useful for stimulating bronchodilation in an asthmatic attack; such bronchodilation helps improve pulmonary ventilation during an asthmatic attack.</td>
</tr>
<tr>
<td>β₃</td>
<td>Adipose</td>
<td>Lipolysis through stimulation of hormone-sensitive lipase</td>
<td>β₃-Agonists may stimulate lipolysis and have potential role as weight-loss aids.</td>
</tr>
</tbody>
</table>

---

**TABLE 2-4. Cholinergic Receptors**

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>PRIMARY LOCATIONS</th>
<th>NORMAL PHYSIOLOGY ASSOCIATED WITH RECEPTOR ACTIVATION</th>
<th>CLINICAL PHARMACOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>M₁</td>
<td>Gastric, CNS</td>
<td>Stimulation of smooth muscle cells; smooth muscle relaxation</td>
<td>N/A</td>
</tr>
<tr>
<td>M₂</td>
<td>Cardiac</td>
<td>Stimulation of smooth muscle cells; smooth muscle relaxation</td>
<td>N/A</td>
</tr>
<tr>
<td>M₃</td>
<td>Smooth muscle</td>
<td>Stimulation of smooth muscle cells; smooth muscle relaxation</td>
<td>N/A</td>
</tr>
<tr>
<td>N₄</td>
<td>Preganglionic-postganglionic junction</td>
<td>Stimulation of smooth muscle cells; smooth muscle relaxation</td>
<td>N/A</td>
</tr>
<tr>
<td>N₅</td>
<td>Neuromuscular junction</td>
<td>Stimulation of smooth muscle cells; smooth muscle relaxation</td>
<td>N/A</td>
</tr>
</tbody>
</table>
IV. Control of Movement

A. Overview

1. The control of movement is complex and involves coordinated functioning of multiple hierarchical structures within the CNS such as the motor cortices, basal ganglia, motor thalamus, cerebellum, upper and lower motor neurons, and the sensory system.

2. Planning, initiation, and modification of movement are dependent on a proper functioning of the complicated interplay between a CNS stimulus, a musculoskeletal effector, and a proprioceptive sensor.

3. Movements are classified as either voluntary or involuntary:
   - **Voluntary movements** require conscious planning, which occurs in cortical centers such as the premotor and motor cortices.
   - **Involuntary movements** or reflexes occur at an unconscious level; they are largely independent of cortical control and dependent on brainstem and spinal cord reflexes.

B. Motor neurons

1. Muscles can be supplied by two types of motor neurons: **alpha motor neurons** and **gamma motor neurons**.

**TABLE 2-4. Cholinergic Receptors**

<table>
<thead>
<tr>
<th>RECEPTOR SUBTYPE</th>
<th>PRIMARY LOCATIONS</th>
<th>NORMAL PHYSIOLOGY ASSOCIATED WITH RECEPTOR ACTIVATION</th>
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</tr>
</thead>
<tbody>
<tr>
<td>M₁</td>
<td>Gastric, central nervous system</td>
<td>Parietal cell activity, neuronal activity</td>
<td>M₁ antagonists (e.g., pirenzepine) useful for treating ulcers</td>
</tr>
<tr>
<td>M₂</td>
<td>Heart</td>
<td>Vagal release of acetylcholine has negative chronotropic effect on the heart and decreases blood pressure</td>
<td>M₂ antagonists (e.g., atropine) useful during surgery to prevent anesthetic-mediated bradycardia</td>
</tr>
<tr>
<td>M₃</td>
<td>Smooth muscle</td>
<td>Contraction of smooth muscle (e.g., intestinal motility)</td>
<td>M₃ agonists (e.g., pilocarpine) for contraction of ciliary muscle in glaucoma</td>
</tr>
<tr>
<td>N₄</td>
<td>Preganglionic-postganglionic junction</td>
<td>Stimulation of both arms of the autonomic nervous system</td>
<td>Low-level nicotine stimulation, high-level nicotine or ganglion blockers such as hexamethonium inhibit autonomic outflow</td>
</tr>
<tr>
<td>N₅</td>
<td>Neuromuscular junction</td>
<td>Generation of an end-plate potential and action potential, resulting in contraction of skeletal muscle</td>
<td>Depolarizing neuromuscular agents (succinylcholine) and nondepolarizing neuromuscular agents (tubocurarine) used during surgeries</td>
</tr>
</tbody>
</table>

2-5: Cholinergic receptors in the autonomic nervous system.

Control of movement: involves motor cortex, basal ganglia, motor thalamus, cerebellum, upper and lower motor neurons, and sensory system.
2. Alpha motor neurons are large, myelinated axons that innervate **extrafusal muscle fibers**, contraction of which causes movement at a joint.

3. Gamma motor neurons are small, myelinated axons that innervate **intrafusal muscle fibers**, contraction of which do not result in movement but does play an important role in muscle tone and joint proprioception.

4. These fibers are summarized in Table 2-5.

C. **Control of voluntary movement**

- Control of voluntary movement by the brain can be thought of as occurring in multiple stages.
  1. The thought of performing the movement arises from the **premotor cortex**.
  2. A specific motor plan is “selected” from the **motor cortex**.
  3. The **basal ganglia** and **thalamus** then grant “permission” for the planned movement.
  4. In the **motor cortex**, neurons “fire,” activating descending **corticospinal fibers**.
  5. These fibers then stimulate **alpha motor neurons**, which stimulate **muscle contraction** (performance of the movement).

D. **Role of the cerebral cortex in movement**

1. The motor cortex of the frontal lobe is responsible for formation and execution of motor plans for voluntary movements.

2. It comprises the premotor, supplementary, and primary motor cortices.

3. Most descending corticospinal fibers originate from the motor cortices of the frontal lobe.

4. Descending corticospinal fibers originate from the motor cortices of the cerebral cortex, decussate in the pyramids of the caudal medulla, and terminate directly on motor neurons in the brainstem and spinal cord. These tracts then stimulate **alpha motor neurons**, which stimulate **muscle contraction** (performance of the movement).

5. Stimulation of the primary motor cortex results in **discrete movements of contralateral muscles** (e.g., moving a finger).

6. Stimulation of the association motor cortices results in more **complex, patterned movements** (e.g., waving the entire arm).

E. **Role of spinal cord tracts in movement** (Table 2-6)

1. Important in **rhythmic movements** such as chewing and swallowing, as well as **reflexive movements** such as withdrawal reflexes.

2. Tracts can be divided anatomically into two categories, pyramidal and extrapyramidal.
   - The **pyramidal tracts** originate in the cerebral cortex, decussate in the pyramids of the caudal medulla, and terminate directly on motor neurons in the brainstem and spinal cord.
     a. They include the corticobulbar, lateral corticospinal, and ventral corticospinal tracts (Fig. 2-6).
   - The **extrapyramidal tracts** originate in the brainstem (pons and medulla) and terminate on neurons adjacent to the ventral horn cells of the spinal cord.
     a. These tracts **indirectly** modulate activity of the ventral horn cells of the spinal cord and play an important role in reflexes, postural control, and locomotion.
     b. Examples include the rubrospinal, pontine and medullary reticulospinal, lateral and medial vestibulospinal, and tectospinal tracts.

3. **Medial descending system (MDS)**
   - **Overview**
     a. The tracts of the MDS terminate in the ventromedial portion of the anterior horn (hence their name).

Anatomy note: The ventral horn is somatotopically organized, such that ventromedially located alpha motor neurons innervate axial and proximal muscles and dorsolaterally located alpha motor neurons control distal limb muscles.
b. They influence activity of alpha motor neurons that control axial and proximal muscles.

c. They contribute to posture control by integrating visual, vestibular, and somatosensory information.

Clinical note: Any lesion of the MDS may cause impaired control of the axial muscles, loss of balance while walking, and loss of corrective reflexes.

- Vestibulospinal tracts
  a. Arise from the vestibular nuclei of the medulla and travel in the anterior funiculus of the spinal cord
  b. Comprise lateral and medial tracts (Fig. 2-7)
  c. The lateral vestibulospinal tract stimulates extensor motor neurons supplying muscles of the trunk and legs, thereby stabilizing posture.
  d. The medial vestibulospinal tract is important in control of eye movements, gaze control, and controlling head and neck position.
Reticulospinal tracts

- Arise from the brainstem reticular formation
- Comprise the pontine (medial) and medullary (lateral) tracts

- The pontine reticulospinal tract descends in the anterior funiculus of the spinal cord and acts in concert with the vestibulospinal tracts, being excitatory to extensor antigravity muscles.

- The medullary reticulospinal tract descends in the lateral funiculus of the spinal cord and is inhibitory to extensor antigravity muscles.
e. Lesions of the reticulospinal tracts can result in **decerebrate** and **decorticate** posturing (Fig. 2-8).

- **Tectospinal tract**
  a. Descends from the *superior colliculus* to the cervical segments of spinal cord.
  b. Important in reflexive movements of the head and neck in response to visual stimuli.

- **Ventral corticospinal tract**
  a. Originates in the primary motor cortex and premotor cortex and descends in the *anterior funiculus* of the spinal cord, projecting bilaterally to the ventromedial portion of the anterior horn at the level at which it synapses.
  b. Important in the control of **axial** and **proximal muscles** (in contrast to the lateral corticospinal tract, which controls more distal muscles).

4. **Lateral corticospinal tract**
- Arises from the primary, premotor, and supplementary motor cortices.
- After decussating in the *caudal medulla*, these tracts descend in the lateral funiculus of the spinal cord and synapse on alpha motor neurons, controlling **distal limb muscles**.
- Lesions result in UMN signs such as the Babinski response (Fig. 2-9)

**Clinical note:** A lesion of the **lateral corticospinal tract** can sometimes be appreciated by the presence of Babinski sign on physical examination. In a healthy patient, stimulation of the plantar aspect of the foot normally results in downward movement of the big toe (plantar flexion). In a patient with a lesion of the pyramidal tract, however, the big toe may move upward (dorsiflexion) in response to plantar stimulation. When this occurs, Babinski sign is said to be present.

5. **Relationship of upper and lower motor neurons**
- The term **upper motor neurons** encompasses motor neurons originating (primarily) from the motor cortices that descend to synapse on lower motor neurons located in the brainstem and spinal cord.
• The term lower motor neurons encompasses motor neurons originating in the brainstem and spinal cord and their path from their origin to the muscle they innervate.
• Upper motor neurons are tonically inhibitory to lower motor neurons.
• A lesion therefore causes disinhibition of lower motor neurons, resulting in spasticity and hyperreflexia (Table 2-7).

Clinical note: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by loss of pyramidal cells in the motor cortex as well as loss of ventral horn cells throughout the spinal cord. The dysfunction of both upper and lower motor neurons results in clinical signs of both types of lesions occurring simultaneously (e.g., hyperreflexia in one limb with hyporeflexia in another).

F. Role of the basal ganglia in movement
1. Overview
• The basal ganglia comprise subcortical (basal) clusters of nuclei (ganglia).
• They are important in the initiation of voluntary movements, becoming activated just before initiation of the movement.
• They include the putamen and caudate nucleus (collectively termed the striatum), globus pallidus, substantia nigra, and subthalamic nucleus (Fig. 2-10; Table 2-8).
• Output of the basal ganglia is to the motor thalamus, which in turn projects to the motor cortex.
  a. Basal ganglia output is always inhibitory in nature.

TABLE 2-7. Lesions of Upper and Lower Motor Neurons

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>UPPER MOTOR NEURON LESION</th>
<th>LOWER MOTOR NEURON LESION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Lesion of cortex or corticospinal tract</td>
<td>Damage to lower motor neurons</td>
</tr>
<tr>
<td>Examples</td>
<td>Amyotrophic lateral sclerosis</td>
<td>Poliomyelitis, trauma, Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Babinski sign</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Paralysis</td>
<td>Spastic</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Muscle wasting</td>
<td>Absent or minimal</td>
<td>Present</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Hyperreflexia or hyporeflexia</td>
<td>Hyperreflexia, clonus</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td>Deep tendon reflexes</td>
<td>Hyperactive</td>
<td>Absent</td>
</tr>
</tbody>
</table>

TABLE 2-8. Basal Ganglia Terms

<table>
<thead>
<tr>
<th>BASAL GANGLIA TERM</th>
<th>COMPOSITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatum</td>
<td>Putamen and caudate nucleus</td>
</tr>
<tr>
<td>Corpus striatum</td>
<td>Striatum and lentiform nucleus</td>
</tr>
<tr>
<td>Lentiform nucleus</td>
<td>Putamen and globus pallidus</td>
</tr>
</tbody>
</table>

2-10: Anatomy of the basal ganglia. (From Weyhenmeyer J, Gallman E: Rapid Review Neuroscience. Philadelphia, Mosby, 2007, Fig. 8-1.)
The basal ganglia influence movement through one of two pathways, the 
indirect pathway.

Lesions of the basal ganglia give rise to contralateral motor deficits.

a. The direct pathway (Fig. 2-11)

- Is activated by binding of dopamine to D1 receptors in the striatum
- This results in direct inhibition of basal ganglia output to the motor thalamus.
- Because the output is always inhibitory, the result is disinhibition of the motor thalamus, thereby allowing excitatory thalamocortical projections to stimulate the motor cortex to promote movement.

b. The indirect pathway (see Fig. 2-11)

- Inhibited by binding of dopamine to D2 receptors in the striatum
- Indirect stimulation, through the subthalamic nucleus, of basal ganglia output to the motor thalamus.
- Because the basal ganglia output is always inhibitory, the result is inhibition of the motor thalamus, and hence inhibition of movement.

Clinical note: Parkinson disease is a degenerative disease involving the loss of dopaminergic neurons in the substantia nigra. The loss of dopaminergic transmission (see Fig. 2-11) causes a relative deficiency of dopamine and excess of ACh in the striatum. Gross specimens show a loss of pigmentation in the substantia nigra. Histology shows Lewy bodies (intracytoplasmic, round, eosinophilic inclusion bodies). Patients present with a resting, “pill-rolling” tremor that disappears with movement, slowing of all voluntary movements, expressionless face (“masked facies”), cogwheel rigidity of limbs, and a wide-based shuffling gait. Treatment consists of dopamine agonists (or precursors such as levodopa) and anticholinergics such as atropine. Research into the implantation of dopamine-producing stem cells has been underway for years and is a matter of ethical controversy.

G. Role of the cerebellum in movement

1. The cerebellum is important in coordinating speed, trajectory, and force of movements as they occur.
2. It is also important in the maintenance of posture and equilibrium.
3. To perform these functions, the cerebellum must process in real time an enormous amount of information received from the body’s muscles, joints, and limbs.
4. In functional terms, the cerebellum is divided into the pontocerebellum, spinocerebellum, and vestibulocerebellum (Fig. 2-12).

   a. Pontocerebellum (neocerebellum, cerebrocerebellum)
      - Consists of the lateral zones of the cerebellar hemispheres, is highly developed, and is crucial to the planning and timing of sequential motor movements
   b. Receives large input from motor cortex
   c. Efferent output from dentate nucleus to red nucleus and thalamus
   d. Lesions of the pontocerebellum result in incoordination of the limbs.
Clinical note: Lateral cerebellar lesions cause a defect known as **decomposition of movement**. The result is a disruption in the timing of the components of a movement, which appear to take place sequentially rather than being coordinated smoothly. However, remaining portions of the motor control system are often able to compensate. Serious and permanent damage occurs when lesions affect the deep cerebellar nuclei—the dentate, interposed, and fastigial nuclei—in addition to the cerebellar cortex.

- **Spinocerebellum (paleocerebellum)**
  a. Responsible for smooth *coordination of movements* of the distal limbs (especially the hands and fingers) for the performance of precise and purposeful movements
  b. Receives input from two areas when a movement is performed:
     - **Direct information** from the **motor cortex and red nucleus** informing the cerebellum of the intended plan of movement
     - **Feedback information** from the peripheral parts of the body (through **muscle spindles** and **Golgi tendon organs**), indicating what actual movement resulted

Clinical note: Lesions of the **interposed nuclei**, which is located in the **spinocerebellum**, result in dysmetria (inability to control range of movement), ataxia (loss of coordination of movements), terminal tremor (attempts to correct abnormal movement result in a tremor), and pendular reflexes (limb oscillates instead of returning to original position and stopping).

- **Vestibulocerebellum (archicerebellum)**
  a. Important in posture, equilibrium, and control of eye movements
  b. Receives input directly from the **vestibular apparatus** through the eighth cranial nerve (CN VIII) and indirectly through the vestibular nuclei
  c. Efferent output is largely from the **fastigial nucleus** to the **vestibular nuclei** and influences the ascending medial longitudinal fasciculus (coordination of eye movements) and the descending medial and lateral vestibulospinal tracts.
  d. Lesions result in pendular **nystagmus** and truncal **ataxia** (Table 2-9).
Clinical note: The cerebellum plays an important role in maintenance of equilibrium. It achieves this by receiving sensory information from the eye and the vestibular apparatus of the inner ear and proprioceptive input from the muscles and joints through the spinocerebellar tracts. Cerebellar disease can be detected by the Romberg test. While performing the Romberg test, the patient is asked to close their eyes and stand with the feet close together. Closing the eyes leaves only vestibular and proprioceptive input to the cerebellum, which is sufficient to maintain balance if they are fully functional. However, in the presence of vestibular disease (e.g., vestibulitis) or sensory deficits (e.g., diabetic neuropathy), the cerebellum may not be able to function effectively, and the patient will be unable to maintain appropriate balance. If vestibular disease and sensory deficits can be ruled out by examination or history, a positive Romberg test implies primary cerebellar disease.

V. The Sensory System

- The sensory system comprises touch, proprioception, vibration, temperature, vision, olfaction, taste, and audition.

A. Sensory receptors

1. **Sensory receptors** are specialized **nerve cells** that detect environmental stimuli and transduce them through neural signals.
   - There are several different types (Table 2-10).
2. A **receptive field** is a focal area of the sensory surface (e.g., skin) to which the application of an approximately intense stimulus will trigger the sensory receptor to initiate an action potential.
3. These receptive fields allow the body to be topographically mapped (by their receptors) throughout the whole nervous system, from the skin to the brain.
4. Some signals need to be transmitted to the CNS rapidly, whereas others can be transmitted more slowly; therefore, different types of sensory fibers have different sizes and velocities.

B. Sensory transduction

1. A process whereby a stimulus is detected, amplified, and “conducted” to its ultimate target.
2. Sensory transduction typically occurs through changes in membrane potential.
3. All sensory receptors have one feature in common: once stimulated, the immediate effect is to change the membrane potential of the receptor.
4. This change is called a **receptor potential**.
5. The receptor potential is achieved by opening ion channels, allowing current to flow.
6. In most cases, the flow is **inward**, and the receptor is **depolarized**.

| TABLE 2-9. Motor Deficits Associated With Cerebellar Lesions*

<table>
<thead>
<tr>
<th>SIGN</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nystagmus</td>
<td>Rapid back-and-forth movements of the eye (e.g., pendular versus vestibular nystagmus), with the fast phase of nystagmus pointing toward the lesion (i.e., direction of eye gaze in fast phase “points” to the lesion)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>Difficulty in producing coherent speech because of inability to coordinate laryngeal muscles (not to be confused with aphasia, caused by damage to the cerebral cortex)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Incoordination of movements or gait (truncal ataxia). Patients typically fall to side of lesion (recall cerebellar lesions produce ipsilateral deficits).</td>
</tr>
<tr>
<td>Intention tremor</td>
<td>Tremor appears only during a voluntary movement.</td>
</tr>
<tr>
<td>Dysdiadochokinesia</td>
<td>Inability to coordinate rapidly alternating movements, such as rapid pronation and supination at the wrist</td>
</tr>
<tr>
<td>Dysmetria</td>
<td>Inability to properly judge distances: overshooting (hypermeteria) or undershooting the target (hypometeria)</td>
</tr>
</tbody>
</table>

*Cerebellar lesions typically give rise to ipsilateral effects (in contrast to lesions of the basal ganglia and cerebral cortex).

| TABLE 2-10. Classification of Sensory Nerve Fibers

<table>
<thead>
<tr>
<th>FIBER TYPE</th>
<th>DIAMETER</th>
<th>CONDUCTION VELOCITY</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia (A-alpha)</td>
<td>Largest</td>
<td>Fastest</td>
<td>Muscle spindles/proprrioception</td>
</tr>
<tr>
<td>Ib (A-alpha)</td>
<td>Largest</td>
<td>Fastest</td>
<td>Golgi tendon organs, proprioception</td>
</tr>
<tr>
<td>II (A-beta)</td>
<td>Medium</td>
<td>Medium</td>
<td>Touch, pressure, and vibration</td>
</tr>
<tr>
<td>III (A-delta)</td>
<td>Small</td>
<td>Medium</td>
<td>Slow pain and temperature</td>
</tr>
<tr>
<td>IV (C)</td>
<td>Smallest</td>
<td>Slowest</td>
<td>Slow pain and temperature, unmyelinated</td>
</tr>
</tbody>
</table>

Sensory receptors: neurons specialized to detect environmental stimuli and transmit them through action potentials.
Receptive field: focal area to which the application of an appropriately intense stimulus will trigger the sensory receptor to initiate an action potential.
Sensory transduction: process in which stimulus is detected, amplified, and conducted to CNS.
Receptor potential: change in membrane potential in sensory cells caused by opening of ion channels; typically cells are depolarized.
7. If the receptor potential is large enough, the membrane potential reaches or exceeds threshold, and action potentials are generated (Fig. 2-13).

8. The signal intensity (e.g., intensity of pain) can be conveyed by recruiting increased numbers of parallel fibers or by increasing the frequency of action potential generation.
   - **Spatial summation:** Increased signal strength is transmitted by using progressively greater numbers of fibers.
   - **Temporal summation:** Increased signal strength is transmitted by increasing the frequency of action potentials in each fiber.

C. Adaptation
1. A special characteristic of all sensory receptors is that they adapt, either partially or completely, to any constant stimulus after a period of time.
2. **Slowly adapting (tonic)** receptors continue to transmit impulses to the brain as long as the stimulus is present.
3. Thus, they keep the brain constantly aware of the status of the body and its relation to its surroundings.
4. They include muscle spindles, pressure receptors, and slow pain receptors.
5. **Rapidly adapting (phasic)** receptors rapidly adapt to a constant stimulus by decreasing their action potential frequency over time.
6. They are stimulated by changes in stimulus strength and primarily alert the brain to the start and stop of a stimulus.
7. They include light touch receptors (e.g., Meissner corpuscles) and deep pressure receptors (e.g., pacinian corpuscles).

D. Sensory pathways
1. A sensory pathway is a group of neurons linked synaptically that share a common function and course.
2. The sensory receptor is stimulated, and a receptor potential is created.
3. The signal from the receptor is received by first-order neurons, the cell bodies of which are located in the dorsal root ganglia (Fig. 2-14).
4. The second-order neurons, located in the spinal cord or brainstem, receive signals from the first-order neurons and transmit them to the thalamus.
5. It is important to note that the axons of these neurons cross the midline at a relay nucleus in the spinal cord or brainstem before synapsing in the thalamus; therefore, sensory information originating on one side of the body communicates with the contralateral thalamic nuclei.
6. The third-order neurons are located in the relay nuclei of the thalamus, the ventral posterior nucleus, and project to the cerebral cortex.

Clinical correlate: Thalamic ischemia due to compromised posterior cerebral artery perfusion can result in the thalamic syndrome (thalamic pain syndrome). Thalamic syndrome is associated with hypersensitivity to stimuli and diffuse body pain and paresthesias. It is difficult to manage clinically.
7. The **fourth-order neurons**, located in the cerebral cortex, confer **conscious perception** of the stimulus.

8. The orientation of these neurons in the cortex creates a **sensory homunculus**, which is essentially a map of the body on the brain (Fig. 2-15).

E. **Specific pathways of the somatosensory system** (Fig. 2-16)

1. **Dorsal column system (DCS): medial lemniscal pathway**
   - The DCS processes the sensations of fine touch, conscious proprioception, two-point discrimination, and vibration.
   - **Primary afferents** travel ipsilaterally up the spinal cord to synapse on the **nucleus gracilis** and **nucleus cuneatus** in the medulla.
   - The **second-order neurons** decussate in the medulla through the internal arcuate fibers and ascend through the **medial lemnisci** to the **contralateral ventral posterolateral nucleus** of the thalamus.
   - Here, **third-order neurons** project to the cortex to synapse with **fourth-order neurons**, and the sensation is made conscious.

**Clinical note:** A lesion of the **DCS** results in a deficit in fine touch, proprioception, two-point discrimination, and vibration on the **ipsilateral** side of the body **below the level of the lesion**. The damage is ipsilateral because the fibers of the DCS do not cross the midline until they reach the medulla. Damage to the DCS is evident in several disease states. For example, in **tabes dorsalis**, a late-stage manifestation of syphilis, neurons in the dorsal root ganglia are destroyed, which in turn causes degeneration of the myelinated afferent fibers in the dorsal columns. Signs include an ataxic wide-based gait, paresthesias, and deficits in touch and proprioception. Damage to the DCS may also be seen in long-term **cobalamin (vitamin B₁₂) deficiency** often secondary to pernicious anemia; this leads to demyelination, axonal degeneration, and eventual neuronal death; the DCS is usually involved, resulting in numbness and paresthesias in the extremities, weakness, and ataxia. **Subacute combined degeneration of spinal cord (Lichtheim’s disease)** may occur if the lateral corticospinal tracts are also affected.
2. Anterolateral system (spinothalamic tract)
   - The spinothalamic tract processes the sensory modalities of pain, temperature, and crude touch.
   - Primary afferents enter the spinal cord and synapse in the dorsal horn (see Fig. 2-16).
   - Second-order neurons then cross the midline in the spinal cord at the anterior commissure and ascend through the anterior and lateral spinothalamic tracts to the contralateral thalamus.
   - Third-order neurons project to the cortex and synapse with fourth-order neurons, as in the DCS.

Clinical note: Lesions of the ALS may result in deficits in pain, temperature, and crude touch sensation on the contralateral side of the body below the level of the lesion. For instance, a lesion at T8 affects everything below that point on the contralateral side; the upper extremity is not affected, because it is above the site of injury. In general, pain and temperature deficits are more prominent than crude touch deficits, because the intact DCS provides an alternative means of experiencing fine touch in the affected areas.

F. Special aspects of the somatosensory system
1. Thalamus
   - Sensory “relay station” between lower-order afferents and the cortex
• Arranged somatotopically such that there is maintenance of spatial organization within the CNS (e.g., sensory information from the foot is carried to the CNS and brain in close juxtaposition to that of the lower leg).
• The specific nuclei of the thalamus, which are beyond the scope of this text, are shown schematically in Figure 2-17.

Clinical note: Thalamic (pain) syndrome is a rare condition in which destruction or ischemia of the thalamus results in hypersensitivity to a variety of stimuli. Most often these stimuli, which may be as benign as touch, cold or heat, or emotional anxiety, can result in significant pain and paresthesias on one side of the body. Unfortunately, there is currently little that can be done for this condition.

2. Physiology of pain perception
• Pain receptors
  a. Pain receptors are free nerve endings that are located in the skin, muscle, and viscera and are responsible for the detection and perception of pain (nociception).
  b. In contrast to other receptors of the body, pain receptors adapt very little and sometimes not at all.
• Pain fibers
  a. Fast pain is carried by group III fibers and is described as sharp, pricking, acute, or electric pain.
  b. It is well localized and has a rapid onset and offset.
An example is pain experienced by stepping on a tack or stubbing a toe.

c. **Slow pain** is carried by C fibers and is described as burning, aching, throbbing, or chronic pain.

d. It is poorly localized and sometimes vague.

Examples include chronic back pain, headache pain, and aching joints.

3. **Dermatomes** (Fig. 2-18; Table 2-11)

- A dermatome is a localized area of skin that is innervated by a single nerve originating from a single nerve root.
- Knowledge of dermatome distribution can help localize nerve injury with physical examination.

**Anatomy note:** Pain from viscera is often referred to sites on the skin; this is called referred pain (Fig. 2-19). The pain is usually experienced in the dermatome supplied by the spinal nerve that enters the spinal cord at the same level as the visceral nerve (Table 2-12).

---

**VI. Special Senses**

A. **Overview**

1. A number of senses are called “special” senses because to function they employ modified and unique CNS components.
2. They comprise vision, hearing (audition), equilibrium (the vestibular system), olfaction, and taste.

B. **Vision**

1. Perception of a visual stimulus occurs in several stages.
2. Light enters the eye through the cornea, the amount of light passing through the cornea being determined by the size of the pupil (Fig. 2-20).
3. It then passes through the lens, the shape of which is adjusted by intraocular muscles to focus light on the retina.
4. Photoreceptors on the retina transmit signals to the brain (through the optic nerve), at which point the visual stimulus is perceived.

- **Structure of the retina** (Fig. 2-21)
  a. The retina is composed of a sheet of photoreceptors on the posterior aspect of the orbit.
  b. It lies in front of epithelium that is filled with the black pigment melanin, which functions to absorb any light not captured by the retina.
  c. It has several layers of different cell types, all of which are necessary for proper vision.
  d. The most posterior layer is composed of the photoreceptor cells, rods, and cones.

**TABLE 2-11. Dermatomes Important in Clinical Diagnosis and Identification of Levels of Spinal Cord Injury**

<table>
<thead>
<tr>
<th>DERMATOME</th>
<th>AREA INNERVATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>Front and back of neck</td>
</tr>
<tr>
<td>C6</td>
<td>Thumb, pointer finger, lateral forearm</td>
</tr>
<tr>
<td>C7</td>
<td>Middle finger</td>
</tr>
<tr>
<td>C8</td>
<td>Ring and little finger, medial hand</td>
</tr>
<tr>
<td>T10</td>
<td>Umbilicus</td>
</tr>
<tr>
<td>L1</td>
<td>Inguinal</td>
</tr>
<tr>
<td>L3</td>
<td>Knee</td>
</tr>
<tr>
<td>L5</td>
<td>Anterior ankle and foot, and first three toes</td>
</tr>
<tr>
<td>S1</td>
<td>Heel, plantar surface of foot (all toes except big toe), and fourth and fifth toes on dorsum of foot</td>
</tr>
<tr>
<td>S3/4</td>
<td>Genital area</td>
</tr>
<tr>
<td>S5</td>
<td>Perianal</td>
</tr>
</tbody>
</table>

Pathway of light → cornea → pupil → lens → retina → optic nerve → LGN of thalamus → optic radiation → occipital lobe

Melanin: black pigment located behind the retina, which absorbs excess light not captured by the retinal photoreceptor cells

Retina: most posterior layer comprising photoreceptor cells rods and cones
e. The optic disc is where the axons of the ganglion cells converge to exit the retina as the optic nerve.
f. There are no rods or cones in the optic disc, which results in a blind spot.

- **Rods**
a. These photoreceptors are very sensitive to light but do not detect color. They are responsible for low-acuity vision at night, when the light supply is poor.
b. They are more numerous than cones and are located diffusely throughout the retina but not in the macula.
c. Their photosensitive element is rhodopsin, which is composed of all-trans-retinal and scotopsin.
d. When exposed to light, rhodopsin decomposes to all-trans-retinal and then to other intermediate compounds; this triggers an electrical impulse that is sent to the occipital lobe of the brain.

Clinical note: Vitamin A is needed to form retinal, which is part of the rhodopsin molecule. In vitamin A deficiency, there is not enough vitamin A to form sufficient amounts of rhodopsin, resulting in poor night vision.

- **Cones**
a. These photoreceptors are less sensitive to light but do detect color. They are responsible for high-acuity color vision during the day, when the light supply is good.
b. They are less numerous than rods and are concentrated in the fovea centralis of the macula.
- Their photosensitive elements are **color pigments**.

5. **Visual pathways**
- After the rods and cones are stimulated by light (photons), the next layer of cells, the **bipolar cells**, becomes activated (see Fig. 2-21).
- The bipolar cells then stimulate **ganglion cells**, which lie in the most anterior layer of the retina; axons of these cells form the **optic nerve**; two accessory cell types in the retina also aid in vision:
  a. **Horizontal cells** transmit signals horizontally in the outer layer from the photoreceptors to the bipolar cells.
  b. **Amacrine cells** transmit signals between the bipolar cells and ganglion cells in the inner layer.
- The optic nerve projects to the **optic chiasm**.
- The optic tract projects from the optic chiasm and synapses with the **lateral geniculate nucleus** (LGN) of the thalamus.
- Ganglion cells from the **nasal hemiretina** project to the **contralateral** LGN, whereas cells from the **temporal hemiretina** project to the **ipsilateral** LGN.
  a. This concept is important in understanding lesions and the visual defects that result (Fig. 2-22).
- The **optic radiation** (geniculocalcarine tract) then projects from the LGN through an upper and lower division to the **visual cortex**.
- The **visual cortex** is retinotopically organized in that the posterior area receives **macular input** (central vision), the intermediate area receives **perimacular input** (peripheral vision), and the anterior area receives monocular input.
- It is in the visual cortex that the signals are finally interpreted and the image is ultimately “seen.”

6. **Ocular reflexes**
- **Pupillary light reflex** (Fig. 2-23)

---

**Compression of the optic chiasm** (e.g., expanding pituitary adenoma) → **bitemporal hemianopia**

**Lesions to the optic tract** → **ipsilateral hemianopia**

**Lesions of upper and lower divisions** → **ipsilateral hemianopsia with macular sparing**

**Massive infarct of occipital lobe** → **contralateral hemianopsia without macular sparing**
a. This reflex prevents excessive radiation from entering the eye when light intensity is high.
b. It can be elicited by shining light in one eye.
   • A normal response is constriction of both pupils.
c. Constriction of the pupil the light is directed at is termed the direct response, and constriction of the other eye is termed the consensual response.
d. Bilateral pupil constriction occurs because
   • Impulses from the retina of the eye into which the light is shone pass through the optic nerve to the pretectal area of the midbrain.
   • Cells in the pretectal area relay the impulse to the Edinger-Westphal (accessory oculomotor) nuclei of both eyes.
   • Each nucleus contains preganglionic parasympathetic neurons that in turn send the signal to the ciliary ganglion of the corresponding eye through the oculomotor nerve.
   • Postganglionic parasympathetic neurons in the ciliary ganglia innervate the smooth muscle of the pupillary sphincters.
   • Thus, pupil constriction is bilateral.

**Clinical note:** Deficits in the pupillary light reflex are evident in several different CNS diseases, including neurosyphilis, alcoholism, and encephalitis. Any damage to the Edinger-Westphal nucleus results in an abnormal or absent pupillary reflex. An Argyll Robertson pupil, often a sign of neurosyphilis, is one that constricts (accommodates) in response to a nearby object but does not constrict (react) in response to light.

- Accommodation reflex (Fig. 2-24)
  a. Reflex that brings nearby objects into proper focus on the retina
  b. When a distant object is brought close to the eyes, the focal point is initially behind the retina, resulting in a blurred image.
Lesion | Visual defect
---|---
1. Optic nerve | Ipsilateral blindness
2. Bilateral lateral compression | Binasal hemianopia
3. Midsagittal transection/pressure | Bitemporal hemianopia
4. Optic tract (left) | Right hemianopia
5. Lower division | Right upper quadrantanopia
6. Upper division | Right lower quadrantanopia
7. Both divisions | Right hemianopia with macular sparing

2-22: The visual pathways, showing the consequences of lesions at various points.

2-23: Pathway of the pupillary light reflex. (From Liporace J: Crash Course: Neurology. Philadelphia, Mosby, 2006, Fig. 6-2.)
c. In the accommodation reflex, parasympathetic outflow from the Edinger-Westphal nuclei causes contraction of the ciliary muscle, resulting in less tension in the suspensory ligaments.

d. This causes the lens to take on a more convex shape, increasing its refractive power so that the image is accurately focused on the retina.

e. Parasympathetic outflow also contracts the radial fibers of the iris (sphincter pupillae), decreasing the amount of light that enters the pupil; this results in better focusing of the light and less scattering.

f. There is simultaneous contraction of the medial recti, which results in convergence of the eyes onto the near object.

C. Audition

1. Structure of the ear (Fig. 2-25)
   - The outer ear consists of the pinna and the external auditory canal.
   - The middle ear comprises the tympanic membrane and three small bones (ossicles): malleus, incus, and stapes.
   - The inner ear is fluid filled and consists of
     a. The bony labyrinth: semicircular canals, cochlea, and vestibule
     b. A series of ducts called the membranous labyrinth
        - Fluid is located both inside the ducts (endolymph) and outside the ducts (perilymph).
        - The cochlea (Fig. 2-26) consists of three tubular canals: the scala vestibuli and scala tympani, both of which contain perilymph (high Na⁺), and the scala media, which contains endolymph (high K⁺).
The cochlea is bordered by the **basilar membrane**, which houses the **organ of Corti**.

1. The **organ of Corti** contains the receptor cells necessary for audition: the **inner and outer hair cells**, which have **cilia** embedded in the **tectorial membrane** of the organ of Corti.

2. **Inner hair cells** are the **primary sensory elements**; they are arranged in single rows and are few in number. They synapse with myelinated neurons, axons of which comprise 90% of the **cochlear nerve**.

3. **Outer hair cells** serve to **reduce the threshold of the inner hair cells**. They are arranged in parallel rows and are greater in number than the inner cells. They synapse with dendrites of unmyelinated neurons, axons of which comprise 10% of the **cochlear nerve**.

### 2. Perception of sound

#### Overview

a. The outer ear directs sound waves into the external auditory canal.

b. The waves travel until they reach the air-filled middle ear, where they cause the **tympanic membrane** to vibrate.

c. This vibration causes the ossicles to vibrate, resulting in **amplification** of the sound energy and **displacement of the fluid** in the inner ear.
Clinical note: Conduction deafness results from impairment of external or middle ear structures that conduct sound into the cochlea. Common causes are cerumen impaction (obstruction), otitis media, and otosclerosis.

- **Auditory transduction**
  a. This is the process in which a sound wave is turned into an electrical message; it occurs in the organ of Corti.
  b. The external and middle structures of the ear collect sound, amplify it, and transmit it to the inner ear, specifically the organ of Corti.
  c. This transmission causes vibrations of the basilar membrane.
  d. Vibrations of the basilar membrane stimulate the cilia of the inner and outer hair cells, causing the hair cells to bend by a shearing force as they push against the tectorial membrane.
  e. Bending of the cilia causes changes in the K⁺ conductance of the hair cell membrane.
  f. Bending in one direction causes depolarization; in the other, hyperpolarization.
  g. The bending back and forth also causes a cochlear microphonic potential, which results in intermittent firing of the cochlear nerves.
  h. On depolarization, the hair cells activate the bipolar cells of the spiral (cochlear) ganglion.
  i. This ganglion projects centrally as the cochlear nerve (CN VIII); its path is as follows (see Fig. 2-26):
     - The cochlear nerve enters the brainstem at the cerebellopontine angle and synapses with the cochlear nuclei.
     - Axons from the cochlear nuclei then project contralaterally to the superior olivary nucleus (sound localization) and then to the lateral lemniscus (Fig. 2-27).
     - Axons project from the lateral lemniscus to the nucleus of the inferior colliculus.
     - These axons then project to the medial geniculate body.
     - Axons of the medial geniculate body then travel through the internal capsule as the auditory radiation, which synapses with the primary auditory cortex.

Clinical note: Cerebellopontine angle tumors are typically benign schwannomas known as acoustic, or more properly, vestibular neuromas. Vestibular neuromas may cause ipsilateral sensorineural hearing loss or deafness, vertigo, and tinnitus.

- **Sound encoding**
  a. Different frequencies of sound stimulate different hair cells, depending on their location along the basilar membrane of the cochlea (Fig. 2-28).
  b. This is sound encoding.
  c. **High frequencies** cause hair cells at the base of the basilar membrane, near the oval and round windows, to vibrate.
  d. **Low frequencies** cause hair cells at the apex of the basilar membrane, near the helicotrema, to vibrate.
  e. Thus, when evaluating hearing loss, the location of damage can be identified on the basis of whether the loss is low or high frequency.

Clinical note: Rinne test is used to compare bone and air conduction. The base of a vibrating tuning fork is placed on the mastoid process until the patient can no longer hear the bone-conducted vibration; at this point, the vibrating end of the fork is repositioned about 1 cm from the external mastoid process.
meatus, and the patient is asked if anything can be heard. Normally and in sensorineural deafness, air conduction is better than bone conduction in both ears; in conduction deafness, bone conduction is better (Table 2-13).

Clinical note: Weber test is performed by placing a vibrating tuning fork on the vertex of the skull and asking the patient whether the sound is the same in both ears. Normally, the sound is heard equally on both sides (see Table 2-13). In conduction deafness, the sound is heard better in the ear most affected by deafness, and in sensorineural deafness, it is heard better in the unaffected ear.
D. The vestibular system (vestibular organ)

- The vestibular system maintains posture and equilibrium (balance) and coordinates head and eye movements.

1. Structure of the vestibular organ (Fig. 2-29)
   - The **vestibular organ** is a membranous labyrinth consisting of three perpendicular semicircular canals, a utricle, and a saccule, all interconnecting and filled with endolymph.
   - The **semicircular canals** detect rotation or angular acceleration.
   - The utricle and the saccule detect linear acceleration.
   - Each semicircular canal contains **hair cells (receptor cells)**.
   - Each hair cell has two types of cilia that are embedded in a gelatinous structure called the **cupula**: a **kinocilium**, the longest cilium on each hair cell, and other smaller cilia called **stereocilia**.
   - The hair cells are innervated by peripheral processes of **bipolar cells**, which are housed in the **vestibular ganglion** of the internal auditory meatus.
   - The central projecting portions of the bipolar cells form the **vestibular portion of CN VIII**, which projects to the vestibular nuclei and flocculonodular lobe of the cerebellum.
   - The **vestibular nuclei**, which receive input from both the hair cells and the flocculonodular lobe, project fibers to:
     a. The flocculonodular lobe and CN III, IV, and VI through the **medial longitudinal fasciculus** (MLF)
     b. The spinal cord through the lateral vestibulospinal tract
     c. The ventral posteroinferior and posterolateral nuclei of the thalamus (both of which project to the postcentral gyrus)

2. Vestibular transduction
   - The process of vestibular transduction is similar to that of auditory transduction in that the bending of hair cells “translates” movement into a change in electrical potential (Fig. 2-30).
   - With rotation, the cupula rotates in the same direction as the movement.
   - Initially, the cupula moves faster than the endolymph, which results in the cilia’s being bent.

---

**TABLE 2-13. Interpretation of Auditory Tests**

<table>
<thead>
<tr>
<th>FINDING</th>
<th>RINNE TEST: COMPARISON OF AIR AND BONE CONDUCTION</th>
<th>WEBER TEST: SOUND LATERALIZES TO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Findings</td>
<td>Air &gt; bone, both ears</td>
<td>(No lateralization)</td>
</tr>
<tr>
<td>Left Ear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduction deafness</td>
<td>Bone &gt; air on left</td>
<td>Left ear</td>
</tr>
<tr>
<td>Partial sensorineural deafness</td>
<td>Air &gt; bone on right</td>
<td></td>
</tr>
<tr>
<td>Right Ear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduction deafness</td>
<td>Bone &gt; air on right</td>
<td>Right ear</td>
</tr>
<tr>
<td>Partial sensorineural deafness</td>
<td>Air &gt; bone on left</td>
<td></td>
</tr>
</tbody>
</table>

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2-29: The vestibular system (anterior view). The hair cells are located in the shaded areas (maculae).
a. If the stereocilia bend toward the kinocilium, the hair cell is **depolarized** and excited.

b. If the stereocilia bend away from the kinocilium, the hair cell is **hyperpolarized** and inhibited.

- Once the endolymph “catches up” with the cupula, the cilia return to an upright position, at which point the hair cells are no longer depolarized or hyperpolarized.

**Clinical note:** Injury to the vestibulocerebellar pathway results in a staggering ataxic gait with a tendency to fall toward the side of the lesion. Injury to this system also results in a spontaneous nystagmus, as discussed later, and vertigo. Nystagmus is normally a corrective reflex.

3. **Vestibular-ocular reflexes**
   - These reflexes stabilize visual images by compensating for head movement.
   - The reflexes are mediated by the vestibular nuclei, MLF, ocular motor nuclei, and CN III, IV, and VI.
   - **Nystagmus**
     a. Reflex used to compensate for head movement; it can be clinically relevant, as noted earlier in vestibulocerebellar injury
     b. It is characterized by an alternating *smooth pursuit* in one direction and fast *saccadic movement* in the other direction.
The direction of nystagmus is defined as the direction of the fast (rapid eye) movement.

The vestibular system drives the slow phase of eye movement, and the brainstem generates the rapid phase.

a. Vestibular (horizontal) nystagmus
   - Resets eye position during sustained rotation of the head
   - The fast phase of nystagmus is in the direction of rotation.
   - The slow phase is in the opposite direction.

b. Postrotatory (horizontal) nystagmus
   - Stabilizes the visual image once the head stops rotating
   - The fast phase of nystagmus is in the opposite direction to that of rotation.
   - The slow phase of nystagmus is in the direction of rotation.

c. Caloric nystagmus (Fig. 2-31)
   - The normal response to cold-water irrigation of the external auditory meatus is nystagmus to the opposite side.
   - The normal response to warm-water irrigation of the external auditory meatus is nystagmus to the same side.

Clinical note: In comatose patients, the nature of the nystagmus elicited by cold-water irrigation can help determine the location of a lesion (see Fig. 2-31).

E. Olfaction

1. Structure of olfactory apparatus (Fig. 2-32)
   - Smell is detected by olfactory receptor cells, which are situated in mucus-coated olfactory epithelium that lines the posterodorsal parts of the nasal cavities.

CONSCIOUS PATIENT

- Brainstem intact
- Bilateral lesion
- Low brainstem lesion

UNCONSCIOUS PATIENT

- Brainstem intact
- Bilateral MLF lesion
- Low brainstem lesion

2-31: Caloric nystagmus. The arrows show the direction of eye movement. MLF, Medial longitudinal fasciculus.

2-32: A and B, Structure of olfactory epithelium and the olfactory bulb. (From Weyhenmeyer J, Gallman E: Rapid Review Neuroscience. Philadelphia, Mosby, 2007, Fig. 11-2.)
Olfactory glands (Bowman glands) secrete a fluid that bathes the cilia of the receptors and acts as a solvent for odorant molecules.

Olfactory receptor cells (first-order neurons) are stimulated by the binding of odor molecules to their cilia.

The axons of the olfactory receptor cells form CN I (olfactory nerve); these project through the cribriform plate at the base of the cranium to synapse with the mitral cells of the olfactory bulb.

The mitral cells of the olfactory bulb are excitatory, second-order neurons.

The output axons of the mitral cells form the olfactory tract and lateral olfactory stria, both of which project to the primary olfactory cortex and the amygdala.

It is at these locations that smell is perceived.

Olfactory receptor cells are the only neurons in the adult human that are regularly replaced.

Anatomy note: Because CN I passes through the cribriform plate on its way to the olfactory bulb, cribriform plate fractures may result in hyposmia (reduced olfaction) or anosmia (no olfaction).

2. Olfactory transduction

- Odoriferous molecules bind to cilia on the olfactory receptor cells.
- Activation of receptors leads to the stimulation of G proteins and, in turn, activation of adenylyl cyclase.
- The activation of adenylyl cyclase leads to an increase in intracellular cyclic adenosine monophosphate (cAMP), which opens Na⁺ channels in the olfactory receptor membrane and results in depolarization of the receptor.
- Depolarization leads to the generation and propagation of action potentials that eventually reach the primary olfactory cortex and culminate in the perception of smell.

F. Taste

1. Functional anatomy

- Taste is detected by taste receptor cells, which are located on specialized papillae of the taste buds and are stimulated by taste chemicals (Fig. 2-33).
- Different areas of the tongue consist of different types of taste buds and communicate with the taste center of the brain through different cranial nerves (see Fig. 2-33).
- Taste buds on the anterior two thirds of the tongue have fungiform papillae and primarily detect sweet and salty tastes.
  a. They send signals centrally through the lingual nerve to the chorda tympani and finally into CN VII (facial).
- Taste buds on the posterior one third of the tongue have circumvallate papillae and foliate papillae, which detect bitter and sour tastes (Fig. 2-34).
Most of them send signals centrally through CN IX (glossopharyngeal); however, some located in the back of the throat and epiglottis send signals centrally through CN X (vagus).

- CN VII, IX, and X synapse with the tractus solitarius (solitary nucleus).
- Second-order neurons leave the solitary nucleus and project ipsilaterally to the ventral posterior medial nucleus of the thalamus.
- Neurons from the thalamus project to the taste cortex located in the primary somatosensory cortex.

2. **Taste transduction**

- The binding of taste chemicals to the taste receptors causes a depolarization of the receptor membrane.
- The depolarization results in an action potential that is propagated centrally until the taste sensation (sweet, sour, salty, or bitter) is perceived.

### VII. Higher Functions of the Cerebral Cortex

#### A. Learning and memory

1. Physiologically, memories are caused by changes in the sensitivity of synaptic transmission between neurons as a result of previous neural activity.
2. These changes result in **memory tracts**, which are facilitated pathways developed for the transmission of signals through the neural circuits of the brain, providing for memory.
3. **Short-term memories** last for seconds or minutes unless they are converted into longer-term memories; the basis of short-term memory involves **synaptic changes**.
4. Intermediate long-term memories last for days to weeks but then are forgotten; they result from temporary chemical and/or structural changes.
5. Long-term memories can be recalled years later.

- The formation of long-term memories involves **structural changes** in the nervous system and the formation of stable memory tracts.

**Clinical note:** Bilateral lesions of the hippocampus prevent the formation of new long-term memories (anterograde amnesia), although the exact mechanism of damage of memory control is not known.
B. Language

1. The major area for **language comprehension** is Wernicke area, located behind the primary auditory cortex in the posterior part of the superior gyrus of the temporal lobe.

   **Clinical note:** Lesions to this area of the brain result in a fluent, **receptive aphasia**, which consists of the inability to comprehend spoken language. The deficit is characterized by fluent verbalization that lacks meaning.

2. The major area for **expressing language** is Broca area, located in the prefrontal and premotor facial region of the cortex.

   **Clinical note:** Damage to this area of the brain results in a nonfluent, **expressive aphasia**, which reflects difficulty piecing together words to produce speech. Patients can understand written and spoken language but are unable to express themselves verbally.

3. In 95% of people, Wernicke and Broca areas are located in the left hemisphere.
   - Even in most left-handed individuals, the left hemisphere is dominant with respect to language.
   - The **right hemisphere** is dominant with respect to facial expression, intonation, spatial tasks, and body language.

C. Brain waves

1. Waves of electrical activity large enough to be electrically recorded from the outer surface of the head by an **electroencephalogram (EEG)**

2. Their **intensity** is determined by the number of neurons that fire in synchrony: the EEG records them only when millions of neurons fire synchronously.

3. Both the **intensity** and **pattern** of electrical activity are determined by the level of excitation of the brain during sleep and wakefulness or in disease states such as epilepsy (Fig. 2-35).
   - **Alpha waves** (8 to 13 per second) are observed in normal adults when they are awake and in a quiet, resting state.
   - **Beta waves** (14 to 80 cycles per second) are observed in awake, alert individuals.
   - **Theta waves** (4 to 7 per second) are observed normally in children; they are also observed in adults with brain disorders or during emotional stress.
   - **Delta waves** include all waves with a frequency of less than 3.5 per second; they are found in very deep sleep, in infants, and in patients with serious organic brain disease.

   ![Electroencephalogram waves](image-url)
D. Sleep

1. The sleep-wake cycle is a circadian (i.e., 24-hour) rhythm.
2. This cycle is driven by the suprachiasmatic nucleus of the hypothalamus, which receives input from the retina.
3. Sleep is divided into two broad types: non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep.
4. NREM and REM occur in alternating cycles, with most time being spent in NREM sleep (Fig. 2-36).
5. On the basis of EEG changes, NREM sleep can be divided into four stages:
   - **Stage 1**
     a. Consists of very light sleep with low-voltage EEG waves
   - **Stage 2**
     a. Is the primary sleep stage during a normal night’s sleep
     b. EEG characterized by sleep spindles, multiple small waves in rapid succession, and K complexes, a negatively deflecting wave immediately followed by a positively deflecting wave
   - **Stage 3**
     a. Is a deeper sleep pattern, with decreased EEG activity and muscle tone; sleep spindles and K complexes may still be seen on the EEG
   - **Stage 4**
     a. Is an even deeper sleep with delta waves on the EEG recording and a further reduction in muscle tone
6. In REM sleep, the EEG resembles that of an awake, resting person or a person in stage 1 sleep; sleep spindles and K complexes should not be present on the EEG.

**Clinical note:** Aging, alcohol, and benzodiazepines decrease the duration of REM sleep.

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**Figure 2-36:** Electroencephalography during the stages of sleep. *(From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 3-35.)*
VIII. Cerebral Blood Supply (Fig. 2-37)
A. Overview
1. The brain is highly vulnerable to ischemia for a variety of reasons (e.g., high metabolic rate, primary dependence on glucose as a fuel source).
2. There are two main systems that ensure adequate blood flow to the brain: the internal carotid system and the vertebrobasilar system.
3. The circle of Willis connects these two major circulatory systems and also provides an alternative blood supply if circulation is compromised in one of them (see Fig. 2-37).

B. Internal carotid system
1. Primarily perfuses the cerebral hemispheres, with the exception of the visual cortex and the posterior inferior surface of the temporal lobe.
2. The anterior cerebral arteries supply blood to the inferior frontal lobes, the medial surfaces of the frontal and parietal lobes, and the anterior corpus callosum.
3. Small penetrating branches supply the limbic structures, the head of the caudate, and the anterior limb of the internal capsule.

**Clinical note:** Occlusion or infarction of the anterior cerebral artery (ACA) may cause weakness and sensory loss of the distal contralateral leg, because the ACA supplies blood to the area of brain that controls the distal contralateral leg, as seen in Figure 2-15.

4. The middle cerebral artery (MCA) supplies blood to most of the cortex and white matter, including the frontal, parietal, temporal, and occipital lobes and the insula.
5. Small penetrating branches of the MCA (lenticulostriate vessels) supply the posterior limb of the internal capsule, the putamen, the outer globus pallidus, and the body of the caudate.

**Clinical note:** The most common stroke syndrome occurs from infarction of tissue in the distribution of the MCA. Infarction damages the cortex and white matter and results in contralateral weakness, sensory loss, homonymous hemianopsia, and, depending on the hemisphere involved, either language disturbance or impaired spatial perception. The weakness and sensory loss affect the face and arm more than the leg (ACA supply), because the MCA supplies blood to the areas of brain that control the contralateral face and upper extremity, as seen in Figure 2-15.
C. Vertebrobasilar system

1. The vertebral and by extension basilar arteries supply the posterior part of the circle of Willis and give rise to the posterior cerebral arteries (PCAs).
2. Through the circle of Willis, the vertebrobasilar system anastomoses with the anterior portion of the circle of Willis supplied by the carotid arteries.
3. The PCA supplies the posterior inferior surface of the temporal lobes, medial occipital lobes, midbrain, and cerebellum.

Clinical note: Thrombosis of the basilar artery may result in the locked-in syndrome. In this condition, the patients’ cognition is intact, but he or she is typically paralyzed with the exception of ocular muscles. These patients are conscious and aware but are unable to communicate other than by blinking or moving their eyes.

Clinical note: Circulatory compromise of the PCA may result in a homonymous hemianopsia (see Fig. 2-15) as a result of injury to the visual cortex. Macular vision is spared, because the occipital pole receives its blood supply from the MCA. If the blockage or infarction is in the proximal portion of the PCA, the thalamus may be affected, which would result in contralateral sensory loss.
I. Hormones
   A. Overview
      1. The primary function of hormones is to maintain homeostasis (e.g., regulate plasma glucose and electrolyte balance) and coordinate physiologic processes such as development, metabolism, and reproduction.
      2. A “master” list of hormones is shown in Table 3-1, and a schematic is shown in Figure 3-1.
      3. Hormones maintain homeostasis by using various feedback mechanisms.
      4. Hormones act slowly relative to the nervous system.
   B. Mechanism of action of hormones
      1. All hormones must interact with a cellular receptor, which then transduces a signal and generates a cellular response.
      2. The effectiveness of a given hormone, therefore, depends on the concentration of free hormone (that which is available for binding), the concentration of hormone receptor, and the effectiveness of the transduction mechanism.
      3. All endocrine diseases are due to a quantitative or qualitative defect in hormone synthesis or altered tissue sensitivity to hormone, usually manifesting as a disruption of a well-characterized homeostatic control system.
   C. Types of hormones and their individual effector mechanisms
      1. Steroid hormones
         • Steroid hormones are lipid-soluble compounds derived from cholesterol that are able to enter all cells of the body by diffusing through the lipid-rich plasma membrane.
         • They produce their effects by binding to receptors in either the cytosol or nucleus of cells in target tissues, and this hormone-receptor complex then activates transcription of specific genes (Fig. 3-2).
         • Because steroid hormones can diffuse freely through lipid membranes, they cannot be stored within intracellular vesicles.
           a. They are therefore produced continually, and synthesis and secretion increase on demand.
         • Furthermore, because steroid hormones are lipid soluble, they must circulate bound to plasma proteins.
           a. Because they are protein-bound they are not freely filtered by the kidney, which contributes to their long half-life relative to most peptide hormones; they are primarily metabolized by the liver.
         • The principal steroid hormones include the sex steroids—testosterone, progesterone, and estrogen—and the adrenal steroids—cortisol and aldosterone.
      2. Thyroid hormones
         • Are unique in that they are derived from the amino acid tyrosine rather than cholesterol
         • Have a mechanism of action similar to steroid hormones (i.e., they diffuse into a cell, bind to a receptor, and alter gene expression)
      3. Proteoglycan, protein, peptide, and amino acid hormones
         • These polar compounds bind to membrane-associated receptors on target cells.
         • The signal transduction mechanism used by these agents varies, depending on the receptor type.
         • Because they are hydrophilic, they can be stored in cytoplasmic vesicles within endocrine cells and released on demand.
### TABLE 3-1. Hormones

<table>
<thead>
<tr>
<th>HORMONES</th>
<th>PHYSIOLOGIC ACTIONS</th>
<th>PATHOPHYSIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypothalamic Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>Stimulates adrenocorticotropic hormone (ACTH) secretion from anterior pituitary</td>
<td>Increase in adrenal insufficiency due to loss of negative feedback</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone (GnRH)</td>
<td>Stimulates gonadotropin secretion from anterior pituitary</td>
<td>Hypothalamic hypogonadotrophic hypogonadism due to hyperprolactinemia — infertility</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone (TRH)</td>
<td>Stimulates thyroid-stimulating hormone (TSH) secretion from anterior pituitary</td>
<td>Increase in hyperthyroidism — ↓ dopamine secretion due to ↑ TRH — hyperprolactinemia</td>
</tr>
<tr>
<td>Growth hormone-releasing hormone (GHRH)</td>
<td>Stimulates growth hormone secretion from anterior pituitary</td>
<td>Decrease in growth hormone (GH)-secreting tumor of anterior pituitary</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Inhibits GH secretion from anterior pituitary</td>
<td>Synthetic version (octreotide) used in GH-secreting pituitary adenomas</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Inhibits prolactin secretion from anterior pituitary</td>
<td>Hypothyroidism — hyperprolactinemia — Antipsychotics — hyperprolactinemia</td>
</tr>
<tr>
<td><strong>Anterior Pituitary Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenocorticotropic hormone (ACTH)</td>
<td>Stimulates glucocorticoid and androgen synthesis in adrenal medulla</td>
<td>Cushing disease — ↓ Cushing syndrome — Paraneoplastic secretion (e.g., small cell lung carcinoma) — Cushing disease: ACTH-hypersecreting pituitary</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH)</td>
<td>Stimulates thyroid hormone synthesis in the thyroid gland</td>
<td>TSH-secreting pituitary adenoma (secondary hypothyroidism) — ↓ in panhypopituitarism</td>
</tr>
<tr>
<td>Luteinizing hormone (LH)</td>
<td>Stimulates testosterone secretion by Leydig cells in testes</td>
<td>Elevated levels: polycystic ovary syndrome (PCOS), testicular failure, premature menopause, Turner syndrome — Decreased levels: hyperprolactinemia, Kallman syndrome, eating disorders (anorexia), hypopituitarism</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
<td>Stimulates spermatogenesis in testes</td>
<td>Elevated levels: testicular failure, premature menopause, Turner syndrome — Increased levels: Kallman syndrome, PCOS, hypopituitarism</td>
</tr>
<tr>
<td></td>
<td>Stimulates estrogen synthesis by granulosa cells in ovarian follicles</td>
<td></td>
</tr>
<tr>
<td>Growth hormone (GH)</td>
<td>Anabolic hormone with multiple anabolic and insulin-antagonizing metabolic effects</td>
<td>Gigantism: excess GH before fusion of epiphyseal plates — Acromegaly: excess GH after fusion of epiphyseal plates — Pituitary dwarfism: GH deficiency resulting in dwarfism with normal body proportions</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Stimulates breast maturation and milk letdown</td>
<td>Prolactinoma: hypersecreting prolactinoma resulting in galactorrhea and infertility in women</td>
</tr>
<tr>
<td><strong>Posterior Pituitary Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidiuretic hormone (ADH)</td>
<td>Stimulates water absorption from the distal nephron</td>
<td>Syndrome of inappropriate antidiuretic hormone (SIADH) — Central diabetes insipidus — Nephrogenic diabetes insipidus</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Stimulates uterine contraction during labor</td>
<td></td>
</tr>
<tr>
<td><strong>Thyroid Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroxine (T₄)</td>
<td>Prohormone that becomes bioactive on peripheral conversion to T₃</td>
<td>Hyperthyroidism: ↑ thyroid gland synthesis of thyroid hormone — Thyrotoxicosis: any cause for ↑ thyroid hormones (e.g., gland destruction, exogenous intake, ↑ synthesis) — Hypothyroidism: ↓ thyroid gland synthesis of thyroid hormone — Thyroiditis: destruction of thyroid gland; can transiently cause hyperthyroidism but ultimately causes hypothyroidism</td>
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<tr>
<td>Triiodothyronine (T₃)</td>
<td>Increases basal metabolic rate by up-regulating expression and insertion of Na⁺,K⁺-ATPase pump</td>
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<tr>
<td><strong>Adrenal Cortex Hormones</strong></td>
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<tr>
<td>Aldosterone</td>
<td>Promotes renal Na⁺ retention and expands plasma volume</td>
<td>Hypersecreted in primary aldosteronism — hypertension with hypokalemic metabolic alkalosis</td>
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<tr>
<td>Cortisol</td>
<td>Helps maintain glucose for glucose-dependent tissues during fasting state by promoting hepatic gluconeogenesis, peripheral resistance to insulin, and lipolysis in adipose tissue</td>
<td>Cushing disease: ACTH-hypersecreting pituitary adenoma — Cushing syndrome: hypercortisolism of any etiology — Adrenal insufficiency: can be primary, secondary, or (rarely) tertiary; most commonly iatrogenic from long-term use of steroids</td>
</tr>
<tr>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>Converted to testosterone in peripheral tissues</td>
<td>Congenital adrenal hyperplasia: oversecretion of androgens results in virilization, precocious puberty, ambiguous genitalia</td>
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# TABLE 3-1. Hormones—cont’d

<table>
<thead>
<tr>
<th>HORMONES</th>
<th>PHYSIOLOGIC ACTIONS</th>
<th>PATHOPHYSIOLOGY</th>
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<tbody>
<tr>
<td><strong>Adrenal Medulla Hormones</strong></td>
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<tr>
<td>Epinephrine</td>
<td>Too numerous to list:</td>
<td>Pheochromocytoma: autonomously catecholamine-hypersecreting adrenal tumor (most common location)</td>
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<tr>
<td></td>
<td>Liver: ↑ glycolysis, gluconeogenesis</td>
<td>Levels ↑ in congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle: ↑ anaerobic metabolism, ↑ insulin resistance</td>
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<td></td>
<td>Adipose: ↑ lipolysis</td>
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<td><strong>Ovarian Hormones</strong></td>
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<tr>
<td>Estrogen</td>
<td>Development of female secondary sexual characteristics</td>
<td>Osteoporosis</td>
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<tr>
<td></td>
<td>Follicular phase of menstrual cycle</td>
<td>Breast cancer</td>
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<td>Bone maturation → fusion of epiphyseal plates in adolescent females</td>
<td>Endometrial cancer</td>
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<td><strong>Testicular Hormones</strong></td>
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<tr>
<td>Testosterone</td>
<td>Development of seminal vesicles, epididymis, vas deferens during embryogenesis</td>
<td>Benign prostatic hyperplasia (BPH)</td>
</tr>
<tr>
<td></td>
<td>Increasing lean muscle mass and bone density</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Dihydrotestosterone (DHT)</td>
<td>Development of the male external genitalia (penis, scrotum) and prostate gland</td>
<td>Androgen insensitivity syndrome (testicular feminization)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Promotes peripheral uptake of glucose in nonfasting (fed) state</td>
<td>Hypoglycemia (factitious, insulinoma, medication induced)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 1 diabetes mellitus: absolute deficiency of insulin due to β cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 2 diabetes mellitus: relative deficiency of insulin (initially) due to peripheral resistance; later in course may have absolute insulin deficiency</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Promotes hyperglycemia and insulin resistance</td>
<td>Glucagonoma</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Inhibits pituitary GH secretion</td>
<td>Used to treat GH-secreting pituitary adenomas</td>
</tr>
<tr>
<td>Vasoactive-intestinal peptide (VIP)</td>
<td>Promotes smooth muscle relaxation and dilation throughout intestines</td>
<td>Vasoactive intestinal polypeptide-secreting tumor (VIPoma); may be associated with multiple endocrine neoplasia type 1 WDHA (watery diarrhea and resultant dehydration, hypokalemia, achlorhydria) syndrome</td>
</tr>
<tr>
<td></td>
<td>Promotes watery/bicarbonate-rich secretions from pancreas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibits gastrin-stimulated HCL secretion in stomach</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Promotes pepsinogen secretion by gastric chief cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Promotes intestinal motility</td>
<td></td>
</tr>
</tbody>
</table>

3-1: Schematic of the hypothalamic-pituitary-endocrine organ axis. **ACTH**, Adrenocorticotropic hormone; **CRH**, corticotropin-releasing hormone; **FSH**, follicle-stimulating hormone; **GH**, growth hormone; **GHRH**, growth hormone–releasing hormone; **GnRH**, gonadotropin-releasing hormone; **LH**, luteinizing hormone; **LHRH**, luteinizing hormone–releasing hormone; **TSH**, thyroid-stimulating hormone. (From Kumar P, Clark M: Kumar and Clark’s Clinical Medicine, 5th ed. Philadelphia, Saunders, 2002, Fig. 18-7.)
• Some travel free as soluble compounds in the blood, whereas others travel mainly bound, associated with specific binding proteins.
  a. In general, free hormones that are not associated with carrier proteins have shorter half-lives than bound hormones.
• There are four primary classes of membrane-spanning receptors to which these hormones can bind:
  a. Tyrosine and serine kinase receptors
  b. Ligand-gated ion channels
  c. Receptor-linked kinases
  d. G protein–coupled receptors

**Biochemistry note:** The four primary classes of membrane-spanning receptors that peptide hormones bind to are (1) tyrosine and serine kinase receptors, (2) receptor-linked kinases, (3) G protein–coupled receptors, and (4) ligand-gated ion channels. As a gross simplification, the “prototypical” agonists for these receptor types can be considered to be growth factors, growth hormones, peptide hormones, and neurotransmitters, respectively.

• Figure 3-3 shows the mechanism underlying G protein signal transduction.

**D. Hormone-binding proteins**
1. Certain hormones circulate bound to hormone-binding proteins.
2. These binding proteins serve several important physiologic functions:
   • They provide a reservoir of hormone, which exists in equilibrium with the free hormone and buffers any moment-to-moment changes in free hormone concentration.
   • They extend the half-life of the bound hormone considerably because it is the free hormone that is excreted by the liver or kidneys.
3. All steroid hormones and a few peptide hormones have plasma binding proteins (Table 3-2).

**Clinical note:** In pregnancy, plasma levels of the hormone-binding protein thyroid-binding globulin and transcortin increase because of the effects of estrogen on the liver, which increases their synthesis. This increases plasma levels of total thyroid hormone and total cortisol hormone but does not affect levels of free thyroid hormone or free cortisol hormone. Therefore, despite elevated levels of total thyroid hormone and cortisol, these women do not manifest symptoms of hyperthyroidism or hypercortisolism. Note, however, that pregnant women can still experience gestational hyperthyroidism and Cushing syndrome, but the pathophysiology of these endocrinopathies is unrelated to altered hormone-binding protein synthesis.
E. Hierarchical control of hormone secretion

1. For several hormonal control systems, a hierarchical axis exists, consisting of the hypothalamus, the anterior pituitary (adenohypophysis), and a specific endocrine gland (Fig. 3-4A).

2. The hypothalamus, at the top of the axis, secretes releasing (and inhibitory) hormones into a capillary bed that converges on the pituitary and then re-expands into another capillary bed within the anterior pituitary (hypothalamic-hypophyseal portal system) (Table 3-3; Fig. 3-4B).

3. The releasing hormones then stimulate specific cell types of the anterior pituitary and stimulate (or inhibit) pituitary hormone secretion.

4. The pituitary hormone, in turn, may act directly on target tissues (e.g., prolactin) or stimulate an endocrine gland to produce an effector hormone (e.g., thyroid-stimulating hormone).

5. The hypothalamus also controls the secretion of the hormones of the posterior pituitary (neurohypophysis), but in a different fashion.

6. Posterior pituitary hormones are synthesized by neurons in the hypothalamus and transported along axons into the posterior pituitary.

7. There they are released into the bloodstream as neurosecretory granules in response to appropriate stimuli.

---

**TABLE 3.2. Hormone Binding in Some Plasma Proteins**

<table>
<thead>
<tr>
<th>PLASMA PROTEIN</th>
<th>HORMONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Multiple lipophilic hormones</td>
</tr>
<tr>
<td>Transthyretin</td>
<td>Thyroxine (T₄)</td>
</tr>
<tr>
<td>Transcortin</td>
<td>Cortisol, aldosterone</td>
</tr>
<tr>
<td>Thyroxine-binding globulin</td>
<td>Triiodothyronine (T₃), T₄</td>
</tr>
<tr>
<td>Sex hormone–binding globulin</td>
<td>Testosterone, estrogen</td>
</tr>
</tbody>
</table>
F. Classification of endocrine diseases

1. A hormone deficiency or excess can occur as the result of a defect anywhere along the hypothalamic-pituitary-target organ axis.
2. It is important to determine the location of the defect to make an accurate diagnosis.
3. In primary endocrine diseases, the defect is in the endocrine organ.
   - For example, if a defect renders the thyroid gland unable to produce thyroid hormone effectively, the disease is known as primary hypothyroidism.
4. In secondary endocrine diseases, the defect is in the pituitary gland.
   - For example, decreased pituitary thyrotropin-releasing hormone secretion causes secondary hypothyroidism.
5. In tertiary endocrine diseases, the defect is in the hypothalamus.
   - For example, decreased hypothalamic thyrotropin-releasing hormone secretion (extremely rare) causes tertiary hypothyroidism.

II. Hormonal Control Systems of the Anterior Pituitary

A. Hypothalamic-pituitary-adrenal axis

1. Overview
   - Functions to maintain physiologically appropriate plasma levels of the hormone cortisol.
- Corticotropin-releasing hormone (CRH) from the hypothalamus stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary through activation of corticotroph cells.
- ACTH then acts on the adrenal cortex to stimulate the synthesis and secretion of glucocorticoids and androgens but not the mineralocorticoid aldosterone (see pathology note below).
- Note that androgens do not feedback-inhibit ACTH secretion.

Pathology note: In certain types of congenital adrenal hyperplasias (CAH), specific enzyme blocks (e.g., 21- and 11-hydroxylase) lead to impaired cortisol synthesis and shunting of proximally located precursors (e.g., 17-hydroxypregnenolone, 17-hydroxyprogesterone) into the androgen biosynthetic pathway. Because androgens do not feedback-inhibit the pituitary, ACTH levels markedly increase. The result is further pathologic androgen production, resulting in precocious puberty in males later in childhood or ambiguous genitalia in female neonates (e.g., clitoris looks like a penis). In severe forms of CAH, salt wasting (hypotension) from insufficient mineralocorticoid production distal to the enzyme block may occur (e.g., 21-hydroxylase deficiency), or salt retention (hypertension) results from increased weak mineralocorticoids like 11-deoxycorticosterone that are proximal to the enzyme block (e.g., 11-hydroxylase deficiency).

- The primary glucocorticoid is cortisol, and the primary adrenal androgen is dehydroepiandrosterone (DHEA), a precursor of testosterone.

2. Regulation of the hypothalamic-pituitary-adrenal axis
- As shown in Figure 3-5, cortisol secretion is stimulated by hypoglycemia or stressful conditions (e.g., surgery), when the sympathetic nervous system is also activated.
  a. This is why cortisol is sometimes referred to as the stress hormone.
- Cortisol secretion is normally inhibited by increased plasma levels of cortisol because of the negative-feedback effect of cortisol on the pituitary and hypothalamus.
- Note from the figure that androgens do not inhibit CRH or ACTH secretion, as discussed in the pathology note above.

Pathology note: A tumor of the adrenal gland that autonomously hypersecretes cortisol exerts negative feedback on the hypothalamus and pituitary and decreases the secretion of ACTH secretion. In this circumstance, the patient will be hypercortisolemic with a low ACTH level, implying the etiology of the hypercortisolism is adrenal in origin.

Androgens: do not feedback-inhibit ACTH secretion
Primary glucocorticoid: cortisol
Primary androgen: DHEA
Cortisol secretion: stimulated by physiologic stressors

3-5: Main determinants of hypothalamic-pituitary-adrenal axis. ACTH, Adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone.
- Cortisol has a **diurnal** pattern of secretion that is based on the daily pattern of ACTH secretion from the pituitary.
- Cortisol levels are **highest in the early morning**, owing to the early-morning surge of ACTH (Fig. 3-6).

### 3. Biosynthetic pathway of adrenal corticosteroids

- The **rate-limiting step** in adrenal steroid synthesis is the **conversion of cholesterol to pregnenolone** (Fig. 3-7).
- The synthetic pathway for each adrenal steroid occurs in a specific region of the adrenal gland.
  - a. Mineralocorticoid synthesis occurs in the **zona glomerulosa**.
  - b. Cortisol synthesis primarily occurs in the **zona fasciculata**.
  - c. Androgen synthesis occurs in the **zona reticularis**.

---

**3-6**: Diurnal secretion of adrenocorticotropic hormone and cortisol. ACTH, Adrenocorticotropic hormone.

**3-7**: Pathways of adrenal steroidogenesis. Note that the primary dehydroepiandrosterone (DHEA) produced by the adrenal is DHEA sulfate, whereas the key DHEA produced by the gonads is DHEA. This is important in working up the cause of hirsutism and virilization. Note also the stimulatory effects of angiotensin II and plasma K⁺ on aldosterone synthesis.
Although the principal mineralocorticoid aldosterone is synthesized in the adrenal cortex, its synthesis is only slightly affected by ACTH.

a. Rather, its secretion is primarily regulated by plasma concentrations of $K^+$ and angiotensin II, the latter increasing conversion of corticosterone to aldosterone by stimulation of 18-hydroxylase.

**Note:** The gonads (ovaries and testes) and the adrenals are the only tissues that convert cholesterol to steroid hormones.

4. **Mechanism of action of cortisol** (see Fig. 3-1)
   - As a steroid hormone, cortisol is able to diffuse through the plasma membrane of cells and bind to a **cytoplasmic receptor**.
   - This hormone-receptor complex then enters the nucleus, binds specific DNA sequences, and regulates the expression of various “steroid-responsive” genes.
   - Because cortisol relies on the intermediary process of gene expression and protein translation, it can take hours to days for its effects to manifest.

5. **Physiologic actions of cortisol** (Fig. 3-8)
   - **Fuel metabolism**
     a. In the **fasting state**, cortisol helps maintain adequate plasma levels of glucose for glucose-dependent tissues such as the central nervous system (CNS).

     **Clinical note:** The CNS is primarily dependent on glucose for a fuel source because it is unable to metabolize fatty acids and proteins to any great extent. Therefore, in patients who experience hypoglycemia (e.g., diabetic patient who takes his pre-meal insulin and then forgets to eat), CNS dysfunction can occur. Symptoms can range from mild confusion and somnolence to coma. Fortunately, unless the hypoglycemia is prolonged, it is rare for brain damage to occur.

     b. It accomplishes this by inhibiting the peripheral utilization of glucose by muscle and adipose tissue while simultaneously stimulating hepatic gluconeogenesis.

     c. Cortisol exerts **catabolic actions** on most tissues, with the exception of the liver, on which it exerts anabolic actions.

     d. Cortisol **stimulates** hepatic **gluconeogenesis** in several ways:
       - It promotes **muscle breakdown**, which releases amino acids (e.g., alanine, aspartate) into the gluconeogenic pathway.
       - It stimulates synthesis of hepatic gluconeogenic enzymes.
       - It potentiates the actions of **glucagon** and **catecholamines** on the liver.
       - Cortisol additionally **stimulates lipolysis in adipose tissue**, which helps maintain plasma levels of **glycerol** and **fatty acids** during the fasting state.
       - These substrates can then be used as **alternative fuel sources** in various tissues (e.g., muscle), thereby **sparing plasma glucose** for the CNS.
       - In the liver, these substrates can be used as an energy source to support gluconeogenesis.

     **Clinical note:** Because of the propensity of cortisol to increase plasma glucose levels, prolonged exposure to supraphysiologic levels of cortisol will often cause **glucose intolerance** and may lead to frank **diabetes mellitus** in a significant number of patients.

     **Metabolic actions of cortisol:**
     - Generally **catabolic**, stimulates **gluconeogenesis**, preserves plasma glucose.

---

### Aldosterone synthesis:
- Regulated by $K^+$ and angiotensin II rather than ACTH

### Steroid hormones:
- Regulate expression of genes containing steroid-responsive elements
- Effects can take hours to days to manifest because they work by altering gene expression

---

3-8: Metabolic actions of cortisol. Note also some of the pathologic affects from prolonged exposure to supraphysiologic concentration.
Effects on blood pressure and plasma volume
a. Cortisol increases blood pressure in several ways.
   • It increases the expression of adrenergic receptors in various tissues.
     (1) For example, stimulation of \( \alpha_1 \)-adrenergic receptors on vascular smooth muscle results in vasconstriction.
     (2) \( \beta \)-Receptor agonism is also important in mediating sympathetic stimulation of the heart, bronchodilation, stimulation of renin secretion, and metabolism, including lipolysis and glycogenolysis.
   • At increased levels, cortisol exerts mineralocorticoid actions on the kidneys because it is similar in structure to aldosterone.
b. This stimulates renal sodium reabsorption and causes plasma volume expansion.

Clinical note: Ordinarily, cortisol is degraded by intracellular enzymes in the cells of mineralocorticoid-responsive tissues such as the colon and kidney. However, at higher levels, these enzymes become saturated, at which point cortisol may bind to mineralocorticoid receptors and exert pathologic effects, such as hypertension and electrolyte abnormalities (e.g., hypokalemia).

Effects on inflammatory and immune responses
a. Cortisol has powerful anti-inflammatory effects.
b. It inhibits activity of the enzyme phospholipase and also inhibits the transcription of various inflammatory cytokines.
c. As shown in Figure 3-9, inhibition of phospholipase leads to decreased arachidonic acid production and, therefore, to decreased production of prostaglandins and leukotrienes, both potent inflammatory mediators.

Effects on bone
a. At supraphysiologic levels, cortisol weakens bones by inhibiting bone-forming cells (osteoblasts) and stimulating bone-degrading cells (osteoclasts).
b. Cortisol also acts to decrease plasma calcium by reducing calcium absorption by the intestines as well as inhibiting the production of 1,25-(OH)_{2}-D (calcitriol) by the kidneys; these actions tend to increase parathyroid hormone secretion, which can promote further bone breakdown.

Pathology note: Increased levels of glucocorticoids can severely compromise the blood supply to certain susceptible bones, resulting in avascular necrosis of the bone. Avascular necrosis most commonly occurs in the femoral head of the hip joint in patients treated with long-term glucocorticoids.

5. Pathophysiology of the CRH-ACTH-cortisol axis
   • Hypercortisolism (Cushing syndrome)
     a. Cushing syndrome refers to the constellation of signs and symptoms associated with hypercortisolism, irrespective of the etiology of the hypercortisolism.
     b. Recall that cortisol promotes hyperglycemia, muscle breakdown, bone loss, and plasma volume expansion.
   • Hypercortisolic states may therefore result in diabetes mellitus, muscle wasting, osteoporosis, and hypertension.

NSAIIDs, Nonsteroidal anti-inflammatory drugs.
c. Hypercortisolism is most commonly physician induced (iatrogenic).
d. The most common endogenous source of elevated cortisol is an ACTH-hypersecreting tumor of the pituitary (pituitary Cushing), a condition formerly referred to as Cushing disease.
e. Other causes of Cushing syndrome (Fig. 3-10) include cortisol-hypersecreting adrenal tumors and ectopic (paraneoplastic) production of ACTH by tumors (e.g., small cell lung cancer).

Clinical note: The dexamethasone suppression test can be used to differentiate between pituitary Cushing and paraneoplastic secretion ACTH in a patient with hypercortisolism and elevated ACTH. In pituitary Cushing, the pituitary retains some responsiveness to feedback inhibition by cortisol or by synthetic glucocorticoids such as dexamethasone. In contrast, ectopic Cushing or adrenal Cushing is not controlled through feedback inhibition by cortisol or dexamethasone. Therefore, although the administration of a high dose of dexamethasone should decrease cortisol levels in pituitary Cushing, it will have no effect on decreasing cortisol levels in ectopic Cushing or adrenal Cushing.

- **Hypocortisolism (adrenal insufficiency)**
  a. Principal pathologic consequences include fatigue and vague abdominal pain, although additional manifestations are numerous and may include orthostatic hypotension, hypoglycemia, hyponatremia, and chronic diarrhea, to name just a few.
  b. Most common cause is iatrogenic, because of the abrupt cessation of chronically administered steroids; in this case, the hypothalamic-pituitary-adrenal axis has been chronically suppressed and needs several weeks to “wake up.”
  c. In primary adrenal insufficiency, ACTH levels should be high, whereas in secondary causes or with chronic use of steroids, ACTH levels should be low.

Symptoms of adrenal insufficiency: nonspecific and vague, include fatigue, nausea, abdominal pain, and diarrhea
Adrenal insufficiency: most commonly iatrogenic from chronic administration of steroids
Primary adrenal insufficiency: ↑ ACTH, hyperpigmentation;
Secondary adrenal insufficiency: ↓ ACTH, no hyperpigmentation

3-10: Classic physical features of Cushing syndrome. The classic physical presentation of Cushing syndrome is central obesity that spares the extremities (extremity wasting may even occur), a rounded face (“moon facies”), abdominal striae, and a dorsocervical fat pad (“buffalo hump”). Although glucocorticoids are lipolytic, they cause fat deposition on the trunk and face. In addition to hyperglycemia, osteoporosis, hypertension, and muscle wasting, hirsutism may be present in the adrenocorticotropic hormone (ACTH)-dependent forms of Cushing syndrome as a result of stimulation of adrenal androgen production by the excess ACTH. Oligomenorrhea, acne, and deepening of the voice can also occur in females as a result of increased levels of androgens.
Clinical note: The exogenous administration of glucocorticoids on a long-term basis normally suppresses the hypothalamic-pituitary-adrenal axis. If steroid therapy is abruptly stopped, patients are susceptible to developing acute adrenal insufficiency. Therefore, whenever steroid therapy is to be stopped, it should be a gradual weaning process, which allows the hypothalamic-pituitary-adrenal axis to recover by the time the steroids are completely stopped.

Chronic adrenal insufficiency also develops when the adrenal cortex is destroyed. Usually, the cause is autoimmune destruction of the adrenals (Addison disease), but sometimes it is tuberculosis or metastatic cancer involving the adrenals. Signs and symptoms of adrenal insufficiency reflect deficiencies in glucocorticoids and mineralocorticoids and include hypotension and salt wasting. Reduced feedback inhibition of the hypothalamic-pituitary axis from deficient cortisol synthesis results in increased ACTH secretion by the pituitary. When ACTH is cleaved from its precursor proopiomelanocortin (POMC), melanocyte-stimulating hormone (MSH) is concurrently released. MSH then stimulates melanin-containing skin cells (melanocytes), causing hyperpigmentation of the skin, which is frequently seen in Addison disease.

6. Hypothalamic-pituitary regulation of adrenal androgen synthesis
   - ACTH stimulates adrenal DHEA and androstenedione synthesis.
   - Both substances are androgen prohormones that are converted in peripheral tissues to testosterone and dihydrotestosterone (DHT).
   - Note that androgens do not cause feedback inhibition of CRH or ACTH secretion.

7. Pathophysiology of congenital adrenal hyperplasias (CAH)
   - This group of disorders is characterized by enzyme defects in the cortisol biosynthetic pathway.
   - In CAH, decreased cortisol production disinhibits the pituitary, causing increased ACTH secretion.
   - The increased ACTH then promotes adrenal hyperplasia.
   - Continued stimulation by ACTH leads to shunting of cortisol precursors to androgens, which may cause precocious puberty in males later in childhood or ambiguous genitalia in female neonates.
   - The most common form of CAH is caused by 21-hydroxylase deficiency (Fig. 3-11).
     a. In addition to producing hypocortisolism, it also produces salt wasting and hypotension as a result of impaired mineralocorticoid synthesis.
Pathology note: The most common cause of congenital adrenal hyperplasia is 21-hydroxylase deficiency, responsible for approximately 95% of cases of CAH. In common use, the term CAH refers to 21-hydroxylase deficiency. In severe forms of 21-hydroxylase deficiency, impaired mineralocorticoid synthesis can result in potentially fatal salt wasting in early life. Less severe forms of CAH (called nonclassic types) cause ambiguous genitalia in female neonates and precocious puberty in males without salt wasting. In contradistinction, the less common 11-hydroxylase deficiency produces salt retention and hypertension, because of an increase in 11-deoxycorticosterone, which is proximal to the enzyme block. It also can cause ambiguous genitalia in female neonates and precocious puberty in males.

8. Pathophysiology of adrenal disorders (Table 3-4)

B. Hypothalamic-pituitary-thyroid axis

1. Overview
   • Functions to maintain physiologically appropriate plasma levels of the thyroid hormones triiodothyronine ($T_3$) and thyroxine ($T_4$)
   • Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates thyroid-stimulating hormone (TSH) secretion from thyrotrophs within the anterior pituitary.
   • TSH stimulates secretion of $T_3$ and $T_4$ from follicular cells within the thyroid gland.
   • Note: The hormone calcitonin, involved in $Ca^{2+}$ regulation, is also secreted by the thyroid gland, but this activity is not under hypothalamic or pituitary control.
     a. Furthermore, calcitonin is secreted by parafollicular cells rather than follicular cells.

2. Steps in the synthesis of thyroid hormones (Fig. 3-12)
   • Plasma iodide ion ($I^-$) is internalized by follicular cells through the iodide pump and extruded into the follicular lumen.
     a. TSH-mediated step
   • $I^-$ is oxidized to iodine $I_2$ by peroxidase.
   • $I_2$ is attached to tyrosine residues on the primary protein of the follicular lumen (thyroglobulin), forming monoiodotyrosine (MIT) and diiodotyrosine (DIT)
     a. This is termed the organification step.
     b. TSH-mediated step
     c. This step is inhibited by the thionamides propylthiouracil (PTU) and methimazole, which are used to treat hyperthyroidism.
   • Coupling of MIT and DIT into $T_4$ and $T_3$
   • Endocytosis of thyroglobulin from colloid

### TABLE 3-4. Adrenal Disorders and Commonly Associated Clinical Features

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>PATHOPHYSIOLOGY</th>
<th>CLINICAL FEATURES</th>
<th>TREATMENT</th>
</tr>
</thead>
</table>
| Primary adrenal insufficiency (Addison disease) | Autoimmune, metastatic, or tubercular destruction of adrenal cortices | $\downarrow$ Aldosterone $\rightarrow$ hypokalemia, metabolic acidosis, sodium wasting, volume depletion, hypotension  
$\downarrow$ Cortisol $\rightarrow$ hypoglycemia, weakness, vulnerability to stress  
$\downarrow$ Adrenal androgens $\rightarrow$ loss of pubic and axillary hair in females  
$\uparrow$ ACTH $\rightarrow$ hyperpigmentation | Glucocorticoid and mineralocorticoid replacement therapy |
| Acute adrenal insufficiency       | Septicemia (e.g., Neisseria meningitidis), iatrogenic (e.g., sudden withdrawal from long-term steroid therapy) | Symptoms of Addison disease (see above)                                             | Treat underlying cause (e.g., septicemia) and initiate steroid replacement therapy |
| Primary hypercortisolism          | Adrenal tumor                                             | $\uparrow$ Cortisol $\rightarrow$ hyperglycemia, central obesity, hypertension, osteoporosis, muscle wasting, purple abdominal striae | Steroid synthesis inhibitors (e.g., ketoconazole, metyrapone) or surgery |
| Secondary hypercortisolism        | Pituitary tumor (pituitary Cushing) or ectopic ACTH production (small cell lung carcinoma) | $\uparrow$ ACTH $\rightarrow$ hypercortisolism, hyperpigmentation  
$\uparrow$ Cortisol $\rightarrow$ same effects as in Cushing syndrome  
$\downarrow$ Androgens $\rightarrow$ hirsutism  
$\downarrow$ ACTH due to feedback inhibition of pituitary | Surgery |

ACTH, Adrenocorticotropic hormone.
Hydrolytic cleavage of T₃ and T₄ from thyroglobulin and diffusion of T₄ and T₃ into plasma
  a. TSH-mediated step

Clinical/pharmacology note: Amiodarone is an iodine-rich drug (approximately 40% by weight) that is commonly used for rate control of tachyarrhythmias such as atrial fibrillation. Unfortunately, amiodarone commonly causes thyroid dysfunction, both hyperthyroidism (commonly) and hypothyroidism (rare), necessitating frequent monitoring of thyroid function. It does this in a myriad of ways, the details of which are beyond the scope of this book.

Pharmacology note: Patients with hyperthyroidism are often treated with the thionamides propylthiouracil (PTU) and methimazole, drugs that inhibit the synthesis of thyroid hormones. These drugs act by inhibiting the oxidation and organification of iodide within the thyroid, thereby reducing the synthesis of thyroid hormones. Because large quantities of thyroid hormones are stored in colloid, it takes several weeks for these drugs to deplete thyroid T₄ levels and return systemic thyroid hormone levels to normal. However, in cases of thyroid storm, when rapid action is required, PTU can act more rapidly than methimazole by inhibiting the peripheral conversion of T₄ to T₃.

3. Physiologic actions of thyroid hormones (Fig. 3-13)
  a. Increased basal metabolic rate (BMR)
  b. The increase in BMR causes heat intolerance, a common symptom of hyperthyroidism.
Potentiation of catecholamine actions

a. Thyroid hormones up-regulate expression and stimulate activity of β-adrenergic receptors in tissues such as the heart and skeletal muscle, resulting in markedly enhanced sensitivity to circulating catecholamines.

b. They also act directly on the heart to stimulate contractility and increase heart rate, and can actually result in high-output congestive heart failure.

c. In skeletal muscle, they may contribute to muscle tremors.

Pharmacology note: By preventing catecholamines from binding to their receptors, β-adrenergic antagonists (β-blockers), such as propranolol, can ameliorate many of the symptoms of hyperthyroidism associated with excessive sympathetic activity (e.g., tachycardia, tremors).
4. Differences between T<sub>4</sub> and T<sub>3</sub>

- The thyroid gland secretes both T<sub>4</sub> and T<sub>3</sub>.
- T<sub>4</sub> is much less potent than T<sub>3</sub>, but it has a longer plasma half-life than T<sub>3</sub>.
- Within target cells, T<sub>4</sub> is converted into the more active T<sub>3</sub> by the enzyme 5'-monodeiodinase.
  a. Therefore, T<sub>4</sub> can essentially be considered a prohormone that serves as a plasma reservoir for T<sub>3</sub>.
  b. Furthermore, because of its prolonged half-life, plasma T<sub>4</sub> is much more abundant than plasma T<sub>3</sub>.
  c. Therefore, it is principally responsible for the feedback inhibition of TRH secretion by the hypothalamus and TSH secretion by the pituitary.

**Clinical note:** In hypothyroid patients, supplementing only T<sub>4</sub> (rather than T<sub>3</sub>) usually provides adequate tissue levels of T<sub>3</sub> from peripheral conversion. However, certain patients respond much better to a T<sub>4</sub>-T<sub>3</sub> combination. Presumably, the peripheral conversion of T<sub>4</sub> to T<sub>3</sub> may be impaired in these patients. Supplementation of thyroid hormone should be titrated to improvement in clinical symptoms and normalization of TSH levels.

5. Pathophysiology

- Hyperthyroidism
  a. Signs and symptoms
    - The increased BMR causes weight loss and heat intolerance.
    - The direct and indirect cardiovascular effects of thyroid hormones increase the cardiac workload and over prolonged periods may cause heart failure (high output type).
    - Atrial fibrillation may also develop.
    - Enhanced sensitivity to catecholamines may cause sinus tachycardia and muscle tremors.
    - Intestinal motility is stimulated, causing diarrhea.
    - Bone resorption is stimulated, which may cause osteoporosis and hypercalcemia.
    - CNS effects may cause agitation and difficulty concentrating.
  b. Laboratory evaluation
    - T<sub>3</sub> and T<sub>4</sub> concentrations are elevated in hyperthyroidism.
    - TRH and TSH concentrations vary depending on the cause of the hyperthyroidism (Table 3-5).
  c. Differential diagnosis (Table 3-6)
    - Graves disease (diffuse toxic goiter)
      1. Most common cause of hyperthyroidism
      2. Stimulatory immunoglobulin G (IgG) autoantibodies bind to TSH receptors in the thyroid (type II hypersensitivity reaction).
      3. Antibodies mimic TSH and excessively stimulate, but do not destroy, the thyroid gland.
    - Toxic multinodular goiter and toxic adenoma
      1. Autonomous thyroid nodules hypersecrete T<sub>3</sub> and T<sub>4</sub>.
    - TSH-secreting pituitary tumor
      2. Rare cause of hyperthyroidism
    - TRH-secreting hypothalamic tumor
      1. Very rare cause of hyperthyroidism
    - Thyroiditis

**Table 3-5. Laboratory Values Associated With Hyperthyroidism**

<table>
<thead>
<tr>
<th>TYPE OF HYPERTHYROIDISM</th>
<th>EXAMPLE</th>
<th>TRH</th>
<th>TSH</th>
<th>T&lt;sub&gt;4&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Graves disease</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Secondary</td>
<td>Pituitary adenoma</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Hypothalamic tumor</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

T<sub>4</sub>: Thyrxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.
(1) Typically caused by viral infection but broad differential (e.g., autoimmune destruction as in Hashimoto thyroiditis).

(2) May cause tissue inflammation and destruction, with release of preformed thyroid hormone, leading to transient thyrotoxicosis; technically this is not a cause of hyperthyroidism because there is not increased synthesis of thyroid hormones.

**Clinical note:** The classic presentation of Graves disease is thyrotoxicosis (e.g., symptoms of hyperthyroidism), diffuse goiter, ophthalmopathy (e.g., exophthalmos), and dermopathy (e.g., pretibial myxedema).

**Clinical note:** In a patient with unintentional weight loss with a preserved or increased appetite, one should consider three diagnoses: hyperthyroidism, diabetes mellitus, and malabsorption syndrome. Infections, vasculitides, and malignancies classically cause weight loss associated with reduced appetite (anorexia).

- Hypothyroidism
  a. Signs and symptoms
  - The decreased BMR causes weight gain and cold intolerance.
  - Cardiac effects include bradycardia.
  - Intestinal effects include constipation.
  - CNS effects include dulled mentation.
  - Congenital hypothyroidism may cause mental retardation (cretinism) and short stature.

---

**TABLE 3-6. Etiology of Thyrotoxicosis (Includes Hyperthyroidism)**

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>PATHOPHYSIOLOGY</th>
<th>PATTERN OF RADIOIODINE UPTAKE</th>
<th>CLASSIC PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially Permanent Causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves disease (diffuse toxic goiter)</td>
<td>Activating IgG antibodies to TSH receptor</td>
<td>Diffuse uptake throughout gland</td>
<td>Goiter, ophthalmopathy, dermopathy</td>
</tr>
<tr>
<td>Toxic multinodular goiter</td>
<td>Multiple hyperactive nodules, may have mutations in genes encoding TSH receptor or G proteins</td>
<td>Uptake in one or a few overly active “hot” nodules Uptake in remainder of thyroid is suppressed</td>
<td>Older adult with history of nontoxic multinodular goiter May have cardiac complications such as atrial fibrillation and/ or heart failure</td>
</tr>
<tr>
<td>Toxic adenoma (Plummer’s disease)</td>
<td>Hyperactive adenoma(s); may have mutations in genes encoding TSH receptor or G proteins</td>
<td>Uptake in one or a few “hot” nodules Uptake in remainder of thyroid is suppressed</td>
<td>Younger adult with a history of a slowly growing “lump” in the neck</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>Hypersecretion of TSH</td>
<td>Diffuse uptake throughout thyroid</td>
<td>May have additional symptoms (e.g., headaches, bitemporal hemianopia, nausea and vomiting)</td>
</tr>
<tr>
<td>Transient Causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune thyroiditis (e.g., Hashimoto disease)</td>
<td>Autoimmune destruction of thyroid</td>
<td>Suppressed uptake throughout thyroid</td>
<td>Thyrotoxicosis initially followed by hypothyroidism</td>
</tr>
<tr>
<td>Subacute thyroiditis (de Quervain thyroiditis)</td>
<td>Likely secondary to viral infection of thyroid Follows upper respiratory tract infection</td>
<td>Suppressed uptake throughout thyroid</td>
<td>Thyroid exquisitely painful to palpation</td>
</tr>
<tr>
<td>Iodine-induced (jodbasedow effect)</td>
<td>Iodine overload may stimulate autonomous nodules, which function independently of TSH stimulation, to hypersecrete thyroid hormone</td>
<td>Suppressed uptake throughout thyroid</td>
<td>Thyrotoxicosis in patient with toxic multinodular goiter following the administration of iodine- rich radiographic contrast media and iodinated drugs such as amiodarone</td>
</tr>
</tbody>
</table>

TSH, Thyroid-stimulating hormone.
Manifestations of hypothyroidism: weight gain, cold intolerance, bradycardia, atrial fibrillation, dulled mentation, short stature
Congenital hypothyroidism: may cause cretinism

Clinical note: Patients with a long history of untreated hypothyroidism are susceptible to the most severe manifestation of hypothyroidism, myxedema coma; such patients may present with profound lethargy or coma, weakness, hypothermia, and hypoglycemia. Such patients may occasionally require emergent treatment with intravenous T4 or T3. Note that if intravenous thyroid hormones are given, steroids should be given first to prevent adrenal crisis (adrenal insufficiency due to the rapidly increased metabolic demands placed on the body from the newly introduced thyroid hormones), which constitutes an enormous physiological stress.

b. Laboratory evaluation (Table 3-7)
c. Differential diagnosis (Table 3-8)

- Euthyroid sick syndrome
  a. Common in sick hospitalized patients
  b. Characterized by low to normal T3 and T4 concentrations but without apparent thyroid dysfunction
  c. Likely caused by increased production of cortisol, which inhibits the peripheral conversion of T4 to T3 but increases the production of reverse T3 (rT3).
  - rT3 is inactive but does bind to the T3 receptor, blocking normal T3 from binding.

d. Take-home message: Due to the difficulty in interpretation of test results, thyroid studies should not be ordered in hospitalized patients unless thyroid disease is strongly suspected as the underlying etiology of the patient’s illness (e.g., new-onset atrial fibrillation).

C. Hypothalamic-pituitary-gonadal axis
- Responsible for the development and maintenance of primary and secondary sexual characteristics, menstrual cycles in females, and spermatogenesis in males.

1. Male reproductive axis (Fig. 3-14)
   - Mechanism of action of testosterone

---

**TABLE 3-7. Laboratory Values Associated With Hypothyroidism**

<table>
<thead>
<tr>
<th>TYPE OF HYPOTHYROIDISM</th>
<th>EXAMPLE</th>
<th>TRH</th>
<th>TSH</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Hashimoto thyroiditis</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Secondary</td>
<td>Pituitary lesion</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Hypothalamic lesion</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

T4, Thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

**TABLE 3-8. Etiology and Differential Diagnosis of Hypothyroidism**

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>PATHOPHYSIOLOGY</th>
<th>PRESENTATION</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endemic cretinism</td>
<td>Dietary iodide insufficiency at early developmental stages</td>
<td>Severe mental retardation; innocent (Christlike) appearing</td>
<td>Iodide replacement; mental retardation may be permanent</td>
</tr>
<tr>
<td>Endemic goiter</td>
<td>Dietary iodide insufficiency in adulthood</td>
<td>Goiter; common in mountainous areas such as the Andes, Himalayas, and Alps</td>
<td>Iodide replacement</td>
</tr>
<tr>
<td>Hashimoto thyroiditis (autoimmune thyroiditis)</td>
<td>Autoimmune destruction of thyroid gland</td>
<td>Initially may present as hyperthyroidism but ultimately causes hypothyroidism</td>
<td>Thyroxine replacement</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Most commonly caused by thyroidectomy Also may occur after radiotherapy for hyperthyroidism</td>
<td>Hypothyroidism</td>
<td>Thyroxine replacement</td>
</tr>
<tr>
<td>Riedel thyroiditis</td>
<td>Chronic fibrosis of thyroid gland</td>
<td>“Woody” thyroid</td>
<td>Steroids</td>
</tr>
<tr>
<td>Subacute granulomatous thyroiditis (de Quervain thyroiditis)</td>
<td>Viral in nature; often develops after upper respiratory tract infection</td>
<td>Thyroid gland is painful and tender on palpation Often preceded by hyperthyroidism</td>
<td>Usually resolves gradually on its own</td>
</tr>
</tbody>
</table>

- Hypothyroidism at any time before closure of the epiphyseal plates may also cause shorter than normal stature.
- Delayed deep tendon reflexes
- Dry skin and brittle hair
a. Testosterone is a steroid hormone that produces its effects by \textbf{stimulating protein synthesis (anabolic effect)}.  
b. In some tissues, especially the prostate and skin, testosterone is converted to a more potent form, \textbf{DHT}, by the enzyme \textbf{5α-reductase} before affecting cellular function.  

\textbf{Pharmacology/pathology note:} In elderly men, the prostate gland often enlarges (benign prostatic hyperplasia) and compresses the urethra as it passes through the prostate, limiting urine flow rates and causing retention of urine in the bladder. One of the most commonly used drugs to treat this condition is \textbf{finasteride}, which inhibits the enzyme \textbf{5α-reductase}, thereby limiting the influence of DHT on the prostate and \textbf{shrinking it}. DHT is partly responsible for \textbf{male pattern baldness}; thus, finasteride is also modestly effective at restoring hair growth in men.

\textbf{• Physiologic actions of testosterone and dihydrotestosterone (DHT)}  
a. Embryologic functions of testosterone and DHT in males  
\begin{itemize}
\item \textbf{Testosterone} is responsible for development of the epididymis, vas deferens, and seminal vesicles from mesonephric duct structures during embryologic development.
\item \textbf{DHT} is responsible for development of the male external genitalia (penis, scrotum) and prostate gland.
\end{itemize}
(1) External female sex organs will develop “by default” in the absence of DHT or appropriate tissue responsiveness to DHT, even if the fetus is genetically male.

\textbf{Clinical note:} In \textbf{androgen insensitivity syndrome (testicular feminization)}, the most common cause of \textbf{male hermaphroditism}, genetic males (46,XY) appear phenotypically female. This syndrome is caused by \textbf{mutations} in the \textbf{androgen receptor gene} located on the X chromosome. The testes produce testosterone, but male accessory structures (e.g., epididymis, seminal vesicles, vas deferens) do not develop because the \textbf{tissues are not responsive to testosterone}. DHT is produced; however, the external genitalia will appear female, and the prostate gland does not develop. The testes, however, do

\textbf{Testosterone:} converted to more potent form (DHT) by 5α-reductase in certain tissues such as skin and prostate

\textbf{Testosterone:} responsible for development of seminal vesicles, epididymis, vas deferens during embryogenesis

\textbf{Absent testosterone:} female sex organs will develop even in genetically male fetus
produce müllerian-inhibiting substance; therefore, müllerian structures such as the fallopian tubes, uterus, and upper one third of the vagina do not develop. However, the lower two thirds of the vagina does develop because it derives from the urogenital sinus; hence, the vagina ends blindly. The testes are located either intra-abdominally or in the inguinal canal (cryptorchid testes). Most patients are reared as females.

b. Testosterone is responsible for increasing both lean muscle mass and bone density.

c. Although testosterone stimulates bone growth, it causes fusion of the epiphyseal plates; therefore, excessive levels during the growing stages may result in short stature.

d. Testosterone stimulates hair growth in a male pattern (face, chest, abdomen).
   • DHT enhances the development of male pattern baldness in genetically prone men.

e. Testosterone lengthens the larynx with deepening of the voice.

f. Testosterone increases the rate of secretion by most of the body’s sebaceous glands, predisposing to acne in pubescent males.

g. Testosterone increases the concentration of red blood cells, accounting for the greater concentration of hemoglobin in males.

Clinical note: During fetal development, müllerian inhibitory factor is important for the transabdominal phase of testes descent and testosterone for the normal descent of the testes from the inguinal canal to the scrotum. Undescended testes (cryptorchidism) is more likely to occur in the absence of testosterone and represents a significant risk factor for testicular cancer. Testosterone may be given to promote testicular descent.

• Regulation of testosterone secretion
   a. Testosterone secretion by the Leydig cells is regulated by the hypothalamic-pituitary axis.
   b. Gonadotropin-releasing hormone (GnRH) secretion by the hypothalamus stimulates the pituitary to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
   c. LH then stimulates testosterone secretion by the Leydig cells, whereas FSH is important in spermatogenesis (discussed later).
   d. Testosterone then feedback-inhibits GnRH secretion by the hypothalamus and LH secretion by the pituitary (see Fig. 3-14).

Pharmacology note: Leuprolide is a synthetic GnRH agonist that, when exogenously administered in a continuous nonpulsatile manner, inhibits the secretion of FSH and LH by the pituitary gonadotrophs. The result is reduced synthesis of testicular androgens in males and reduced ovarian estrogens and progesterins in females. In patients with prostate cancer, a reduction in androgen synthesis is desirable because the growth of the prostate cancer is DHT dependent.

• Puberty in males
   a. At the onset of puberty, increased GnRH secretion by the hypothalamus stimulates LH secretion and consequently increased testosterone secretion.
   b. The increased testosterone stimulates expression of male secondary sexual characteristics and enlargement of male primary sex organs.

• Spermatogenesis
   a. Process of sperm maturation in which a haploid male gamete is produced
   b. Occurs in the seminiferous tubules of the testicles
   c. Testosterone is important in stimulating the growth and division of testicular germinal cells, the ultimate source of sperm cells.
   d. FSH, which is secreted by the anterior pituitary in response to GnRH, stimulates the Sertoli cells of the seminiferous tubules to facilitate sperm maturation.
   e. The Sertoli cells also produce a substance called inhibin, which inhibits the secretion of FSH by the anterior pituitary (see Fig. 3-14).
Clinical note: FSH is required for sperm maturation within the testes. By inhibiting FSH secretion by the pituitary, inhibin might be able to prevent spermatogenesis and could therefore be used as a male contraceptive. Indeed, clinical trials using inhibin are currently underway.

2. Female reproductive axis (Fig. 3-15)
   - Physiologic actions of estrogen
     a. Estrogen and progesterone are both unnecessary for the development of female primary sex organs.
     b. Estrogen is responsible for the development of female secondary sexual characteristics and also plays a critical role in the menstrual cycle.
     c. With the onset of puberty, increased estrogen levels induce breast maturation by causing proliferation of stromal tissue, development of the ductule system, and deposition of fat.
     d. Estrogen stimulates fat deposition, particularly on the hips and buttocks and in the subcutaneous tissues.
     e. Estrogen is also critical in skeletal maturation, causing increased bone density and fusion of the epiphyseal plates in adolescent females.
     - Note that in just the first 3 years of menopause, there is an approximate 30% reduction in bone mass because of the drop in estrogen levels, highlighting the importance of estrogen in maintaining strong bones.

Clinical note: It was long felt that providing supplemental estrogen (with or without progesterone) to postmenopausal women would have beneficial effects in terms of preventing osteoporosis, hip fractures, and cardiovascular disease. Instead, a large randomized placebo-controlled trial (the Women’s Health Initiative trial, published in 2002) showed that postmenopausal women receiving estrogen were far more likely to develop breast cancer, stroke, thrombotic embolic disease, and modestly more likely to develop heart disease. Therefore, supplemental estrogen is currently recommended only to those postmenopausal women experiencing intractable postmenopausal symptoms such as persistent hot flashes that are refractory to other medications such as selective-serotonin-reuptake-inhibitors (SSRIs).
Physiologic actions of progesterone
a. Stimulation of breast development, regulation of the menstrual cycle, and maintenance of pregnancy
b. Both estrogen and progesterone antagonize the effects of prolactin on the breast, explaining why pregnant women with hyperprolactinemia (normal during pregnancy) do not experience galactorrhea or milk letdown.

Regulation of secretion of estrogen and progesterone
a. A complex cyclical pattern of FSH and LH secretion occurs in females.
b. Hypothalamic release of GnRH causes the gonadotrophs in the anterior pituitary to secrete FSH and LH.
c. FSH stimulates estrogen synthesis by granulosa cells in the ovarian follicles, and LH stimulates progesterone synthesis by theca cells.
   • Aromatase in the granulosa cells converts testosterone synthesized by the theca interna outside the developing follicle into estradiol.
d. Both estrogen and progesterone control FSH and LH secretion by feedback inhibition (see Fig. 3-15).
e. As occurs in males, females reach puberty when the hypothalamus begins secreting increased levels of GnRH.

Menstrual cycle (Fig. 3-16)
a. Follicular (proliferative) phase
   • Most variable phase of the menstrual cycle
   • The menstrual cycle begins with the first day of uterine bleeding (day 1; menses).
   • At this point, estrogen and progesterone levels are low, so FSH levels begin to gradually increase as a result of reduced feedback inhibition.
   • FSH stimulates multiple follicles to develop and increases synthesis of aromatase in granulosa cells to increase estrogen synthesis and secretion.
   • Eventually, a single dominant follicle emerges and the remaining follicles undergo atresia.
   • Although increasing levels of estrogen then begin to inhibit FSH secretion, the enlarging follicles or dominant follicle becomes increasingly sensitive to FSH, and estrogen levels continue to increase.
   • When plasma estrogen levels reach a critical threshold, they paradoxically cause a surge in both LH and FSH secretion through a positive-feedback mechanism at the pituitary, with LH increasing greater than FSH (LH surge).
   • The LH surge causes ovulation.
   • After ovulation, the cells that lined the ovarian follicle form the corpus luteum, which secretes estrogen and progesterone.
If an ovum is not fertilized, the corpus luteum degenerates, menses begins, and the cycle begins again.

- If the ovum is fertilized, the developing embryo will synthesize human chorionic gonadotropin (hCG), which acts similarly to LH and maintains the corpus luteum and its synthesis of progesterone.
- In 8 to 10 weeks, the developing placenta assumes the role of progesterone synthesis, which correlates with the time that the corpus luteum begins to involute.
  1. If the placenta is not synthesizing enough progesterone at this time, the patient may start bleeding and lose the pregnancy.
- The time between the first day of menses and ovulation is referred to as the follicular phase, because the follicles are developing.
  1. It is also called the proliferative phase, because estrogen stimulates proliferation of the endometrial lining.

**Pharmacology note:** Estrogen-containing oral contraceptives function by inhibiting the LH surge that is responsible for ovulation. Estrogen-containing contraceptives provide a constant level of estrogen that maintains a continual negative feedback on pituitary gonadotropin secretion, thereby stabilizing FSH and LH secretion.

In contrast, progesterone-only pills are only about 50% effective in inhibiting ovulation. Rather, they work primarily by thickening the cervical mucus and altering the motility and secretions of the fallopian tubes, as well as thinning the endometrium. All these changes make the uterus a less hospitable environment for implantation of a fertilized embryo. Some people may be ethically opposed to use of the progesterone-only pill because, whereas it inhibits implantation and therefore pregnancy, it does not prevent fertilization.

**b. Luteal (secretory) phase**
- Least variable phase of the menstrual cycle
- The time between ovulation and menses is referred to as the luteal phase (because the corpus luteum is present).
- During the follicular (proliferative) phase, the estrogen secreted by the ovaries stimulates proliferation of the uterine endometrium.
- When ovulation occurs, the progesterone secreted by the corpus luteum causes the endometrial glands to become more secretory, preparing the endometrial lining for implantation of the ovum.
  1. Secretions initially develop beneath the nucleus and produce subnuclear vacuoles, a key indicator of ovulation.
- If fertilization and implantation of the ovum do not occur, the corpus luteum degenerates and stops secreting estrogen and progesterone.
- Sloughing off of the endometrial lining (menses) occurs when estrogen and progesterone levels drop, although menses is triggered primarily by the drop in progesterone.
  1. The drop in these hormones is a signal for apoptosis of the cells within the endometrial glands.

**Clinical note:** In some reproductive-aged females, menses does not occur (amenorrhea). This is often the result of a failure to ovulate (anovulatory infertility); with anovulation, there will be no spike and subsequent decline in progesterone levels to trigger menses because the corpus luteum will not develop. To determine whether anovulation is the cause, these females can be given a 10-day course of progesterone; if they begin menstruating shortly after the course of progesterone, this is compelling evidence that anovulation is causing the amenorrhea.

3. Pathophysiology of reproductive disorders (Table 3-9)

**D. Prolactin**

1. **Physiologic actions**
   - Promotes breast maturation and differentiation of mammary alveoli cells such that they are able to secrete milk (lactogenesis) in post-pregnant females.
a. The pituitary gland approximately doubles in size during pregnancy as a result of proliferation of prolactin-secreting lactotrophs; this is why women in the third trimester may experience visual difficulties such as a bitemporal hemianopsia.

- Actual lactation during pregnancy is inhibited because of the high amounts of estrogen and progesterone secreted by the placenta, which inhibit the actions of prolactin.
- After delivery and expulsion of the placenta, there is a drop in maternal estrogen and progesterone; prolactin is then able to stimulate lactation in response to suckling by the infant.
- In addition, elevated levels of prolactin serve as a “natural contraceptive” for breastfeeding females by inhibiting the hypothalamic secretion of GnRH.
  a. This explains why it is more difficult for mothers who are breastfeeding to become pregnant.

Clinical note: Prolactin plays a more limited role in the male than in the female. However, hyperprolactinemia in males also inhibits hypothalamic GnRH secretion, causing impotence and loss of libido because of a drop in testosterone. Therefore, hyperprolactinemia should always be considered in the differential diagnosis of impotence and depression in men.

2. Prolactin secretion
   - Stimulated by breastfeeding or excessive nipple stimulation, antidopaminergic agents (e.g., typical antipsychotics), and hypothyroidism, through TRH-induced prolactin secretion.
     a. Other causes of hyperprolactinemia include a hypersecreting-pituitary adenoma and head trauma resulting in severing of the pituitary stalk, which disinhibits dopamine secretion by the pituitary.
     b. Inhibited by dopamine agonists such as bromocriptine and cabergoline, which are used to treat prolactinomas.

Pharmacology note: Antipsychotic drugs used to treat schizophrenia function largely by blocking dopamine receptors. Consequently, these drugs can block the inhibitory effect that dopamine has on prolactin secretion, resulting in hyperprolactinemia and its attendant consequences (e.g., reduced libido). Indeed, prolactin levels are frequently monitored in patients taking antipsychotic agents to see if they are actually taking their medications (some readers may recall the movie A Beautiful Mind).
3. **Pathophysiology** (Fig. 3-17)

- Elevated levels of prolactin (**hyperprolactinemia**) in nonpregnant females can result in abnormal milk discharge from the nipples (**galactorrhea**) and **anovulatory infertility**.
- Hyperprolactinemia in men can cause **decreased energy** and **lack of libido**.
  a. Difficult to diagnose because men do not present with galactorrhea or amenorrhea

**Pharmacology note:** Dopamine agonists such as **bromocriptine** (used in the treatment of Parkinson disease) can be used to treat **hyperprolactinemia**. Schizophrenia is believed to be related to excess dopamine activity, and dopamine agonists such as bromocriptine can precipitate psychotic symptoms, because of increased dopaminergic effects.

---

E. **Growth hormone (GH)**

1. **Anabolic actions**

- Promotes tissue growth, particularly of the musculoskeletal system but also of the visceral organs, resulting in **organomegaly**
- Stimulates the liver to secrete **insulin-like growth factor-1** (**IGF-1**), which mediates many of the anabolic actions of GH (Fig. 3-18)

**Pathology note:** Excess GH levels may cause abnormal increased longitudinal bone growth before epiphyseal plate closure and may result in **gigantism**, whereas a deficiency of GH may cause **pituitary dwarfism**. After closure of the epiphyseal plate, longitudinal bone growth does not occur. However, transverse bone growth (i.e., thickening) in response to GH can continue throughout adulthood and occurs in **acromegaly**.

2. **Metabolic actions**

- GH acts on muscle, adipose tissue, and liver to promote fat metabolism, enhance protein synthesis, and preserve body carbohydrate.
- **Stimulates lipolysis in adipose tissue**, which increases the delivery of “combustible” fatty acids to the cells of the body.
- Simultaneously inhibits protein breakdown and stimulates new protein synthesis in skeletal muscle.
- Finally, it conserves body stores of carbohydrate by **stimulating hepatic gluconeogenesis** and **preventing glucose utilization** by the peripheral tissues, which forces them to burn fats (see Fig. 3-18).
These actions are helpful in stressful conditions such as fasting or starvation.

- Plasma glucose is preserved for the insulin-independent tissues, such as the CNS (to maintain consciousness), and skeletal muscle protein is preserved as much as possible.
- Notice that these actions essentially are antagonistic to those of insulin.

- Prolonged exposure to excessive levels of GH may therefore cause hyperglycemia and even overt diabetes mellitus, which is why GH (like cortisol) is considered a diabetogenic hormone.
- Note that in rare states of GH deficiency, chronic hypoglycemia may develop.

3. Regulation of secretion

- GH is secreted from pituitary somatotrophs mainly during sleep but also in response to other stimuli, such as various forms of stress caused by fasting or hypoglycemia.
- Secretion is regulated by hypothalamic growth hormone–releasing hormone (GHRH), which stimulates GH release, and by somatostatin, which inhibits GH release.
- The IGF-1 that is produced in response to GH stimulation of the liver also influences the hypothalamus and anterior pituitary by feedback inhibition.

Clinical note: GH is a diabetogenic hormone that acts to increase plasma glucose levels. GH secretion is in turn suppressed by increased plasma glucose levels, a fact that can be exploited clinically when evaluating patients with a suspected GH-hypersecreting pituitary adenoma. In the growth hormone suppression test, an oral load of glucose (typically 75 to 100 g) is rapidly administered. This will increase plasma glucose levels, which should inhibit GH secretion and IGF-1 (more sensitive than GH) in a healthy adult. If plasma levels of GH do not decrease substantially (to less than 2 ng/mL) in response to the glucose load, a GH-hypersecreting pituitary adenoma is indicated, which may facilitate a diagnosis of gigantism or acromegaly.
As one might expect, because hyperglycemia inhibits GH secretion, hypoglycemia stimulates its secretion. This fact can also be exploited in cases of suspected GH hyposecretion by intentionally provoking hypoglycemia by administering insulin. Needless to say, this should only be performed under careful monitoring in a hospitalized setting. The failure of GH secretion to increase following provoked hypoglycemia is evidence of pituitary GH hyposecretion or panhypopituitarism, or both.

Pharmacology note: Octreotide, a synthetic somatostatin analogue, is used to treat GH-secreting tumors of the anterior pituitary.

III. Hormonal Control Systems of the Posterior Pituitary

A. Overview
1. The posterior pituitary is composed of axonal extensions from several of the hypothalamic nuclei.
2. The axonal terminals of these neurons secrete posterior pituitary hormones, and their activity is independent of hypothalamic releasing hormones.

B. Hormones of the posterior pituitary
1. Antidiuretic hormone (ADH, arginine vasopressin, vasopressin)
   - **Physiologic actions**
     a. Stimulates free water reabsorption by the kidneys (concentrates urine), which increases plasma volume and decreases plasma osmolarity.
     b. At higher concentrations, also promotes systemic vasoconstriction and increased arterial blood pressure.
   - **ADH secretion**
     a. Regulated by hypothalamic osmoreceptors.
     b. These specialized cells either shrink or swell in response to changing plasma osmolarity, respectively triggering or inhibiting ADH secretion.
     c. Although ADH secretion occurs in response to only slight increases in plasma osmolarity, marked reductions in plasma volume (see Fig. 4-43 in Chapter 4), as might occur with hemorrhage and severe dehydration, can also trigger substantial ADH secretion.
   - **Pathophysiology of diabetes insipidus (DI)**
     a. Caused by a deficiency of functional ADH (central DI) or by tissue insensitivity (collecting tubule) to circulating ADH (nephrogenic DI).
     b. Characterized by production of large volumes of dilute urine as the result of inability of the kidneys to reabsorb water and concentrate urine.
     - Kidneys are always diluting and never concentrating urine.

Clinical note: Diabetes insipidus is more common in the population than many suppose. Just think of all the frequent water drinkers you might know. These individuals may have diabetes insipidus but despite making large amounts of dilute urine each day, because they ingest large amounts of water and ingest adequate amounts of effective osmoles, they do not become dehydrated or develop hypernatremia. However, once these individuals become elderly, when their thirst mechanism may become impaired, they are more susceptible to developing diabetes insipidus. Then take these individuals and place them in the intensive care unit or a nursing home, where they will not have unfettered access to water, and full-blown signs and symptoms of diabetes insipidus (e.g., hypernatremia, altered mental status, respectively) may develop.

c. Central diabetes insipidus
   - Impaired ADH secretion from hypothalamus
   - Responds to administration of synthetic ADH (i.e., urine becomes concentrated)

d. Nephrogenic diabetes insipidus
   - Renal resistance to ADH
   - Will not respond to synthetic ADH
   - Commonly caused by long-term lithium use
Clinical note: Central diabetes insipidus can be caused by head trauma, hypothalamic lesions, neoplasms, and gene mutations in the vasopressin gene. Patients with central diabetes insipidus will be responsive to exogenously administered ADH, because there is nothing wrong with their kidneys. In contrast, patients with nephrogenic diabetes insipidus will not respond to ADH. This difference in responsiveness serves as the basis for clinical differentiation between these two etiologies. For example, if one administers ADH to a patient and the urine becomes concentrated, the patient has central DI; whereas if there is no effect on urine concentration, the patient has nephrogenic DI.

- Pathophysiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)
  a. In certain pathologic situations (e.g., pronounced pain, nausea, various medications, pulmonary infections), the posterior pituitary may secrete excessive amounts of ADH irrespective of plasma osmolarity or plasma volume.
  b. Alternatively, ectopic secretion of ADH can occur from tumors such as small cell lung cancer.
  c. Regardless of the cause, increased levels of ADH will cause excessive free water reabsorption by the kidneys, resulting in reduced plasma osmolarity and dilutional hyponatremia.
  
  - In SIADH, the patient is always concentrating urine and never diluting urine.
  d. Urine osmolality will be inappropriately concentrated given the low plasma sodium concentration.
  - One would expect a positive free water clearance in the setting of hyponatremia; however, in SIADH, it is frequently negative, indicating inappropriate urine concentration (see Chapter 6).

2. Oxytocin
- Promotes uterine contractions in response to dilation of the cervix during labor
- Stimulates contraction of myoepithelial cells of the breast in response to suckling during breastfeeding
- Secretion often stimulated simply by the sight and sounds of a newborn

Pharmacology note: Oxytocin is often administered during labor to augment labor. It is also given to reduce postpartum hemorrhage, because the uterine contractions it stimulates clamp down on the uterine blood vessels, thereby minimizing blood loss.

IV. Hormonal Control Systems Independent of Pituitary Regulation
A. Endocrine pancreas
1. Comprises the islets of Langerhans, a cluster of specialized endocrine cells that secrete various hormones important in metabolism
2. The main specialized cell types are the α cells that secrete glucagon, the β cells that secrete insulin, and the δ cells that secrete somatostatin (Table 3-10).
3. Insulin
- Key hormone of the fed state.
- Mechanism of action
  a. As a peptide hormone, insulin acts by binding to a cell surface receptor, the tyrosine kinase receptor.
  b. Insulin stimulates a wide variety of intracellular events, such as the insertion of glucose transporters (GLUT4) into cell membranes of skeletal muscle and adipose tissue and the transcriptional stimulation of genes involved in glycolysis.
  c. Onset of the effects of insulin is immediate for some (e.g., GLUT4 insertion into membranes) but can take hours or days for others (e.g., new protein synthesis).

<table>
<thead>
<tr>
<th>TABLE 3-10. Physiologic Actions of Pancreatic Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELL TYPE</strong></td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>α</td>
</tr>
<tr>
<td>β</td>
</tr>
<tr>
<td>δ</td>
</tr>
</tbody>
</table>

SIADH: common in hospitalized patients; triggered by pain, medications, lung infections and tumors

Oxytocin: promotes uterine contractions and milk letdown

Islets of Langerhans: β cells secrete insulin; α cells secrete glucagon; δ cells secrete somatostatin
**Metabolic actions** (Table 3-11; Fig. 3-19)

a. The principal role of insulin is to **maintain plasma glucose levels** within normal ranges.

b. The major **stimulus** for insulin secretion is **plasma glucose**, with increasing plasma glucose levels stimulating proportionally more insulin secretion.
   * Note that amino acids and hyperkalemia also stimulate insulin secretion, but less potently so than elevated plasma glucose.

c. The major **inhibitor** of insulin secretion is **low plasma glucose**.
   * Because $K^+$ is cotransported into cells with glucose, hypokalemia also inhibits insulin secretion.

d. Insulin **stimulates glucose uptake** in various target tissues, especially skeletal muscles and adipose tissue.

e. Insulin also **stimulates glycolysis** and various anabolic pathways, including the synthesis of glycogen (**glycogenesis**), fat (**lipogenesis**), cholesterol, and protein.

f. Certain tissues, such as the CNS, utilize glucose as their primary energy source and are able to take up glucose **without** the assistance of insulin.

---

**TABLE 3-11. Actions of Insulin on Target Tissues**

<table>
<thead>
<tr>
<th>TARGET TISSUE</th>
<th>STIMULATES</th>
<th>INHIBITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose</td>
<td>Fatty acid uptake, triglyceride synthesis and storage, glucose uptake</td>
<td>Lipolysis</td>
</tr>
<tr>
<td>Liver</td>
<td>Glycolysis, glycogenesis, amino acid and glucose uptake, fat synthesis, cholesterol synthesis</td>
<td>Gluconeogenesis, β-oxidation of fatty acids, ketogenesis</td>
</tr>
<tr>
<td>Muscle</td>
<td>Glucose uptake, glycogenesis, glycolysis, protein synthesis</td>
<td>Protein catabolism</td>
</tr>
</tbody>
</table>

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3-19: Regulation of insulin secretion and physiologic actions of insulin. GLUT-2 is insulin-independent. GH, Growth hormone; GI, gastrointestinal; GLUT, glucose transporter; TG, triglyceride; VLDL, very-low-density lipoprotein.
• This ability becomes critically important during the fasting state, when plasma levels of insulin (and sometimes glucose) are low.

- When insulin levels are low, the skeletal muscles, adipose tissue, and liver do not take up significant amounts of glucose; this preserves glucose for insulin-independent tissues such as the CNS.

- In capillary endothelial cells, insulin stimulates the synthesis of the enzyme capillary-lipoprotein lipase (CPL), which liberates free fatty acids from very-low-density lipoproteins (VLDL) and chylomicrons and allows these fatty acids to enter adipocytes, where they are used to synthesize triglycerides.

**Pharmacology note:** A class of drugs known as the fibrin acid derivatives (e.g., clofibrate, gemfibrozil) reduces plasma triglyceride levels by stimulating lipoprotein lipase synthesis, causing increased clearance of triglyceride. This is important because elevated triglycerides, like low-density lipoprotein (LDL) cholesterol, are a risk factor for development of coronary artery disease. Extremely high levels of triglycerides are also a risk factor for pancreatitis.

**Clinical note:** Because glucose and potassium are simultaneously cotransported into cells, insulin stimulates potassium uptake. This effect is often exploited therapeutically in patients with hyperkalemia, in whom injection of insulin can reduce the plasma potassium level significantly.

- **Pathophysiology of type 1 diabetes mellitus**
  a. The primary defect in type 1 diabetes mellitus (previously termed insulin-dependent diabetes mellitus, or IDDM) is a deficiency of insulin, typically caused by autoimmune and antibody destruction of the pancreatic β cells.
  b. Because insulin is cosecreted with C peptide by pancreatic β cells, plasma levels of C peptide are typically low in type 1 diabetes, because these patients have few functional β cells.
  c. The insulin deficiency causes hyperglycemia.
  d. The resulting increased glucose “load” delivered to the kidneys may result in loss of glucose in the urine, resulting in glucosuria, osmotic diuresis, and polyuria.
    - This diuresis in turn stimulates thirst (polydipsia).
  e. In addition, because insulin is a potent anabolic hormone, a catabolic state characterized by unintentional weight loss and muscle wasting occurs.
  f. This causes an increase in appetite (polyphagia).
  g. Together, these phenomena account for the clinical presentation of type 1 diabetes mellitus: polyuria, polydipsia, and unintentional weight loss with polyphagia.
    - Although the classic presentation for type 1 diabetes mellitus is weight loss, polydipsia, and polyuria, these patients often present initially in diabetic ketoacidosis (DKA), as discussed next.

- **Diabetic ketoacidosis**
  a. DKA is characterized by hyperglycemia, volume depletion, and acidosis.
  b. It is caused by an absolute deficiency of the anabolic hormone insulin.
  c. DKA can occur in type 1 diabetic patients who are noncompliant with their insulin regimen, or it can be triggered by stressors such as infection.
  d. In the absence of insulin, “runaway” lipolysis and β-oxidation occur in adipose tissue and liver, respectively.
    - Moreover, the lipolysis in adipose tissue continues to “feed” β-oxidation precursors to the liver, which metabolizes these fatty acids to ketone bodies.
  e. Several of these ketone bodies are acids (e.g., acetone) that reduce the plasma pH and cause an anion gap metabolic acidosis.
  f. This acidosis is further exacerbated by the hyperglycemia, because the hyperglycemia causes an osmotic diuresis, which results in volume depletion.
    - With plasma volume contraction, the glomerular filtration rate (GFR) drops, and the kidneys are less able to excrete acid.

**Clinical note:** Patients presenting with DKA are typically volume depleted, have an increased anion gap metabolic acidosis, and are hyperkalemic despite reduced body stores of potassium (this is due to the transcellular shift of K⁺ for H⁺ ions, which occurs for a variety of reasons, e.g., solvent drag effect).
These patients need sodium-containing fluids (to expand plasma volume), insulin (to treat the hypoglycemia), and perhaps potassium, in that order. If their initial potassium level is quite high and associated with electrocardiographic changes (peaked T waves), emergent calcium gluconate with or without subcutaneous insulin should be administered to prevent cardiac arrhythmias.

Pathophysiology of type 2 diabetes mellitus

a. The primary defect in type 2 diabetes mellitus (previously termed non–insulin-dependent diabetes mellitus, or NIDDM) is insulin resistance: the abnormal resistance of target tissues (e.g., muscle, adipose tissue) to circulating insulin.
   - This resistance is particularly common in obese persons, because an increase in adipose causes down-regulation of insulin receptor synthesis.
   - Another even more important mechanism for insulin resistance is postreceptor abnormalities (e.g., tyrosine kinase defects; GLUT4 abnormalities).

b. Insulin levels are initially elevated in type 2 diabetes, although it should be realized that they are still relatively deficient given the degree of hyperglycemia; C-peptide and pro-insulin levels may also be elevated in early diabetes.

c. As type 2 diabetes mellitus progresses, a secondary defect, β-cell dysfunction with impaired insulin secretion, begins to play a greater role.
   - There are various speculations as to why this happens, including pancreatic exhaustion, glucotoxicity, and amylin deposition in the islets.

d. DKA does not typically occur in type 2 diabetes, because the insulin that is present is capable of inhibiting hepatic ketogenesis but not abundant enough to prevent hyperglycemia.
   - However, if the diabetes is poorly managed or a major illness (e.g., pneumonia) ensues, plasma glucose and plasma osmolarity may become pathologically elevated, resulting in signs and symptoms.
   - This is termed hyperosmolar hyperglycemic nonketotic coma (HHNC), although the most recent terminology is hyperosmolar hypertonic syndrome (HHS).
   - HHS is caused by severe volume depletion that is caused by a prolonged hyperglycemic diuresis in which compensatory fluid intake is inadequate.

(1) Elderly patients with type 2 diabetes are particularly susceptible to HHS because of inadequate fluid intake and preexisting renal disease (i.e., renal glucose clearance is already compromised).

Clinical note: Plasma levels of C peptide are typically high in the early stages of type 2 diabetes, because type 2 diabetes is characterized by insulin resistance and hyperinsulinemia. Therefore, plasma levels of C peptide can help distinguish between type 1 and type 2 diabetes. However, this is an imperfect test, given that fairly high levels of C peptide may be present in type 1 diabetics diagnosed very early, and fairly low levels in type 2 diabetics diagnosed very late, after the β cells have started “failing.”

Clinical note: Plasma C peptide levels can also help determine the cause of hypoglycemia. For example, in a malingering patient who injects insulin (exogenous sources of insulin do not contain C-peptide) to cause hypoglycemia, plasma levels of C peptide will be very low (insulin synthesis is suppressed by hypoglycemia). In contrast, a patient with a rare insulin-secreting tumor (insulinoma) will have high plasma levels of C peptide and insulin.

Pharmacology note: One way to reduce plasma glucose is to stimulate the β cells to secrete more insulin. The sulfonylurea drugs (e.g., tolbutamide, glyburide) stimulate insulin secretion by closing membrane-spanning K⁺ channels on pancreatic β cells, resulting in depolarization, followed by calcium influx that triggers insulin secretion. These drugs are primarily useful in type 2 diabetes, because their mechanism of action is dependent on the presence of functional β cells. However, these drugs carry a significant risk for hypoglycemia, and their misuse often leads to a visit to the emergency department.

4. Glucagon
   - Primary hormone of the fasting state
   - Like insulin, glucagon is a primary regulator of plasma glucose homeostasis.
Glucagon functions primarily to increase plasma glucose levels, thereby opposing the actions of insulin.

**Regulation of secretion**

a. Paradoxically, the primary stimulus for glucagon secretion from islet cells is amino acids rather than low plasma glucose.
b. However, glucagon secretion is also stimulated by low plasma glucose levels and inhibited by high levels.

**Physiologic actions**

a. At physiologic concentrations in the fasting state, glucagon primarily promotes hepatic glycogenolysis and gluconeogenesis.
b. Glucagon further stimulates β-oxidation of fats by the liver, which liberates energy that can be used to support hepatic gluconeogenesis.
c. Glucagon exerts only minimal metabolic actions on adipose tissue and muscle.

These actions include stimulation of lipolysis in adipose tissue and inhibition of glucose utilization by the peripheral tissues.

**Pathology note:** Given its secretion directly into the portal circulation, glucagon normally has minimal extrahepatic actions because of the first-pass effect, whereby it is largely inactivated by the liver. Increased glucagon levels may be associated with a rare tumor of the islet α cells termed a glucagonoma. At higher glucagon levels, the extrahepatic effects may become significant, and many of these patients will present with hyperglycemia.

### B. Adrenal mineralocorticoids

1. **Aldosterone** is the primary mineralocorticoid secreted from the adrenal gland.

2. **Physiologic actions of aldosterone**

   • The main function of aldosterone is to maintain intravascular volume and thereby maintain arterial blood pressure and adequate organ perfusion.

   • Aldosterone acts on the kidneys to stimulate sodium (and therefore water) reabsorption, potassium secretion, and hydrogen ion secretion.

   • The net effect is an increase in blood pressure through stimulation of plasma volume expansion.

   • If high levels of aldosterone are present (e.g., aldosterone-secreting adrenal adenoma), this may also result in pathologically elevated blood pressure (hypertension), hypokalemia, and a metabolic alkalosis.

3. **Regulation of aldosterone secretion**

   • Aldosterone is primarily secreted in response to increasing plasma levels of angiotensin II and potassium.

   • ACTH has only a minimal effect on aldosterone synthesis.

### C. Adrenal catecholamines

1. **Overview**

   • The adrenal catecholamines include epinephrine, norepinephrine, and dopamine, which are all synthesized from the amino acid tyrosine in the adrenal medulla.

   • These agents are responsible for the physiologic manifestations of the fight-or-flight response, in which a severe threat to life elicits a coordinated physiologic response to counter that threat.

   • All catecholamines have short half-lives (seconds), so their effects are short lived.

   • Epinephrine is synthesized and secreted by the adrenal gland in much larger amounts than either norepinephrine or dopamine, and it is responsible for the major catecholamine-mediated physiologic responses resulting from sympathetic stimulation of the adrenal medulla.

   • **Note:** Norepinephrine is the catecholamine released by postganglionic nerves of the sympathetic nervous system.

2. **Physiologic actions of catecholamines** (Fig. 3-20)

   - **Cardiovascular effects**
     a. Blood pressure is increased, because catecholamines increase heart rate and cardiac contractility by stimulating β1-adrenergic receptors.
     b. Catecholamines also cause peripheral vasoconstriction by stimulating α1-adrenergic receptors on vascular smooth muscle cells, which increases peripheral vascular resistance and further increases arterial pressure.
Catecholamines simultaneously stimulate vasodilation in skeletal muscle by stimulating \( \beta_2 \)-adrenergic receptors, allowing greater blood flow to active muscles.

- Metabolic effects
  a. Catecholamines are like other “stress” hormones such as cortisol and function to maintain adequate levels of plasma fuels such as glucose and free fatty acids.
  b. For example, epinephrine potently stimulates glycogenolysis and gluconeogenesis in the liver, as well as lipolysis in adipose tissue.

3. Regulation of secretion of epinephrine
   - The secretion of epinephrine by the adrenal medulla is under the control of the autonomic nervous system.
   - Preganglionic fibers of the sympathetic division of the autonomic nervous system synapse on chromaffin cells of the adrenal medulla and stimulate them to synthesize and release catecholamines.
   - A major stimulus of epinephrine secretion is hypoglycemia.
   - The surge in epinephrine stimulates glycogenolysis and gluconeogenesis in the liver.

Pathology note: Chromaffin cell tumors of the adrenal medulla, or of sites along the tract by which neural crest cells migrate to form the adrenal medulla, can arise and secrete large quantities of catecholamines. These tumors often release catecholamines in spurs, causing symptomatic episodes of hypertension, tachycardia, palpitations, sweating, and headache. Catecholamines are degraded to metanephrines and vanillylmandelic acid; therefore, increased urine levels of these metabolites may be used to diagnose a pheochromocytoma. Definitive treatment of a pheochromocytoma is surgical excision.

V. Calcium and Phosphate Homeostasis: Parathyroid Hormone (PTH), Vitamin D, and Calcitonin
   A. Calcium homeostasis
      1. The body maintains plasma calcium levels within a narrow range because of the adverse effects caused by abnormally reduced or elevated levels of calcium.
2. The endocrine regulation of calcium depends mainly on the actions of PTH and calcitriol (active vitamin D).
3. A third hormone, calcitonin, contributes minimally to calcium homeostasis.
4. Most calcium (approximately 99%) is found in the bones.
5. Aside from playing an important structural role, this calcium serves as a large reservoir to replenish and maintain plasma calcium levels.
6. Within the plasma, calcium exists either as free ionized calcium or as bound calcium associated with plasma proteins such as albumin.
   - The ionized calcium is biologically active, and it is this portion of total body calcium that is tightly regulated by the hormones PTH, calcitriol, and calcitonin.
   - The percentage of plasma calcium that exists as free ionized calcium can be altered by changes in plasma pH and plasma protein levels.
   - Alkalosis tends to decrease free ionized calcium, mainly because of greater calcium binding to negatively charged sites on albumin, and acidosis tends to increase ionized calcium.
   - Changes in plasma protein levels (particularly albumin) are more likely to affect total plasma calcium than ionized calcium.
     a. For example, total plasma calcium levels are decreased in hypoalbuminemia, but the levels of free ionized calcium are normal.
     b. Therefore, before making a diagnosis of hypocalcemia, one should consider excluding hypoalbuminemia; hyperalbuminemia is so rare that it need not be considered in hypercalcemia.
7. Calcium stabilizes membrane potentials; therefore, hypocalcemia can lead to various manifestations of enhanced membrane excitability, including muscle spasms (tetany), cardiac arrhythmias, and seizures.
8. Hypercalcemia, on the other hand, reduces membrane excitability, leading to such manifestations as muscle weakness and stupor.

Clinical note: Students should be familiar with the many causes of hypercalcemia, always a board favorite. The two most common causes include primary hyperparathyroidism in outpatients and hypercalcemia of malignancy in ill hospitalized patients. Other causes of hypercalcemia include milk-alkali syndrome, granulomatous diseases such as tuberculosis and sarcoidosis, lymphoma, paraneoplastic syndromes in which there is ectopic secretion of PTH-related protein (PTHrP), vitamin D toxicity, and familial hypocalciuric hypercalcemia.

B. Parathyroid Hormone (Fig. 3-21)
1. PTH functions to increase plasma calcium and to decrease plasma phosphate and bicarbonate.
2. PTH is released by parathyroid chief cells, mainly in response to hypocalcemia, but also in response to hyperphosphatemia.
3. PTH causes bone resorption, which liberates calcium into the plasma, and stimulates renal calcium reabsorption.
4. PTH further stimulates the synthesis of 1,25-dihydroxyvitamin D₃ (calcitriol) by the kidneys by increasing the synthesis of 1α-hydroxylase in proximal tubule cells; it is this active form of vitamin D (calcitriol) that increases calcium absorption in the intestines.

Clinical note: Because PTH stimulates bone resorption, conditions such as primary hyperparathyroidism are associated with bone loss, osteoporosis, and pathologic fractures. Paradoxically, recent trials have shown that the intermittent administration of PTH actually stimulates new bone synthesis and prevents bone loss.

Pathology note: Primary hyperparathyroidism can result in several adverse manifestations. Excessive bone resorption can cause osteoporosis as well as cysts in areas of extensively demineralized bone; this latter condition is referred to as osteitis fibrosa cystica. Hypercalcemia can cause renal calculi (most common symptomatic presentation) as well as weakness and mental status changes. These manifestations are responsible for the clinical description of hyperparathyroidism: “stones, bones, groans, and psychological overtones.” A hypersecreting adenoma of one of the parathyroid glands is the most common cause of primary hyperparathyroidism.
1. 1,25-Dihydroxyvitamin D$_3$ (calcitriol) is the metabolically active form of vitamin D.

2. Vitamin D ingested in the diet or formed in the skin from exposure to sunlight must first be converted to 25-hydroxyvitamin D (calcidiol) in the liver and then to its metabolically active form, 1,25-dihydroxyvitamin D$_3$, in the kidneys.

3. PTH stimulates the synthesis of 1,25-dihydroxyvitamin D$_3$ in the kidneys by increasing the synthesis of the enzyme 1α-hydroxylase in the proximal tubules (Fig. 3-22).

4. Calcitriol affects calcium homeostasis in the following ways:
   - Most important, it stimulates calcium and phosphate absorption in the intestine.
   - To a lesser extent, it stimulates calcium and phosphate reabsorption in the kidneys.
   - It also stimulates calcium mobilization from bone.

**Pathology note:** Osteoclastogenic molecules such as PTH and calcitriol act on stromal cells and osteoblasts to produce RANKL (receptor for activation of nuclear factor kappa B). RANKL, in turn, interacts with its receptors on mononuclear progenitors of the monocyte-macrophage family, causing them to fuse together to become multinucleated cells known as osteoclasts.
Pathology note: Although calcitriol stimulates bone resorption, its indirect effects on stimulating bone mineralization appear to outweigh its direct effects on stimulating bone resorption, given that vitamin D deficiencies result in conditions associated with impaired bone mineralization. For example, inadequate vitamin D levels in children lead to rickets, in which the bones are inadequately mineralized and the weight placed on them causes bowing of the legs and increased unmineralized osteoid in the epiphyses of the ribs (rachitic rosary) and skull (craniotabes). In adults, vitamin D deficiency weakens the bones, predisposing to fractures; in these cases, the disease is referred to as osteomalacia. Vitamin D probably stimulates bone mineralization because of its actions to increase plasma calcium and phosphate levels, which facilitates plasma calcium deposition into newly formed bone.

D. Phosphate homeostasis
1. Phosphate levels are less tightly controlled than plasma calcium levels, because similar shifts in plasma phosphate do not tend to produce serious adverse effects.
2. Phosphate is important in normal bone mineralization.
   • Without adequate levels of phosphate, osteoid calcification cannot occur, leading to osteomalacia (soft bone).
   • This explains why normal children have higher serum phosphate levels than adults in order to mineralize their rapidly growing bone.
3. PTH and phosphate (see Table 3-12)
   • By stimulating bone resorption, PTH causes both calcium and phosphate to be released into the plasma.
   • The released phosphate can complex with calcium and decrease plasma calcium levels.

Pathology note: In pathologic conditions such as hypercalcemia or renal failure associated with hyperphosphatemia, the level of the calcium-phosphate “product” can be so high that calcium-phosphate deposition occurs throughout the tissues; this pathologic process is referred to as metastatic calcification (refers to calcium depositing in normal tissue, e.g., basement membrane of collecting tubules, skin).

- Hypocalcemia does not typically result, however, because PTH also inhibits phosphate reabsorption by the proximal tubules, thus causing greater renal excretion of phosphate.

4. 1,25-Dihydroxyvitamin D<sub>3</sub> and phosphate (see Table 3-12 and Fig. 3-21)
   • 1,25-Dihydroxyvitamin D<sub>3</sub> stimulates intestinal absorption of both calcium and phosphate and, in contrast to PTH, stimulates renal phosphate reabsorption.
   • In turn, increased levels of phosphate inhibit renal 1,25-dihydroxyvitamin D<sub>3</sub> synthesis through a negative-feedback mechanism.
   • In addition, the active form of vitamin D inhibits further vitamin D synthesis, another negative-feedback mechanism.
Clinical note: Hypocalcemia often develops in patients with chronic renal failure because of disruptions in several mechanisms. When renal tissue is destroyed, less 1,25-dihydroxyvitamin D$_3$ is synthesized by the kidney, resulting in less calcium absorption in the intestine. This is the primary mechanism for the development of the hypocalcemia. In addition, less phosphate is excreted because of reduced renal filtration, causing phosphate to accumulate. This phosphate can complex with plasma calcium and decrease ionized calcium levels. The increased plasma phosphate further inhibits the already compromised renal synthesis of 1,25-dihydroxyvitamin D$_3$.

Parathyroid secretion of PTH is strongly stimulated by hypocalcemia. When PTH is secreted at increased amounts in response to hypocalcemia, it is referred to as secondary (or compensatory) hyperparathyroidism. The excess PTH can cause severe bone wasting in patients with renal disease. The reduced vitamin D synthesis in renal failure and its attendant hypocalcemia contribute to bone wasting. Both of these processes contribute to renal osteodystrophy. In severe cases of renal osteodystrophy, diffuse cystic areas of demineralized bone (osteitis fibrosa cystic) may occur.
I. Cardiac Mechanics
   A. Cardiac cycle: composed of systole and diastole
      1. Systole
         • Systole is that part of the cardiac cycle in which the heart contracts and blood is ejected.
         • In atrial systole, the atria pump blood into the relaxed ventricles, whereas in ventricular systole, the ventricles pump blood into the blood vessels.
         • Blood pressure is greatest during systole and is referred to as the systolic blood pressure (SBP).
      2. Diastole
         • Diastole is that part of the cardiac cycle in which the heart relaxes and fills with blood.
         • Blood pressure is lowest during diastole and is referred to as the diastolic blood pressure (DBP).
         • The pulse pressure is the difference between the systolic and diastolic pressures. A typical value is approximately 40 mm Hg, as shown below.
           \[
           \text{Pulse pressure} = \text{SBP} - \text{DBP} = 120\text{mm Hg} - 80\text{mm Hg} = 40\text{mm Hg}
           \]
           
           **Clinical note:** Pulse pressure may be increased in conditions such as hyperthyroidism (increased systolic pressure and decreased diastolic pressure) and aortic regurgitation (increased systolic pressure and decreased diastolic pressure) and decreased in conditions such as aortic stenosis (decreased systolic pressure).
   B. Heart valves
      • Function to establish one-way flow of blood in the heart (Fig. 4-1)
      1. Atrioventricular valves: mitral and tricuspid valves
         • The atrioventricular (AV) valves prevent blood from flowing back into the atria during ventricular systole.
         • The mitral (bicuspid) valve prevents backflow from the left ventricle into the left atrium.
         • The tricuspid valve prevents backflow from the right ventricle into the right atrium.
      2. Semilunar valves: aortic and pulmonic valves
         • The semilunar valves separate the left ventricle from the aorta.
         • The pulmonic valve separates the right ventricle from the pulmonary artery.
         • Both valves normally have three cusps.
   C. Principal heart sounds
      • Reflect valve closure and/or pathologic states
      1. S1: closure of AV valves
         • Produced by closure of the AV valves in early systole as a result of the rapidly increasing ventricular pressure
         • Heard loudest at the apex
- Has **mitral (M₁) and tricuspid (T₁)** components that do not vary with the respiratory cycle (i.e., S₁ split during inspiration or expiration is not normal).
- Mitral valve closes just before the tricuspid (0.01 second before).
- Closure of these valves is therefore interpreted as a single sound on auscultation.

**Clinical note:** In certain circumstances, S₁ may be accentuated. This occurs when the valve leaflets are “slammed” shut in early systole from a greater than normal distance because they have not had time to drift closer together. Three conditions that can result in an accentuated S₁ are a shortened PR interval, mild mitral stenosis, and high cardiac-output states or tachycardia.

2. **S₂:** closure of semilunar valves
   - Produced by closure of the semilunar valves in early diastole
   - Diastolic pressures in the aorta and pulmonary artery exceed the pressures in the relaxing ventricles, causing the semilunar valves to close.
   - Has aortic (A₂) and pulmonic (P₂) components (A₂:P₂), which vary with the respiratory cycle (Fig. 4-2)
   - During inspiration, when intrathoracic pressures decrease, the reduced pulmonary artery pressure decreases the back pressure responsible for pulmonic valve closure, resulting in delayed closure of the pulmonic valve and a “split” S₂.
     a. Furthermore, despite the increased preload, for unclear reasons the aortic valve closes earlier during inspiration.
     b. S₂ can be best appreciated on auscultation at the 2nd or 3rd left intercostal space.

**Clinical note:** Paradoxical or “reversed” splitting occurs when S₂ splitting occurs with expiration and disappears on inspiration. Moreover, in paradoxical splitting, the pulmonic valve closes before the aortic valve, such that P₂ precedes A₂. The most common cause is left bundle branch block (LBBB). In LBBB, depolarization of the left ventricle is impaired, resulting in delayed left ventricular contraction and aortic valve closure.

3. **S₃:** ventricular gallop
   - An S₃ is sometimes heard in early to middle diastole, during rapid ventricular filling.
Caused by a sudden limitation of ventricular expansion (some authors believe it is caused by sudden tensing of the chordae tendineae)

May be normal in children and young adults but usually represents disease in older adults

Typically caused by a **volume-overloaded heart**, as may be seen in congestive heart failure or advanced mitral regurgitation, in which the rate of early diastolic filling is increased

**Clinical note:** An \( S_3 \) is usually caused by volume overload in congestive heart failure. It can also be associated with valvular disease, such as advanced mitral regurgitation, in which the “regurgitated” blood increases the rate of ventricular filling during early diastole.

- Caused by atrial contraction against a stiff ventricle, often heard after an acute myocardial infarction

**Clinical note:** An \( S_4 \) usually indicates decreased ventricular compliance (i.e., the ventricle does not relax as easily), which is commonly associated with ventricular hypertrophy or myocardial ischemia. An \( S_4 \) is almost always present after an acute myocardial infarction. It is loudest at the apex with the patient in the left lateral decubitus position (lying on their left side).

4. \( S_4 \): atrial gallop

- An \( S_4 \) is sometimes heard in late diastole and is caused by atrial contraction against a stiffened (noncompliant) ventricle.
- An \( S_4 \) almost always indicates **cardiac disease** and should be further evaluated; it is commonly noted during or shortly after an acute myocardial infarction.

**Clinical note:** An \( S_4 \) is sometimes heard in late diastole and is caused by atrial contraction against a stiffened (noncompliant) ventricle.

4. Systole
   - \( S_1 \): due to closure of AV valves in early systole from \( \\uparrow \) ventricular pressure
   - \( S_2 \): due to closure of semilunar valves in early diastole because pulmonic/aortic pressures exceed intraventricular pressures

D. **Ventricular pressure changes during the cardiac cycle** (Fig. 4-3)

- During diastole, the ventricles gradually increase in volume, causing **ventricular pressures to gradually increase** (A).
- The slight “hump” before systole (B) represents **atrial contraction** in the final “topping off” phase of ventricular filling.
- When systole begins, the increasing ventricular pressures close the AV valves (C).
- Pressure continually builds until the ventricular pressure exceeds that of the aorta (left ventricle) or the pulmonary artery (right ventricle) (D).
- The aortic valve (left ventricle) or the pulmonic valve (right ventricle) then opens (E).
- Blood is ejected into the circulation (F).
- After the ventricles have finished contracting, they begin to relax, and **intraventricular pressures decrease**.
  a. When the intraventricular pressure is less than the aortic pressure (left ventricle) or the pulmonary artery pressure (right ventricle), the aortic and pulmonic valves close (G).
  b. After closure of the semilunar valves, the ventricles continue to relax, and intraventricular pressures continue to decrease (H).
Once intraventricular pressures are less than atrial pressures, the AV valves open (I), and the ventricular filling of diastole begins again.

**Note:** The normal phonocardiogram in Figure 4-3 parallels the ventricular pressure curve.

a. S1 occurs at the beginning of systole with AV valve closure (C), and S2 occurs at the beginning of diastole with semilunar valve closure (G).

b. If an S3 were present, it would occur in early diastole, because it is caused by rapid ventricular filling.

c. If an S4 were present, it would occur in late diastole, because it is caused by atrial contraction against a stiff ventricle.

**Note:** Rapid ventricular filling occurs in the early part of diastole, when the pressure gradients for blood flow between the pulmonary veins and left ventricle are greatest and the mitral valve is wide open.

II. Cardiac Performance

- Cardiac performance is often assessed by measuring the cardiac output, which is the volume of blood pumped out of the heart each minute.

A. **Cardiac output**

1. Cardiac output (CO) is the **product of heart rate** (HR) and **stroke volume** (SV).

2. HR is primarily under the influence of the autonomic nervous system.

3. In a healthy adult, the CO is approximately 5 L/minute:

   \[
   \text{CO} = \text{HR} \times \text{SV}
   \]

   \[
   = 70 \text{ beats/minute} \times 70 \text{ mL/beat}
   \]

   \[
   = 4900 \text{ mL/minute}, \text{ or } 4.9 \text{ L/minute}
   \]

4. CO can also be calculated by measuring whole body oxygen consumption.

   - The **Fick principle** states that oxygen consumption by the body is a function of the amount of blood delivered to the tissues (cardiac output, CO) and the amount of \( \text{O}_2 \) extracted by the tissues (arteriovenous \( \text{O}_2 \) difference):

   \[
   \text{O}_2 \text{ consumption} = \text{CO} \times ([\text{O}_2]_a - [\text{O}_2]_v)
   \]

   where \([\text{O}_2]_a\) = arterial \( \text{O}_2 \) concentration (~200 mL \( \text{O}_2 / \text{L} \) blood) and \([\text{O}_2]_v\) = venous \( \text{O}_2 \) concentration (~150 mL \( \text{O}_2 / \text{L} \) blood).

5. This equation can be rearranged to calculate the cardiac output:

   \[
   \text{CO} = \frac{\text{O}_2 \text{ consumption}}{\text{A} - \text{V} \text{ O}_2 \text{ gradient}}
   \]

   where oxygen consumption is monitored by analysis of expired air, mixed venous blood is sampled by inserting a catheter into the pulmonary artery, and arterial blood is obtained from any peripheral artery.

6. For example, the CO for a healthy 70-kg man is calculated as follows:

   \[
   \text{CO} = 250 \text{ mL/min} / (200 - 150 \text{ mL } \text{O}_2 / \text{L blood}) = 5 \text{ L/min}
   \]

- While this is an important physiologic concept, CO is rarely measured in this way.
B. Stroke volume

1. **Stroke volume** (SV) is the volume of blood ejected from the ventricle during systole.
   - SV is a major determinant of pulse pressure.
   - SV is equal to the difference between end diastolic volume and end systolic volume
   - In a typical adult, the SV is calculated as follows:

\[
SV = EDV - ESV
\]

\[
= 120 \text{ mL} - 50 \text{ mL} = 70 \text{ mL}
\]

2. **Ejection fraction**
   - Ejection fraction (EF) is the percentage of blood in the ventricle at the end of diastole that is pumped into the circulation with each heartbeat.
   - In other words, it is the SV divided by the EDV.
   - In a typical adult, the EF is calculated as follows:

\[
EF = \frac{SV}{EDV} = \frac{70}{120} = 60\%
\]

Clinical note: If the heart muscle is not contracting efficiently (e.g., after a myocardial infarction), the EF may be decreased. If the ejection fraction is equal to or less than 40%, patients are said to have **systolic heart failure**. Multiple studies have shown that these patients benefit from taking angiotensin-converting-enzyme inhibitors (ACE inhibitors), which reduce pathologic ventricular remodeling in heart failure. Note that some patients may have a “preserved” ejection fraction on echocardiography but still have heart failure; in these cases, they would have **diastolic heart failure**.

3. **Determinants of stroke volume**
   - SV is determined by three principal factors: preload, contractility, and afterload.
   - **Preload**
     a. Preload is the degree of tension or “load” on the ventricular muscle when it begins to contract.
     b. This load is mainly determined by the volume of blood within the ventricle at the end of diastole (EDV), which in itself is primarily dependent on venous return.
     c. An increased EDV causes an increased SV (Fig. 4-4).
     d. Precisely why an increased EDV increases SV remains controversial, but there are two prominent theories.
       - The **Frank-Starling relationship**, also called the length-tension relationship of the heart theory, postulates that the increased ventricular wall tension associated with increased EDV stretches ventricular myocytes and results in a greater overlap of actin and myosin filaments.
         (1) This greater overlap causes more forceful contractions and increases the SV.
       - The second theory postulates that the contractile apparatus of cardiac myocytes becomes more sensitive to cytoplasmic calcium (Ca\(^{2+}\)) as the myocytes (and therefore sarcomeres) are stretched under conditions associated with increased preload.
         (1) This concept is similar to the myogenic theory proposed to explain autoregulation of blood flow, to be discussed later.
• **Contractility**
  a. Contractility is a measure of the **forcefulness of contraction at any given preload** (i.e., independent of myocardial wall tension at EDV) (Fig. 4-5).
  b. It is commonly referred to as the **inotropic state** of the heart.
  c. **Drugs** (e.g., digitalis), **sympathetic excitation**, and **heart disease** may all affect contractility.

• **Afterload**
  a. Afterload is the pressure or resistance against which the ventricles must pump blood, including systemic blood pressure and any obstruction to outflow from the ventricle, such as a **stenotic** (narrowed) **aortic valve**.
  b. At a given preload and contractility, if afterload increases, SV will decrease (Fig. 4-6).

4. **Mechanical characterization of contraction**

• **Wall tension**
  a. When pressure is increased inside a vessel, it causes a distending force.
  b. The force that opposes this distention is the **tension or stress in the vessel wall**.
  c. The **Laplace equation** relates these two forces:

\[
\sigma = \frac{P \times r}{2h}
\]

where \(\sigma\) = wall tension, \(P\) = intraluminal pressure, \(r\) = intraluminal radius, and \(h\) = wall thickness.

d. Think of the ventricle as a very thick-walled vessel, and use the Laplace equation to determine that, if the ventricle must generate a greater intraventricular pressure to overcome an afterload, **myocardial wall tension will increase**.

e. Left ventricular hypertrophy with the **addition of sarcomeres in parallel** (↑H) then occurs as a compensatory response to increased wall tension.

• **Stroke work**
  a. Stroke work is a measure of the mechanical work performed by the ventricle with each contraction.

4-5: Stroke volume versus contractility. For any given end diastolic volume (A), addition of a positive inotropic agent (e.g., epinephrine) increases stroke volume and cardiac output by increasing contractility (B). Similarly, addition of a negative inotropic agent (e.g., antagonist of circulating epinephrine or norepinephrine) decreases stroke volume and cardiac output by decreasing contractility (C). Note that in heart failure, a new preload “set point” (D) is established to optimize cardiac output.

4-6: Determinants of stroke volume.
b. Stroke work will increase in two scenarios: by increasing stroke volume against a constant afterload or by maintaining a given SV while afterload increases.

c. Stroke work has two main components.
   - **Pressure-volume work** is work used to push the SV into the high-pressure arterial system and is equal to the systemic arterial pressure multiplied by the SV (P × SV).
     (1) This is the **primary component** of stroke work.
   - **Kinetic energy work** is work supplied by ventricular contraction that is used to move the ejected blood at a certain velocity.
     (1) Under normal conditions, kinetic energy work is a **minor component** of the stroke work.

C. Venous return

1. **Effect of venous return on cardiac output by influencing preload**
   - The rate of venous return is determined by the **pressure gradient** between the systemic veins and the right atrium.
   - Increased venous return increases preload and CO (Fig. 4-7).
   - At **increased right atrial pressures** (e.g., pulmonary hypertension), venous return is reduced because the pressure gradient driving venous return is reduced.
   - When right atrial pressure equals systemic venous pressure, there is **no pressure gradient** and therefore **no flow**.
   - Contraction of the veins or infusion of volume increases the **systemic venous pressure** and therefore the driving force for venous return to the right side of the heart, increasing venous return (Fig. 4-8, point B) at a given right atrial pressure.

![Diagram of venous return vs. right atrial pressure](image)

**4-8**: Rate of venous return as a function of right atrial pressure.
Alternatively, loss of blood or dilation of the veins reduces systemic venous pressure and decreases venous return (see Fig. 4-8, point C).

Clinical note: Patients experiencing massive blood loss (e.g., trauma patients) are given large volumes of intravenous fluids to increase systemic venous pressure and to increase venous return, thereby increasing preload and CO.

- The situation becomes more complex when the CO curve is superimposed on the venous return curve (Fig. 4-9).
- Recall that as preload increases, CO increases by the Frank-Starling relationship.
- Increased preload also increases right atrial pressure, which reduces venous return and acts to reduce CO.
  a. There is, therefore, a continual balance.
  b. The right atrial pressure maintains the preload required for a given CO, but the pressure is not so great that it prevents the venous return required to maintain the CO.
  c. Thus, CO and venous return are perfectly matched!

2. Other determinants of venous return
- Skeletal muscle pump
  a. During physical exercise, muscle contraction increases the pressure in the veins in the skeletal muscles, which increases the pressure gradient for venous return and thus increases the rate of venous return.
  b. This extravascular compression is a major force for venous return during exercise.
  c. The skeletal muscle pump is particularly important in the lower extremities, where the force of gravity has a tendency to cause venous pooling.
  d. Muscle contraction pushes the blood through one-way valves in the lower extremities, facilitating its return to the heart.
- Respiratory pump
  a. Venous return is facilitated during inspiration because of an increased venous pressure gradient associated with inspiration.
  b. As the chest wall expands outward in inspiration, intrathoracic pressure decreases.
  c. At the same time, abdominal pressure increases (partly because of the descending diaphragm).
  d. The net result of these pressure changes is an increased pressure gradient driving increased venous return to the right atrium.

\[
\text{Right atrial pressure (mm Hg)} \quad \text{Cardiac output curve} \\
\text{Venous return curve} \quad \text{Equilibrium point} \\
\text{Mean systemic filling pressure} \\
\text{or end diastolic volume (mL)}
\]

4-9: Intersection of cardiac output curve and venous return curve. At the equilibrium point in a healthy person, CO and venous return are perfectly matched.
Clinical note: The presence of an inspiratory S$_2$ split on cardiac auscultation can be explained by increased venous return to the right atrium during inspiration, which increases the EDV and necessitates a longer systole to eject the additional blood into the pulmonary artery. Pulmonary vascular resistance also decreases somewhat during inspiration, which decreases the pulmonary back pressure needed to close the pulmonic valve. These two factors delay closure of the pulmonary valve during inspiration.

D. Ventricular pressure-volume loops
1. Cardiac function is commonly characterized graphically by pressure-volume loops.
2. There are four phases (Fig. 4-10).
   - **Phase I: ventricular filling in diastole**
     a. This phase begins with opening of the mitral valve and the beginning of ventricular filling.
     b. Notice that as ventricular volume increases, the intraventricular pressure also increases gradually, increasing preload.
   - **Phase II: isovolumic contraction**
     a. This phase begins at the onset of systole and closure of the mitral valve.
     b. The ventricle is contracting, but not shrinking, because sufficient pressure must develop to exceed pressures in the aorta (pulmonary artery for the right ventricle).
     c. The greater the afterload, the more the ventricular pressure must increase to overcome it.
   - **Phase III: ejection period**
     a. This phase begins as pressures in the left ventricle exceed those in the aorta, causing the aortic valve to open.
     b. Blood is then continually ejected until the pressures in the aorta exceed those in the ventricle, and the aortic valve closes.
   - **Phase IV: isovolumic relaxation**
     a. This phase begins immediately after closure of the aortic valve.
     b. During this time, the ventricular muscle is relaxing, but no blood is flowing into the ventricle from the atria because the pressures in the ventricle still exceed pressures in the atria.
     c. The ventricular volume does not change.
     d. At the end of phase IV, the pressure in the ventricle becomes less than the pressure in the atria, causing the AV valves to open and allowing ventricular filling to begin again (phase I).
E. Atrial pressure changes during the cardiac cycle (Fig. 4-11)
1. A slight pressure increase (a wave) is caused by atrial contraction.
2. A large pressure increase (c wave) is caused by isovolumic ventricular contraction and inward bulging of the AV valves.
3. A rapid reduction in pressure (x descent) is caused by initiation of the ventricular ejection phase; sometimes referred to as the vacuum effect.
4. A gradual pressure increase (v wave) is caused by atrial filling after closure of the AV valves.
5. A gradual pressure decrease (y descent) is caused by ventricular filling after opening of the AV valves.

Clinical note: Measurement of atrial pressures can be helpful in determining the cause of various cardiac disorders. Elevated right atrial and pulmonary artery pressures can often be appreciated on examination by simply looking for jugular venous distention or by performing echocardiography. However, a more invasive procedure, using a pulmonary wedge device or Swan-Ganz catheter, is required to evaluate left atrial pressure. This catheter is inserted into a peripheral vein and threaded through the venous circulation until it becomes “wedged” in one of the small branches of the pulmonary artery. Equilibration of blood from the pulmonary veins then allows an indirect measurement of left atrial pressure.

F. Pathophysiology of the major valvular diseases
1. Aortic stenosis
   • The cross-sectional area of the aortic valve becomes pathologically decreased, causing substantial resistance to ejection of blood through the valve.
   • This increase in resistance increases afterload, which decreases the SV and consequently decreases CO.
   • Figure 4-12A shows a pressure-volume loop in a patient with aortic stenosis.

Aortic stenosis: ↑ afterload; ↓ stroke volume, pulsus parvus et tardus

4-12: Pressure-volume changes in aortic stenosis. Ao, Aorta; AV, atriointerventricular; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; LVH, left ventricular hypertrophy; MV, mitral valve; PA, pulmonary artery; PMI, point of maximal impulse; PV, pulmonary valve; RA, right atrium, RV, right ventricle; SV, stroke volume; SVC, superior vena cava; TV, tricuspid valve. (B, From Goljan EF: Rapid Review Pathology, 3rd ed. Philadelphia: Mosby; 2010, Fig. 10-18.)
• Notice how an increased **intraventricular pressure** must be attained to overcome the significant afterload produced by the stenotic valve.
• The heart expends more energy developing increased pressures; therefore, less energy is available for the ejection phase, so the **SV** is decreased.
• Development of the pressure necessary to overcome the afterload also takes time, which means that it takes longer for a pulse to appear after closure of the AV valves ($S_1$).
• The combination of reduced SV (which reduces the pulse pressure) and delayed pulse from the increased afterload is responsible for the description of the pulse seen in aortic stenosis: **pulsus parvus et tardus** (weak and late) (see Fig. 4-12B).

**Pathology note:** In some individuals, the aortic valve is **congenitally bicuspid**. These bicuspid valves are predisposed to early calcification and stenosis, often causing significant **aortic stenosis** in individuals in their late 40s or early 50s. More commonly, aortic stenosis in elderly people is caused by calcification of the normal tricuspid valve, a condition known as **severe calcific aortic stenosis**. Another cause of aortic stenosis is rheumatic fever, but this disease is becoming rare in developed nations because of the use of antibiotics.

**Clinical note:** A **stenotic aortic valve** increases the rate of blood flow through the aortic valve, producing turbulent flow and consequently a **systolic ejection murmur** (while blood is being ejected across the valve).

### 2. Aortic regurgitation (insufficiency)

- The aortic valve does not normally prevent backflow of blood into the left ventricle.
- In aortic regurgitation, a significant fraction of the blood ejected into the aorta with each heartbeat returns to the left ventricle (Fig. 4-13A). Naturally, this decreases the **CO**.
- The increased preload that occurs from blood regurgitating back into the ventricle increases the **SV** (although not necessarily the **effective SV**), which helps maintain a relatively normal systolic pressure.
- However, diastolic pressure may be substantially reduced because of this “backward flow,” thus explaining the **widened pulse pressure** commonly seen in aortic regurgitation and the bounding and forceful pulses, the so called Water Hammer pulse (Fig. 4-13B).

---

### Aortic regurgitation:
- ↓ effective SV, widened pulse pressure

### Aortic regurgitation:
- Increased SV and decreased diastolic pressure — Water Hammer pulse on exam

---

**A** and **B**, Pathologic and clinical findings often seen with aortic regurgitation. Ao, Aorta; AV, atrioventricular; IVC, inferior vena cava; 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 Damjanov I: Pathophysiology. Philadelphia: Saunders; 2008, Fig. 4-53; **B**, from Goljan EF: Rapid Review Pathology, 3rd ed. Philadelphia: Mosby; 2010, Fig. 10-19.)
Pathology note: Aortic regurgitation may involve several different pathogenetic mechanisms. The most common causes are connective tissue defects that weaken the supporting aortic and valvular structures (e.g., Marfan syndrome, Ehlers-Danlos syndrome) and inflammatory diseases of the heart and/or aorta (e.g., endocarditis, syphilitic aortitis).

3. Mitral stenosis
- In early diastole, the mitral valve opens and provides negligible resistance to blood flow from the left atrium to the left ventricle.
- In mitral stenosis (Fig. 4-14), the mitral valve becomes stenotic owing to abnormal structural changes.
- This results in a large diastolic pressure gradient between the left atrium and left ventricle.
- Resistance to blood flow across the mitral valve increases, and adequate ventricular filling can occur only at pathologically elevated atrial filling pressures.

Pathology note: Rheumatic fever remains the most common cause of mitral stenosis. Symptoms of mitral stenosis (dyspnea, exercise intolerance) usually develop about 20 years after an acute episode of rheumatic fever.

- As left atrial pressures become elevated, the hydrostatic pressures in the pulmonary veins and capillaries also become elevated, causing net transudation of fluid into the pulmonary interstitium.
- Initially, the pulmonary lymphatics can reabsorb this fluid and prevent pulmonary edema.
- Once the left atrial pressure exceeds 30 to 40 mm Hg, however, the compensatory capacity of the lymphatics is overwhelmed, and fluid begins to accumulate in the lungs.
- This fluid accumulation causes the symptoms of mitral stenosis, such as dyspnea and reduced exercise capacity.
- If the degree of stenosis is severe, repair (mitral commissurotomy), percutaneous balloon valvuloplasty, or replacement of the mitral valve is necessary to prevent fatal progression of the disease.

4. Mitral regurgitation (insufficiency)
- In early systole, ventricular contraction is isovolumic when both the semilunar and AV valves are closed.
- This allows the entire left ventricular output to move “forward” into the aorta once the aortic valve opens.
- In mitral regurgitation, however, the mitral valve does not form a good “seal” and allows backward flow of blood into the left atrium during early systole.
- Figure 4-15 shows the hemodynamic changes in mitral regurgitation. Note that both the left atrium and left ventricle are enlarged.

Mitral stenosis: rheumatic fever still most common cause
Mitral stenosis: associated with large diastolic pressure difference between left atrium and ventricle
Mitral stenosis: ↑ left atrial pressures → ↑ hydrostatic pressures in pulmonary circulation → pulmonary edema
Mitral regurgitation: mitral valve does not form good seal → blood flows into left atrium during early systole

4-14: Schematic of mitral stenosis illustrating some of the pathologic anatomic and hemodynamic changes that may occur. Ao, Aorta; AV, aortic valve; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; LVPH, 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. (From Goljan EF: Rapid Review Pathology, 3rd ed. Philadelphia: Mosby; 2010, Fig. 10-14.)
Symptoms of mitral regurgitation therefore may be associated with reduced forward flow CO, elevated left atrial pressures, and/or left ventricular volume overload because of the additional preload imposed on the left ventricle by the addition of the “regurgitated” blood to the normal venous return.

The precise symptoms primarily depend on the temporal course of the mitral regurgitation.

In acute settings (e.g., rupture of papillary muscle in myocardial infarction), severe and even fatal pulmonary edema may develop because the “unprepared” left atrium is small and relatively noncompliant and the increase in atrial pressure is therefore rapidly transmitted to the pulmonary vasculature.

Furthermore, the pulmonary lymphatics have not adapted to reabsorb more interstitial fluid.

In chronic settings (e.g., ischemic cardiomyopathy causing gradual valvular dysfunction), the left atrium has had time to enlarge and become more compliant, and the pulmonary lymphatics have had time to augment their function.

Although pulmonary complications are less likely, increasingly larger fractions of the left ventricular SV are diverted into the low-pressure left atrium, thereby decreasing SV and causing symptoms attributable to low cardiac output (e.g., fatigue, weakness).

Pathology note: Mitral regurgitation can be caused by mitral valve prolapse, in which the mitral leaflets billow into the left atrium during ventricular systole. It classically gives rise to a midsystolic “click” on auscultation. Mitral regurgitation is the most common form of valvular disease. It is usually asymptomatic.

5. Pathophysiology of murmurs

- Blood flow through most of the cardiovascular system is normally laminar and silent.
- In certain circumstances, flow velocity is increased or viscosity is decreased, and nonlaminar (turbulent) flow occurs that can produce noise (murmurs or bruits) (Fig. 4-16).

Murmurs: most likely with high-flow velocity in large vessels
• Turbulent flow typically occurs when the Reynolds’ number is elevated, exceeding approximately 2500.
• The Reynolds’ number (Re) can be calculated as follows:

\[ Re = \frac{2rv}{\eta} \]

where \( r \) = radius of the vessel, \( v \) = velocity of flow, \( \rho \) = density of the fluid, and \( \eta \) = viscosity of the fluid.

### III. Myocardial Oxygen Supply and Demand

#### A. Main determinants of myocardial O₂ supply

1. **Coronary blood flow**
   - Myocardial O₂ supply is directly related to the rate of blood flow within the coronary arteries, which is dependent on the length of diastole, the diastolic perfusion pressure, and the vascular resistance of the coronary arteries.
   - **Length of diastole** (Fig. 4-17)
     a. The increased extravascular pressures generated during left ventricular systole compress the coronary vessels, causing little or no myocardial blood flow during systole.
     b. Consequently, left ventricular perfusion is largely dependent on the length of time spent in diastole, this time being inversely proportional to heart rate.
c. In contrast, the right ventricle receives most of its blood flow during systole, because the extravascular compressive forces during systole are much weaker in the right ventricle than in the left ventricle.

d. Therefore, right ventricular blood flow is largely independent of the time spent in diastole.

- **Diastolic perfusion pressure**
  a. The driving force for coronary blood flow is equal to the diastolic pressure within the proximal aorta.
  b. Equivalent to the diastolic pressure within the proximal aorta.
  c. Decreases in conditions that decrease diastolic pressures within the aorta (e.g., aortic regurgitation, hypotension), resulting in compromised myocardial O₂ supply.

**Clinical note:** In severely ill patients who are hypotensive (e.g., after a myocardial infarction), the diastolic perfusion pressure of the aorta may be insufficient to maintain adequate coronary blood flow. The resulting myocardial ischemia can compromise cardiac function, and the decreased CO further decreases the diastolic perfusion pressure. To increase this perfusion pressure, an intra-aortic balloon pump is inserted into the distal thoracic aorta. The balloon is designed to inflate during diastole, thereby increasing the aortic back pressure and the diastolic perfusion pressure. The result is improved diastolic coronary blood flow, which improves cardiac function and increases CO. It also deflates during systole, and the “vacuum” effect augments cardiac output.

- **Coronary vascular resistance**
  a. The resistance of the coronary vessels is governed by their radii; a decreased radius causes greater resistance and reduced flow.
  b. External compression during systole essentially halts left ventricular coronary blood flow by decreasing vessel radius.
  c. During diastole, the vessels open and perfusion occurs.
  d. Aside from these extravascular compressive forces, the local production of various vasoactive substances by metabolically active cardiac tissue is a major determinant of coronary vessel diameter and, hence, coronary vascular resistance and coronary blood flow.
  e. These vasoactive substances include mediators that cause vasodilation, such as adenosine, hydrogen ions (H⁺), and potassium (K⁺).
  f. Atherosclerotic narrowing of the coronary vessels also increases coronary vascular resistance.

2. **Arterial O₂ content**
   - The arterial O₂ content primarily depends on the O₂-carrying capacity of the blood, determined by the concentration of hemoglobin, and the efficiency of gas exchange by the lungs.
   - Normally, the arterial O₂ content is constant; therefore, it does not regulate myocardial O₂ supply.
   - In severe anemia, however, the decreased arterial O₂ content can compromise myocardial O₂ supply, causing myocardial ischemia.

B. **Determinants of myocardial O₂ demand**

1. **Heart rate** is most important.
   - When the heart rate increases, proportionally more time is spent in systole, which increases the cardiac workload and therefore increases the myocardial O₂ demand.
   - Additionally, because less time is spent in diastole, myocardial O₂ supply is simultaneously compromised; this sets the stage for “supply-demand mismatch.”

2. **Myocardial wall tension**
   - Increased wall tension may occur with increased preload, increased contractility, or increased afterload.
   - Each of these will result in increased myocardial O₂ demand.

**Clinical note:** When the heart is exposed to increased afterloads, as occurs in hypertension and aortic stenosis, it hypertrophies. Although this increase in muscle mass reduces wall tension, it nonetheless increases overall myocardial O₂ demand, predisposing to myocardial ischemia.
3. Contractility
   • Myocardium in a positive inotropic state ejects a greater SV than when in a normal or negative inotropic state.
   • Stroke work is increased, and therefore myocardial O₂ demand is increased.

Clinical note: Young men without coronary artery disease often present to the emergency department with anginal chest pain (and occasionally acute myocardial infarction) in a setting of recent cocaine use. This supply-demand mismatch occurs in part because of the potent inotropic effect that cocaine has on the myocardium, which increases myocardial O₂ demand. However, cocaine can also compromise myocardial O₂ supply by causing coronary artery vasospasm.

C. Pathophysiology of angina pectoris
1. Angina occurs when myocardial O₂ demand exceeds O₂ supply.
2. When this occurs, the ventricular myocytes begin to use anaerobic respiration.
3. Lactic acid accumulation may cause the pain of angina (as it does in overworked skeletal muscles).
4. Causes of angina pectoris include:
   • Atherosclerotic narrowing of coronary vessels in coronary artery disease
     a. This increases resistance and reduces blood flow.
   • Anginal pain associated with coronary artery disease typically becomes noticeable or more pronounced when myocardial O₂ demand increases (e.g., with exertion).
   • Spasm of the coronary arteries in Prinzmetal angina, which reduces coronary blood flow so much that the pain may occur at rest

Pharmacology note: Bearing in mind the determinants of myocardial O₂ supply and demand, it is clear why nitrates such as nitroglycerin are so effective in relieving anginal pain. Nitrates primarily function by reducing wall tension generated during systole, thus reducing the myocardial O₂ demand. They reduce wall tension by dilating both veins and arteries, which reduces preload and afterload, respectively. In addition, nitrates may prevent vasospasm of coronary arteries by causing vasodilation, thereby alleviating anginal pain in patients with Prinzmetal angina.

IV. Pathophysiology of Myocardial Adaptations
• Cardiac muscle, much like skeletal muscle, can adapt to increased workloads.
A. Adaptations to increased afterload (Fig. 4-18)
1. Significant afterloads (e.g., systemic hypertension, aortic stenosis) cause thickening of the heart muscle.
2. Myocytes cannot proliferate, but they can thicken by adding sarcomeres in parallel within a myocyte, decreasing the amount of tension that each sarcomere has to generate to overcome the afterload.
3. This process of adaptive thickening is known as concentric hypertrophy.
4. Concentric hypertrophy occurs at the expense of decreased ventricular compliance.
5. An increasingly stiff ventricle results in impaired diastolic ventricular filling, in which adequate ventricular filling may occur only at pathologically elevated atrial filling pressures, thereby predisposing to pulmonary venous congestion and pulmonary edema.

Pathology note: In a congenital cardiac disease known as hypertrophic cardiomyopathy, the myocardial muscle hypertrophies without a physiologic stimulus. This hypertrophy usually occurs asymmetrically, with the cardiac septum exhibiting the most hypertrophy. During systole, this enlarged septum may cause left ventricular outflow obstruction, resulting in a systolic murmur. This obstruction of left ventricular outflow can be so severe during intense exercise that it can cause syncope or even sudden death. Treatments include alcohol ablation of the apical region of hypertrophied septum, negative inotropic agents such as beta-blockers, cessation of vigorous exercise, and placement of an implantable cardioverter-defibrillator (ICD).
B. Adaptations to increased preload (see Fig. 4-18)
1. Larger-than-normal preloads (e.g., aortic regurgitation, mitral regurgitation) cause the heart to dilate, and the ventricular chamber then increases in diameter with only a minimal increase in ventricular wall thickness.
2. In contrast to concentric hypertrophy caused by increased afterload, the response to increased preload is to add sarcomeres in series. This is referred to as eccentric hypertrophy.
3. Although the ventricular myocardium does not appreciably thicken as a result, it does elongate, which accounts for the increased ventricular chamber size.
4. The elongation decreases preload by decreasing the amount of tension on each sarcomere at end diastole.
5. Hearts that are subject to increased preload are often referred to as volume-overloaded hearts.

Pathology note: In certain pathologic situations, the heart may dilate without being volume overloaded. Most commonly, this happens for unknown reasons and is known as idiopathic dilated cardiomyopathy. The most common known cause of dilated cardiomyopathy unrelated to volume overload is excessive use of alcohol.

V. Electrophysiology of the Heart
A. Overview
1. Action potentials spontaneously generated by the sinoatrial (SA) node are rapidly conducted throughout the heart through the Purkinje system and the intercalated disks of myocytes, causing coordinated myocardial contraction.
2. The SA node discharges at its own inherent rate (approximately 80 times per minute) in the absence of neurohumoral input.
3. If the SA node fails to discharge, other backup nodes become active and discharge at their own inherent rates, distribute an action potential throughout the heart, and cause myocardial contraction.
**B. Electrophysiologic basis of spontaneous depolarization of SA node and other backup nodes (Fig. 4-19)**

1. The membrane potential in nodal tissues is never stable.
   - The membranes gradually depolarize at rest (phase 4) because they are fairly permeable to sodium ions (Na\(^+\)).
2. When the membrane potential depolarizes to reach a certain **threshold potential**, voltage-gated calcium channels open, allowing a *slow current* of Ca\(^{2+}\) to enter the cells (phase 0), generating an action potential.
3. After causing the action potential, the calcium channels in the nodal tissues close spontaneously, and K\(^+\) flows out of the cells, restoring the membrane potential (phase 3).
4. **The process then begins again because of the Na\(^+\) leak.**
5. **Note:** Nodal cells do not demonstrate phases 1 and 2, which are observed in the action potentials of Purkinje fibers and cardiac myocytes.

**C. Autonomic influence on heart rate**

- The **rate of action potential generation by the SA node**, and thus the HR, may be influenced by several electrophysiologic mechanisms.

  1. **Maximum diastolic potential**
     - The maximum diastolic potential is the most negative membrane potential of the SA node.
     - The more negative this value, the longer the nodal cells must depolarize to reach the **threshold potential** (at which point an action potential is triggered); the result is a **reduction in HR**.
     - This is one way in which the parasympathetic nervous system, through the vagus nerve, slows the HR.

  2. **Rate of depolarization in phase 4**
     - The more permeable nodal cells are to Na\(^+\), the more rapidly they depolarize during phase 4 and reach threshold potential, **increasing the HR**.
     - The less permeable nodal cells are to Na\(^+\), the more slowly they depolarize, decreasing the HR.
     - Catecholamines produced by sympathetic excitation increase the HR, in part by **increasing the slope of phase 4 depolarization**.
       - In contrast, the parasympathetic nervous system decreases the HR, in part by **decreasing the slope of phase 4 depolarization**.

  3. **Threshold for generating action potentials**
     - The higher the threshold for generating action potentials, the longer phase 4 depolarization takes to reach this threshold and cause an action potential.
     - Therefore, raising the threshold (i.e., making it less negative) decreases the HR.
     - The sympathetic nervous system raises the threshold, whereas the parasympathetic nervous system lowers the threshold, for action potential generation in nodal cells.

**D. Backup pacemakers**

- “Backup” nodes such as the AV node are ordinarily not as permeable to Na\(^+\) as is the SA node, so they do not spontaneously depolarize as rapidly during phase 4.
- An action potential initiated by the SA node typically forces the backup nodes to depolarize together with other cardiac tissue.
After such depolarization, the backup nodes slowly begin to depolarize again, but because their membranes are not as permeable to Na\(^+\), the SA node depolarizes first and repeats the cycle.

a. This process is known as overdrive suppression.

b. Normally, only if the SA node does not fire soon enough does one of the backup nodes initiate an action potential that is conducted throughout the heart.

**E. Conduction pathway of action potentials** (Fig. 4-20)

1. After a spontaneous action potential is generated in the SA node, the action potential is distributed throughout the atria and is also rapidly conducted to the AV node through specialized internodal fibers.

2. **Conduction through the AV node** then occurs very slowly, which gives the atria sufficient time to contract and “top off” the ventricles before ventricular systole occurs.

3. From the AV node, impulses travel through the AV bundle as it traverses the fibrous septum that provides electrical “insulation” between the atria and the ventricles.

4. Action potentials then travel through the right and left bundle branches of the interventricular septum and are finally distributed to the ventricular myocardium via specialized Purkinje fibers and myocyte gap junctions.

**F. Action potentials in cardiac muscle**

1. **Phases in cardiac myocytes** (Fig. 4-21)

   a. In atrial and ventricular myocytes and Purkinje fibers, the resting membrane potential is maintained at a very negative level (approximately −90 mV).

   b. At this potential, the fast, voltage-gated Na\(^+\) channels are generally closed, but they are “primed” to be opened if triggered by an incipient action potential.
c. Notice the isoelectric nature of phase 4 of the action potential in cardiac muscle, which contrasts with the upward slope of phase 4 of the nodal action potential (see Fig. 4-21).

- **Phase 0: depolarization**
  a. This phase is characterized by rapid cell depolarization caused by the opening of fast, voltage-gated Na\(^+\) channels in response to action potentials coming from the cardiac conduction system.
  b. Na\(^+\), which is much more abundant extracellularly than intracellularly, rushes into the cell and **causes the membrane potential to become increasingly positive**.

- **Phase 1: transient repolarization**
  a. This phase is caused by a transient rapid efflux of K\(^+\) with simultaneous **cessation of Na\(^+\) efflux**.
  b. These effluxes result in a slight repolarization that is almost immediately counteracted by the opening of calcium channels and Ca\(^{2+}\) influx.

- **Phase 2: calcium plateau**
  a. This phase is characterized by a **balance between K\(^+\) efflux and Ca\(^{2+}\) influx**, resulting in no net change in membrane potential.
  b. It accounts for the long duration of the cardiac myocyte action potential.
  c. The entry of calcium is responsible for initiating contraction of cardiac myocytes.

- **Phase 3: repolarization**
  a. This phase is characterized by a **simultaneous rapid efflux of K\(^+\)** and **cessation of Ca\(^{2+}\)** influx.
  b. The result is repolarization and even hyperpolarization of cells.

2. **Differences in action potential generation in nodal cells and myocytes**
   - The **resting membrane potential** is approximately −70 mV in nodal cells (see Fig. 4-19), and it is approximately −90 mV in non-nodal cells (see Fig. 4-21).
   - The less negative resting membrane potential in nodal cells effectively eliminates the contribution of the fast voltage-gated Na\(^+\) channels to action potential generation, because at this potential they are almost all in a conformation that cannot be triggered to open.
   - The resting membrane potential in phase 4 slopes upward and depolarizes spontaneously in nodal cells, whereas it is level in non-nodal cells.
   - Notice the slow phase 0 depolarization due to slow influx of Ca\(^{2+}\) in nodal cells, compared with the steeply sloping phase 0 in non-nodal cells caused by the rapid influx of Na\(^+\).

3. **Refractory period**
   - Immediately after depolarization, cardiac muscle cells cannot be excited again.
   - The Na\(^+\) channels responsible for phase 0 depolarization are inactivated by depolarization.
   - There is a certain “recovery” period during which these Na\(^+\) channels cannot be stimulated to initiate an action potential.
   - This **period of inexcitability** has two important physiologic roles.
     a. First, it **prevents tetany** (sustained contraction), which can occur in skeletal muscle from rapid stimulation, but which in the heart would cause perpetual systole.
     b. Second, it **places an upper limit on the heart rate** of approximately 180 to 200 beats per minute.

G. **Excitation-contraction coupling**
   1. Excitation-contraction coupling reflects the “coupling” of an **increase in membrane potential (excitation) to cell contraction**.
   2. In a cardiac myocyte, the first step that occurs is the generation of an action potential at the cell surface.
   3. As this action potential spreads along the sarcolemma and transverse tubules, extracellular Ca\(^{2+}\) enters the cell, triggering Ca\(^{2+}\) release from the sarcoplasmic reticulum.
     - This phenomenon is referred to as Ca\(^{2+}\)-**induced Ca\(^{2+}\)** release.
   4. The intracellular Ca\(^{2+}\) then stimulates contraction through a **sliding filament mechanism of contraction** similar to that in skeletal muscle (i.e., Ca\(^{2+}\) binds troponin, which promotes actin and myosin cross-bridge formation).
   5. The **force of contraction is proportional to the intracellular Ca\(^{2+}\) level**.
6. For the ventricles to relax, \( \text{Ca}^{2+} \) must be pumped out of the cytosol back into the sarcoplasmic reticulum or into the extracellular fluid.
- This process, like excitation-contraction coupling, also requires energy.

7. **Sympathetic excitation** of the heart increases contractility in large part by increasing the influx of extracellular \( \text{Ca}^{2+} \), causing a greater \( \text{Ca}^{2+} \)-induced \( \text{Ca}^{2+} \) release.
- It also stimulates reuptake of \( \text{Ca}^{2+} \), thereby accelerating the rate of ventricular relaxation and facilitating ventricular filling during the shortened period of diastole.

**Pharmacology note:** Non-dihydropyridine calcium channel blocking drugs (e.g., diltiazem, verapamil) have a **negative inotropic effect** on the heart by preventing the influx of extracellular \( \text{Ca}^{2+} \) during the cardiac action potential. Such a negative inotropic effect may be beneficial in patients with **chronic heart failure** (by reducing myocardial \( \text{O}_2 \) demand) and **hypertension** (by reducing CO). These drugs also exert a negative chronotropic effect on the heart, which is useful in “rate control” of supraventricular tachycardias such as atrial fibrillation.

**Pharmacology note:** The cardiac glycoside **digitalis** has a **positive inotropic effect** on the heart because it increases cytoplasmic \( \text{Ca}^{2+} \). It does this indirectly by inhibiting the sodium-potassium adenosine triphosphatase pump (\( \text{Na}^+,\text{K}^+\)-ATPase pump), which increases intracellular \( \text{Na}^+ \). The increased intracellular \( \text{Na}^+ \) reduces the \( \text{Na}^+ \) gradient that drives a \( \text{Na}^+\text{Ca}^{2+} \) antiport, allowing more \( \text{Ca}^{2+} \) to accumulate in the cytosol. Because of this positive inotropic effect, digitalis may provide significant symptomatic relief in patients with heart failure, in whom cardiac contractility may be severely impaired. However, it has not been shown to provide a mortality benefit to patients with congestive heart failure.

**II. Autonomic innervation of the heart (Fig. 4-22)**

1. **Sympathetic (adrenergic) innervation**
   - **Sympathetic innervation to the heart** is extensive, with innervation to the nodal tissues, atria, and ventricles.
   - **Norepinephrine** released from sympathetic nerves binds to adrenergic receptors in the heart, resulting in **increased heart rate** (positive **chronotropic** effect) and **increased contractility** (positive **inotropic** effect).

**Pharmacology note:** The \( \beta_1 \)-adrenergic receptor is primarily responsible for mediating sympathetic excitation of HR and contractility. **\( \beta \)-Blocking drugs** such as metoprolol antagonize this receptor and slow HR and reduce contractility. However, despite being marketed as \( \beta \)-specific antagonists, drugs such as metoprolol also bind to \( \beta_2 \)-adrenergic receptors and can occasionally worsen breathing in patients with asthma or chronic obstructive pulmonary disease. At low doses, nebulol is a truly \( \beta_1 \)-selective antagonist that can be used in such susceptible patients.

2. **Parasympathetic (cholinergic) innervation**
   - **Parasympathetic innervation** of the heart is limited to the nodal tissues and the atria (see Fig. 4-22).
   - There is essentially no **parasympathetic innervation** to the ventricles.
• Acetylcholine released from parasympathetic nerves (the vagus) binds to muscarinic receptors.
• Parasympathetic stimulation decreases HR by increasing the maximum diastolic potential, raising the threshold potential and decreasing the rate of phase 4 depolarization in nodal cells.

Clinical note: In extreme conditions such as vasovagal syncope, marked parasympathetic outflow to the heart can cause the heart to stop beating transiently, resulting in syncope from inadequate cerebral perfusion. Parasympathetic outflow can stop the heart transiently because cholinergic stimulation impairs both action potential generation in nodal tissue and conduction of action potentials from the atria to the ventricles, resulting in heart block. However, because the ventricles do not receive parasympathetic input, ventricular pacemaker cells free from parasympathetic control are able to initiate de novo action potentials if they are not overdrive-suppressed by another action potential. Ventricular function is then able to resume at some level with the creation of a ventricular escape rhythm, allowing the person to regain consciousness.

Pharmacology note: The drug atropine blocks the muscarinic receptors in the heart and increases HR. It is therefore useful in treating patients with acute symptomatic bradycardia.

VI. The Electrocardiogram
A. Overview
1. The electrocardiogram (ECG) monitors electrical activity in the heart by recording electrical changes at the surface of the body.
2. The important “leads” to be familiar with are the bipolar limb leads (I, II, and III), the unipolar limb leads (aVR, aVL, and aVF), and the precordial leads (V₁ through V₆).
3. The bipolar and unipolar limb leads detect electrical activity in the vertical (frontal) plane; the precordial leads detect current in the transverse plane.
B. The normal ECG (Fig. 4-23)
1. The P wave corresponds to atrial depolarization.
2. The PR interval corresponds to impulse conduction through the AV node.
3. The QRS complex corresponds to ventricular depolarization.
4. The T wave corresponds to ventricular repolarization.
C. Determination of axis
1. The mean QRS axis is calculated in the frontal plane.
2. The two leads typically used for axis determination are leads I and aVF, although a simplified approach is discussed below.
3. A normal QRS axis is typically defined as lying between –30 and +90 degrees.
Left axis deviation (LAD; i.e., superior and leftward) is defined from $-30$ to $+90$ degrees (Fig. 4-24).

Right axis deviation (RAD; i.e., inferior and rightward) is defined from $+90$ to $+150$ degrees.

4. A simplified approach to determine QRS axis is as shown in Figure 4-25.

- Left axis deviation (LAD; i.e., superior and leftward) is defined from $-30$ to $+90$ degrees (Fig. 4-24).
- Right axis deviation (RAD; i.e., inferior and rightward) is defined from $+90$ to $+150$ degrees.

D. Correlation of ECG with cardiac events

E. Abnormal ECGs (Figs. 4-26 to 4-34)

**TABLE 4-1. Correlation of Electrocardiogram With Cardiac Events**

<table>
<thead>
<tr>
<th>ELECTROCARDIOGRAM ABNORMALITY</th>
<th>POSSIBLE DIAGNOSES</th>
<th>POSSIBLE PATHOPHYSIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-segment elevation</td>
<td>Acute myocardial infarction</td>
<td>Prolonged repolarization</td>
</tr>
<tr>
<td>Split R wave</td>
<td>Bundle branch block</td>
<td>Depolarization of right and left bundle branches no longer occurs simultaneously</td>
</tr>
<tr>
<td>PR interval &gt; 200 msec</td>
<td>Heart block</td>
<td>Excessive vagal outflow, drugs that slow atrioventricular conduction, or conduction disease (common in the elderly)</td>
</tr>
<tr>
<td>Pathologic Q wave</td>
<td>“Transmural” myocardial infarction</td>
<td>—</td>
</tr>
<tr>
<td>Deviation of mean QRS axis</td>
<td>Myocardial infarction or ventricular hypertrophy</td>
<td>Left ventricular hypertrophy in response to increased afterload (e.g., hypertension, aortic stenosis) or right ventricular hypertrophy in response to massive pulmonary embolism</td>
</tr>
<tr>
<td>Inverted T wave</td>
<td>Ischemia</td>
<td>Prolonged ventricular depolarization and ventricular ischemia from coronary artery disease</td>
</tr>
</tbody>
</table>
VII. Arterial Pressure Maintenance

A. Determinants of mean arterial pressure (MAP)

1. MAP is dependent on two variables: cardiac output (CO) and total peripheral resistance (TPR):

\[ \text{MAP} = \text{CO} \times \text{TPR} \]

- CO is a function of SV and HR (see section IIA on cardiac output).

2. Resistance (R) to fluid flow through a tube (vessel) is described by Poiseuille equation:

\[ R = 8\eta l/r^4 \]

where \( \eta \) = viscosity; \( l \) = length of the vessel; and \( r \) = radius of the vessel.

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4-26: Atrial fibrillation with a rapid ventricular response in a patient with hyperthyroidism. (From Goldberger A: Clinical Electrocardiography, 7th ed. Philadelphia: Mosby; 2006, Fig. 15-5.)

4-27: Atrial fibrillation with a slow ventricular response, in this case due to digitalis toxicity. (From Goldberger A: Clinical Electrocardiography, 7th ed. Philadelphia: Mosby; 2006, Fig. 18-4.)

4-28: Atrial flutter. A, Note the presence of flutter waves in leads II and III. B, Note that carotid sinus pressure showed the ventricular rate but interestingly did not affect the atrial flutter rate. (From Goldberger E: Treatment of Cardiac Emergencies, 5th ed. St. Louis: Mosby; 1990.)
First-Degree AV block: PR interval uniformly prolonged > 0.2 second

Mobitz type 1 second-degree AV block: PR interval lengthens progressively until P wave is “dropped”

Second-degree heart block (Mobitz type 2): not all P waves are conducted, so some P waves will not give rise to a QRS complex

Third-degree AV block: no relationship between P waves and QRS complex

Ventricular tachycardia: often a precursor to potentially fatal ventricular fibrillation

Wolff-Parkinson-White syndrome: note the presence of the delta wave

4-29: First-degree atrioventricular block. PR interval prolonged beyond 0.2 second with each beat. (From Goldberger A: Clinical Electrocardiography, 7th ed. Philadelphia: Mosby; 2006, Fig. 17-1.)

4-30: Mobitz type 1 second-degree AV block. The PR interval lengthens progressively with successive beats until one sinus P wave is not conducted at all. Then the cycle repeats itself. Notice that the PR interval after the nonconducted P wave is shorter than the PR interval of the beat just before it. (From Goldberger A: Clinical Electrocardiography, 7th ed. Philadelphia: Mosby; 2006, Fig. 17-2.)

4-31: Second-degree heart block (Mobitz type 2). Note how not all P waves are conducted, resulting in a dropped QRS complex after the third P wave. (From Lim E, Loke YK, Thompson A: Medicine and Surgery. New York: Churchill Livingstone; 2007, Fig. 1-4C.)

4-32: Complete heart block with underlying sinus rhythm characterized by independent atrial (P) and ventricular (QRS complex) activity. The PR intervals are completely variable. Some sinus P waves fall on the T wave, distorting its shape. Others may fall in the QRS complex and be “lost.” (From Goldberger A: Clinical Electrocardiography, 7th ed. Philadelphia: Mosby; 2006, Fig. 17-3.)

4-33: Ventricular tachycardia (VT) and ventricular fibrillation (VF) recorded during cardiac arrest (monitor leads). The rapid sine-wave type of ventricular tachycardia seen here is sometimes referred to as ventricular flutter. (From Goldberger A: Clinical Electrocardiography, 7th ed. Philadelphia: Mosby; 2006, Fig. 19-2.)

Because it is the fourth power of the radius that determines resistance to fluid flow, vessel constriction or dilation can have powerful effects on fluid resistance and mean arterial pressure. In the circulatory system, resistance is governed primarily by the diameter of the arterioles, rather than the large arteries or capillaries (Fig. 4-35).

Pharmacology note: Sympathetic stimulation of arteriolar vascular smooth muscle contraction is mediated by $\alpha_1$-receptors. $\alpha_1$-Blocking drugs such as prazosin antagonize this receptor and inhibit vasoconstriction, thereby lowering blood pressure.

3. Tonic sympathetic outflow through the medullary vasomotor center
   - Tonic sympathetic outflow from the medullary vasomotor center increases TPR and maintains vasomotor tone.
   - When vasomotor tone is normal, most of the body’s arterioles are at least partly constricted, helping to maintain arterial blood pressure.
   - The medullary vasomotor center is also involved in reflex regulation of blood pressure; see discussion of baroreceptor reflex below.
   - It receives input regarding the arterial blood pressure from a variety of sources, including baroreceptors located in large-diameter arteries, peripheral and central chemoreceptors, and even higher brain centers such as the hypothalamus and motor cortex (Fig. 4-36).

B. Rapid blood pressure control by the autonomic nervous system
   1. Baroreceptor reflex (Fig. 4-37)
      - This neural reflex works rapidly to compensate for changes in arterial blood pressure and is dependent on specialized mechanoreceptors located within the aortic arch and the carotid sinuses.
      - When exposed to higher arterial blood pressures, the mechanoreceptors become deformed and “fire” action potentials that are relayed to the vasomotor center and other nuclei in the brainstem.

   4-35: Blood pressure oscillations throughout the vasculature. Resistance to flow dampens the pressure oscillations caused by each heartbeat and also causes the pressures to drop as blood traverses the cardiovascular system. Most of the pressure drop occurs in the arterioles, where the vascular resistance is the greatest.

   4-36: Regulatory input to the medullary vasomotor center. CNS, Central nervous system.
Response of the baroreceptor reflex to acute hemorrhage, represented by the drop in mean arterial pressure ($P_a$). CVLM, Caudal ventrolateral medulla; NTS, nucleus of tractus solitarius; RVLM, rostral ventrolateral medulla; TPR, total peripheral resistance. (A, From Roberts J, Hedges J: Clinical Procedures in Emergency Medicine, 5th ed. Philadelphia: Saunders; 2009, Fig. 11-5; B, from Costanzo L: Physiology, 3rd ed. Philadelphia: Saunders; 2002, Fig. 4-32.)
• This signal is inhibitory, so that medullary sympathetic outflow is blocked and parasympathetic outflow is stimulated.
• The decreased sympathetic outflow causes arteriolar dilation and also decreases sympathetic drive to the heart, decreasing the HR.
• The parasympathetic outflow decreases HR by reducing the firing frequency of the SA node.
• The combined result of vasodilation and reduced cardiac output is a rapid compensatory drop in blood pressure.
• If the blood pressure decreases, the opposite sequence of events occurs.
• The baroreceptors fire less frequently, reducing inhibition of sympathetic outflow.
• The resulting increase in CO and peripheral vascular resistance acts rapidly to prevent a further decline in blood pressure, in an attempt to maintain adequate organ perfusion.

Clinical note: Pressure on the carotid sinuses, which might occur when checking for the carotid pulse, can also cause deformation of the baroreceptors. This action may be interpreted by the medullary vasomotor center as an elevated blood pressure. The resulting decreased sympathetic outflow and increased parasympathetic outflow can cause a rapid "compensatory" drop in blood pressure and possibly even syncope.

Pharmacology note: When a person moves rapidly from a supine to a standing position, blood pressure decreases because of venous pooling in the legs. This decline is transient only because decreased baroreceptor firing frequency stimulates sympathetic outflow, which increases the HR and causes vasoconstriction to maintain adequate blood pressure. Certain antihypertensive medications, such as the \( \alpha \)-blockers and dihydropyridine calcium channel blockers, can cause marked orthostatic hypotension, because they block the receptors required for this vasoconstriction.

2. Central nervous system (CNS) ischemic response
• When blood flow to the medullary vasomotor center is compromised (e.g., severe hypotension), sympathetic outflow from the vasomotor center is strongly stimulated.
• Brainstem ischemia in stroke may also activate the CNS ischemic response.
• Note that activation of the CNS ischemic response occurs irrespective of the type of feedback the vasomotor center may be receiving from the peripheral baroreceptors and chemoreceptors.

Clinical note: Head injury that causes significantly increased intracranial pressure may activate the CNS ischemic response, decreasing blood flow to the medullary vasomotor center and causing hypertension. When this occurs and bradycardia develops, it is referred to as Cushing sign.

C. Autoregulation of local blood flow
1. Autoregulation is the ability of tissues to self-regulate local blood flow in the face of varying systemic pressures.
2. There are two principal mechanisms of autoregulation.
   • Metabolic mechanism
     a. Local metabolism regulates local blood flow through the production of vasoactive substances, such as adenosine and lactic acid.
     b. Demand regulates supply.
   • Myogenic mechanism
     a. Stretching of vascular smooth muscle cells increases calcium permeability, which stimulates contraction and compensatory vasoconstriction (Fig. 4-38).
     b. This helps minimize fluctuations in local perfusion.

D. Vascular compliance
1. Vascular compliance refers to the distensibility of a vessel.
2. A compliant vessel is able to withstand an increase in volume without causing a significant increase in pressure.
3. Mathematically, it is expressed as the volume (V) required to increase the pressure (P) by 1 mm Hg:
   \[ C = \frac{\Delta V}{\Delta P} \]
Pathology note: If the arteries are not very compliant, as in arteriosclerosis, they are unable to “accept” large volumes of blood without a substantial increase in arterial pressure. This is precisely what happens in isolated systolic hypertension due to arteriosclerosis, which often occurs in the elderly.

4. Note: Veins are significantly more compliant than arteries, which allows them to accept large volumes of blood without considerable increases in pressure.

E. Long-term control through regulation of intravascular volume by the kidneys

1. Overview
   - Intravascular volume is a major determinant of blood pressure (BP) and is primarily controlled by the kidneys.
   - Elevated intravascular volume increases systemic venous pressure, which in turn increases venous return.
     a. This increases preload and CO, which elevates blood pressure.
   - Therefore, by either increasing or decreasing intravascular volume, the kidneys have a powerful effect on CO and MAP (Fig. 4-39).

2. Pressure diuresis
   - In persons with normal renal function, increases in systemic blood pressure result in increased diuresis by the kidneys.
   - This phenomenon, known as pressure diuresis, takes place because of the increased renal blood flow that occurs at elevated arterial pressures, which causes a higher-than-normal glomerular filtration rate (GFR) (Fig. 4-40).
   - The increased GFR results in increased filtration and excretion of sodium (pressure natriuresis) as well as water.
   - The resulting loss of sodium and water reduces intravascular volume, which reduces CO and normalizes the arterial pressure.
   - If systemic pressure decreases, the opposite sequence of events is set into motion.
   - Decreased renal perfusion causes the kidneys to retain more sodium and water, which increases intravascular volume and restores the blood pressure.
     a. Therefore, many believe that there is some component of renal disease in all patients with hypertension.

3. Renin-angiotensin-aldosterone system
   - The renin-angiotensin-aldosterone system (RAAS) is a system for preserving intravascular volume and mean arterial pressure.
The primary stimulus for the RAAS is reduced renal blood flow, which typically occurs in conditions associated with reduced intravascular volume (e.g., dehydration).

Reduced renal blood flow is sensed by a group of specialized cells located in the walls of the afferent arterioles (part of the juxtaglomerular apparatus).

Renin secretion by these cells initiates an enzymatic cascade that ultimately results in the production of angiotensin II (Fig. 4-41).

Clinical note: Activation of the RAAS may also occur in euvolemic and even hypervolemic states, such as renal artery stenosis or congestive heart failure (CHF). In these states, the kidney is underperfused despite a normal or elevated intravascular volume. Long-term activation of the RAAS may not be an appropriate physiologic response; in fact, it may exacerbate the underlying disease (e.g., cause hypertension in renal artery stenosis or a more rapid decline in cardiac function in CHF).

Actions of angiotensin II
a. Angiotensin II increases arterial blood pressure in numerous ways.
b. It stimulates expansion of intravascular volume by stimulating Na⁺ reabsorption in the proximal nephron and stimulating thirst (Fig. 4-42).
c. It also is a powerful stimulator of systemic vasoconstriction, which increases arterial blood pressure by increasing TPR.
d. In contrast to stimulating plasma volume expansion, which can take hours to days, increased arterial vasoconstriction causes a rapid increase in arterial blood pressure, which may be an important protective mechanism during hemorrhage.

Pharmacology note: Blood pressure can be reduced in patients with hypertension by inhibiting the production of angiotensin II. This can be achieved by inhibiting the actions of angiotensin-converting enzyme (ACE), which converts angiotensin I to angiotensin II (see Fig. 4-41). This is precisely how ACE inhibitors function to reduce blood pressure.
**Actions of aldosterone**
- Stimulates Na\(^+\) reabsorption and K secretion from the distal nephron.
- Acts to increase intravascular volume and maintain arterial blood pressure.
- In excess can contribute to the development of hypertension and electrolyte abnormalities such as hypernatremia, hypokalemia, and metabolic alkalosis.

**Clinical note:** Although renal artery stenosis is still the most common secondary cause of hypertension, primary hyperaldosteronism (Conn syndrome) is now felt to be much more prevalent than previously thought.

**Pharmacology note:** Because aldosterone acts to expand plasma volume, aldosterone antagonists such as spironolactone are useful in managing congestive heart failure. In patients with dyspnea with minimal exertion or at rest (these patients are referred to as having stage 3 or 4 heart failure per the New York Heart Association [NYHA] criteria), the use of aldosterone antagonists is clinically indicated.

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**4. CNS osmoreceptors and antidiuretic hormone**
- **Antidiuretic hormone (ADH)** is a hormone secreted from the posterior pituitary that plays an important role in the regulation of plasma osmolality and volume.
- It is secreted by hypothalamic osmoreceptors in response to either slight increases in plasma osmolarity or marked reductions in plasma volume (Fig. 4-43).
- The primary mechanism of action of ADH is to stimulate water reabsorption by the collecting tubules of the distal nephron.
- At higher levels, it also stimulates systemic vasoconstriction.
- Both of these actions are aimed at increasing MAP.

**4-42:** Diagrammatic representation of physiologic actions of angiotensin II.

**4-43:** Differential sensitivity of secretion of antidiuretic hormone (ADH) to plasma osmolarity and plasma volume status. The dotted line illustrates the differential sensitivity to ADH secretion by the two stimuli.

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**ADH secretion:** More sensitive to ↑ plasma osmolarity than ↓ plasma volume.
Pharmacology note: ADH (vasopressin) exerts its effects through two different receptors. Its vasoconstrictive effects are mediated by a receptor (AVPR1A) located on vascular smooth muscle cells. Its effects on renal water reabsorption are mediated by a receptor (AVPR2) on the renal tubules. Loss-of-function mutations in this latter receptor result in nephrogenic diabetes insipidus.

5. Low-pressure stretch receptors that monitor venous return
   - In contrast to the high-pressure stretch receptors in the aortic arch and carotid sinuses, low-pressure stretch receptors in the atria and vena cava are ideally positioned to monitor venous return.
   - If large volumes of blood return to the right side of the heart, these receptors send signals through the vagus nerve that stimulate selective renal vasodilation, causing diuresis by the kidneys in an effort to decrease plasma volume.
   - In response to increased venous return these receptors also increase the HR (Bainbridge reflex).
     a. This action increases CO and renal perfusion, further increasing diuresis.
   - Atrial stretch from increased venous return causes the atria to secrete atrial natriuretic peptide (ANP), which further promotes diuresis.

Clinical note: Brain natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to volume expansion and pressure overload in the ventricle. It is clinically useful in diagnosing left-sided heart failure (increased), in excluding left-sided heart failure (normal), and as a predictor of survival.

VIII. Fluid Exchange in the Capillaries
A. Overview
   1. Fluid exchange across the capillary membrane is dependent on the permeability characteristics of the capillary bed and the net filtration pressure generated across the capillary bed.
   2. The net filtration pressure (NFP) depends on the interaction between plasma and interstitial hydrostatic and osmotic forces, which are known as Starling forces.
   3. The end result of this interaction is the production of an NFP that drives fluid from the capillaries into the interstitium or from the interstitium into the capillaries, depending on the relative contribution of each force.
B. Starling forces
   1. Hydrostatic pressure of the capillary (Pc)
      - This is the outward force exerted by pressurized fluid within the blood vessel; it is greater on the arterial end of the capillary (approximately 35 mm Hg) than it is on the venous end (approximately 15 mm Hg).
      - The hydrostatic pressure difference along the capillary results in net loss of fluid from the arterial end and reabsorption of interstitial fluid from the venous end (Fig. 4-44).
      - In conditions such as venous obstruction, the hydrostatic pressure may become abnormally elevated, resulting in increased loss of fluid to the interstitium and causing edema.

4-44: Starling forces in a capillary. HP, Hydrostatic pressure (mm Hg); OP, oncotic pressure (mm Hg); ΔP, difference in pressure (HP – OP).

Low-pressure stretch receptors response to ↑ venous return: ↑ renal perfusion, ↑ HR (Bainbridge reflex), ↑ ANP secretion, ↑ diuresis

ANP: atrial stretching ↑ secretion → promotes diuresis

BNP: ventricular stretching ↑ secretion → promotes diuresis

| Capillary hydrostatic pressures: hemorrhage, hypotension, hypoalbuminemia

| Capillary hydrostatic pressure forces fluid into the interstitium, causing edema.
Pathology note: In conditions associated with rapid loss of intravascular volume, such as hemorrhage, the hydrostatic pressure of the capillaries may become too low to cause fluid movement into the interstitium. Instead, there is net movement of interstitial fluid into the capillaries, which helps restore intravascular volume. This explains why there is a drop in hematocrit many hours after an acute bleed.

2. **Plasma oncotic pressure or plasma colloid osmotic pressure** ($\pi_c$)
   - This is the inward force on fluid movement exerted by plasma proteins that are too large to diffuse out of the capillaries; oncotic pressure draws fluid from the interstitium into the capillaries.
   - Plasma albumin concentration is the primary determinant of the plasma oncotic pressure.
   - In patients with hypoalbuminemia, the low oncotic pressure causes fluid to move from the vascular compartment into the interstitium, resulting in edema.

3. **Interstitial hydrostatic pressure** ($P_{IF}$)
   - Interstitial fluid exerts an inward force.
   - The force is normally slightly negative because the lymphatics are constantly draining interstitial fluid.

4. **Interstitial oncotic pressure** ($\pi_{IF}$)
   - This is the outward force exerted by interstitial proteins.
   - The concentration of proteins in the interstitial fluid is normally much less than that of the plasma, so this force is less than the opposing force of capillary oncotic pressure.

Pathology note: In inflammatory states, increased vascular permeability may result in increased levels of interstitial proteins, which increases interstitial oncotic pressure and drives fluid into the interstitium, causing edema. This type of fluid is protein rich (>3 g/dL) and is cell rich (contains numerous neutrophils) and is called an exudate. Unlike a transudate, it remains localized because of its increased viscosity and does not pit with pressure.

C. **Starling equation**
1. The sum of the Starling forces determines the NFP across a capillary bed.
2. **Starling forces** vary significantly in different tissues, but the NFP in a typical capillary bed is expressed as follows:
   \[
   \text{NFP} = (P_c + \pi_{IF}) - (P_{IF} + \pi_c)
   \]
   \[
   = (17.3 + 8) - (-3 + 28)
   \]
   \[
   = 0.3 \text{ mm Hg}
   \]
   where NFP = net filtration pressure; $P_c$ = hydrostatic pressure of capillary; $P_{IF}$ = interstitial hydrostatic pressure; $\pi_c$ = plasma oncotic pressure; and $\pi_{IF}$ = interstitial oncotic pressure.
3. **Note:** A very small NFP drives filtration across the capillary membrane.
   - This small driving pressure is sufficient because of the highly permeable nature of the capillary membrane.
   - The average NFP over the entire capillary is very low, but at any given point, it could be much higher or much lower (see Fig. 4-44).
   - Note also that the example above was for a typical capillary bed.
   a. The Starling forces in the glomerular capillary bed, for example, will vary markedly from that shown above.
D. Pathophysiology of edema
1. The reabsorption of fluid at the venous end of the capillary is typically slightly less than the loss of fluid at the arterial end of the capillary.
2. Therefore, there is a constant “leakage” of fluid from the vascular compartment into the interstitial compartment.
3. One of the primary functions of the lymphatic system is to return this excess fluid to the vascular compartment through the thoracic duct.
4. This capacity can be overwhelmed by significant alterations in the Starling forces or increased capillary permeability.
5. Dysfunction of the lymphatic system also may result in severe edema (Table 4-2).

IX. Pathophysiology of Heart Failure
A. Definition
- Heart failure may be thought of as any state in which cardiac output is inadequate to meet the body’s metabolic demands or can be maintained only at the expense of pathologically elevated ventricular filling pressures.

B. Systolic heart failure: “pump” failure
1. The pathogenesis of systolic heart failure involves either impaired ventricular contractility or pathologic increases in afterload; the end result is a decrease in SV and CO (decreased ejection fraction).
2. Impaired contractility: myocardial ischemia, myocardial infarction, chronic volume-overloaded states such as aortic or mitral regurgitation, dilated cardiomyopathy
3. Pathologic increases in afterload: poorly controlled hypertension, aortic stenosis

C. Diastolic heart failure
1. Ventricular filling during diastole is impaired.
2. Ejection fraction remains normal owing to increased left atrial contraction.
3. Reduced ventricular filling occurs as the result of one of two distinct pathophysiologic mechanisms: either a reduction in ventricular compliance or an obstruction of left ventricular filling.  
   - Reduced ventricular compliance may result from a variety of conditions:
     a. In left ventricular hypertrophy and hypertrophic cardiomyopathy, the thickened myocardium does not relax well.
     b. In restrictive cardiomyopathy, deposition of substances within the myocardium (e.g., iron, amyloid) causes fibrosis, reducing ventricular compliance.
     c. In myocardial ischemia, the O\textsubscript{2} supply is not sufficient to support the normal energy requirements of active diastolic relaxation.
   - Obstruction to left ventricular filling may occur in:
     a. Mitral stenosis and cardiac tamponade (fluid accumulates in the pericardial space and opposes ventricular filling)
     b. Restrictive pericarditis
       - Scarring of the pericardium limits ventricular expansion and filling

Pathology note: Myocardial ischemia may contribute to both systolic and diastolic dysfunction because ventricular contraction during systole and ventricular relaxation during diastole are both energy-requiring processes that depend on an adequate O\textsubscript{2} supply. The underlying cause of myocardial ischemia is typically coronary artery disease.

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>PHYSIOLOGIC MECHANISM OF EDEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease</td>
<td>↓ Plasma protein → ↓ plasma oncotic pressure</td>
</tr>
<tr>
<td>Inflammation</td>
<td>↑ Vascular permeability → ↑ proteins in interstitial fluid → ↑ oncotic pressure of interstitial fluid</td>
</tr>
<tr>
<td>Venous obstruction</td>
<td>Back-pressure resulting in capillary congestion → ↑ capillary hydrostatic pressure</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Back-pressure resulting in venous congestion → increased capillary hydrostatic pressure</td>
</tr>
<tr>
<td>Myxedema</td>
<td>↑ Glycoproteins in interstitial fluid → ↑ oncotic pressure of interstitial fluid</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Proteinuria → ↓ plasma protein → ↓ plasma oncotic pressure</td>
</tr>
<tr>
<td>Obstruction of lymphatics (e.g., filariasis, tumor)</td>
<td>Impaired lymphatic drainage of interstitium</td>
</tr>
</tbody>
</table>
D. High-output heart failure

1. Heart failure can be precipitated by “peripheral” conditions in which the body’s tissues require an ever-increasing CO.

2. For example, with large arteriovenous fistulas or in conditions such as thyrotoxicosis or severe anemia, the demand for CO becomes pathologically elevated.

3. The healthy heart is initially able to meet this increased demand, but over time the strain imposed on the heart may become too great, at which point the heart begins to fail.

E. Compensatory mechanisms in heart failure

1. The primary compensatory responses for low CO (systolic failure) include use of the Frank-Starling relationship, myocardial hypertrophy, and neurohormonal activation.

2. Table 4-3 presents the “triggers” for these compensatory responses.

3. Initially, these compensatory mechanisms may have a beneficial effect in preserving CO.

4. However, if the underlying cause of the heart failure (e.g., hypertension, coronary artery disease, valvular disease) is not addressed, the chronic activation of these compensatory mechanisms may have deleterious effects.

X. Circulatory Insufficiency

A. Signs and symptoms

1. Circulatory insufficiency, or shock, is a state of inadequate tissue perfusion, which most often occurs in hypotensive states. This inadequate tissue perfusion invokes powerful compensatory responses from the sympathetic nervous system through diversely located baroreceptors and chemoreceptors.

2. The signs and symptoms of shock, which include cold and clammy skin, rapid and weak pulse, confusion, and reduced urinary output, result as much from the inadequate tissue perfusion as from the compensatory sympathetic response.

B. Pathophysiologic basis for classification of shock

1. Overview

   • In the human circulatory system, three basic pathophysiologic processes can cause circulatory insufficiency, or shock (Tables 4-4 and 4-5).

   • Regardless of the precise pathophysiologic abnormality, the end result is impaired tissue perfusion.

2. Cardiogenic shock

   • In cardiogenic shock, the heart fails as a pump; it is unable to maintain a CO sufficient to meet the body’s metabolic demands in the presence of an adequate intravascular volume.
The most common cause is **severe left ventricular dysfunction**, which may occur after a large left-sided myocardial infarction.

a. Other causes include valvular disease (e.g., rupture of papillary muscle, causing mitral regurgitation) and myocarditis.

3. **Distributive shock**
   - In distributive types of shock, widespread vasodilation decreases the peripheral resistance substantially, thereby lowering the blood pressure to inadequate levels.
   - There are several causes of distributive shock:
     a. **Neurogenic shock**: sympathetic tone to the vasculature is removed (e.g., by severing the spinal cord in the cervical region), resulting in massive vasodilation
     b. **Septic shock**: cytokines released in response to toxins cause widespread vasodilation (called “warm” shock)
     c. **Anaphylactic shock**: histamine and **prostaglandins** released in response to allergens cause widespread vasodilation and increased capillary permeability, resulting in **fluid loss into the interstitium**

4. **Hypovolemic shock**
   - In hypovolemic shock, there is simply not enough fluid within the vascular compartment to produce an effective circulating volume through no fault of the “pump” or of the “pipes.”
   - Hypovolemic shock occurs mainly as a **result of hemorrhage**, but it may also occur in conditions such as **dehydration**.

---

**TABLE 4-5. Types of Shock**

<table>
<thead>
<tr>
<th>TYPE OF SHOCK</th>
<th>PATHOPHYSIOLOGY</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic</td>
<td>Failure of the heart to pump effectively (i.e., reduced ejection fraction), resulting in reduced cardiac output</td>
<td>Myocardial infarction, viral myocarditis</td>
</tr>
<tr>
<td>Distributive</td>
<td>Disruption of autonomic outflow from the spinal cord, which abolishes normal tonic stimulation of arteriolar contraction by sympathetic nerves</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>Septic</td>
<td>Bacterial infection of blood → release of bacterial toxins and cytokines → high fever and massive vasodilation → ↓ vascular resistance</td>
<td>Severe bacteremia</td>
</tr>
<tr>
<td>Anaphylactic</td>
<td>Massive immunoglobulin E-mediated histamine release</td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Hypovolemic</td>
<td>Hypovolemia → ↓ venous return → ↓ cardiac output</td>
<td>Hemorrhage, vomiting, diarrhea, burns, dehydration</td>
</tr>
</tbody>
</table>

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Distributive shock:
vasodilation → ↓ peripheral resistance → hypotension → tissue ischemia

**Cardiovascular Physiology 137**
I. Overview
A. Because it is essential for metabolism, oxygen must be provided in relatively large amounts to most cells.
B. Oxygen delivery has three stages
  1. External respiration
     • Gas exchange between the external environment (alveolar air) and the blood (pulmonary capillaries)
     • Any process that impairs ventilation (e.g., asthma flare) or gas exchange at the alveoli (e.g., interstitial lung disease) may impair this process
  2. Internal respiration
     • Gas exchange between the blood (systemic capillaries) and the interstitial fluid
     • Example: inhibited by carbon monoxide, which shifts the oxygen binding curve to the left (more on this later)
  3. Cellular respiration
     • Gas exchange between the interstitial fluid and the inner mitochondrial membrane of cells
     • Example: inhibited by cyanide (CN) and carbon monoxide (CO), both of which inhibit cytochrome oxidase in the electron transport chain

II. Functional Anatomy of the Respiratory System
A. Overview
   1. The respiratory system is composed of large conducting airways, which conduct air to the smaller respiratory airways.
   2. Gas exchange occurs in the respiratory airways.
   3. Because conducting airways do not directly participate in gas exchange, the space within them is termed anatomic dead space.
B. Conducting airways
   1. These include the nose, mouth, pharynx, larynx, trachea, bronchi, and conducting bronchioles.
   2. Despite their larger size, airway resistance is greater than in the respiratory airways because the conducting airways are arranged in series and airflow resistance in series is additive.
   3. Bronchi (Table 5-1)
      • The bronchi are large airways (>1 mm in diameter) that contain supportive cartilage rings.
         a. If not for these cartilage rings, the bronchi would be more likely to collapse during expiration, when intrathoracic pressures increase substantially.
         • As the bronchi branch into successively smaller airways, they have fewer cartilage rings.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>BRONCHI</th>
<th>CONDUCTING BRONCHIOLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth muscle</td>
<td>Present (many layers)</td>
<td>Present (1-3 layers)</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Epithelium</td>
<td>Pseudostratified columnar</td>
<td>Simple cuboidal</td>
</tr>
<tr>
<td>Ciliated</td>
<td>Yes</td>
<td>Yes (less)</td>
</tr>
<tr>
<td>Diameter</td>
<td>Independent of lung volume</td>
<td>Depends on lung volume</td>
</tr>
<tr>
<td>Location</td>
<td>Intraparenchymal and extraparenchymal</td>
<td>Embedded directly within connective tissue of lung</td>
</tr>
</tbody>
</table>

O2: required to synthesize adenosine triphosphate (ATP)
External respiration: inhibited by hypoventilation and impaired gas exchange at pulmonary membrane
Internal respiration: inhibited by CO
Cellular respiration: inhibited by CO and CN by interfering with electron transport chain
Gas exchange occurs in the respiratory airways.
Space within conducting airways is termed anatomic dead space.
Conducting airways: resistance because arranged in series
Bronchi contain supportive cartilage rings that prevent airway collapse during expiration.
Bronchioles: lack cartilage
a. Bronchial branches that have no cartilage and are less than 1 mm in diameter are termed **bronchioles**.

- Bronchi are not physically embedded in the lung parenchyma; this allows them to dilate and constrict independently of the lung, which helps them stay open during expiration so the lungs can empty.

**Clinical note:** In asthma, the smooth muscle of the medium-sized bronchi becomes hypersensitive to certain stimuli (e.g., pollens), resulting in bronchoconstriction. This airway narrowing produces **turbulent** airflow, which is often appreciated on examination as expiratory wheezing.

4. **Mucociliary tract**

- Bronchial epithelium comprises pseudostratified columnar cells, many of which are ciliated, interspersed with mucus-secreting goblet cells.

- The mucus traps inhaled foreign particles before they reach the alveoli.
  a. It is then transported by the beating cilia proximally toward the mouth, so that it can be swallowed or expectorated.
  b. This process is termed the **mucociliary escalator**.

**Clinical note:** Primary ciliary dyskinesia is an autosomal recessive disorder that renders cilia in airways unable to beat normally (absent dynein arm). The result is a chronic cough and recurrent infections. When accompanied by the combination of **situs inversus**, **chronic sinusitis**, and **bronchiectasis**, it is known as **Kartagener syndrome**. Cigarette smoke causes a secondary ciliary dyskinesia. Cystic fibrosis and ventilation-associated pneumonia are other examples of conditions associated with dysfunction of the mucociliary tract.

5. **Conducting bronchioles** (see Table 5-1)

- In contrast to the bronchi, these small-diameter airways are physically embedded within the lung parenchyma and do not have supportive cartilage rings.

- Therefore, as the lungs inflate and deflate, so too do these airways.

C. **Respiratory airways** (Table 5-2)

1. These include **respiratory bronchioles**, **alveolar ducts**, and **alveoli**, where gas exchange occurs.

2. Despite their smaller size, **airway resistance** is less than in conducting airways, because the respiratory airways are arranged in parallel, and airflow resistances in parallel are added reciprocally.

3. Similar to the smaller of the conducting bronchioles, the respiratory airways have no cartilage and are embedded in lung tissue; therefore, their diameter is primarily dependent on **lung volume**.

D. **Pulmonary membrane: the “air-blood” barrier** (Fig. 5-1)

1. This is a thin barrier that separates the alveolar air from the pulmonary capillary blood, through which gas exchange must occur.

2. It comprises multiple layers, including, from the alveolar space “inward”:
   a. A **surfactant-containing fluid layer** that lines the alveoli
   b. **Alveolar epithelium** composed of pneumocytes (both type I and type II)
   c. **Epithelial and capillary basement membranes**, separated by a thin interstitial space (fused in areas)
   d. **Capillary endothelium**

<table>
<thead>
<tr>
<th>TABLE 5-2. Comparison of Conducting and Respiratory Airways</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARAMETER</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Presence of cartilage</td>
</tr>
<tr>
<td>Resistance</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Type II pneumocytes:** synthesize surfactant; repair cell of lung.
Pathology note: The alveolar epithelium is primarily populated by type 1 epithelial cells, which play an important role in gas exchange. Type 2 epithelial cells are much less numerous but are important in producing surfactant (stored in lamellar bodies). When the pulmonary membrane has been damaged, type 2 epithelial cells are able to differentiate into type 1 epithelial cells and effect repair of the pulmonary membrane.

III. Mechanics of Breathing

A. Overview

1. Ventilation is the process by which air enters and exits the lungs.
2. It is characterized by inspiratory and expiratory phases.
3. Note that ventilation is a separate process from gas exchange.

Pathology note: Gas exchange may be impaired in certain conditions in which pulmonary ventilation is nevertheless normal or even increased. Two examples are anemia and high-altitude respiration.

B. Inspiration

1. Overview
   - Inspiration is an active process that requires substantial expansion of the thoracic cavity to accommodate the inspired air (Fig. 5-2).
     a. This expansion occurs primarily as a result of diaphragmatic contraction and, to a lesser extent, contraction of the external intercostal muscles (see Fig. 5-2).
   - During forceful breathing (e.g., exercise, lung disease), contraction of accessory muscles such as the sternocleidomastoid, scalenes, and pectoralis major may be necessary to assist in expanding the thorax (see Fig. 5-2A).
Clinical note: During normal inhalation at rest, abdominal pressure increases secondary to diaphragmatic contraction. This is evident by watching a supine person’s abdomen rise during quiet breathing (as long as the person is not trying to “suck in their gut”). In patients with respiratory distress, the abdomen may actually be “sucked in” while the accessory muscles of inspiration are contracting. This is known as paradoxical breathing and is an indicator of impending respiratory failure.

2. Driving force for inspiration
   - A negative intrapleural pressure is created by movement of the diaphragm downward and the chest wall outward.
     a. This acts like a vacuum and “sucks open” the airways, causing air to enter the lungs.
   - The relationship between intrapleural pressure and lung volume is expressed by Boyle’s law:

\[ P_1V_1 = P_2V_2 \]

where
- \( P_1 \) = intrapleural pressure at start of inspiration
- \( P_2 \) = intrapleural pressure at end of inspiration
- \( V_1 \) = lung volume at start of inspiration
- \( V_2 \) = lung volume at end of inspiration

a. Boyle’s law shows that as lung volume increases during inspiration, the intrapleural pressure must decrease (become more negative).

b. The pressure and volume changes that occur during the respiratory cycle are shown in Figure 5-3.

3. Sources of resistance during inspiration
   - Airway resistance: friction between air molecules and the airway walls, caused by inspired air coursing along the airways at high velocity
   - Compliance resistance: intrinsic resistance to stretching of the alveolar air spaces and lung parenchyma
Tissue resistance: friction that occurs when the pleural surfaces glide over each other during inspiration

Expiration during normal breathing: passive process due to elastic recoil of lungs and chest wall

Expiration during exercise or in lung disease: active process requiring use of accessory muscles

**C. Expiration**

1. **Overview**
   - Usually a passive process in which relaxation of the diaphragm, combined with elastic recoil of the lungs and chest wall, forces air from the lungs.
   - During forceful breathing (e.g., exercise, lung disease), expiration becomes an active process employing accessory muscles such as the internal intercostals and abdominal wall muscles (e.g., rectus abdominis).
     - a. Contraction of these muscles helps to depress the rib cage, which compresses the lungs and forces air from the respiratory tree.

2. **Driving forces for expiration**
   - An increase in intrapleural pressure is created by movement of the diaphragm upward and the chest wall inward.
     - a. This increase is then transmitted to the terminal air spaces (alveolar ducts and alveoli) and compresses them, causing air to leave the lungs.
     - b. Additionally, the recoil forces from the alveoli that were stretched during inspiration promote expiration.
   - During forced expiration, this elastic recoil of the diaphragm and chest wall is accompanied by contraction of the abdominal muscles, all of which increase the intrapleural pressure.

3. **Sources of resistance during expiration**
   - As the volume of the thoracic cavity decreases during expiration, the intrathoracic pressure increases (recall Boyle’s law—the inverse relationship of pressure and volume).
   - The increased pressure compresses the airways and reduces airway diameter.
     - a. This reduction in airway diameter is the primary source of resistance to airflow during expiration.
       - Figure 5-4 shows a flow-volume curve recorded during inspiration and expiration in a normal subject.
       - Note the linear decline during most of expiration.
       - Note also the contribution of radial fibers, which exert traction on these small airways to help prevent collapse during expiration.

**Clinical note:** If the lung were a simple pump, its maximum attainable transport of gas in and out would be limited by exhalation. During expiration, the last two thirds of the expired vital capacity is largely independent of effort. The best way to appreciate this is to do it yourself. No matter how hard you try, you cannot increase flow during the latter part of the expiratory cycle. The reduction in small airway diameter with resultant increase in airway resistance is the major determinant of this phenomenon. In contrast, large airways are mostly spared from collapse by the presence of cartilage. One can imagine the difficulty asthmatic individuals face during exhalation with the addition of bronchoconstriction.
D. Work of breathing

1. Overview

- This is the **pressure-volume work** performed in moving air into and out of the lungs.
- Because expiration is usually passive, most of this work is performed during inspiration.
- Work must be performed to overcome the three primary sources of resistance encountered during inspiration.

2. Airway resistance

- As inspired air courses along the airways, friction, and therefore airway resistance, is generated **between air molecules and the walls of conducting airways**.
  a. Airway resistance normally accounts for approximately 20% of the work of breathing.
- Because air is essentially a fluid of low viscosity, airflow resistance can be approximated by Poiseuille’s equation:

  \[
  R = \frac{8\eta l}{\pi r^4}
  \]

  - In the lung, air viscosity and airway length are basically unchanging constants, whereas airway radius can change dramatically.
  - Even slight changes in **airway diameter** have a dramatic impact on airflow resistance because of the inverse relationship of resistance to the fourth power of radius, as demonstrated in Poiseuille’s equation.

  **Pathophysiology note:** Airway diameter can be reduced (and airway resistance thereby increased) by a number of mechanisms. For example, airway diameters are reduced by smooth muscle contraction and excess secretions in **obstructive airway diseases** such as **asthma** and **chronic bronchitis**. Work caused by airway resistance increases markedly as a result.

  Note that this description is a simplification, because Poiseuille’s equation is based on the premise that airflow is laminar. Although this is true for the smaller airways, in which the total cross-sectional area is large and the airflow velocity is slow, airflow in the **upper airways** is typically **turbulent**, as evidenced by the **bronchial sounds** heard during auscultation.

- Contribution of large and small airways to resistance
  a. Under normal conditions, most of the total airway resistance actually comes from the **large conducting airways**.
  - This is because they are arranged in series, and airflow resistances in series are **additive**, such that

  \[
  R_{\text{total}} = R_1 + R_2 + R_3 + \ldots + R_n
  \]
b. By contrast, the small airways (terminal bronchioles, respiratory bronchioles, and alveolar ducts) provide relatively little resistance.
• This is because they are arranged in parallel, and airflow resistances in parallel are added reciprocally, such that
\[
1/R = 1/R_1 + 1/R_2 + 1/R_3 + \ldots + 1/R_n
\]

c. Resistance is low in smaller-diameter airways despite the fact that Poiseuille’s equation states that resistance is inversely proportional to the fourth power of airway radius.
• This is because the branches of the small airways have a total cross-sectional area that is greater than that of the larger airways from which they branch.
• Additionally, flow in these small airways is laminar rather than turbulent, and it is very slow.

Pharmacology note: Many classes of drugs affect large-airway diameter by affecting bronchial smooth muscle tone. For example, \( \beta_2 \)-adrenergic agonists such as albuterol directly stimulate bronchodilation. Most other classes work by preventing bronchoconstriction or by inhibiting inflammation (which reduces airway diameter); these include steroids, mast cell stabilizers, anticholinergics, leukotriene-receptor antagonists, and lipooxygenase inhibitors.

3. Compliance resistance (work)
• As the lungs inflate, work must be performed to overcome the intrinsic elastic recoil of the lungs.
• This work, termed compliance work, normally accounts for the largest proportion (~75%) of the total work of breathing (Fig. 5-5).

Pathology note: In emphysema, compliance work is reduced because of the destruction of lung tissue and the loss of elastin and collagen. In pulmonary fibrosis, compliance work is increased, because the fibrotic tissue requires more work to expand.

4. Tissue resistance
• As the pleural surfaces slide over each other during the respiratory cycle, friction and therefore resistance is generated.
• A small amount of pleural fluid in the pleural space acts to lubricate these surfaces, thereby minimizing the friction.
• Under normal conditions, tissue resistance accounts for a small portion (perhaps 5%) of the total work of breathing.
Pathology note: In certain pleuritic conditions, inflammation or adhesions are formed between the two pleural surfaces, which increases tissue resistance substantially. An example is empyema, in which there is pus in the pleural space.

E. Pulmonary compliance (C)
1. This is a measure of lung distensibility.
   • Compliant lungs are easy to distend.
2. Defined as the change in volume (ΔV) required for a fractional change of pulmonary pressure (ΔP):
   \[ C = \frac{\Delta V}{\Delta P} \]
3. Compliance of the lungs (Fig. 5-6)
   • In the schematic, note that the inspiratory curve has a different shape than the expiratory curve.
   • The lagging of an effect behind its cause, in which the value of one variable depends on whether the other has been increasing or decreasing, is referred to as hysteresis.
   • Hysteresis is an intrinsic property of all elastic substances, and the compliance curve of the lungs represents the difference between the inspiratory and expiratory curves.
   • Note also that compliance is greatest in the midportion of the inspiratory curve.
4. Compliance of the combined lung–chest wall system (Fig. 5-7)
   • In the schematic, note that at functional residual capacity (FRC), the lung–chest wall system is at equilibrium.
   • In other words, at FRC, the collapsing pressure from the elastic recoil of the lungs is equal to the outward pressure exerted from the chest wall.

Pathology note: In emphysema, destruction of lung parenchyma results in increased compliance and a reduced elastic recoil of the lungs because of destruction of elastic tissue by neutrophil-derived elastases. At a given FRC, the tendency is therefore for the lungs to expand because of the unchanged outward pressure exerted by the chest wall. The lung–chest wall system adopts a new higher FRC to balance these opposing forces. This is part of the reason patients with emphysema breathe at a higher FRC. Breathing at a higher FRC also keep more airways open, which decreases airway resistance and minimizes dynamic airway compression during expiration.

F. Pulmonary elastance
1. Elastance is the property of matter that makes it resist deformation.
   • Highly elastic structures are difficult to deform.
2. Pulmonary elastance (E) is the pressure (P) required for a fractional change of lung volume (ΔV):
   \[ E = \frac{\Delta P}{\Delta V} \]

5-6: Compliance curve of the lungs: lung volume plotted against changes in transpulmonary pressure (the difference between pleural and alveolar pressure). During inspiration, maximal compliance occurs in the midportion of the inspiratory curve. The difference between the inspiration curve and the expiration curve is referred to as hysteresis. Hysteresis is an intrinsic property of all elastic substances.
3. As elastance increases, increasingly greater pressure changes will be required to distend the lungs.

**Clinical note:** In restrictive lung diseases such as silicosis and asbestosis, inspiration becomes increasingly difficult as the resistance to lung expansion increases in response to increased lung elastance, resulting in reduced lung volumes and total lung capacity. In obstructive lung diseases such as emphysema, there is reduced lung elastance secondary to destruction of lung parenchyma and loss of proteins that contribute to the elastic recoil of the lungs (e.g., collagen, elastin). Expiration may therefore become an active process (rather than a passive one), even while at rest, because the easily collapsible airways “trap” air in the lungs. “Pursed-lip breathing,” an attempt to expire adequate amounts of air, is often seen; it creates an added pressure within the airways that keeps them open and allows for more effective expiration.

**G. Surface tension**

1. The fluid lining the alveolar membrane is primarily water.
2. The water molecules are attracted to each other through noncovalent hydrogen bonds and are repelled by the hydrophobic alveolar air.
3. The **attractive forces between water molecules** generate **surface tension** \( T \), which in turn produces a **collapsing pressure**, which acts to collapse the alveoli.
4. **Laplace’s law** states that collapsing pressure is inversely proportional to the alveolar radius, such that smaller alveoli experience a larger collapsing pressure:

   \[
   CP = \frac{T}{R}
   \]

   where
   
   \( CP \) = collapsing pressure
   
   \( R \) = alveolar radius
   
   \( T \) = surface tension

5. Figure 5-8 demonstrates that saline-inflated lungs are more compliant than air-inflated lungs because of reduced surface tension and collapsing pressures.

---

Surface tension: created by attractive forces between water molecules; produces a collapsing pressure.

Compliance of saline-inflated lungs: greater than air-filled lungs because of reduced surface tension and alveolar collapsing pressure.

Laplace’s law: collapsing pressure inversely proportional to alveolar radius; \( CP = \frac{T}{R} \).
Clinical note: The collapse of many alveoli in the same region of lung parenchyma leads to **atelectasis**. Atelectatic lung may result from **external compression**, as may occur with pleural effusion or tumor; a prolonged period of "shallow breaths," as may occur with pain (e.g., rib fracture) or diaphragmatic paralysis; or **obstruction of bronchi** (e.g., tumor, pus, or mucus).

H. **Role of surfactant**

1. **Surfactant** is a **complex phospholipid** secreted onto the alveolar membrane by **type 2 epithelial cells**.
   - It minimizes the interaction between alveolar fluid and alveolar air (Fig. 5-9), which reduces surface tension.
   - This increases lung compliance, which reduces the work of breathing.

2. **Surfactant reduces compliance resistance** (work) of the lungs.
   - A moderate amount of surface tension is beneficial because it generates a collapsing pressure that contributes to the elastic recoil of the lungs during expiration.
   - However, if collapsing pressure were to become pathologically elevated, lung inflation during inspiration would become impaired.
   - So a balance needs to be reached, and this is mediated by surfactant.
Clinical note: The collapsing pressure of alveoli in infants born before approximately 34 weeks of gestation may be pathologically elevated for two reasons: (1) the alveoli are small, which contributes to an elevated collapsing pressure (recall Laplace’s law); and (2) surface tension may be abnormally increased because surfactant is not normally produced until the third trimester of pregnancy. There is therefore a high risk for respiratory failure and neonatal respiratory distress syndrome (hyaline membrane disease) in these infants. Mothers in premature labor are frequently given corticosteroids to stimulate the fetus to produce surfactant. After birth, exogenous surfactant or artificial respiration may also be required.

IV. Gas Exchange
A. Overview
1. Gas exchange across the pulmonary membrane occurs by diffusion.
2. The rate of diffusion is dependent on the partial pressure (tension) of the gases on either side of the membrane and the surface area available for diffusion, among other factors (Fig. 5-10).
B. Partial pressure of gases
1. According to Dalton’s law, the partial pressure exerted by a gas in a mixture of gases is proportional to the fractional concentration of that gas:

$$P_x = P_B \times F$$

where

- $P_x$ = partial pressure of the gas (mm Hg)
- $P_B$ = barometric pressure (mm Hg)
- $F$ = fractional concentration of the gas
2. The partial pressure of $O_2$ in the atmosphere ($P_O_2$) at sea level, which has a fractional concentration of 21%, is calculated as follows:

$$P_x = P_B \times F$$

$$P_O_2 = 760 \text{ mm Hg} \times 0.21 = 160 \text{ mm Hg}$$

3. The partial pressure of $O_2$ in humidified tracheal air is calculated as follows:

$$P_x = (P_B - P_{H_2O}) \times F$$

$$P_O_2 = (760 - 47) \times 0.21 = 150 \text{ mm Hg}$$

- Note that the addition of $H_2O$ vapor decreases the percent concentration of $O_2$ in alveolar air and hence decreases its partial pressure (Table 5-3).
- This “dilution” of partial pressures by $H_2O$ vapor becomes very important at high altitudes, where atmospheric oxygen tension is already low.

Example: Assume a mountain climber at high altitude is exposed to an atmospheric pressure of 460 mm Hg. What would the partial pressure of alveolar oxygen be in this person?

Again we have to consider the dilution of inspired air with water vapor. Assuming a fractional concentration of $O_2$ of 21% and an atmospheric pressure of 460 mm Hg:
\[ P_{A02} = (P_B - P_{H, O}) \times F \]
\[ P_{A02} = (460 - 47) \times 0.21 \]
\[ P_{A02} = 413 \times 0.21 = 86.7 \text{ mm Hg} \]

Note that the value of 86.7 mm Hg is less than the \( P_{A02} \) of 97 mm Hg that would be expected in the absence of dilution of inspired air with water vapor.

### TABLE 5-3: Comparison of Partial Gas Pressures (mm Hg)

<table>
<thead>
<tr>
<th>GAS</th>
<th>ATMOSPHERIC</th>
<th>ALVEOLAR</th>
<th>ARTERIAL</th>
<th>VENOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>( O_2 )</td>
<td>160</td>
<td>100</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>( CO_2 )</td>
<td>0.3</td>
<td>40</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>( N_2 )</td>
<td>600</td>
<td>573</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>( H_2O )</td>
<td>0</td>
<td>47</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

### C. Diffusion

1. The **diffusion rate** of oxygen across the pulmonary membrane depends on:
   - The **pressure gradient** (\( \Delta P \)) between alveolar oxygen and oxygen within the pulmonary capillaries
   - The **surface area** (A) of the pulmonary membrane
   - The **diffusion distance** (T) across which \( O_2 \) must diffuse

2. These variables are expressed in **Fick’s law of diffusion**, where the solubility coefficient for oxygen (S) is an unchanging constant; its importance relates to the concept that the rate of diffusion is in part proportional to the concentration gradient of \( O_2 \) across the pulmonary membrane.

\[
D = \frac{\Delta P \times A \times S}{T}
\]

**Pathophysiology note:** Oxygen diffusion is impaired by any process that decreases the \( O_2 \) pressure gradient (e.g., high altitude), decreases the surface area of the pulmonary membrane (e.g., emphysema), or increases the diffusion distance (e.g., pulmonary fibrosis).

### D. Diffusing capacity of the pulmonary membrane

1. This is the **volume of gas** that can diffuse across the pulmonary membrane in 1 minute when the pressure difference across the membrane is 1 mm Hg.
   - It is often measured using **carbon monoxide** (Fig. 5-11).

2. The diffusing capacity of the lungs is normally so great that \( O_2 \) exchange is **perfusion limited**: that is, the amount of \( O_2 \) that enters the arterial circulation is limited only by the amount of blood flow to the lungs (cardiac output).

3. In various types of lung disease, the diffusing capacity may be reduced to such an extent that \( O_2 \) exchange becomes **diffusion limited**.

**Diffusing capacity (D\(_{LCO}\))**

- Requires:
  - \( CO \) reach alveoli
  - \( CO \) cross septum
  - \( CO \) bind to Hb in RBCs

**5-11:** Showing diffusion of \( CO \) across the pulmonary membrane and binding to hemoglobin (Hb). RBC, Red blood cell. *(From Goljan EF, Sloka K: Rapid Review Laboratory Testing in Clinical Medicine. Philadelphia, Mosby, 2008, Fig. 3-7.)*
Pathophysiology note: A number of pathophysiologic mechanisms reduce diffusing capacity: (1) increased thickness of the pulmonary membrane in restrictive diseases (the primary factor in silicosis and idiopathic pulmonary fibrosis); (2) collapse of alveoli and lung segments (atelectasis), which contributes to a decreased surface area available for gas exchange (e.g., with bed rest after surgery); (3) poor lung compliance, resulting in insufficient ventilation (e.g., silicosis); and (4) destruction of alveolar units, which also decreases surface area (e.g., emphysema).

E. Perfusion-limited and diffusion-limited gas exchange

1. Perfusion-limited exchange
   • Gas equilibrates early along the length of the pulmonary capillary such that the partial pressure of the gas in the pulmonary capillary equals that in the alveolar air.
   • Diffusion of that gas can be increased only if blood flow increases.
   • Figure 5-12 shows the perfusion-limited uptake of nitrous oxide and O₂ (under normal conditions).

2. Diffusion-limited exchange
   • Gas does not equilibrate by the time the blood reaches the end of the pulmonary capillary such that the partial pressure difference of the gas between alveolar air and arterial blood is maintained.
   • Diffusion continues as long as a partial pressure gradient exists.
   • Can occur with O₂ under abnormal conditions, for example, with exercise in interstitial lung disease and in healthy people who are vigorously exercising at very high altitudes
   • Figure 5-12 illustrates that diffusion of carbon monoxide across the pulmonary membrane is diffusion limited.

V. Pulmonary Blood Flow

A. Pressures in the Pulmonary Circulation
   • Despite receiving the entire cardiac output, pressures in the pulmonary circulation are remarkably low compared with the systemic circulation.

5-12: Uptake of N₂O, O₂, and CO across the pulmonary membrane. (From West JB: Respiratory Physiology: The Essentials, 8th ed. Philadelphia, Lippincott Williams & Wilkins, 2008, Fig. 3-2.)
1. Figure 5-13 compares pressures in the pulmonary and systemic circulation.
2. Note the markedly lower pressures in the pulmonary circulation.
3. Note also the relatively small pressure drop across the pulmonary capillary bed, which contrasts with the large pressure drop across the systemic capillary beds.

B. "Zones" of pulmonary blood flow (Fig. 5-14)
1. In the upright position, when the effects of gravity are apparent, the lung apices are relatively underperfused, whereas the lung bases are relatively overperfused.
   • For this reason, pulmonary blood flow is often described as being divided into three different zones.
2. Zone 1 blood flow
   • Zone 1 has no blood flow during the cardiac cycle, a pathologic condition that does not normally occur in the healthy lung.
   • The lack of perfusion that occurs with zone 1 pulmonary blood flow quickly leads to tissue necrosis and lung damage.
   • Zone 1 conditions occur when hydrostatic arterial and venous pressures are lower than alveolar pressures.
     a. This can occur in the lung apices, where arterial hydrostatic pressures are reduced relative to the pressures in arteries supplying the lower lung fields.
     b. Under these conditions, the blood vessel is completely collapsed, and there is no blood flow during either systole or diastole.

---

**Figure 5-13:** Comparison of pressures in the pulmonary and systemic circulations. Cap, Capillaries; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (From West JB: Respiratory Physiology: The Essentials, 8th ed. Philadelphia, Lippincott Williams & Wilkins, 2008, Fig. 4-1.)

**Figure 5-14:** Zones of pulmonary blood flow. Note the vertical position of the heart relative to the lung zones. $P_{av}$, Alveolar partial pressure; $P_{art}$, arterial partial pressure; $P_{ven}$, venous partial pressure.
3. **Zone 2 blood flow**
   - Zone 2 has *intermittent* blood flow during the cardiac cycle, with no blood flow during diastole.
     a. This is typically exhibited by the **upper two thirds of the lungs**.
   - Alveolar pressures cause collapse of pulmonary capillaries during diastole, but pulmonary capillary pressures during systole exceed alveolar pressures, resulting in perfusion during systole.
4. **Zone 3 blood flow**
   - Zone 3 has **continuous blood flow** during the cardiac cycle.
     a. This pattern of blood flow is characteristic of the **lung bases**, which are situated below the heart.
   - Pulmonary capillary pressures are greater than alveolar pressures during systole and diastole, which means that the pulmonary capillaries remain patent throughout the cardiac cycle.

**Clinical note:** Zone 3 conditions are exploited during hemodynamic monitoring with the use of a **Swan-Ganz** or pulmonary artery catheter. The catheter is inserted through a central vein and advanced into the pulmonary artery. An inflated balloon at the distal tip of the catheter allows it to "wedge" into a distal branch of the pulmonary artery. Under zone 3 conditions, a static column of blood extends from the catheter, through the pulmonary capillary bed, to the left atrium, and ultimately to the left ventricle. When the balloon is inflated, the pulmonary artery occlusion pressure or "wedge pressure" is obtained. This is an indirect measurement of the left ventricular end-diastolic pressure (LVEDP). LVEDP is a surrogate measurement of left ventricular end-diastolic volume, which is an indicator of cardiac performance and volume status.

C. **Ventilation-perfusion (V/Q) matching** (Fig. 5-15)

1. For gas exchange to occur *efficiently* at the pulmonary membrane, pulmonary ventilation and perfusion should be well “matched.”
2. Optimal matching minimizes unnecessary ventilation of nonperfused regions and perfusion of nonventilated areas.
3. Figure 5-15 shows V/Q matching in different parts of the lung at rest.
   - The value of V/Q at rest is approximately 0.8, with alveolar ventilation of about 4 L/minute and cardiac output of 5 L/minute.
   - The lung apices at rest are underperfused and relatively overventilated (V/Q ratio, ~3.3), but compared with the lung bases, they do not receive as much ventilation.
   - The high V/Q ratio indicates the discrepancy between the amount of blood flow and ventilation. Conversely, the lung bases at rest are relatively overperfused (V/Q ratio, ~0.6).
4. **Mechanisms of maintaining V/Q matching**
   - Optimal matching of pulmonary ventilation and perfusion is achieved by **hypoxia-induced vasoconstriction** and by changes in response to **exercise**.

![V/Q matching chart](image)

**C. Ventilation-perfusion (V/Q) matching (Fig. 5-15)**

<table>
<thead>
<tr>
<th>V/Q ratio</th>
<th>Ventilation (L/min)</th>
<th>Perfusion (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung apices</td>
<td>3.3</td>
<td>4</td>
</tr>
<tr>
<td>Lung bases</td>
<td>0.6</td>
<td>6</td>
</tr>
</tbody>
</table>

5-15: Ventilation-perfusion (V/Q) matching in the different parts of the lungs (at rest).
• Hypoxia-induced vasoconstriction
  a. In most capillary beds, hypoxia stimulates vasodilation (e.g., myogenic response of autoregulation; see Chapter 4).
  b. However, in the pulmonary vasculature, hypoxia stimulates vasoconstriction of pulmonary arterioles, essentially preventing the perfusion of poorly ventilated lung segments (e.g., as might occur in pulmonary disease).
  c. This hypoxia-induced vasoconstriction allows the lungs to optimize V/Q matching for more efficient gas exchange.

Clinical note: Hypoxia-induced vasoconstriction is particularly well demonstrated in the nonventilated fetal lungs. The resulting vasoconstriction of the pulmonary vessels shunts most of the blood from the pulmonary circulation to the rest of the body. After delivery, when ventilation is established, the pulmonary vascular resistance drops quickly, and blood is pumped through the lungs for oxygenation.

Pathology note: At high altitudes, where the alveolar partial pressure of O₂ is low, pulmonary vasoconstriction may become harmful, leading to a global hypoxia-induced vasoconstriction. This further inhibits gas exchange and increases pulmonary vascular resistance, contributing to the development of right-sided heart failure (cor pulmonale).

• Changes with exercise
  a. Only about one third of the pulmonary capillaries are open at rest.
  b. During exercise, additional capillaries open (recruitment) because of increased pulmonary artery blood pressure.
  c. Capillaries that are already open dilate to accommodate more blood (distension) (Fig. 5-16).
  d. During exercise, ventilation and perfusion (and hence gas exchange) occur more efficiently because
    • With increased cardiac output, blood flow is increased to the relatively underperfused lung apices.
    • Ventilation is increased to the relatively underventilated lung bases.

5-16: Increased pulmonary perfusion occurs through two mechanisms: opening (recruitment) of previously closed capillaries and dilation (distension) of already open capillaries. (From West JB: Respiratory Physiology: The Essentials, 8th ed. Philadelphia, Lippincott Williams & Wilkins, 2008, Fig. 4-5.)
Clinical note: At rest, a typical red blood cell (RBC) moves through a pulmonary capillary in approximately 1 second. O₂ saturation takes only approximately 0.3 second. This “safety cushion” of approximately 0.7 second is essential for O₂ saturation of hemoglobin during exercise, when the velocity of pulmonary blood flow greatly increases and the RBC remains in the pulmonary capillary for much less time.

D. Shunts
1. A shunt refers to blood that bypasses the lungs or for another reason does not participate in gas exchange (Table 5-4).
   • There are two types of shunts: anatomic and physiologic
2. Anatomic shunt
   • This occurs when blood that would normally go to the lungs is diverted elsewhere.  
   • Fetal blood flow is the classic example.
     a. In the fetus, gas exchange occurs in the placenta, so most of the cardiac output either is shunted from the pulmonary artery to the aorta through the ductus arteriosus or passes through the foramen ovale between the right and left atria.
   • Intracardiac shunting is another example.
     a. Right-to-left shunts result in the pumping of deoxygenated blood to the periphery, as occurs in a ventricular septal defect.
     • Hypoxia results and cannot be corrected with oxygen administration.
     b. Left-to-right shunts do not cause hypoxia but can cause bilateral ventricular hypertrophy.
     • Patent ductus arteriosus is an example.
3. Physiologic shunt
   • This occurs when blood is appropriately directed to the lungs but is not involved in gas exchange.
   • The classic example here is the bronchial arterial circulation.
     a. The bronchial arteries supply the bronchi and supporting lung parenchyma but are not involved in gas exchange at the level of the alveoli.
   • In pathologic states such as pneumonia or pulmonary edema, impaired ventilation may result in perfusion of unventilated alveoli.
     a. This is another example of a physiologic shunt.

<table>
<thead>
<tr>
<th>TABLE 5.4. Types of Shunt</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Physiologic</td>
</tr>
<tr>
<td>Anatomic</td>
</tr>
<tr>
<td>Left-to-right</td>
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<tr>
<td>Right-to-left</td>
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</table>

VI. Lung Volumes
A. Overview
1. Total lung capacity comprises several individual pulmonary volumes and capacities.
   • Spirometry is used to measure these (Fig. 5-17).
2. There are four pulmonary volumes (tidal volume, inspiratory reserve, expiratory reserve, and residual volume).
3. All but residual volume can be measured directly with volume recorders.

Clinical note: Lung volumes tend to decrease in restrictive lung diseases (e.g., pulmonary fibrosis) because of limitations of pulmonary expansion, and they tend to increase in obstructive lung diseases (e.g., emphysema) as a result of increased compliance. Note that in patients with both restrictive and obstructive disease, lung volumes may remain relatively normal.
B. Tidal volume (VT)
1. The volume of air inspired or expired with each breath
2. Varies with such factors as age, activity level, and position
3. In a resting adult, a typical tidal volume is about **500 mL**

C. Inspiratory reserve volume (IRV)
1. The maximum volume of air that can be inspired beyond a normal tidal inspiration
2. Typically about **3000 mL**

D. Expiratory reserve volume (ERV)
1. The maximum volume of air that can be exhaled after a normal tidal expiration
2. Typically about **1100 mL**

E. Residual volume (RV)
1. The amount of air remaining in the lungs after maximal forced expiration
2. Typically slightly more than **1000 mL**
   - The lungs cannot be completely emptied of air, because cartilage in the major airways prevent their total collapse; furthermore, not all alveolar units completely empty before the small conducting airways that feed them collapse, owing to lack of cartilage support against elastic recoil pressures.
3. Measurement of residual volume
   - Spirometry measures the volume of air entering and leaving the lungs.
     a. It cannot measure static volumes of air in the lungs such as residual volume, total lung capacity, or functional residual capacity.
   - The residual volume can, however, be measured by **helium dilution**.
     a. In this technique, a spirometer is filled with a mixture of helium (He) and oxygen (Fig. 5-18).
b. After taking several breaths at FRC, the concentration of He becomes equal in the spirometer and lung.

c. Because no helium is lost from the spirometer-lung system (helium is virtually insoluble in blood), the amount of He present before equilibrium \( \frac{C_1}{V_1} \) equals the amount after equilibrium \( \frac{C_2}{V_1 + V_2} \).

d. Rearranging yields the following:

\[
\frac{C_1}{V_1} = \frac{C_2}{(V_1 + V_2)} = \frac{V_1}{C_1 - C_2} \]

where

- \( V_1 \) = volume of gas in spirometer
- \( V_2 \) = total gas volume (volume of lung + volume of spirometer)
- \( C_1 \) = initial concentration of helium
- \( C_2 \) = final concentration of helium

\[ V_2 = V_1 \frac{C_1}{C_2} \]

Clinical note: Expiration is compromised in obstructive airway diseases, and residual volume may progressively increase because inspiratory volumes are always slightly greater than expiratory volumes. This explains the “barrel-chested” appearance of patients with emphysema. Dynamic air trapping during exercise is a major limitation to rigorous activity in patients with chronic obstructive pulmonary disease (COPD).

C. Inspiratory capacity (IC)
- The maximum volume of air that can be inhaled after a normal tidal expiration:

\[
IC = V_T + IRV = 500 \text{ mL} + 3000 \text{ mL} = 3500 \text{ mL}
\]

D. Vital capacity (VC)
- The maximum volume of air that can be expired after maximal inspiration; hence, it is sometimes called the forced vital capacity (FVC):

\[
VC = IRV + V_T + ERV = IC + ERV = 3000 \text{ mL} + 500 \text{ mL} + 1100 \text{ mL} = 4600 \text{ mL}
\]
Clinical note: Although patients with restrictive lung disease do not have difficulty emptying their lungs, FVC typically decreases because they are unable to adequately fill their lungs during inspiration.

E. Forced expiratory volume (FEV\textsubscript{1}) and FEV\textsubscript{1}/FVC ratio

1. FEV\textsubscript{1} is the maximum amount of air that can be exhaled in 1 second after a maximal inspiration.
2. In healthy individuals, the FEV\textsubscript{1} typically constitutes about 80% of FVC; this relationship is usually expressed as a ratio:
   \[
   \text{FEV}_1 / \text{FVC} = 0.8
   \]
3. The FEV\textsubscript{1}/FVC ratio is clinically useful in helping to distinguish between restrictive and obstructive lung disease.
   - The FEV\textsubscript{1}/FVC ratio decreases in obstructive lung disease and increases in restrictive lung disease.
   - Figure 5-19 depicts a flow-volume loop recorder which illustrates the differences in airflow patterns between obstructive and restrictive lung disease.

Pathology note: Although FEV\textsubscript{1} and FVC are both reduced in lung disease, the degree of reduction depends on the nature of the disease:

In restrictive diseases, inspiration is limited by noncompliance of the lungs, which limits expiratory volumes. However, because the elastic recoil of the lungs is largely preserved (if not increased), the FVC is typically reduced more than is the FEV\textsubscript{1}, resulting in an FEV\textsubscript{1}/FVC ratio that is normal or increased.

In obstructive diseases, expiratory volumes are reduced because of airway narrowing and sometimes a loss of elastic recoil in the lungs. Total expiratory volumes are largely preserved, but the ability to exhale rapidly is substantially reduced. Therefore, FEV\textsubscript{1} is reduced more than FVC, and the FEV\textsubscript{1}/FVC ratio is reduced.

F. Total lung capacity (TLC)

- The maximum volume of air in the lungs after a maximal inspiration:
  \[
  \text{TLC} = \text{IRV} + \text{Vr} + \text{ERV} + \text{RV}
  = 3000 \text{ mL} + 500 \text{ mL} + 1100 \text{ mL} + 1200 \text{ mL}
  = 5800 \text{ mL}
  \]

VIII. Pulmonary Dead Space

A. Overview

1. Refers to portions of the lung that are ventilated but in which no gas exchange occurs
2. There are three types of dead space: anatomic, alveolar, and physiologic

\[\text{Fig. 5-19: Flow-volume loop showing the difference between an obstructive (A), normal, and restrictive (B) airflow pattern. (From Goljan EF, Sloka K: Rapid Review Laboratory Testing in Clinical Medicine. Philadelphia, Mosby, 2008, Fig 3-4.)}\]
B. Anatomic dead space
1. Before inspired air reaches the terminal respiratory airways, where gas exchange occurs, it must first travel through the conducting airways.
   • Anatomic dead space is the volume of those conducting airways that do not exchange oxygen with the pulmonary capillary blood.
2. It is estimated as approximately 1 mL per pound of body weight for thin adults, or about 150 mL in a 150-pound man.

Clinical note: In patients who require mechanical ventilation, the amount of anatomic dead space increases considerably. This is because the volume of space occupied by the respiratory apparatus from the patient’s mouth to the ventilator must be considered to be anatomic dead space. Therefore, alveolar ventilation (described later) is altered, and care must be taken to ensure adequate oxygenation.

C. Alveolar dead space
1. Volume of alveoli that are ventilated but not supplied with blood (e.g., as might occur with pulmonary embolism).
   • This volume of air does not contribute to the alveolar $P_{ACO_2}$ (see later discussion).
2. In healthy young adults, alveolar dead space is almost zero.

D. Physiologic dead space
1. This is the total volume of lung space that does not participate in gas exchange.
2. It is the sum of the anatomic and alveolar dead spaces.
3. Can be calculated as follows:
   $$ V_D = \frac{V_T}{P_{ACO_2}} \times \left( \frac{P_{CO_2} - P_{ECO_2}}{P_{CO_2}} \right) $$
   where
   - $V_D$ = physiologic dead space (mL)
   - $V_T$ = tidal volume (mL)
   - $P_{ACO_2}$ = $P_{CO_2}$ of arterial blood (mm Hg)
   - $P_{ECO_2}$ = $P_{CO_2}$ of expired air (mm Hg)

Clinical note: Alveolar dead space is typically of minimal significance. However, in pulmonary airway or vascular disease, it can become substantial, and it may contribute substantially to a pathologically elevated physiologic dead space.

E. Alveolar ventilation
1. Because not all inspired air reaches the alveoli, pulmonary ventilation needs to be differentiated from alveolar ventilation.
2. The minute ventilation rate (i.e., pulmonary ventilation per minute) is calculated as follows (typical values):
   $$ \text{Minute ventilation} (V) = \text{respiratory rate} \times \text{tidal volume} $$
   $$ = 12 \text{ breaths/minute} \times 500 \text{ mL/breath} $$
   $$ = 6 \text{ L/minute} $$
3. To calculate alveolar ventilation, the physiologic dead space must be taken into account.
   • In a 150-pound healthy man with a physiologic dead space of 150 mL:
     $$ \text{Alveolar ventilation} (V_A) = \text{respiratory rate} \times \left( \text{tidal volume} - \text{physiologic dead space} \right) $$
     $$ = 12 \text{ breaths/minute} \times (500 \text{ mL/breath} - 150 \text{ mL}) $$
     $$ = 4.2 \text{ L/minute} $$
   • In the same man, if obstructive lung disease resulted in a substantial increase in physiologic dead space, from 150 to 350 mL, there would be a drastic reduction in alveolar ventilation:
     $$ V_A = 12 \text{ breaths/minute} \times (500 \text{ mL/breath} - 350 \text{ mL}) $$
     $$ = 1.8 \text{ L/minute} $$
Clinical note: If alveolar ventilation falls to a level too low to provide sufficient oxygen to the tissue, patients must compensate by increasing the rate of breathing (tachypnea) or by taking larger-volume tidal breaths. Taking larger tidal breaths would be better because it minimizes the effect of dead space on alveolar ventilation.

IX. Oxygen Transport
A. Overview
1. Oxygen is transported in the blood in two forms, dissolved (unbound) oxygen and oxygen bound to the protein hemoglobin.
2. Because O\textsubscript{2} is poorly soluble in plasma, it is transported in significant amounts only when bound to hemoglobin.
B. Oxygen tension: free dissolved oxygen
1. Just as carbonated soft drinks are “pressurized” by dissolved carbon dioxide, so too is blood pressurized by dissolved O\textsubscript{2}.
2. The pressure this dissolved oxygen exerts in blood is termed the oxygen tension or \( P_{\text{O}_2} \), which typically approximates 100 mm Hg in arterial blood.
3. The amount of dissolved O\textsubscript{2} that it takes to exert a pressure of 100 mm Hg is small, representing approximately 2% of the total volume of oxygen in blood.
4. The \( P_{\text{O}_2} \) is directly measured in the clinical laboratory.
   • A decreased \( P_{\text{O}_2} \) (<75 mm Hg) is called hypoxemia.

Clinical note: The alveolar-arterial (A-a) gradient is helpful in detecting inadequate oxygenation of blood, in which case it is increased. It is the difference between the alveolar oxygen tension (\( P_{\text{AO}_2} \)) and the arterial oxygen tension (\( P_{\text{aO}_2} \)):

\[
\text{A-a gradient} = P_{\text{AO}_2} - P_{\text{aO}_2}
\]

The \( P_{\text{aO}_2} \) is determined by an arterial blood gas (ABG) analysis, and the \( P_{\text{AO}_2} \) is calculated as follows:

\[
P_{\text{AO}_2}(\text{mm Hg}) = (F_iO_2 \times (P_{\text{atm}} - P_{H_2O})) - (P_{\text{CO}_2}/R)
\]

where \( F_iO_2 \) = fractional inspired oxygen concentration (0.21 mm Hg for room air), \( P_{\text{atm}} \) = atmospheric pressure (in mm Hg), \( P_{H_2O} \) = partial pressure of water (47 mm Hg at normal body temperature), \( P_{\text{CO}_2} \) = arterial CO\textsubscript{2} tension, and \( R \) = respiratory quotient (an indicator of the relative utilization of carbohydrates, proteins, and fats as “fuel”; although \( R \) varies depending on “fuel” utilization, a value of 0.8 is typically used).

\( P_{\text{aO}_2} \) decreases and the normal A-a gradient increases with age, and the A-a gradient ranges from 7 to 14 mm Hg when breathing room air. Conditions associated with an elevated A-a gradient are caused by V/Q mismatch, shunts, and diffusion defects. Examples are listed in Table 5-5.

C. Oxygen content of the blood
1. Includes the amount of O\textsubscript{2} bound to hemoglobin and dissolved in plasma
2. Most (~98%) of this O\textsubscript{2} is bound to hemoglobin, with relatively little dissolved in blood.
   • Each gram of hemoglobin can bind between 1.34 and 1.39 mL of O\textsubscript{2}.
   • Therefore, a typical man with a hemoglobin concentration of 15 g/dL has an oxygen-carrying capacity of ~20 mL/dL, or 20%.

<table>
<thead>
<tr>
<th>V/Q MISMATCH</th>
<th>SHUNT</th>
<th>DIFFUSION DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>Intracardiac (e.g., VSD)</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Airway obstruction</td>
<td>Intrapulmonary (e.g., pulmonary AVM, pneumonia, CHF)</td>
<td>Emphysema</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Atelectasis</td>
<td>Asbestosis</td>
</tr>
</tbody>
</table>

AVM, Arteriovenous malformation; CHF, congestive heart failure; V/Q, ventilation-perfusion; VSD, ventricular septal defect.
3. To calculate the amount of dissolved $\text{O}_2$ in blood we can invoke Henry’s law, as shown:

$$C_x = P_x \times S$$

where

$C_x =$ concentration of dissolved gas ($\text{mL gas/100 mL blood}$)

$P_x =$ partial pressure of the gas ($\text{mm Hg}$) in the liquid phase

$S =$ solubility of gas in the liquid

• Therefore, the calculation for dissolved $\text{O}_2$ in blood is as shown below, assuming $\text{O}_2$ solubility constant of $0.003 \text{ mL/100 mL blood}$ is shown as:

$$\text{Dissolved}[\text{O}_2] = 100 \text{ mm Hg} \times 0.003 \text{ mL O}_2/100 \text{ mL blood/mm Hg}$$

$$= 0.3 \text{ mL O}_2/100 \text{ mL blood}$$

Pathology note: Conditions associated with a reduced oxygen-carrying capacity include anemia and methemoglobinemia.

D. Hemoglobin

1. Types of hemoglobin

• Tetrameric protein with two $\alpha$-subunits and two $\beta$-subunits held by covalent bonds
  a. Each subunit binds one $\text{O}_2$ molecule.
  b. A hemoglobin molecule can therefore carry a maximum of four $\text{O}_2$ molecules at once.

• Fetal hemoglobin ($\text{Hb F}$) comprises two $\alpha$- and two $\gamma$-subunits. $\text{Hb F}$ has a higher affinity for oxygen than adult hemoglobin does.
  a. This causes increased release of oxygen to the fetal tissues, which is important for survival of the fetus in its relatively hypoxemic environment.

2. $\text{O}_2$ binding to hemoglobin

• Each of the four hemoglobin subunits contains a heme group, which is an iron-containing porphin moiety that contains iron in the ferrous state ($\text{Fe}^{2+}$).
  • This heme group binds $\text{O}_2$ in a cooperative manner; that is, within a hemoglobin molecule, the binding of $\text{O}_2$ to one heme group enhances the binding of $\text{O}_2$ to another heme group, and so on.
  • Hemoglobin in the taut or deoxyhemoglobin form has a low affinity for $\text{O}_2$.
  • Upon binding of $\text{O}_2$ to deoxyhemoglobin, however, hemoglobin takes on a relaxed form that has a much higher affinity for $\text{O}_2$.

Clinical note: Methemoglobin is an altered form of hemoglobin in which the ferrous ($\text{Fe}^{2+}$) iron of heme are oxidized to the ferric ($\text{Fe}^{3+}$) state. Oxidizing agents include nitrates, nitrites, and sulfa compounds. The ferric form of hemoglobin is unable to bind $\text{O}_2$, so patients with methemoglobinemia have functional anemia. Patients present with cyanosis (decreased $\text{O}_2$ saturation) despite having a normal $\text{PaO}_2$. The blood may appear blue, dark red, or a chocolate color and does not change with the addition of oxygen. Methemoglobinemia may be congenital, or it may occur secondary to certain drugs or exposures (e.g., trimethoprim, aniline dyes, sulfonamides).

3. Hemoglobin-$\text{O}_2$ dissociation curve

• The hemoglobin-$\text{O}_2$ dissociation curve (Fig. 5-20) has a sigmoidal shape, which represents the increasing affinity of hemoglobin for $\text{O}_2$ with increasing $\text{PaO}_2$ (“loading phase”) and the decreasing affinity of hemoglobin for $\text{O}_2$ with decreasing $\text{PaO}_2$ (“unloading phase”).

Clinical note: Carbon monoxide ($\text{CO}$) is a colorless, odorless gas formed by hydrocarbon combustion that diffuses rapidly across the pulmonary capillary membrane. Hemoglobin has a very high affinity for $\text{CO}$ (240 times its affinity for $\text{O}_2$). $\text{CO}$ avidly binds to hemoglobin to form carboxyhemoglobin, which has greatly diminished ability to bind $\text{O}_2$. Nonsmokers may normally have up to 3% carboxyhemoglobin at baseline; this may increase to 10% to 15% in smokers.
When CO binds to hemoglobin, the conformation of the hemoglobin molecule is changed in a way that greatly diminishes the ability of the other O2-binding sites to offload oxygen to tissues. Blood Po2 tends to remain normal because Po2 measurement usually reflects O2 dissolved in blood, not that bound to hemoglobin. Carbon monoxide poisoning is treated with 100% oxygen and/or hyperbaric oxygen. When carboxyhemoglobin reaches a level of approximately 70% of total hemoglobin, death can occur from cerebral ischemia or cardiac failure. Autopsy shows bright red tissues because of the failure of CO to dissociate from hemoglobin. The blood and skin appear bright red secondary to the inability of O2 to dissociate from hemoglobin (myoglobin).

- O2 saturation (SaO2)
  a. Each hemoglobin molecule contains four Fe2+-containing groups to which oxygen can bind.
  b. The percentage of the available heme groups that are bound to oxygen is termed the O2 saturation, or the Sao2 when referring to arterial blood.
  c. In a healthy person, Sao2 is approximately 98% at a typical O2 tension (PaO2) of 100 mm Hg.
     - An Sao2 of less than 80% produces clinical evidence of cyanosis, a bluish discoloration of the skin caused by the presence of ≥ 5 g/dL of deoxygenated hemoglobin in the blood.
  d. O2 saturation is measured in arterial, oxygenated blood, usually by using a sensor attached to a finger (pulse oximeter).
  e. The Sao2 can be calculated or directly measured in the clinical laboratory.

- Increased O2 delivery to the tissues
  a. Right shift of the O2 dissociation curve (see Fig. 5-20) indicates a decrease in the affinity of hemoglobin for O2 and a corresponding increased degree of oxygen unloading into the tissues.
     - There is an increase in P50, the pressure of oxygen (Po2) at which hemoglobin is half saturated (i.e., two O2 molecules are bound to each hemoglobin molecule), which facilitates the release of O2 to the metabolically active tissues.
  b. Factors that shift the curve to the right include binding of 2,3-diphosphoglycerate (2,3-DPG), increased H+ ions (acidosis), and CO2 to hemoglobin, as well as increased body temperature.
     - Note that each of these increases during exercise.

- Decreased O2 delivery to the tissues
  a. Left shift of the O2 dissociation curve occurs when there is increased affinity of hemoglobin for O2:
     - The P50 decreases, and unloading of oxygen into the tissues is decreased.
  b. Factors that cause a leftward shift of the hemoglobin-O2 dissociation curve include increased pH, decreased Po2, decreased body temperature, decreased 2,3-DPG, fetal hemoglobin, and carbon monoxide.

X. Carbon Dioxide (CO2) Transport

A. Overview
  1. CO2 is a byproduct of cellular respiration.
  2. It diffuses across cell and capillary membranes into the bloodstream.
  3. Most (~70%) of the CO2 then crosses the RBC membrane.
4. Once inside the RBC, it is converted to bicarbonate ion ($\text{HCO}_3^-$).
5. The rest of the $\text{CO}_2$ travels in the blood as either carbaminohemoglobin ($\sim 20\%$ of total $\text{CO}_2$), or dissolved $\text{CO}_2$ ($\sim 10\%$).

Clinical note: Whereas $\text{PaO}_2$ decreases and the A-a gradient widens with normal aging, the $\text{PCO}_2$ does not change with age.

B. Bicarbonate ion
1. Approximately 70% of $\text{CO}_2$ is transported in the blood as $\text{HCO}_3^-$ (Fig. 5-21).
2. Carbonic anhydrase, present in abundance in RBCs, catalyzes the hydration of $\text{CO}_2$ to $\text{H}_2\text{CO}_3$.
   - This dissociates to form $\text{HCO}_3^-$ and $\text{H}^+$.
     a. The $\text{HCO}_3^-$ is exchanged for chloride ions ($\text{Cl}^-$) across the RBC membrane to maintain a balance of charge.
     b. This countertransport is termed the chloride shift.
   - $\text{HCO}_3^-$ then travels to the pulmonary capillaries through the venous blood.
3. A reverse chloride shift and reversal of all these reactions occurs in the RBCs in the pulmonary capillaries.
   - This reverse reaction produces $\text{CO}_2$, which is expired.
4. Low $\text{PACO}_2$ and a high solubility coefficient stimulate diffusion of $\text{CO}_2$ from pulmonary capillaries into the alveolar air.
   - The consequent decrease in $\text{PCO}_2$ allows hemoglobin to bind oxygen more effectively (left shift; see Fig. 5-20).

C. Carbaminohemoglobin
1. Approximately 20% of $\text{CO}_2$ is transported in the blood in a form that is chemically bound to the amino groups of hemoglobin.
2. The binding of $\text{CO}_2$ to hemoglobin decreases the $\text{O}_2$ affinity of hemoglobin, causing a right shift of the hemoglobin-$\text{O}_2$ dissociation curve (Bohr effect), which promotes unloading of $\text{O}_2$ to the tissues.

D. Dissolved $\text{CO}_2$ ($\text{PCO}_2$)
1. Approximately 10% of $\text{CO}_2$ is transported as dissolved $\text{CO}_2$ (compared with 0.3% of $\text{O}_2$), because of the high solubility constant of $\text{CO}_2$, which is approximately 20 times greater than that of $\text{O}_2$.
2. The arterial $\text{PCO}_2$ is directly measured in the laboratory; a normal value is approximately 40 mm Hg.

E. Buffering effect of deoxyhemoglobin
1. For every $\text{HCO}_3^-$ ion produced in the RBCs, one $\text{H}^+$ ion is also produced.
   - Most of these ions are buffered by deoxyhemoglobin, resulting in only a slight drop in plasma pH between arterial and venous end of capillaries (see Fig. 5-21).
2. Hydrogen binding to hemoglobin also increases $\text{O}_2$ unloading at the tissues, corresponding to a right shift of the dissociation curve.
XI. Control of Respiration

A. Overview
1. Respiration is tightly controlled to maintain optimal PaO₂ and PaCO₂ under varying environmental and physiologic conditions.
2. The act of breathing is under central (brainstem) control and is modulated by input from several types of peripheral receptors, including chemoreceptors and mechanoreceptors.

B. Central control
1. Overview
   • Basic control of respiratory rhythm originates from two neuronal “groups” within the medulla, the dorsal and ventral respiratory groups.
   • Fine control of inspiration and expiration originates from the pons (pneumotaxic and apneustic groups) of the brainstem (Fig. 5-22).
   • More complex regulation (behavioral control) by higher brain centers such as the thalamus and cerebral cortex is superimposed on these levels of control.

   **Clinical note:** Control by higher brain centers can override the basic controls of the brainstem, which makes it possible to induce one’s own hyperventilation. For example, in some mental illnesses, patients may engage in voluntary suppression of breathing or hyperventilation.

2. Dorsal respiratory group
   • Located along the entire length of the dorsal medulla
   • Controls the basic rhythm of respiration.
     a. This is accomplished by neurons that spontaneously generate action potentials (similar to the sinoatrial node), which stimulate inspiratory muscles.
   • Input to the dorsal respiratory group from other respiratory centers and higher brain centers can have a significant effect on activity.

   **Clinical note:** Ondine curse, a rare respiratory disorder, is a fascinating illustration of the dual control of respiration by higher brain centers (voluntary control) and brainstem respiratory centers (involuntary control). In this condition, the autonomic control of respiration may be impaired to such an extent that affected individuals must consciously remember to breathe. These patients may need mechanical ventilatory assistance while sleeping in order to prevent death.
3. Ventral respiratory group
   - Located on the ventral aspect of the medulla
   - **Stimulates expiratory muscles**
     a. These muscles, which are inactive during normal quiet respiration because expiration is a passive process under normal conditions, become important only when ventilation is high (e.g., with exercise).

4. **Pneumotaxic center**
   - Located in the superior pons; its neurons project to the dorsal respiratory group
   - **Inhibits inspiration**, limiting the size of tidal volume, and secondarily increasing the breathing rate

5. **Apneustic center**
   - Located in the inferior pons; it projects to the dorsal respiratory group
   - Increases the duration of inspiratory signals, increasing the duration of diaphragmatic contraction and resulting in more complete lung filling and a decreased breathing rate

C. **Chemoreceptors**
   - Groups of nerve terminals that are very sensitive to changes in pH, $\text{Pao}_2$, and $\text{Paco}_2$, which lead to the firing of these afferent nerves to the brainstem respiratory centers

1. **Central chemoreceptors (chemosensitive areas)**
   - Located on the ventral surface of the medulla
   - Function to keep $\text{Paco}_2$ within normal limits, having an indirect response to the amount of $\text{CO}_2$ dissolved in cerebrospinal fluid (CSF) (Fig. 5-23)
     a. Through the central chemoreceptors, high $\text{Paco}_2$ (hypercapnia) and to a lesser extent decreasing pH stimulate hyperventilation.
     b. Effects are transient as a result of desensitization of central chemoreceptors.
       - They have a very slow response to increased plasma $\text{H}^+$, because $\text{H}^+$ does not cross the blood-brain and blood-CSF barriers.

Clinical note: At high altitudes, hypoxia (decreased $\text{Pao}_2$) stimulates hyperventilation through peripheral chemoreceptors, leading rapidly to decreased $\text{Paco}_2$ and decreased $[\text{H}^+]$, both of which antagonize hypoxia-induced hyperventilation. Renal compensation for the respiratory alkalosis involves increased $\text{HCO}_3^-$ excretion and decreased $\text{H}^+$ ion secretion and this typically takes 1 to 2 days. After 1 to 2 days, the central chemoreceptors become sufficiently desensitized, and hypoxia is able to strongly stimulate hyperventilation. Climbers must ascend mountains slowly for this reason.
2. Peripheral chemoreceptors
   - Located in the carotid and aortic bodies
     a. Afferent fibers travel from the carotid bodies along the glossopharyngeal nerve (cranial nerve [CN] IX), and from the aortic bodies along the vagus nerve (CN X), to the dorsal respiratory group in the medulla.
     b. They respond to pH, \( P_{aCO_2} \), and \( P_{aO_2} \).
     c. Although mild hypoxemia does not strongly stimulate them, they are strongly stimulated by a \( P_{aO_2} \) less than 60 mm Hg.
     d. When pH or \( P_{aO_2} \) decreases or when \( P_{aCO_2} \) increases, breathing rate is increased.
   - They can also trigger hyperventilation.
     a. High \( P_{aCO_2} \) (hypercapnia) or acidosis stimulates production of action potentials, which travel along afferents to the dorsal respiratory group, leading to hyperventilation.

Clinical note: Hypoxia has a limited ability to stimulate hyperventilation, because hyperventilation rapidly decreases \( P_{aCO_2} \) and \( H^+ \), thereby inhibiting the process. However, in conditions in which \( P_{aCO_2} \) and \( H^+ \) do not decrease in response to hyperventilation (e.g., emphysema, pneumonia), hypoxia may remain a potent inducer of ventilation. Supplemental \( O_2 \) should be administered with great caution in these circumstances, because removal of the hypoxic stimulant to ventilation can inhibit ventilatory drive, leading to death from severe hypercapnia and acidosis.

D. Mechanoreceptors and pulmonary reflexes
   1. Irritant receptors
      - Located between the cells of large-diameter airways, primarily the trachea, bronchi, bronchioles
      - Respond to the presence of noxious gases, smoke, and dust, and mediate reflexes such as bronchoconstriction, coughing, and sneezing
   2. Stretch receptors: the Hering-Breuer reflex
      - Located in the muscular walls of the bronchi and bronchioles
      - Activated by distension of the airways in response to large tidal inspirations, they inhibit further inspiration and thereby play a protective role in preventing excessive filling of the lungs.
      a. The afferent nerve fibers travel through the glossopharyngeal (CN IX) and vagus (CN X) nerves to the dorsal respiratory group.

E. Effects of exercise
   1. Hyperventilation in response to exercise is poorly understood but is thought to involve stimulation of respiratory centers by higher brain centers.
      - For example, descending corticospinal fibers from the motor cortex may have a stimulatory effect on brainstem respiratory centers as they pass through.
      - In the initial stages of exercise, hyperventilation occurs even before changes in blood gas levels are detectable, indicating that hyperventilation is unlikely to be mediated through the actions of either the central or peripheral chemoreceptors.
   2. Body movements, especially of the arms and legs, stimulate ventilation through excitatory signals from joint and muscle proprioceptors to the respiratory center.

XII. Respiratory Responses to Stress
A. Hypoxemia and hypoxia
   1. Overview
      - The distinction between these conditions is important.
        a. Hypoxemia refers to insufficient \( O_2 \) in the blood.
        b. Hypoxia refers to insufficient \( O_2 \) supply to the body or tissues.
      - Hypoxia is caused either by a reduction in cardiac output or by hypoxemia (Table 5-6).
      - Hypoxemia has many causes, including high altitude, anemia, carbon monoxide poisoning, hypoventilation, diffusion defects (fibrosis, pulmonary edema), V/Q defects, and shunts.
   2. Physiologic responses to hypoxemia
      - When \( P_{aO_2} \) drops, chemoreceptors increase their firing, and the central breathing centers up-regulate the respiratory rate (tachypnea) and heart rate (tachycardia) and cause large tidal volume breaths (hyperpnea); these actions all serve to increase oxygenation at the pulmonary membrane and increase delivery of oxygen to the tissues.
Clinical note: Treatment of hypoxia may vary depending on the type of hypoxia. For example, supplemental oxygen therapy may completely alleviate symptoms caused by hypoxic hypoxia (e.g., as with lung disease or high-altitude respiration), but it does little to improve symptoms associated with histotoxic hypoxia (e.g., cyanide poisoning).

3. High-altitude respiration (Fig. 5-24)
   - At high altitudes, atmospheric pressure and therefore $P_{\text{AO}_2}$ is decreased
   - Several physiologic responses enable the body to acclimatize to this change, maintaining adequate oxygenation of tissues; the reduced $P_{\text{AO}_2}$ triggers
     a. An increase in ventilation
     b. An increase in pulmonary vascular resistance, as a result of hypoxia-induced vasoconstriction of the pulmonary vasculature
     c. A right shift of the hemoglobin-O$_2$ dissociation curve
   - Hypoxia-induced polycythemia, an increase in number of RBCs, is responsible for longer-term acclimatization to high altitude.
     a. It increases the O$_2$-carrying capacity of the blood, compensating for the lower $P_{\text{AO}_2}$.
     b. It is an additional cause of increased pulmonary vascular resistance, because it increases blood viscosity.

Clinical note: Hypoxia-induced polycythemia is a form of secondary polycythemia that occurs as a result of the increased renal secretion of erythropoietin in response to hypoxia. Erythropoietin stimulates RBC production in the bone marrow. In addition to high-altitude acclimatization, hypoxia-induced polycythemia can also be seen in smokers and in patients with lung and heart disease severe enough to cause hypoxia. Other types of secondary polycythemia occur in a hypoxia-independent manner (e.g., erythropoietin-secreting renal tumors). Primary polycythemia (often termed polycythemia vera), by contrast, occurs from an intrinsic proliferative abnormality within the bone marrow. Unlike in the secondary polycythemias, erythropoietin levels are low in this condition.
B. Breathing disorders (Table 5-7)

- Altered breathing patterns often signify an underlying disease process.

**Clinical note:** In Kussmaul respiration, which is associated with metabolic acidosis (e.g., diabetic ketoacidosis), patients may breathe rapidly (tachypnea) and deeply.
I. Overview

A. General functions of the kidneys
1. The kidneys are an extraordinarily effective recycling facility into which the body’s extracellular fluid compartment is cycled many times a day.
2. Substances that are not needed, such as excess water, electrolytes, and potentially toxic end products of metabolism, are discarded into the urine.
3. Substances that are needed, such as most of the filtered sodium, water, glucose, and bicarbonate, are reclaimed and returned to the circulation.
4. The kidneys have particularly strong control over homeostasis of water, sodium, potassium, calcium, phosphate, bicarbonate, and the nonvolatile acids.
5. This allows them to regulate extracellular fluid (ECF) volume, osmolality, and acid-base balance.

B. Functional anatomy of the kidney (Fig. 6-1)
1. To achieve their recycling functions, the kidneys receive a substantial fraction (20% to 25%) of the cardiac output despite comprising less than 2% of body weight.
2. This blood supply is through the renal arteries.
3. The basic functional unit of the kidney is the nephron, where blood is filtered; there are approximately 1 million nephrons per kidney.
4. Fluid and compounds that are not recycled (urine) drain from the nephron into the calyceal system.
5. This in turn drains into the renal pelvis, ureter, and bladder.

C. Structure of the filtration unit: the nephron (Fig. 6-2)
1. Filtering of the blood occurs in the glomerulus of each nephron.
2. Each glomerulus is an expansion of an afferent arteriole into a diffuse capillary bed, the glomerular capillaries, which have an extensive surface area for filtration; these capillaries are surrounded by an expansion of the renal tubular system (Fig. 6-3).
3. The ultrafiltrate of plasma created in the glomerulus flows into the tubular system, where selective reabsorption and secretion of solutes and water occurs along the various segments of the nephron.
4. The terminal segments of the nephron empty into the calyceal system.
1. Renal corpuscle
2. Proximal convoluted tubule
3. Proximal straight tubule
4. Descending thin limb
5. Ascending thin limb
6. Distal straight tubule (thick ascending limb)
7. Macula densa
8. Distal convoluted tubule
9. Connecting tubule
10. Cortical collecting duct
11. Outer medullary collecting duct
12. Inner medullary collecting duct


D. The glomerular filtration barrier

- For substances in the lumen of the glomerular capillaries to be filtered into the renal tubular system, they must traverse the three component layers of the glomerular filtration barrier (Fig. 6-4).

1. Function of the filtration barrier

- Effectively prevents the passage of cells and large-molecular-weight proteins into the glomerular ultrafiltrate, thereby preventing their loss into the urine

2. Layers of the filtration barrier

- Each of these layers is highly specialized for filtration.
  a. **Endothelial cells**
     - These cells are fenestrated (have many holes), which markedly increases capillary permeability and so permits the production of large volumes of filtrate (see Fig. 6-4).
  b. **Basement membrane**
     - The basement membrane is negatively charged, which helps prevent filtration (and subsequent loss in the urine) of negatively charged plasma proteins such as albumin (see Fig. 6-4).
  c. **Visceral epithelial cells (podocytes)**
     - The overlying visceral epithelial cells, or podocytes, project foot processes that overlie the glomerular basement membrane.
     - These podocytes, and their adjoining slit pores, form a final negatively charged barrier for filterable molecules to traverse before they enter Bowman space (see Fig. 6-4).

**Pathology note:** In a condition known as minimal change disease (lipoid nephrosis), the negative charges on the glomerular filtration barrier are lost for unknown reasons. Certain proteins are then able to pass through the basement membrane, resulting in proteinuria. This disease is the most common cause of the nephrotic syndrome (loss of >3.5 g of protein per day into the urine) in children and is usually responsive to treatment with corticosteroids. Of note, the positively charged immunoglobulin light chains, which are overproduced in multiple myeloma, are small enough to pass through the glomerular filtration barrier (and therefore into the urine) without any pathologic changes in the glomerulus. Therefore, if one suspects a paraproteinemia or multiple myeloma, a negative urine dipstick (which detects negatively charged proteins) does not rule out such a diagnosis. In these cases, precipitation of all proteins in the urine can be performed with sulfosalicylic acid (SSA); this will detect the presence of globulins and Bence-Jones proteins.

II. Regulation of Glomerular Function

A. Filtration forces at the glomerulus (Fig. 6-5)

1. The forces that drive fluid across the glomerular membrane and into Bowman space are the same as the Starling forces that cause fluid movements in systemic capillaries.

2. Forces that promote filtration are the hydrostatic pressure in the glomerular capillaries ($P_{GC}$) and the oncotic pressure in Bowman space ($P_{BS}$); however, because most proteins are not readily filtered into Bowman space, the latter is typically negligible.
3. Forces that oppose fluid movement across the glomerular membrane are the hydrostatic pressure in Bowman space \( (P_{BS}) \) and the oncotic pressure in the glomerular capillaries \( (P_{GC}) \).

4. Summation of these forces yields the net filtration pressure (NFP), which is the pressure gradient driving filtration across the glomerulus.

5. For a typical adult:

\[
NFP = (P_{GC} + \Pi_{BS}) - (P_{BS} + \Pi_{GC}) \\
= (60 + 0) - (18 + 32) \\
= 10 \text{ mm Hg}
\]

Clinical note: In the presence of a damaged basement membrane (e.g., membranous nephropathy), where protein can be filtered across the glomerular membrane, the resulting increase in oncotic pressure in Bowman space can result in an elevated NFP and increased filtrate production. Review of systems in such patients with nephrotic syndrome may be significant for the presence of foamy or frothy urine due to the lowering of surface tension by the severe proteinuria.

B. Glomerular filtration rate (GFR)

1. Overview
   - The GFR quantifies the total filtration volume by all of the glomeruli each minute (mL/minute).
   - The GFR is dependent on the filtration forces acting at the glomerulus and the unit permeability \( (L_p) \) and available surface area \( (S) \) of the glomerular capillaries.
   - In the healthy kidney, the product of these two factors \( (L_pS) \) is equal to approximately 12.5 mL/minute per mm Hg filtration pressure.
Because the NFP is equal to approximately 10 mm Hg, GFR can therefore be approximated as follows:

\[ \text{GFR} = (L_p \times S) \times \text{NFP} \]
\[ = 12.5 \text{ mL/min/mm Hg} \times 10 \text{ mm Hg} \]
\[ = 125 \text{ mL/min} \]

- Typical values for GFR in healthy adults are approximately 90 mL/minute in women and 120 mL/minute in men.
- This rate of filtration exceeds that seen in muscle capillaries by more than 1,000-fold.
- This is due to the high Lp of the glomeruli capillaries, which are 50 to 100 times greater than that of muscle capillaries, and the high glomerular hydrostatic pressure of the glomerular capillaries, approximately 60 mm Hg versus 30 mm Hg in a typical capillary bed.

2. **Calculation of GFR**
- Can be estimated by measuring the clearance of a **glomerular marker**
- The substance inulin is an ideal marker for measuring GFR because it is freely filtered and neither reabsorbed nor secreted along the nephron (more on this later)

\[ C_{\text{inulin}} \sim \text{GFR} = U_{\text{inulin}} \times V / P_{\text{inulin}} \]

where
- \( C_{\text{inulin}} = \) clearance of inulin (mL/minute)
- \( \text{GFR} = \) glomerular filtration rate (mL/minute)
- \( U_{\text{inulin}} = \) urine concentration of inulin (mg/mL)
- \( V = \) urine flow rate (mL/minute)
- \( P_{\text{inulin}} = \) plasma concentration of inulin (mg/mL)

3. **Filtration fraction**
- The percentage of renal plasma flow (RPF) that is filtered across the renal glomerular capillaries

\[ \text{Filtration fraction} = \frac{\text{GFR}}{\text{RPF}} \]

- A typical value is about 20%.

4. **Regulation of GFR**
   - **Overview**
     - Although alteration of any of the determinants of NFP at the glomerulus can alter GFR, the primary mechanism through which GFR is normally regulated is through regulation of the **glomerular hydrostatic pressure**.
     - The glomerular hydrostatic pressure depends on the systemic arterial pressure and afferent and efferent arteriolar resistances, respectively.
     - The **sympathetic nervous system** and hormones such as angiotensin II primarily regulate GFR by varying the degree of afferent and efferent arteriolar resistance; this is discussed later in the context of overall plasma volume regulation.
   - **Systemic arterial pressure**
     - As systemic arterial pressure increases, the increased renal perfusion tends to increase glomerular hydrostatic pressure and GFR.
     - However, the changes in glomerular hydrostatic pressure are relatively small compared with the often substantial fluctuations in systemic arterial pressure.
     - This attenuation is due to **intrinsic autoregulatory mechanisms** in the kidneys, which maintain relatively constant renal perfusion despite fluctuations in systemic arterial pressure (see later discussion and Fig. 6-7).
     - Consequently, the contribution of systemic arterial pressure is typically minor, and the primary determinants of glomerular hydrostatic pressure are afferent and efferent arteriolar resistance.
   - **Afferent arteriolar resistance** (Fig. 6-6; Table 6-1)
     - Dilation of the afferent arteriole through prostaglandins such as prostaglandin \( E_2 \) increases renal blood flow, glomerular hydrostatic pressure, and, hence, GFR.
     - Vasoconstriction has the opposite effect.
Afferent arteriole | Glomerulus | Efferent arteriole

**6-6**: Effects of afferent and efferent vasoconstriction on glomerular forces and glomerular filtration rate (GFR). $P_{GC}$, Hydrostatic pressure in glomerular capillary; $RPF$, renal plasma flow. *(Modified from Rose BD, Rennke KG: Renal Pathophysiology: The Essentials. Baltimore, Williams & Wilkins, 1994.)*

**TABLE 6-1.** Effect of Changes in Starling Forces on Renal Plasma Flow, Glomerular Filtration Rate, and the Filtration Fraction

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>RPF</th>
<th>GFR</th>
<th>FILTRATION FRACTION (GFR/RPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constriction of afferent arteriole</td>
<td>↓</td>
<td>↓</td>
<td>NC</td>
</tr>
<tr>
<td>Constriction of efferent arteriole</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Increased plasma protein concentration</td>
<td>NC</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Decreased plasma protein concentration</td>
<td>NC</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Constriction of the ureter</td>
<td>NC</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

GFR, Glomerular filtration rate; NC, no change; RPF, renal plasma flow.


- **Efferent arteriolar resistance**
  a. **Mild to moderate vasoconstriction** of the efferent arteriole (angiotensin II) increases glomerular hydrostatic pressure, resulting in increased filtration across the glomerulus.
  b. However, this increased GFR comes at the expense of reducing overall renal blood flow and increasing the filtration fraction at the glomerulus, which in turn increases the glomerular oncotic pressure that opposes filtration.
  c. Therefore, with **marked vasoconstriction** of the efferent arteriole, GFR typically decreases, because the reduced renal blood flow and increased glomerular oncotic pressure overcome the effects of the increased glomerular hydrostatic pressure on GFR (see Fig. 6-6).
5. Renal Blood Flow
   - Overview
     a. Highly perfused, receiving approximately 25% of cardiac output
     b. Blood supply through the renal arteries
     c. Vasodilatory prostaglandins maintain afferent arteriolar dilatation, whereas the sympathetic nervous system and angiotensin II promote vasoconstriction with preferential vasoconstriction of the efferent arteriole (Fig. 6-7).

   Clinical note: Narrowing of the renal arteries (renal artery stenosis) most commonly occurs as a result of atherosclerosis or fibromuscular hyperplasia. In unilateral renal artery stenosis, hypertension may occur because decreased perfusion of the affected kidney is incorrectly “interpreted” as intravascular volume depletion, which triggers a neurohormonal cascade response (the renin-angiotensin-aldosterone system and antidiuretic hormone [ADH]; see Chapter 3), causing fluid retention and vasoconstriction resulting in hypertension. When both renal arteries are affected (bilateral renal artery stenosis), renal blood flow may become so compromised that the kidneys are unable to perform their normal recycling functions, resulting in the toxic accumulation of metabolic byproducts.

   • Autoregulation of renal blood flow
     a. Process in which intrinsic renal mechanisms act to maintain fairly constant renal perfusion, GFR, and distal flow in the nephron in the face of widely varying systemic arterial pressures
     b. This is accomplished by the kidneys by altering renal vascular resistance
     c. At very high or very low arterial blood pressures, autoregulatory mechanisms fail, and renal blood flow parallels changes in systemic arterial pressure (Fig. 6-8); this is why at the extremes of blood pressure, hypotension and malignant hypertension, acute kidney injury may occur as a result of renal ischemia or damage from pathologically elevated glomerular hydrostatic pressures, respectively.

   6-7: Effect of prostaglandins and angiotensin II on renal perfusion. GFR, Glomerular filtration rate; RBF, renal blood flow. (From Oh W, Guignard J-P, Baumgart S: Nephrology and Fluid/Electrolyte Physiology: Neonatology Questions and Controversies. Philadelphia, Saunders, 2008, Fig. 5-3.)

   6-8: Autoregulation of renal blood flow. At extremes of blood pressure, systemic arterial pressure and renal blood flow are in direct proportion.
d. Autoregulation occurs through the **myogenic mechanism** and **tubuloglomerular feedback**, as discussed below.

e. Both function largely by regulating renal vascular resistance in the absence of neural or hormonal input.

**Myogenic mechanism**

a. **Response to increased arteriolar pressure**
   - As in other arterioles, an increase in pressure in the afferent arteriole stimulates reflexive vasoconstriction by stimulating smooth muscle cell contraction.
   - This minimizes the increase in glomerular hydrostatic pressure and GFR that would otherwise occur.
   - It also minimizes damage to the glomerular capillaries, which already function at hydrostatic pressures that are much greater than those in the systemic capillaries.

b. **Response to decreased arteriolar pressure**
   - A decrease in pressure in the afferent arteriole stimulates reflexive vasodilation, which increases glomerular blood flow and GFR.
   - This helps to ensure adequate removal of toxins by the kidneys when systemic arterial pressures drop.

**Tubuloglomerular feedback**

a. In this mechanism, the rate of NaCl delivery to the distal nephron significantly influences the glomerular blood flow and therefore the GFR.
   - The rate of NaCl delivery to the distal tubule is dependent on the tubular concentration of NaCl as well as the tubular flow rate.

b. This mechanism is dependent on the presence of a specialized structure termed the **macula densa**, which is located at the end of the thick ascending limb and abuts the glomerulus adjacent to the afferent arteriole (Fig. 6-9; see Figs. 6-2 and 6-3).

c. The macula densa and the specialized cells within the glomerulus and the walls of the afferent arteriole are referred to as the **juxtaglomerular apparatus**.

d. The mechanism has three components:
   - A **signal**: NaCl delivery to the distal tubule
   - A **sensor**: macula densa
   - An **effector**: vascular smooth muscle cells within the wall of the afferent arteriole

e. When filtration increases, through an unclear mechanism the increased NaCl delivery to the macula densa triggers vasoconstriction of the afferent arteriole (see Fig. 6-9).
   - The result is reduced renal blood flow (RPF) and therefore decreased GFR, which reduces delivery of NaCl to the macula densa.

---

**6-9: Tubuloglomerular feedback.** Because of the hairpin loop structure of each nephron, the macula densa is located adjacent to its originating glomerulus and is positioned adjacent to the afferent and efferent arterioles that supply that glomerulus. **GFR**, Glomerular filtration rate; **JGA**, juxtaglomerular apparatus. (From Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 32-19.)
f. When filtration decreases, decreased NaCl delivery to the macula densa triggers vasodilation of the afferent arteriole, which increases GFR and increases delivery of NaCl to the macula densa.

g. Again, the “goal” of this mechanism is to maintain constant RBF and distal tubular flow.

**Pharmacology note:** The juxtaglomerular apparatus is informed of NaCl in the tubular lumen by virtue of its transport into the cells of the macula densa by the same Na\(^+\)-K\(^+\)-2Cl\(^-\)/cotransporter that is inhibited by loop diuretics. One reason for the potency of loop diuretics is their ability to blunt tubuloglomerular feedback and thereby maintain GFR (and urine production) despite increased NaCl traffic past the macula densa.

**Clinical note:** Acute tubular necrosis (ATN) is a common cause of acute renal failure, which results when hypotension (ischemia, hypoxemia) or tubular toxins damage renal tubular epithelial cells. In ATN, owing to dysfunction of these cells, sodium and water reabsorption in the proximal tubule, where most of the NaCl and fluid reabsorption normally occurs, is impaired. Large amounts of NaCl and water are therefore presented to the macula densa. Through tubuloglomerular feedback, this decreases renal blood flow and GFR by stimulating vasoconstriction of the afferent arteriole. The subsequent decrease in GFR, despite causing acute renal failure, may play a role in limiting potentially life-threatening losses of sodium and water that might otherwise occur in ATN.

### III. Measuring Renal Function

#### A. Overview

1. The term **renal function** is used to refer to the rate at which the kidneys remove toxins from the circulation.
2. The main mechanism of toxin removal is filtration of toxin-laden plasma through the glomerulus, leaving the toxins behind in the tubule and reabsorbing 99% of the filtrate.
3. Plasma that has undergone this process has been “cleared.”

#### B. Clearance

1. Clearance is the **volume of plasma** from which a substance has been completely cleared by the kidneys per unit of time.
2. If a substance is freely filtered across the glomerulus and then neither reabsorbed nor secreted into the tubule (e.g., inulin), its rate of clearance is equivalent to GFR.
3. Therefore, measures of renal function involve use of the concept of clearance to directly measure or estimate GFR.

#### C. Calculating clearance

1. If a substance is present in the blood at a concentration of 1 mg per 100 mL, the clearance of the substance from 100 mL of blood per minute will result in 1 mg of this substance being excreted into the urine each minute.
2. If the amount of the substance excreted in the urine is divided by its plasma concentration (\(P_x\), in milligrams per milliliter), the quotient reflects the volume of plasma that has been cleared of that substance in 1 minute, called its **clearance** (\(C_x\));

\[
\text{Clearance} = \frac{\text{Amount excreted in urine in 1 minute}}{\text{Plasma concentration}}
\]

3. This can be expressed in terms of urinary flow rate (\(V\), in mL/minute) and urinary concentration (\(U_x\), in mg/mL):

\[
C_x = \frac{V \times U_x}{P_x}
\]

4. Example: Given a typical excretion rate of urea into the urine of 15 mg/minute and a typical plasma concentration of urea of 0.2 mg/mL, the clearance of urea can be calculated as follows:

\[
C_{\text{urea}} = \frac{15}{0.2} = 75 \text{ mL/min}
\]

5. Note that the \(C_{\text{urea}}\) is less than the typical GFR, which is approximately 90 to 120 mL/minute, consistent with net reabsorption of urea along the nephron.

6. A clearance value that is greater than GFR indicates net secretion of the substance along the nephron.
D. Measuring the GFR

1. Creatinine clearance (Fig. 6-10)
   - Creatinine is formed continually as a breakdown product in skeletal muscle and released into the bloodstream.
   - Creatinine is freely filtered across the glomeruli and neither reabsorbed nor secreted to a significant extent (in actuality it is slightly secreted but we will ignore this fact for purposes of the current discussion).
   - The amount that enters the urine is therefore approximately equal to the amount that is filtered across the glomeruli.
   - Thus, the plasma concentration of creatinine is a good approximation of renal function.
   - The amount of creatinine that enters the urine in 1 minute is equal to the product of the urinary flow rate (V) and the urinary creatinine concentration (V \times U_{cr}).
   - The amount of creatinine that filters across the glomeruli is equal to the product of the plasma creatinine concentration and the GFR (P_{cr} \times GFR).
   - Because these two expressions define the same quantity, they can be equated and solved for the GFR, as follows:
     \[ V \times U_{cr} = P_{cr} \times GFR \]
     so that
     \[ GFR = \frac{V \times U_{cr}}{P_{cr}} \]
   - This is the same equation as the equation for creatinine clearance (C_{cr} = V \times U_{cr}/P_{cr}); therefore, creatinine clearance is approximately the same as the GFR.
   - Creatinine clearance is used clinically as an estimate of GFR; however, because there is in fact a mild degree of tubular secretion of creatinine (\sim 10\%), it is actually a slight overestimate of GFR.
   - Note that if GFR decreases, plasma creatinine will increase until a new steady state is reached, at which point urinary excretion of creatinine will again match daily creatinine production.

Clinical note: In clinical settings, clearance is calculated from the serum concentration of a substance and the substance’s concentration in a timed urine sample (typically a 24-hour sample).
Clinical note: Because measuring renal clearance involves collecting urine and is a nuisance for patients, plasma creatinine concentration is usually measured as a surrogate marker of renal function. However, because the plasma creatinine concentration is dependent on both muscle mass and renal function, this method may significantly overestimate renal function in patients with reduced muscle mass and, hence, lower creatinine production. Similarly, renal function may be underestimated in very muscular individuals and in situations, such as crush injury, in which extensive muscle damage leads to increased creatinine release into the circulation.

2. Inulin clearance
   - Inulin is a nonmetabolized polysaccharide that is freely filtered at the glomerulus.
   - Unlike creatinine, it is neither reabsorbed nor secreted along the tubule, so inulin clearance is a more accurate measurement of the GFR.

Clinical note: Unlike creatinine, inulin must be administered intravenously and is therefore almost never used clinically except in clinical research, in which precise assessments of GFR are required. So while it is a better marker of GFR, its use clinically is impractical.

E. Clearance and reabsorption/secretion

1. Overview
   - After filtration at the glomerulus, substances can be either reabsorbed or filtered (Fig. 6-11).
   - The clearance value for a given substance provides useful information about renal handling of that substance (Fig. 6-12).

2. Renal clearance for a given substance approximates GFR if that substance is freely filtered and does not undergo net reabsorption or secretion along the nephron (e.g., inulin).

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2. Renal clearance for a given substance approximates GFR if that substance is freely filtered and does not undergo net reabsorption or secretion along the nephron (e.g., inulin).
3. If a substance undergoes net **reabsorption** along the nephron, its clearance is less than GFR because some of it is returned to the plasma from which it was initially “cleared” (e.g., urea).

4. If a substance undergoes net **secretion** along the nephron (e.g., para-aminohippuric acid [PAH]), its clearance is greater than GFR because it is removed both from the filtered plasma at the glomerulus and from the unfiltered plasma in the peritubular capillaries. Notice that the clearances of substances that are freely filtered but then actively reabsorbed (e.g., sodium, glucose, amino acids) are quite low (Table 6-2).

F. **Using clearance values to estimate effective renal plasma flow**

1. If a substance were filtered and secreted so efficiently that it was completely eliminated from plasma by the time blood leaves the kidney (i.e., concentration in renal vein = 0), its clearance would give a very good approximation of RPF, because the amount of plasma cleared of the substance would represent all the plasma that initially entered the kidney, including the filtered fraction at the glomerulus and the unfiltered fraction in the peritubular capillaries.

2. An example of such a substance is para-aminohippuric acid (PAH), an organic acid that is not metabolized and needs to be administered intravenously.

3. If PAH is administered, it is freely filtered and very efficiently secreted but not reabsorbed.

4. If PAH is present in relatively low amounts in the plasma, approximately 90% of the amount entering the kidney is removed in its first pass. (See 6. on next page to understand why 100% of PAH is not removed in first pass.)

5. Therefore, the rate at which PAH is excreted in the urine ($U_{PAH} \times V$) approximates the rate at which PAH is delivered to the kidneys ($P_{PAH} \times RPF$) (Fig. 6-13).

   In other words, PAH clearance approximates RPF:

   $$U_{PAH} \times V \approx P_{PAH} \times RPF$$

   since

   $$C_{PAH} = U_{PAH} \times V / P_{PAH}$$

   this becomes

   $$RPF \approx C_{PAH}$$

   **Effective RPF = $C_{PAH}$**

---

**TABLE 6-2. Summary of Important Clearance Values**

<table>
<thead>
<tr>
<th>SUBSTANCE</th>
<th>APPROXIMATE CLEARANCE RATE (AS % OF GFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>50</td>
</tr>
<tr>
<td>Inulin</td>
<td>100</td>
</tr>
<tr>
<td>Creatinine</td>
<td>100</td>
</tr>
<tr>
<td>Para-aminohippuric acid (PAH)</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Sodium</td>
<td>1</td>
</tr>
<tr>
<td>Potassium</td>
<td>10</td>
</tr>
<tr>
<td>Glucose</td>
<td>0</td>
</tr>
<tr>
<td>Amino acids</td>
<td>0</td>
</tr>
</tbody>
</table>

GFR, Glomerular filtration rate.
6. Estimating RPF from this calculation yields the effective RPF rather than the true RPF, because a small amount of blood leaving the efferent arterioles (~10%) perfuses the vasa recta in the medulla rather than the peritubular capillaries, and this PAH cannot be secreted into the tubules of the nephron.

7. More precision can be achieved by correcting for this factor:

\[
\text{True RPF} = \frac{C_{PAH}}{0.90}
\]

8. Even more precision can be achieved by inserting a catheter into the renal vein and measuring the concentration of PAH in the renal vein.

9. Note that most clinicians speak in terms of renal blood flow (RBF) rather than renal plasma flow (RPF).

10. Although RBF is not normally measured clinically, it can be calculated from the hematocrit as follows:

\[
RBF = \frac{RPF}{1 - \text{Hematocrit}}
\]

**Clinical note:** Renal blood flow is not normally measured in routine clinical practice because it involves the intravenous administration of PAH and catheterization of the renal vein to determine the concentration of PAH in the renal venous plasma. However, this is more commonly performed in clinical research investigations, for example, when evaluating a new drug to see whether it affects renal hemodynamics.

### IV. Renal Transport Mechanisms

#### A. Overview

1. A huge amount of glomerular filtrate is delivered into the tubules each day.
2. Potentially life-threatening fluid and electrolyte disturbances would rapidly occur if the tubules did not reclaim most of this filtrate.
3. Therefore, the tubules of the nephron undertake a complex array of activities to excrete unneeded substances (excess electrolytes, toxins, hydrogen ions) while reclaiming the rest.

#### B. General tubular function

1. As a consequence of selective reabsorption and secretion, the solute composition of tubular fluid, which is initially plasmalike, changes dramatically along the course of the nephron.
2. The reabsorption and secretion of fluids and solutes from the tubular fluid is accomplished by a variety of tubular epithelial cell types, which have distinctly different transport capabilities and are located in different segments of the nephron.
3. There are two basic routes of transport across the tubular epithelium into the peritubular capillaries, the transcellular and paracellular routes, as discussed below (Fig. 6-14):
   - **Transcellular route**
     a. Transport across tubular epithelial cells by way of channels, pumps, or transporters
b. Substances are transported from the tubular lumen into tubular epithelial cells across the luminal (apical) membrane and from inside the tubular epithelial cells into the interstitium (and peritubular capillaries) across the basolateral membrane.

c. Responsible for bulk of tubular transport to peritubular capillaries

d. The bulk of Na\(^+\) reabsorption occurs through the transcellular route, as discussed later.

- **Paracellular route**
  
a. Transport across so-called **tight junctions** between tubular epithelial cells
  - Important for electrolytes such as K\(^+\) and Ca\(^{2+}\)
  
b. The leakiness in the proximal tubule facilitates the reabsorption of large amounts of fluid and solute through the paracellular route.
  
c. In contrast, paracellular transport in the collecting tubules is much more limited; steep concentration gradients can be maintained across the very tight junctions that separate tubular and interstitial fluids.

C. **Reabsorption of salt and water**

1. **Reabsorption from the proximal tubule**
   - Approximately two thirds of the glomerular filtrate is reabsorbed from the proximal tubule.
   - However, reclamation of components in the filtered load is not uniform (Fig. 6-15).
     a. For example, reabsorption of glucose and amino acids in the proximal tubule is almost complete, whereas only about 67% of filtered sodium is reabsorbed at this site.
     
   - The primary driving force behind transcellular proximal tubular reabsorption is the active transport of sodium out of the tubular epithelial cells and into the
interstitium through the \( \text{Na}^+, \text{K}^+ \)-ATPase pump \( \text{located on the basolateral membrane of the tubular epithelial cell.} \)

- This pump creates a favorable electrochemical gradient that facilitates further sodium entry into the cell from the tubular lumen through the luminal membrane by maintaining:
  a. A low intracellular sodium concentration
  b. A negatively charged intracellular environment, owing to the stoichiometry of the pump, which exchanges three \( \text{Na}^+ \) ions for two \( \text{K}^+ \) ions

- Despite this favorable electrochemical gradient, because it is a charged ion, sodium cannot simply pass out of and into tubular epithelial cells through the lipid bilayer.

- Instead, it moves through the luminal membrane by way of cotransporters (e.g., \( \text{Na}^+-\text{glucose}, \text{Na}^+-\text{amino acid}, \text{Na}^+-\text{phosphate} \)) and countertransporters (\( \text{Na}^+-\text{H}^+ \)) (Fig. 6-16).

- This solute movement into the tubular epithelial cells increases the intracellular osmolality relative to tubular fluid osmolality, which then causes water to move from the lumen into the cells through water channels in the luminal membrane of the tubular epithelial cells (Fig. 6-17).
  a. This osmotic flow of water through the transcellular and paracellular routes promotes reabsorption of solutes such as \( \text{K}^+ \) and \( \text{Ca}^{2+} \) through solvent drag (see figure below).

---

**6-16:** Steps in proximal tubular solute and water reabsorption: (1) the \( \text{Na}^+, \text{K}^+ \)-ATPase pump creates a favorable intracellular electrochemical gradient for further entry of \( \text{Na}^+ \); (2) luminal sodium cotransporters and countertransporters move solute into the cell, which increases intracellular osmolality; (3) water enters the cell through luminal water channels in response to the increased intracellular osmotic gradient; (4) basolaterally located cotransporters and water channels transport water and solute into the interstitial space.

**6-17:** Schematic illustrating the concept of solvent drag. (From Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 33-4.)
Cotransporters and water channels located in the basolateral membrane then move solute and water into the interstitial space (see Fig. 6-16).

Although osmotic forces are involved in reabsorbing water and sodium from the proximal tubule, the net changes are such that the osmolarity of the tubular fluid does not change along the proximal tubule.

a. This is referred to as isosmotic reabsorption.

2. Reabsorption into the peritubular capillaries

- The peritubular capillaries emerge from the efferent arteriole of the glomerulus and drain into the renal veins.

- Starling forces are responsible for reabsorption of fluid from the renal interstitium into the peritubular capillaries.

- Because a significant amount of protein-free plasma is filtered across the glomerulus, the plasma that remains in the efferent arteriole and peritubular capillaries is protein enriched, creating a strong oncotic pressure that draws fluid into these capillaries.

- This may also be responsible for glomerulotubular balance (discussed later).

- Additionally, because the blood has already passed through the resistance beds of the afferent arteriole, the hydrostatic pressure in the peritubular capillaries (P_{H2}) is low, favoring reabsorption from the interstitium (Fig. 6-18).

3. Glomerulotubular balance

- Despite a varying GFR, when total body sodium balance is normal, a relatively constant fraction of the filtrate (approximately 67%) is reabsorbed from the proximal tubule.

- This phenomenon, termed glomerulotubular balance, tends to minimize the effects of a fluctuating GFR on sodium and water excretion, thereby promoting a constant plasma volume.

a. However, glomerulotubular balance can be altered by changes in the ECF volume, as discussed later.

b. Imagine a volume-depleted state whereby the increased glomerular filtration fraction results in protein-enriched peritubular fluid.

- In this setting, the increase in reabsorption from the proximal tubule will serve to decrease urinary losses and thereby help restore ECF volume.

c. In contrast, in a volume-expanded state, the decreased glomerular filtration fraction results in protein-poor peritubular fluid.

- In this setting, the decrease in reabsorption from the proximal tubule will serve to increase urinary losses and help restore normal ECF volume.

Note: Glomerulotubular balance and tubuloglomerular feedback are easy to confuse. In glomerulotubular balance, proximal tubular reabsorption is related to GFR (and filtration fraction) by virtue of peritubular capillary oncotic pressure. In tubuloglomerular feedback, the rate of delivery of NaCl to the macula densa influences GFR by regulating afferent arteriolar tone. For example, in glomerulotubular balance, a volume-contrasted state will increase peritubular oncotic pressure and increase proximal tubular reabsorption in an attempt to expand plasma volume and RBF. In tubuloglomerular feedback, a volume-contracted state will decrease the rate of NaCl delivery to the macula densa and increase RBF through afferent arteriolar vasodilation.
D. Transport maximum (T<sub>m</sub>)
1. This is the maximum rate at which a substance can be reabsorbed from the tubular fluid.
2. It exists for certain substances because their reabsorption is dependent on membrane receptor proteins that have a finite transport capacity (i.e., they are saturable).
3. The importance of the T<sub>m</sub> is its relationship to the filtered (renal) load, which describes the amount of any substance delivered to the renal tubular system.
4. The filtered load for a given substance can be calculated as the product of the plasma concentration of that substance and GFR.
5. If the renal load exceeds the T<sub>m</sub>, as might occur with an abnormal increase in the plasma concentration of a substance, that substance will begin to accumulate in the urine, as shown for glucose in Figure 6-19.
6. The renal load for glucose is as shown below:

\[
\text{Renal load for glucose} = \frac{[P_{\text{glucose}}]}{C_2} \times \text{GFR} = 100 \text{ mg/dL} \times 125 \text{ mL/minute} = 125 \text{ mg/min}
\]

where \( P_{\text{glucose}} \) = plasma glucose concentration in mg/dL

6-19: A typical concentration of plasma glucose of 100 mg/dL corresponds to a glucose load of 125 mg/minute (point A), which is well below the transport maximum (T<sub>m</sub>) for glucose of 320 mg/minute. As plasma glucose levels become pathologically elevated (e.g., in diabetes), a threshold value (point B) is reached, at which point glucose begins to appear in the urine. At still higher plasma levels of glucose (point C), the transport maximum is reached. At this point, all transporter proteins are saturated, and excess glucose is lost in the urine.

Clinical note: The threshold value for plasma glucose (i.e., the level at which glucose begins to appear in the urine) is 180 mg/dL, which corresponds to a glucose load of 225 mg/minute (assuming a GFR of 125 mL/minute). Given that 225 mg/minute is still well below the T<sub>m</sub> for glucose (320 mg/minute), it may seem strange that glucose begins to appear in the urine at 180 mg/dL. This is believed to reflect the fact that there is variation in the transport capacity of different nephrons. Consequently, the glucose reabsorptive capacity of some nephrons may become saturated sooner than others, spilling the remainder into the urine, whereas other nephrons may still be able to increase reabsorption until their higher T<sub>m</sub> is reached.

E. Tubular secretion
1. A number of substances are not filtered at the glomerulus but still gain access to the tubular lumen by virtue of being secreted.
2. Proximal tubular epithelial cells play an important role in the secretion of organic ions into the tubular lumen.
3. The substances being secreted enter the interstitial space from the peritubular capillaries and are transported into the tubular epithelial cells by organic transporters localized on the basolateral membrane (Fig. 6-20).
4. Luminal membrane localized transporters then facilitate movement into the tubular lumen.
5. The transporters move endogenous substances, typically toxic end products of metabolism such as bile salts, uric acid, and ketoacids, as well as exogenous drugs.
6. The relative lack of specificity of these transporters allows them to serve as an important route of elimination of a number of different drugs and exogenous chemicals (Table 6-3).
Clinical note: With the exception of spironolactone, an aldosterone receptor antagonist, diuretics must gain access to the tubular lumen to reach their site of action. Because they are highly protein bound, they are not filtered through the glomerulus. Instead, they are transported into the tubular lumen through the organic ion transporters located in the basolateral membrane of the proximal tubular epithelial cells. Diuretics become less effective in individuals with renal failure. This diminished efficacy occurs in part because other organic ions accumulate in renal failure and compete with diuretics for transport into the tubular lumen. Large doses of diuretics, particularly loop diuretics, are given in renal failure to overcome this competition for tubular secretion.

7. The transporters are saturable (i.e., they have a $T_m$) and demonstrate competitive inhibition.
8. Figure 6-20 illustrates the mechanisms of organic anion (OA$^-$) transport across the proximal tubule.

Pharmacology note: Probenecid and penicillin use organic anion transporters for elimination into the urine. Probenecid can be used clinically to reduce elimination of penicillin because it competes for the anion transporter, thereby increasing plasma penicillin levels.

F. Pathophysiology of Renal Transport Mechanisms
• Impaired transport along the various nephron segments result in numerous conditions, as shown in Table 6-4.

| TABLE 6-3. Some Organic Cations Secreted by the Proximal Tubule |
|---------------------|-------------------|
| **ENDOCYNOUS**      | **DRUGS**         |
| Creatinine          | Atropine          |
| Dopamine            | Isoproterenol     |
| Epinephrine         | Cimetidine        |
| Norepinephrine      | Morphine          |
|                     | Quinine           |
|                     | Amiloride         |
|                     | Procainamide      |

V. Handling of Specific Substances along the Nephron

A. Sodium and water

1. Overview

- The kidneys filter a massive amount of Na\(^+\) and water each day.
- Given a GFR of 125 mL/minute, approximately 180 L of filtrate is produced per day.
- Assuming the GFR above and a plasma Na\(^+\) concentration of 140 mEq/L, approximately 25,000 mEq of Na\(^+\) are filtered each day (Fig. 6-21).
- Because dietary Na\(^+\) intake is small, ranging between 80 and 250 mEq/day, most (>99%) of Na\(^+\) must be reabsorbed from the tubular fluid.
- Assuming water intake of no more than a few liters per day and normal urine output, it is clear that most of the water must also be reabsorbed from the tubular fluid.
- The above approximations highlight the critical role of the kidneys in preventing excess loss of NaCl and water.
- Most of NaCl and water reclamation occurs in the proximal tubule, although substantial reabsorption also occurs in the loop of Henle, with fine regulation of reabsorption occurring in the distal nephron (Fig. 6-22; Table 6-5).

**Table 6-4. Function of Nephron Segments**

<table>
<thead>
<tr>
<th>NEPHRON SEGMENT</th>
<th>PRIMARY FUNCTIONS</th>
<th>HORMONAL REGULATION</th>
<th>ASSOCIATED DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal convoluted tubule</td>
<td>Reabsorption and secretion</td>
<td>Ang II, PTH</td>
<td>Fanconi syndrome, carbonic anhydrase deficiency</td>
</tr>
<tr>
<td>Loop of Henle</td>
<td>Concentration followed by dilution of tubular fluid</td>
<td>ADH</td>
<td>Nephrogenic diabetes insipidus, volume derangements</td>
</tr>
<tr>
<td>Thin ascending limb</td>
<td>Permeable to water</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thick ascending limb</td>
<td>Impermeable to water, dilution of tubular fluid through activity of Na(^+)-K(^+)-2Cl(^-) channel</td>
<td>Aldosterone and ADH</td>
<td>Diuretic-induced volume depletion, Bartter syndrome (chronic metabolic alkalosis)</td>
</tr>
<tr>
<td>Distal tubule</td>
<td>Site of macula densa, tubuloglomerular feedback</td>
<td>ADH, aldosterone, PTH</td>
<td>Gitelman syndrome</td>
</tr>
<tr>
<td>Cortical collecting tubules</td>
<td>Baseline permeability to urea</td>
<td>ADH, aldosterone, PTH</td>
<td>Hyperkalemia secondary to potassium-sparing diuretics</td>
</tr>
<tr>
<td>Medullary collecting tubules</td>
<td>Permeability to urea depends on presence or absence of ADH</td>
<td>ADH</td>
<td>Liddle syndrome, pseudohypoaldosteronism</td>
</tr>
</tbody>
</table>

ADH, Antidiuretic hormone; Ang II, angiotensin II; PTH, parathyroid hormone.

**Example of net reabsorption of Na\(^+\)**

\[
\text{Filtered load} = \text{GFR} \times P_{Na^+} = 180 \text{ L/day} \times 140 \text{ mEq/L} = 25,200 \text{ mEq/day}
\]

\[
\text{Reabsorption} = \text{filtered load} - \text{excretion} = 25,200 \text{ mEq/day} - 100 \text{ mEq/day} = 25,100 \text{ mEq/day}
\]

\[
\text{Excretion} = V \times U_{Na^+} = 1 \text{ L/day} \times 100 \text{ mEq/L} = 100 \text{ mEq/day}
\]

6-21: Na\(^+\) handling along the nephron. GFR, Glomerular filtration rate; \(U_{Na^+}\), urine concentration of sodium; \(V\), volume of urine produced per day. (From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 6-13A.)
2. General Mechanisms of Na\(^+\) Reabsorption
   a. Pathway of Na\(^+\) Reabsorption
      • Na\(^+\) enters the peritubular epithelial cells from the tubular lumen through selective Na\(^+\) channels and cotransporters, which transport Na\(^+\) into the cell along with other charged substances such as glucose (Fig. 6-23).
      1) This is a type of secondary active transport, with energy supplied by the basolaterally located Na\(^+\),K\(^+\)-ATPase pump (more on this later).
      • Na\(^+\) then leaves the peritubular epithelial cell and enters the interstitium through the Na\(^+\),K\(^+\)-ATPase pump.
      • From the interstitium, Na\(^+\) is returned to the systemic circulation through the peritubular capillaries.
   b. Role of the Na\(^+\),K\(^+\)-ATPase pump
      • Because of the stoichiometry of the Na\(^+\),K\(^+\)-ATPase pump, in which three Na\(^+\) ions are exchanged for two K\(^+\) ions, the intracellular Na\(^+\) concentration is kept low, which promotes Na\(^+\) influx.
      • Activity of this pump also creates an intracellular electronegative potential, which also promotes Na\(^+\) influx.
      • This electrochemical gradient is so strong that it allows for the cotransport of other charged substances against their concentration gradient, a type of transport referred to as secondary active transport.

3. Reabsorption along the proximal tubule
   • Approximately two thirds of Na\(^-\) and water and most of the filtered amino acids, phosphate, glucose, and other organic solutes are reabsorbed in the proximal tubule.
   • Most of these other substances are reabsorbed because of cotransport with Na\(^+\).

---

**TABLE 6-5. Sodium Handling Along the Nephron**

<table>
<thead>
<tr>
<th>TUBULAR SEGMENT</th>
<th>FILTERED SODIUM REABSORBED (%)</th>
<th>MECHANISM OF SODIUM ENTRY</th>
<th>REGULATORY FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule</td>
<td>67</td>
<td>Na(^+)-H(^+) countertransport, Na(^+) cotransport with glucose, phosphate, amino acids, and other substances</td>
<td>Angiotensin II, epinephrine GFR</td>
</tr>
<tr>
<td>Loop of Henle</td>
<td>25</td>
<td>Na(^+)-K(^+)-2Cl(^-) channel</td>
<td>Flow dependent</td>
</tr>
<tr>
<td>Distal tubule</td>
<td>5</td>
<td>Na(^+)-Cl(^-) channel</td>
<td>Flow dependent</td>
</tr>
<tr>
<td>Collecting tubules</td>
<td>3</td>
<td>Na(^+) channels</td>
<td>Aldosterone, atrial natriuretic factor</td>
</tr>
</tbody>
</table>

Data from Rennke HG, Denker BM: Renal Pathophysiology: The Essentials, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2006, Table 1-1.
Cotransporters include Na⁺-glucose, Na⁺-phosphate, Na⁺-citrate, and Na⁺-H⁺ transporters. The Na⁺-H⁺ transport facilitates excretion of an H⁺ ion into the lumen in exchange for entry of an Na⁺ ion into the tubular epithelial cell (see clinical note later). This secretion of H⁺ ions facilitates HCO₃⁻ reabsorption because the H⁺ combines with HCO₃⁻ to produce carbonic acid, which then dissociates into CO₂ and water, as shown below.

\[
CO₂ + H₂O \rightarrow H₂CO₃ \rightarrow H^+ + HCO₃^-
\]

Clinical note: In volume-depleted states, in which the proximal tubular epithelial cells avidly retain filtered Na⁺ in an attempt to maintain ECF volume, a contraction alkalosis can result from the loss of H⁺ ions. Clinical scenarios resulting in a contraction alkalosis include dehydration, chronic diarrhea (acute diarrhea causes a metabolic acidosis due to loss of HCO₃⁻), and overdiuresis with diuretics.

- Removal of solutes from the lumen reduces luminal osmolality, creating an osmotic gradient for H₂O reabsorption.
- Water is transported across the proximal tubule through aquaporin channels as well as across “leaky” tight junctions.
  a. Because the proximal tubule is so permeable to water, concentration and osmotic gradients are difficult to maintain, resulting in a filtrate that is isosmotic relative to plasma.
  b. High permeability to water limits the ability of the proximal tubule to concentrate solutes. This limitation exists for two reasons:
    - Substances directly linked to Na⁺ reabsorption are reabsorbed in equivalent amounts as Na⁺ and water and therefore their concentration in the tubular fluid remains unchanged.
    - Substances indirectly linked to Na⁺ reabsorption (e.g., urea) will not have their concentration change along the proximal tubule because Na⁺-induced water reabsorption raises the concentration of these solutes, which then promotes diffusion out of the proximal tubule.
- By contrast, tight junctions in the distal nephron are much more “tight” and therefore allow for the development of significant osmotic and concentration gradients. This serves two purposes:
  a. Allow for the excretion of concentrated urine
  b. Allow for the excretion of a significant acid load
4. Reabsorption of Na⁺ and H₂O along the loop of Henle (LOH)
   - Approximately 25% of filtered Na⁺ is reabsorbed in the thick ascending limb of the LOH.
   - Because the ascending limb lacks aquaporin channels, it is impermeable to water; therefore, reabsorption of Na⁺ exceeds that of water.
   - The tubular fluid is therefore diluted in the ascending limb, and this also plays an important role in the countercurrent mechanism and production of concentrated urine (discussed later).
   - Figure 6-24 illustrates Na⁺ uptake in the thick ascending limb of the LOH through the electroneutral Na⁺-K⁺-2Cl⁻/C⁰ channel.
     a. This lumen positivity also drives cation (Na⁺, Ca²⁺, Mg²⁺) transport across the tight junctions in the ascending limb; for example, the thick ascending limb of the LOH is the major site of Mg²⁺ reabsorption in the nephron.

**Pharmacology note:** Loop diuretics inhibit activity of the Na⁺-K⁺-2Cl⁻ channel by binding to the Cl⁻ binding site on the transporter, thereby promoting a vigorous diuresis. By blocking the Na⁺-K⁺-2Cl⁻ channel they may also cause hyponatremia, hypokalemia, and a hypochloremic metabolic alkalosis (through loss of H⁺ ions as well as volume depletion).

5. Reabsorption of Na⁺ and H₂O in the distal nephron
   - Typically responsible for reabsorption of approximately 5% to 8% of filtered NaCl
   - The primary mechanism of Na⁺ reabsorption is through cotransport with Cl⁻ (Fig. 6-25).
   - Because the distal nephron is relatively impermeable to water, the intraluminal NaCl concentration drops to approximately 40 mEq/L.
   - It is this fall in the concentration of Cl⁻, rather than Na⁺, that limits further NaCl reabsorption in the LOH and distal tubule. It does this in two ways:
     a. Because the activity of the Na⁺-K⁺-2Cl⁻ channel is primarily dependent on luminal Cl⁻ concentration, a low Cl⁻ concentration inhibits activity of this channel.
     b. A falling concentration of NaCl in the lumen creates a gradient for backflux of Na⁺ and Cl⁻ from the interstitium into the lumen through tight junctions.
   - Net reabsorption therefore ceases when rate of Na⁺ entry into cell equals rate of backflux.
   - For this reason, it may be that the transport of Na⁺ and Cl⁻ in the distal nephron is flow dependent (see clinical note).
6. Regulation of Na\(^+\) Balance

   • Overview
      a. Na\(^+\) with its associated anions Cl\(^-\) and HCO\(_3\)\(^-\) are the primary solutes of the ECF.
      b. Therefore, the amount of Na\(^+\) in the ECF determines the ECF volume, which affects total body weight, blood volume, and blood pressure.
      c. A variety of neurohormonal mechanisms play a critical role in regulating Na\(^+\) balance and by extension ECF volume and blood volume (Fig. 6-26).
      d. Na\(^+\) balance and regulation of ECV volume are discussed in greater detail in Chapters 8 and 9.

VI. Concentration and Dilution of Urine

A. Overview
   1. The kidney is the body’s major route of excretion of solute and water.
   2. It can excrete urine ranging from very dilute to very concentrated.
   3. If this were not the case and reabsorption of fluid and electrolytes along the nephron occurred in an isosmotic fashion (as it does in the proximal tubule), urine would have an osmolality equivalent to that of plasma.
   4. Consequently, maintenance of plasma osmolality in the tight range that is physiologically required would fall largely to regulation of dietary intake, which would not be feasible.

B. Obligatory urine output
   1. This is the minimum amount of urine that must be produced each day in order to excrete the nonvolatile waste products of daily metabolism.
   2. It is determined by the kidney’s concentrating capacity and solute production and is approximately 500 mL, reflecting a normal maximum concentrating capacity of 1200 milliosmoles per liter (mOsm/L) and typical daily solute production of 600 mOsm.

C. The interstitial osmotic gradient from cortex to medulla
   1. In order to regulate total body sodium and water balance, the kidney must be able to excrete urine across a high range of concentrations.
   2. To remove excess water, the kidney must be able to excrete a dilute urine.
6-26: Overall regulation of Na⁺ balance. $P_C$, Oncotic capillary pressure; ANP, atrial natriuretic peptide; EABV, effective arterial blood volume; ECF, extracellular fluid; GFR, glomerular filtration rate. (From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Figs. 6-27 and 6-28.)
3. The nephron does this by reabsorbing solute and retaining water in the tubular lumen (because the water channels across the tubular epithelial cells are closed).
   - Excretion of this dilute urine eliminates the excess water.
4. To remove excess solute, the kidney must be able to excrete a concentrated urine.
5. This is achieved by the collecting ducts passing through a hyperosmolar region of the kidney, with open water channels across the tubular epithelial cells.
6. Water moves out of the tubule into the interstitial space, and the remaining solute-rich urine can be excreted.
   - Excretion of this concentrated urine eliminates the excess solute.
7. The ability of the kidney to produce a concentrated urine hinges on the creation and maintenance of a region of high interstitial osmolality.
   - **The countercurrent mechanism**
     a. The kidney’s ability to establish an osmotic gradient rests primarily in the structure of the **loop of Henle**, which folds back on itself to form a physiologic **countercurrent system** (Fig. 6-27).
     b. Other factors, such as the active transport of NaCl from the ascending limb of the loop of Henle and **urea trapping** within the medullary interstitium, are also important.
     c. The unique structure of the vas recta also plays a contributory role (more on this later).
   - **The loop of Henle as a countercurrent system**
     a. The loop of Henle functions as a countercurrent system in which the flows in the individual limbs “interact” with one another (Fig. 6-28).
     b. As in the example in Figure 6-27B, in which the heat from the ascending tube was used to heat the cold water in the descending tube, the salts removed from the ascending limb are used to concentrate the fluid within the descending limb, by creating a hyperosmotic interstitium.
       - In the **descending limb**, which is permeable to water but not to salts, water is removed and solute remains, increasing the concentration and causing an increase in tubular fluid osmolality.
       - In the **thick ascending limb** (see Fig. 6-2), which is permeable to salts but not water, the removal of solute dilutes the tubular fluid and helps generate and maintain the interstitial osmotic gradient.
     c. Note that the loop of Henle functions as an imperfect countercurrent system, because the fluid emerging from the ascending limb is more dilute (~100 mOsm/L) than the fluid entering (~300 mOsm/L).
     d. This is partly because the hyperosmotic tubular fluid in the **thin ascending limb** (see Fig. 6-2) draws in water from the medullary interstitium (which also helps maintain the hyperosmolar interstitium of the medulla).

6-27: Flow-through and countercurrent systems. **A**, In a flow-through system, initially the water in the tube is at 0°C; as it passes through the beaker, it draws heat from the fluid such that it emerges from the tube at a different temperature (100°C). This arrangement represents a flow-through system. The capillaries in the renal cortex (as in most tissues) can be thought of as flow-through capillaries that rapidly equilibrate with the surrounding interstitial fluid. **B**, In a countercurrent system with a hairpin bend (such as the loop of Henle), the fluid emerges from the tube unchanged from its initial temperature of 0°C. Thus, countercurrent systems isolate environments despite intimate contact. For the countercurrent mechanism to work efficiently, two requirements must be met: the fluid must be moving slowly, and the two vertical “limbs” of the “U” must be contiguous.
Pharmacology note: Recall that a slow flow rate is required for a countercurrent system to work effectively. If the tubular flow rate increases substantially within the loop of Henle, its ability to function as a countercurrent system and maintain a hyperosmolar interstitium will become compromised. Dilute urine will then be produced in large amounts. This is one mechanism by which loop diuretics function in promoting diuresis—by increasing the tubular flow rate and compromising the ability of the loop of Henle to function as a countercurrent system.

- **Antidiuretic hormone and control of urine concentration**
  a. The distal nephron delivers a very dilute tubular fluid to the collecting tubules.
  b. If fluid intake has been high, this dilute fluid is excreted.
  c. However, if solute load is such that fluid retention is needed (recall that Na\(^+\) balance determines ECF volume), mechanisms must be in place to allow the needed water to be reclaimed.

- **Plasma osmolality**
  a. Plasma osmolality is determined by the ratio of solute to plasma water.
  b. The major plasma solute is sodium and its accompanying anions, so plasma osmolality is typically equal to slightly more than two times the plasma sodium concentration.

  Clinical note: Plasma osmolality can be formally calculated by the following equation: \( P_{\text{osm}} = 2 \times [\text{Na}^+] + \text{glucose}/18 + \text{urea}/2.8 \)

c. Plasma osmolality is tightly regulated and normally is 275 to 290 mOsm/L.
d. The addition of water (or the removal of solute) decreases the osmolality of plasma (Fig. 6-29).

- **Renal responses to changes in plasma osmolality** (see Fig. 6-29)
  a. The cortical collecting ducts are permeable to water at all times.
  b. By contrast, the permeability of the medullary collecting tubules to water is determined by secretion of ADH, which is controlled by the response of hypothalamic osmoreceptors to plasma osmolality and volume.
  c. When ADH is secreted, it travels to the kidney, where it stimulates insertion of water channels (aquaporin) into the membranes of the tubular epithelial cells of the collecting tubules, allowing water to move by osmosis into the hypertonic interstitium (Fig. 6-30).
  d. In response to decreased plasma osmolality (addition of water or loss of solute), osmoreceptors trigger cessation of the release of ADH, so the collecting tubules remain relatively impermeable to water (Fig. 6-31).
e. Because of this, the excess water is excreted into the urine; the loss of this excess water returns plasma osmolality to normal.

f. In response to raised plasma osmolality (addition of solute or loss of water), the osmoreceptors stimulate ADH secretion.

g. As a result, the collecting tubules become permeable to water, allowing water to move by osmosis into the hypertonic interstitium, so less water is excreted, and plasma osmolality returns to normal.

h. Note that the osmoreceptors that regulate ADH secretion may also stimulate thirst, leading to increased water intake.

i. The combination of water retention, solute excretion, and increased water intake serves to lower the plasma osmolality toward normal.

- **Urea trapping** (Fig. 6-32)
  a. Approximately one half of the solute that contributes to the medullary concentrating gradient is urea.
  b. Urea is freely filtered through the glomerulus and only partially reabsorbed in the proximal tubule.
  c. The cortical and outer medullary portions of the collecting tubules are impermeable to urea, whereas the inner medullary collecting tubules are variably permeable to urea.
  d. In the presence of ADH, urea concentration in the collecting tubules becomes quite high, because water is removed through open water channels.
6-30: Production of concentrated urine with presence of ADH. ADH, Antidiuretic hormone. (From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 6-41.)

6-31: Production of dilute urine in the absence of ADH. ADH, Antidiuretic hormone. (From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 6-42.)
e. ADH further increases the permeability of the inner medullary collecting tubules to urea, allowing more urea to diffuse into the medullary interstitium.

f. This creates a more hypertonic medulla, which enables further concentration of the urine.

• **Vasa recta**
  a. This is the capillary network that supplies the nephron.
  b. The vascular supply to the loop of Henle and collecting tubules could easily wash away the medullary concentrating gradient if the vessels traveled past the nephron in a manner similar to the flow-through model depicted in Figure 6-27A.
  c. However, the vasa recta also have a **hairpin configuration** that prevents these vessels from dissipating the concentrating gradient and the blood flow is slow (Fig. 6-33).
  d. The ascending portions of the vasa recta remove water reabsorbed from the collecting tubules, which helps maintain the medullary hypertonicity.
  e. These vessels also supply the **oxygen** and **nutrients** required by the tubular epithelial cells.
  f. Because of their hairpin configuration, oxygen can diffuse from the descending vessels into the ascending vessels, leaving the tubular epithelial cells at the innermost part of the loop of Henle in a relatively **oxygen-poor** environment.

Clinical note: The poor oxygenation of tubular epithelial cells makes them susceptible to hypoxia or hypotension. A hypotensive insult that leaves the heart, liver, and brain unscathed can cause **acute renal failure** (injury) because of **hypoxic injury** to tubular epithelial cells. This leads to one of the most common causes of acute renal failure, **acute tubular necrosis**. Of note, blood flow through the vasa recta is of necessity very slow to help maintain the countercurrent exchange. However, particularly in hypercoagulable states and sickle cell crisis, this can predispose them to thrombosis resulting in **renal papillary necrosis**.
VII. Renal Control of Plasma Potassium

A. Overview
1. Most potassium is intracellular (140 mEq/L), and only approximately 2% is extracellular (~4.5 mEq/L).
2. Therefore, a shift of only a small fraction of intracellular potassium to or from the plasma can have a significant impact on the plasma potassium concentration.
3. The distribution of sodium and potassium between the intracellular and extracellular compartments is maintained by the activity of the Na\(^+\),K\(^+\)-ATPase pump, which moves sodium out and potassium into cells.
4. The kidneys play a major role in regulating potassium excretion; in fact, in acute kidney failure (injury), hyperkalemia typically occurs as a result of the decreased ability of the kidney to excrete potassium.

Clinical note: Regulation of the extracellular potassium pool is extremely important, because modest changes in plasma levels can precipitate neuromuscular symptoms and lethal cardiac arrhythmias. These occur because the resting membrane potentials of nerves and muscle are directly related to the ratio of intracellular and extracellular potassium concentrations.

B. Regulation of potassium distribution
1. The activity of the Na\(^+\),K\(^+\)-ATPase pump is regulated by insulin, catecholamines, and K\(^+\) concentration.
2. Regulation by K\(^+\) concentration is particularly important after ingestion of a potassium-containing meal.
3. The meal-induced increase in insulin activates the Na\(^+\),K\(^+\)-ATPase channel, which moves the absorbed potassium into the intracellular compartment; this circumvents the large increase in extracellular potassium that would otherwise occur.
4. Catecholamines also stimulate intracellular movement of potassium.
5. Activation of \(\beta_2\)-adrenergic receptors promotes entry of potassium into cells; \(\alpha\)-receptors impair this movement.
6. Extracellular pH can also prompt shifts in the distribution of potassium, especially in certain types of metabolic acidosis in which large amounts of the H\(^+\) excess are buffered intracellularly.
7. In order to maintain mandatory electroneutrality, K\(^+\) shifts to the extracellular location to offset an increase in positive charges caused by intracellular movement of H\(^+\).
8. The result is an increase in plasma K\(^+\) concentration of 0.2 to 1.7 mEq/L for every 0.1-unit fall in extracellular pH.
Clinical note: In diabetic ketoacidosis (DKA), the profound metabolic acidosis results in hyperkalemia (in part) due to shifting of intracellular $K^+$ to the plasma in exchange for $H^+$ ions. Despite the hyperkalemia, these patients are often whole body potassium–depleted because the osmotic diuresis in DKA results in significant losses of potassium. For this reason, despite a normal or mildly elevated plasma potassium concentration, in addition to insulin and aggressive hydration, these patients require potassium as long as their kidneys are working and they are producing urine. In fact, following the administration of insulin and glucose and the correction of the acidosis, one has to be very cautious about the development of hypokalemia.

9. $H^+$ shifts are much less prominent with metabolic alkalosis, and $K^+$ levels typically exhibit only small decreases.

Pharmacology note: Several drugs can affect potassium distribution. Digitalis is a drug commonly used in the treatment of congestive heart failure; overdose impairs the activity of $Na^+,K^+-ATPase$ and can cause severe hyperkalemia because of the inability of potassium to be moved intracellularly. Other drugs that affect potassium distribution are insulin and albuterol (a $\beta_2$-receptor agonist). Because of their ability to shift potassium to the intracellular location, these drugs are used to treat severe hyperkalemia.

C. Control of potassium homeostasis

1. Overview
   - Ultimately, control of potassium balance requires the excretion of excess potassium by the kidneys.
   - Under normal circumstances, the kidneys maintain potassium homeostasis simply by matching potassium excretion with potassium intake.
   - The colon also plays a minor role in potassium excretion.

2. Renal handling of potassium
   - Most potassium (~90%) is reabsorbed in the proximal nephron (primarily the proximal convoluted tubule and the thick ascending limb).
   - The result is a fairly limited delivery of potassium to the distal nephron (late distal tubule and cortical collecting tubules) (Fig. 6-34).
   - The distal nephron has the ability to either reabsorb or secrete potassium and therefore is the site that ultimately determines renal potassium handling.
   - Under normal conditions, the distal nephron favors potassium secretion over potassium reabsorption, because this is normally what is required to maintain potassium balance.

Distal nephron has final say on potassium handling.

6-34: Renal handling of potassium. Because the absorption of $K^+$ is so complete, most urinary potassium is derived primarily from secreted rather than filtered potassium. This diagram depicts the typical situation of dietary potassium excess. In potassium-depleted states, net reabsorption of potassium might occur in the distal nephron.
This secretory ability is so powerful that if there is high dietary intake of potassium, the amount of urinary potassium actually exceeds the filtered potassium load.

a. Mechanism of potassium secretion by distal nephron

- In the distal nephron, Na⁺,K⁺-ATPase pumps on the basolateral membrane of tubular principal cells pump sodium out and potassium into the cells (Fig. 6-35).
- The potassium that accumulates in the cells then passively diffuses into the tubular lumen via luminal potassium channels.
- Therefore, anything that affects the electrochemical gradient for passive potassium diffusion from cell to tubular lumen affects potassium secretion in the distal nephron.
- If the tubular flow rate is increased, less potassium accumulates in the tubular lumen, and this maintains a larger electrochemical gradient for potassium diffusion into the tubules, increasing potassium secretion.
- If the Na⁺,K⁺-ATPase is more active, this increases intracellular potassium levels in the tubular cells and causes increased potassium diffusion into the tubules.
- The transcellular electrical potential affects potassium secretion: more negative luminal potentials increase the diffusion of the positively charged potassium ions.
- Such an increase in transcellular potential occurs with increased sodium movement from the tubular lumen into the cells via the luminal sodium channels (see Fig. 6-35).

b. Regulation of renal potassium secretion and reabsorption

- Aldosterone and plasma K⁺ concentration are the major regulators of K⁺ secretion by the kidney.
- Small increases (0.1 mEq/L) in plasma potassium concentration promote significant increases in aldosterone secretion by the adrenal glands.
- Aldosterone has two effects on the potassium-secreting principal cells in the kidney:
  1. It increases the activity of the Na⁺,K⁺-ATPase pump in the basolateral membrane.
  2. It causes a marked increase in the number of open Na⁺ and K⁺ channels in the luminal membrane.
- These factors favor potassium secretion into the urine as outlined in the previous section, and hence excretion of potassium from the body.
- Plasma potassium levels themselves can regulate renal potassium excretion:
  1. An increase in plasma K⁺ concentration, and thus interstitial K⁺ concentration, replicates all the activities of aldosterone (Fig. 6-36).
  2. The response to potassium depletion is a decrease in the release of aldosterone and a fall in intracellular potassium concentration in the distal portions of the nephron.

Clinical note: In renal failure (injury), the GFR is reduced. This reduces the rate of flow through the renal tubules, limiting the amount of potassium that can be excreted. This is one of several reasons hyperkalemia is a common complication of renal dysfunction.
This effectively shuts down potassium secretion into the tubular lumen by the principal cells; however, reabsorption must be employed to reclaim potassium that is still present in the tubular lumen.

A second cell type, the intercalated cell, plays an active role in distal potassium reabsorption.

These cells have a luminal H⁺,K⁺-ATPase pump that reabsorbs K⁺ and secretes H⁺ (Fig. 6-37).

The activity of this pump increases with K⁺ depletion and promotes reabsorption of potassium.

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**Intercalated cells:** secretes H⁺ ions; critical role in acid-base balance

**6-36:** Effect of aldosterone and hyperkalemia on potassium excretion. Aldosterone or elevated interstitial K⁺ concentrations generate changes in the principal cell that favor potassium excretion. The activity of Na⁺,K⁺-ATPase is increased, and the number of open sodium and potassium channels on the luminal membrane is increased.

**6-37:** K⁺ secretion in the principal cell and K⁺ reabsorption in the intercalated cell. ATP, Adenosine triphosphate. (From Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 33-9.)

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**Illustration:**
- Tubular lumen
- Principal cell
- Interstitial space
- Sodium (Na⁺) and potassium (K⁺) transport across cell membranes.
- Aldosterone stimulation.
- ATPase activity.
- Channel permeability changes.
Pharmacology note: The volume depletion triggered by carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics stimulates aldosterone secretion. Because this increases the number of open sodium and potassium channels in the collecting tubule, the high distal flow rates and sodium retention at this site set the stage perfectly for high levels of potassium secretion into the tubule. Hypokalemia commonly results. This potassium-wasting property of diuretics is so consistently observed that the one class of diuretics that does not prompt hypokalemia is distinguished by being known as the “potassium-sparing” diuretics (see later discussion). The potassium-sparing diuretics are those that act in the collecting tubule to decrease the number of open sodium channels in principal cells; examples include amiloride, triamterene, and spironolactone.

VIII. Renal Contribution to Control of Phosphate and Calcium Homeostasis
A. Overview
1. The contribution of the kidney to phosphate homeostasis involves a more complex regulatory system than does its contribution to acid-base, bicarbonate, and potassium homeostasis, all of which involve near-complete absorption from the gut with a matching of daily intake to urinary losses.
2. Regulation of plasma phosphate levels is tightly linked to regulation of plasma calcium and is influenced by the same compounds, parathyroid hormone (PTH) and vitamin D.
3. Gut absorption of phosphate and calcium is highly variable and is controlled by PTH and vitamin D, as is the distribution of high concentrations of calcium and phosphate in the bone in the form of hydroxyapatite.
4. Renal excretion of phosphate is controlled by PTH (Fig. 6-38).

B. Parathyroid hormone
1. PTH is secreted by the parathyroid gland, the primary role of which is the precise regulation of serum calcium levels (Fig. 6-39).
2. A decrease in serum calcium increases circulating PTH; this triggers increased gut absorption of calcium and phosphate, increased mobilization of calcium and phosphate from stores in bone, and decreased renal calcium excretion.
3. These factors raise plasma calcium back to normal.

HANDLING OF PHOSPHATE ALONG NEPHRON

6-38: Phosphate handling in the nephron. PCT, proximal convoluted tubule; Pi, inorganic phosphate; PST, proximal straight tubule. (From Boron W, Boulpaep E: Medical Physiology, 2nd ed. Philadelphia, Saunders, 2009, Fig. 36-14A.)
4. However, in the absence of renal control, this would also have the unwanted effect of increasing serum phosphate.
5. This does not occur because PTH also increases renal phosphate excretion.
6. It does this by causing a marked decrease in the number of Na\(^+\)-Pi cotransporters located in the luminal membrane, thus increasing renal phosphate excretion. Energy for phosphate transport is derived from the basolateral Na\(^+\),K\(^+\)-ATPase. Phosphate is transported into the interstitium for absorption into the circulation.

**C. Vitamin D**

1. 1,25 dihydroxyvitamin D\(_3\) (calcitriol), the most active form of vitamin D, is the primary hormone that responds to changes in phosphate balance.
2. **Vitamin D (cholecalciferol)** is obtained from the diet and also is synthesized in skin exposed to ultraviolet light.
3. In the liver, a hydroxyl group is added in the 25 position to yield calcidiol, which then travels through the circulation to the kidney.
4. In the kidney, calcidiol is hydroxylated at the 1 position to yield calcitriol.
5. **Hypophosphatemia stimulates renal calcitriol production.**
6. **Hyperphosphatemia inhibits renal calcitriol production.**
7. Changes in plasma calcitriol concentration normalize phosphate balance by regulating the absorption of dietary phosphate and phosphate mobilization from bone.
increased calcitriol increases bone formation/mineralization and decreases bone resorption/mobilization (see Chapter 3).

8. Calcitriol also modulates **PTH production**: a low calcitriol level stimulates PTH production, and a high calcitriol level decreases PTH production.

D. **Hypophosphatemia and hyperphosphatemia**

1. Physiologic responses to hypophosphatemia include the following:
   - Increased number of Na\(^+\)-Pi cotransporters, which serves to increase proximal phosphate reabsorption
   - Increased calcitriol synthesis, which increases phosphate availability from the gut and bone
   - Suppression of PTH secretion, which further increases the activity of the proximal Na\(^+\)-Pi cotransporters and lowers urinary phosphate losses

2. The reverse happens in response to hyperphosphatemia, which is commonly seen in individuals with moderate renal failure:
   - A reduction in proximal tubular phosphate reabsorption occurs because of reduced production of the Na\(^+\)-Pi cotransporter.
   - Calcitriol levels fall.
   - Increased PTH secretion further lowers Na\(^+\)-Pi cotransporter activity.
   - The net result is a decrease in serum phosphorus levels toward normal.

**Clinical note:** In primary hyperparathyroidism, the primary problem is overproduction of PTH by the parathyroid glands. The typical laboratory findings in this disease are hypercalcemia and hypophosphatemia. Secondary (compensatory) hyperparathyroidism is commonly seen with chronic kidney disease. Impaired 1,25-dihydroxyvitamin D production by the diseased kidney, hypophosphatemia due to impaired renal phosphate excretion, and mild hypocalcemia combine to increase PTH production. The hyperparathyroidism tends to normalize calcium levels and increase renal phosphorus excretion. The result is that both calcium and phosphorus levels may be normal. The price for this normalcy is sustained elevation of PTH, which can induce bone disease because of the continued stimulatory effects of PTH in mobilizing bone stores of calcium and phosphate. In an attempt to preserve bone health, nephrologists often use calcimimetics to keep PTH levels low and prevent renal osteodystrophy and osteitis fibrosa cystica.

IX. **Diuretics**

A. **Overview**

- Diuretics primarily reduce extracellular volume by preventing reabsorption of **sodium** and **water** from the tubular lumen.

B. **Diuretics and sodium**

1. **Sodium**, the most abundant plasma electrolyte, is freely filtered through the glomerulus and then almost completely reabsorbed through transporters located at several different sites along the nephron.
2. The basolaterally located Na\(^+\),K\(^-\)-ATPase is important at each of these sites; however, the mechanism of sodium entry through the luminal membrane differs.
3. Different classes of diuretics act at different **nephron sites**, because each class of diuretics interacts with one type of luminal sodium transporter (Fig. 6-41; Table 6-6).
4. The ability of diuretics to increase sodium excretion is dependent on the amount of sodium absorbed at the site of diuretic action and the ability of more distal sites in the nephron to increase their sodium reabsorption.
TABLE 6-6. Differences Among Classes of Diuretics

<table>
<thead>
<tr>
<th>CLASS OF DIURETIC</th>
<th>SITE OF ACTION</th>
<th>MECHANISM</th>
<th>POTENCY</th>
<th>CLINICAL USE</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>Proximal convoluted</td>
<td>Promote metabolic acidosis by inhibiting bicarbonate reclamation (i.e., increase bicarbonate excretion), weak diuretic effect by inhibiting Na⁺ reabsorption</td>
<td>Weak diuretic effect because of the capacity of more distal sites, particularly the Na⁺-K⁺-2Cl⁻ cotransporter in the loop of Henle, to increase sodium reabsorption</td>
<td>High-altitude sickness, glaucoma</td>
<td>Metabolic acidosis, ↓ K</td>
</tr>
<tr>
<td>(acetazolamide)</td>
<td>tubule</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Distal convoluted</td>
<td>Inhibit the activity of the Na⁺-Cl cotransporter</td>
<td>Relatively weak because act at sites where smaller amounts of sodium (5%-10%) are reabsorbed</td>
<td>Hypertension</td>
<td>Hyponatremia, hypercalcemia, ↓ K</td>
</tr>
<tr>
<td>(HCTZ, metolazone)</td>
<td>tubule</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
<td>Collecting tubule</td>
<td>Decreasing the number of open Na⁺ channels in principal cells of the tubule</td>
<td>Relatively weak because act at sites where smaller amounts of sodium (3%-5%) are reabsorbed</td>
<td>Cirrhosis Added to thiazides to avoid ↓ K</td>
<td>Hyperkalemia (rarely), gynecomastia (spironolactone)</td>
</tr>
<tr>
<td>(spironolactone, triamterene,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amiloride)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Loop of Henle</td>
<td>Inhibit Na⁺-K⁺-2Cl⁻ carrier in thick ascending limb of loop of Henle</td>
<td>More potent because act at a site responsible for reabsorption of approximately 25% of filtered sodium</td>
<td>Pulmonary edema associated with congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>(furosemide)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmotic diuretics</td>
<td>—</td>
<td>Osmotic diuresis</td>
<td>—</td>
<td>Cerebral edema</td>
<td>Vascular space expansion with volume overload</td>
</tr>
<tr>
<td>(mannitol)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Data from Stevenson F: Crash Course: Renal and Urinary Systems. Philadelphia, Mosby, 2005, Fig. 3-19.

6-41: Sites of actions of diuretics along the nephron. ADH, Antidiuretic hormone; PTH, parathyroid hormone. (From Pazdernik T, Kerecsen L: Rapid Review Pharmacology, 2nd ed. Philadelphia, Mosby, 2007, Fig. 15-1.)
CHAPTER 7
GASTROINTESTINAL PHYSIOLOGY

I. Structure and Function of the Gastrointestinal Tract
A. Functional anatomy
1. Overview
   • The gastrointestinal (GI) tract is essentially a **hollow digestive tube** that extends from the mouth to the anus.
   • Secretions from accessory digestive structures such as the salivary glands, pancreas, and liver empty into this tube and are essential for efficient digestion and absorption.
   • The digestive tract can be subdivided into three sections based on embryologic origin and vascular supply (Fig. 7-1).
   • The **foregut** extends from the esophagus to the second part of the duodenum and is supplied by the **celiac artery**.
   • The **midgut** extends from the second part of the duodenum to the splenic flexure of the colon and is supplied by the **superior mesenteric artery**.
   • The **hindgut** extends from the splenic flexure of the colon to the anus and is supplied by the **inferior mesenteric artery**.
   • Venous return of all three arterial beds is through the **portal vein** into the liver.

Pathology note: The portal vein normally carries nutrient-rich blood from the intestines to the liver, after which the blood is shunted to the inferior vena cava through the hepatic vein. In [cirrhosis](https://en.wikipedia.org/wiki/Cirrhosis), a variety of pathophysiologic changes result in elevated portal vein pressures, termed **portal hypertension**. Because the portal vein has multiple [anastomoses with systemic veins](https://en.wikipedia.org/wiki/Portal_hypertension), pressures likewise increase in these vessels. These systemic veins may then become abnormally dilated and are at increased risk for rupture. In the anterior abdominal wall, venous dilatation can result in **caput medusae**, a rather harmless clinical examination finding that nonetheless indicates severe liver disease. In the esophagus, venous dilatation can result in **esophageal varices**. Rupture of esophageal varices can be rapidly fatal.

Vascular supply of intestinal tract: foregut—celiac artery; midgut—SMA; hindgut—IMA

7-1: Splanchnic circulation, which is derived entirely from the celiac artery, the superior mesenteric artery, and the inferior mesenteric artery.
2. **Layers of the gut wall**
   - Throughout most of the GI tract, the gut wall is composed of four layers; from inside to outside, these are the mucosa, submucosa, muscularis propria, and serosa (Fig. 7-2).
   - **Mucosa**
     - The mucosa is composed of three distinct layers: the **mucosal epithelium**, the **lamina propria**, and the **muscularis mucosae**.
     - The structure of the **mucosal epithelium** varies depending on its location in the GI tract.
     1. **Stratified squamous** mucosal epithelium is present in the esophagus.
     2. In contrast, **columnar** mucosal epithelium is present in the rest of the GI tract, except for the rectum, where it changes back to squamous at the dentate line.
     3. In the stomach, the mucosa is folded into **rugae**.
     4. In the small intestine, there are folds of cells in the mucosa (**villi**) and projections on individual cells (**microvilli**), which increase the surface area for absorption (Fig. 7-3).
     5. In the large intestine, there are **crypts** but no villi.
Pathology note: In gastroesophageal reflux disease (GERD), the mucosal epithelium of the esophagus takes on the appearance of the gastric mucosal epithelium—it differentiates from a stratified squamous epithelium into a columnar epithelium. This process, whereby one cell type transforms into another, is termed metaplasia. Columnar metaplasia in the lower esophagus is called Barrett esophagus, which can be detected by endoscopy and substantially increases the risk for development of esophageal adenocarcinoma and stricture from scarring. Patients who develop Barrett esophagus require periodic endoscopic surveillance.

- The lamina propria is a thin sheet of connective tissue just outside the mucosa.
  (1) It contains capillaries, a central lymph vessel, lymphoid tissue, and glands with ducts that allow for mucus and serous secretions onto the mucosal surface.
- The muscularis mucosa is composed of multiple thin layers of smooth muscle, which separate the lamina propria from the submucosa.
  (1) Contraction of these layers helps expel the contents of the glandular crypts to the mucosal surface.

b. Submucosa
- Layer of loose connective tissue that connects the mucosa to the underlying muscularis propria
- Contains blood vessels, lymphatic vessels, and nerves that supply the overlying mucosa
- Site of the submucosal plexus, which innervates the muscularis mucosae (more on this later)

- Muscularis propria (externa)
  - Thick muscular layer composed of inner circular and outer longitudinal muscle layers that extend the entire length of the intestinal tract
  - Plays an important role in intestinal motility (e.g., peristalsis)

Anatomy note: In the colon, the outer longitudinal muscle layer is discontinuous and clustered into three distinct strips called the taeniae coli.

d. Serosa
- Outermost cellular membrane present in most of the intestinal tract that is continuous with the peritoneal lining
- Cells secrete a serous fluid that helps reduce friction from muscle movement
- The serosa is absent in certain retroperitoneal portions of the intestinal tract, such as the esophagus and portions of the colon.
  (1) These portions instead are bounded by a fibrous covering termed the adventitia.

Clinical note: Absence of the serosa from much of the esophagus may contribute to the tendency for esophageal cancers to spread locally before they are detected, in part explaining the poor prognosis associated with esophageal cancer.

3. Neural regulation of the gastrointestinal tract
- Enteric nervous system
  a. Overview
    - Contained entirely within the gut wall
    - Composed of the submucosal and myenteric plexuses
    - These plexuses regulate entirely different aspects of intestinal activity, as discussed later.
  b. Submucosal (Meissner) plexus
    - Located between the muscularis mucosa and the muscularis propria
    - Gives rise to efferent fibers that synapse directly on mucosal epithelial cells, with the primary goal of stimulating secretions required for digestion

Enteric nervous system: composed of submucosal and myenteric plexuses and entirely contained within gut wall

Submucosal plexus: stimulates secretion, promotes digestion
Pathology note: In Hirschsprung disease (aganglionic megacolon), the neural crest cells that form the myenteric plexus fail to migrate to the colon. Newborns with this condition are likely to be severely constipated, and imaging studies may reveal a massively dilated colon proximal to the aganglionic segment.

c. Myenteric (Auerbach) plexus
   - Located between the inner circular and the outer longitudinal muscle layer of the muscularis propria
   - Primary role is coordination of intestinal motility
     - Stimulation of the myenteric plexus increases intestinal motility mainly by stimulating peristalsis and also by inhibiting contraction of sphincter muscles throughout the intestinal tract.
   - Extrinsic regulation: autonomic nervous system (Fig. 7-4)
     a. The parasympathetic nervous system (PNS) generally promotes digestion and absorption by stimulating GI secretions and peristalsis while inhibiting sphincter muscle contraction.
     b. In contrast, the sympathetic nervous system (SNS) generally inhibits digestion and absorption, stimulates sphincter muscle contraction, and causes vasoconstriction in the splanchnic circulation (Table 7-1).

Clinical note: The PNS stimulates intestinal motility by releasing acetylcholine onto neurons of the myenteric plexus. Therefore, cholinergic drugs should never be given to a patient if an intestinal obstruction is suspected. The resulting increase in pressure could rupture a viscus, resulting in potentially lethal peritonitis.

Myenteric plexus: promotes motility of intestinal tract

PNS: promotes digestion and absorption by stimulating secretions and intestinal motility

SNS: inhibits digestion and absorption in part through vasoconstriction of the splanchnic circulation

7-4: Innervation of the gastrointestinal tract by the autonomic nervous system. The myenteric plexus synapses mainly on the inner circular and outer longitudinal muscles, whereas the submucosal plexus synapses mainly on the muscularis mucosae and epithelial cells of the mucosa. (From Damjanov I: Pathophysiology. Philadelphia, Saunders, 2008, Fig. 7-5.)

### TABLE 7-1. Effect of the Autonomic Nervous System on the Gastrointestinal Tract

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>PARASYMPATHETIC</th>
<th>SYMPATHETIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motility</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Sphincter tone</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Secretion</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>No effect</td>
<td>+</td>
</tr>
</tbody>
</table>
• **Anatomy of reflex loops**
  
a. Local reflexes, such as the gastrocolic reflex, involve afferent and efferent arcs that are contained entirely within the enteric nervous system.

b. Vagovagal reflexes, such as receptive relaxation of the stomach in response to swallowing of food, involve afferent fibers from the gut that travel through the vagus nerve to the brainstem and then back to the gut through the vagus nerve.

c. Afferent fibers from the gut may travel to the spinal cord (or sympathetic ganglia) and then back to the gut.

d. Some of the afferent fibers that travel to the spinal cord synapse, directly or indirectly, on lower-order neurons of the anterolateral system and send pain signals to the brain.
  
  * These afferent fibers that sense pain typically travel to the spinal cord together with the nerves of the SNS.

B. **Gastrointestinal functions**

1. **Motility**

   • **Electrical basis for intestinal motility: slow waves**
     
a. Similar to cardiac nodal cells, intestinal smooth muscle cells (SMCs) have a constantly changing **resting membrane potential**.

b. Rather than constantly generating action potentials, intestinal smooth muscle cells are subject to undulating oscillations in resting membrane potential.

c. These **slow waves** have a resting membrane potential that varies between approximately −60 and −30 mV (Fig. 7-5).

d. In the absence of spike potentials, the slow waves are **unable to elicit smooth muscle contractions**, except in the stomach.
  
  * However, if the peak of the slow wave reaches the threshold potential, an **action (spike)** potential may be initiated, which then stimulates smooth muscle contraction.

e. This **rhythmic contraction** results in the intermittent propulsion of intestinal contents toward the anus.

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**Pharmacology note:** Metoclopramide is a D2 receptor antagonist and 5-HT3 antagonist that is a prokinetic agent useful in the treatment of nausea and vomiting, particularly in patients who have delayed gastric emptying (gastroparesis).

**Clinical note:** Patients with a long history of poorly controlled diabetes mellitus can sometimes develop severe gastric motility dysfunction, termed **gastroparesis**. In diabetes, gastroparesis can occur as a result of damage to the autonomic nerves supplying the stomach. These patients may suffer from intractable **nausea** and **vomiting** because of the failure of the stomach to empty after a meal. In such patients, promotility agents such as metoclopramide can provide substantial symptomatic relief. A more aggressive option is to surgically implant a gastric pacemaker, although this is rarely done.

---

• **Types of contractions**

  a. **Peristalsis**

  * Distension of the gut wall by a food bolus triggers reflexive contractions of smooth muscle (mainly the inner circular and outer longitudinal muscle layers) that **push the food bolus forward along the intestinal tract**.

  * This forward propulsion requires smooth muscle contraction just proximal to the food bolus and simultaneous relaxation just distal to the food bolus (Fig. 7-6A).

---

**7-5:** Slow waves of the enteric nervous system. The tension occurs slightly after the action (spike) potentials, and the magnitude of the tension depends on the frequency of the spike potentials.
The myenteric plexus is almost entirely responsible for coordination of peristalsis. In its absence, peristaltic contractions may be severely impaired or even absent.

Pathology note: In a condition called achalasia, esophageal peristalsis is severely compromised because of damage to the myenteric plexus (see later discussion).

- **Segmentation**
  - The primary function of segmentation is to assist digestion by promoting mixing of the intestinal contents (e.g., food, digestive enzymes, bile salts).
  - This is achieved by simultaneous contractions both proximal and distal to the food bolus (Fig. 7-6B).
  - In contrast to peristalsis, segmentation does not result in forward propulsion of the food bolus.

- **Tonic contractions**
  - The tonic contractions of sphincter muscles throughout the intestinal tract separates different segments of the tract and prevents premature passage of intestinal contents into the next segment.

2. **Digestion**
   - Digestion entails the enzymatic hydrolysis of macromolecules (fats, carbohydrates, and proteins) into smaller compounds.
   - These can then be absorbed across the intestinal epithelial barrier.

3. **Absorption**
   - Absorption involves the transport of luminal substances across the mucosal barrier.
   - Absorption is facilitated by the large surface area of the mucosal epithelium, particularly in the small intestine.

II. **Salivation and Mastication**
   A. **Salivation**
      1. **Composition and functions of saliva**
         - Salivation plays several important roles in facilitating digestion in addition to its vital role in maintaining oral health (Table 7-2).
Clinical note: Sjögren syndrome is an autoimmune disorder characterized by lymphocytic infiltration of exocrine glands, mainly affecting the salivary and lacrimal glands. It is relatively common in elderly people (3% to 5% of those >60 years of age) and is characterized by dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca). Low levels of saliva may cause dysphagia (difficulty swallowing) and increased dental caries; a deficiency in tear production may cause corneal ulceration and scarring. Pilocarpine, a muscarinic receptor agonist, is effective in increasing salivary production, and artificial tears can be used for treating dry eyes.

2. Mechanism of saliva production
- Secretions from the salivary acinus are very similar in tonicity to plasma (i.e., they are isotonic).
- However, as these secretions move along the salivary duct, they are constantly modified.
- The salivary ducts are relatively impermeable to water entry, and sodium is continually reabsorbed.
- Therefore, saliva is usually hypotonic relative to plasma by the time it is secreted (Fig. 7-7).

3. Types of salivary glands
- There are two types of salivary glands: serous and mixed.
- Serous glands (e.g., parotid), which are primarily composed of serous cells, secrete a nonviscous saliva containing water, electrolytes, and enzymes.
- Mixed glands (submandibular, sublingual), which are composed of serous and mucous cells (Fig. 7-8), secrete a viscous saliva rich in mucin glycoproteins.

4. Regulation of salivation
- Salivation is primarily controlled by the autonomic nervous system (ANS).
- Both branches of the ANS stimulate salivation, but the PNS does so much more strongly than the SNS.

Pharmacology note: The muscarinic acetylcholine receptor mediates the effects of the PNS on the salivary glands. Blockade of this receptor can substantially decrease salivary secretions. This effect is associated with several classes of drugs, most notably antimuscarinic drugs (e.g., atropine, ipratropium), but also with drugs that have anticholinergic side effects, especially the antipsychotics and tricyclic antidepressants.
B. Mastication
1. Mastication (chewing) is the first step in the breakdown of complex foodstuffs.
2. It serves several important functions.
3. Not only does it break large food pieces into smaller pieces, which increases the surface area available for digestion, but it also lubricates food with saliva, which facilitates swallowing.
4. The muscles of mastication are the masseter, temporalis, and medial and lateral pterygoids.
5. They are all innervated by the mandibular division of the trigeminal nerve (cranial nerve V). 

Clinical note: Of the many neurologic deficiencies that may be seen in patients with a cerebrovascular accident, difficulties with mastication and swallowing are particularly common. Often the deficiency is subtle (e.g., silent aspiration). For this reason, all patients admitted to the hospital with a cerebrovascular accident undergo formal speech and swallow evaluation, which often includes a modified barium swallow.

III. Esophagus
A. Functional anatomy
1. The upper and lower esophageal sphincters are located at the top and bottom of the esophagus, respectively.
2. Alternating contraction and relaxation of these sphincter muscles helps coordinate movement of the food bolus from the pharynx to the stomach.

B. Esophageal motility
1. Overview
   - Esophageal motility is under both voluntary and involuntary control.
   - This reflects the differential distribution of striated and smooth muscle fiber throughout the esophagus.
   - The upper third of the esophagus is composed of striated muscle fibers, whereas the lower third is composed mainly of smooth muscle fibers.
   - The middle third is composed of a mixture of striated and smooth muscle fibers.
2. **Opening of the upper esophageal sphincter**
   - Relaxation of the upper esophageal sphincter allows food to enter the esophagus from the pharynx.
   - The sphincter then closes immediately after the food bolus passes to prevent reflux into the pharynx.

3. **Peristalsis: coordinated muscular contraction**
   - Swallowing or distension of the esophagus by a food bolus triggers a series of local reflexes, which result in coordinated esophageal contractions that move the food bolus toward the stomach.
   - **Primary peristalsis** is triggered by swallowing, whereas **secondary peristalsis** is triggered by esophageal distension.

4. **Opening of the lower esophageal sphincter (LES)**
   - When not eating, the LES is normally tonically constricted, in part because of the additional sphincteric pressure provided by the diaphragm.
   - This helps prevent reflux of gastric contents into the esophagus.
   - When eating, the LES relaxes in response to swallowing (deglutition) and distension of the esophagus.
   - This relaxation is mediated both by vagal stimulation and by some intrinsic properties of the LES (Fig. 7-9).

**Pathology note:** In a **sliding hiatal hernia**, the esophagogastric junction herniates upward through the esophageal hiatus in the diaphragm. This removes the contribution to LES tone provided by the diaphragm and predisposes to reflux. In a **rolling (paraesophageal) hiatal hernia**, the esophagogastric junction remains fixed in place, and LES tone remains largely preserved. These patients therefore are less likely to suffer from reflux, although there is some concern for incarceration.

**Clinical note:** In **achalasia**, destruction of the myenteric plexus of the enteric nervous system causes dysregulation of esophageal smooth muscle activity. Pressure-recording studies (esophageal manometry) show decreased or absent peristaltic activity in the distal esophagus, impaired LES relaxation, and increased LES pressure. The result is that food cannot pass easily into the stomach. There may be difficulty swallowing (dysphagia), chest pain from esophageal distension, and frequent bouts of pneumonia from aspiration of esophageal contents. Achalasia is most commonly idiopathic, but it can also be seen in **Chagas disease**, which is caused by infection with the protozoan parasite, *Trypanosoma cruzi* (found in South America). In Chagas disease, the myenteric plexus of the colon may also be destroyed, causing **toxic megacolon**.

**IV. Stomach (Fig. 7-10)**

**A. Overview**
1. The stomach functions mainly as a “holding area” for food waiting to be digested in the small intestine.
2. It also prepares food for digestion in the small intestine by converting the food into chyme and then regulating the release of this chyme into the duodenum.
B. Gastric response to a meal: phases of digestion (Fig. 7-11)

1. Multiple cues can trigger the stomach to prepare for the process of digestion.
2. In the cephalic phase, the sight or even the mere thought of food can stimulate gastric secretions.
3. In the gastric phase, after eating has begun, the presence of food in the stomach and the distension it causes can also stimulate gastric secretions.
4. In the enteric or intestinal phase, the entry of gastric contents into the small intestine stimulates the release of multiple factors, which then inhibit gastric activity.

C. Receptive relaxation of the stomach

1. As the food bolus travels through the lower esophagus, the stomach reflexively begins to relax.
2. This anticipatory relaxation is referred to as receptive relaxation.
3. This phenomenon allows the stomach to accept large amounts of food with only a minimal increase in gastric pressure; it also minimizes esophageal reflux.
4. The stomach also relaxes in response to distension of the stomach itself, which also allows the stomach to accept and to store larger quantities of food; this process is termed gastric accommodation.

D. Gastric cell types and their secretions

1. Parietal cells (Table 7-3)
   - Parietal cells secrete hydrogen ions, which creates a low gastric pH.
   - This low pH serves many functions:
     a. It denatures proteins.
     b. It activates protein-digesting enzymes such as pepsinogen.
     c. It creates a harsh environment for bacterial growth.
   - Parietal cell activity is promoted by vagal stimulation (through acetylcholine) and by the hormones histamine and gastrin.
   - Parietal cells also secrete intrinsic factor, which binds vitamin B₁₂ in protein-rich foods such as meats to prevent its degradation in the small intestine and to allow absorption in the terminal ileum.
Clinical note: In pernicious anemia, autoimmune destruction of parietal cells results in the deficient secretion of intrinsic factor by parietal cells, causing impaired absorption of vitamin B₁₂ (cobalamin). This produces a macrocytic anemia (more specifically, a megaloblastic anemia), because vitamin B₁₂ is required for DNA synthesis in erythrocyte progenitor cells within the bone marrow. There is also a loss of hydrochloric acid producing a hypochloremic metabolic alkalosis. Of note, severe prolonged cobalamin deficiency can also cause neurological symptoms (e.g., peripheral neuropathy, abnormal gait) and rarely can cause subacute combined degeneration of the spinal cord (see Chapter 2 for further discussion).

- Figure 7-12 shows how certain drugs regulate parietal cell activity.
- Figure 7-13 shows the mechanism by which hydrogen ions are generated and secreted from parietal cells into the gastric lumen.
7-12: Pharmacologic regulation of parietal cell activity. Parietal cell activity can be inhibited with antihistamines (H₂-blockers such as ranitidine) and anticholinergics (e.g., atropine). Proton pump inhibitors (PPIs; such as omeprazole) inhibit the final common pathway of acid secretion in parietal cells (H⁺,K⁺-ATPase pump on the apical surface) and are the most potent agents for reducing gastric acid secretion. ACh, Acetylcholine; cAMP, cyclic adenosine monophosphate; CCK, cholecystokinin; ECL, enterochromaffin-like; H⁺,K⁺-ATPase, hydrogen-potassium-adenosine triphosphatase pump. (From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 8-18.)

7-13: Mechanism of secretion by parietal cells. Plasma CO₂ is generated within the parietal cells or diffuses into parietal cells, where it reacts with water to form HCO₃⁻ and H⁺ ions. H⁺ ions are then secreted into the gastric lumen in exchange for K⁺ ions, and HCO₃⁻ diffuses from parietal cells into the plasma in exchange for chloride. This results in a brief "alkaline tide" after a meal. The reason that large meals do not precipitate a metabolic alkalosis is because these secretions are counteracted by the secretion of HCO₃⁻ into the gut lumen by organs such as the pancreas. ADP, Adenosine diphosphate; ATP, adenosine triphosphate; CA, carbonic anhydrase.
2. G cells
- G cells secrete the hormone gastrin, which promotes parietal cell activity.
- Gastrin release is stimulated mainly by the presence of protein in the stomach, and its secretion is feedback-inhibited by H\(^+\) ions (i.e., reduced pH indirectly inhibits parietal cell activity).

Clinical note: In atrophic gastritis, many of the glands containing acid-secreting parietal cells are destroyed, thereby limiting the extent of gastric acidification. This lack of acid production (achlorhydria) causes a loss of feedback inhibition of gastrin secretion. Use of proton pump inhibitors such as omeprazole will also cause a loss of gastrin feedback inhibition. Both situations can therefore result in hypergastrinemia, a metabolic anomaly that is largely benign. However, for boards, realize that a patient with peptic ulcer disease who is taking a proton pump inhibitor and has hypergastrinemia on testing almost certainly does not have Zollinger-Ellison syndrome.

3. Chief cells
- Protein digestion (hydrolysis of proteins to peptides and amino acids) begins in the stomach because of the activity of chief cells (see Table 7-3).
- These cells secrete the inactive precursor protein, pepsinogen, which is activated to the proteolytic enzyme, pepsin, in the presence of acid and/or small amounts of active pepsin.
- Pepsin functions optimally at a pH of approximately 2.

4. Mucous cells (see Table 7-3)
- If it were not for the protective activity of mucous cells, which secrete mucus and HCO\(_3\)^–, the low gastric pH would continually damage the gastric mucosa and predispose to ulcers.
- The mucous layer protects the gastric mucosa by preventing back diffusion of H\(^+\) ions into the gastric mucosa (Fig. 7-14).
- Beneath this mucous layer, a layer rich in HCO\(_3\)^– neutralizes H\(^+\) as it passes through the mucous barrier.
- In addition, the alkaline HCO\(_3\)^– layer prevents activation of any pepsinogen that “escapes” through the mucous layer.

Clinical note: Mucosal blood flow is highly dependent on the local production of prostaglandins. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, can impair mucosal blood flow by inhibiting prostaglandin synthesis. This compromises the protective abilities of the mucosa (mucus and HCO\(_3\)^– secretion) and can cause irritation of the mucosa (gastritis) or even ulceration (peptic ulcer disease). In fact, it is not uncommon for elderly people to be admitted to the hospital with active upper intestinal bleeding, with concomitant anemia, owing to the recent use of NSAIDs.
E. Gastric motility: regulation of gastric emptying

1. Overview
- When the pyloric sphincter relaxes, chyme enters the duodenum.
- Depending on the composition of the meal (e.g., fats take much longer), approximately half of the stomach contents will empty into the small bowel within 1 hour.
- Gastric motility and pyloric sphincter tone are primarily regulated by hormones produced in the small intestine.
- The production of these hormones is in turn somewhat dependent on the volume and composition of chyme entering the small intestine (e.g., high-fat versus low-fat content) (Table 7-4).

Clinical note: Gastric emptying may be impaired by medications such as opiates and anticholinergics as well as in conditions such as gastroparesis, often seen with long-standing diabetes. Symptoms of impaired gastric emptying include postprandial nausea, bloating, and vomiting. In a gastric emptying study, a patient eats a radiolabeled meal, and a scanner is placed over the patient’s stomach to measure the rate at which the radiolabeled food empties from the stomach. If impaired gastric emptying is confirmed, prokinetic agents such as metoclopramide and erythromycin can be given.

Clinical note: A normally functioning pyloric sphincter is tonically contracted and relaxes only periodically to allow small volumes of chyme to enter the duodenum. If the pyloric sphincter is incompetent, as is often caused by gastric surgery, large volumes of hypertonic chyme may enter the duodenum, resulting in massive loss of water from the circulation and the extracellular fluid. The ensuing hypovolemia may result in dizziness, tachycardia, sweating, flushing, and vasomotor collapse; this is called dumping syndrome. Symptoms occur shortly after eating. Treatment consists primarily of eating very small meals to limit the hyperosmolar load to the duodenum.

2. Secretin
- The entry of acidic chyme into the small intestine stimulates the release of the hormone secretin from specialized S cells in the duodenum (Fig. 7-15).

| TABLE 7.4. Hormones Produced in the Duodenum |
|-------------------------------|------------------|------------------|------------------|
| HORMONE                       | STRUCTURE OF ORIGIN | PRIMARY STIMULI               | ACTIONS                                      |
| Secretin                      | S cells            | Acidic chyme entering duodenum | Gastric emptying, ↑ HCO₃⁻ secretion from ductal cells of pancreas to buffer acidic chyme |
| Cholecystokinin               | I cells            | Fatty acids                   | ↑ Enzyme-rich secretion by pancreatic acinar cells, ↑ Gallbladder contraction, ↑ Tone of sphincter of Oddi, ↓ Gastric emptying |
| Gastric inhibitory peptide   | Mucosa             | Carbohydrates, proteins, and fatty acids entering duodenum | ↓ Gastric activity |
| Somatostatin                  | Mucosa (also δ cells of pancreas) | ↓ pH of duodenum, ↑ Levels of various gastrointestinal hormones | Various inhibitory actions |

Clinical note: Gastric emptying is delayed by a high-fat meal.
Secretin then stimulates the release of a $\text{HCO}_3^-$-rich secretion from the ductal cells of the pancreas to neutralize the acidic chyme and to allow pancreatic digestive enzymes to function close to their pH optima.

Secretin also stimulates the secretion of $\text{HCO}_3^-$ by the duodenum and inhibits further gastric emptying.

3. Cholecystokinin (CCK)
   - The entry of chyme that is abundant in fatty acids into the small intestine stimulates the release of CCK.
   - CCK then powerfully inhibits relaxation of the pyloric sphincter to prevent further gastric emptying; it also promotes gallbladder contraction to facilitate delivery of bile to the small intestine.
   - This occurs because fats require more time to digest than proteins or carbohydrates.

4. Other hormones
   - The hormone **gastric inhibitory peptide** is released in response to a variety of substances, particularly carbohydrates. It interferes with numerous aspects of gastric activity.
   - Likewise, the hormone **somatostatin**, which is released from the duodenal mucosa and pancreatic $\delta$ cells, globally inhibits gastric activity (Fig. 7-16).

V. Pancreas
   A. Functional anatomy (Fig. 7-17)
      1. The pancreas is a retroperitoneal organ located behind the stomach.
      2. Although the pancreas serves critical endocrine functions (e.g., regulation of plasma glucose), most of this organ is devoted to exocrine functions that are critical for the efficient digestion of macromolecules.
Anatomy note: During embryologic development of the pancreas, the ventral and dorsal pancreatic buds may become abnormally fused as they rotate around the second part of the duodenum. If this occurs, it can cause duodenal obstruction and is termed annular pancreas. Newborns with annular pancreas may present with projectile vomiting in the first few days of life. It is also a rare cause of chronic pancreatitis in adults.

B. Pancreatic secretions
1. The exocrine secretions of the pancreas that ultimately drain into the small bowel are derived from two distinct cells, ductal cells and acinar cells.
2. Acinar secretions are enzyme-rich secretions that provide the enzymes necessary for digestion.
3. Ductal secretions are HCO\textsubscript{3}\textsuperscript{-}-rich and neutralize acidic chyme to allow for proper function of pancreatic enzymes (Fig. 7-18).

C. Pathophysiology
1. With loss of pancreatic exocrine function, as may occur in pancreatitis or pancreatic insufficiency, fewer digestive enzymes are secreted, which impairs nutrient digestion and absorption.
2. The most common causes of pancreatitis are alcohol abuse and gallstones.
3. Other well established but less common causes include significant hereditary pancreatitis, marked hypercalcemia and hypertriglyceridemia, abdominal trauma, and various drugs such as azathioprine.

Pathology note: In the genetic disease cystic fibrosis, thick secretions into the pancreatic duct may obstruct the duct and cause pancreatic insufficiency. Usually fat digestion is affected to the greatest extent, resulting in a fatty diarrhea (steatorrhea) in which the feces may float, have an oily appearance, and be particularly foul-smelling. These patients are often treated with supplementary pancreatic enzymes.

VI. Liver and Biliary Tree
A. Functional anatomy
• The functional anatomy of the liver and biliary tree is shown in Figure 7-19.
B. Gallbladder
1. The gallbladder stores and releases bile that is initially produced in the liver.
2. The bile within the gallbladder serves several functions:
   • Digestion and absorption of dietary fats through formation of lipid micelles, which enable fatty acid absorption across the intestinal mucosa (Table 7-5)
   • Removal of waste products such as bilirubin and excess cholesterol
   • Solubilization of cholesterol to prevent precipitation and stone formation
When fatty acids enter the duodenum, they stimulate the release of CCK, which stimulates the gallbladder to contract and excrete bile into the small intestine and to inhibit gastric emptying. In biliary dyskinesia (acalculous cholecystitis), the gallbladder does not contract effectively in response to CCK, which can be shown by performing a hepatobiliary iminodiacetic acid (HIDA) scan. Often, the symptoms of biliary dyskinesia and biliary obstruction by gallstones (e.g., right upper quadrant abdominal pain) are similar.

C. Enterohepatic circulation

1. The term enterohepatic circulation describes the cycling of substances between the liver and intestinal tract; it does not refer to a distinct anatomic circulation (Fig. 7-20).
2. For example, bile salts are synthesized by the liver and secreted into the duodenum.
3. Most bile acids (>90%) are then reabsorbed in the terminal ileum and returned to the liver.
4. The small percentage of bile acids that are not reabsorbed in the distal ileum are eliminated in the feces.
5. This is the primary mechanism of excretion of excess cholesterol.

Clinical note: When fatty acids enter the duodenum, they stimulate the release of CCK, which stimulates the gallbladder to contract and excrete bile into the small intestine and to inhibit gastric emptying. In biliary dyskinesia (acalculous cholecystitis), the gallbladder does not contract effectively in response to CCK, which can be shown by performing a hepatobiliary iminodiacetic acid (HIDA) scan. Often, the symptoms of biliary dyskinesia and biliary obstruction by gallstones (e.g., right upper quadrant abdominal pain) are similar.

Clinical note: Bile-sequestering agents, such as cholestyramine, act by preventing reabsorption of bile in the distal ileum, thereby depleting hepatic stores of bile acids. Because bile acids are synthesized from cholesterol, compensatory hepatic synthesis of new bile acids necessitates increased uptake of plasma low-density lipoprotein (LDL) cholesterol by the liver, resulting in decreased plasma LDL. Unfortunately, inhibiting the actions of bile in the small intestines also leads to a reduced ability to digest fats, potentially resulting in steatorrhea and a deficiency of fat-soluble vitamins.

VII. Small Intestine

A. Functional anatomy

1. The small intestine extends from the pylorus to the ileocecal valve and is composed of the duodenum, jejunum, and ileum.
2. Most absorption occurs in the duodenum and proximal jejunum, although important fat-soluble vitamins, bile acids, and vitamin B₁₂ are absorbed in the distal ileum.
B. Digestion and absorption

1. Carbohydrates (Table 7-6)
   - Complex carbohydrates are long-chain polymers of simple sugars such as glucose.
   - Complete degradation to the monosaccharides glucose, galactose, and fructose is necessary for absorption across the intestinal mucosa (Fig. 7-21).
   - Although this degradation begins in the mouth in the presence of salivary amylase, most carbohydrate digestion occurs in the small intestine through pancreatic amylase.
   - Pancreatic amylase mainly breaks down carbohydrates to disaccharides, which are then further hydrolyzed to monosaccharides by intestinal brush border enzymes (disaccharidases) such as sucrase, lactase, and maltase.

Clinical note: In disaccharidase-deficient states, such as lactase deficiency, the osmotically active disaccharide lactose is delivered to the colon, where it is fermented by colonic bacteria to produce gases such as hydrogen and carbon dioxide and lactic acid. Symptoms include flatulence, bloating, cramping, diarrhea, and an acidic stool.

TABLE 7-6. Digestion and Absorption of the Major Fuels

<table>
<thead>
<tr>
<th>FUEL</th>
<th>ENZYMES USED IN DIGESTION</th>
<th>STRUCTURAL FORM ABSORBED</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteins</td>
<td>Pepsin in stomach Protease in pancreas</td>
<td>Amino acids and small peptides</td>
<td>Small peptides broken down into amino acids in enterocytes</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Amylase in saliva Amylase in pancreas Disaccharidases in intestinal mucosa</td>
<td>Monosaccharides</td>
<td></td>
</tr>
<tr>
<td>Fats</td>
<td>Lipase in saliva and stomach Lipase/collipase in pancreas</td>
<td>Free fatty acids</td>
<td>Bile acids/salts emulsify for digestion and form micelles to facilitate absorption Resynthesized to triglycerides and packed into chylomicrons by enterocytes</td>
</tr>
</tbody>
</table>
2. **Proteins** (see Table 7-6)
   - Protein digestion begins in the stomach because of the acidic pH and the presence of the enzyme pepsin, but most protein digestion occurs in the small intestine.
   - By neutralizing the acidic chyme, the HCO₃⁻-rich ductal secretions allow the pancreatic proteases to function optimally in degrading proteins and large peptides into small peptides and amino acids.
   - Products of protein digestion are absorbed as small peptides (major) and free amino acids (minor) through **cotransport with Na⁺** into enterocytes.
   - In the cytoplasm of enterocytes, the peptides are degraded to amino acids, which then enter the portal blood destined for the liver.
   - Note that the gastric contribution to protein digestion is so minor that even patients with achlorhydria (such as in patients with pernicious anemia or in those taking protein pump inhibitors such as omeprazole) have no observable impairment of protein assimilation.

3. **Lipids** (Fig. 7-22; see Table 7-6)
   - Overview
     a. In most people, with the possible exception of vegetarians, intake of fats (lipids) is in the form of **triglycerides**.
     b. Most triglyceride digestion occurs in the small intestine, although a small amount (no more than 10%) occurs in the mouth because of **lingual lipase** and in the stomach because of **gastric lipase**.
   - **Digestion**
     a. In the presence of bile and the phospholipid lecithin, mechanical mixing in the stomach and small intestine converts large lipid droplets to much smaller lipid globules by the process of **emulsification**.
     b. This process markedly increases the surface area for water-soluble digestive enzymes such as **pancreatic lipase**.
     c. Pancreatic lipase (and colipase) then hydrolyzes triglycerides into free fatty acids and monoglycerides.
     d. **Micelles** formed by bile salts then efficiently absorb these free fatty acids.

---

**Pharmacology note:** Carbohydrate digestion can be intentionally impaired in patients with diabetes mellitus by **α-glucosidase inhibitors** such as **acarbose**. These drugs competitively inhibit intestinal enzymes such as sucrase, maltase, and amylase, thus impairing carbohydrate digestion and therefore intestinal glucose absorption. Reduced intestinal absorption of glucose facilitates glucose control in diabetes. However, because carbohydrates remain in the gut, these drugs typically cause adverse effects such as **flatulence**, **nausea**, and **diarrhea**.
e. This is a critical step in fat digestion, because the free fatty acids and monoglycerides would otherwise rapidly recombine to form triglycerides, which are unable to diffuse across the intestinal mucosa.

- **Absorption**
  a. Once lipids in the form of fatty acids and monoglycerides are absorbed across the intestinal mucosa, they are re-esterified to produce triglycerides.
  b. The triglycerides are then packaged as **chylomicrons** and transported through the intestinal **lymphatics** to the **thoracic duct** and then to the **left subclavian vein**, not the portal vein.

**Pathology note:** In **celiac sprue** (celiac disease), massive loss of intestinal surface area occurs because of a hypersensitivity reaction to the gliadin component of the protein gluten, found in grains such as wheat. This hypersensitivity reaction results in autoimmune destruction of intestinal villi, which causes malabsorption of numerous nutrients and predisposition to a variety of nutrient deficiency diseases. Patients with celiac sprue may respond dramatically to elimination of gluten from the diet.

4. **Absorption of other substances**
- **Sodium**
  a. The intestinal lumen–intracellular sodium gradient can be used to drive absorption of numerous substances, including glucose, amino acids, dipeptides, and water-soluble vitamins (Fig. 7-23).
- **Vitamin B₁₂ (cobalamin)**
  a. Vitamin B₁₂ complexes with R protein in the mouth and with intrinsic factor in the duodenum after the R protein is cleaved off by pancreatic enzymes (Fig. 7-24).
    - Pancreatic dysfunction (e.g., chronic pancreatitis) leads to malabsorption of vitamin B₁₂ because R protein blocks the complexing of the vitamin with intrinsic factor.
  b. It is then absorbed in the distal ileum of the small intestine.
  c. Patients with disease of the distal ileum (e.g., **Crohn disease**) are likely to have impaired intestinal absorption of vitamin B₁₂.

**Clinical note:** Disease involvement of the distal ileum can also impair reabsorption of bile salts, resulting in fat malabsorption (**steatorrhea**) as well as impaired absorption of the **fat-soluble vitamins** (vitamins A, D, E, and K).
Iron (Fe)
a. Dietary iron is released in relatively large amounts after the digestion of proteins such as myoglobin and hemoglobin, which are abundant in meats.
b. Fe is absorbed primarily in the duodenum and proximal jejunum.
c. It is converted to the ferrous (Fe$^{2+}$) form for absorption.
d. Within the cell, it is bound by one or more iron-binding proteins and delivered to the basolateral membrane, where it complexes with transferrin (Fig. 7-25).
e. After absorption, it is transported in plasma bound to transferrin and stored within cells as ferritin.

Clinical note: Iron is essential for the production of red blood cells within the bone marrow (erythropoiesis). A deficiency of iron may therefore result in impaired erythropoiesis and a microcytic anemia. The term microcytic refers to the small size of the red blood cells, which results from a lack of hemoglobin within the cytoplasm. Patients susceptible to iron deficiency anemia include premenopausal women with heavy menstrual bleeding, vegetarians with limited dietary intake of meat, and patients with chronic blood loss (e.g., intestinal bleeding from an ulcer or colon cancer).

C. Motility: migrating myoelectric complex
1. During the interdigestive period, a pattern of motor activity functions to clear food debris from the intestinal tract, including the stomach, small intestine, and large intestine.
2. Bursts of peristalsis occur at 90-minute intervals during fasting.
3. The hormone motilin, secreted by duodenal mucosa, is thought to play an important role in this process.
4. The migrating myoelectric complex is characterized by three phases:
   - Phase I: long period in which peristalsis is absent
   - Phase II: sporadic contractions
   - Phase III: short period of intense peristalsis to clear the lumen of debris

Pharmacology note: The antibiotic erythromycin, often referred to as “erythroterrible” because of its common side effects (e.g., nausea, diarrhea) is sometimes used specifically because of these side effects; for example, as a laxative in constipated adults. It is believed to produce these effects by stimulating the motilin receptor. Erythromycin is also implicated as a cause of hypertrophic pyloric stenosis. Infants who are given the drug orally have about a 10-fold increased risk for developing hypertrophic pyloric stenosis.

D. Reflexes
1. Gastric and/or duodenal distension after a meal stimulates various reflexes.
2. These reflexes are controlled entirely by the enteric nervous system, as shown by their continuation after autonomic denervation.

3. Perhaps the best known is the **gastrocolic reflex**, which results from distension of the stomach, stimulating bowel movements after meals.

4. The **gastroileal** (gastroenteric) reflex promotes passage of intestinal contents from the small intestine into the colon by stimulating intestinal peristalsis and relaxation (opening) of the ileocecal valve.

5. The **enterogastric reflex**, which is triggered by the entry of acidic chyme into the duodenum, inhibits further gastric emptying.

VIII. **Large Intestine**

A. **Functional anatomy** (Fig. 7-26)

1. The large intestine has much less mucosal surface area available for absorption than does the small intestine, reflecting the absence of villi and fewer microvilli on epithelial cells (Table 7-7).

2. The main functions of the colon are **absorption of salt and water** and **storage and elimination of feces**.

3. Initially, the fecal contents in the right colon are fairly liquid; they gradually become more solid as they move through the large intestine.

B. **Electrolyte movements**

1. **Sodium**
   - Absorption of sodium by the large intestine is very efficient.
   - **Aldosterone** and high doses of **glucocorticoids** increase sodium absorption and potassium secretion.

2. **Bicarbonate and potassium**
   - The colon actively secretes bicarbonate.
   - Therefore, a patient with **acute** diarrhea may lose large amounts of **bicarbonate** and have a **metabolic acidosis**.
   - The colon also secretes potassium, so large volumes of diarrhea can also precipitate **hypokalemia**.

C. **Defecation reflex**

1. When the rectum becomes distended with feces, it initiates a spinal reflex that causes relaxation of the internal and external anal sphincters.

2. Fortunately, we can consciously override the relaxation of the external anal sphincter when we wish to.

![Image](7-26: Anatomy of the large intestine.)

**TABLE 7-7. Structural Comparison of Small and Large Intestines**

<table>
<thead>
<tr>
<th></th>
<th>SMALL INTESTINE</th>
<th>LARGE INTESTINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plicae circularis</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Villi</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Microvilli</td>
<td>+</td>
<td>Fewer in number</td>
</tr>
<tr>
<td>Glycocalyx</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Peyer patches</td>
<td>+ (ileum)</td>
<td>–</td>
</tr>
<tr>
<td>Brunner glands</td>
<td>+ (Duodenum)</td>
<td>–</td>
</tr>
<tr>
<td>Outer longitudinal muscle</td>
<td>Continuous sheet</td>
<td>Arranged as taeniae coli</td>
</tr>
</tbody>
</table>
Chapter 8

Acid-Base Balance

I. Acid and Base

A. Overview

1. The pH (i.e., \(-\log [H^+]\)) of the body is maintained within a very narrow range to allow for proper protein functioning.

2. Normal plasma \([H^+]\) is therefore very low at approximately 40 nmol; Table 8-1 provides a comparison to that of other plasma ions.

3. Such tight control is due to the presence of buffers in all of the body compartments, removal of volatile acids by the lungs, and excretion of nonvolatile acids by the kidneys.

4. Daily metabolism of fats and carbohydrates to \(CO_2\) produces a substantial volatile acid load in the form of \(CO_2\) (approximately 15,000 mmol), which forms \(H^+\) ions through the following reaction: \(H_2O + CO_2 \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-\).

   • However, because \(CO_2\) is rapidly removed through alveolar respiration, the above reaction is driven to the left, so \(H^+\) ions do not accumulate.

5. Daily metabolism of proteins produces a much smaller acid load (approximately 50 to 100 mEq) in the form of nonvolatile acids such as sulfate and phosphate.

   • These nonvolatile acids are excreted in the urine in the form of ammonium (\(NH_4^+\)) and titratable acids.

6. The primary buffer of the extracellular fluid (ECF) compartment is bicarbonate, which buffers the daily load of acid generated by metabolism.

7. The lungs contribute to acid-base balance by excreting \(CO_2\), although in acid-base disorders (e.g., metabolic alkalosis), they can “compensate” by retaining \(CO_2\).

8. The kidneys contribute to acid-base balance by removing nonvolatile acids such as sulfate and phosphate; they also reclaim most of the filtered bicarbonate and create de novo bicarbonate through deamination of the amino acid glutamine.

9. Diagnosis of an acid-base disorder can often be made by the presence of electrolyte abnormalities alone with a suggestive history (e.g., high \([HCO_3^-]\), low \([Cl^-]\) after vomiting suggests a metabolic alkalosis).

   • However, an arterial blood gas (ABG) analysis is required for definitive diagnosis as the same high \([HCO_3^-]\) above could represent metabolic compensation for a respiratory acidosis.

10. A low plasma pH is referred to as an acidemia, whereas a process resulting in the production of excess acids is termed an acidosis, irrespective of the pH.

11. A high plasma pH is referred to as an alkalemia, whereas a process resulting in the production of excess base is termed an alkalosis.

   • Of note, patients with a coexisting acidosis and alkalosis, a so-called mixed disorder, may have a perfectly normal pH.

### Table 8-1. Normal Concentrations of Cations and Anions in Plasma

<table>
<thead>
<tr>
<th>CATIONS (mEq/L)</th>
<th>ANIONS (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na(^+) 140</td>
<td>Cl(^-) 103</td>
</tr>
<tr>
<td>K(^+) 4</td>
<td>HCO_3(^-) 25</td>
</tr>
<tr>
<td>Ca(^{2+}) 5 (2.5 mmol/L)</td>
<td>Proteins 16</td>
</tr>
<tr>
<td>Mg(^{2+}) 2 (1 mmol/L)</td>
<td>Organic 4</td>
</tr>
<tr>
<td>H(^+) 0.000040 (40 nmol/L)</td>
<td>Other inorganics 3</td>
</tr>
</tbody>
</table>

B. Acids, bases, and buffers

1. Acids are compounds that can donate a hydrogen ion, whereas bases are compounds that can accept a hydrogen ion.
   - For example, carbonic acid ($\text{H}_2\text{CO}_3$) is an acid, whereas after it donates a hydrogen ion, it becomes bicarbonate ($\text{HCO}_3^-$), its (conjugate) base.

2. Assuming the reaction $\text{HA} \rightarrow \text{H}^+ + \text{A}^-$, the higher the concentration of a conjugate base ($\text{A}^-$) relative to its acidic form (HA), the higher will be the $\text{pH}$.

3. This relationship is demonstrated by the Henderson-Hasselbalch equation, shown below.
   \[
   \text{pH} = \text{pK}_a + \log \frac{\text{A}^-}{[\text{HA}]}
   \]
   which can be rewritten as:
   \[
   \text{pH} = \text{pK}_a + \log \frac{\text{A}^-}{[\text{HA}]}
   \]

4. Note that the $\text{pK}_a$ equals the pH at which the acid is half dissociated; in other words, the pH at which $[\text{A}^-] = [\text{HA}]$.
   - Buffering systems typically work best at a pH near their $\text{pK}_a$.

5. In the plasma, the most important buffer is the bicarbonate/carbon dioxide system.

6. In this system, carbonic acid ($\text{H}_2\text{CO}_3$), a weak acid, rapidly dissociates into either CO$_2$ or HCO$_3^-$, as shown here:
   \[
   \text{H}_2\text{O} + \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-
   \]

7. The bicarbonate buffer system is an effective buffering system despite the fact that the $\text{pK}_a$ for the above reaction is 6.1, far from the normal plasma pH of 7.4, because the end-products of the reaction (CO$_2$ and HCO$_3^-$) are able to be rapidly excreted by the lungs and kidneys, respectively.

C. Role of the kidneys in acid-base balance

1. Overview
   - The kidneys filter approximately 4500 mEq of bicarbonate daily (24 mEq/L × 180 L/day); most of this is reclaimed.
   - The kidneys also synthesize de novo bicarbonate to offset nonvolatile acid production; this occurs through the process of ammoniagenesis (see Fig. 8-3).

2. Bicarbonate reclamation
   - More than 99.9% of filtered plasma bicarbonate is reabsorbed in the kidney: approximately 80% in the proximal tubule, 10% in the thick ascending limb, and 10% in the distal nephron.
   - A single mechanism operates at all sites in the nephron (Fig. 8-1).
   - Hydrogen ions are secreted into the tubular lumen, where they react with filtered bicarbonate to form carbonic acid, which dissociates into CO$_2$ and water in a reaction catalyzed by carbonic anhydrase.

---

**8-1: Bicarbonate reclamation. CA, Carbonic anhydrase.**
**Pharmacology note:** Because sodium reabsorption in the proximal tubule is indirectly coupled to bicarbonate reabsorption, carbonic anhydrase inhibitors such as acetazolamide exert a diuretic effect by blunting sodium reabsorption. However, this diuretic action is weak because of the capacity of more distal sites, particularly the Na\(^+\)-K\(^+\)-2Cl\(^-\) cotransporter in the loop of Henle, to increase sodium reabsorption. They also interfere with reclamation of bicarbonate in the proximal tubule, the site at which 80% of filtered bicarbonate is reclaimed (the distal sites do not have a capacity to greatly increase their bicarbonate absorption). The loss of bicarbonate can cause acidosis (normal anion gap type) when carbonic anhydrase inhibitors are used as diuretics. In fact, clinically, carbonic anhydrase inhibitors are used much more often for their ability to increase bicarbonate excretion and thus treat a metabolic alkalosis (e.g., contraction alkalosis in an overly diuresed patient) than they are used as a diuretic.

### 3. De novo bicarbonate synthesis
- The removal of a hydrogen ion is the biochemical equivalent of bicarbonate generation, so the kidney needs to excrete hydrogen ions to generate bicarbonate and to prevent acidosis.
- If H\(^+\) were excreted as free ions in the urine, this would lower urine pH to physiologically intolerable levels; in fact, negligible amounts of free H\(^+\) ions are excreted because the kidney uses urinary buffers to facilitate H\(^+\) excretion.
- The buffers used are filtered weak acids that make up what is called titratable acidity and ammonium; using bicarbonate as a buffer would accomplish nothing, because the effect of losing H\(^+\) would be offset by the simultaneous loss of HCO\(_3^-\).
  - **Titratable acidity**
    - Filtered phosphate (HPO\(_4^{2-}\)) is the major contributor to titratable acidity (Fig. 8-2); less abundant acids with less favorable pKa values (e.g., creatinine and uric acid) also contribute.
    - The amount of titratable acidity present in the urine can be determined by determining the amount of OH\(^-\) required to titrate the urine pH back to 7.4; hence, the name *titratable acidity*.
    - Normally, about 10 to 40 mEq of H\(^+\) that has been secreted into the tubular lumen is buffered in this manner each day.
b. **Ammonium production**

- The deamination of the amino acid glutamine in the proximal tubule cells yields two ammonium (NH$_4^+$) molecules and two bicarbonate molecules (Fig. 8-3).
- The bicarbonate molecules are transported across the basolateral membrane and diffuse into the peritubular capillaries.
- The NH$_4^+$ is transported across the luminal membrane by substitution of NH$_4^+$ on the Na$^+$-H$^+$ countertransporter.
- In the collecting tubule, lipid-soluble ammonia (NH$_3$) diffuses across the luminal membrane, where it combines with secreted H$^+$ ions to form the polar, nondiffusible NH$_4^+$, which is then trapped in the tubular lumen.

**Note:** The model of nondiffusible NH$_4^+$ being trapped in the tubular lumen is an oversimplification of renal NH$_4^+$ handling. In fact, NH$_4^+$ is produced, partially reabsorbed, and then dissociated to NH$_3$, which is recycled in the renal medulla, where its high concentration prompts diffusion back into the tubular lumen; there, it combines again with secreted H$^+$ to form NH$_4^+$. The net result is that NH$_4^+$ ends up back in the tubular lumen.

**Clinical note:** In renal failure, in which the GFR is substantially reduced, less H$^+$ ions may be secreted into the tubular fluid because of a reduced number of functioning nephrons. The result is an accumulation of acid in the plasma, leading to the metabolic **acidosis** that is characteristic of advanced renal failure.

c. **Regulation of de novo bicarbonate synthesis**

- Under normal physiologic circumstances, all of the filtered bicarbonate is reabsorbed, and the additional amount of bicarbonate required to offset the 40 to 80 mEq of H$^+$ produced daily is generated in the kidney by excretion of titratable acids and ammonium.
- Renal acid excretion, and hence bicarbonate synthesis, varies to adapt to different physiologic circumstances:
- The amount of H$^+$ excreted varies inversely with extracellular pH; as systemic pH falls, the activities of the kidney’s Na$^+$-H$^+$ countertransporter, H$^+$-ATPase cotransporter, and Na$^+$-HCO$_3^-$ cotransporter increase.
- The capacity of titratable acidity to increase is fairly limited, so the required increase in renal buffering capacity is derived from increased production of NH$_4^+$.
- Systemic alkalosis results in a reversal of these H$^+$-secreting processes and a decrease in bicarbonate reabsorption.
- These processes are so efficient that enormous amounts of bicarbonate can be ingested without generating a significant increase in bicarbonate concentration.
D. Metabolic acidosis

1. Overview

- Caused by excess acid production or impaired renal acid excretion
- Characterized by low pH, low $\text{HCO}_3^-$ (<22 mEq/L) and low $\text{PCO}_2$ (from respiratory compensation)

  a. Note that a low $\text{HCO}_3^-$ can also be seen in compensation for a respiratory alkalosis, although in this case the pH would be high rather than low.

- Metabolic acidoses can be divided into anion gap and normal anion gap acidoses.

- Causes of anion gap metabolic acidoses are numerous and can be recalled by the mnemonic MUDPILES:

  Causes of anion gap metabolic acidosis: MUDPILES
  Methanol ingestion
  Uremia
  Diabetic, starvation, alcohol ketoacidosis
  Paraldehyde ingestion
  Isoniazid ingestion
  Lactic acidosis
  Ethylene glycol ingestion
  Salicylate toxicity

  a. Anion gap acidoses are typically emergent conditions that require aggressive therapy.

- Normal gap acidoses include renal and extrarenal causes.

  a. Renal causes include early acute renal failure, distal renal tubular acidosis (type 1), proximal renal tubular acidosis (type 2), and hyporeninemic hypoaldosteronemic renal tubular acidosis (type 4).

  b. Extrarenal causes include diarrhea, “dilutional” acidosis (typically from normal saline infusion), and ureteral-colonic fistulas.

- Anion gap (AG)

  a. The anion gap can be calculated by subtracting measured anions from measured cations.

  b. Because the primary measured plasma cation is Na$^+$ and the primary measured anions are $\text{HCO}_3^-$ and Cl$^-$; the anion gap can be calculated as shown:

$$\text{AG} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$$

  which can be rewritten as

$$\text{AG} = \text{unmeasured anions} - \text{unmeasured cations}$$

  c. The presence of unmeasured plasma anions such as lactate, sulfate, and phosphate explains why the anion gap is normally positive; that is, if all plasma anions were composed of $\text{HCO}_3^-$ and Cl$^-$, the anion gap would approach zero.

  d. Because electroneutrality must be maintained, in an anion gap metabolic acidosis, there is consumption of $\text{HCO}_3^-$ (used up in buffering H$^+$ ions) and production of an unmeasured anion such as lactate or sulfate.

- Urinary anion gap (UAG)

  a. The UAG can be calculated by subtracting the major measured urinary anion (Cl$^-$) from the major measured urinary cations (Na$^+$, K$^+$), as shown.

$$\text{UAG} = (U_{\text{Na}^+} + U_{\text{K}^+} - U_{\text{Cl}^-})$$

  b. Note that the primary unmeasured urinary anion is $\text{HCO}_3^-$, whereas the primary unmeasured urinary cation is NH$_4^+$.

  c. The UAG can be helpful in determining the etiology of a normal AG metabolic acidosis by differentiating between renal and extrarenal etiologies.

  d. If the kidneys are functioning normally, they will produce significant amounts of ammonium (NH$_4^+$) through ammoniagenesis; this NH$_4^+$ is paired with urinary Cl$^-$ to maintain electroneutrality.
c. In a setting of a normal anion gap metabolic acidosis, if the kidneys are working normally, urinary [Cl\(^{-}\)] should therefore be high, and the UAG should be negative, indicating an extrarenal cause of the acidosis, such as diarrhea.

d. A failure to excrete ammonium during an acidemia will yield a positive urine anion gap; an acidosis resulting from such a failure by the kidney to excrete NH\(_4^+\) is termed renal tubular acidosis (RTA).

2. Respiratory compensation
   - Metabolic acidosis stimulates the peripheral and central chemoreceptors, promoting hyperventilation to “blow off” CO\(_2\).
   - The increased minute ventilation induced is mainly a result of increased tidal volumes rather than increased respiratory rate.
   - The expected P\(_{\text{CO}_2}\) is shown.

   \[\text{Expected } P_{\text{CO}_2} = 1.5 \times [\text{HCO}_3^-] + 8 \pm 2\]

   - Typically the P\(_{\text{CO}_2}\) will decrease by 1.2 mm Hg for every 1 mEq/L drop in plasma [HCO\(_3^-\)].

3. Causes of anion-gap metabolic acidosis
   - **Renal failure**
     a. Caused by inability of kidneys to excrete an appropriate amount of acid; this is caused by too few functional nephrons rather than a specific acid secretory defect. See Box 8-2 for a clinical example of renal failure.
   b. Renal failure can result in an anion gap metabolic acidosis as well as a normal anion gap acidosis if due to renal tubular acidosis.
   c. Of note, the RTAs can also cause a metabolic acidosis; in these cases, there are specific defects in acid excretory mechanisms.
   - **Lactic acidosis**
     a. Due to overproduction of lactic acid through anaerobic respiration
       - This typically occurs with tissue hypoperfusion and hypoxia but can also occur in states associated with high O\(_2\) demand (e.g., prolonged grand mal seizure).

### BOX 8-1 SAMPLE CASE: NORMAL ANION GAP METABOLIC ACIDOSIS

A 67-year-old woman is admitted to the hospital for evaluation of several days of profuse watery diarrhea. She is extremely fatigued. She has tachycardia (HR 125) and tachypnea (RR 20) and appears dehydrated on exam. Blood work reveals the following:

- Na\(^+\) 138
- K\(^+\) 4.2
- Cl\(^-\) 110
- HCO\(_3^-\) 16
- Anion gap 12
- P\(_{\text{CO}_2}\) 32

**Case Discussion**

This patient’s diarrhea has resulted in the loss of HCO\(_3^-\)-rich intestinal fluid, causing a hyperchloremic metabolic acidosis. Note that this is a normal anion gap metabolic acidosis because there is no production of an unmeasured anion. Based on Winter’s formula, appropriate respiratory compensation (through hyperventilation) should result in a drop in P\(_{\text{CO}_2}\) from 40 to approximately 32 (expected P\(_{\text{CO}_2}\) = 1.5 \times [16] + 8 \pm 2). Therefore, this patient is experiencing a normal anion gap metabolic acidosis (from diarrhea) with appropriate respiratory compensation. She needs aggressive hydration.

### TABLE 8-2. Renal Tubular Acidosis

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PATHOPHYSIOLOGY</th>
<th>URINE pH</th>
<th>DEGREE OF ACIDOSIS</th>
<th>SERUM K(^+)</th>
<th>EXCRETION OF HCO(_3^-) AFTER HCO(_3^-) LOAD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal RTA (Type I)</td>
<td>Inability to secrete H(^+) in distal tubule</td>
<td>$&gt;5.3$</td>
<td>Severe (serum HCO(_3^-) often $&lt;10$)</td>
<td>Decreased</td>
<td>$&lt;3$</td>
</tr>
<tr>
<td>Proximal RTA (Type II)</td>
<td>Inhibition of carbonic anhydrase (e.g., acetazolamide) and/or HCO(_3^-) reclamation in proximal tubule</td>
<td>$&lt;5.3$</td>
<td>Modest (serum HCO(_3^-) 12-16)</td>
<td>Decreased</td>
<td>$&gt;15$</td>
</tr>
<tr>
<td>Hyporeninemic</td>
<td>Destruction of juxtaglomerular apparatus causes hyporeninemic hypoadosteronism</td>
<td>$&lt;5.3$</td>
<td>Mild (serum HCO(_3^-) 14-20)</td>
<td>Increased</td>
<td>$&lt;3$</td>
</tr>
<tr>
<td>hyperaldosteronism</td>
<td>(hyperkalemic) RTA (Type IV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A negative UAG in a setting of a normal anion gap metabolic acidosis indicates an extrarenal etiology for the acidosis.

If the UAG is positive, RTA is likely.

To determine type of RTA: examine urine pH, serum pH, serum [K\(^+\)], and the fractional excretion of HCO\(_3^-\) after a bicarbonate load (Table 8-2)

Respiratory compensation for metabolic acidosis: hyperventilation to “blow off” CO\(_2\)

Winter’s formula: P\(_{\text{CO}_2}\) = 1.5 \times [HCO\(_3^-\)] + 8 \pm 2

Respiratory compensation for metabolic acidosis: P\(_{\text{CO}_2}\) should drop by 1.2 mm Hg for each 1 mEq/L drop in [HCO\(_3^-\)]

Pathophysiology of renal failure causing metabolic acidosis: due to too few functional nephrons and decreased glomerular filtration rate rather than specific acid secretory defect

Acute renal failure: can cause an anion gap or a normal anion gap metabolic acidosis

Lactic acidosis: generally caused by diffuse tissue hypoperfusion
A 43-year-old man with diabetes and hypertension experiences several days of vomiting and diarrhea from a presumptive viral gastroenteritis. The ibuprofen he has been taking has not relieved his symptoms. He is evaluated by his primary care physician. Labs during this visit reveal acute renal failure (ARF), with elevated plasma [Cr] of 6.5 (normal, <1 mg/dL), anion gap of 22 (normal, <16), HCO₃⁻ of 16 (normal, 24 mmol/L), and K⁺ of 6.5 (normal, 3.0 to 4.5).

**Case Discussion**

This patient has ARF as a result of hypovolemia from his vomiting and diarrhea as well as from renal hypoperfusion due to the renal vasoconstricting effects from the nonsteroidal anti-inflammatory agent ibuprofen. Renal hypoperfusion resulted in a low glomerular filtration rate, which reduced the acid excretory capacity of the kidneys. This decreased acid excretory capacity led to a metabolic acidosis. It is an anion gap metabolic acidosis because of the reduced ability of the kidneys to excrete nonvolatile acids such as lactate and sulfate, both unmeasured anions.

b. Tissue hypoperfusion can occur with sepsis, shock, hypovolemic states, prolonged sepsis, or even prolonged strenuous exercise.

c. In these conditions, not only is there excess production of lactic acid but conversion of lactic acid to glucose by the liver is also decreased because of reduced hepatic blood flow.

**Diabetic ketoacidosis (DKA)**

- **a.** DKA classically occurs in patients with type 1 diabetes, often as their initial presentation. See Box 8-3 for a clinical example of diabetic ketoacidosis.
- **b.** Characterized by hyperglycemia, volume depletion, ketosis, and anion gap metabolic acidosis.
- **c.** It results from an absolute deficiency in the anabolic hormone insulin.
- **d.** In the absence of insulin, “runaway” lipolysis occurs in the adipose tissue, and β-oxidation occurs in the liver.
- **e.** The lipolysis in adipose tissue continues to “feed” β-oxidative precursors to the liver, which metabolizes these fatty acids to ketone bodies.
- **f.** Several of these ketone bodies are acids that reduce the plasma pH, resulting in an anion gap metabolic acidosis.
- **g.** This acidosis is further exacerbated by the hyperglycemia, because the hyperglycemia causes an osmotic diuresis which results in volume depletion.
- **h.** With plasma volume contraction, the glomerular filtration rate (GFR) drops, and the kidneys are less able to excrete acid; there may also be a component of generalized tissue hypoperfusion and lactic acidosis.
- **i.** DKA is often associated with hyperkalemia despite total body potassium wasting.
- **j.** The hyperkalemia is caused by transcellular shifting of potassium due to the metabolic acidosis (H⁺ enters cells for buffering in exchange for K⁺), a solvent drag effect from the hyperglycemia, and the lack of insulin and/or insulin resistance.

**Acetylsalicylic (aspirin) toxicity**

- **a.** Acetylsalicylic acid is a commonly used antipyretic and analgesic that is rapidly converted into the bioactive salicylic acid in the body.
- **b.** Salicylic acid toxicity can cause tinnitus, vertigo, and nausea and in severe cases can cause seizures and death; in children and adolescents, it can also cause Reye syndrome.
- **c.** In terms of acid-base disturbances, salicylic acid toxicity can cause a respiratory alkalosis by stimulating the medullary respiratory center, causing hyperventilation, and a metabolic acidosis by inhibiting oxidative metabolism.

**Methanol ingestion**

- **a.** Methanol is a simple alcohol (CH₃OH) commonly used as an industrial solvent.
- **b.** Ingestion of methanol can result in blindness, due to destruction of the optic nerve, and death, from central nervous system (CNS) depression.
- **c.** Methanol is metabolized to formic acid, through formaldehyde, in a reaction catalyzed by the enzyme alcohol dehydrogenase.
- **d.** Formic acid exerts toxic effects by inhibiting mitochondrial cytochrome c oxidase, thereby causing cellular hypoxia and an anion gap metabolic acidosis (Fig. 8-4).
- **e.** The toxic effects of the metabolites of methanol can be prevented by competitively inhibiting the enzyme alcohol dehydrogenase with ethanol or fomepizole.
- **f.** Such inhibition allows the methanol to be excreted by the kidneys (or dialyzed by the nephrologist) rather than metabolized by the liver.
Ethylene glycol toxicity
a. Ethylene glycol is a sweet-tasting organic compound frequently used in automotive antifreeze.
b. Children and animals may ingest large amounts of it owing to its sweet taste if they are exposed to antifreeze.
c. As with methanol, the toxicity from ethylene glycol ingestion is from its metabolites (Fig. 8-5), glycolic and oxalic acid; discussion of the myriad toxic effects are beyond the scope of this book.

4. Causes of normal anion gap metabolic acidosis
   • Diarrhea
     a. Most common cause of normal anion gap metabolic acidosis
b. Diarrhea increases intestinal transit time and prevents \( \text{HCO}_3^-/\text{Cl}^- \) exchange, resulting in low \( \text{HCO}_3^- \) with retention of \( \text{Cl}^- \), and causing a hyperchloremic metabolic acidosis.

c. The anion gap is not increased because the fall in \( \text{HCO}_3^- \) is counterbalanced by a rise in \( \text{Cl}^- \) (a measured anion).

d. It is classically acute diarrhea that causes a metabolic acidosis; chronic diarrhea can actually cause a metabolic alkalosis because of volume contraction.

• **Renal tubular acidosis**
  a. An acidosis resulting from impaired renal excretion of \( \text{NH}_4^+ \)
  b. Although the details of the RTAs are beyond the scope of this book, the three principle types are summarized in Table 8-2.

**E. Metabolic alkalosis**

1. **Overview**
   
   • Characterized by a high \( \text{HCO}_3^- \) (>28 mEq/L), high pH, and high \( \text{PCO}_2 \) as a result of respiratory compensation. See Box 8-4 for a clinical example of metabolic alkalosis.
   
   • Recall that a high \( \text{HCO}_3^- \) may also represent renal compensation for a respiratory acidosis, although in this case the pH would be low.

   • If hypokalemia is present, this also indicates a likely metabolic etiology because of stimulation of the renin-angiotensin-aldosterone system.

   • Metabolic alkalosis is frequently associated with volume-depleted states (e.g., vomiting, hyperreninemic and/or hyperaldosteronemic states).

   • It can also occur with transcellular shifts (e.g., in hypokalemia, \( \text{K}^+ \) exits the cells in exchange for \( \text{Na}^+ \) and \( \text{H}^+ \) ions) and by the administration of \( \text{HCO}_3^- \).

   • Of note, respiratory compensation for a metabolic alkalosis (i.e., hypoventilation) is limited because the resulting hypoxemia will inhibit the alkalemia-induced hypoventilation.

2. **Specific causes of metabolic alkalosis**
   
   • **Vomiting**
     
     a. Characterized by high \( \text{HCO}_3^- \), low \( \text{Cl}^- \), high \( \text{PCO}_2 \) as a result of respiratory compensation, and high pH.
b. Loss of gastric contents is a powerful stimulant of metabolic alkalosis because it works through three separate but additive mechanisms: direct loss of H⁺, loss of Cl⁻, and volume depletion.

c. Loss of gastric secretions directly results in a decrease in H⁺ and Cl⁻ and an increase in pH.

d. Loss of Cl⁻ ions will additionally inhibit HCO₃⁻ secretion in the distal nephron because of decreased Cl⁻/HCO₃⁻ exchange by intercalated cells in an attempt to maintain electroneutrality, further increasing plasma HCO₃⁻ levels.

e. Vomiting will also cause a volume-contracted state, and because Na⁺ and HCO₃⁻ reclamation in the proximal nephron are linked, volume depletion results in increased sodium and bicarbonate reclamation.

f. Volume depletion also stimulates the renin-angiotensin-aldosterone system; the increased aldosterone promotes Na⁺ reabsorption in exchange for K⁺ and H⁺ in the distal tubule.

• Mineralocorticoid excess

  a. Classically characterized by volume expansion, hypertension, hypokalemia, hypernatremia, and metabolic alkalosis.

  b. Can be seen in a variety of conditions, including primary hyperaldosteronism (Conn syndrome), hypercortisolism (Cushing syndrome), Bartter syndrome, Gitelman syndrome, Liddle disease, 11β-(OH)-steroid dehydrogenase deficiency, and licorice ingestion (Table 8-3).

c. In most of the above conditions, the mineralocorticoid effects on the kidney produce a metabolic alkalosis by promoting H⁺ (and K⁺) secretion in exchange for Na⁺.

---

**BOX 8.4 SAMPLE CASE: METABOLIC ALKALOSIS**

A 49-year-old man with a history of systolic congestive heart failure (CHF) and an ejection fraction of 30% is evaluated for gradually worsening shortness of breath and fatigue. He is diagnosed with a CHF exacerbation and admitted to the hospital and placed on intravenous furosemide. His symptoms improve dramatically, but his urine output drops precipitously on the third day, and his urine specific gravity indicates concentrated urine. An arterial blood gas measurement reveals the following:

- pH 7.47
- Pco₂ 51 mm Hg
- HCO₃⁻ 40 mEq/L
- Po₂ 100 mm Hg

**Case Discussion**

The above patient likely has a *contraction alkalosis* caused by furosemide, a potent loop diuretic. His HCO₃⁻ is increased 16 mEq/L above normal. Given that the expected respiratory compensation for a metabolic alkalosis is a rise in Pco₂ of 0.7 mm Hg for every 1 mEq/L rise in HCO₃⁻, we would expect a rise in Pco₂ of approximately 11 mm Hg above the normal value of 40 mm Hg; therefore, the patient above has a metabolic alkalosis with appropriate respiratory compensation. Although in this case the hypoventilation resulted in appropriate respiratory compensation, recall that the ability of the lungs to compensate for a metabolic alkalosis is limited because significant hypoventilation will cause hypoxemia.

**TABLE 8-3. Mineralocorticoid Excess States Resulting in Metabolic Alkalosis**

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>PATHOPHYSIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conn syndrome</td>
<td>The action of aldosterone in the distal tubule results in an increase in H⁺ (and K⁺) secretion in exchange for Na⁺</td>
</tr>
<tr>
<td>Cushing disease</td>
<td>Levels of cortisol exert mineralocorticoid effects on the kidney</td>
</tr>
<tr>
<td>Bartter syndrome</td>
<td>Defective Na⁺/K⁺/Cl⁻ transporter in the loop of Henle (mimics the effect of a loop diuretic)</td>
</tr>
<tr>
<td>Gitelman syndrome</td>
<td>Defective Na⁺/Cl⁻ transporter (mimics the effect of a thiazide diuretic)</td>
</tr>
<tr>
<td>Liddle disease</td>
<td>A defect in the Na⁺ channel in the distal tubule that is normally stimulated by aldosterone results in a channel being permanently activated (mimics mineralocorticoid excess; in this setting spironolactone will not work so one must use triamterene or amiloride instead)</td>
</tr>
<tr>
<td>11β-(OH)-steroid dehydrogenase deficiency</td>
<td>Defect of the enzyme that normally breaks down cortisol within aldosterone-responsive cells causes cortisol to build up and activate the mineralocorticoid receptor</td>
</tr>
<tr>
<td>Licorice ingestion</td>
<td>Contains a substance that inhibits 11β-OH-SD</td>
</tr>
</tbody>
</table>
3. **Respiratory compensation**
   - The reduced [H⁺] stimulates hypoventilation through the respiratory chemoreceptors; the hypoventilation acts to increase P\(_{CO_2}\).
   - For every 1 mEq/L rise in [HCO\(_3^-\)], the P\(_{CO_2}\) typically rises 0.7 mm Hg.
   - Assuming a normal [HCO\(_3^-\)] of 24 mEq/L, a metabolic alkalosis with an [HCO\(_3^-\)] of 34 mEq/L should result in a rise in P\(_{CO_2}\) of 7 mm Hg.
   - If the rise in P\(_{CO_2}\) is different from expected, there is a coexisting respiratory alkalosis or acidosis.

F. **Respiratory acidosis**

1. **Overview**
   - Almost always caused by alveolar hypoventilation (inability to remove CO\(_2\)) rather than an increase in CO\(_2\) production (>45 mm Hg). See Box 8-5 for a clinical example of respiratory acidosis.
   - Characterized by high P\(_{CO_2}\), low pH, and high HCO\(_3^-\); the degree to which the HCO\(_3^-\) is reflecting the extent of renal compensation.
   - Complications may include lethargy and coma (“CO\(_2\) narcosis”), increased intracranial pressure (ICP), cardiac dysrhythmias, impaired cardiac contractility, and hypoxemia.
   - It should be realized that hypoventilation as a compensatory response to metabolic alkalosis will **not** cause hypoxemia.
   - Alveolar ventilation can be impaired in a variety of settings, such as with opiates or sedatives, anesthetics, neurologic disorders such as myasthenia crisis and Guillain-Barré syndrome, and a host of other scenarios (Table 8-4 provides further details).
   - Therapy will often involve mechanical intubation.

2. **Specific causes of respiratory acidosis** (see Table 8-4)

3. **Metabolic compensation** (Table 8-5)
   - Acute compensation
     a. Compensation for acute respiratory acidosis involves use of intracellular proteins such as hemoglobin, which act as buffers by sequestering H\(^+\) ions, as shown.
     \[
     H_2CO_3 + buffer^- \rightarrow HCO_3^- + H^- + buffer
     \]
     b. These buffering actions produce new HCO\(_3^-\), as shown above.
     c. The increase in plasma [HCO\(_3^-\)] averages approximately 1 mEq/L for every 10 mm Hg rise in P\(_{CO_2}\).
   - Chronic compensation
     a. Chronically elevated P\(_{CO_2}\) stimulates renal H\(^+\) secretion, which acts to increase renal production of HCO\(_3^-\) and increase plasma [HCO\(_3^-\)].
     b. This response becomes maximally effective within 3 to 5 days.
     c. In this case, the increase in plasma [HCO\(_3^-\)] averages approximately 3.5 mEq/L for every 10 mm Hg rise in P\(_{CO_2}\).

G. **Respiratory alkalosis**

1. **Overview**
   - Caused by alveolar hyperventilation. See Box 8-6 for a clinical example of respiratory alkalosis.
   - Alveolar hyperventilation may occur in response to hypoxemia (e.g., lung disease) or as a result of a central cause (e.g., pain, anxiety, CNS disease); see Table 8-5 for further causes.

### Table 8-4. Causes of Respiratory Acidosis

<table>
<thead>
<tr>
<th>CAUSES OF HYPERCAPNIA</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung disease</td>
<td>Chronic bronchitis, bronchiectasis</td>
</tr>
<tr>
<td>Central hyperventilation</td>
<td>Sedatives, central nervous system trauma, pickwickian syndrome</td>
</tr>
<tr>
<td>Neuromuscular disorders</td>
<td>Myasthenia gravis, Guillain-Barré, amyotrophic lateral sclerosis, muscular dystrophy, poliomyelitis</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>Acute airway obstruction, laryngospasm, obstructive sleep apnea</td>
</tr>
<tr>
<td>Thoracic cage abnormalities</td>
<td>Pneumothorax, flail chest, scoliosis</td>
</tr>
<tr>
<td>O(_2) administration</td>
<td>In chronic bronchitis patient with chronic hypercapnia</td>
</tr>
</tbody>
</table>

### Table 8-5. Compensation for Acute and Chronic Respiratory Acidosis

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>PRIMARY CHANGE</th>
<th>EXPECTED COMPENSATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory acidosis</td>
<td>Increased P(_{CO_2})</td>
<td>Increased HCO(<em>3^-) = 0.1 \times \Delta P</em>{CO_2}</td>
</tr>
<tr>
<td>Chronic respiratory acidosis</td>
<td>Increased P(_{CO_2})</td>
<td>Increased HCO(<em>3^-) = 0.35 \times \Delta P</em>{CO_2}</td>
</tr>
</tbody>
</table>
BOX 8-5  SAMPLE CASE: RESPIRATORY ACIDOSIS

A 38-year-old obese woman with obstructive sleep apnea is evaluated by the medical service for confusion and lethargy shortly after undergoing a laparoscopic cholecystectomy. Her postoperative pain had been controlled with intravenous morphine. Examination reveals an obese somnolent woman who is obviously confused. She is breathing at a rate of 8 breaths per minute. An arterial blood gas measurement reveals the following:
- pH 7.28
- $P_{CO_2}$ 120 mm Hg
- $HCO_3^-$ 32 mEq/L
- $P_O_2$ 75 mm Hg

Case Discussion
This patient has respiratory acidosis caused by depression of the medullary respiratory center by the opiate morphine, resulting in hypoventilation, hypercapnia, and hypoxemia; her obesity and obstructive sleep apnea were undoubtedly contributing factors. The kidneys compensate for a respiratory acidosis by more avidly retaining filtered $HCO_3^-$, excreting a greater acid load, and by producing de novo bicarbonate from the deamination of glutamine. The kidneys are able to compensate much more effectively for a chronic respiratory acidosis than for an acute respiratory acidosis. In an acute respiratory acidosis, we would expect the $HCO_3^-$ to increase by approximately 1 mEq/L for every increase in $P_{CO_2}$ of 10 mm Hg whereas the $HCO_3^-$ should increase by 3.5 mEq/L for every increase in $P_{CO_2}$ of 10 mm Hg for compensation of a chronic respiratory acidosis. In this patient, the $P_{CO_2}$ has increased by 80 mm Hg and the $HCO_3^-$ has increased by only 8 mEq/L, representing renal compensation for an acute respiratory acidosis. This woman has “$CO_2$ narcosis” and needs to be intubated.

TABLE 8-6. Causes of Respiratory Alkalosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>PRIMARY CHANGE</th>
<th>EXPECTED COMPENSATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory alkalosis</td>
<td>Decreased $P_{CO_2}$</td>
<td>Decreased $HCO_3^-$ = 0.2 x $\Delta P_{CO_2}$</td>
</tr>
<tr>
<td>Chronic respiratory alkalosis</td>
<td>Decreased $P_{CO_2}$</td>
<td>Decreased $HCO_3^-$ = 0.4 x $\Delta P_{CO_2}$</td>
</tr>
</tbody>
</table>

- Characterized by low $P_{CO_2}$ (<33 mm Hg), high pH, and low $HCO_3^-$, the degree to which the $HCO_3^-$ is lowered reflecting the extent of renal compensation.
- Maximal compensation by the kidneys takes a couple of days.
- Of note, it is “easier” for the kidneys to excrete bicarbonate than to retain it when a respiratory acid-base disturbance exists, resulting in greater compensation for a respiratory alkalosis.

2. Specific causes of respiratory alkalosis (Table 8-6)
3. Metabolic compensation (Table 8-7)
   - Acute compensation
     a. Initial response involves buffering by transeellular shift whereby $H^+$ ions leave cells and combine with $HCO_3^-$ in the extracellular fluid, in the reaction shown below.
        \[ H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O \]
     b. This lowers plasma $[HCO_3^-]$ within minutes.
     c. The $H^+$ ions from above are donated from intracellular proteins, hemoglobin, and phosphate.
     d. Such buffering typically lowers plasma $[HCO_3^-]$ by 2 mEq/L for every 10 mm Hg decrease in the $P_{CO_2}$.

TABLE 8-7. Compensation for Respiratory Alkalosis

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>PRIMARY CHANGE</th>
<th>EXPECTED COMPENSATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory alkalosis</td>
<td>Decreased $P_{CO_2}$</td>
<td>Decreased $HCO_3^-$ = 0.2 x $\Delta P_{CO_2}$</td>
</tr>
<tr>
<td>Chronic respiratory alkalosis</td>
<td>Decreased $P_{CO_2}$</td>
<td>Decreased $HCO_3^-$ = 0.4 x $\Delta P_{CO_2}$</td>
</tr>
</tbody>
</table>

- Respiratory alkalosis: $P_{CO_2}$, high pH, and low $HCO_3^-$. Kidneys better able to compensate for respiratory alkalosis than for respiratory acidosis
- Intracellular shift of $H^+$ ions: due to “release” of $H^+$ ions from intracellular proteins, hemoglobin, phosphate
- Acute compensation for respiratory alkalosis: $[HCO_3^-]$ by 2 mEq/L for every 10 mm Hg ↓ in $P_{CO_2}$
Chronic compensation

A. Kidneys increase $\text{HCO}_3^-$ urinary excretion and decrease urinary ammonium ($\text{NH}_4^+$) excretion.

B. The reduced ammonium excretion decreases the acid excretory capacity of the kidney, which helps retain acid in the body.

C. These renal responses begin within approximately 2 hours but are not complete for 3 to 5 days.

D. The combination of the cell buffers and the renal compensation typically lowers plasma $[\text{HCO}_3^-]$ by approximately 4 mEq/L for every 10 mm Hg decrease in the $P_{\text{CO}_2}$.

**BOX 8-6 SAMPLE CASE: RESPIRATORY ALKALOSIS**

A 62-year-old woman recovering from hip surgery 3 days earlier is evaluated for sudden onset of shortness of breath. The medicine intern is called to evaluate the patient. The woman appears in moderate respiratory distress, and her $O_2$ saturation is low at 80% (normal 95%). An arterial blood gas measurement reveals the following:

- $\text{pH} = 7.48$
- $P_{\text{CO}_2} = 20$ mm Hg
- $\text{HCO}_3^- = 20$ mEq/L
- $P_{O_2} = 80$ mm Hg

**Case Discussion**

The above scenario is a classic presentation of acute pulmonary embolism. The patient has had recent surgery (endothelial trauma) and has likely been immobile in bed for several days (stasis). Moreover, her dyspnea is abrupt in onset, and she is hypoxemic with an A-a gradient of 20 mm Hg. Assuming this represents an acute respiratory alkalosis (from hypoxemia-induced hyperventilation), the expected drop in plasma $\text{HCO}_3^-$ would be 0.2 times the change in $P_{\text{CO}_2}$. Because $P_{\text{CO}_2}$ has dropped by 20 mm Hg, we would expect a drop in $\text{HCO}_3^-$ of 4 mm Hg. The arterial blood gases therefore support a diagnosis of acute respiratory alkalosis that is being compensated by cellular buffers and limited renal compensation. A word of caution here: although the history here is classic for abrupt development of pulmonary embolism, studies have shown that patients with pulmonary embolism can present with respiratory alkalosis, respiratory acidosis, metabolic acidosis, and without hypoxemia. In short, the ABG is actually of limited diagnostic value for diagnosing PE.

- Chronic compensation
  
  a. Kidneys increase $\text{HCO}_3^-$ urinary excretion and decrease urinary ammonium ($\text{NH}_4^+$) excretion.
  
  b. The reduced ammonium excretion decreases the acid excretory capacity of the kidney, which helps retain acid in the body.
  
  c. These renal responses begin within approximately 2 hours but are not complete for 3 to 5 days.
  
  d. The combination of the cell buffers and the renal compensation typically lowers plasma $[\text{HCO}_3^-]$ by approximately 4 mEq/L for every 10 mm Hg decrease in the $P_{\text{CO}_2}$. 

Chronic compensation for respiratory alkalosis: ↓ $[\text{HCO}_3^-]$ by 4 mEq/L for every 10 mm Hg ↓ in $P_{\text{CO}_2}$. 

Rapid Review Physiology
I. Body Fluids
   A. Distribution of body fluids
      1. Fluid compartments (Fig. 9-1)
         • Approximately 50% to 60% of total body weight consists of water (approximately 50% in women, 60% in men, and 70% in infants).
         • Roughly two thirds of total body water (TBW) is located within cells (intracellular fluid, ICF), with the remainder located in the extracellular fluid (ECF) compartment.
         • The ECF is composed of interstitial fluid (IF; ~75%) and plasma (~25%), with a minute fraction consisting of transcellular fluids.
         • Transcellular fluids include many small fluid compartments such as the peritoneal, pleural, synovial, pericardial, and cerebrospinal fluids and the aqueous humor of the intraocular compartment.
           a. Although transcellular fluids normally comprise a minute fraction of the ECF, in disease states such as ascites from liver disease, this fraction can increase substantially.

   Total body water (TBW)
   \[ 0.6 \times \text{Body weight} \]
   \[ 42 \text{ L} \]

   Extracellular fluid (ECF)
   \[ 0.2 \times \text{Body weight} \]
   \[ 14 \text{ L} \]

   Intracellular fluid (ICF)
   \[ 0.4 \times \text{Body weight} \]
   \[ 28 \text{ L} \]

   Interstitial fluid
   \[ \frac{3}{4} \text{ of ECF} \]
   \[ 10.5 \text{ L} \]

   Plasma
   \[ \frac{1}{4} \text{ of ECF} \]
   \[ 3.5 \text{ L} \]

   Transcellular fluid compartment (normal)
   Transcellular fluid compartment in disease states (e.g., massive ascites)

   9-1: Fluid compartments in the “typical” 70-kg man. (From Levy MN, Koeppen BM, Stanton BA: Berne & Levy Principles of Physiology, 4th ed. Philadelphia, Mosby, 2007, Fig. 38-1.)

TBW: ~50% (women) to 60% (men) of body weight
Approximately two thirds of TBW is ICF, one third ECF
ECF: composed of IF, plasma, transcellular fluids
In disease states such as ascites or pleural effusion, the transcellular compartment can increase substantially
As an example, a 70-kg man should have approximately 35 liters of TBW, 23 liters of ICF, and 12 liters of ECF; the ECF would comprise 9 liters of IF, whereas the plasma would comprise 3 liters of water.

Clinical note: In conditions associated with decreased arterial oncotic pressure (e.g., hypoalbuminemia in liver disease and nephrotic syndrome), fluid can shift from the intravascular space to the interstitium (so-called third spacing), resulting in edema, and often transcellular compartments such as the peritoneal cavity, resulting in ascites. If third spacing results in significant accumulation of fluid in compartments such as the peritoneal cavity or pleural space, the transcellular fluid volume becomes pathologically increased and the effective circulatory volume may become pathologically reduced, resulting in tissue hypoperfusion and prerenal azotemia.

### Composition of fluid compartments

#### Intracellular fluid
- Relative to ECF, the ICF has large amounts of protein, potassium, calcium, and phosphate and low levels of sodium and chloride.
- Approximately 98% of total body potassium is located within cells; this potassium can play an important role in buffering of a metabolic acidosis.
- Most total body phosphate is also located within cells; this phosphate is important in adenosine triphosphate (ATP) generation as well as in intracellular buffering.
- The large amounts of proteins are necessary for cellular function and also play an important buffering and osmotic role.
- The low $[\text{Na}^+]$ and $[\text{Cl}^-]$ are due to activity of the $\text{Na}^+,\text{K}^+\text{-ATPase}$ pump, which maintains the electrochemical gradient across the cell membrane.

#### Extracellular fluid
- **Interstitial fluid**
  - Interstitial fluid is separated from the plasma compartment by a barrier that is freely permeable to water and many electrolytes but not to red blood cells (RBCs) and most proteins.
  - Interstitial fluid has high amounts of sodium and chloride and low amounts of potassium and phosphate; it is also relatively protein poor because of the selectively permeable capillary plasma membrane.
  - Proteins that do leak into the interstitial compartment from the blood are typically returned to the vascular compartment through the lymphatics.

- **Plasma**
  - Plasma is the fluid component of blood that remains after blood cells (primarily RBCs) are removed.
  - It normally comprises about 60% of blood volume.

Clinical note: In conditions associated with increased vascular permeability (e.g., infections, inflammatory states), proteins leave the intravascular space and enter the interstitium. If the lymphatics are unable to keep up with this transudation of fluid, interstitial edema results. In the lungs, this process can result in acute respiratory distress syndrome (ARDS).

### Measurement of fluid compartments

1. This requires the use of an **indicator substance**, which is **diffusion-restricted** to a particular fluid compartment.
   - Note that indicator substances are used in research and rarely used in clinical medicine.
2. **Deuterium** and **tritiated water** diffuse throughout the TBW; they can therefore be used to measure TBW.
3. **Inulin** and **mannitol** are diffusion-restricted to the ECF compartment; they can therefore be used to measure ECF volume.
4. **Radiolabeled albumin** ($^{125}\text{I}\text{-albumin}$) is diffusion restricted to the vascular compartment; it can therefore be used to measure plasma volume.

### Regulation of Sodium and Water Balance

#### General principles
1. Sodium and water are regulated differently.
2. In the normal state, volume is regulated through sodium balance, whereas osmolarity and sodium concentration are regulated through water balance.
3. The kidneys regulate ECF volume by adjusting the rate of sodium excretion.
   - To be more precise, it is the effective circulating volume (ECV) that is regulated by
     the body, not the ECF volume (discussed later).
4. Under normal circumstances, ECF osmolarity and sodium concentration are
   regulated through water balance via ADH secretion.
   - A low Na\(^+\) concentration (hyponatremia) results in swelling of the cells (by osmosis)
     and inhibition of antidiuretic hormone (ADH) secretion from specialized
     osmoreceptors in the hypothalamus.
   - Conversely, a high Na\(^+\) concentration (hypernatremia) results in shrinking of
     osmoreceptors cells and stimulates ADH secretion.
   - Note that ECF Na\(^+\) concentration does not necessarily correlate with ECF volume.

Clinical note: Under normal conditions, ADH does not work to regulate ECF volume. Instead, ADH
normally functions to regulate the reabsorption of free water in the collecting duct in response to
changes in body fluid osmolarity. However, when ECV is severely compromised (e.g., congestive heart
failure, cirrhosis, nephrotic syndrome), the secretion of ADH by the posterior pituitary is stimulated.
Thus, with significant hypovolemia, the function of ADH changes to help preserve volume rather than
osmolality. Treatment of both conditions involves inhibition of the pathologically stimulated renin-
angiotensin-aldosterone neurohormonal cascade.

B. Effective circulatory volume
1. The effective circulatory volume is that portion of the ECF contained within the
   vascular space that is effectively perfusing tissues; it is not a separate fluid compartment.
2. Extracellular sodium content is the primary determinant of ECV volume.
3. ECF volume is directly proportional to total body sodium content because sodium, as
   the primary extracellular solute, acts to retain fluid within the extracellular space.
4. The body has no way to directly monitor ECF volume; instead, various pressure and
   volume detectors located throughout the circulatory system (in the atria, aortic arch,
   carotid sinuses, and afferent arterioles of the kidney) monitor plasma “volume” and,
   through various mechanisms, stimulate or inhibit renal Na\(^+\) excretion.
5. The renin-angiotensin-aldosterone system is probably the most important of these
   mechanisms.

Clinical note: The ECV is not directly proportional to extracellular volume in certain conditions such as
congestive heart failure and cirrhosis with ascites. In the former, the impaired cardiac output is unable
to stretch the baroreceptors; this leads to the perception of inadequate circulating volume, which
triggers further fluid retention. In cirrhosis, fluid sequestration in ascitic fluid and in the dilated
splanchnic bed results in a markedly expanded extracellular volume. However, this expanded volume is
effectively invisible to the detectors of effective circulating volume, which trigger further fluid retention
and consequent exacerbation of the ECF excess. Hyponatremia is common in both conditions due to
pathologically increased secretion of ADH, and its presence is a poor prognostic factor.

- Response to decrease in effective circulating volume
  a. The body perceives the ECV in relation to the pressure that is perfusing the arterial
     stretch receptors in the carotid sinus, the aortic arch, and the glomerular afferent artery.
  b. When stretch receptors are activated by reduced blood flow, they send signals to
     the brainstem to increase sympathetic outflow.
  c. The increase in sympathetic outflow alters the circulatory system in several ways:
     - It increases cardiac contractility and heart rate, thereby increasing cardiac output.
     - It promotes venoconstriction, which moves blood into the arterial circulation;
       approximately 70% of blood is usually in the venous system, and a shift of some
       of this volume to the arterial circulation increases the effective circulating
       volume (recall the Frank-Starling relationship discussed in Chapter 4).
     - It stimulates arteriolar constriction, which raises systemic blood pressure and
       increases arterial perfusion pressure.
     - It stimulates renin production by the juxtaglomerular apparatus of the nephron,
       which in turn stimulates angiotensin II synthesis, which promotes sodium retention
       by the kidneys, and at higher concentrations, promotes systemic vasoconstriction.
     - It stimulates sodium retention by the kidneys, which increases intravascular
       volume (recall, sodium balance determines ECV volume).
Through angiotensin II, there is preferential constriction of the efferent arteriole, which helps maintain an adequate glomerular filtration pressure in a setting of hypovolemia.

d. A reduced ECV can occur in conditions such as diarrhea, adrenal insufficiency, and volume depletion (dehydration), as shown in Figure 9-2; note the differential effects these conditions have on the composition of the ECF.

- **Secretory diarrhea (e.g., cholera, traveler’s diarrhea)**
  1. In secretory diarrhea, there is a loss of isosmotic fluid, resulting in an isosmotic decrease in ECF volume (**isosmotic volume contraction**).
  2. ECF osmolarity remains unchanged, so there is no fluid shift from the ICF compartment to the ECF compartment.

- **Water loss (e.g., diabetes insipidus, insensible water loss from fever)**
  1. With water deprivation, there is loss of hyposmotic fluid, resulting in reduced ECF volume and increased ECF osmolarity (**hyperosmotic volume contraction**).
  2. Water shifts from the ICF compartment to the hyperosmolar ECF until the osmolarities are equal.
  3. The end result is a reduction in ECF and ICF volume with increased osmolarity in both compartments.

- **Adrenal insufficiency (Addison disease)**
  1. In adrenal insufficiency, reduced aldosterone, and to a lesser extent cortisol, results in excess loss of NaCl from the nephron, resulting in decreased ECF volume and osmolarity (**hyposmotic volume contraction**).
  2. Water shifts to the relatively hyperosmolar ICF compartment.
  3. In the new steady state, ECF volume is reduced with a reduced osmolarity, and ICF volume is increased with a reduced osmolarity.

- **Response to increased effective circulating volume**
  a. All the changes in the previous section are reversed:

    - The increased cardiac output causes stretching of baroreceptors, which triggers cessation of sympathetic outflow from the brainstem.
    - Reduced sympathetic outflow has multiple effects, including vasodilation, reduced cardiac contractility, and decreased renal fluid retention, which lower cardiac output and blood pressure, thereby reducing baroreceptor stretch.

  b. Multiple conditions can cause a volume-expanded state; note the differential effects these conditions have on the composition of the ECF (Fig. 9-3).

    - **Isotonic NaCl infusion**
      1. With isotonic saline infusion, there is an increase in ECF volume, but because there is no oncotic difference between the ICF and the ECF, there are no fluid shifts between the compartments.
      2. Therefore, only the ECF volume increases (**isosmotic volume expansion**).

    - **High NaCl intake**
      1. Increased NaCl intake, in the absence of excess water, increases ECF volume and osmolarity (**hyperosmotic volume expansion**).
(2) Water therefore shifts from the ICF compartment to the ECF compartment, reducing ICF volume and increasing ECF volume.
(3) However, osmolarity of both the ECF and ICF compartments is increased.
   - SIADH (e.g., small cell carcinoma of lung)
     (1) In the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, ADH secretion occurs irrespective of ECF osmolarity or intravascular volume status (i.e., ADH secretion is nonphysiologic).
     (2) ADH promotes excessive free water reabsorption from the kidneys, which expands both the ECF and ICF volumes without signs of volume overload such as edema.
     (3) This free water reabsorption decreases ECF and ICF osmolarity (hyposmotic volume expansion).
     (4) Note that although SIADH is typically classified as a euvolemic cause of hyponatremia, there is in fact a mild increase in ECV volume; however, this is not significant enough to be recognized on exam.

# Common Laboratory Values

<table>
<thead>
<tr>
<th>TEST</th>
<th>CONVENTIONAL UNITS</th>
<th>SI UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood, Plasma, Serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT, GPT at 30°C)</td>
<td>8–20 U/L</td>
<td>8–20 U/L</td>
</tr>
<tr>
<td>Amylase, serum</td>
<td>25–125 U/L</td>
<td>25–125 U/L</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST, GOT at 30°C)</td>
<td>8–20 U/L</td>
<td>8–20 U/L</td>
</tr>
<tr>
<td>Bilirubin, serum (adult): total; direct</td>
<td>0.1–1.0 mg/dL; 0.0–0.3 mg/dL</td>
<td>2–17 μmol/L; 0–5 μmol/L</td>
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<tr>
<td>Calcium, serum (Ca++)</td>
<td>8.4–10.2 mg/dL</td>
<td>2.1–2.8 mmol/L</td>
</tr>
<tr>
<td>Cholesterol, serum</td>
<td>Rec: &lt;200 mg/dL</td>
<td>&lt;5.2 mmol/L</td>
</tr>
<tr>
<td>Cortisol, serum</td>
<td>8:00 AM: 6–23 μg/dL</td>
<td>170–650 nmol/L; 80–410 nmol/L</td>
</tr>
<tr>
<td></td>
<td>8:00 PM: ≤50% of 8:00 AM</td>
<td>Fraction of 8:00 AM: ≤0.50</td>
</tr>
<tr>
<td>Creatine kinase, serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male: 25–90 U/L</td>
<td>25–90 U/L</td>
<td></td>
</tr>
<tr>
<td>Female: 10–70 U/L</td>
<td>10–70 U/L</td>
<td></td>
</tr>
<tr>
<td>Creatinine, serum</td>
<td>0.6–1.2 mg/dL</td>
<td>53–106 μmol/L</td>
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<tr>
<td>Electrolytes, serum</td>
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<tr>
<td>Sodium (Na⁺)</td>
<td>136–145 mEq/L</td>
<td>135–145 mmol/L</td>
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<tr>
<td>Chloride (Cl⁻)</td>
<td>95–105 mEq/L</td>
<td>95–105 mmol/L</td>
</tr>
<tr>
<td>Potassium (K⁺)</td>
<td>3.5–5.0 mEq/L</td>
<td>3.5–5.0 mmol/L</td>
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<tr>
<td>Bicarbonate (HCO₃⁻)</td>
<td>22–28 mEq/L</td>
<td>22–28 mmol/L</td>
</tr>
<tr>
<td>Magnesium (Mg²⁺)</td>
<td>1.5–2.0 mEq/L</td>
<td>1.5–2.0 mmol/L</td>
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<tr>
<td>Estriol, total, serum (in pregnancy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24–28 wk; 32–36 wk</td>
<td>30–170 ng/mL; 60–280 ng/mL</td>
<td>104–590 nmol/L; 208–970 nmol/L</td>
</tr>
<tr>
<td>28–32 wk; 36–40 wk</td>
<td>40–220 ng/mL; 80–350 ng/mL</td>
<td>140–760 nmol/L; 280–1210 nmol/L</td>
</tr>
<tr>
<td>Ferritin, serum</td>
<td>Male: 15–200 ng/mL</td>
<td>15–200 μg/L</td>
</tr>
<tr>
<td></td>
<td>Female: 12–150 ng/mL</td>
<td>12–150 μg/L</td>
</tr>
<tr>
<td>Follicle-stimulating hormone, serum/plasma (FSH)</td>
<td>Male: 4–25 mIU/mL</td>
<td>4–25 U/L</td>
</tr>
<tr>
<td></td>
<td>Female:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Premenopause, 4–30 mIU/mL</td>
<td>4–30 U/L</td>
</tr>
<tr>
<td></td>
<td>Midcycle peak, 10–90 mIU/mL</td>
<td>10–90 U/L</td>
</tr>
<tr>
<td></td>
<td>Postmenopause, 40–250 mIU/mL</td>
<td>40–250 U/L</td>
</tr>
<tr>
<td>Gases, arterial blood (room air)</td>
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<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35–7.45</td>
<td>[H⁺] 36–44 nmol/L</td>
</tr>
<tr>
<td>P&lt;sub&gt;CO₂&lt;/sub&gt;</td>
<td>33–45 mm Hg</td>
<td>4.4–5.9 kPa</td>
</tr>
<tr>
<td>P&lt;sub&gt;O₂&lt;/sub&gt;</td>
<td>75–105 mm Hg</td>
<td>10.0–14.0 kPa</td>
</tr>
<tr>
<td>Glucose, serum</td>
<td>Fasting: 70–110 mg/dL</td>
<td>3.8–6.1 mmol/L</td>
</tr>
<tr>
<td></td>
<td>2 hr postprandial: &lt;120 mg/dL</td>
<td>&lt;6.6 mmol/L</td>
</tr>
<tr>
<td>Growth hormone–arginine stimulation</td>
<td>Fasting: &lt;5 ng/mL</td>
<td>&lt;5 μg/L</td>
</tr>
<tr>
<td></td>
<td>Provocative stimuli: &gt;7 ng/mL</td>
<td>&gt;7 μg/L</td>
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<tr>
<td>Immunoglobulins, serum</td>
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</tr>
<tr>
<td>IgA</td>
<td>76–390 mg/dL</td>
<td>0.76–3.90 g/L</td>
</tr>
<tr>
<td>IgE</td>
<td>0–380 IU/mL</td>
<td>0–380 kIU/L</td>
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Continued
<table>
<thead>
<tr>
<th>TEST</th>
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</tr>
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<tbody>
<tr>
<td>IgG</td>
<td>650–1500 mg/dL</td>
<td>6.5–15 g/L</td>
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<tr>
<td>IgM</td>
<td>40–345 mg/dL</td>
<td>0.4–3.45 g/L</td>
</tr>
<tr>
<td>Iron</td>
<td>50–170 µg/dL</td>
<td>9–30 µmol/L</td>
</tr>
<tr>
<td>Lactate dehydrogenase, serum</td>
<td>45–90 U/L</td>
<td>45–90 U/L</td>
</tr>
<tr>
<td>Luteinizing hormone, serum/plasma (LH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male: 6–23 mIU/mL</td>
<td>6–23 U/L</td>
<td></td>
</tr>
<tr>
<td>Female:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular phase, 5–30 mIU/mL</td>
<td>5–30 U/L</td>
<td></td>
</tr>
<tr>
<td>Midcycle, 75–150 mIU/mL</td>
<td>75–150 U/L</td>
<td></td>
</tr>
<tr>
<td>Postmenopause, 30–200 mIU/mL</td>
<td>30–200 U/L</td>
<td></td>
</tr>
<tr>
<td>Osmolality, serum</td>
<td>275–295 mOsm/kg</td>
<td>275–295 mOsm/kg</td>
</tr>
<tr>
<td>Parathyroid hormone, serum, N-terminal</td>
<td>230–630 pg/mL</td>
<td>230–630 ng/L</td>
</tr>
<tr>
<td>Phosphatase (alkaline), serum (p-NPP at 30°C)</td>
<td>20–70 U/L</td>
<td>20–70 U/L</td>
</tr>
<tr>
<td>Phosphorus (inorganic), serum</td>
<td>3.0–4.5 mg/dL</td>
<td>1.0–1.5 mmol/L</td>
</tr>
<tr>
<td>Prolactin, serum (hPRL)</td>
<td>&lt;20 ng/mL</td>
<td>&lt;20 µg/L</td>
</tr>
<tr>
<td>Proteins, serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (recumbent)</td>
<td>6.0–8.0 g/dL</td>
<td>60–80 g/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5–5.5 g/dL</td>
<td>35–55 g/L</td>
</tr>
<tr>
<td>Globulin</td>
<td>2.3–3.5 g/dL</td>
<td>23–35 g/L</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, serum or plasma (TSH)</td>
<td>0.5–5.0 µU/mL</td>
<td>0.5–5.0 µU/L</td>
</tr>
<tr>
<td>Thyroidal iodine (123I) uptake</td>
<td>8–30% of administered dose/24 hr</td>
<td>0.08–0.30/24 hr</td>
</tr>
<tr>
<td>Thyroxine (T4), serum</td>
<td>4.5–12 µg/dL</td>
<td>58–154 nmol/L</td>
</tr>
<tr>
<td>Triglycerides, serum</td>
<td>35–160 mg/dL</td>
<td>0.4–1.81 mmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T3), serum (RIA)</td>
<td>115–190 ng/dL</td>
<td>1.8–2.9 nmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T3) resin uptake</td>
<td>25–38%</td>
<td>0.25–0.38</td>
</tr>
<tr>
<td>Urea nitrogen, serum (BUN)</td>
<td>7–18 mg/dL</td>
<td>1.2–3.0 mmol urea/L</td>
</tr>
<tr>
<td>Uric acid, serum</td>
<td>3.0–8.2 mg/dL</td>
<td>0.18–0.48 mmol/L</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell count</td>
<td>0–5 cells/mm³</td>
<td>0–5 × 10³/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>118–132 mEq/L</td>
<td>118–132 mmol/L</td>
</tr>
<tr>
<td>Gamma globulin</td>
<td>3–12% total proteins</td>
<td>0.03–0.12</td>
</tr>
<tr>
<td>Glucose</td>
<td>50–75 mg/dL</td>
<td>2.8–4.2 mmol/L</td>
</tr>
<tr>
<td>Pressure</td>
<td>70–180 mm H₂O</td>
<td>70–180 mm H₂O</td>
</tr>
<tr>
<td>Proteins, total</td>
<td>&lt;40 mg/dL</td>
<td>&lt;0.40 g/L</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding time (template)</td>
<td>2–7 min</td>
<td>2–7 min</td>
</tr>
<tr>
<td>Erythrocyte count</td>
<td>Male: 4.3–5.9 million/mm³</td>
<td>4.3–5.9 × 10¹²/L</td>
</tr>
<tr>
<td></td>
<td>Female: 3.5–5.5 million/mm³</td>
<td>3.5–5.5 × 10¹²/L</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (Westergren)</td>
<td>Male: 0–15 mm/hr</td>
<td>0–15 mm/hr</td>
</tr>
<tr>
<td></td>
<td>Female: 0–20 mm/hr</td>
<td>0–20 mm/hr</td>
</tr>
<tr>
<td>Hematocrit (Hct)</td>
<td>Male: 40–54%</td>
<td>0.40–0.54</td>
</tr>
<tr>
<td></td>
<td>Female: 37–47%</td>
<td>0.37–0.47</td>
</tr>
<tr>
<td>Hemoglobin A₁C</td>
<td>≤6%</td>
<td>≤0.06%</td>
</tr>
<tr>
<td>Hemoglobin, blood (Hb)</td>
<td>Male: 13.5–17.5 g/dL</td>
<td>2.09–2.71 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Female: 12.0–16.0 g/dL</td>
<td>1.86–2.48 mmol/L</td>
</tr>
<tr>
<td>Hemoglobin, plasma</td>
<td>1–4 mg/dL</td>
<td>0.16–0.62 mmol/L</td>
</tr>
<tr>
<td>Leukocyte count and differential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>4500–11,000/mm³</td>
<td>4.5–11.0 × 10³/L</td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td>54–62%</td>
<td>0.54–0.62</td>
</tr>
<tr>
<td>Bands</td>
<td>3–5%</td>
<td>0.03–0.05</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1–3%</td>
<td>0.01–0.03</td>
</tr>
<tr>
<td>Basophils</td>
<td>0–0.75%</td>
<td>0–0.0075</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>25–33%</td>
<td>0.25–0.33</td>
</tr>
<tr>
<td>Monocytes</td>
<td>3–7%</td>
<td>0.03–0.07</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (MCH)</td>
<td>25.4–34.6 pg/cell</td>
<td>0.39–0.54 fmol/cell</td>
</tr>
<tr>
<td>TEST</td>
<td>CONVENTIONAL UNITS</td>
<td>SI UNITS</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration (MCHC)</td>
<td>31–37% Hb/cell</td>
<td>4.81–5.74 mmol Hb/L</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV)</td>
<td>80–100 μm³</td>
<td>80–100 fl</td>
</tr>
<tr>
<td>Partial thromboplastin time (activated) (aPTT)</td>
<td>25–40 sec</td>
<td>25–40 sec</td>
</tr>
<tr>
<td>Platelet count</td>
<td>150,000–400,000/mm³</td>
<td>150–400 x 10⁹/L</td>
</tr>
<tr>
<td>Prothrombin time (activated) (aPTT)</td>
<td>12–14 sec</td>
<td>12–14 sec</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>0.5–1.5% of red cells</td>
<td>0.005–0.015</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>&lt;2 sec deviation from control</td>
<td>&lt;2 sec deviation from control</td>
</tr>
<tr>
<td>Volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>Male: 25–43 mL/kg</td>
<td>0.025–0.043 L/kg</td>
</tr>
<tr>
<td></td>
<td>Female: 28–45 mL/kg</td>
<td>0.028–0.045 L/kg</td>
</tr>
<tr>
<td>Red cell</td>
<td>Male: 20–36 mL/kg</td>
<td>0.020–0.036 L/kg</td>
</tr>
<tr>
<td></td>
<td>Female: 19–31 mL/kg</td>
<td>0.019–0.031 L/kg</td>
</tr>
<tr>
<td>Sweat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>0–35 mmol/L</td>
<td>0–35 mmol/L</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>100–300 mg/24 hr</td>
<td>2.5–7.5 mmol/24 hr</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Male: 97–137 mL/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female: 88–128 mL/min</td>
<td></td>
</tr>
<tr>
<td>Estriol, total (in pregnancy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 wk</td>
<td>6–18 mg/24 hr</td>
<td>21–62 μmol/24 hr</td>
</tr>
<tr>
<td>35 wk</td>
<td>9–28 mg/24 hr</td>
<td>31–97 μmol/24 hr</td>
</tr>
<tr>
<td>40 wk</td>
<td>13–42 mg/24 hr</td>
<td>45–146 μmol/24 hr</td>
</tr>
<tr>
<td>17-Hydroxycorticosteroids</td>
<td>Male: 3.0–9.0 mg/24 hr</td>
<td>8.2–25.0 μmol/24 hr</td>
</tr>
<tr>
<td></td>
<td>Female: 2.0–8.0 mg/24 hr</td>
<td>5.5–22.0 μmol/24 hr</td>
</tr>
<tr>
<td>17-Ketosteroids, total</td>
<td>Male: 8–22 mg/24 hr</td>
<td>28–76 μmol/24 hr</td>
</tr>
<tr>
<td></td>
<td>Female: 6–15 mg/24 hr</td>
<td>21–52 μmol/24 hr</td>
</tr>
<tr>
<td>Osmolality</td>
<td>50–1400 mOsm/kg</td>
<td></td>
</tr>
<tr>
<td>Oxalate</td>
<td>8–40 μg/mL</td>
<td>90–445 μmol/L</td>
</tr>
<tr>
<td>Proteins, total</td>
<td>&lt;150 mg/24 hr</td>
<td>&lt;0.15 g/24 hr</td>
</tr>
</tbody>
</table>
This page intentionally left blank
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