Student | CONSULT

Activate at studentconsult.com

Searchable Full Text Online

Rapid Review

PHYSIOLOGY

SECOND EDITION

THOMAS A. BROWN

Series Editor: EDWARD F. GOLJAN

ELSEVIER
MOSBY

RAPID REVIEW
PHYSIOLOGY

Rapid Review Series

SERIES EDITOR
Edward F. Goljan, MD

BEHAVIORAL SCIENCE, SECOND EDITION
Vivian M. Stevens, PhD; Susan K. Redwood, PhD; Jackie L. Neel, DO; Richard H. Bost, PhD; Nancy W. Van Winkle, PhD; Michael H. Pollak, PhD

BIOCHEMISTRY, THIRD EDITION
John W. Pelley, PhD; Edward F. Goljan, MD

GROSS AND DEVELOPMENTAL ANATOMY, THIRD EDITION
N. Anthony Moore, PhD; William A. Roy, PhD, PT

HISTOLOGY AND CELL BIOLOGY, SECOND EDITION
E. Robert Burns, PhD; M. Donald Cave, PhD

MICROBIOLOGY AND IMMUNOLOGY, THIRD EDITION
Ken S. Rosenthal, PhD; Michael J. Tan, MD

NEUROSCIENCE
James A. Weyhenmeyer, PhD; Eve A. Gallman, PhD

PATHOLOGY, THIRD EDITION
Edward F. Goljan, MD

PHARMACOLOGY, THIRD EDITION
Thomas L. Pazdernik, PhD; Laszlo Kerecsen, MD

PHYSIOLOGY, SECOND EDITION
Thomas A. Brown, MD

LABORATORY TESTING IN CLINICAL MEDICINE
Edward F. Goljan, MD; Karlis I. Sloka, DO

USMLE STEP 2
Michael W. Lawlor, MD, PhD

USMLE STEP 3
David Rolston, MD; Craig Nielsen, MD

RAPID REVIEW

PHYSIOLOGY

SECOND EDITION

Thomas A. Brown, MD
Clinical Educator and Hospitalist
Department of Medicine
St. Mary's Hospital
Waterbury, Connecticut
Assistant Professor of Medicine
Yale University School of Medicine
New Haven, Connecticut

MOSBY
ELSEVIER

ELSEVIER
MOSBY

1600 John F. Kennedy Blvd.
Suite 1800
Philadelphia, PA 19103-2899

RAPID REVIEW PHYSIOLOGY, SECOND EDITION ISBN: 978-0-323-07260-1

International Standard Book Number: 978-0-323-07260-1

Senior Acquisitions Editor: James Merritt
Developmental Editor: Christine Abshire
Publishing Services Manager: Anne Altepeter
Senior Project Manager: Beth Hayes
Design Direction: Steve Stave

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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

—TAB

This page intentionally left blank

CONTRIBUTORS

The following contributors are thanked for their input in the previous edition, which continues to add value to the book:

TEXT

David D. Brown, DO
Neurologist
Private Practice
Fountain Valley, California

Thomas A. Brown, MD
Clinical Educator and Hospitalist
Department of Medicine
St. Mary's Hospital
Waterbury, Connecticut
Assistant Professor of Medicine
Yale University School of Medicine
New Haven, Connecticut

Courtney Cuppett, MD
Resident, Obstetrics and Gynecology
West Virginia University School of Medicine
Ruby Memorial Hospital
Morgantown, West Virginia

Jason B. Harris, MD, MPH
Assistant Professor of Pediatrics
Harvard Medical School
Division of Infectious Diseases
Massachusetts General Hospital
Boston, Massachusetts

Jennie J. Hauschka, MD
Resident, Obstetrics and Gynecology
Carolinas Medical Center
Charlotte, North Carolina

Karen MacKay, MD
Associate Professor of Medicine and Nephrology
West Virginia University School of Medicine
Ruby Memorial Hospital
Morgantown, West Virginia

Ronald Mudry, MD
Fellow, Pulmonary and Critical Care Medicine
West Virginia University School of Medicine
Ruby Memorial Hospital
Morgantown, West Virginia

John Parker, MD
Chief, Section of Pulmonary and Critical Care Medicine
West Virginia University School of Medicine
Ruby Memorial Hospital
Morgantown, West Virginia

QUESTIONS

David D. Brown, DO
Neurologist
Private Practice
Fountain Valley, California

Thomas A. Brown, MD
Clinical Educator and Hospitalist
Department of Medicine
St. Mary's Hospital
Waterbury, Connecticut
Assistant Professor of Medicine
Yale University School of Medicine
New Haven, Connecticut

Courtney Cuppett, MD
Resident, Obstetrics and Gynecology
West Virginia University School of Medicine
Ruby Memorial Hospital
Morgantown, West Virginia

John Haughey, MD
Resident, Emergency Medicine
Albert Einstein College of Medicine
Beth Israel Medical Center
New York, New York

Ched Lohr, MD
Resident, Department of Radiology
Mercy Hospital
Pittsburgh, Pennsylvania

Quincy Samora, MD
Resident, Orthopedic Medicine
West Virginia University School of Medicine
Ruby Memorial Hospital
Morgantown, West Virginia

Alex Wade, MD
Resident, Internal Medicine
West Virginia University School of Medicine
Ruby Memorial Hospital
Morgantown, West Virginia

Melanie Watkins, MD
Resident, Department of Gynecology and Obstetrics
Emory University School of Medicine
Atlanta, Georgia

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.
- **Visual elements:** Abundant two-color schematics and summary tables enhance your study experience.
- **Two-color design:** Colored text and headings make studying more efficient and pleasing.

New! Online Study and Testing Tool

- A minimum of **350 USMLE Step 1–type MCQs:** Clinically oriented, multiple-choice questions that mimic the current USMLE format, including high-yield images and complete rationales for all answer options.
- **Online benefits:** New review and testing tool delivered via the USMLE Consult platform, the most realistic USMLE review product on the market. Online feedback includes results analyzed to the subtopic level (discipline and organ system).
- **Test mode:** Create a test from a random mix of questions or by subject or keyword using the timed **test mode.** USMLE Consult simulates the actual test-taking experience using NBME's FRED interface, including style and level of difficulty of the questions and timing information. Detailed feedback and analysis shows your strengths and weaknesses and allows for more focused study.
- **Practice mode:** Create a test from randomized question sets or by subject or keyword for a dynamic study session. The **practice mode** features unlimited attempts at each question, instant feedback, complete rationales for all answer options, and a detailed progress report.
- **Online access:** Online access allows you to study from an Internet-enabled computer wherever and whenever it is convenient. This access is activated through registration on www.studentconsult.com with the pin code printed inside the front cover.

Student Consult

- **Full online access:** You can access the complete text and illustrations of this book on www.studentconsult.com.
- **Save content to your PDA:** Through our unique Pocket Consult platform, you can clip selected text and illustrations and save them to your PDA for study on the fly!
- **Free content:** An interactive community center with a wealth of additional valuable resources is available.

Preface

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

This page intentionally left blank

ACKNOWLEDGMENT OF REVIEWERS

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:

Brent M. Ardaugh, Boston University School of Public Health

Merrian Brooks, Ohio University College of Osteopathic Medicine

Michael Cheng, David Geffen School of Medicine, University of California, Los Angeles

Amanda C. Chi, David Geffen School of Medicine, University of California, Los Angeles

Jarva Chow, MS, MPH, Georgetown University School of Medicine

Betty M. Chung, School of Osteopathic Medicine, University of Medicine and Dentistry of New Jersey

Rebecca Colleran, National University of Ireland, Galway

Mausam R. Damani, David Geffen School of Medicine, University of California, Los Angeles

Andrew J. Degnan, The George Washington University School of Medicine

Caroline Foust-Wright, MD, Maine Medical Center

Shari T. Jawetz, MD, New York Presbyterian Hospital–Weill Cornell

Victoria Kuohung, Boston University/Tufts University Combined Dermatology Residency Program

Jean-Pierre Muhumuza, Morehouse School of Medicine

Adaobi I. Nwaneshiudu, Temple University School of Medicine

Ike S. Okwuosa, Georgetown University School of Medicine

David Rand, Philadelphia College of Osteopathic Medicine

Michael E. Tedrick, West Virginia School of Osteopathic Medicine

Christopher S. Thom, University of Pennsylvania School of Medicine

We also thank the following reviewers of the first edition:

Jacob Babu, Sophie Davis School of Biomedical Education, City University of New York

Jay Bhatt, Philadelphia College of Osteopathic Medicine

Stephen Dolter, University of Iowa College of Medicine

Timothy Fagen, University of Missouri–Kansas City

Katherine Faricy, Jefferson Medical College

Veronica L. Hackethal, Columbia College of Physicians and Surgeons

Michael Hoffman, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey

Caron Hong, University of Hawaii at Manoa

Justin Indyk, State University of New York Stony Brook

David A. Kasper, DO, MBA, Philadelphia College of Osteopathic Medicine

Tyler J. Kenning, MD, Albany Medical Center

Maria Kirzhner, Kresge Eye Institute

Caroline Koo, State University of New York Downstate Medical Center

Michelle Koski, MD, Vanderbilt University Medical Center

Barrett Levesque, New York Medical College

James Massullo, Northeastern Ohio Universities College of Medicine

Todd J. Miller, University of Utah School of Medicine

Tiffany Newman, New York University School of Medicine

Adaobi Nwaneshiudu, Temple University School of Medicine

Josalyn Olsen, University of Iowa College of Medicine

Daniel Osei, University of Pennsylvania School of Medicine

Sachin S. Parikh, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey

Neil Patel, David Geffen School of Medicine, University of California, Los Angeles

Brad Picha, Case Western Reserve University School of Medicine

Stephan G. Pill, MD, MSPT, Hospital of the University of Pennsylvania

Keith R. Ridel, University of Cincinnati College of Medicine

Arjun Saxena, Jefferson Medical College

Sarah Schlegel, MD, Stony Brook University Hospital

Tana Shah, School of Osteopathic Medicine, University of Medicine and Dentistry of New Jersey

Yevgeniy Shildkrot, Kresge Eye Institute

Julia C. Swanson, Oregon Health & Science University

Ian Wong, MD, St. Vincent Hospital, Indiana University

Michael Yee, Sophie Davis School of Biomedical Education, City University of New York

Acknowledgments

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 naiveté, 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.

This page intentionally left blank

Contents

Chapter 1 Cell Physiology 1

Chapter 2 Neurophysiology 25

Chapter 3 Endocrine Physiology 65

Chapter 4 Cardiovascular Physiology 102

Chapter 5 Respiratory Physiology 138

Chapter 6 Renal Physiology 168

Chapter 7 Gastrointestinal Physiology 205

Chapter 8 Acid-Base Balance 228

Chapter 9 Sodium and Water Balance, Fluid Compartments 241

Common Laboratory Values 247

Index 251

This page intentionally left blank

CHAPTER 1

CELL PHYSIOLOGY

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).**

Cells: basic structural and functional unit of body

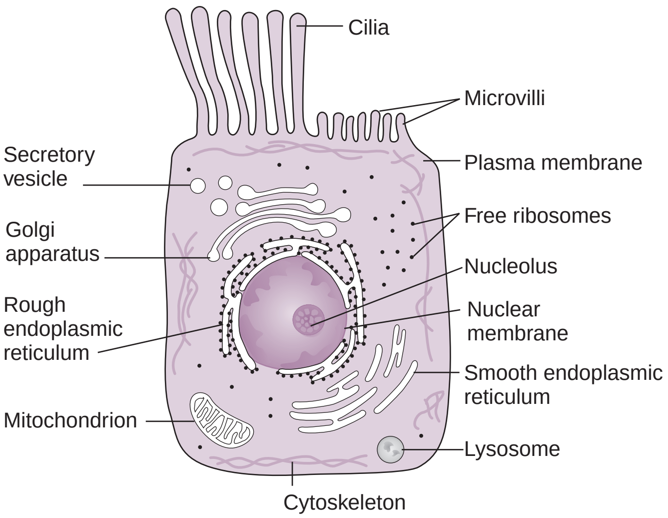
B. The cell membrane

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.

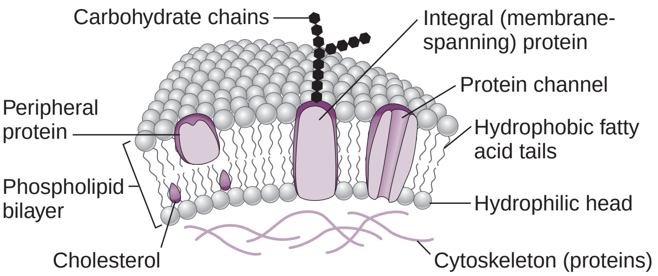
Cell membrane: lipid bilayer composed of phospholipids

Plasma membrane: permeable to steroids and other fat-soluble substances

Plasma membrane: impermeable to most hydrophilic substances, which require pores or transporter systems to penetrate membrane



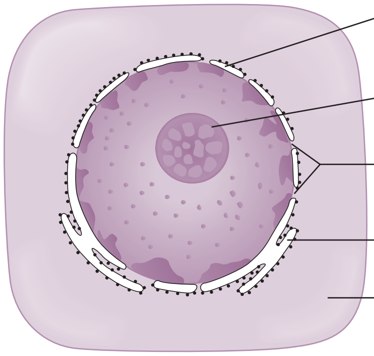
1-1: Structure of the generalized cell. Cells have specialized structures depending on their origin and function; the components common to most human cells are shown here.



1-2: The cell membrane.

TABLE 1-1. Types of Membrane Proteins

TYPE	FUNCTION	EXAMPLE	PATHOPHYSIOLOGY
Channel proteins	Transport of substances into the cell	Nicotinic receptor on muscle cells (ligand-gated Na^+ channel)	Myasthenia gravis
Enzymes	Catalyze reactions	Luminal carbonic anhydrase in the proximal convoluted tubule of the nephron	Proximal renal tubular acidosis
Receptor proteins	Mediate an intracellular response to extracellular ligands (e.g., hormones)	Insulin receptor	Insulin resistance in type 2 diabetes mellitus
Anchor proteins	Cell stabilization	Spectrin, Dystrophin	Hereditary spherocytosis Duchenne muscular dystrophy
Carrier proteins	Required for facilitated transport	GLUT4 (glucose-sodium symporter)	Diabetes mellitus
Identifier proteins	Identify a cell as "self" or "foreign" to the immune system	Major histocompatibility complex I	Expression down-regulated in virally infected cells



1-3: The nucleus. The outer layer of the nuclear envelope and the space between the two layers are continuous with rough endoplasmic reticulum (rER). Both the rER and the outer layer are studded with ribosomes. Chromatin is seen as heterochromatin, a highly compacted form that appears dark in micrographs, and euchromatin, a less compact form containing transcriptionally active DNA sequences.

Fluid mosaic model: describes ability of proteins to move freely within lipid bilayer

- The cell membrane is commonly described as a **fluid mosaic** because proteins can freely move within the phospholipid bilayer.

2. **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.

In select cell types, the plasma membrane is folded to ↑ surface area.

C. 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).**

Nucleus: contains most of a cell's DNA; complexed with histones as chromatin

Roles of the nucleus: transcription, regulation of cell division

Nucleolus: housed within the nucleus; synthesizes ribosomal RNA

D. 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.

Composition of cytosol: differs markedly from extracellular fluid in terms of electrolytes and pH

TABLE 1-2. Comparison of Intracellular and Extracellular Fluid Composition

COMPONENT	INTRACELLULAR FLUID	EXTRACELLULAR FLUID
Sodium (mEq/L)	5-15	145
Potassium (mEq/L)	140	5
Calcium (mEq/L)	10^{4-}	1-2
Mg^{2+} (mEq/L)	0.5	1-2
Cl^- (mEq/L)	5-15	110
pH	7.2	7.4

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.

Rough ER: protein synthesis

Smooth ER: drug detoxification; lipid and carbohydrate synthesis

   - **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

Golgi apparatus: post-translational modification of proteins, packaging of substances for intracellular or extracellular delivery, maintenance of plasma membrane

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.

Lysosomes: important in endocytosis, phagocytosis, autophagy

Acidic pH of lysosomes: removes M6P tags from proteins delivered to lysosomes from 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.

Mitochondria: contain their own DNA encoding for mitochondrial proteins and transfer RNA

Mitochondrial energy production: occurs through aerobic metabolism; defective in LHON (see clinical note below)

Mitochondrial DNA: inherited maternally

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.

Cytoskeleton: provides structural support and flexibility to cell, aids in cell motility and division

Microfilaments: myriad functions; composed of G actin

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 1-3. Lysosomal Storage Diseases

DISEASE	DEFECT	PATHOPHYSIOLOGY	INHERITANCE
Niemann-Pick disease	Deficiency of sphingomyelinase	Accumulation of sphingomyelin and cholesterol	Autosomal recessive; death by age 3 yr
Tay-Sachs disease	Absence of hexaminosidase	Accumulation of GM_2 ganglioside	Autosomal recessive; death by age 3 yr; cherry-red spot on macula
Krabbe disease	Absence of galactosylceramide β-galactosidase	Accumulation of galactocerebroside	Autosomal recessive; optic atrophy, spasticity, early death
Gaucher disease	Deficiency of β-glucocerebrosidase	Glucocerebroside accumulation in liver, brain, spleen, and bone marrow	Autosomal recessive; "crinkled paper" appearance of cells
Fabry disease	Deficiency of α-galactosidase A	Accumulation of ceramide trihexosidase	X-linked recessive
Hurler syndrome	Deficiency of α-L-iduronidase	Clouding of cornea, mental retardation	Autosomal recessive
Hunter syndrome	Deficiency of iduronate sulfatase	Mild form of Hurler syndrome; no corneal clouding, mild mental retardation	X-linked recessive

TABLE 1-4. Overview of Cytoskeletal Proteins

COMPONENTS	PROTEIN	SIZE	CELL LOCATION	FUNCTIONS	PATHOPHYSIOLOGY
Microfilaments	G actin	Small (5-9 nm), thin, and flexible	Form cortex layer just under the plasma membrane	Mechanical support of cell membrane, cell flexibility, cell motility, polarity of the plasma membrane	*Listeria monocytogenes* spreads from cell to cell by inducing actin polymerization.
Intermediate filaments	Heterogeneous group of proteins	Intermediate (∼10 nm)	Widely distributed	Mechanical stability to cells	Epidermolysis bullosa—blister formation in response to mechanical stress
Microtubules	Tubulin	Large (∼25 nm), wide, and stiff	One end attached to a centrosome	Cell division, intracellular movement of organelles Components of cilia and flagella	Antimitotic drugs (e.g., colchicine, vincristine, vinblastine) inhibit microtubule function. Dysfunction can lead to disorders such as immotile cilia syndrome and male infertility.

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.**

Microtubules: composed of tubulin; components of cilia and flagella

Intermediate filaments: most abundant of cytoskeletal elements

Intermediate filaments: form desmosomes and hemidesmosomes; example: spectrin

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.

Microvilli: projections of plasma membrane which ↑ surface area; present in small intestines and proximal tubule of nephron

Centrioles: composed of microtubules; present in centrosome; spindle fibers separate chromosome pairs

Cilia: motile or nonmotile; defective in Kartagener syndrome

Kartagener syndrome: ciliary dysmotility, bronchiectasis, chronic sinusitis, situs inversus

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.

Flagella: important in cell locomotion; present on sperm

Ribosomes: complexes of RNA and protein, which catalyze protein synthesis using messenger and transfer RNA

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.

Function of tight junctions: prevent most movement between cells, maintain membrane polarity in terms of protein distribution between apical and basolateral membranes

Gap junctions: connect the cytoplasm of adjacent cells; important in cardiac muscle and skin

Desmosomes: cell-to-cell spot adhesions present on lateral membrane of cells, which help resist shearing forces in squamous epithelium

Hemidesmosomes: serve to attach a cell to the ECM; composed of cell adhesion proteins such as integrin

- 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 **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 **GPIIb/IIIa** receptor on platelets, thereby preventing platelet aggregation and thrombus formation. Integrilin is commonly used during angioplasty in high-risk cardiac patients.

Simple diffusion: movement of substance down its concentration gradient across semipermeable membrane; no energy or transporter required

Diffusion of uncharged substances: $J = PA(\Delta C)$

Diffusion of charged substances: may not necessarily flow down their concentration gradient depending on electrical potential across membrane

Cations: tend to diffuse into cells

Anions: tend to diffuse out of cells

Nonpolar substances such as gases easily diffuse across lipid bilayer

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** (ΔC), 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 (ΔP), the **surface area** of the cell (A), the **diffusivity coefficient** (d), and the **thickness** of the membrane (T):

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

Diffusion of gases: $V_g = \Delta P \times A \times d/T$

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
        - Osmotic pressure increases with increased solute concentration.
     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 (π) 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 (σ; varies from 0 to 1), the gas constant (R), and the absolute temperature (T).
     b. van't Hoff's law estimates osmotic force as

$$\pi = gC\sigma RT$$

        - 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.

Osmosis: diffusion of water from high to lower concentration across semipermeable membrane

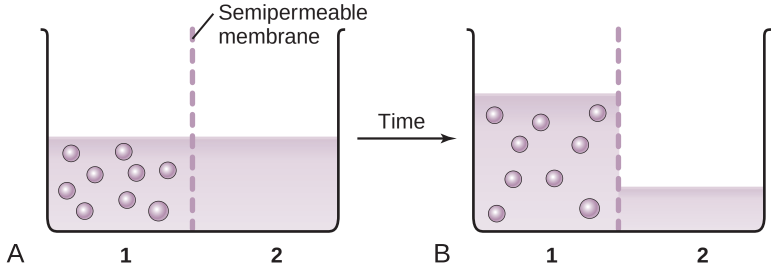
Osmotic pressure: generated by solute concentration gradient across semipermeable membrane, promotes osmosis

van't Hoff's law: $\pi = gC\sigma RT$

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, D-glucose but not L-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, D-galactose binds to and is transported by the same GLUT4 transporter as D-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_m)** has been reached; the substance can no longer bind to its carrier and therefore cannot pass through the membrane (Fig. 1-5).

Stereospecificity of transport proteins: recognize only a single isomer of a substance

Transport maximum: above this transport rate, the substance can no longer be transported into cells

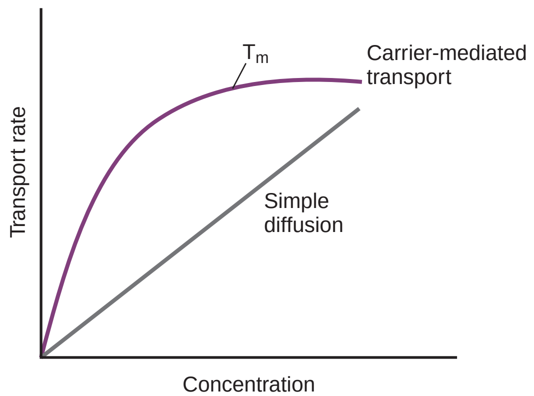


1-4: Osmosis. **A,** Solution 1 has higher osmotic pressure (hypertonic) than solution 2 (hypotonic). **B,** Water has flowed from the hypotonic solution into the hypertonic solution as a result of the driving force of osmotic pressure.

TABLE 1-5. Examples of Transmembrane Transport Molecules

MECHANISM AND ENERGY SOURCE	TRANSPORTER	FUNCTION	CLINICAL AND THERAPEUTIC RELEVANCE
Facilitated diffusion: No additional energy required	Glucose- facilitated transporter 4 (GLUT4)	Transport glucose into cells	Deficient expression in diabetes results in impaired glucose metabolism.
	Voltage-gated Na^+ channel	Generation and propagation of action potentials	Inhibited by tetrodotoxin (puffer fish) and saxitoxin (contaminated shellfish)
Primary active transport: ATP hydrolysis	Na^+,K^+-ATPase (sodium) pump	Electrogenic pump that contributes to maintenance of resting membrane potential	Inhibited by digitalis (naturally occurring toxin); derivative, digoxin, used in treatment of congestive heart failure
	Ca^{2+}-ATPase	Maintains low cytoplasmic concentration of calcium	Inhibited by dantrolene (used in treatment of malignant hyperthermia)
	H^+,K^+-ATPase (sodium) pump	Contributes to low pH of gastric secretions and acid secretion of distal convoluted tubule of the nephron	Inhibited by omeprazole (used to treat GERD and peptic ulcer disease)
Secondary active transport (cotransport): Energy derived from transport of Na^+ down its concentration gradient	Na^+-glucose cotransporter	Actively transports glucose into cells against concentration gradient, along with 2 Na^+ Located in gastrointestinal mucosa and PCT of the nephron	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^+.
	Na^+-K^+-$2Cl^-$ cotransporter	Pumps 1 Na^+, 1 K^+, and 2 Cl^- into cells Has important role in thick ascending limb of loop of Henle	Inhibited by loop diuretics (e.g., furosemide). The nephron becomes unable to concentrate urine, resulting in loss of NaCl, K^+, and fluid.

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.

Facilitated transport: occurs *down* electrochemical gradient; requires carrier transport molecules

- **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.

- **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 **Ca^{2+}-ATPase pump** in muscle cells.

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, Ca^{2+}-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^+-Ca^{2+} countertransporter** of heart muscle cells moves Ca^{2+} against its concentration gradient as Na^+ moves down its concentration gradient) (Fig. 1-6).

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

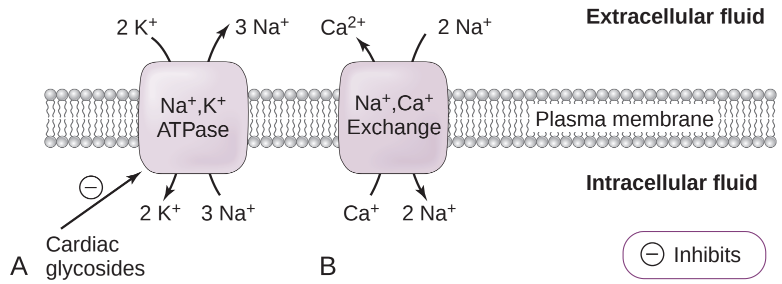
Countertransport: substances move in opposite directions

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 Ca^{2+}-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.**

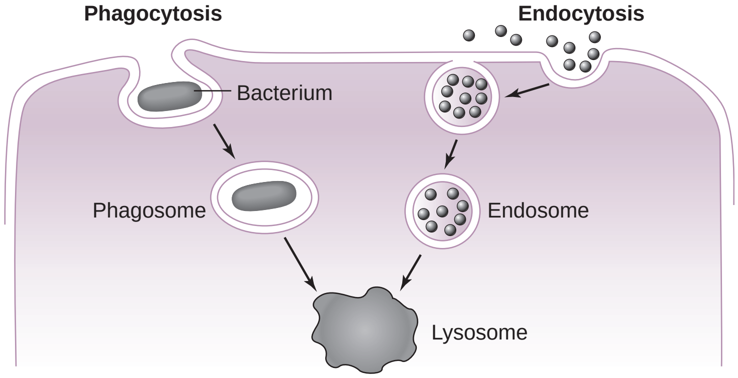
Endocytosis: internalization of a membrane-bound vesicle containing extracellular material

Pinocytosis: random sampling of extracellular fluid through endocytotic vesicles



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^+,Ca^{2+} countertransporter.

1-7: Vesicular transport.



Receptor-mediated endocytosis: receptors located on clathrin-coated pit → complex is internalized after ligand binding

Fusing of the internalized clathrin-coated vesicle with acidic environment of early endosome → recycling of clathrin to cell membrane

Examples of substances transported through receptor-mediated endocytosis: LDL, transferrin

- When a ligand binds to its receptor, this clathrin-coated pit invaginates and forms an endocytotic 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: actin-mediated process whereby membranous extensions engulf solid particles and internalize them

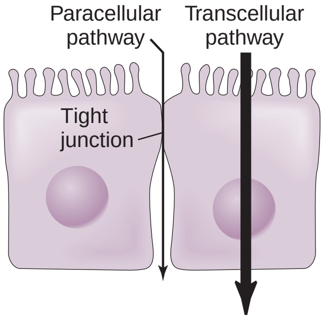
Oxidative burst: critical for degradation of phagosomal contents

Phagocytosis: part of innate immunity; carried out in neutrophils and macrophages; defects result in diseases such as chronic granulomatous disease

- **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_2O_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.



1-8: Transcellular and paracellular transport.

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.

Exocytosis: triggered by ↑ in intracellular calcium

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.

Paracellular transport: occurs across "leaky" tight junctions; example: proximal convoluted tubule of nephron

Transcellular transport: facilitated by polarized nature of epithelial and endothelial membranes

Convection: transport of substances by the movement of a medium

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.**

RMP: dependent on concentration difference and on permeant ions across cell membrane as well as equilibrium potential of ions

RMP is a negative value in most cells.

Negative RMP "powers" 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:

Selective permeability of membranes: a dynamic property; just think of changes in membrane permeability to various ions during an action potential

Equilibrium potential: membrane potential at which there is no *net* diffusion of the ion across the membrane

$E_X = -61 \log([X_{in}]/[X_{out}])$

$E_{K+} = -61 \log 150/5 = -90$ mV

$$E_{K^+} = \frac{-61 \log 150}{5}$$
$$= -90\,mV$$

- 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.

No net K^+ flux when membrane potential is −90 mV

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).

$Em = P_{Na}(E_{Na}) + P_K(E_K) + P_{Cl}(E_{Cl})$

RMP: reflects equilibrium potential of most permeable ions and those with highest equilibrium potential

Contribution of K^+ to RMP: most permeable ion → makes largest contribution to RMP

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^+).

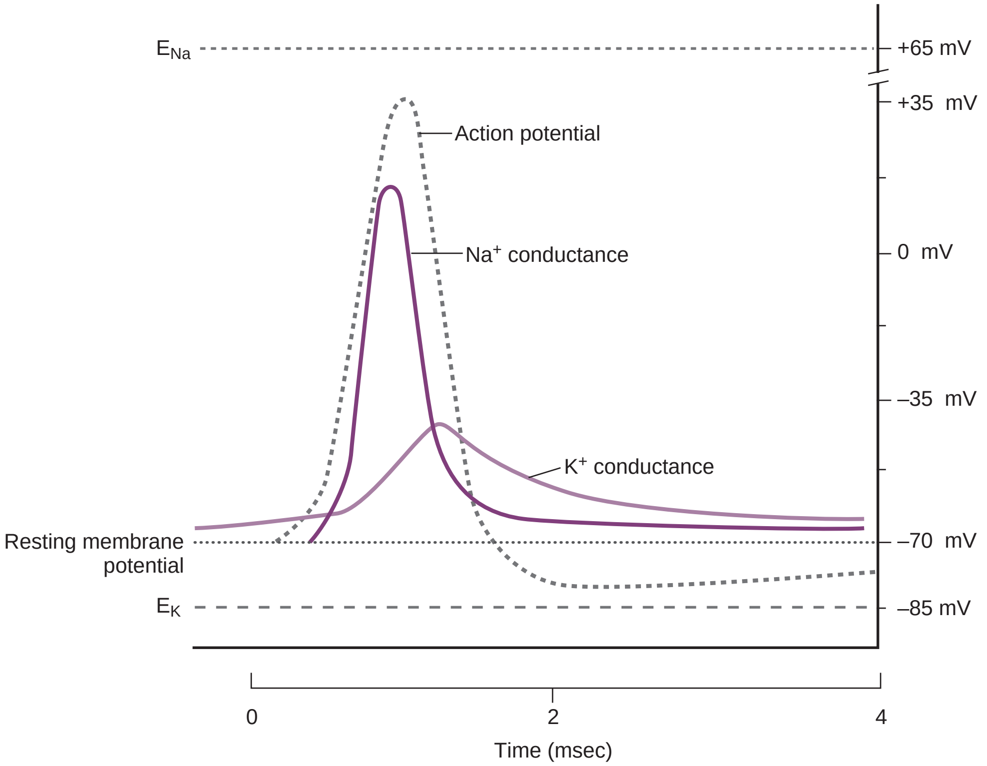
Intracellular fixed anions: unable to diffuse out of cells; draw in cations such as K^+

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.

Na^+,K^+-ATPase pump: maintains concentration gradient for Na^+ and K^+ across cell membrane

Na^+,K^+-ATPase pump: electrogenic by virtue of removing 3 Na^+ ions for every 2 K^+ ions that enter the cell—that is, creates negative intracellular electrical potential

B. Action potentials (Fig. 1-9)



1-9: Changes during generation of an action potential. *E_K*, Equilibrium potential for K^+; *E_{Na}*, equilibrium potential for Na^+.

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.

Action potential: rapid alteration in membrane potential that occurs in *excitable* tissues in response to various stimuli

Threshold value: membrane potential once reached at which fast, voltage-gated Na^+ channels open

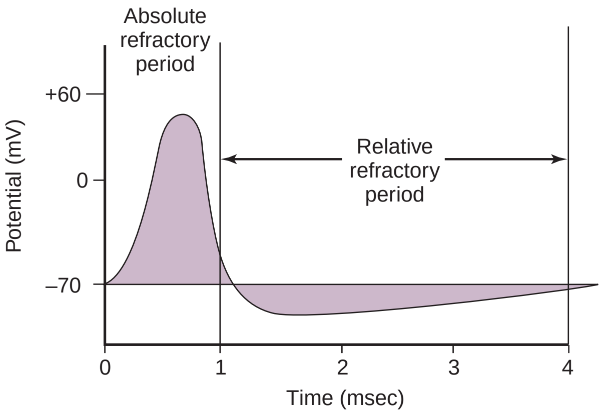
Hyperpolarization phase: slight delay in which Na^+, K^+-ATPase pump reestablishes the original transmembrane Na^+ and K^+ gradients

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

↑ Stimulus intensity →↑ frequency of action potential generation, although action potential amplitude will remain unchanged.

Refractory periods: prevent tetany

Absolute refractory period: action potential cannot be generated regardless of stimulus intensity; occurs during depolarization phase



1-10: Refractory periods.

Relative refractory period: only much larger than normal stimulus intensity can generate an action potential; occurs during repolarization phase

- 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.

e. **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.

Action potentials travel along axon without decrease in signal strength because of insulating protein myelin.

Where myelin is absent (nodes of Ranvier), the action potential travels by saltatory conduction.

- **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.

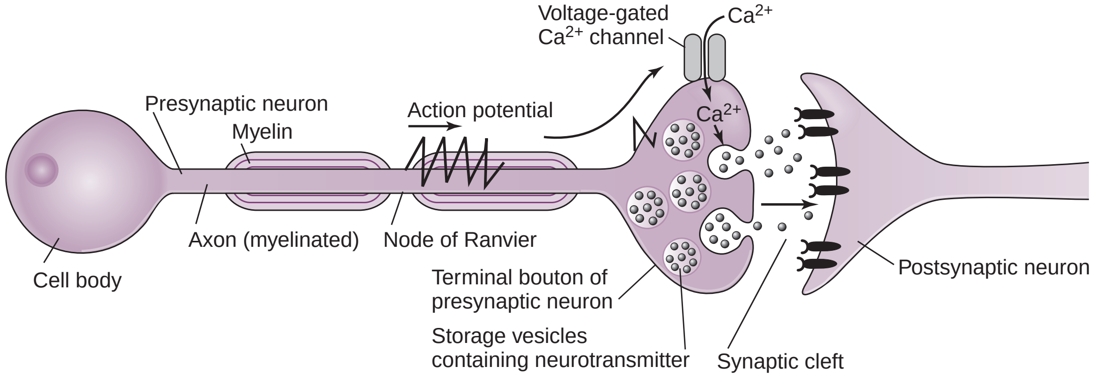
Electrical transmission: action potentials transmitted from cell to cell through gap junctions; occurs in cardiac and smooth muscle

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

Chemical transmission: primary form by which action potentials are generated



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.

Chemical transmission: neurotransmitter binds postsynaptic ligand-gated receptor → depolarization → action potential

Action potential traveling to terminal bouton triggers Ca^{2+} influx and release of neurotransmitter into synaptic cleft

Binding of neurotransmitter to postsynaptic ligand-gated receptor → EPSP or IPSP

If summation of EPSPs and IPSPs reaches threshold at axon hillock → action potential generated

Synaptic neurotransmitters degraded by enzymes in synaptic cleft or removed by endocytosis to prevent excessive postsynaptic stimulation

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.

Conduction velocity: dependent on myelin and axon diameter

Unmyelinated axons: much slower conduction velocity because of absence of nodes of Ranvier

↓ Distance between nodes of Ranvier → ↓ conduction velocity

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.

Pathophysiology of cholinergic transmission: myasthenia gravis, Parkinson disease, Alzheimer dementia

- 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.**

Glutamate: primary stimulatory neurotransmitter of the central nervous system; excess activity → 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.

GABA: primary inhibitory neurotransmitter of the brain; pathophysiology: Huntington disease

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.

Glycine: primary inhibitory neurotransmitter of spinal cord; pathophysiology: tetanus toxicity

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 spasmic 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)**.

Monoamines: norepinephrine, serotonin, dopamine; degraded by MAO and 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.

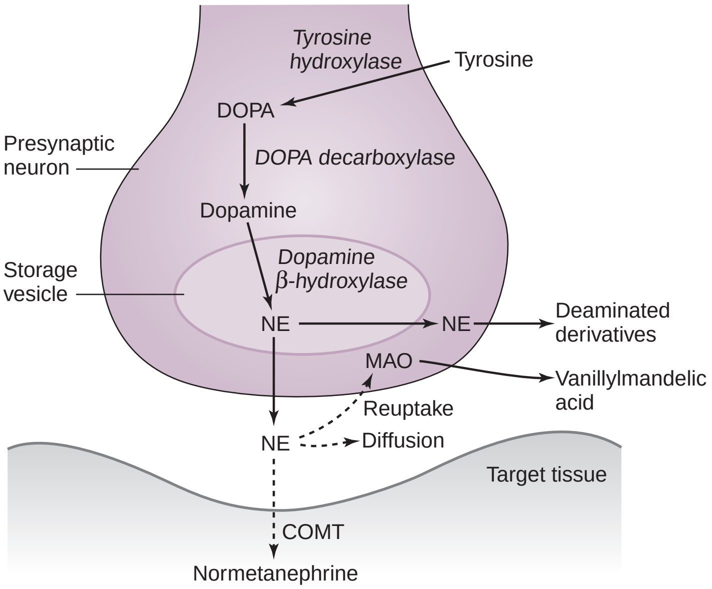
- **Norepinephrine: adrenergic transmission** (Fig. 1-12)
  a. Derived from the amino acid **tyrosine**
  b. Synthesized and released by the **sympathetic nervous system, adrenal medulla,** and **locus ceruleus** of the central nervous system

Norepinephrine: synthesized by sympathetic neurons, adrenal medulla, locus ceruleus

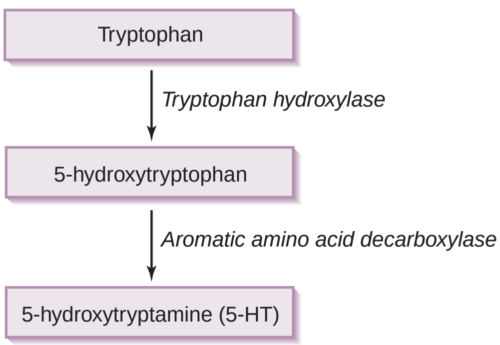
Clinical note: Cocaine is a centrally acting norepinephrine reuptake inhibitor.

- **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.

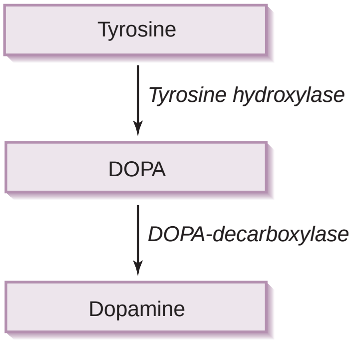
Serotonin: although most is located in the enteric nervous system, serotonin is best known for its role in depression and mood disorders



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



1-13: Synthesis of serotonin (5-hydroxytryptamine).



1-14: Synthesis of dopamine. *DOPA*, L-dihydroxyphenylalanine.

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

Dopaminergic pathways: nigrostriatal, mesolimbic, tuberoinfundibular pathways

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.

Neuropeptides: alter gene expression → longer duration of action

Cotransmission: release of multiple substances simultaneously from presynaptic neuron, allowing for more complex communication between neurons

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.

NMJ: composed of a presynaptic motor neuron, synaptic cleft, and postsynaptic membrane; synonymous with motor end plate

AP triggers exocytosis of ACh from presynaptic neuron by influx of Ca^{2+}.

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.**

Synaptic delay: time required for ACh to diffuse across synaptic cleft and bind postsynaptic nicotinic receptors

End-plate potential: local postsynaptic membrane depolarization created by binding of ACh to nicotinic receptors

If end-plate potential reaches threshold → action potential generated

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).

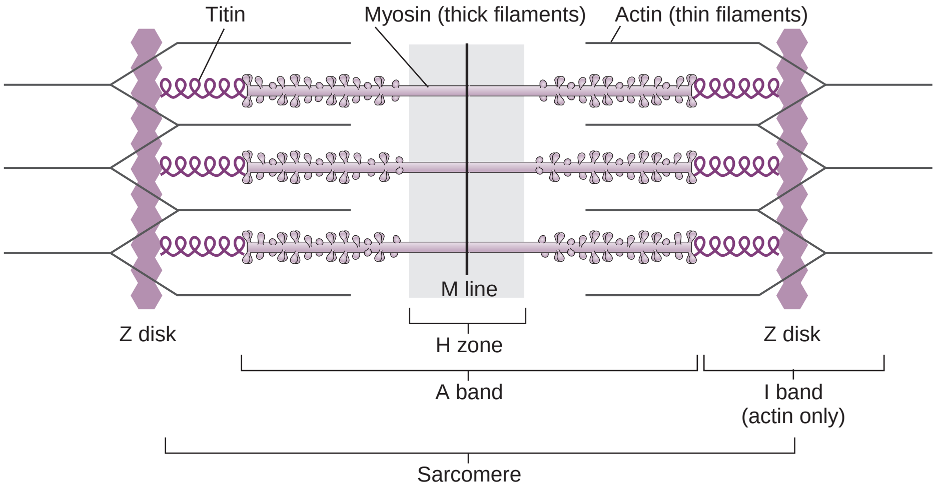
TABLE 1-6. Comparison of the Steps Involved in Synaptic Transmission at Neuron-to-Neuron Junctions and the Neuromuscular Junction

NEURON TO NEURON	NEUROMUSCULAR JUNCTION
An action potential in presynaptic neuron causes release of neurotransmitter from vesicles stored in terminal bouton.	An action potential in presynaptic neuron causes release of acetylcholine (ACh) from vesicles stored in terminal bouton.
Diffusion of neurotransmitter across synaptic cleft	Diffusion of ACh across synaptic cleft
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.	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).
To prevent repetitive stimulation, neurotransmitters are either degraded in the presynaptic cleft or taken up by endocytosis in presynaptic cell.	Acetylcholinesterase breaks down ACh into acetyl coenzyme A and choline, which are taken up into the presynaptic cell.

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

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

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



1-15: Structure of the sarcomere.

IV. Skeletal Muscle

A. Structure

Skeletal muscle: joins bone to bone; cells large diameter and multinucleated

Transverse (T) tubules: interconnect sarcolemma membrane and sarcoplasmic reticulum

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).

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**

Calcium-induced Ca^{2+} release: action potential transmitted from sarcolemma to T tubules → Ca^{2+} release from sarcoplasmic reticulum

Binding of Ca^{2+} to troponin → conformational change in troponin → tropomyosin displaced → myosin binding to actin (cross-bridging)

Sliding of filaments: dependent on repetitive cycles of cross-bridging, pivoting, and detachment of actin and myosin

Cross-bridge cycling shortens the sarcomeres, pulling the Z disks closer together, and muscle contracts.

Muscle relaxation: energy-requiring process dependent on pumping Ca^{2+} back into sarcoplasmic reticulum

Absence of Ca^{2+} → ↓ binding to troponin → tropomyosin resumes original conformation → no more actin-myosin binding

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.

Strength of contraction: depends on number of muscle fibers recruited

Tetanus: high-frequency stimulation → summation of muscle twitches → tetany

Isotonic muscle contraction: constant force produced in setting of changing muscle length

Isometric muscle contraction: constant force produced in setting of unchanging muscle length

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).
   - If the sarcomere is shortened, the actin and myosin have less room to overlap and develop tension.
   - 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

Motor unit: a single α-motor neuron and all of the corresponding muscle fibers it innervates

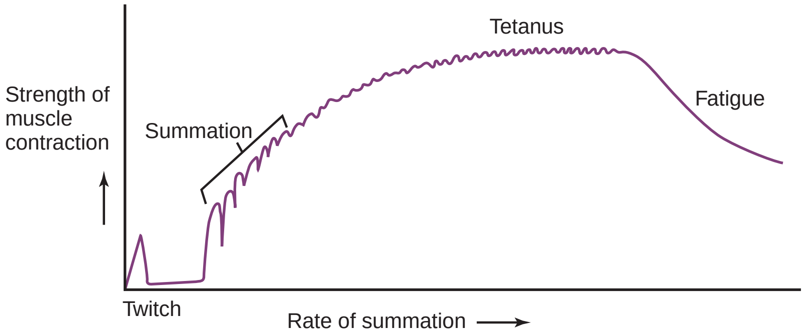
The smaller the motor unit (i.e., the fewer muscle fibers supplied by a motor unit), the more precise the control of the muscle

Creation of muscle tension: determined by degree of actin-myosin myofilament overlap

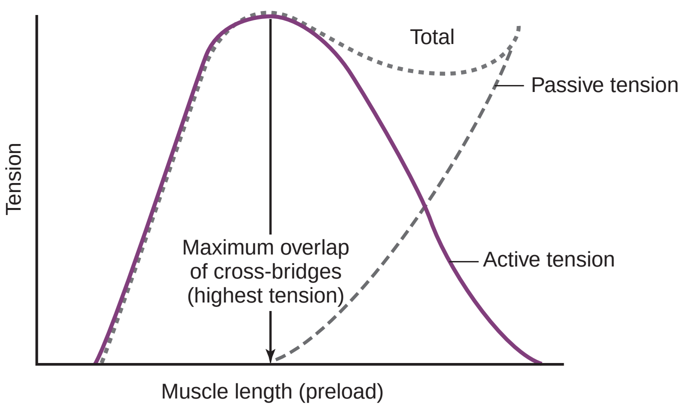
Length-tension relationship: similar to the Frank Starling relationship in cardiac physiology: the greater the length and corresponding actin-myosin overlap (to a point), the greater the tension developed

Fast-twitch fibers: use glycogen and anaerobic metabolism → fatigue easily but good for explosive high-intensity activity of short duration

Fast-twitch fibers: very little myoglobin → whitish in color



1-16: Types of muscle contraction.



1-17: Length-tension relationship in skeletal muscle.

TABLE 1-8. Types of Skeletal Muscle Fiber

CHARACTERISTIC	SLOW-TWITCH	FAST-TWITCH
Appearance	"Red" muscle	"White" muscle
Example	Soleus	Stapedius
Metabolism	Primarily aerobic	Primarily anaerobic
Diameter of fiber	Small	Large
Mitochondria	More	Fewer
Capillary supply	Higher	Lower
Myoglobin	Higher	Lower
Sensitivity to hypoxia	Higher	Lower
Resistance to fatigue	Higher	Lower

Slow-twitch fibers: use aerobic metabolism so do not fatigue easily; rich in myoglobin → red appearance; common in muscles controlling posture

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

Smooth muscle: typically arranged around hollow organs; contraction reduces lumen diameter

Smooth muscle cells: nonstriated in appearance because of lack of sarcomeres

Absence of sarcomeres → contraction *not* dependent on length-tension relationship

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

Visceral smooth muscle: predominant type of smooth muscle in body; functions as syncytium

Unstable RMP of smooth muscle in intestinal tract: gives rise to slow waves and spike potentials

Multiunit smooth muscle: much less abundant than single-unit smooth muscle; does not function as syncytium; regulated by the autonomic nervous system

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.

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 interstitium, 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.

Slow waves → spike potentials → muscle contraction

Sustained contraction: involves Ca^{2+} binding to calmodulin and activating myosin light-chain kinase

Smooth muscle relaxation: requires active pumping of Ca^{2+} into sarcoplasmic reticulum

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.

Smooth muscle contraction: typically not under voluntary control but can be affected by the autonomic nervous system

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.

Cardiomyocytes: interconnected through gap junctions → syncytium; sarcomeres cause striated 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.

Cardiac mechanism of contraction: sliding filament mechanism; extracellular Ca^{2+} plays important role; contraction in "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.**

RMP potential of cardiac cells: unstable → pacemaker activity

Effects of SNS: + chronotropy, + dromotropy, + inotropy, + lusitropy

Effects of PNS: − chronotropy, − dromotropy, − inotropy

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

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

CREST, Calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia.

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.

Chapter 2

Neurophysiology

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.

Nervous system: allows one to think, move, feel, experience, and manipulate one's environment

CNS: comprises the brain and spinal cord

Nervous system: anatomically divided into CNS and PNS

PNS: functionally divided into somatic and autonomic components

Somatic nervous system: controls voluntary actions

Somatic nervous system: comprises afferent and efferent loops; requires conscious processing

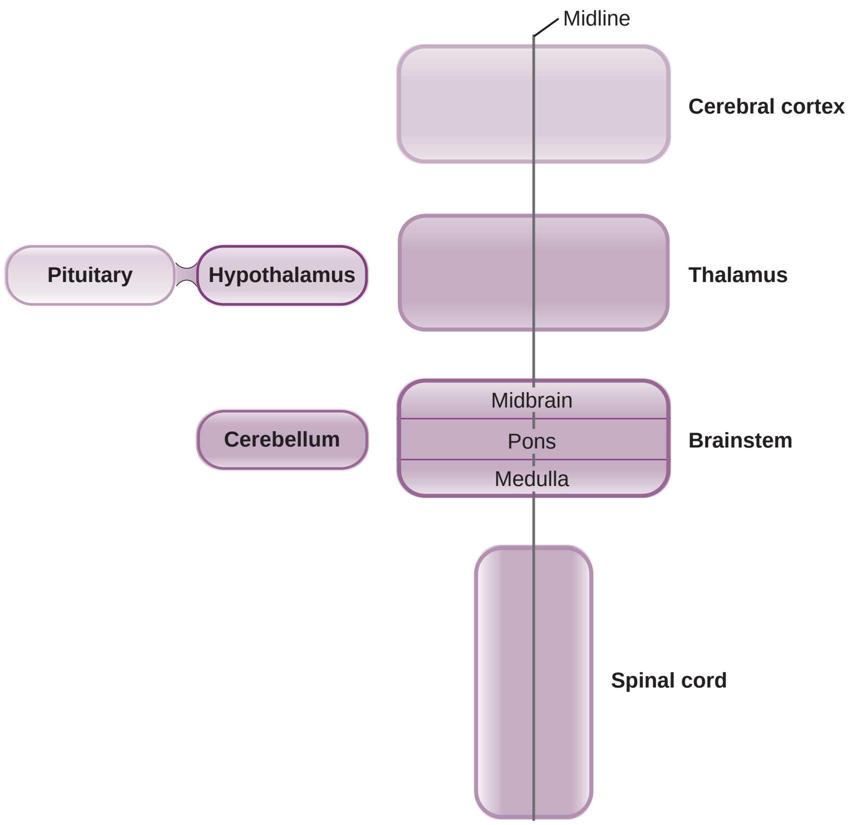
Autonomic nervous system: controls involuntary actions; active at subconscious level

ANS comprises sensory and motor loops between visceral organs and CNS.

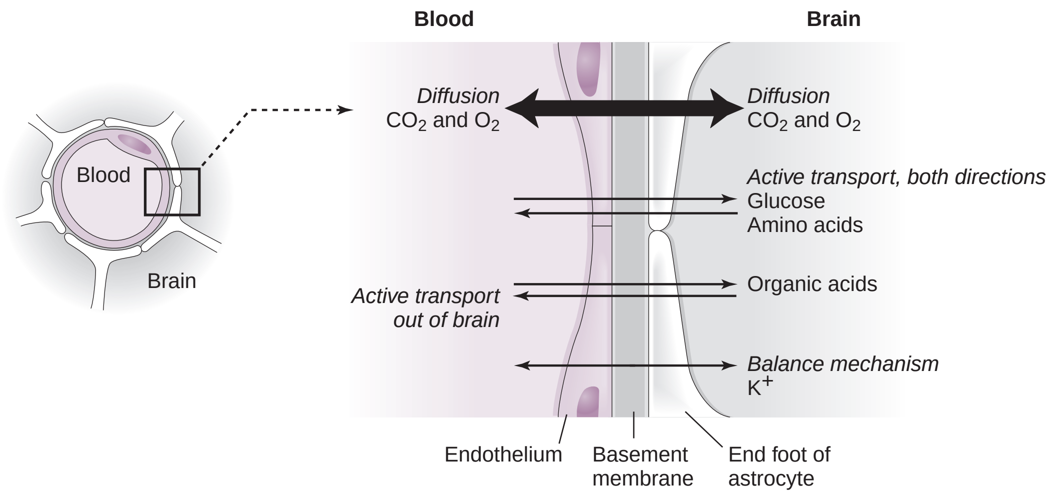
ANS: subdivided into parasympathetic, sympathetic, and enteric nervous systems

Protection of the brain: ensured by blood-brain barrier and blood-CSF barrier

BBB: endothelial cells connected by tight junctions with underlying basement membrane and surrounding astrocytes



2-1: Components of the central nervous system. *(From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 3-2.)*



2-2: Blood-brain barrier.

BBB: lipid-soluble substances cross easily

BBB: active transport systems in place for substances such as organic acids and K^+ ions

Parts of brain outside BBB: pineal gland, chemoreceptor trigger zone

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^+ 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.

Blood-CSF barrier: comprises highly vascular choroid plexus epithelial cells connected by tight junctions

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.

ANS: controls visceral functions of the body such as heart and respiratory rate through hypothalamic and brainstem "centers"

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.

Operation of the ANS: acts through visceral reflexes

ANS efferents: travel through sympathetic or parasympathetic nerves

ENS: regulates gastrointestinal activity but greatly influenced by both arms of the ANS

Example of visceral reflex: shivering and peripheral vasoconstriction in response to cold

Sympathetic nervous system: fight-or-flight system

Sympathetic nervous system–mediated actions: tachycardia, dilated pupils, diaphoresis, gluconeogenesis, ↓ blood flow to intestines and kidneys

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

TARGET ORGAN	SYMPATHETIC	PHYSIOLOGIC MECHANISM	PARASYMPATHETIC	PHYSIOLOGIC MECHANISM
Eyes	Pupil dilation (mydriasis)	Pupil dilation from contraction of dilator pupillae (radial fibers of iris)	Pupil constriction (miosis)	Contraction of sphincter pupillae (circular fibers of iris)
Bronchioles	Bronchodilation	β_2-Mediated smooth muscle relaxation	Bronchoconstriction	M3-mediated smooth muscle contraction
Kidney	↓ Renal perfusion, ↑ renin secretion	α_1-Mediated vasoconstriction and β_2- mediated renin secretion	Very limited innervation	No
Heart	↑ Heart rate, ↑ stroke volume, ↑ cardiac output	↑ Permeability nodal tissue to Na^+ ions, ↑ sensitivity of cardiomyocytes to calcium ions	↓ Heart rate, ↓ stroke volume, ↓ cardiac output	Increased permeability of nodal tissue to potassium ions
Gastrointestinal tract	↓ Digestion and motility	Stimulates sphincter muscle contraction and splanchnic vasoconstriction	Promotes digestion	Stimulates intestinal secretions and peristalsis, inhibits sphincter muscle contraction
Bladder	Urinary retention	Constricts sphincter, relaxes detrusor muscle	Stimulates urination	Relaxes sphincter, contracts detrusor muscle
Sweat glands	↑ Sweating	Postganglionic sympathetic cholinergic transmission	↑ Sweating	Postganglionic parasympathetic cholinergic transmission
Penis	Ejaculation		Erection	Vasodilation

- 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)

Anatomy of sympathetic nerves: comprises preganglionic and postganglionic fibers

Sympathetic preganglionics: originate from T1 to L2

- 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 through the white rami 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

Sympathetic postganglionics: project from paravertebral or peripheral ganglion to effector organ

Adrenal medulla: can be considered a specialized ganglion of sympathetic nervous system

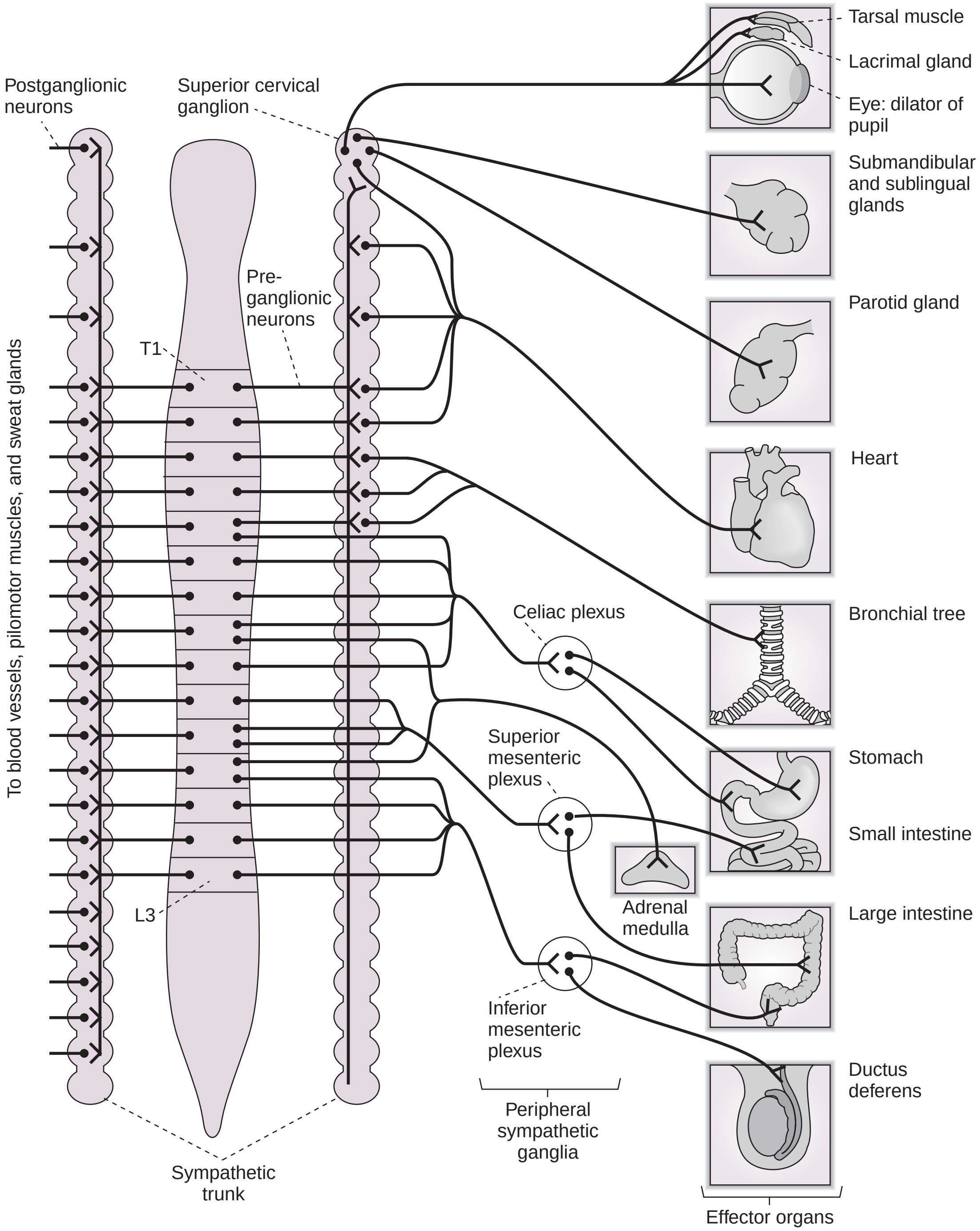
- The **postganglionic** fiber then exits the ganglion and projects to the **effector organ.**
- The **adrenal medulla** is a specialized ganglion of the **sympathetic division** that synthesizes and secretes **epinephrine** and **norepinephrine.**
- Preganglionic sympathetic fibers pass, without synapsing, 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.

Parasympathetic nervous system: rest-and-digest system

PNS-mediated actions: pupil constriction, glycogen storage, intestinal activity promoted, relaxation of skeletal muscle

c. The **parasympathetic division: "rest and digest" system**

- The parasympathetic nervous system is called the *rest-and-digest system* because it is most active in times of rest, relaxation, and rejuvenation.
- For instance, when a person is relaxed, his or her parasympathetic nervous system is in control.
- Pupils are constricted, glycogen is being stored, and digestion is occurring.



2-3: The sympathetic nervous system. *L*, Lumbar; *T*, thoracic.

- 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.**

Anatomy of parasympathetic nerves: also comprise preganglionic and postganglionic fibers

PNS: "craniosacral" outflow from brainstem and S2-S4 of spinal cord

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

	AUTONOMIC		SOMATIC	
CHARACTERISTIC	SYMPATHETIC	PARASYMPATHETIC	SENSORY	MOTOR
Preganglionic neuron origin of ANS or location of cell body of first-order neuron in somatic nervous system	Spinal cord segments T1-12, L1-3	Cranial nerve nuclei III, VII, IX, and X; spinal cord segments S2-4	Dorsal root ganglia	Anterior horn of spinal cord
Preganglionic neuron length	Short	Long		
Preganglionic neurotransmitter	ACh	ACh		
Ganglia location	Paravertebral chain	Near effector organ		
Postganglionic receptor	Nicotinic	Nicotinic		
Postganglionic neuron length	Long	Short		
Postganglionic neurotransmitter	Norepinephrine (except sweat glands, which are ACh)	ACh	ACh (at synapses in spinal cord)	ACh (at synapse in neuromuscular junction)
Effector organs	Cardiac and smooth muscle, glands	Cardiac and smooth muscle, glands	Brain and spinal cord	Skeletal muscle
Effector organ receptors	α_1, α_2, β_1, β_2	Muscarinic	Nicotinic	Nicotinic

ACh, Acetylcholine; *ANS,* autonomic nervous system.
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.

Anatomy of PNS: long preganglionics to effector organ; short postganglionics

Enteric nervous system: comprises submucosal and myenteric plexuses; entirely contained within gut wall

- 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 inhibits peristalsis and increases sphincter tone, thereby inhibiting digestion.
  (2) The parasympathetic system promotes peristalsis and relaxes the sphincters, thereby enhancing digestion.

Effect of ANS on ENS: sympathetic—inhibits peristalsis, ↑ sphincter tone, inhibits digestion; parasympathetic—relaxes sphincters, stimulates peristalsis and 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 "aganglionic" 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).

Acetylcholine: neurotransmitter used in PNS, CNS, and ANS and in motor division of somatic nervous system

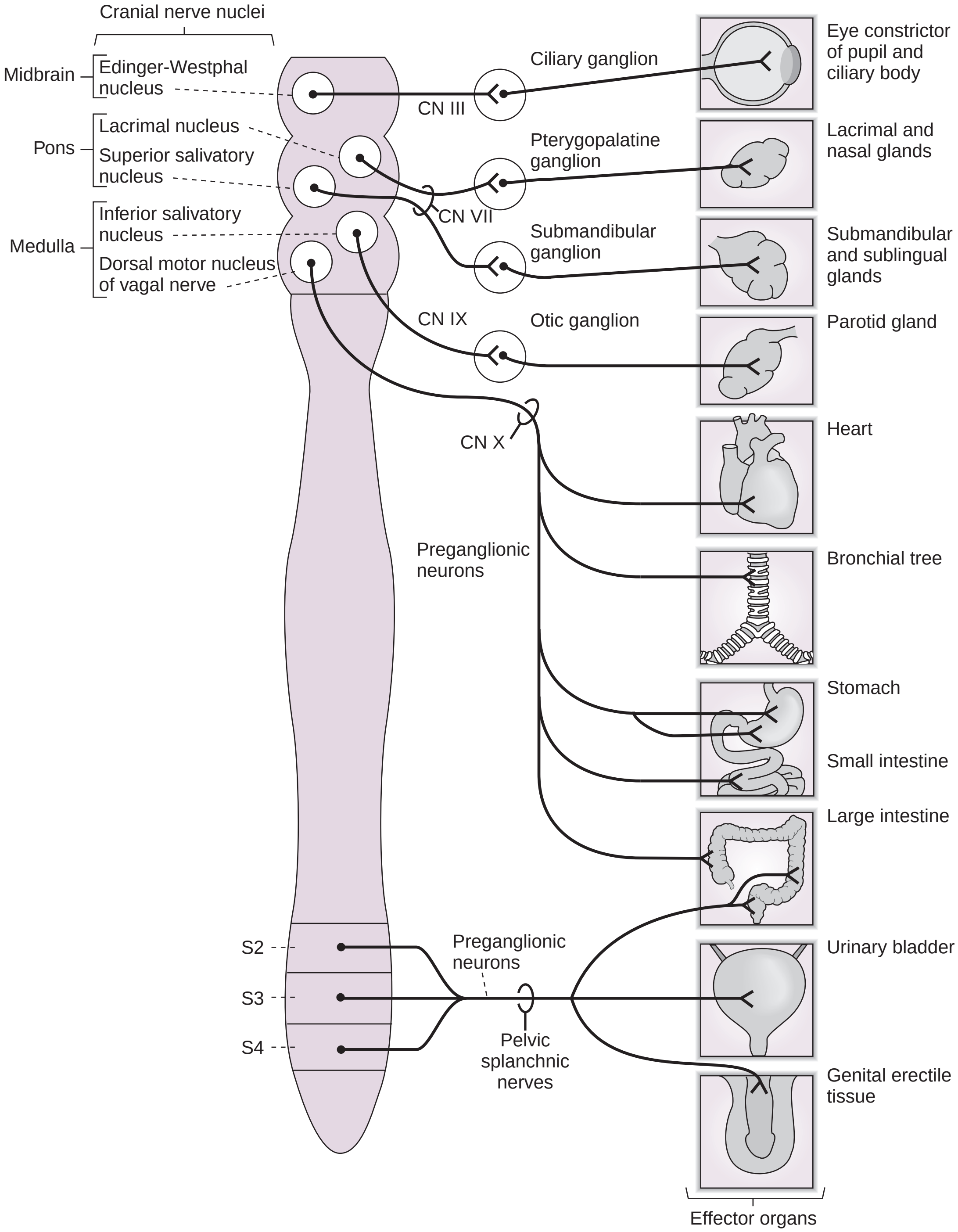
Norepinephrine: adrenergic neurotransmitter released from most postganglionic neurons of the SNS

VIP and substance P: peptidergic neurotransmitters colocalized with ACh in some parasympathetic postganglionics

Dopamine synthesis: occurs in substantia nigra, ventral tegmental area, and hypothalamus

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



2-4: The parasympathetic nervous system. *CN*, Cranial nerve; *S*, sacral.

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

Nitric oxide: vascular smooth muscle relaxation, penile erection

- 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 β_1 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 sometimes referred to as the sympathoadrenal system.
   - NE has preferential affinity for **α-receptors,** whereas **epinephrine** binds 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: **N_N (preganglionic-postganglionic junction)** and **N_M (neuromuscular junction).**

Norepinephrine: preferential affinity for α-adrenergic receptors

Epinephrine: equal affinity for α- and β-adrenergic receptors

Location of cholinergic receptors: preganglionic junctions of both arms of ANS, parasympathetic effector organs, postsynaptic membrane of myocytes

Muscarinic receptors: M1 (gastric, CNS), M2 (cardiac), M3 (smooth muscle)

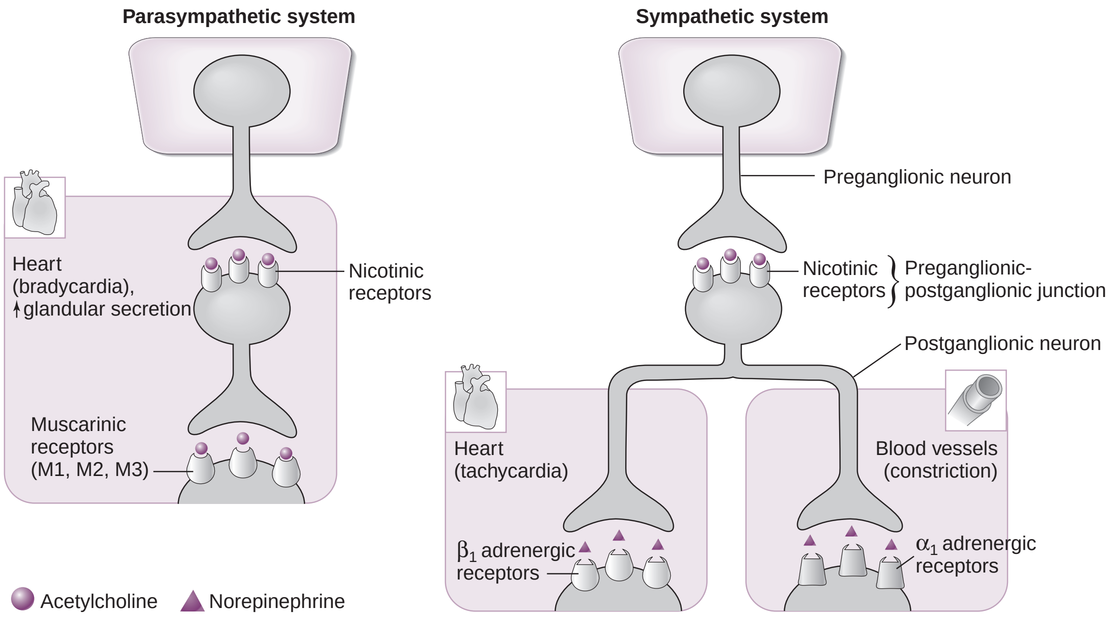
Nicotinic receptors: N_N (preganglionic junction), N_M (neuromuscular junction)

TABLE 2-3. Adrenergic Receptors

RECEPTOR SUBTYPE	PRIMARY LOCATIONS	NORMAL PHYSIOLOGY ASSOCIATED WITH RECEPTOR ACTIVATION	CLINICAL PHARMACOLOGY
α_1	Vascular smooth muscle cells	Binding of catecholamines stimulates contraction, usually through Gq subunit, causing vasoconstriction and increased blood pressure	α-Blockers (e.g., prazosin) lower blood pressure by reducing total peripheral resistance
α_2	Presynaptic	Binding of synaptic norepinephrine results in feedback inhibition through Gi subunit to regulate release of neurotransmitter	Centrally acting α_2-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).
β_1	Heart	Binding of catecholamines is generally stimulatory in nature, increasing cardiac contractility (positive inotropy) and heart rate (positive chronotropy)	Dopamine indicated for hypovolemic shock (e.g., arterial hemorrhage); increases cardiac output but simultaneously stimulates renal vasodilation, thereby preserving renal perfusion. β_1-blockers such as metoprolol lower blood pressure by reducing cardiac stroke volume and heart rate, both of which lower cardiac output.
β_2	Vascular and nonvascular smooth muscle cells	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)	β_2- blockers (e.g., propranolol) useful antihypertensives; β-agonists (e.g., albuterol) useful for stimulating bronchodilation in an asthmatic attack; such bronchodilation helps improve pulmonary ventilation during an asthmatic attack.
β_3	Adipose	Lipolysis through stimulation of hormone-sensitive lipase	β_3-Agonists may stimulate lipolysis and have potential role as weight-loss aids.

TABLE 2-4. Cholinergic Receptors

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



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

IV. Control of Movement

A. Overview

Control of movement: involves motor cortex, basal ganglia, motor thalamus, cerebellum, upper and lower motor neurons, and sensory system

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.**

Alpha motor neuron: supply extrafusal muscle fibers → movement

Gamma motor neurons: supply intrafusal muscle fibers → joint proprioception

Voluntary movements: requires "permission" from basal ganglia and motor thalamus

Motor cortex: comprises premotor, supplementary, and primary motor cortices

Stimulation of primary motor cortex → discrete movement

Stimulation of association motor cortices → complex, patterned movement

Role of spinal cord in movement: important in rhythmic and reflexive movements

Spinal cord tracts controlling movement: pyramidal and extrapyramidal

Lesions → paraplegia, quadriplegia, spinal or neurogenic shock, upper motor neuron (UMN) signs, lower motor neuron (LMN) signs

Pyramidal tracts: decussate in the caudal medulla

Pyramidal tracts: corticobulbar, lateral corticospinal, and ventral corticospinal

Pyramidal tracts: originate primarily from motor cortex and terminate directly on motor neurons in the brainstem and spinal cord

Lesions → UMN signs

Extrapyramidal tracts: originate in brainstem; do not directly innervate lower motor neurons

Role of extrapyramidal tracts: reflexes, postural control, control of movement

Lesions → inability to initiate movement (akinesia), inability to remain still (akathisia); extrapyramidal symptoms: tardive dyskinesia, muscle spasms (dystonia) of neck (torticollis)

TABLE 2-5. Classification of Motor Nerve Fibers

FIBER TYPE	DIAMETER	CONDUCTION VELOCITY	FUNCTION
Alpha (A-alpha)	Largest	Fastest	Supply extrafusal muscle fibers
Gamma (A-gamma)	Medium	Medium	Supply intrafusal muscle fibers
Preganglionic autonomic fibers (B)	Small	Medium	Control and regulate cardiac muscle, smooth muscle, and glands
Postganglionic autonomic fibers (C)	Smallest	Slowest	Control and regulate cardiac muscle, smooth muscle, and glands

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 corticobulbar and corticospinal fibers travel through the **internal capsule** en route to their target nuclei in the brainstem and spinal cord, respectively.
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.

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.

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

TABLE 2-6. Overview of Spinal Cord Tracts

TRACT	ORIGIN	COURSE	TERMINATION	FUNCTION
Pyramidal				
Ventral corticospinal	Cerebral cortex at premotor cortex (Brodman 6) and primary motor cortex (Brodman 4)	Telencephalon: posterior limb of internal capsule Midbrain: crus cerebri Pons: basilar portion of pons Medulla: medullary pyramids	Spinal cord and synapse bilaterally with ventromedial cell column and adjoining portions of intermediate-zone horn motor neurons	Mediates voluntary skilled motor activity, primarily axial muscles
Lateral corticospinal	Cerebral cortex at premotor cortex (Brodman 6), primary motor cortex (Brodman 4), and primary sensory cortex (Brodman 3, 1, and 2)	Telencephalon: posterior limb of internal capsule Midbrain: crus cerebri Pons: basilar portion of pons Medulla: medullary pyramids where the fibers decussate	Contralateral spinal cord, on motor nuclei in lateral part of anterior horn and to interneurons in the intermediate zone	Mediates voluntary skilled motor activity of the distal limbs and coarse regulation of the proximal limbs
Corticobulbar	Frontal eye fields (Brodman 8, 6), precentral gyrus (Brodman 4), postcentral gyrus (Brodman 3, 1, and 2)	Frontal eye field: caudal portions of anterior limb of internal capsule in telencephalon Precentral gyrus: genu of internal capsule Postcentral gyrus: rostral portions of posterior limb of internal capsule	Frontal eye field: rostral interstitial nucleus of medial longitudinal fasciculus and paramedian pontine reticular formation, which project to the nuclei of III, IV and VI Precentral and postcentral gyrus: nuclei of cranial nerves V, VII, XI and XII, and nucleus ambiguus	Controls muscles of head and face
Extrapyramidal				
Rubrospinal	Red nucleus	Crosses to opposite side in the ventral tegmental decussation of lower brainstem and follows a course immediately adjacent and anterior to the corticospinal tracts	Interneurons in lateral columns of spinal cord	Stimulates flexors and inhibits extensors
Pontine reticulospinal	Nuclei in the pons	Descends in ventral column of spinal cord	Ipsilateral ventromedial spinal cord neurons	Stimulates flexors and extensors, with predominant effect on extensors
Medullary reticulospinal	Medullary reticular formation	Descends in ventral column of spinal cord	Spinal cord interneurons in intermediate gray area (synapses bilaterally with ipsilateral preponderance)	Inhibits extensors and flexors, with predominant effect on extensors
Lateral vestibulospinal	Dieters' nucleus	Descends in ventral column of spinal cord	Ipsilateral motoneurons and interneurons	Stimulates extensors and inhibits flexors
Tectospinal	Superior colliculus	Fibers cross in posterior tegmental decussation and descend in ventral column of spinal cord	Cervical spinal cord	Control of neck 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.

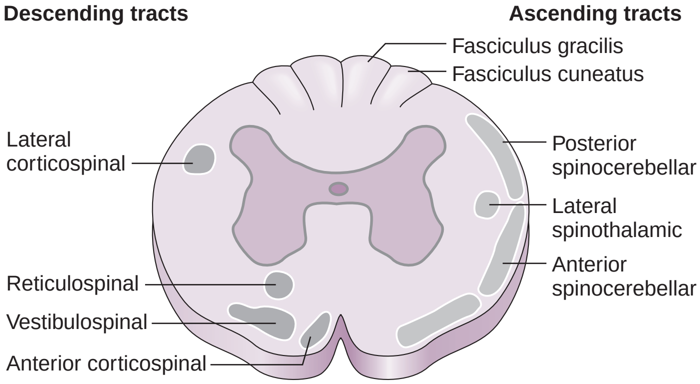
Role of medial descending system: control of posture

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.

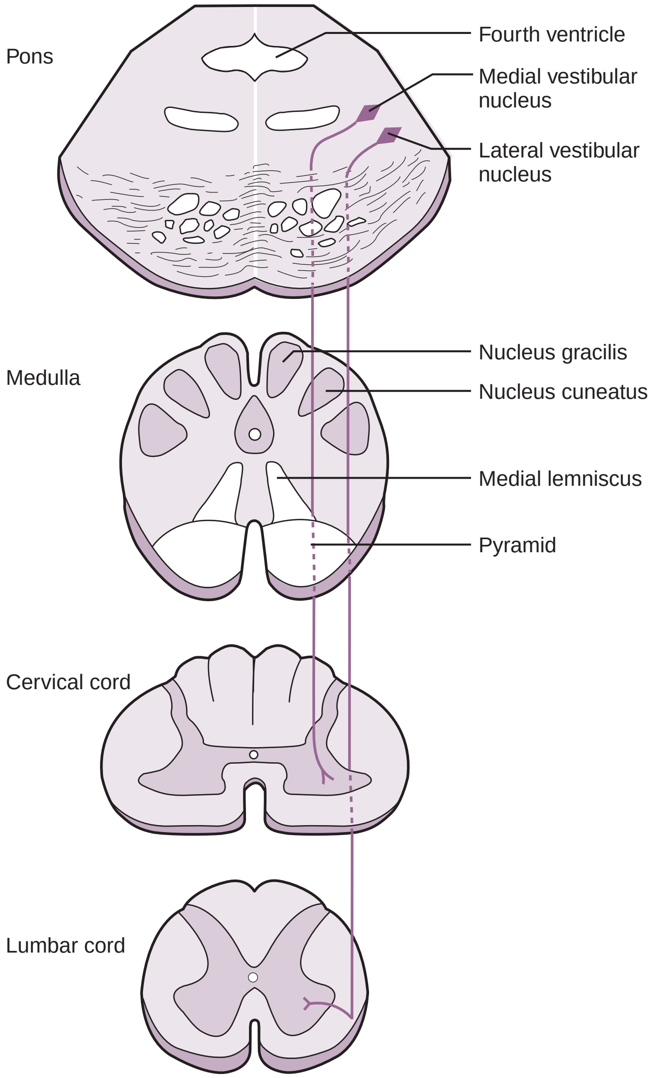
Role of lateral vestibulospinal tracts: stabilizes posture through stimulation of extensor (antigravity) muscles; promotes equilibrium

Role of medial vestibulospinal tracts: eye movements, gaze control, head and neck positioning

- **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.



2-6: Motor tracts of the spinal cord (also showing the sensory tracts, fasciculus gracilis, and fasciculus cuneatus).



2-7: Pathway of the vestibulospinal tracts. *(From Crossman A, Neary D: Neuroanatomy: An Illustrated Colour Text, 3rd ed. London, Churchill Livingstone, 2006, Fig. 8-20.)*

Role of pontine reticulospinal tracts: stimulates extensor antigravity muscles

Role of medullary reticulospinal tracts: to inhibit extensor antigravity muscles

- **Reticulospinal tracts**
  a. Arise from the brainstem reticular formation
  b. Comprise the pontine (medial) and medullary (lateral) tracts
  c. The p**ontine 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.**
  d. 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)

Lesion at level of superior colliculus → decerebrate posturing or rigidity, also referred to as *extensor posturing*

Role of tectospinal tracts: reflexive movements of head and neck in response to visual stimuli

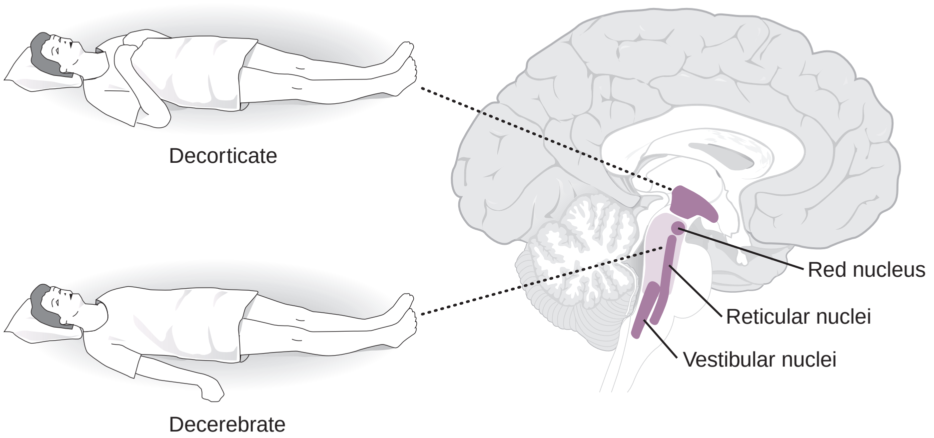
Ventral corticospinal tract: descends in anterior funiculus of spinal cord; controls axial and proximal muscles

Lateral corticospinal tract: synapses on alpha lower motor neurons; controls distal limb muscles

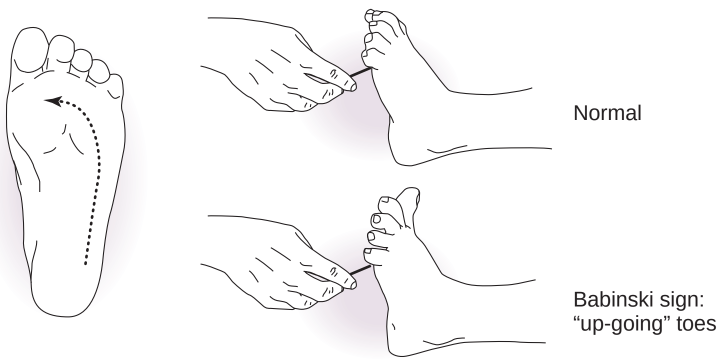
Lesions → UMN signs: hyperreflexia, spasticity, clonus, Babinski sign

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.



2-8: Decorticate and decerebrate posturing. *(From Weyhenmeyer J, Gallman E: Rapid Review Neuroscience. Philadelphia, Mosby, 2007, Fig. 15-2.)*



2-9: Babinski response. *(From Weyhenmeyer J, Gallman E: Rapid Review Neuroscience. Philadelphia, Mosby, 2007, Fig. 17-1.)*

Upper motor neurons: tonically inhibitory to lower motor neurons

UMN lesion → disinhibition of LMN activity → UMN lesion signs

- 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

Basal ganglia: important in initiation of voluntary movements

Basal ganglia output: always inhibitory in nature

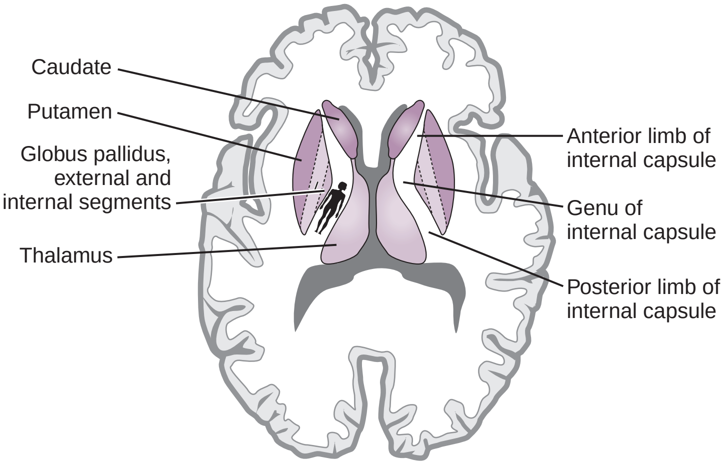
- The basal ganglia comprise subcortical *(basal)* clusters of nuclei *(ganglia).*
- They are important in the initiation of **voluntary movements**, becoming activated just before initiation of the movement.
- They include the putamen and caudate nucleus (collectively termed the ***striatum***), globus 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

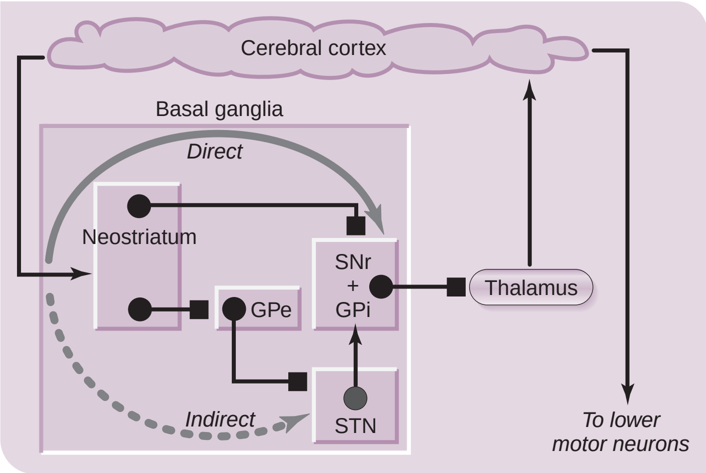
PARAMETER	UPPER MOTOR NEURON LESION	LOWER MOTOR NEURON LESION
Cause	Lesion of cortex or corticospinal tract	Damage to lower motor neurons
Examples	Amyotrophic lateral sclerosis	Poliomyelitis, trauma, Guillain-Barré syndrome
Clinical Signs		
Babinski sign	Present	Absent
Paralysis	Spastic	Flaccid
Muscle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

TABLE 2-8. Basal Ganglia Terms

BASAL GANGLIA TERM	COMPOSITION
Striatum	Putamen and caudate nucleus
Corpus striatum	Striatum and lentiform nucleus
Lentiform nucleus	Putamen and globus pallidus



2-10: Anatomy of the basal ganglia. *(From Weyhenmeyer J, Gallman E: Rapid Review Neuroscience. Philadelphia, Mosby, 2007, Fig. 8-1.)*



2-11: The direct and indirect pathways. Changes seen in Parkinson disease are also shown. *GPe,* Globus pallidus external segment; *GPi,* globus pallidus internal segment; *SNr,* sinus node receptor; *STN,* subthalamic nucleus. *(From Weyhenmeyer J, Gallman E: Rapid Review Neuroscience. Philadelphia, Mosby, 2007, Fig. 9-3.)*

- The basal ganglia influence movement through one of two pathways, the **direct** or 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 ***dis*inhibition** 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.**

Direct pathway: *dis*inhibition of motor thalamus → promotes movement

Lesions → difficulty initiating movements (e.g., Parkinson disease)

Indirect pathway: inhibition of motor thalamus → inhibits movement

Lesions → unintentional or spontaneous movements (e.g., Huntington disease)

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

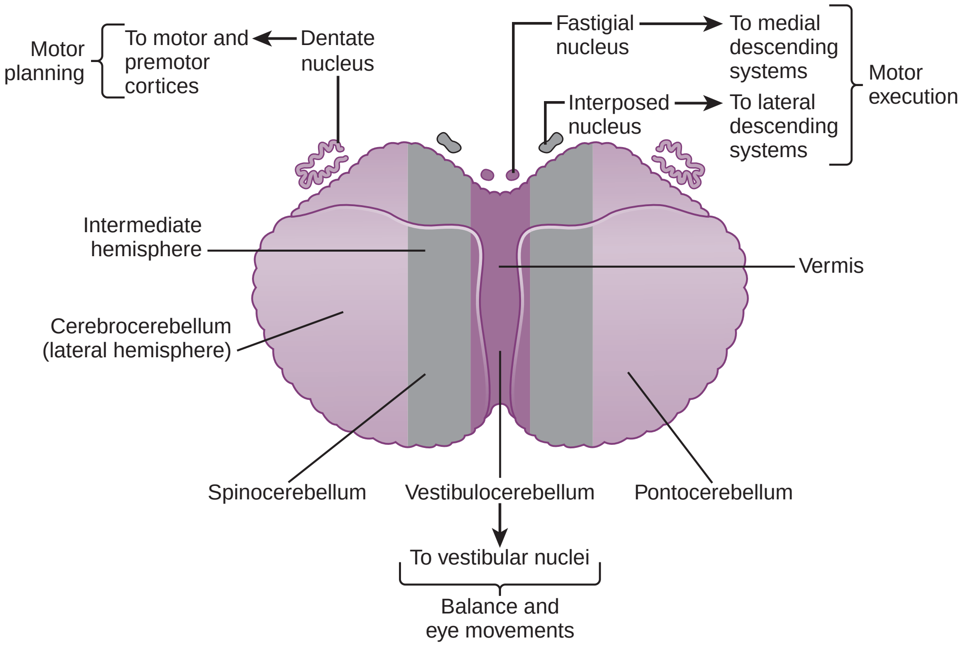
1. The cerebellum is important in coordinating **speed, trajectory,** and **force** of movements *as they occur.*
2. It is also important in the maintenance of **posture** and **equilibrium.**
3. To perform these functions, the cerebellum must process *in real time* an enormous amount of information 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).
   - **Pontocerebellum (neocerebellum, cerebrocerebellum)**
     a. 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.

Cerebellum: coordinates speed, trajectory, and force of movements *as they occur;* important in posture and equilibrium

Cerebellar divisions: pontocerebellum, spinocerebellum, vestibulocerebellum

Role of neocerebellum: planning and timing of sequential motor movements

Neocerebellar lesions → incoordination of limbs



2-12: Functional components of the cerebellum. *(From FitzGerald MJT, Gruener G, Mtui E: Clinical Neuroanatomy and Neuroscience, 5th ed. London, Saunders, 2007, Fig. 25-1.)*

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

Role of spinocerebellum: control of precise and purposeful movements

Spinocerebellar lesions → ataxia, tremor, pendular reflexes

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).

Role of vestibulocerebellum: posture, equilibrium, eye movements

Vestibulospinal lesions → pendular nystagmus, ataxia

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

SIGN	DESCRIPTION
Nystagmus	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)
Dysarthria	Difficulty in producing coherent speech because of inability to coordinate laryngeal muscles (not to be confused with aphasias, caused by damage to the cerebral cortex)
Ataxia	Incoordination of movements or gait (truncal ataxia). Patients typically fall to side of lesion (recall cerebellar lesions produce ipsilateral deficits).
Intention tremor	Tremor appears only during a voluntary movement.
Dysdiadochokinesia	Inability to coordinate rapidly alternating movements, such as rapid pronation and supination at the wrist
Dysmetria	Inability to properly judge distances: overshooting (hypermetria) or undershooting the target (hypometria)

*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

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

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 the 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

Sensory receptors: neurons specialized to detect environmental stimuli and transmit them through action potentials

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).

Receptive field: focal area to which the application of an appropriately intense stimulus will trigger the sensory receptor to initiate an action potential

2. A **receptive field** is a focal area of the sensory surface (e.g., skin) to which the application of an appropriately 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.

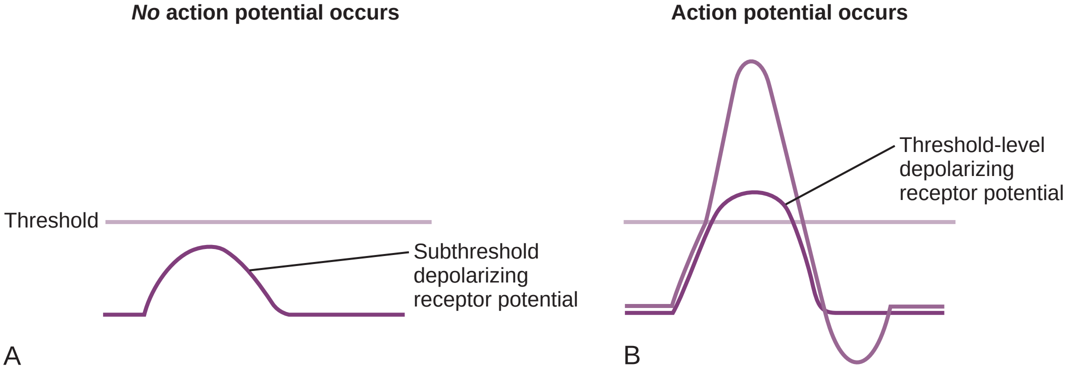
B. Sensory transduction

Sensory transduction: process in which stimulus is detected, amplified, and conducted to CNS

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.

Receptor potential: change in membrane potential in sensory cells caused by opening of ion channels; typically cells are depolarized

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.**



2-13: **A** and **B,** Receptor potentials. Threshold potential must be reached for action potential generation to occur. *(From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 3-4.)*

If membrane potential > threshold potential → action potential (AP) generated

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.

Spatial summation: "firing" of greater numbers of nerve fibers → ↑ signal intensity

Temporal summation: ↑ frequency of AP generation → ↑ signal intensity

C. Adaptation

Adaptation: sensory receptors adapt (change frequency of AP generation) to varying extents in the presence of a constant stimulus

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).

Tonic receptors: continue to generate APs as long as stimulus is present

Examples of tonic receptors: muscle spindles, pressure receptors, slow pain receptors

Phasic receptors: rapidly ↓ frequency of AP generation in response to a constant stimulus

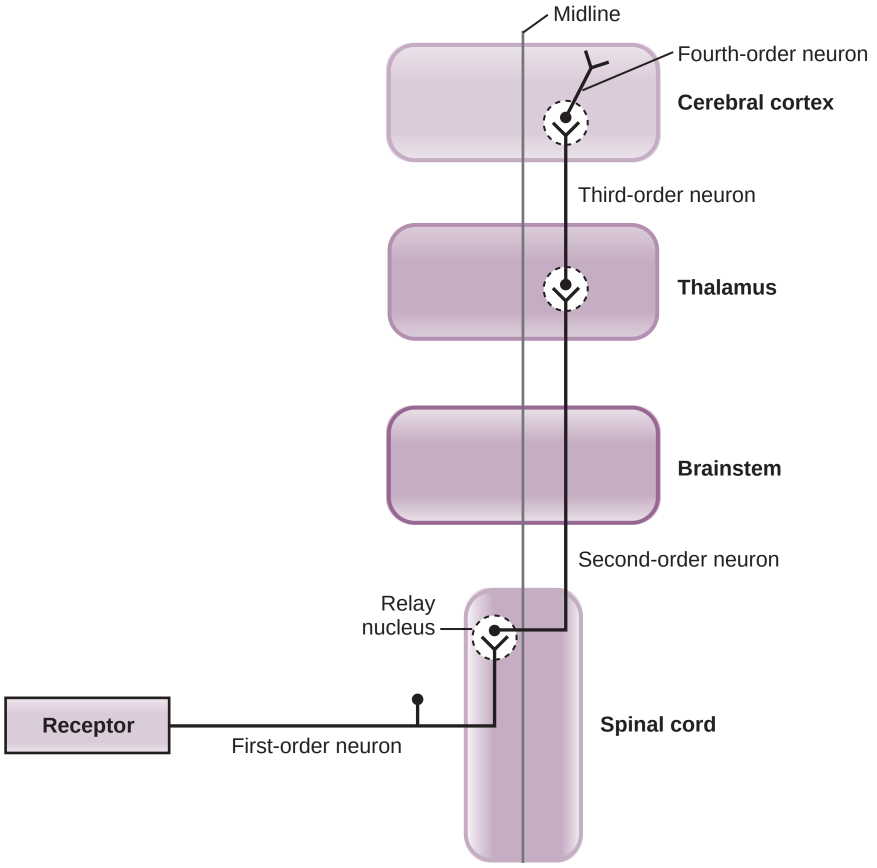
Examples of phasic receptors: Meissner and pacinian corpuscles

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.

A thalamic or cortical stroke will result in sensory deficits on the opposite side of the body.

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.



2-14: Anatomy of sensory pathway. *(From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 3-3.)*

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**)**

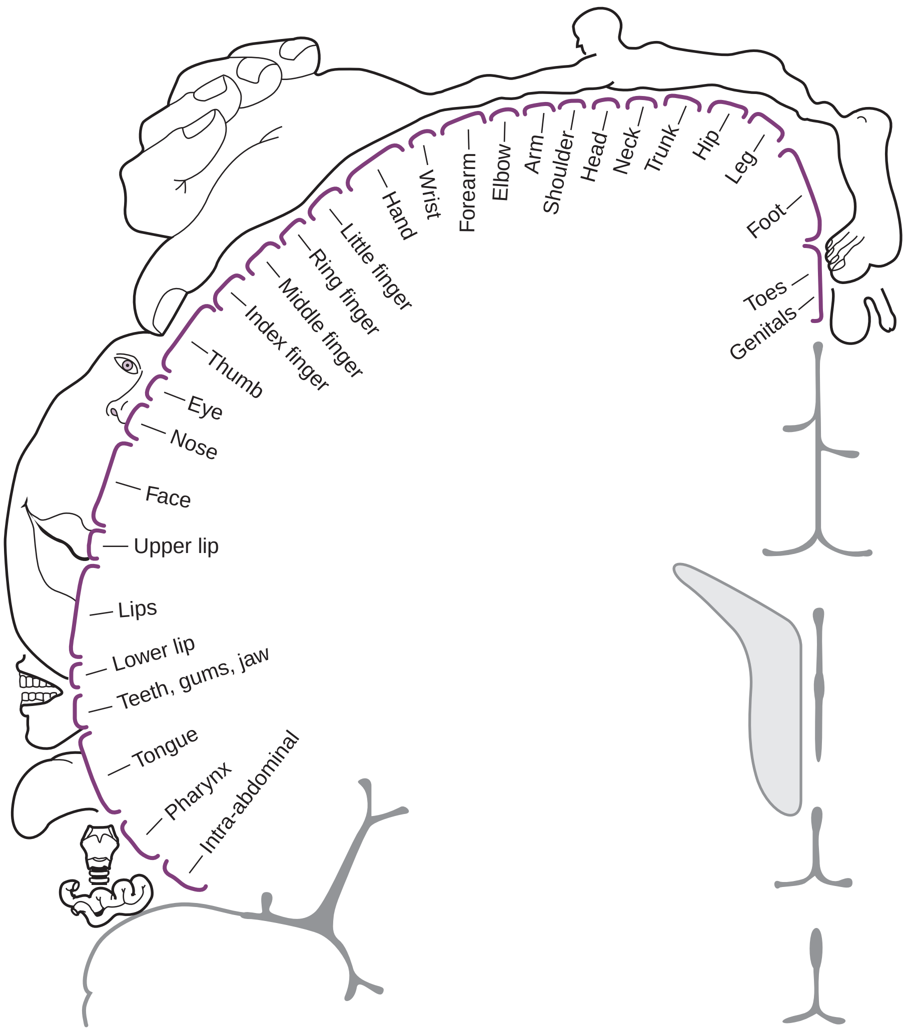
1. **Dorsal column system (DCS): medial lemniscal pathway**
   - The DCS processes the sensations of fine touch, conscious proprioception, two-point discrimination, and vibration.
   - **Primary afferents** travel ipsilaterally up the spinal cord to synapse on the **nucleus gracilis** and **nucleus cuneatus** 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.

Sensory modalities detected by dorsal columns: fine touch, conscious proprioception, two-point discrimination, vibration

Second-order neurons decussate in the brainstem (medulla) rather than in the spinal cord.

Dorsal column lesions → ipsilateral sensory deficits below level of the lesion

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 B_{12}) 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.



2-15: Sensory homunculus. Note that the face, hands, and fingers—areas where precise localization is critical—represent the largest areas of the homunculus.

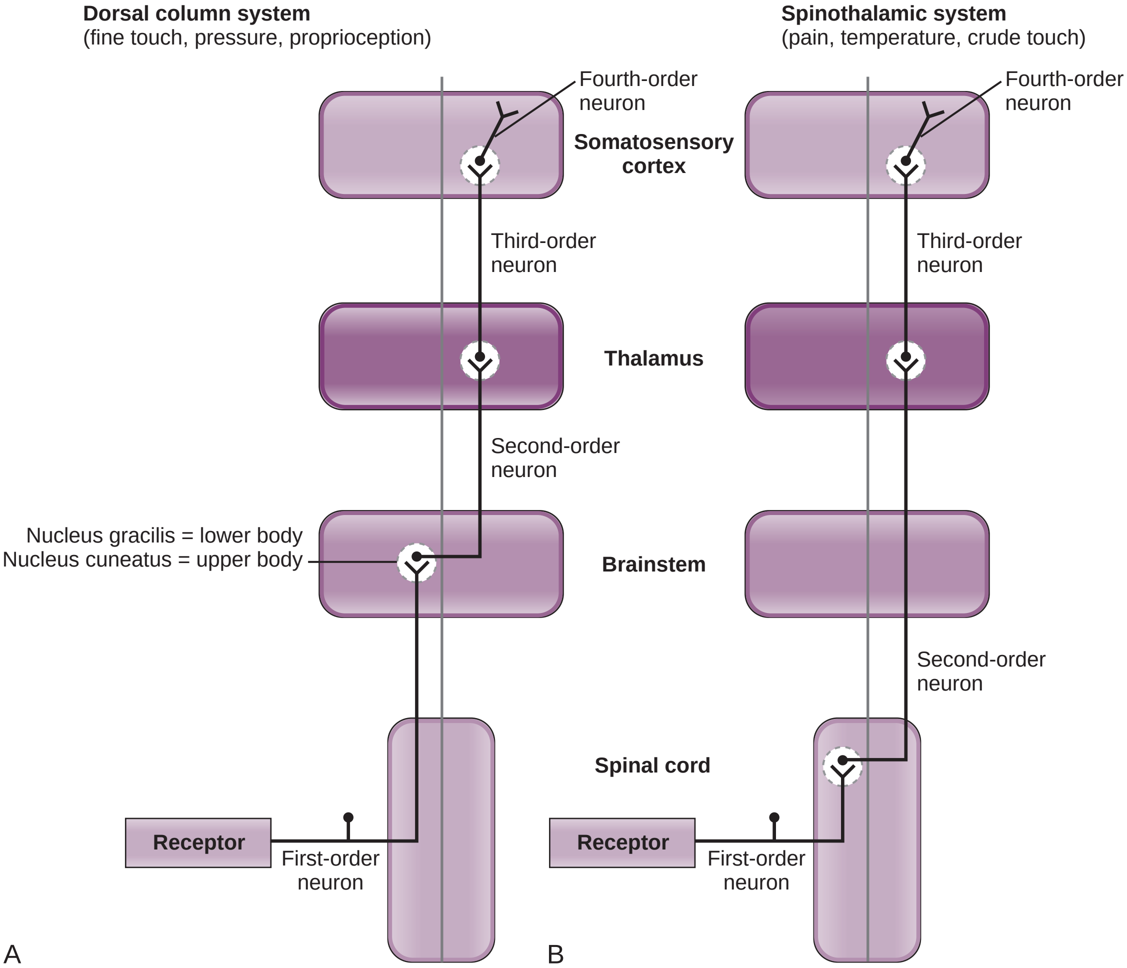
Sensory modalities detected by spinothalamic system: pain, temperature, crude touch

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



2-16: **A** and **B,** Somatosensory pathways. Anatomy of the dorsal column and spinothalamic systems. *(From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 3-10.)*

- 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.

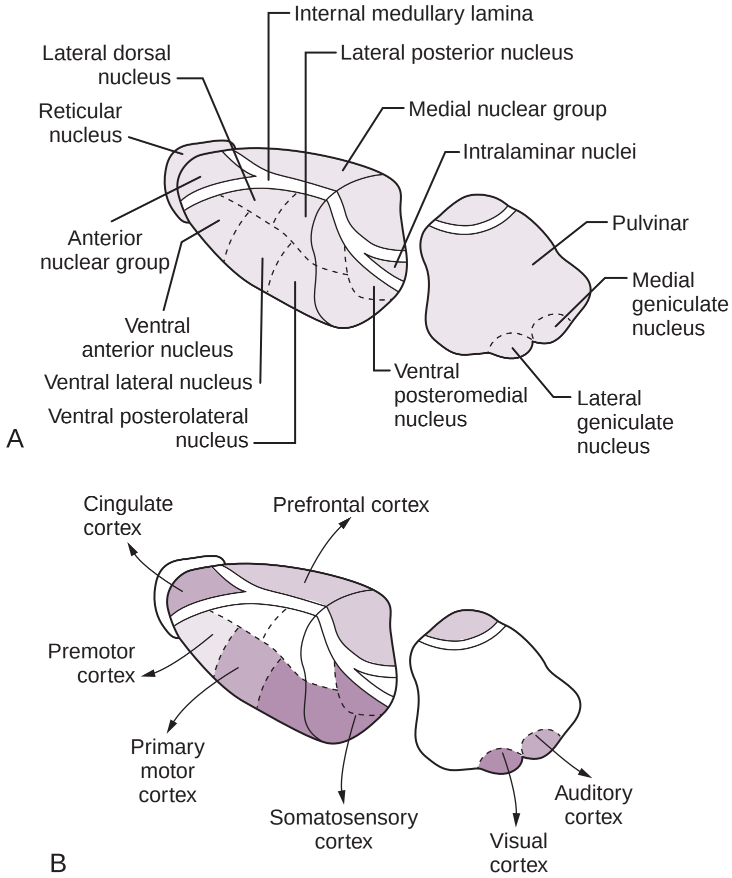
Thalamus: arranged somatotopically; lesions → contralateral sensory deficits

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.

Pain receptors: adapt very little or not at all

2-17: **A** and **B,** The thalamus. *(From Crossman A, Neary D: Neuroanatomy: An Illustrated Colour Text, 3rd ed. London, Churchill Livingstone, 2006, Fig. 12-6.)*



Fast pain: well localized, sharp in nature, rapid onset and offset, carried by group III fibers

Slow pain: poorly localized

Dermatome: area of skin innervated by single spinal nerve

- 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

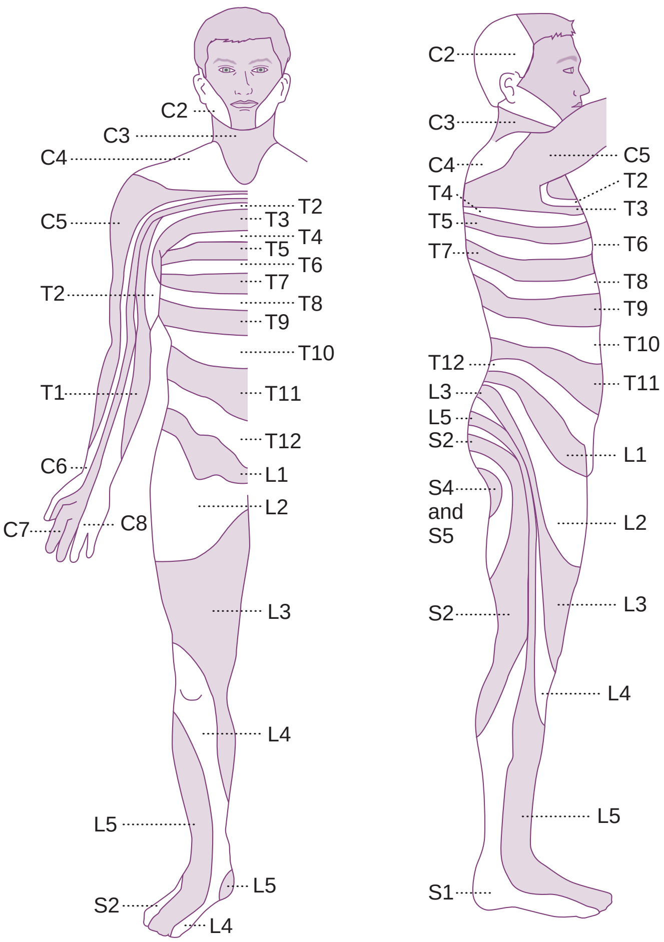
A. Overview

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.

Special senses: vision, hearing, equilibrium, olfaction, 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.**



2-18: Dermatomes. *C,* Cranial; *L,* lumbar; *S,* sacral; *T,* thoracic.

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

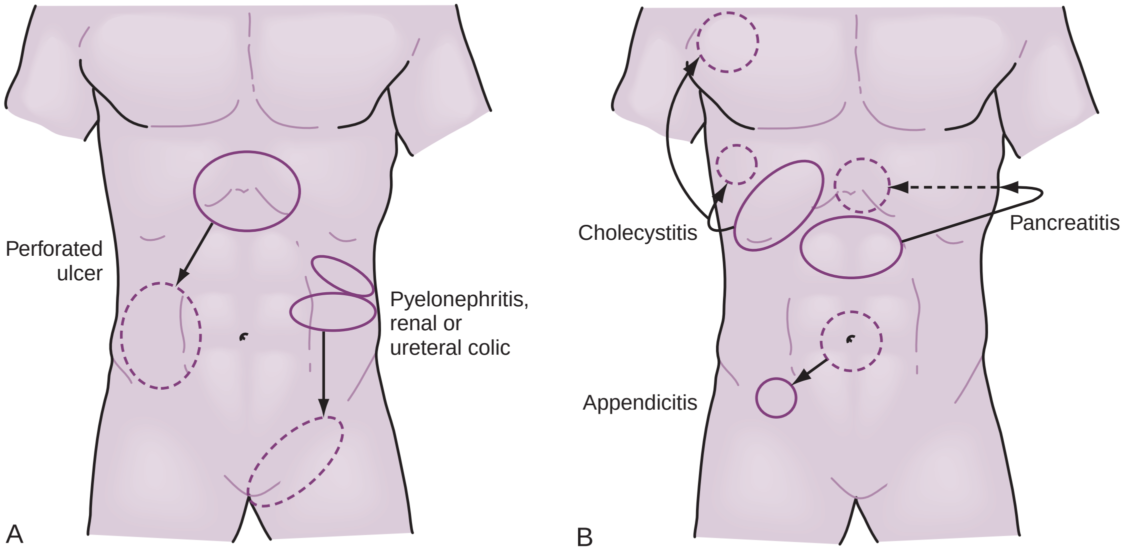
DERMATOME	AREA INNERVATED
C3	Front and back of neck
C6	Thumb, pointer finger, lateral forearm
C7	Middle finger
C8	Ring and little finger, medial hand
T10	Umbilicus
L1	Inguinal
L3	Knee
L5	Anterior ankle and foot, and first three toes
S1	Heel, plantar surface of foot (all toes except big toe), and fourth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

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.

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



2-19: **A** and **B,** Referred pain. *Solid circles* are primary or most intense sites of pain. *(From Townsend C, Beauchamp RD, Evers BM, Mattox K: Sabiston Textbook of Surgery, 18th ed. Philadelphia, Saunders, 2008, Figs. 45-5 and 45-6.)*

TABLE 2-12. Referred Pain

SITE OF PAIN	ORGANS FROM WHICH PAIN IS REFERRED
Lower abdomen (above pubic bone)	Large bowel Bladder
Umbilical region	Small bowel Pancreas
Upper abdomen	Duodenum Stomach
Behind sternum	Esophagus Trachea
Tip of shoulder	Diaphragm
Chest (central), arms (usually left arm), neck, abdomen (occasionally)	Heart
Back of head and neck	Meninges

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*.

Optic disc: retinal *blind spot* due to absence of rods and cones

- **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.

Rods: low-acuity night vision; more numerous than cones

c. Their photosensitive element is **rhodopsin,** which is composed of **11-*cis*-retinal** and **scotopsin.**

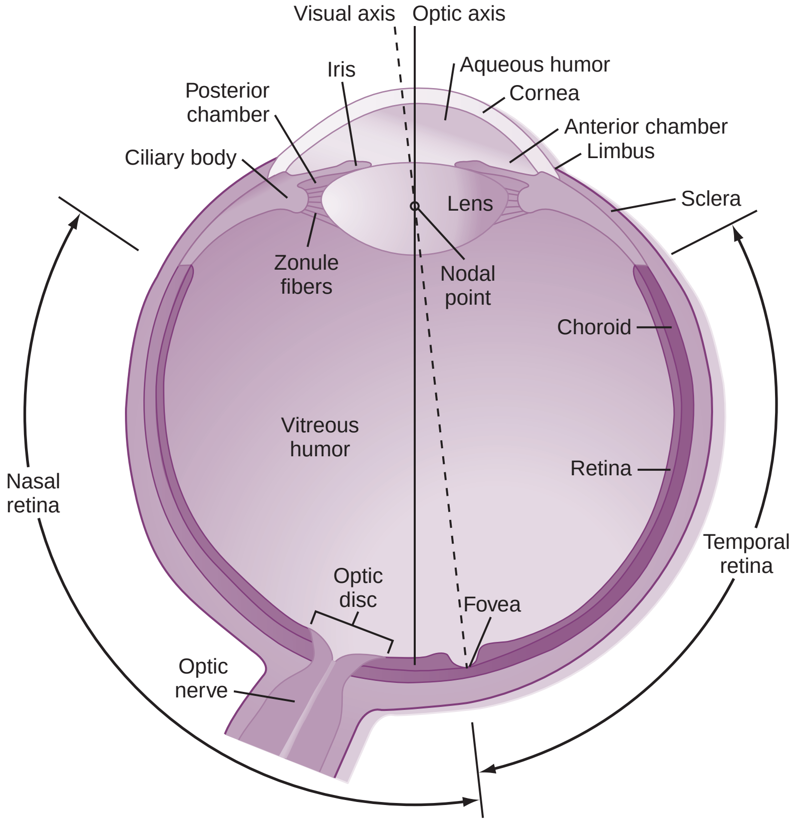
d. When exposed to light, rhodopsin decomposes to **all-*trans*-retinal** and then to other intermediate compounds; this triggers an electrical impulse that is sent to the occipital lobe of the brain.

Rhodopsin → all-*trans*-retinal → nerve impulse to occipital lobe

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.



2-20: The eye. *(From Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 8-1.)*

b. They are less numerous than rods and are concentrated in the fovea centralis of the macula.
   - Their photosensitive elements are **color pigments.**

Cones: responsible for high-acuity color vision; less numerous than rods; concentrated in fovea centralis

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."

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

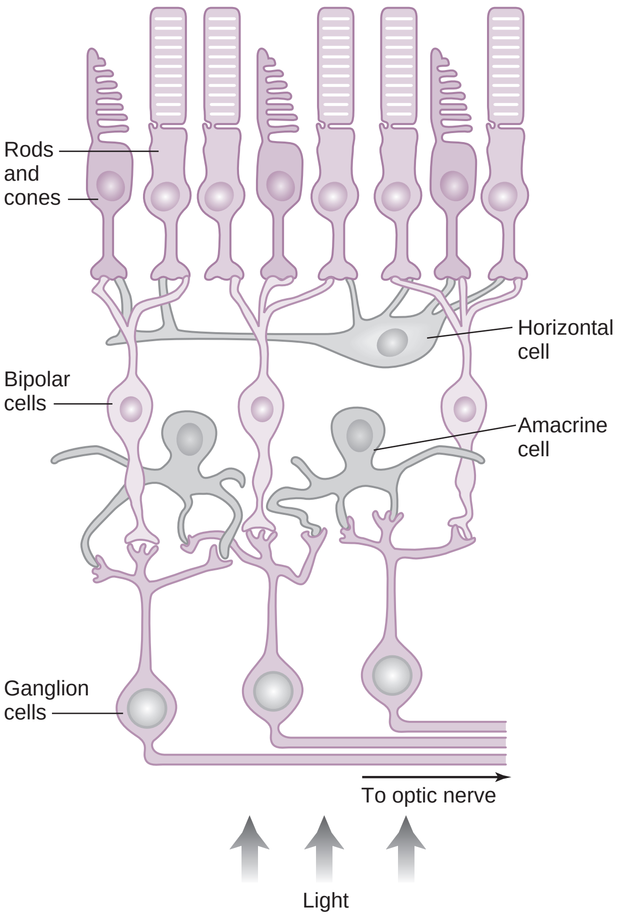
Lesions to the optic tract → ipsilateral hemianopia

Lesions of upper and lower divisions → ipsilateral hemianopia with macular sparing

Massive infarct of occipital lobe → contralateral hemianopsia without macular sparing

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

2-21: Layers of the retina.



Pupillary light reflex: regulates intensity of light entering the eye by controlling pupil diameter

Shining light in one eye: normal response is constriction of *both* pupils

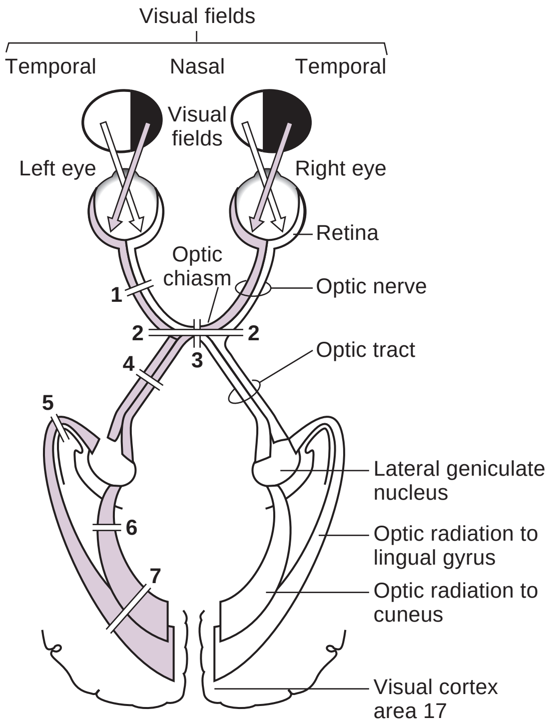
Direct response: constriction of pupil in eye exposed to light

Consensual response: constriction of pupil in eye not exposed to light

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.

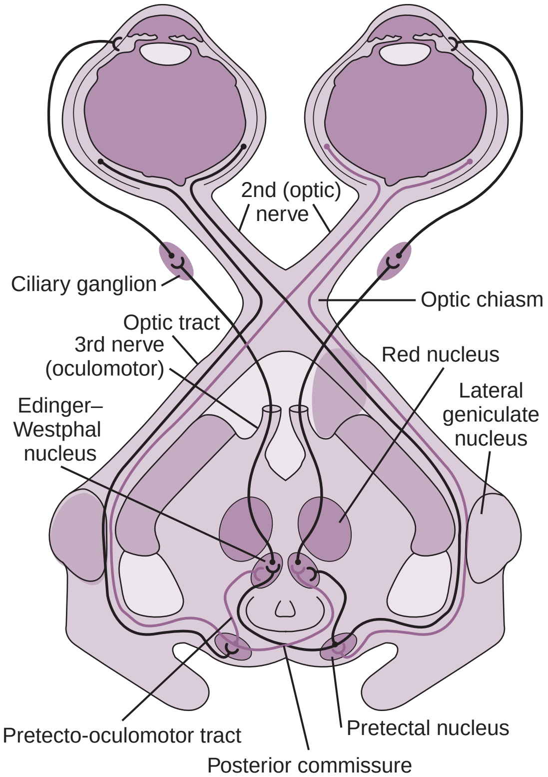
Clinical note: Deficits in the pupillary light reflex are evident in several different CNS diseases, including neurosyphilis, alcoholism, and encephalitis. Any damage to the Edinger-Westphal nucleus results in an abnormal or absent pupillary reflex. An **Argyll Robertson pupil,** often a sign of neurosyphilis, 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.

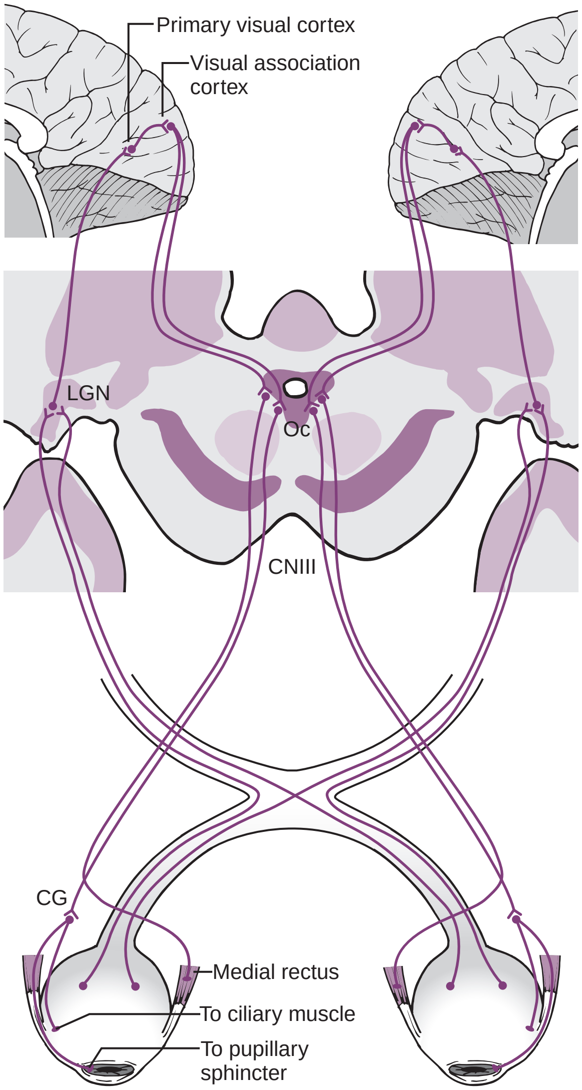


Lesion	Visual defect
1. Optic nerve	Ipsilateral blindness (1)
Optic chiasm 2. Bilateral lateral compression	Binasal hemianopia (2)
3. Midsagittal transection/pressure	Bitemporal hemianopia (3)
4. Optic tract (left)	Right hemianopia (4)
Optic radiation (left) 5. Lower division	Right upper quadrantanopia (5)
6. Upper division	Right lower quadrantanopia (6)
7. Both divisions	Right hemianopia with macular sparing (7)

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.)*



2-24: Accommodation reflex. *CG*, Ciliary ganglion; *CN*, cranial nerve; *LGN*, lateral geniculate nucleus; *Oc*, optic chiasm. *(From Nolte J: Elsevier's Integrated Neuroscience. Philadelphia, Mosby, 2007, Fig. 12-18.)*

Accommodation reflex: brings nearby objects into focus

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.

Outer ear: comprises pinna and external auditory canal

Middle ear: comprises tympanic membrane, malleus, incus, and stapes

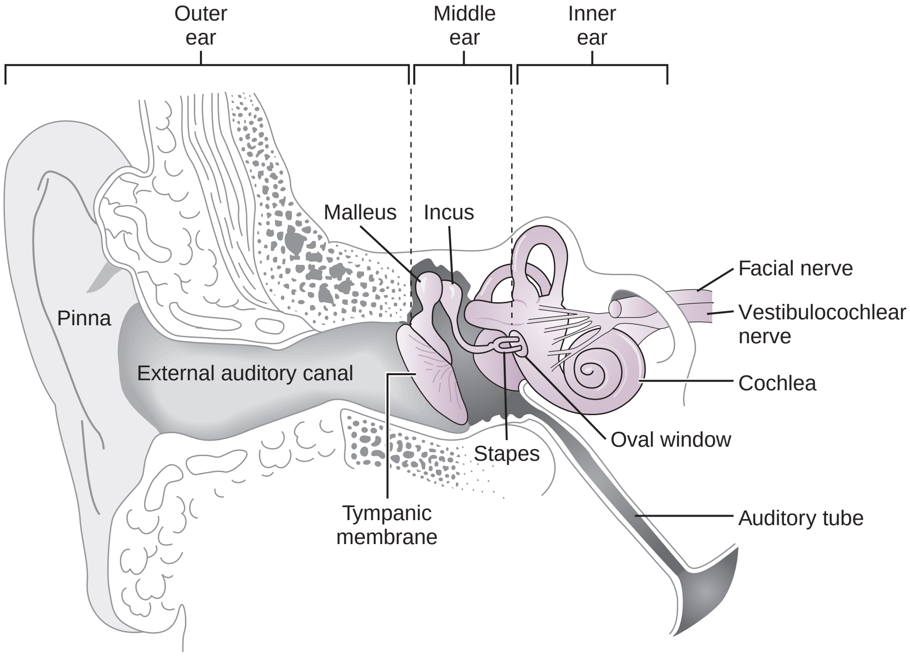
Inner ear: comprises bony labyrinth (semicircular canals, cochlea, vestibule) and fluid-filled membranous labyrinth

Scala vestibuli and tympani: contain Na^+-rich perilymph

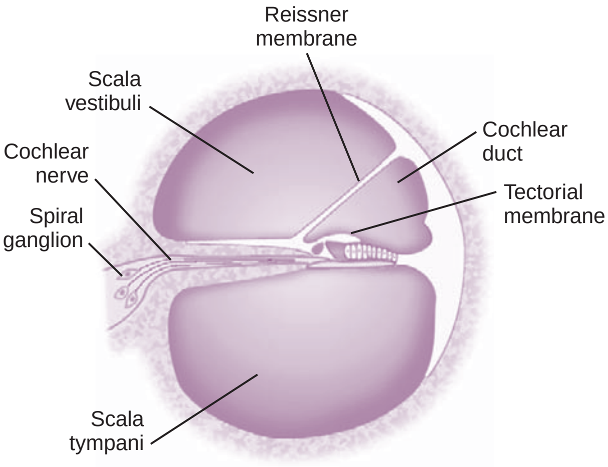
Scala media: contains K^+-rich endolymph

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^+).



2-25: Structure of the ear (anterior view). *(From Weyhenmeyer J, Gallman E: Rapid Review Neuroscience. Philadelphia, Mosby, 2007, Fig. 13-1.)*



2-26: Cross section of one turn of the cochlea. *(From Nadeau S, et al: Medical Neuroscience. Philadelphia, Saunders, 2004, Fig. 10-9.)*

- 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.**

Organ of Corti: contains inner and outer hair cells needed for audition; these cells have cilia embedded in tectorial membrane

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.

Pathway of sound: sound waves directed into external auditory canal → tympanic membrane vibrates → ossicles vibrate → fluid displaced in 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.**

Basilar membrane: vibrations force hair cells against tectorial membrane → changes in K^+ conductance → hyper/depolarization

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.**

- 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.**

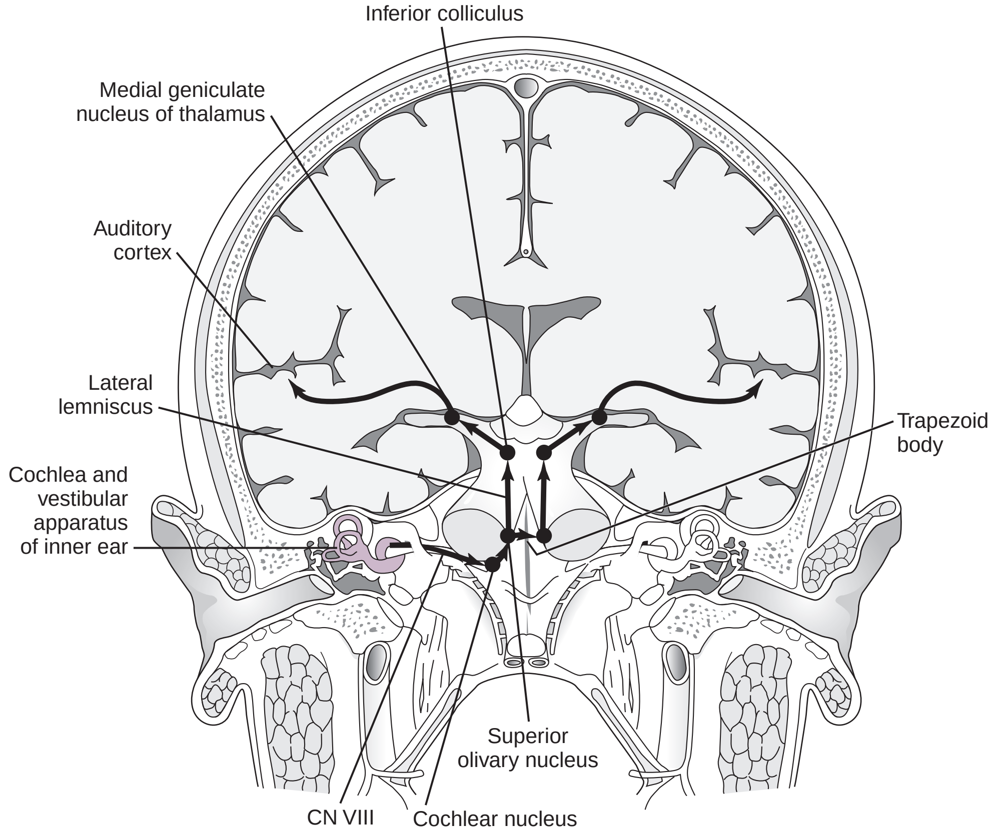
Clinical note: Sensorineural deafness is caused by damage to the inner ear, auditory nerve, or central auditory pathway. In **presbycusis,** a common condition in older adults associated with high-frequency (4000 to 8000 Hz) hearing loss, degenerative disease of the base of the basilar membrane and loss of hair cells in the organ of Corti are the primary reasons for the hearing loss.

- 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.

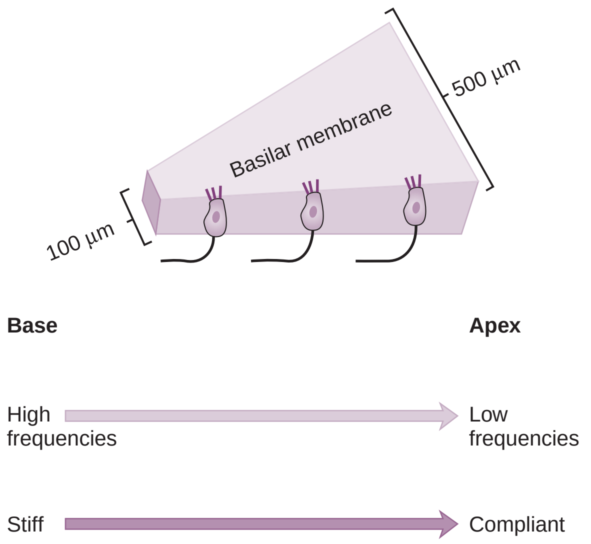
High-frequency sounds: stimulate hair cells at base of basilar membrane to vibrate

Low-frequency sounds: stimulate hair cells at apex of basilar membrane to vibrate

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



2-27: Pathway of auditory transduction. *CN,* Cranial nerve. *(From Weyhenmeyer J, Gallman E: Rapid Review Neuroscience. Philadelphia, Mosby, 2007, Fig. 13-4.)*



2-28: Effect of sound frequency on location of basilar membrane stimulation. *(From Costanzo L: Physiology, 3rd ed. Philadelphia, Saunders, 2006, Fig. 3-21.)*

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.

Role of vestibular system: posture, balance, control of head and eye movements

Role of semicircular canals: detect rotation and angular acceleration

Role of utricle and saccule: detect linear acceleration

Kinocilium: longest cilium on each hair cell

Vestibular transduction: bending of hair cells with movement → generation of an action potential

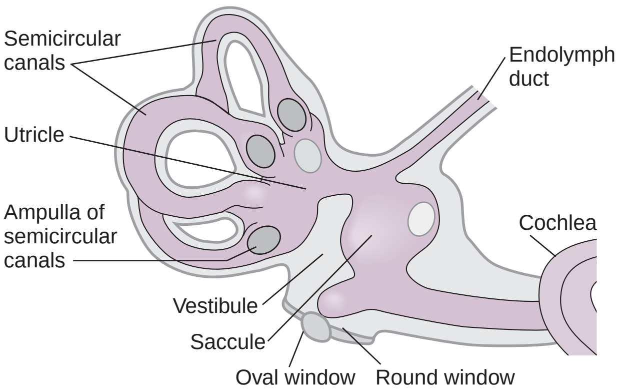
D. The vestibular system (vestibular organ)

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

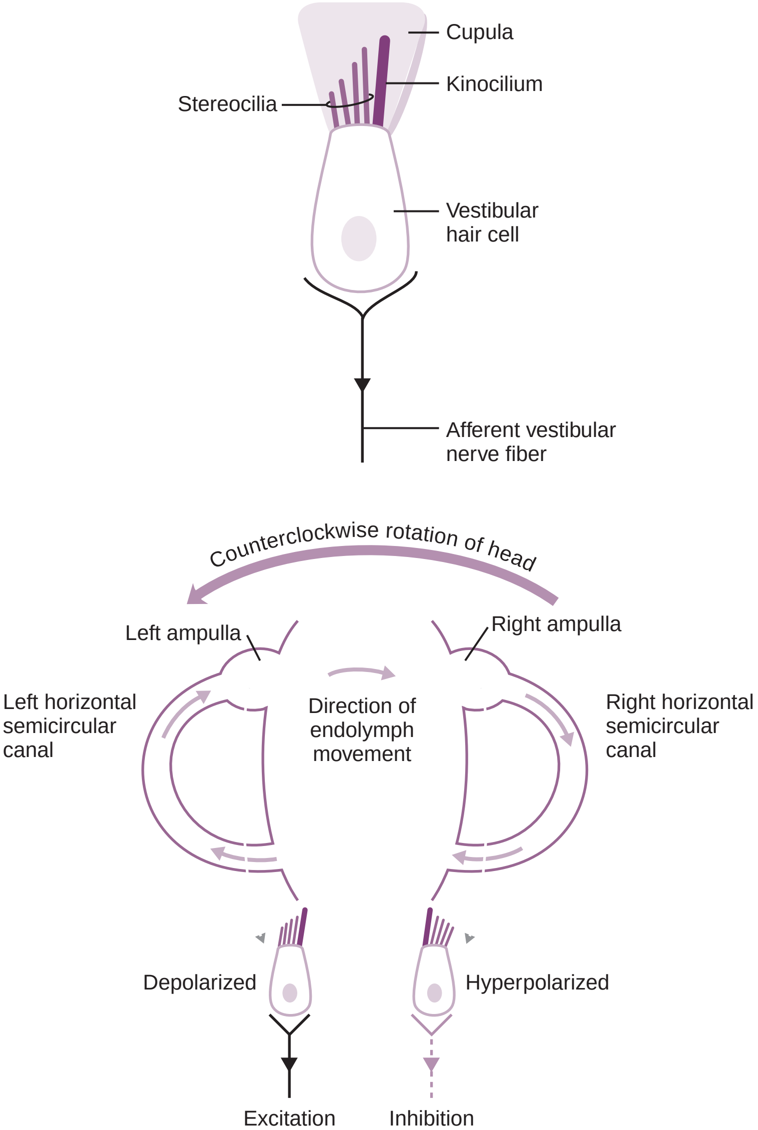
1. **Structure of the vestibular organ** (Fig. 2-29)
   - The **vestibular organ** is a membranous labyrinth consisting of three perpendicular semicircular canals, a utricle, and a saccule, all interconnecting and filled with endolymph.
   - The **semicircular canals** detect **rotation** or angular 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

FINDING	RINNE TEST: COMPARISON OF AIR AND BONE CONDUCTION	WEBER TEST: SOUND LATERALIZES TO
Normal Findings	Air > bone, both ears	(No lateralization)
Left Ear		
Conduction deafness	Bone > air on *left* Air > bone on *right*	*Left* ear
Partial sensorineural deafness	Air > bone, both ears	*Right* ear
Right Ear		
Conduction deafness	Bone > air on *right* Air > bone on *left*	*Right* ear
Partial sensorineural deafness	Air > bone, both ears	*Left* ear



2-29: The vestibular system (anterior view). The hair cells are located in the shaded areas (maculae).



2-30: Vestibular transduction. *(From Costanzo L: Physiology, 3rd ed. Philadelphia, Saunders, 2006, Fig. 3-23.)*

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.

Stereocilia bend *toward* kinocilium → hair cell depolarized/excited

Stereocilia bend *away* from kinocilium → hair cell hyperpolarized/inhibited

Hair cells no longer stimulated or inhibited once endolymph "catches up" with cupula

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.

Vestibular-ocular reflexes: stabilize visual images by compensating for head movement

Nystagmus: may indicate vestibulocerebellar injury

Direction of nystagmus: defined as direction of the fast phase of eye movement

Vestibular system: drives slow phase of nystagmus; brainstem: drives fast phase of nystagmus

- 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.

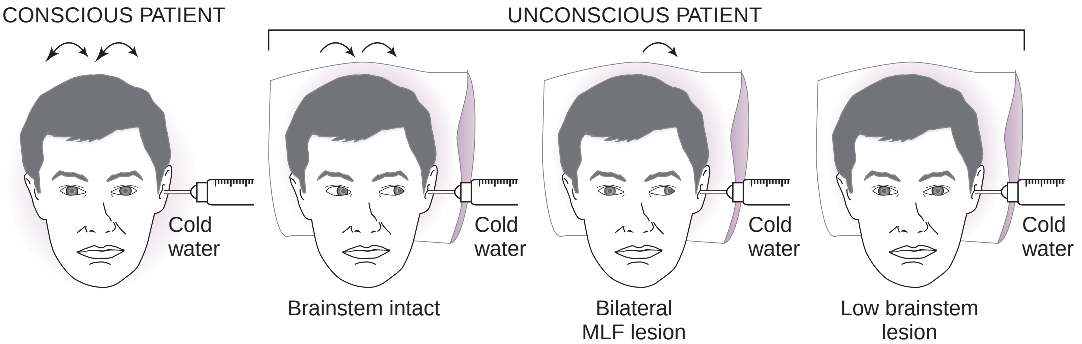
Clinical note: In comatose patients, the nature of the nystagmus elicited by cold-water irrigation can help determine the location of a lesion (see Fig. 2-31).

E. Olfaction

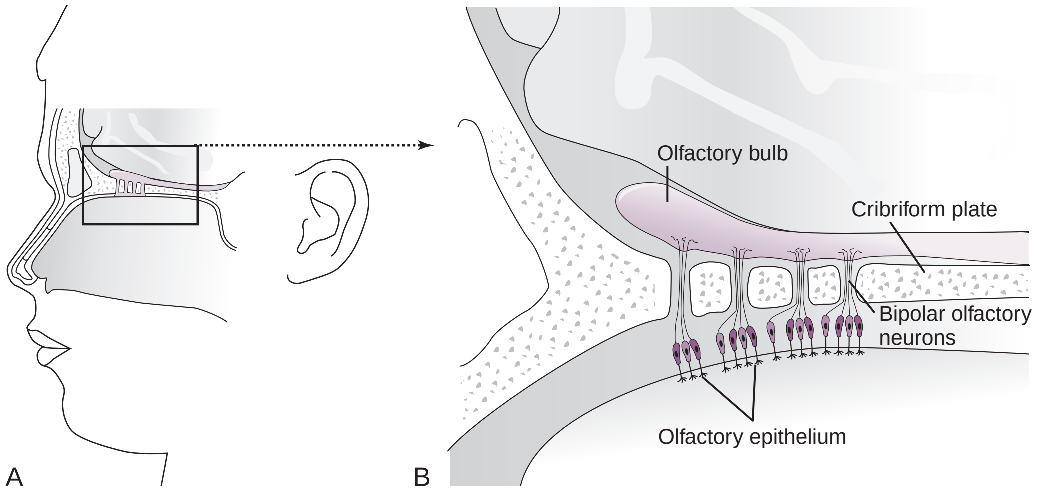
1. **Structure of olfactory apparatus** (Fig. 2-32)

Smell: detected by olfactory receptor cells on olfactory epithelium

- Smell is detected by **olfactory receptor cells,** which are situated in mucus-coated **olfactory epithelium** that lines the posterodorsal parts of the nasal cavities.



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.

Axons of olfactory receptor cells: form the first cranial nerve (CN I)

Axons of mitral cells: form the olfactory tract/stria, which project to olfactory cortex and amygdala

Olfactory receptor cells: only regenerative neurons in adult human

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).

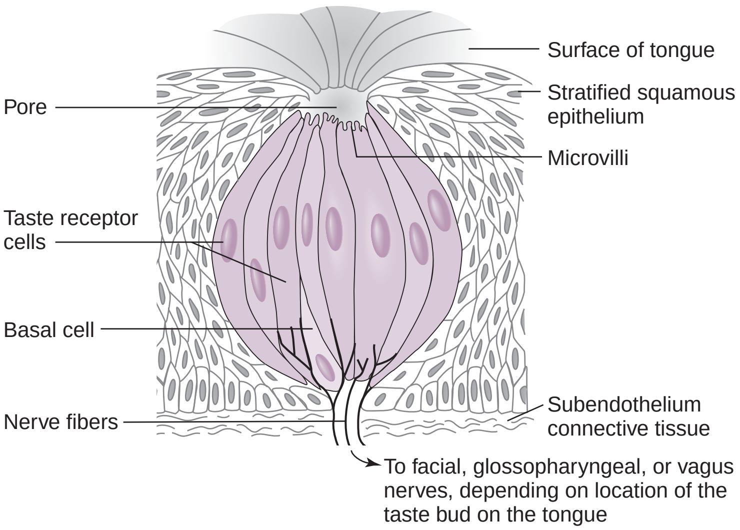
2. **Olfactory transduction**
   - Odoriferous molecules bind to cilia on the olfactory receptor cells.
   - Activation of receptors leads to the **stimulation of G proteins** and, in turn, activation of **adenylate cyclase.**
   - The activation of adenylate cyclase leads to an **increase** in **intracellular 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.

Binding of odoriferous molecules to cilia on olfactory cells: ultimately results in action potential generation and transduction of signal to olfactory cortex

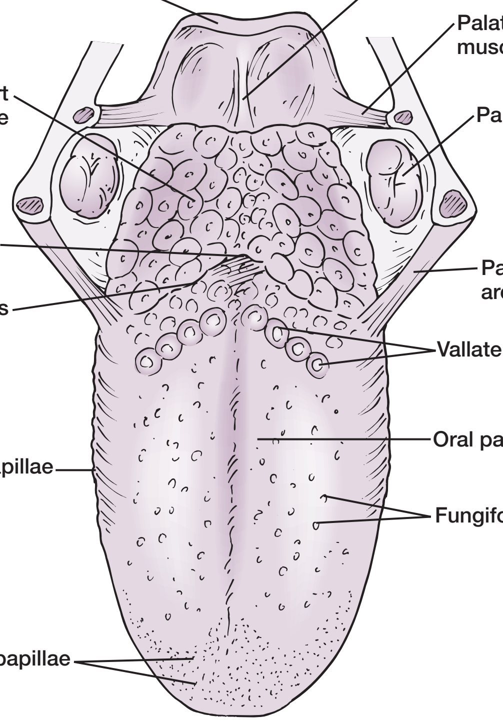
F. Taste

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).

Taste buds on anterior two thirds of tongue: detect sweet and salty tastes; transmit through lingual nerve to facial nerve



2-33: Taste bud.



2-34: Papillae of the tongue. *(From Telser A, Young J, Baldwin K: Elsevier's Integrated Histology. Philadelphia, Mosby, 2007, Fig. 11-8.)*

Taste buds on posterior third of tongue: detect bitter and sour tastes; transmit through glossopharyngeal and vagus nerves

- 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).**
  a. CN VII, IX, and X synapse with the tractus solitarius (solitary nucleus).
  b. Second-order neurons leave the solitary nucleus and project ipsilaterally to the ventral posterior medial nucleus of the thalamus.
  c. 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

Memory tracts: facilitated pathways for signal transmission important in formation of memories

Short-term memories: last only for seconds or minutes unless converted to long-term memories

Intermediate long-term memories: last for days to weeks unless converted to long-term memories

Long-term memories: last for years; mechanism involves synaptic structural and chemical changes

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.

Language comprehension: Wernicke area; lesions cause receptive aphasia

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.

Verbalization of language: Broca area; lesions cause expressive aphasia

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.

Language center: present in left hemisphere in most individuals, even if left-handed

Right middle cerebral artery strokes can present with left-sided weakness and sensory deficits, dysarthria and dysphagia but *not* aphasia, and left-sided neglect

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.

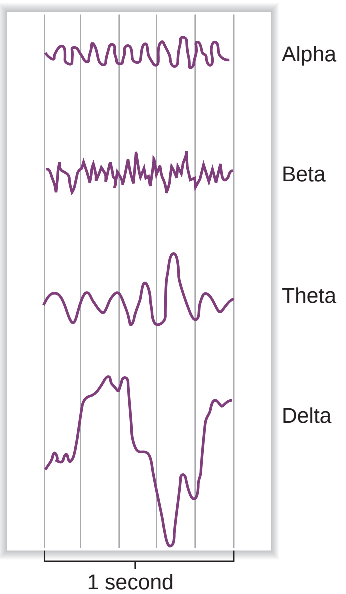
Brain waves: synchronous firing of millions of neurons can be detected on surface of the head by EEG

Alpha waves: seen in awake but resting state

Beta waves: seen in awake but alert state

Theta waves: seen in healthy children and in adults with brain disorders

Delta waves: seen in very deep sleep, infants, and patients with severe brain disease



2-35: Electroencephalogram waves.

Sleep-wake cycle: driven by the suprachiasmatic nucleus of hypothalamus

Classification of sleep: divided into NREM and REM sleep

Most sleep time is spent in NREM sleep.

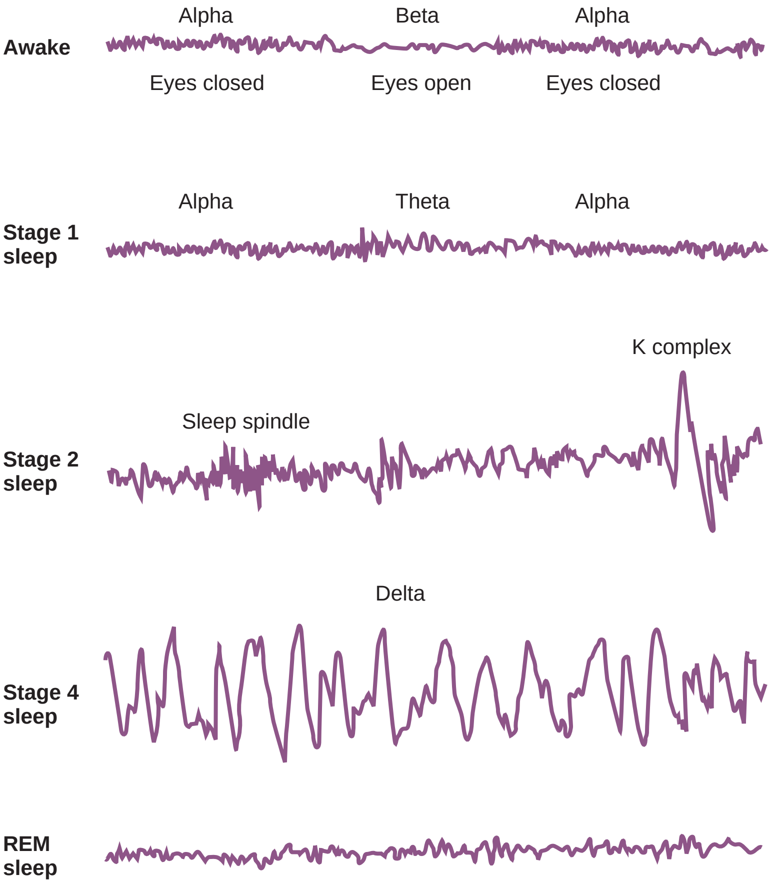
Stage 2 NREM: most of time spent in this phase, characterized by sleep spindles and K complexes on EEG

NREM sleep: progress from very light sleep (stage 1) to stage 2, where most time is spent, to very deep sleep (stages 3 and 4)

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.



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.

Brain is vulnerable to ischemia as a result of high metabolic rate and dependence on glucose as fuel source.

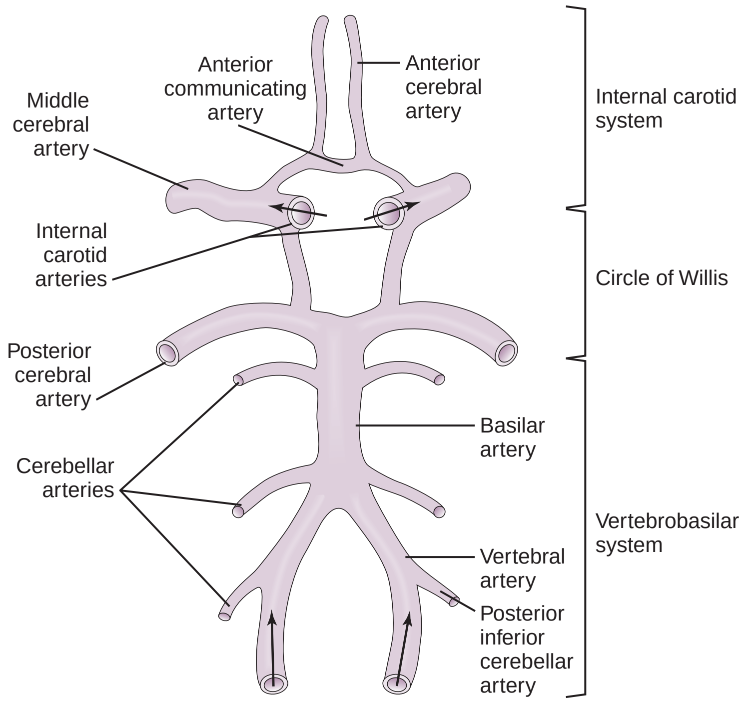
Internal carotid arteries: >70% stenosis in the setting of an acute cerebrovascular accident → indication for carotid endarterectomy

Circle of Willis: interconnects the internal carotid and vertebrobasilar systems to ensure adequate cerebral perfusion

A stroke involving the anterior cerebral artery may present as contralateral lower extremity weakness.

Cerebrovascular accident involving proximal MCA and lenticulostriate branches may cause contralateral arm weakness and dysarthria.

Cerebrovascular accident of distal left MCA can cause *cortical* deficits such as aphasia.



2-37: Cerebral blood supply, showing the arteries at the base of the brain (viewed from below).

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.

Thrombosis of the vertebral artery can cause severe brainstem ischemia and may result in the so-called locked-in syndrome

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.

CHAPTER 3
ENDOCRINE PHYSIOLOGY

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.

Hormones maintain homeostasis by regulating processes such as development, metabolism, and reproduction.

Hormones: maintain homeostasis through feedback loops

Hormones: act slowly relative to 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.

Endocrinopathies: due to qualitative or quantitative defect in hormone synthesis and/or tissue sensitivity to hormone

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.

Steroid hormones: produced continuously, cannot be stored, synthesis and secretion ↑ on demand

Steroid hormones: circulate bound to proteins, diffuse freely through cell membranes

Sex steroids: testosterone, progesterone, estrogen

Adrenal steroids: aldosterone, cortisol

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)

Thyroid hormones: derived from amino acid tyrosine, not cholesterol

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.**

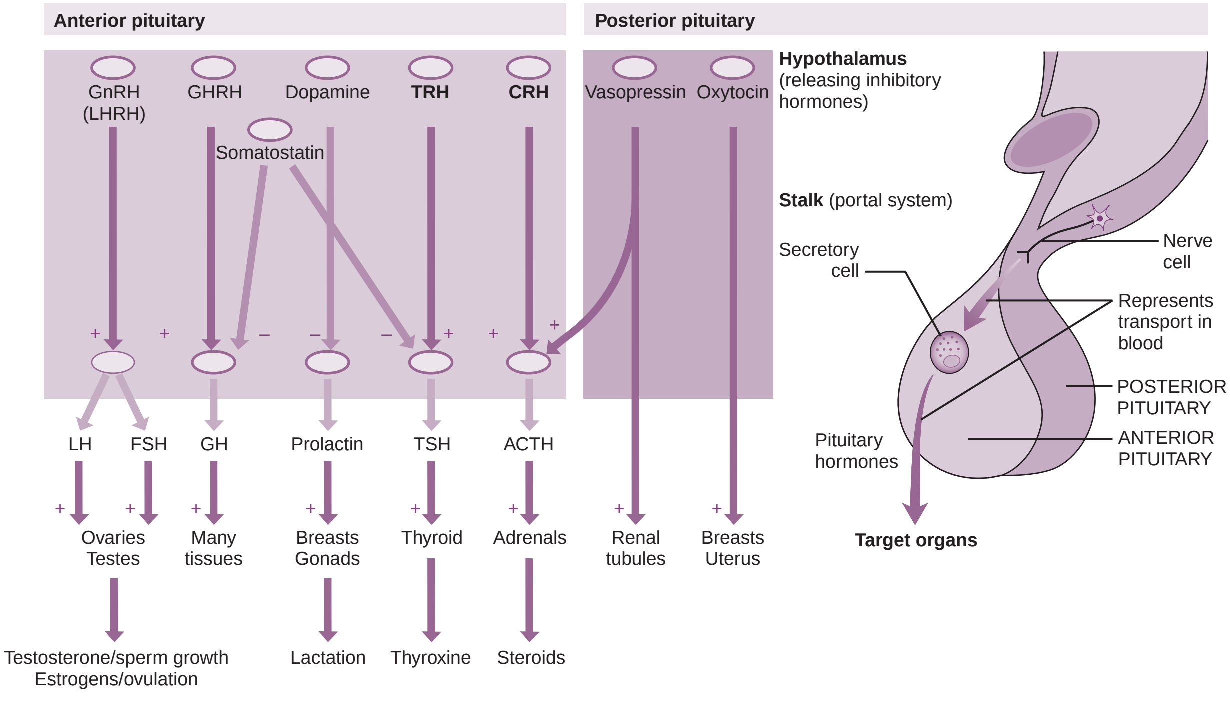
Protein, peptide, amino acid hormones: hydrophilic, stored in vesicles, released on demand, bind membrane-bound receptors

TABLE 3-1. Hormones

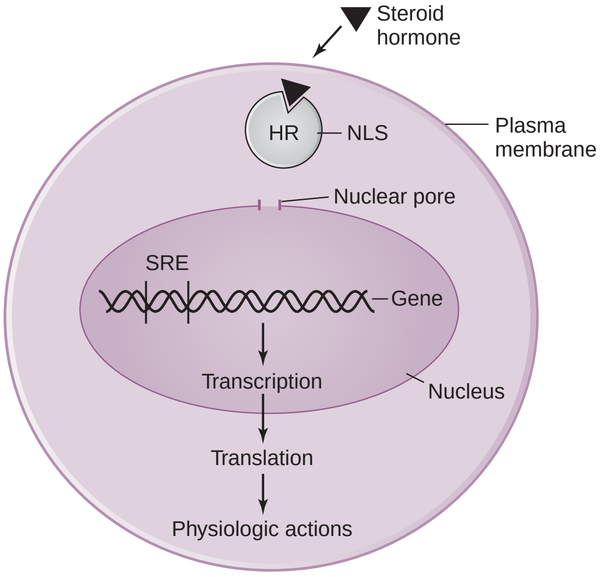
HORMONES	PHYSIOLOGIC ACTIONS	PATHOPHYSIOLOGY
Hypothalamic Hormones		
Corticotropin-releasing hormone (CRH)	Stimulates adrenocorticotropic hormone (ACTH) secretion from anterior pituitary	Increase in adrenal insufficiency due to loss of negative feedback
Gonadotropin-releasing hormone (GnRH)	Stimulates gonadotropin secretion from anterior pituitary	Hypothalamic hypogonadotrophic hypogonadism due to hyperprolactinemia → infertility Increase in hypothyroidism → ↓ dopamine secretion due to ↑ TRH → hyperprolactinemia
Thyrotropin-releasing hormone (TRH)	Stimulates thyroid-stimulating hormone (TSH) secretion from anterior pituitary	Decrease in primary or secondary hyperthyroidism due to feedback inhibition
Growth hormone-releasing hormone (GHRH)	Stimulates growth hormone secretion from anterior pituitary	Decrease in growth hormone (GH)-secreting tumor of anterior pituitary
Somatostatin	Inhibits GH secretion from anterior pituitary	Synthetic version (octreotide) used in GH-secreting pituitary adenomas
Dopamine	Inhibits prolactin secretion from anterior pituitary	Hypothyroidism → hyperprolactinemia Antipsychotics → hyperprolactinemia
Anterior Pituitary Hormones		
Adrenocorticotropic hormone (ACTH)	Stimulates glucocorticoid and androgen synthesis in adrenal medulla	Cushing disease ↓ Cushing syndrome Paraneoplastic secretion (e.g., small cell lung carcinoma) Cushing disease: ACTH-hypersecreting pituitary
Thyroid stimulating hormone (TSH)	Stimulates thyroid hormone synthesis in the thyroid gland	TSH-secreting pituitary adenoma (secondary hyperthyroidism) ↓ in panhypopituitarism
Luteinizing hormone (LH)	Stimulates testosterone secretion by Leydig cells in testes Stimulates progesterone synthesis in women Stimulates ovulation and corpus luteum development	Elevated levels: polycystic ovary syndrome (PCOS), testicular failure, premature menopause, Turner syndrome Decreased levels: hyperprolactinemia, Kallman syndrome, eating disorders (anorexia), hypopituitarism
Follicle-stimulating hormone (FSH)	Stimulates spermatogenesis in testes Stimulates estrogen synthesis by granulosa cells in ovarian follicles	Elevated levels: testicular failure, premature menopause, Turner syndrome Decreased levels: Kallman syndrome, PCOS, hypopituitarism
Growth hormone (GH)	Anabolic hormone with multiple anabolic and insulin-antagonizing metabolic effects	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
Prolactin	Stimulates breast maturation and milk letdown	Prolactinoma: hypersecreting prolactinoma resulting in galactorrhea and infertility in women
Posterior Pituitary Hormones		
Antidiuretic hormone (ADH)	Stimulates water absorption from the distal nephron	Syndrome of inappropriate antidiuretic hormone (SIADH) Central diabetes insipidus Nephrogenic diabetes insipidus
Oxytocin	Stimulates uterine contraction during labor	
Thyroid Hormones		
Thyroxine (T_4)	Prohormone that becomes bioactive on peripheral conversion to T_3	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 Euthyroid sick syndrome: impaired peripheral conversion of T_4 to T_3
Triiodothyronine (T_3)	Increases basal metabolic rate by up-regulating expression and insertion of Na^+,K^+-ATPase pump	
Adrenal Cortex Hormones		
Aldosterone	Promotes renal Na^+ retention and expands plasma volume	Hypersecreted in primary aldosteronism → hypertension with hypokalemic metabolic alkalosis
Cortisol	Helps maintain glucose for glucose-dependent tissues during fasting state by promoting hepatic gluconeogenesis, peripheral resistance to insulin, and lipolysis in adipose tissue	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
Dehydroepiandrosterone (DHEA)	Converted to testosterone in peripheral tissues	Congenital adrenal hyperplasia: oversecretion of androgens results in virilization, precocious puberty, ambiguous genitalia

TABLE 3-1. Hormones—cont'd

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



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.)*



3-2: After diffusing through the plasma membrane, most steroid hormones bind to a cytoplasmic receptor. This hormone-receptor complex then undergoes a conformational change, which uncovers a nuclear localization site that allows access to the nucleus. The complex then binds to and activates genes that contain the appropriate steroid response element within their sequence. *HR,* Hormone receptor; *NLS,* nuclear localization sequence; *SRE,* steroid response element.

- 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.

Membrane-spanning receptors: kinase receptors, ligand-gated ion channels, receptor-linked kinases, G protein–coupled receptors

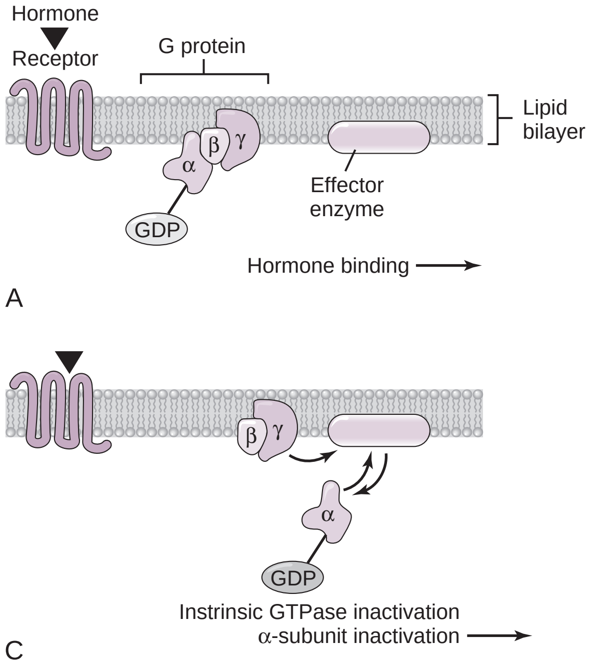
- Figure 3-3 shows the mechanism underlying G protein signal transduction.

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).

Hormone-binding proteins: extend half-life of bound hormone, levels often ↑ in pregnancy

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.



3-3: G protein signal transduction cascade. The first step **(A)** is the binding of hormone (triangle) to a G protein–associated membrane receptor. This hormone binding stimulates the receptor to undergo a conformational change **(B),** which causes the α-subunit of the G protein to release guanosine diphosphate (GDP) and bind guanosine triphosphate (GTP). This causes the α-subunit to dissociate from the β-γ complex. The α-subunit and the β-γ complex are then free to diffuse laterally within the lipid bilayer and activate or inhibit the activity of various effector molecules, such as adenylate cyclase **(C).** After several seconds, intrinsic GTPase activity of the α-subunit degrades the GTP to GDP. The GDP-bound α-subunit is inactive and also binds to the β-γ complex **(D),** restoring the system to its original condition. The intrinsic adenosine triphosphatase (ATPase) activity of the α-GTP complex limits the duration of the response.

TABLE 3-2. Hormone Binding in Some Plasma Proteins

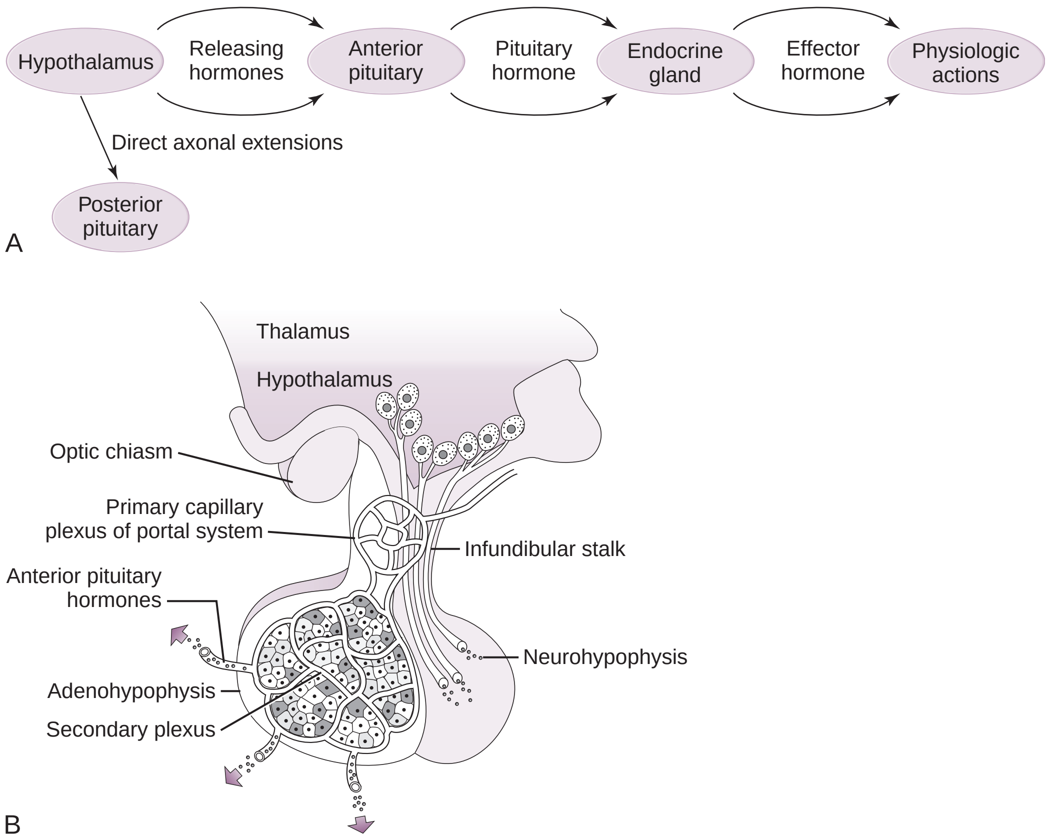
PLASMA PROTEIN	HORMONE
Albumin	Multiple lipophilic hormones
Transthyretin	Thyroxine (T_4)
Transcortin	Cortisol, aldosterone
Thyroxine-binding globulin	Triiodothyronine (T_3), T_4
Sex hormone–binding globulin	Testosterone, estrogen

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.

Hypothalamic-hypophyseal portal system: targets delivery of hypothalamic hormones to adenohypophysis with minimal systemic distribution

Posterior pituitary: composed of axonal extensions originating from hypothalamus



3-4: **A,** Hierarchical control of hormone secretion. **B,** Hypothalamic-hypophyseal portal system.

TABLE 3-3. Effect of Hormones Released by the Hypothalamus on the Anterior Pituitary

HORMONE	EFFECT ON ANTERIOR PITUITARY
Growth hormone–releasing hormone (GHRH)	Stimulates growth hormone (GH) secretion
Prolactin-inhibitory factor (dopamine)	Inhibits prolactin secretion
Somatostatin	Inhibits GH secretion
Gonadotropin-releasing hormone (GnRH)	Stimulates luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion
Corticotropin-releasing hormone (CRH)	Stimulates adrenocorticotropic hormone (ACTH) secretion
Thyrotropin-releasing hormone (TRH)	Stimulates thyroid-stimulating hormone (TSH) secretion

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 thyroid-stimulating 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.**

Location of defect: primary disease: endocrine gland; secondary disease: pituitary; tertiary disease: hypothalamus

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.**

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-hydroxlase) 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.

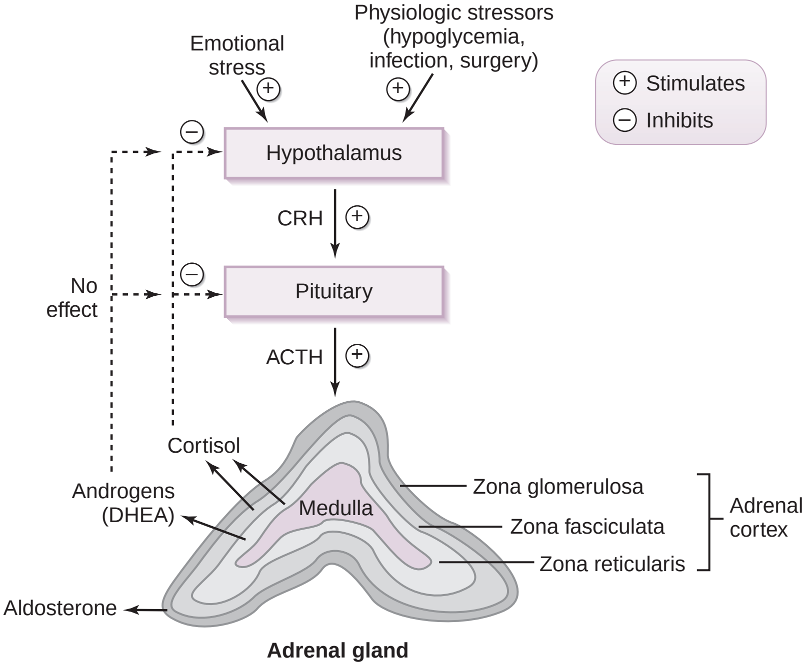
Primary glucocorticoid: cortisol

Primary androgen: DHEA

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.

Cortisol secretion: stimulated by physiologic stressors

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.



3-5: Main determinants of hypothalamic-pituitary-adrenal axis. *ACTH*, Adrenocorticotropic hormone; *CRH*, corticotropin-releasing hormone; *DHEA*, dehydroepiandrosterone.

Cortisol secretion: diurnal pattern, highest in morning

- 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).

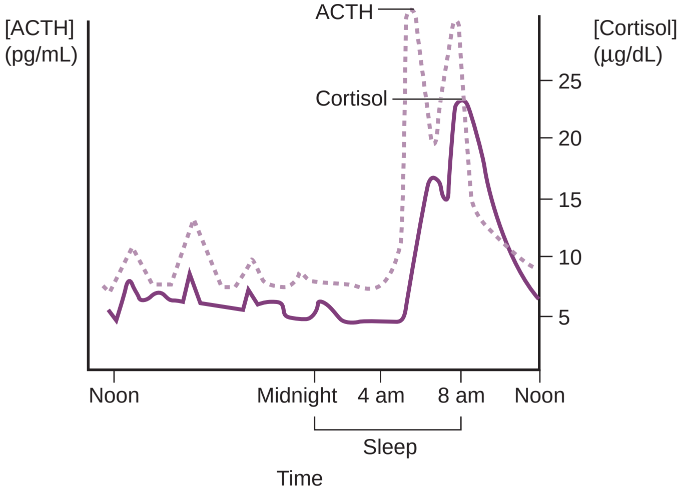
3. **Biosynthetic pathway of adrenal corticosteroids**

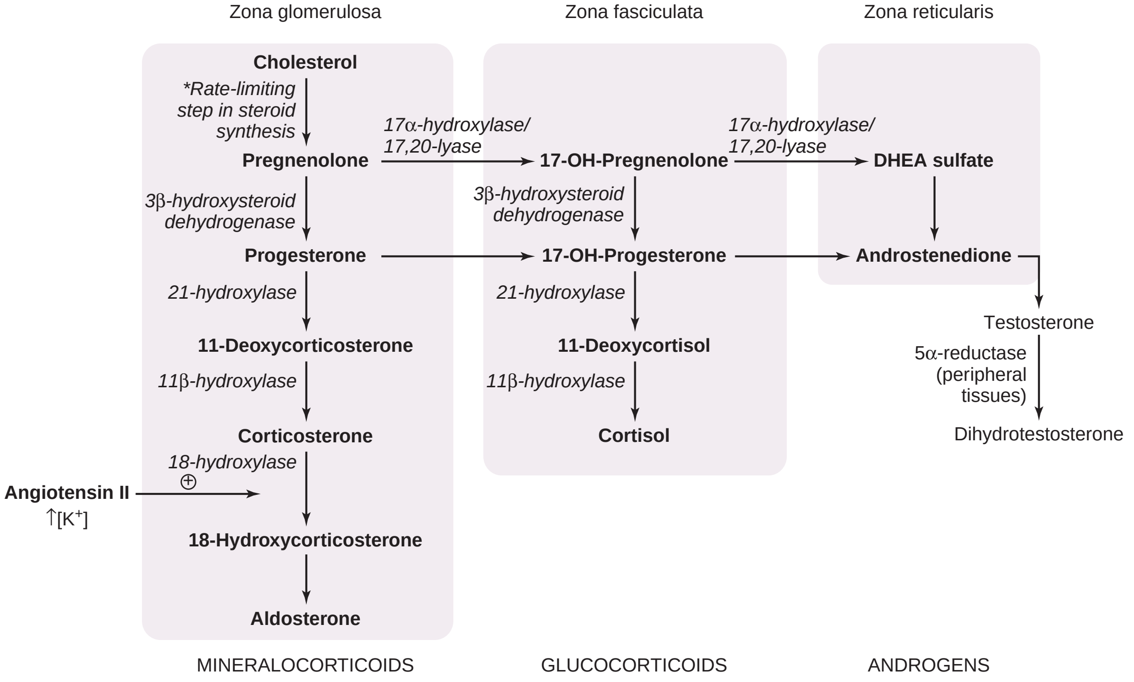
Rate-limiting step in steroid hormone synthesis: conversion of cholesterol to pregnenolone

- 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.**

Layers of adrenal cortex: "GFR" for zona *g*lomerulosa, *f*asciculata, and *r*eticularis

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.

Aldosterone synthesis: regulated by K^+ and angiotensin II rather than ACTH

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).

Steroid hormones: regulate expression of genes containing steroid-responsive elements

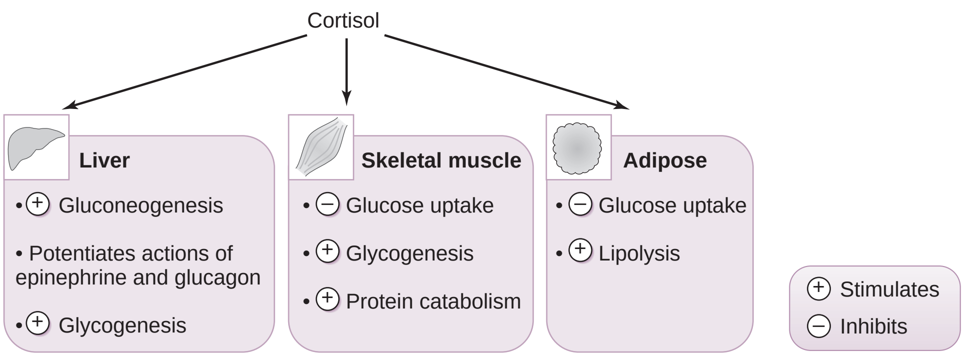
Steroid hormones: effects can take hours to days to manifest because they work by altering gene expression

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.

Metabolic actions of cortisol: generally catabolic, stimulates gluconeogenesis, preserves plasma glucose

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.



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 **α_1-adrenergic receptors** on vascular smooth muscle results in **vasoconstriction.**
      (2) β-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.**

Cortisol: exerts mineralocorticoid effects at higher plasma concentrations

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.

Cortisol: potent anti-inflammatory but with myriad acute and chronic side effects

Cortisol: inhibits osteoblasts, stimulates osteoclasts

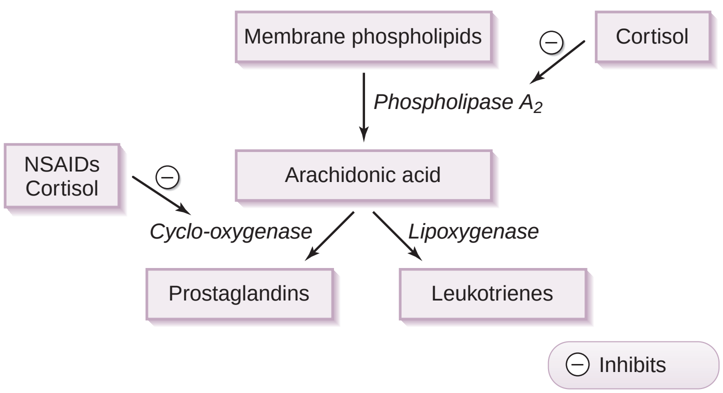
Avascular necrosis: steroids may precipitate; most commonly occurs in hip

Cortisol: inhibits intestinal Ca^{2+} absorption; inhibits calcitriol synthesis

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.**

Manifestations of chronic hypercortisolism: diabetes mellitus, muscle atrophy, osteoporosis, hypertension



3-9: Anti-inflammatory action of cortisol. *NSAIDs*, 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**).

Cushing syndrome: most often iatrogenic

Pituitary Cushing: most common pathologic cause of Cushing syndrome; caused by ACTH-hypersecreting pituitary adenoma

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.

Pituitary Cushing: ACTH should partially suppress in response to high-dose dexamethasone; ectopic and adrenal Cushing do not suppress

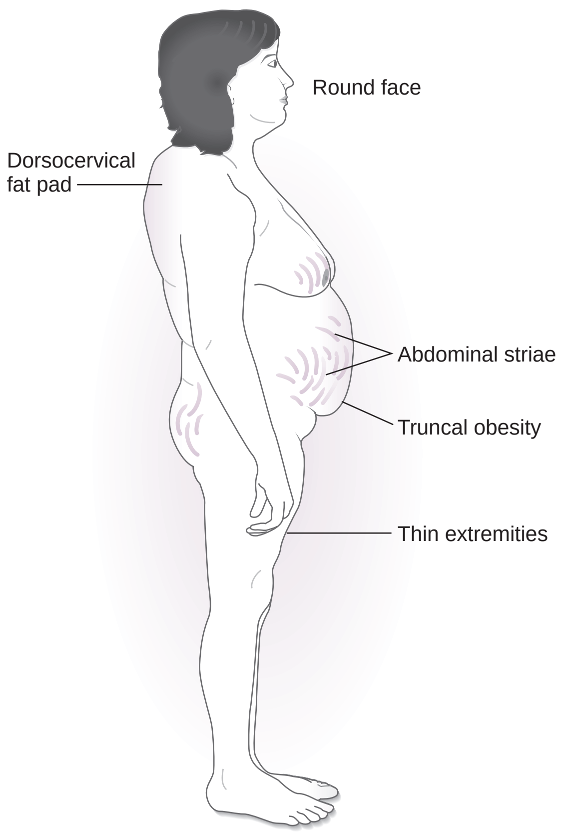
- **Hypocortisolism (adrenal insufficiency)**

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.

ACTH: stimulates adrenal androgen synthesis

Androgens: do *not* feedback-inhibit ACTH secretion

Congenital adrenal hyperplasias: relatively rare disorders characterized by enzyme defects in cortisol biosynthetic pathway

CAH: ↑ ACTH → adrenal hyperplasia → ↑ shunting of cortisol precursors to androgens

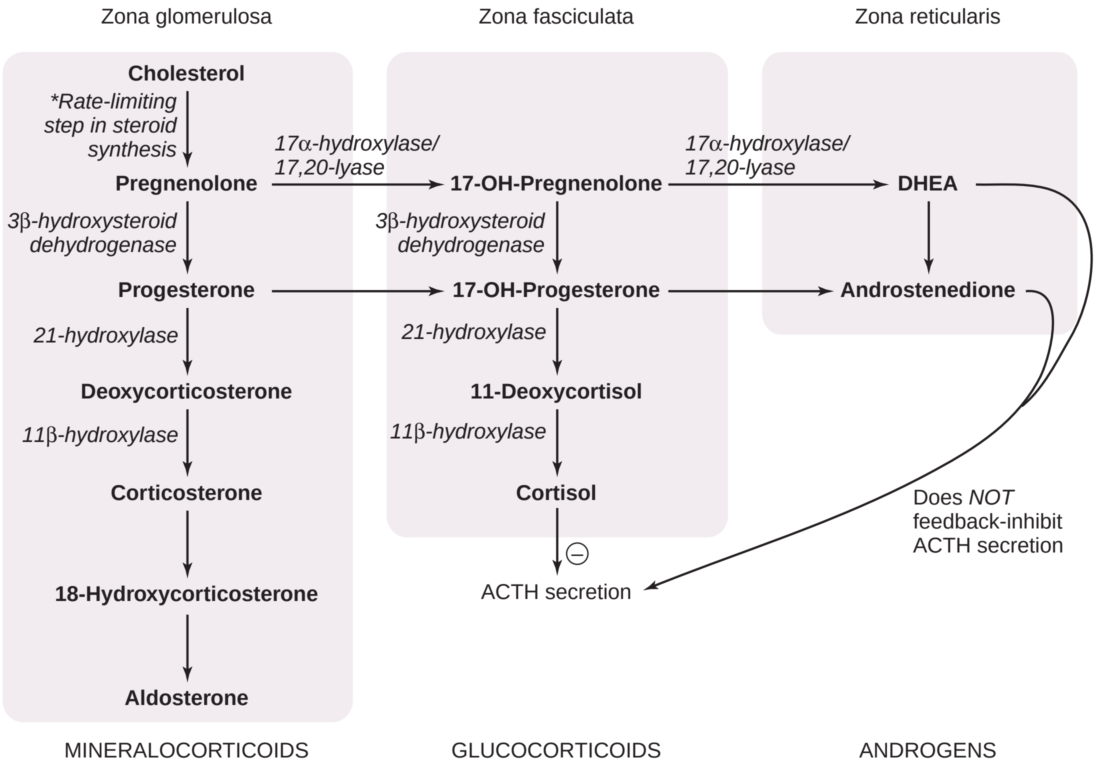
Congenital adrenal hyperplasias: precocious puberty in male children, ambiguous genitalia in female neonates

Most common causes of CAH: 21-hydroxylase deficiency; salt wasting, hypotension

21-hydroxylase deficiency: most common cause of CAH

11β-hydroxylase deficiency: rare

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.**



3-11: Pathways of adrenal steroidogenesis. *ACTH*, Adrenocorticotropic hormone; *DHEA*, dehydroepiandrosterone.

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

TRH → TSH → T_3 + T_4 → physiologic actions

Calcitonin: secreted by parafollicular cells, involved in Ca^{2+} regulation; *not* regulated by hypothalamic-pituitary-thyroid axis

Thyroglobulin: primary protein of follicular lumen; substrate on which thyroid hormones are produced

Plasma thyroglobulin: levels can be used to detect and monitor certain types of thyroid cancer

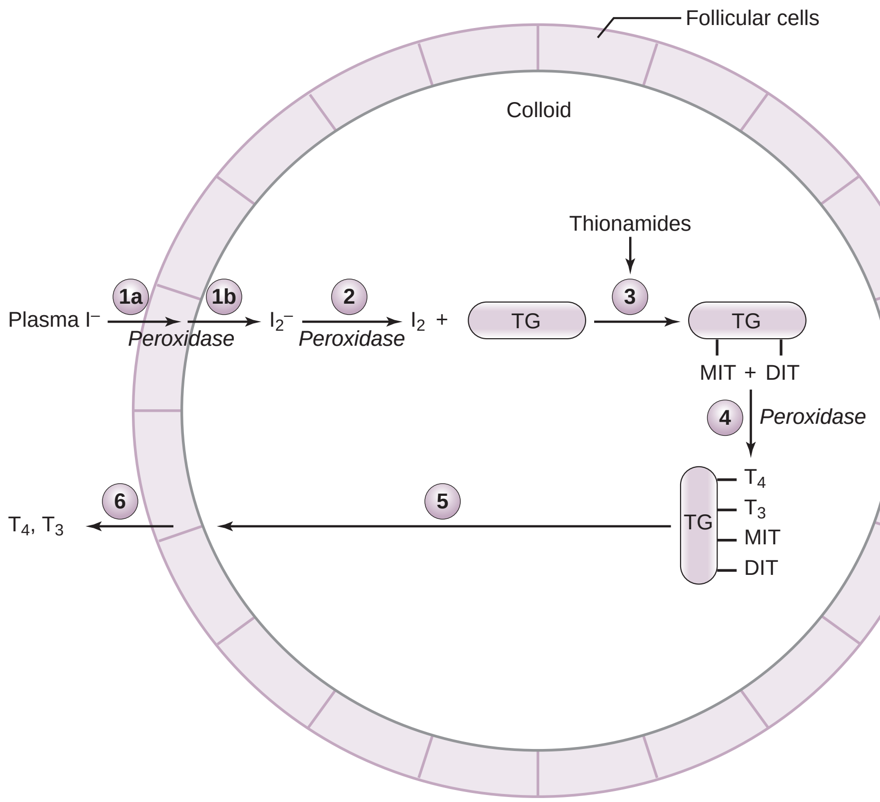
Thionamides: inhibit the organification step

Colloid: large storage depot for thyroid hormones

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

DISORDER	PATHOPHYSIOLOGY	CLINICAL FEATURES	TREATMENT
Primary adrenal insufficiency (Addison disease)	Autoimmune, metastatic, or tubercular destruction of adrenal cortices	↓ Aldosterone → hyperkalemic metabolic acidosis, sodium wasting, volume depletion, hypotension ↓ Cortisol → hypoglycemia, weakness, vulnerability to stress ↓ Adrenal androgens → loss of pubic and axillary hair in females ↑ ACTH → 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	↑ Cortisol → 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)	↑ ACTH → hypercortisolism, hyperpigmentation ↑ Cortisol → same effects as in Cushing syndrome ↑ Androgens → hirsutism ↓ ACTH due to feedback inhibition of pituitary	Surgery

ACTH, Adrenocorticotropic hormone.



3-12: Thyroid hormone synthesis in the thyroid follicle. (1) Uptake of plasma I^- by iodide pump of thyroid follicular cells (a) and extrusion into follicular lumen (b). (2) Oxidation of I^- to I_2 by peroxidase. (3) Organification: I_2 is attached to tyrosine residues attached to thyroglobin (TG), forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). (4) Coupling of MIT and DIT to T_4 and T_3. (5) Endocytosis of TG from colloid. (6) Hydrolytic cleavage of T_3 and T_4 from TG and diffusion of T_4 and T_3 into plasma. T_3, Triiodothyronine; T_4, thyroxine.

- Hydrolytic **cleavage of T_3 and T_4 from thyroglobulin** and diffusion of T_4 and T_3 into plasma
  a. TSH-mediated step

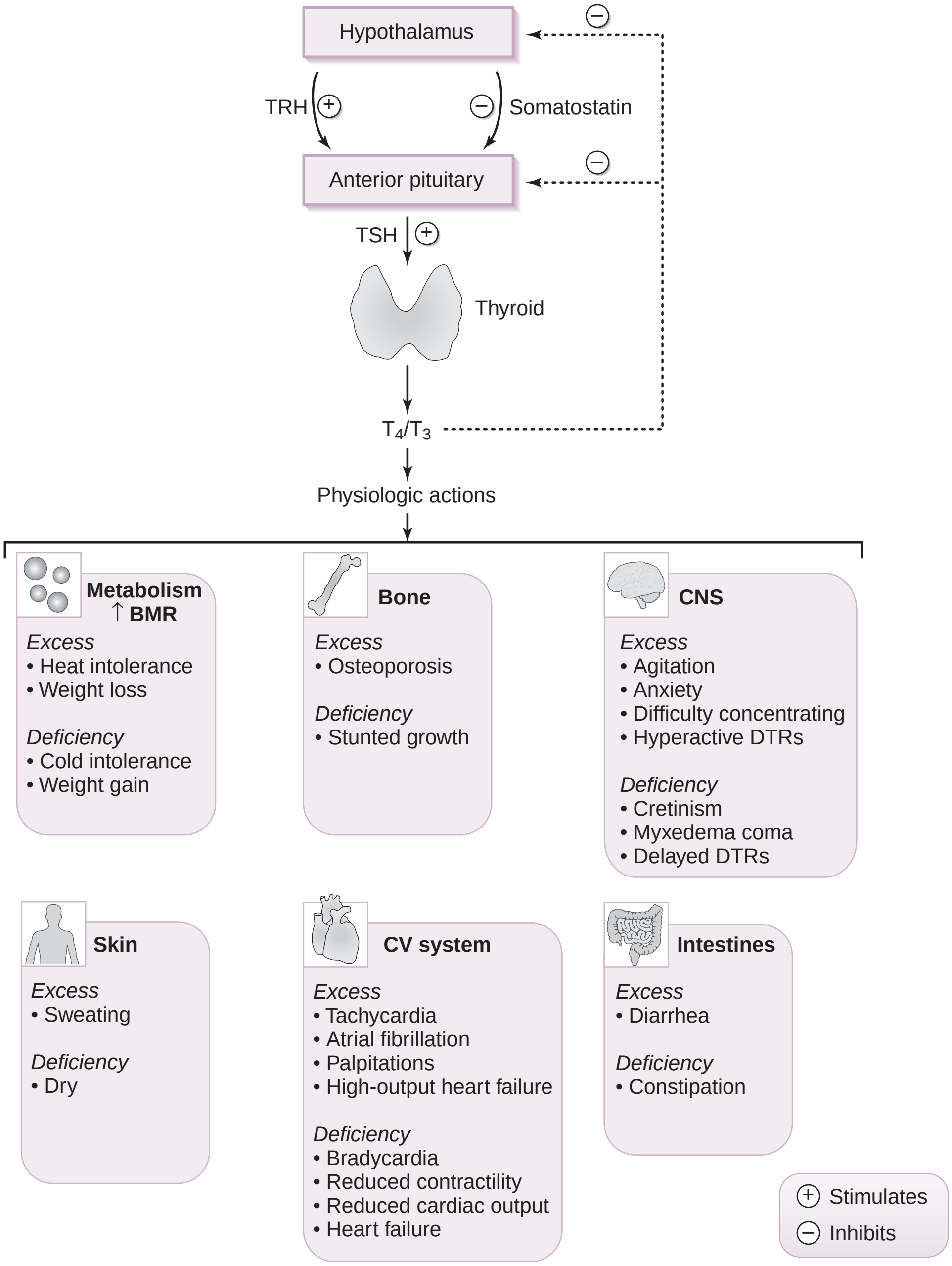
Amiodarone: can cause both hypothyroidism and hyperthyroidism

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 T_4 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 T_4 to T_3.

Thyroid hormones: up-regulate expression of Na^+,K^+-ATPase pump

3. **Physiologic actions of thyroid hormones** (Fig. 3-13)
   - Increased basal metabolic rate (BMR)
     a. Thyroid hormones increase the BMR primarily by **up-regulating expression** and **increasing activity** of the sodium-potassium adenosine triphosphatase pump **(Na^+,K^+-ATPase pump)** in most tissues.
     b. The increase in BMR causes heat intolerance, a common symptom of hyperthyroidism.



3-13: Thyroid regulation, physiology, and pathophysiology. *BMR,* Basal metabolic rate; *CHF,* congestive heart failure; *CNS,* central nervous system; *CV,* cardiovascular; *DTR,* deep tendon reflex; T_3, triiodothyronine; T_4, thyroxine; *TRH,* thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone.

- **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.**

Thyroid hormones: excessive levels → enhanced sensitivity to circulating catecholamines → palpitations, tremors; symptoms may respond to β-blockers

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_4 and T_3**
   - The thyroid gland secretes both T_4 and T_3.
   - **T_4** is much **less potent** than T_3, but it has a **longer** plasma **half-life** than T_3.
   - Within target cells, T_4 is converted into the more active T_3 by the enzyme **5′-monodeiodinase.**
     a. Therefore, T_4 can essentially be considered a prohormone that serves as a plasma reservoir for T_3.
   - Furthermore, because of its prolonged half-life, plasma T_4 is much more abundant than plasma T_3.
   - Therefore, it is principally responsible for the feedback inhibition of TRH secretion by the hypothalamus and TSH secretion by the pituitary.

Thyroxine (T_4): basically a prohormone; T_3 much more active

T_4: much more abundant than T_3 so primarily responsible for feedback inhibition of pituitary

Clinical note: In **hypothyroid patients,** supplementing only T_4 (rather than T_3) usually provides adequate tissue levels of T_3 from peripheral conversion. However, certain patients respond much better to a T_4-T_3 combination. Presumably, the peripheral conversion of T_4 to T_3 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.**
         (1) Note that weight loss occurs in a setting of *increased* appetite.
       - The direct and indirect cardiovascular effects of thyroid hormones **increase the cardiac workload** and over prolonged periods may cause **heart failure (high output type).**
         (1) **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_3 and T_4 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_3 and T_4.
       - **TSH-secreting pituitary tumor**
         (2) Rare cause of hyperthyroidism
       - **TRH-secreting hypothalamic tumor**
         (1) Very rare cause of hyperthyroidism
       - Thyroiditis

Hyperthyroidism: refers only to a pathologic increase in *synthesis* of thyroid hormone

Thyrotoxicosis: symptomatology associated with pathologically elevated levels of thyroid hormones irrespective of the etiology (e.g., gland destruction; increased synthesis)

Manifestations of hyperthyroidism: include weight loss with *increased* appetite, heat intolerance, diarrhea, and often atrial fibrillation

Graves disease: most common cause of hyperthyroidism

Graves disease: IgG antibodies mimic TSH and stimulate TSH receptor on thyroid

TSH-secreting pituitary tumor: rare cause of hyperthyroidism

TRH-secreting hypothalamic tumor: *very* rare cause of hyperthyroidism

TABLE 3-5. Laboratory Values Associated With Hyperthyroidism

TYPE OF HYPERTHYROIDISM	EXAMPLE	TRH	TSH	T_4
Primary	Graves disease	↓	↓	↑
Secondary	Pituitary adenoma	↓	↑	↑
Tertiary	Hypothalamic tumor	↑	↑	↑

T_4, Thyroxine; *TRH,* thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone.

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

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

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.

Thyroiditis: release of preformed thyroid hormone → transient thyrotoxicosis

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.

- 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

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 T_4 or T_3. 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 T_3 and T_4 concentrations but without apparent thyroid dysfunction
  c. Likely caused by increased production of cortisol, which inhibits the peripheral conversion of T_4 to T_3 but increases the production of reverse T_3 (rT_3)
    - **rT_3 is inactive but does bind to the T_3 receptor, blocking normal T_3 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).

Euthyroid sick syndrome: low to normal T_3 and T_4 in ill patients with no apparent signs of thyroid dysfunction; very common in hospitalized patients

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**

Reverse T_3 (rT_3): binds T_3 receptor, blocking normal T_3 from binding

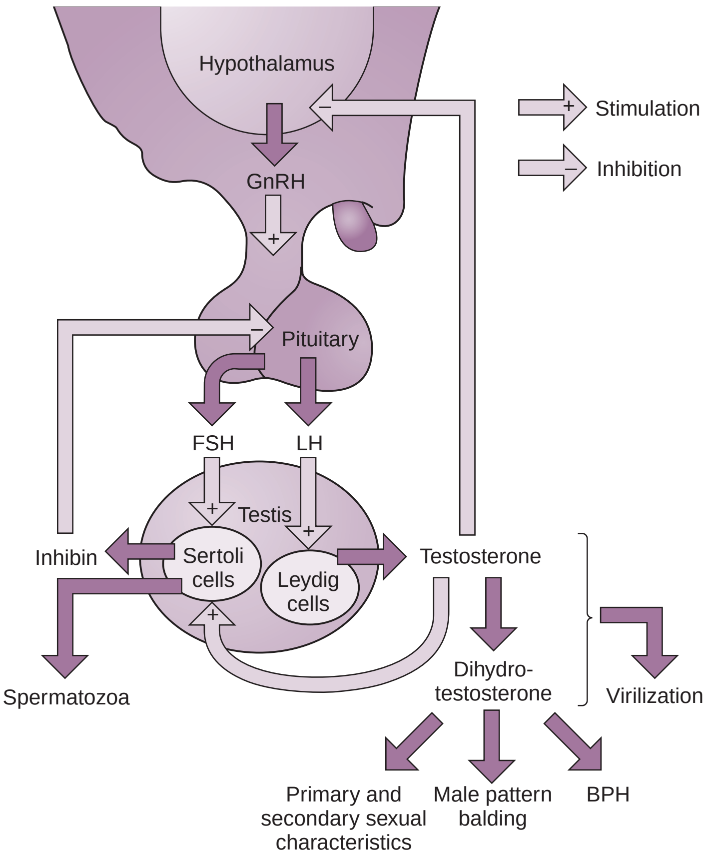
TABLE 3-7. Laboratory Values Associated With Hypothyroidism

TYPE OF HYPOTHYROIDISM	EXAMPLE	TRH	TSH	T_4
Primary	Hashimoto thyroiditis	↑	↑	↓
Secondary	Pituitary lesion	↑	↓	↓
Tertiary	Hypothalamic lesion	↓	↓	↓

T_4, Thyroxine; *TRH*, thyrotropin-releasing hormone; *TSH*, thyroid-stimulating hormone.

TABLE 3-8. Etiology and Differential Diagnosis of Hypothyroidism

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



3-14: Male axis. *BPH,* Benign prostatic hyperplasia; *FSH,* follicle-stimulating hormone; *GnRH,* gonadotropin-releasing hormone; *LH,* luteinizing hormone. *(Modified from Marshall W, Bangert S: Clinical Chemistry, 6th ed. Mosby, 2008, Fig. 7-4.)*

a. Testosterone is a steroid hormone that produces its effects by **stimulating protein synthesis (anabolic effect).**
b. In some tissues, especially the prostate and skin, testosterone is converted to a more potent form, **DHT**, by the enzyme **5α-reductase** before affecting cellular function.

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

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 **finasteride,** which inhibits the enzyme **5α-reductase,** thereby limiting the influence of DHT on the prostate and **shrinking it.** DHT is partly responsible for **male pattern baldness;** thus, finasteride is also modestly effective at restoring hair growth in men.

- **Physiologic actions of testosterone and dihydrotestosterone** (DHT)
  a. Embryologic functions of testosterone and DHT in males
    - **Testosterone** is responsible for development of the epididymis, vas deferens, and seminal vesicles from mesonephric duct structures during embryologic development.
    - **DHT** is responsible for development of the male external genitalia (penis, scrotum) and prostate gland.
      (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.

Testosterone: responsible for development of seminal vesicles, epididymis, vas deferens during embryogenesis

Absent testosterone: female sex organs will develop even in genetically male fetus

Clinical note: In **androgen insensitivity syndrome (testicular feminization),** the most common cause of **male hermaphroditism,** genetic males (46,XY) appear phenotypically female. This syndrome is caused by **mutations** in the **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 **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

(cont'd)
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.

Testosterone: ↑ lean muscle mass, bone density

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.

DHT: responsible for male pattern baldness in genetically prone men

Testosterone: responsible for the development of lean muscle mass, deepening of voice in 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).

Leuprolide: synthetic GnRH agonist given in nonpulsatile manner; cessation of menses in woman; ↓ androgen production in men with prostate cancer

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 progestins 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).

Spermatogenesis: process of sperm maturation in which a haploid male gamete is produced

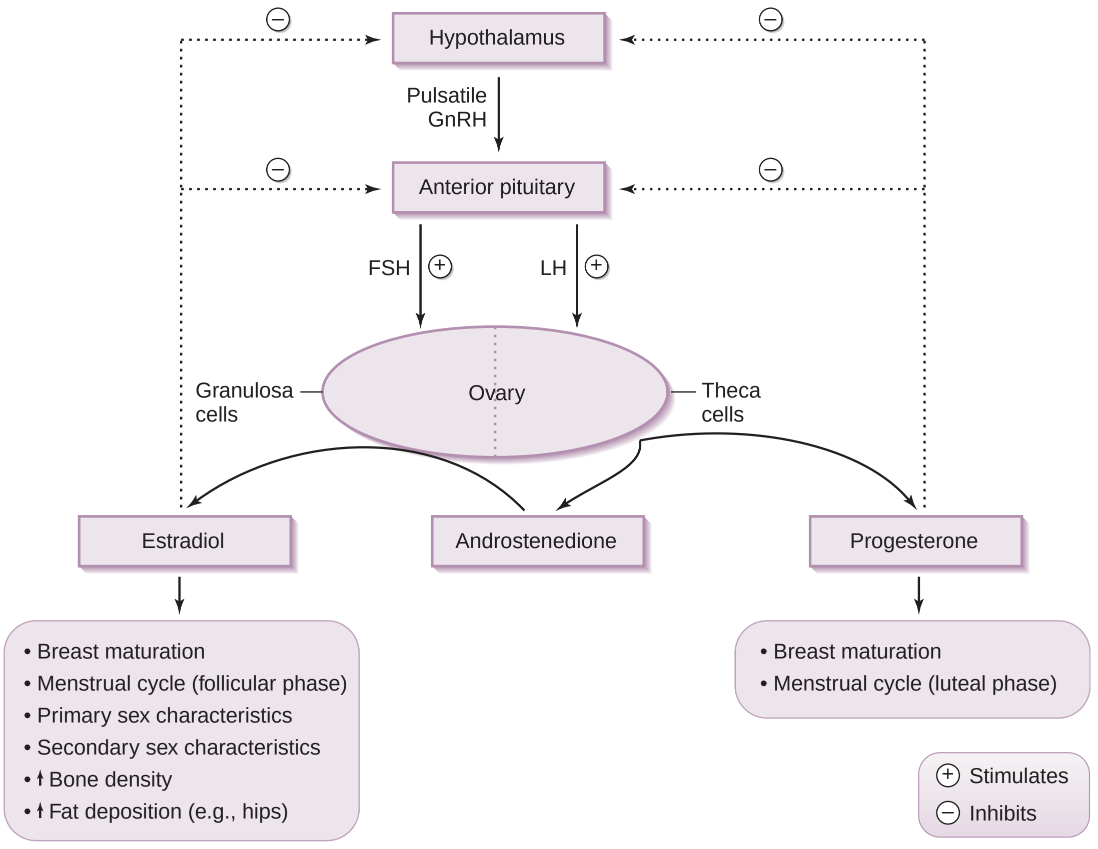
Clinical note: FSH is required for sperm maturation within the testes. By inhibiting FSH secretion by the pituitary, **inhibin** might be able to **prevent spermatogenesis** and could therefore be used as a **male contraceptive.** Indeed, clinical trials using inhibin are currently underway.

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.

Estrogen and progesterone: unnecessary for development of female primary sex organs

Estrogen: responsible for development of female secondary sexual characteristics (e.g., breast maturation, fat deposition on hips and buttocks)

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).



3-15: Female axis. *FSH,* Follicle-stimulating hormone; *GnRH,* gonadotropin-releasing hormone; *LH,* luteinizing hormone.

- **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.

Actions of progesterone: breast development, regulation of menstrual cycle, maintenance of pregnancy

Estrogen and progesterone: antagonize effects of prolactin → prevent milk letdown in pregnant women

- **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.

FSH stimulates estrogen synthesis by granulosa cells.

LH stimulates progesterone synthesis by theca cells.

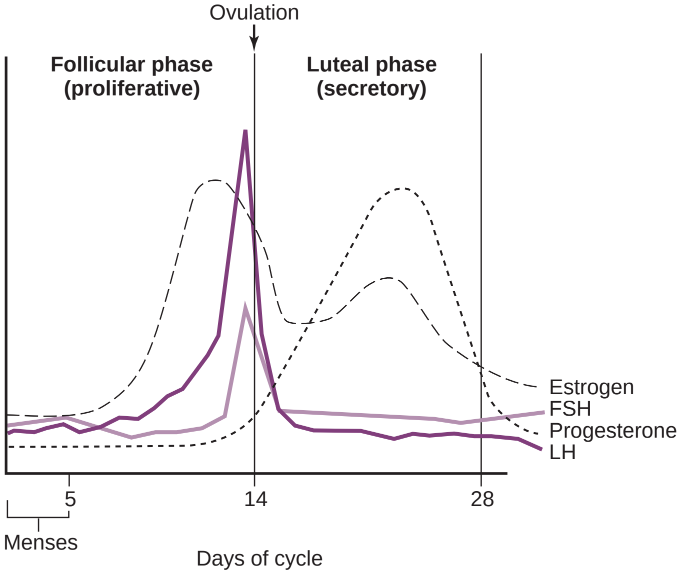
- Menstrual cycle (Fig. 3-16)
  a. Follicular (proliferative) phase
     - Most variable phase of the menstrual cycle
     - The menstrual cycle begins with the first day of **uterine bleeding** (day 1; **menses**).
     - At this point, **estrogen** and **progesterone levels are low,** so **FSH levels** 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.**

Dominant follicle: ultimately emerges, and remaining follicles undergo atresia

Dominant follicle: becomes increasingly sensitive to FSH → ↑ estrogen levels → switch from negative to positive feedback on pituitary → LH and FSH surge

LH surge: causes ovulation

3-16: Menstrual cycle. *FSH,* Follicle-stimulating hormone; *LH,* luteinizing hormone.



- 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.

Corpus luteum: composed of cells lining dominant ovarian follicle; secretes estrogen and progesterone

Corpus luteum: if ovum *not* fertilized, corpus luteum degenerates; if fertilized, corpus luteum maintained by hCG secretion from embryo

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.

Follicular phase: time between first day of menses and ovulation; since luteal phase fixed, differences in length of this phase account for cycle length differences

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.

Luteal phase: secretory phase; period between ovulation and menses

Menses: sloughing off of endometrial lining, triggered by drop in estrogen and progesterone

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.

TABLE 3-9. Pathophysiology of Some Reproductive Disorders

DISORDER	GENETICS	PATHOPHYSIOLOGY	CLINICAL COMMENTS
Precocious puberty	Normal karyotype	Premature maturation of arcuate nucleus in hypothalamus	Treat with GnRH agonists (e.g., leuprolide)
5α-Reductase deficiency	Normal karyotype	Insufficient conversion of testosterone to active dihydrotestosterone form	Female develops external male genitalia during puberty
Klinefelter syndrome	47,XXY karyotype	Meiotic nondisjunction of X chromosome	Male with eunuchoid body and gynecomastia
Androgen insensitivity syndrome (male pseudohermaphroditism)	XY karyotype	Androgen receptor defect Male internal genitalia but incompletely virilized, ambiguous, or female external genitalia	These individuals do not have male internal genitalia (no epididymis, seminal vesicles, vas deferens, prostate), and most have normal female-looking external genitalia with a blind-ending vaginal pouch.
Female pseudohermaphroditism	46,XX karyotype	Gonads are ovaries, but virilization of external genitalia	Congenital adrenal hyperplasia (21-hydroxylase deficiency)
True hermaphroditism	46,XX karyotype, most common, followed by 46,XX/46,XY mosaicism	Presence of both ovarian and testicular tissues	Ovulation and spermatogenesis may both occur.
Turner syndrome	45,XO karyotype with absent Barr body	Meiotic nondisjunction	Streaked ovaries, amenorrhea, short stature, webbed neck, aortic coarctation

GnRH, Gonadotropin-releasing hormone.

Prolactin: promotes breast maturation and lactogenesis in 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.

Lactation during pregnancy: despite high prolactin levels, is inhibited by high levels of estrogen and progesterone

Hyperprolactinemia with breastfeeding: serves as natural (but imperfect!) contraceptive by inhibiting GnRH secretion

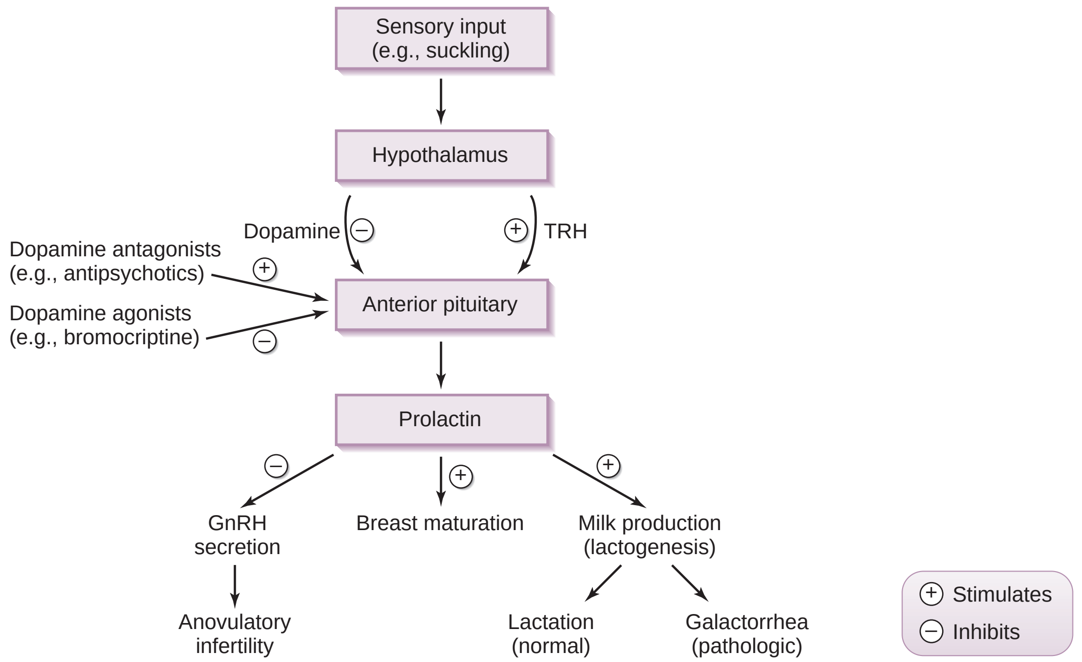
Clinical note: Prolactin plays a more limited role in the male than in the female. However, hyperprolactinemia in males also inhibits hypothalamic GnRH secretion, causing **impotence** and **loss of libido because of a drop in testosterone.** Therefore, hyperprolactinemia should always be considered 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.
   - Inhibited by **dopamine agonists** such as bromocriptine and cabergoline, which are used to treat prolactinomas.

Prolactin secretion: stimulated by breastfeeding, excessive nipple stimulation, typical antipsychotics, hypothyroidism, severing of the pituitary stalk

Prolactin secretion: inhibited by dopamine agonists such as bromocriptine; used in treatment of pituitary 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*).



3-17: Physiologic actions of prolactin. *TRH,* Thyrotropin-releasing hormone.

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

Hyperprolactinemia in nonpregnant women: galactorrhea, anovulatory infertility

Hyperprolactinemia in men: hard to diagnose; may cause depression and ↓ libido

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)

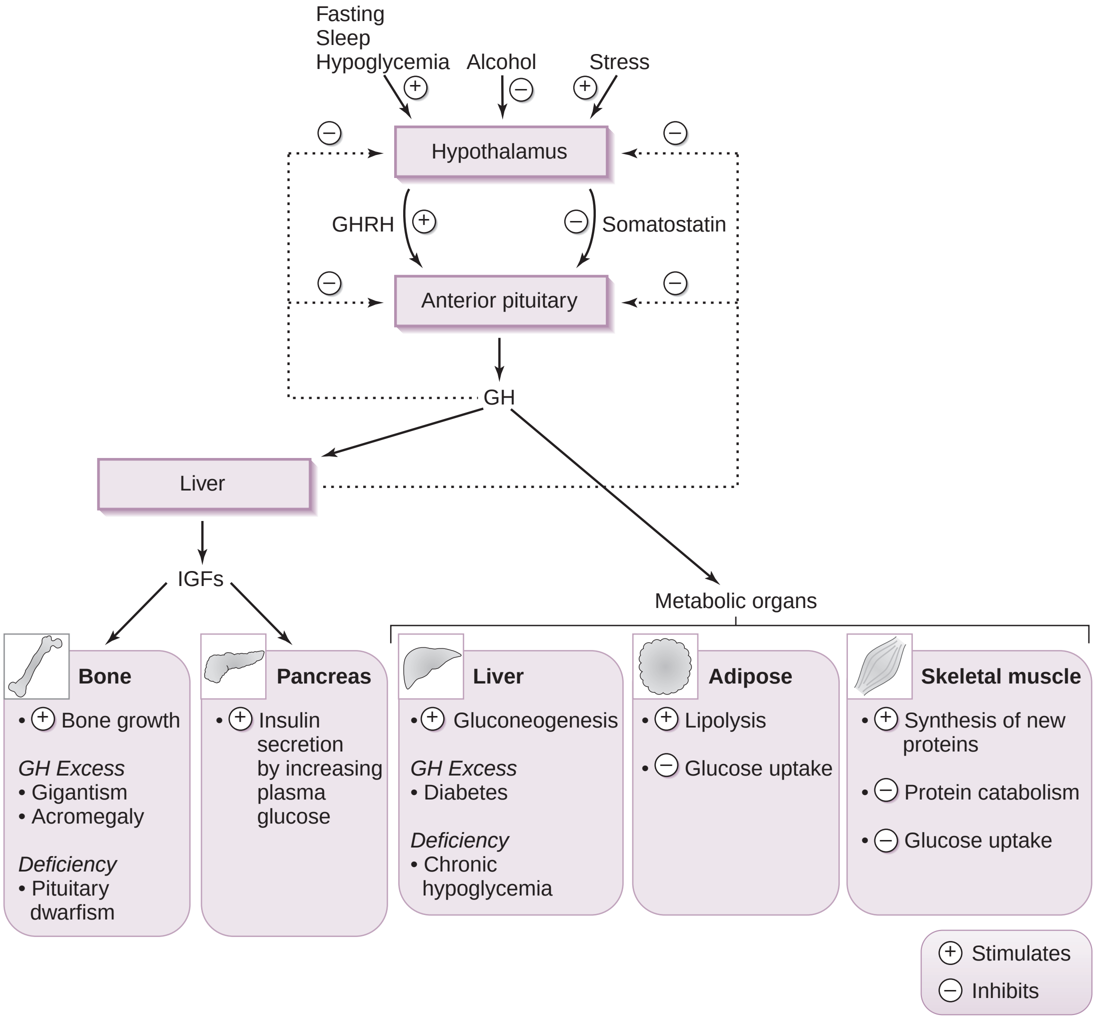
GH actions: anabolic; primarily mediated through IGF-1

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).

GH/IGF-1: stimulates lipolysis, inhibits peripheral utilization of glucose, stimulates gluconeogenesis to preserve plasma glucose

GH/IGF-1: preserves skeletal protein in an attempt to maintain ability of organism to “hunt and gather” during starvation



3-18: Physiologic actions of growth hormone. *GH*, Growth hormone; *GHRH*, growth hormone–releasing hormone; *IGF*, insulin-like growth factor.

GH: diabetogenic hormone; chronically excessive levels → diabetes

GH deficiency: intentional provocation of hypoglycemia should ↑ GH secretion if hypothalamic-pituitary axis functioning normally

GH secretion: stimulated by sleep, stress, hypoglycemia; inhibited by alcohol

- These actions are helpful in stressful conditions such as fasting or starvation.
  a. 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.
  a. 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.

Posterior pituitary: composed of axonal extension from hypothalamus; independent of hypothalamic releasing hormones, which only influence the anterior pituitary

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
        - Absence of ADH leads to dilution of urine with a loss of free water.

     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

ADH: stimulates (1) free water reabsorption and (2) systemic vasoconstriction → maintains plasma osmolarity and ↑ blood pressure

ADH secretion: triggered by ↑ plasma osmolarity and ↓ plasma volume

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

Central diabetes insipidus: common with head trauma; urine should concentrate following administration of synthetic ADH

Nephrogenic diabetes insipidus: commonly caused by lithium; urine will *not* concentrate with synthetic ADH

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 osmolarity 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).

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

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

Oxytocin: promotes uterine contractions and milk letdown

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).

Islets of Langerhans: β cells secrete insulin; α cells secrete glucagon; δ cells secrete somatostatin

TABLE 3-10. Physiologic Actions of Pancreatic Hormones

CELL TYPE	HORMONE SECRETED	PRIMARY ACTIONS	PRIMARY STIMULATORS
α	Glucagon	Stimulates hepatic glycogenolysis and gluconeogenesis to increase plasma glucose	Hypoglycemia, amino acids
β	Insulin	Anabolic actions through stimulation of glucose and amino acids in tissues; decreases levels of plasma glucose	Glucose, amino acids, hyperkalemia
δ	Somatostatin	Inhibits insulin and glucagon secretion; has inhibitory effects on all digestive processes	Glucose, amino acids, fatty acids

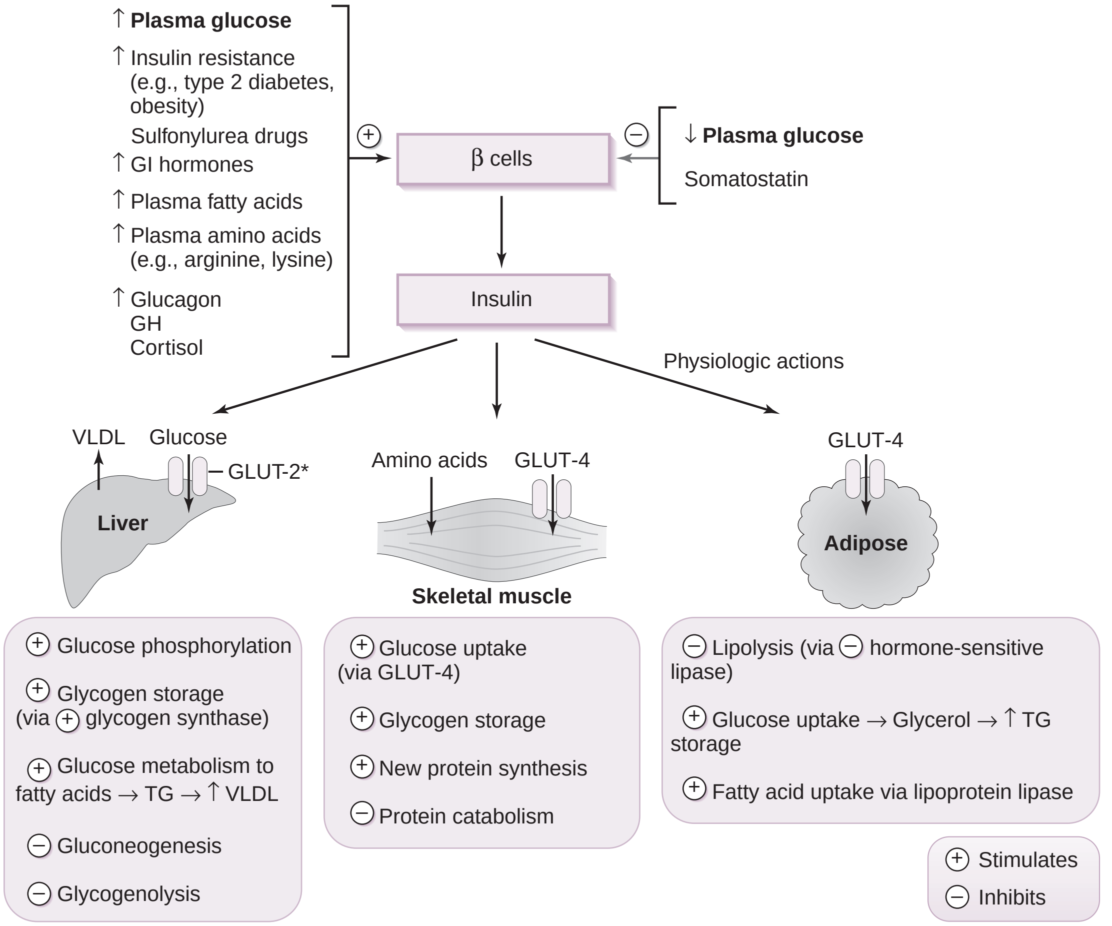
- **Metabolic actions** (Table 3-11; Fig. 3-19)
  a. The principal role of insulin is to **maintain plasma glucose levels** within normal ranges.
  b. The major **stimulus** for insulin secretion is **plasma glucose,** with increasing plasma glucose levels stimulating proportionally more insulin secretion.
    - 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.

Insulin: stimulates glucose uptake in various tissues

Insulin: promotes glucose use in multiple ways; stimulates glycolysis, glycogenesis, and glucose uptake in adipose and muscle

TABLE 3-11. Actions of Insulin on Target Tissues

TARGET TISSUE	STIMULATES	INHIBITS
Adipose	Fatty acid uptake, triglyceride synthesis and storage, glucose uptake	Lipolysis
Liver	Glycolysis, glycogenesis, amino acid and glucose uptake, fat synthesis, cholesterol synthesis	Gluconeogenesis, β-oxidation of fatty acids, ketogenesis
Muscle	Glucose uptake, glycogenesis, glycolysis, protein synthesis	Protein catabolism



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.

g. 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.

h. 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**.

Insulin-independent tissues: CNS is mainly dependent on glucose as fuel source, does not need insulin to internalize glucose, allowing the CNS to function at low glucose levels when plasma [insulin] is low

Pharmacology note: A class of drugs known as the **fibric 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**.

Type 1 diabetes mellitus: caused by autoimmune and antibody destruction of pancreatic β cells

Hyperglycemia: filtered load of glucose exceeds renal capacity for glucose reabsorption, resulting in glucosuria and osmotic diuresis

Classic presentation of diabetes mellitus: polydipsia, polyuria, and unintentional weight loss with a preserved or increased appetite (polyphagia)

DKA: absolute deficiency in insulin; anion gap metabolic acidosis, hyperglycemia, volume depletion

DKA: often triggered by noncompliance with insulin or by infections

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).

Type 2 diabetes mellitus: insulin levels initially elevated but still inadequate because of target tissue insensitivity to insulin from decreased receptors and postreceptor abnormalities

Type 2 diabetes mellitus: β-cell dysfunction with impaired insulin secretion plays a larger role in later stages of diabetes

HHS: characterized by marked volume depletion, much more so than with DKA, and a much more elevated [glucose]; absent ketogenesis results from the presence of some insulin

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: primary hormone of the fasting state

- 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.
- These extrahepatic actions also contribute to increased plasma glucose levels.

Glucagon secretion: stimulated by amino acids and low plasma glucose

Glucagon: acts primarily on liver to promote gluconeogenesis and glycogenolysis; weakly stimulates lipolysis in adipose tissue; inhibits glucose utilization by 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.

Aldosterone: acts to maintain blood pressure by increasing intravascular volume

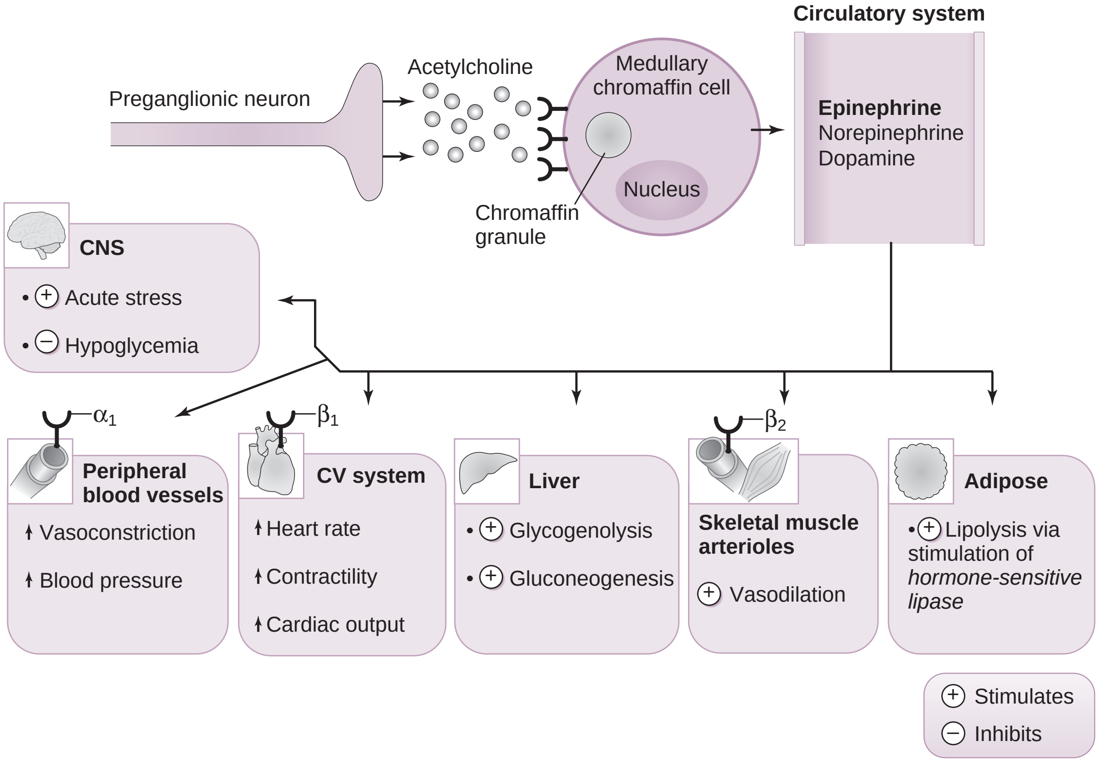
Hyperaldosteronism: moderate common cause of secondary hypertension, hypokalemia, and metabolic alkalosis

Aldosterone secretion: regulated by K^+ and angiotensin II, minimal effect by ACTH

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 β_1-adrenergic receptors.
     b. Catecholamines also cause **peripheral vasoconstriction** by stimulating α_1-adrenergic receptors on vascular smooth muscle cells, which increases peripheral vascular resistance and further increases arterial pressure.

Adrenal catecholamines: epinephrine, norepinephrine, and dopamine

Epinephrine: secreted by medulla in larger amounts than epinephrine or dopamine



3-20: Synthesis and physiologic actions of catecholamines. *CNS,* Central nervous system; *CV,* cardiovascular.

- Catecholamines simultaneously **stimulate vasodilation in skeletal muscle** by stimulating β_2-adrenergic receptors, allowing greater blood flow to active muscles.

c. In addition, catecholamines cause **bronchodilation** by stimulating β_2-adrenergic receptors in the bronchioles, allowing greater oxygen delivery to the lungs.

Catecholamines: ↑ heart rate and contractility, ↑ total peripheral resistance by stimulating arterial vasoconstriction, stimulate bronchodilation

- **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.

Metabolic actions of catecholamines: maintain plasma glucose by stimulating hepatic glycogenolysis and gluconeogenesis and 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.

Epinephrine secretion: primarily under control of autonomic nervous system

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 spurts, 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.**

Calcium regulation: dependent on PTH, calcitriol, and (minimally) calcitonin

Calcium: approximately 99% is located in the bones

Calcium regulation: it is the *ionized* calcium that is tightly regulated

Alkalosis: ↓ ionized Ca^{2+} as a result of ↑ Ca^{2+} binding to negatively charged sites on albumin

Calcium: stabilizes membrane potentials; hypocalcemia → muscle spasms (tetany), cardiac arrhythmias, and seizures

Manifestations of hypercalcemia: confusion, muscle weakness, osmotic diuresis → dehydration and possibly (prerenal) renal failure

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.**

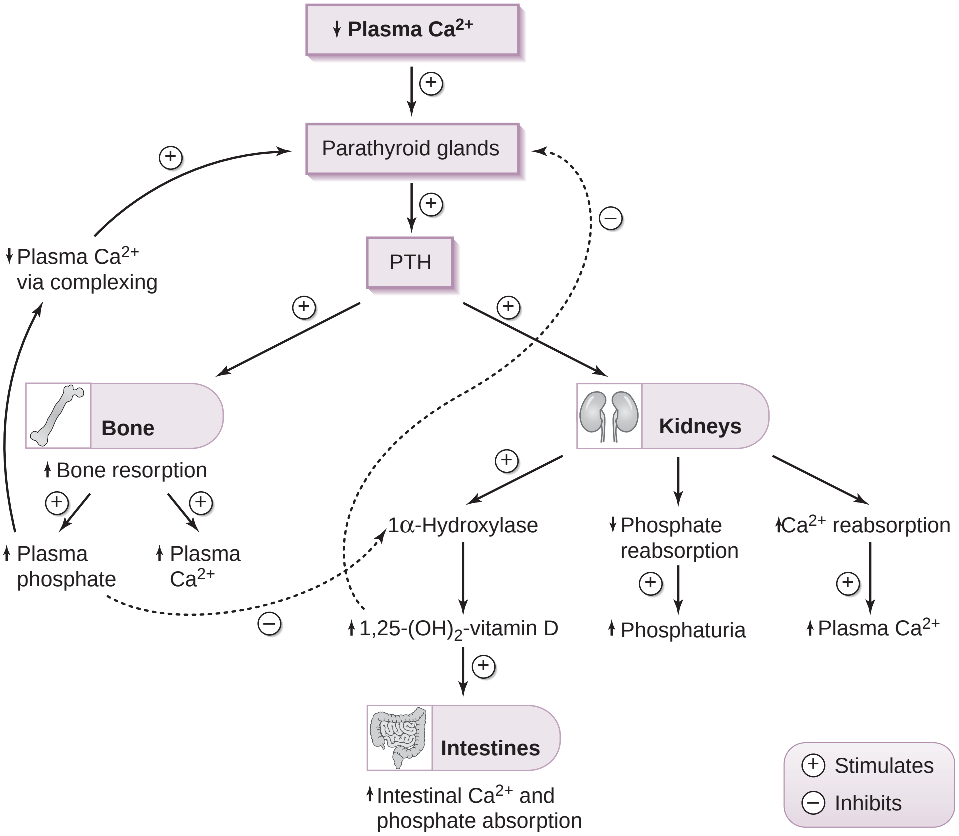
B. Parathyroid Hormone (Fig. 3-21)

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 D_3** (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.

PTH: secreted by parathyroid chief cells primarily in response to hypocalcemia but also to hyperphosphatemia

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.



3-21: Parathyroid hormone (PTH) overview.

TABLE 3-12. Organ Effects of Parathyroid Hormone and 1,25-Dihydroxyvitamin D_3

HORMONE	KIDNEY	INTESTINE	BONE
Parathyroid hormone	Stimulates calcium reabsorption and phosphate excretion	Stimulates calcium absorption through increasing synthesis of active vitamin D	Stimulates bone resorption
1,25-Dihydroxyvitamin D_3	Stimulates calcium and phosphate reabsorption	Stimulates calcium and phosphate absorption	Stimulates bone resorption by osteoclasts Stimulates bone formation indirectly by increasing plasma calcium and phosphate levels

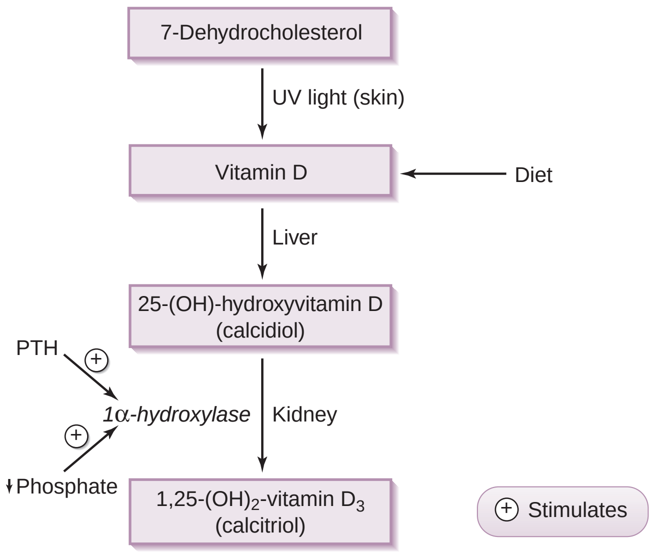
C. 1,25-Dihydroxyvitamin D_3 (Table 3-12)

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.

Vitamin D from diet or skin → 25-hydroxyvitamin D (liver) → 1,25-dihydroxyvitamin D_3 (kidney)

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*.

3-22: Vitamin D synthesis. *PTH,* Parathyroid hormone; *UV,* ultraviolet.



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.

Metastatic calcification: can occur when the calcium-phosphate product level is pathologically elevated

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_3 and phosphate** (see Table 3-12 and Fig. 3-21)
   - 1,25-Dihydroxyvitamin D_3 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_3 synthesis through a negative-feedback mechanism.
   - In addition, the active form of vitamin D inhibits further vitamin D synthesis, another negative-feedback mechanism.

1,25-Dihydroxyvitamin D_3: stimulates intestinal absorption of calcium *and* phosphate; also stimulates renal reabsorption of phosphate

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.

Compensatory (secondary) hyperparathyroidism: occurs in response to chronic renal failure due to hypocalcemia and hyperphosphatemia

CHAPTER 4

CARDIOVASCULAR PHYSIOLOGY

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).

Pulse pressure: ↑ in hyperthyroidism, aortic regurgitation; ↓ in aortic stenosis

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.

$$\begin{aligned}\text{Pulse pressure} &= \text{SBP} - \text{DBP}\\ &= 120\text{mm Hg} - 80\text{mm Hg}\\ &= 40\text{mm Hg}\end{aligned}$$

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)

Atrioventricular valves: prevent backflow of blood into atria during systole

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.

Semilunar valves: prevent backflow of blood into ventricles during diastole

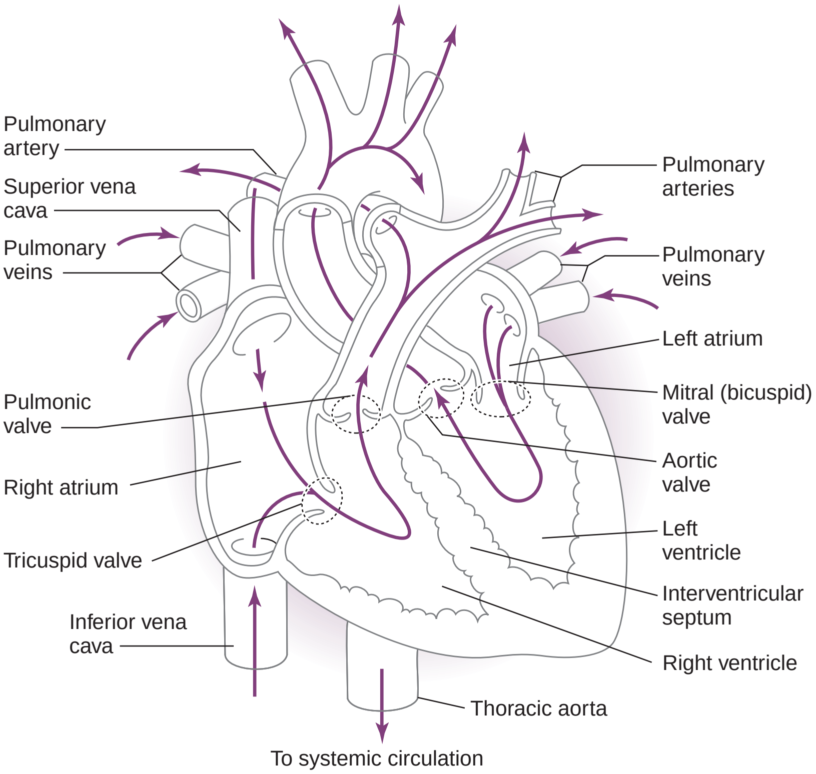
2. **Semilunar valves: aortic and pulmonic valves**
    - The **semilunar valves** prevent blood from flowing back into the ventricles during ventricular diastole.
    - The **aortic valve** separates the left ventricle from the aorta.
    - The **pulmonic valve** separates the right ventricle from the pulmonary artery.
    - Both valves normally have three cusps.

C. **Principal heart sounds**

- **Reflect valve closure and/or pathologic states**

S_1: closure of AV valves; typically auscultated as a single sound

1. **S_1: 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



4-1: One-way flow of blood through the heart valves.

- Has **mitral (M_1) and tricuspid (T_1)** components that do ***not* vary with the respiratory cycle** (i.e., S_1 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, S_1 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 S_1 are a **shortened PR interval, mild mitral stenosis,** and **high cardiac-output states** or **tachycardia.**

S_2: normally "split" during inspiration

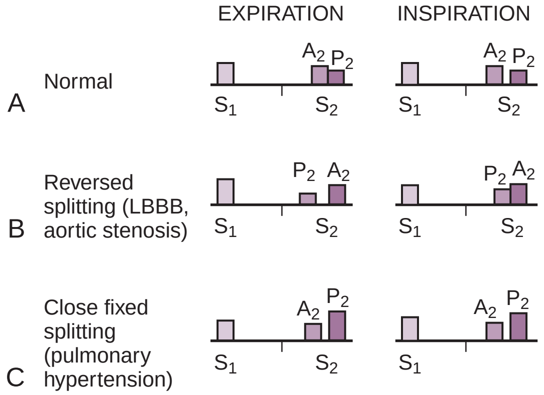
2. **S_2: closure of semilunar valves**
   - Produced by **closure of the semilunar valves** in early diastole
   - Diastolic pressures in the aorta and pulmonary artery exceed the pressures in the relaxing ventricles, causing the semilunar valves to close.
   - Has aortic (A_2) and pulmonic (P_2) components (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" S_2.
     a. Furthermore, despite the increased preload, for unclear reasons the **aortic valve closes earlier during inspiration**.
     b. S_2: can be best appreciated on auscultation at the 2nd or 3rd left intercostal space

S_2: best appreciated in the 2nd or 3rd left intercostal space

Clinical note: Paradoxical or "reversed" splitting occurs when S_2 **splitting occurs with expiration** and **disappears on inspiration.** Moreover, in paradoxical splitting, the pulmonic valve closes *before* the aortic valve, such that P_2 precedes A_2. **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.

S_3: presence reflects volume-overloaded state

3. **S_3: ventricular gallop**
   - An S_3 is sometimes heard in early to middle diastole, during rapid ventricular filling.



4-2: **A,** Relationship of splitting of S_2 to respiration in normal subjects. **B,** Reversed splitting of S_2 associated with delayed aortic closure, most commonly caused by left bundle branch block (LBBB). **C,** Fixed splitting of S_2 characteristic of severe pulmonary hypertension. *A_2,* Aortic valve closure; *P_2,* pulmonic valve closure; *PA,* pulmonic artery; *S_1,* first heart sound. *(From Fowler NO: Diagnosis of Heart Disease. New York: Springer-Verlag; 1991, p 31.)*

- 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.

S_4: atrial contraction against a stiff ventricle, often heard after an acute myocardial infarction

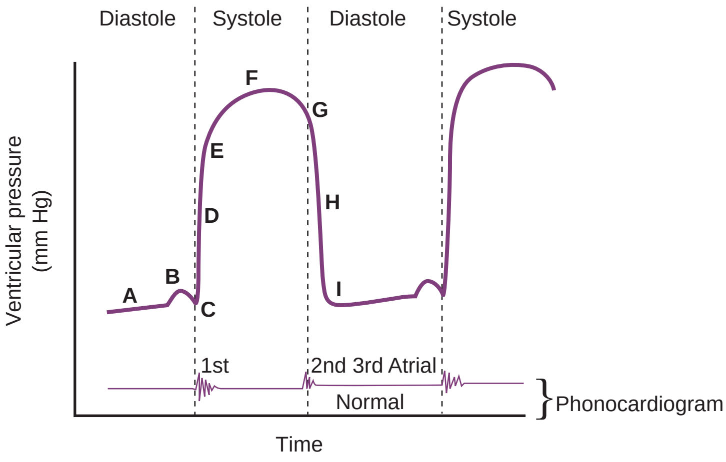
4. **S_4: atrial gallop**
   - An S_4 is sometimes heard in late diastole and is caused by atrial contraction against a stiffened (noncompliant) ventricle.
   - An S_4 almost always indicates **cardiac disease** and should be further evaluated; it is commonly noted during or shortly after an acute myocardial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

Clinical note: An S_4 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).

S_1: due to closure of AV valves in early systole from ↑ 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).**
- After closure of the semilunar valves, the ventricles continue to relax, and intraventricular pressures continue to decrease **(H).**



4-3: Ventricular pressure changes during the cardiac cycle.

- 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. S_1 occurs at the beginning of systole with AV valve closure **(C),** and S_2 occurs at the beginning of diastole with semilunar valve closure **(G).**
  b. If an S_3 were present, it would occur in early diastole, because it is caused by **rapid ventricular filling.**
  c. If an S_4 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: assessed by measuring cardiac output

- 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

$CO = HR \times SV$

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:

$$\begin{aligned} CO &= HR \times SV \\ &= 70 \text{ beats/minute} \times 70 \text{ mL/beat} \\ &= 4900 \text{ mL/minute, or } 4.9 \text{ L/minute} \end{aligned}$$

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 O_2 extracted by the tissues **(arteriovenous O_2 difference):**

$$O_2 \text{ consumption} = CO \times ([O_2]_a - [O_2]_v)$$

   where $[O_2]_a$ = arterial O_2 concentration (~200 mL O_2/L blood) and $[O_2]_v$ = venous O_2 concentration (~150 mL O_2/L blood).
5. This equation can be rearranged to calculate the cardiac output:

$$CO = O_2 \text{ consumption}/A - V\ O_2 \text{ gradient}$$

$$CO = \frac{O_2 \text{ consumption}}{A - V\ O_2 \text{ gradient}}$$

   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:

$$CO = 250 \text{ mL/min}/(200 - 150 \text{ mL } O_2/\text{L blood}) = 5 \text{ L/min}$$

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

Stroke volume = EDV − ESV

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:

$$SV = EDV - ESV$$
$$= 120\text{ mL} - 50\text{ mL} = 70\text{ mL}$$

Ejection fraction = SV/EDV

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.
     a. In other words, it is the SV divided by the EDV.
   - In a typical adult, the EF is calculated as follows:

$$EF = SV/EDV = 70/120 = 60\%$$

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.**

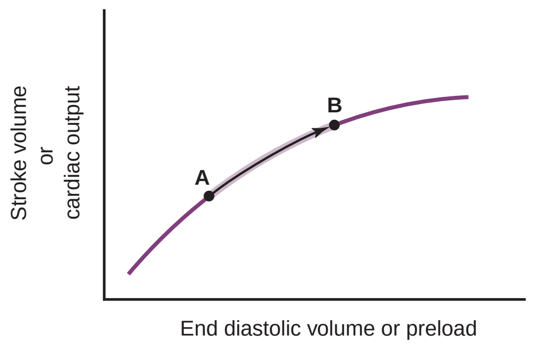
Stroke volume: dependent on preload, contractility, and afterload

Preload: "load" placed on ventricle at start of systole; equivalent to EDV

Frank-Starling relationship: increased preload (to a point) results in increased CO

Increased preload → ↑ stretching of sarcomeres → ↑ sensitivity to Ca^{2+}

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.



4-4: Stroke volume versus preload. Atrial pressure at ventricular end diastole correlates with ventricular end diastolic volume and pressure and is often used as a surrogate marker of preload. Note that cardiac output increases from point A to point B as the preload increases.

- 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.

Contractility: ↑ with digitalis, sympathetic stimulation; ↓ in heart failure

- 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).

Afterload: ↑ in aortic stenosis and hypertension, ↓ with intra-aortic balloon pump

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:

$$\sigma = P \times r/2h$$

where σ = wall tension, P = intraluminal pressure, r = intraluminal radius, and h = wall thickness.

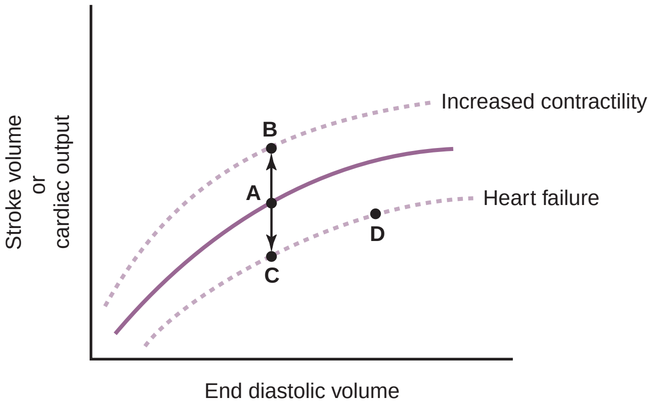
  d. Think of the ventricle as a very thick-walled vessel, and use the Laplace equation to determine that, if the ventricle must generate a greater intraventricular pressure to overcome an afterload, **myocardial wall tension will increase.**
  e. Left ventricular hypertrophy with the **addition of sarcomeres in parallel** (↑H) then occurs as a compensatory response to increased wall tension.

Laplace relationship: myocardial wall tension needs to ↑ in order to generate an ↑ intraventricular pressure to overcome an ↑ afterload

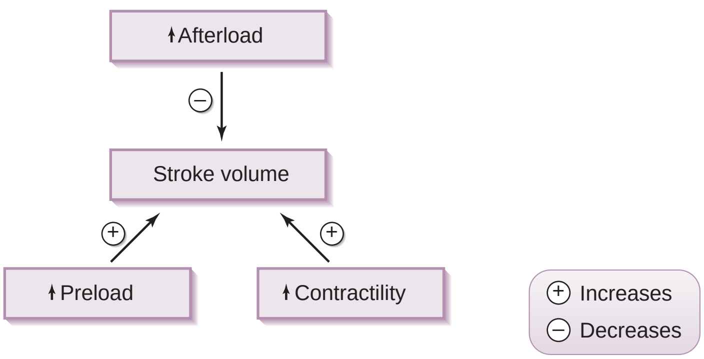
Left ventricular hypertrophy: occurs by addition of sarcomeres in *parallel*

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

Stroke work: ↑ with increasing SV or by maintaining constant SV in face of ↑ afterload



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.

Pressure-volume component of stroke work: work used to push SV into high-pressure arterial system (major component)

Kinetic-energy component of stroke work: work used to move ejected SV at a certain velocity (minor component)

C. Venous return

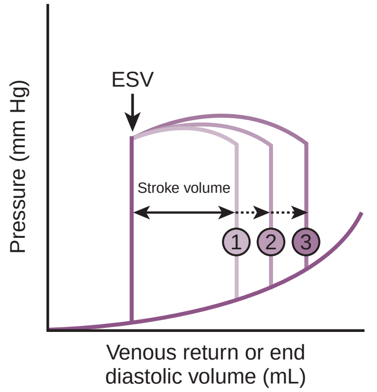
1. **Effect of venous return on cardiac output by influencing preload**
   - The rate of venous return is determined by the **pressure gradient** between the systemic veins and the right atrium.
   - Increased venous return increases preload and CO (Fig. 4-7).
   - At **increased right atrial pressures** (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.

Venous return: rate determined by pressure gradient between systemic veins and right atrium

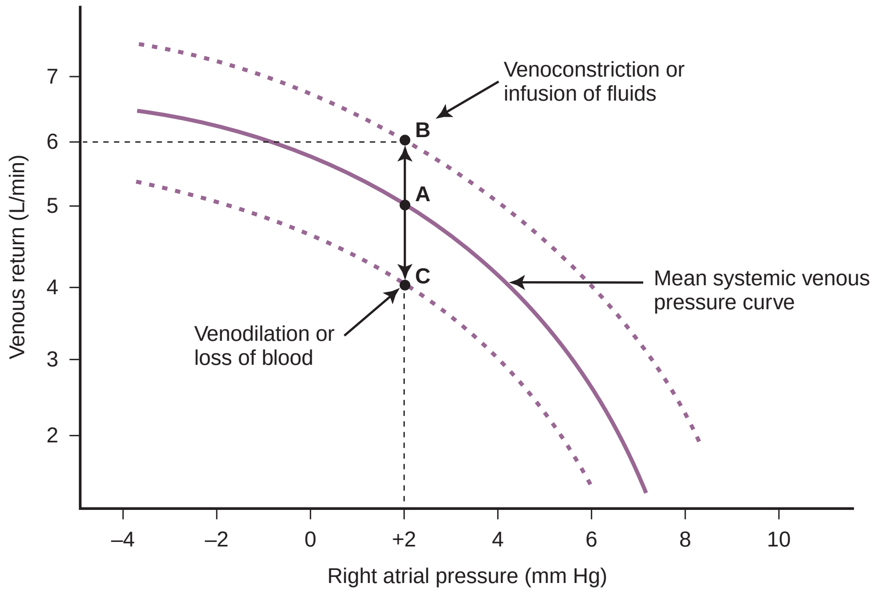
Venous return is decreased at increased right atrial pressures.

Venoconstriction or intravenous volume infusion → ↑ systemic venous pressure → ↑ venous return and CO

Venodilation or loss of blood → ↓ systemic venous pressure → ↓ venous return and CO



4-7: Relationship of preload to stroke volume. *ESV,* End systolic volume. *(From Lilly LS: Pathophysiology of Heart Disease, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2003, Fig. 9-5A.)*



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).

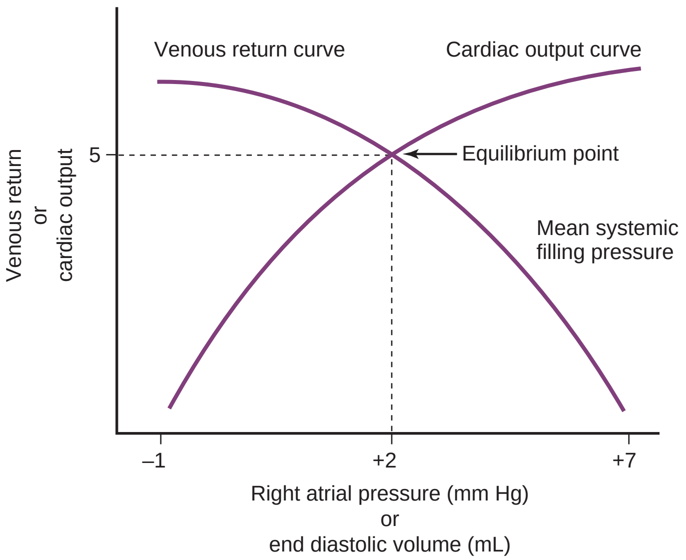
Clinical note: Patients experiencing **massive blood loss** (e.g., **trauma patients**) are given large volumes of intravenous fluids to increase systemic venous pressure and to increase venous return, thereby increasing preload and CO.

- 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!

On average, CO and venous return need to be perfectly matched to ensure adequate CO and arterial perfusion and prevention of venous congestion.

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.

Respiratory pump: ↑ VR during inspiration due to ↓ intrathoracic and ↑ abdominal pressures



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 after opening of mitral valve

- **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 ventricular contraction after closing of mitral valve

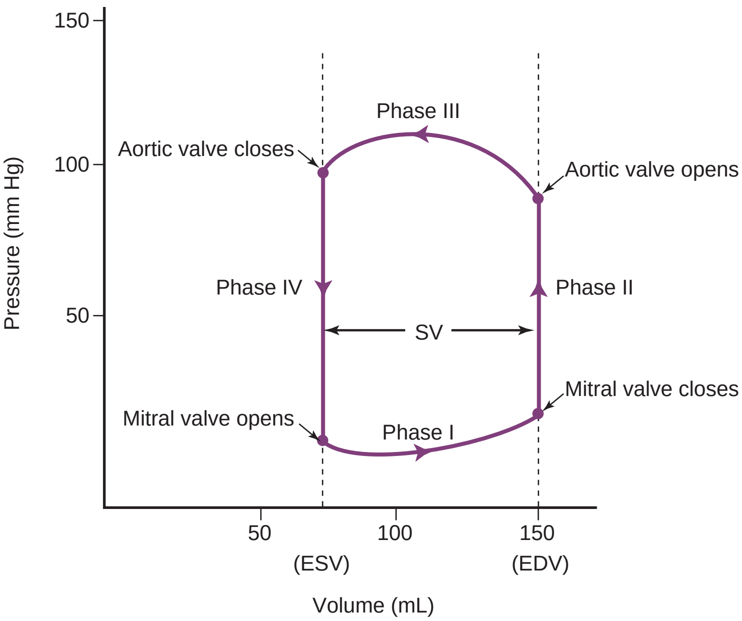
- **Phase II: isovolumic contraction**
  a. This phase begins at the **onset of systole** and **closure of the mitral valve.**
  b. The ventricle is contracting, but not shrinking, because sufficient pressure must develop to exceed pressures in the aorta (pulmonary artery for the right ventricle).
  c. The greater the afterload, the more the ventricular pressure must increase to overcome it.

Phase III: ejection of blood after opening of aortic valve

- **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 ventricular contraction after closing of aortic valve

- **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).



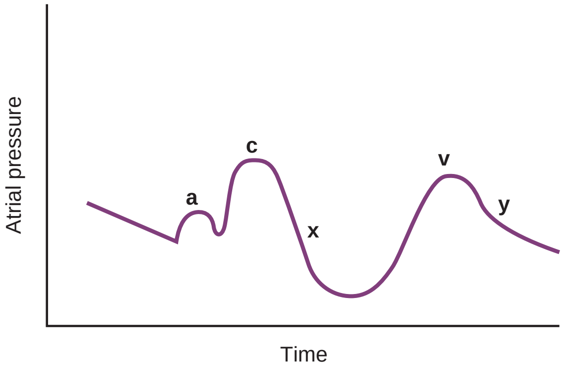
4-10: Left ventricular pressure-volume loop. *EDV,* End diastolic volume; *ESV,* end systolic volume; *SV,* stroke volume.

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.

a wave: atrial contraction → slight ↑ in atrial pressure

c wave: isovolumic ventricular contraction and inward bulging of AV valves → large ↑ in atrial pressure

x descent: start of ventricular ejection → rapid ↓ in atrial pressure



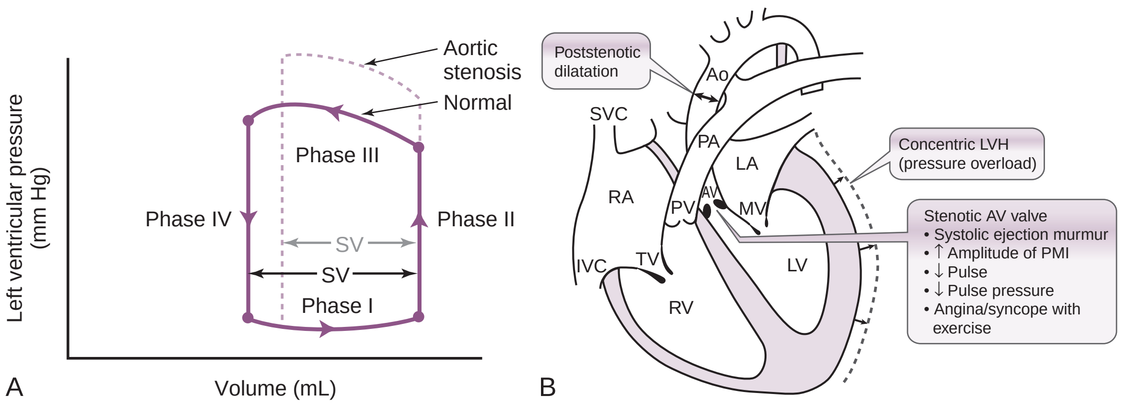
4-11: Atrial pressure curve. The *a wave* would be absent during atrial fibrillation.

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.

v wave: **atrial filling** after closure of AV valves → gradual ↑ in 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,* atrioventricular; *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).

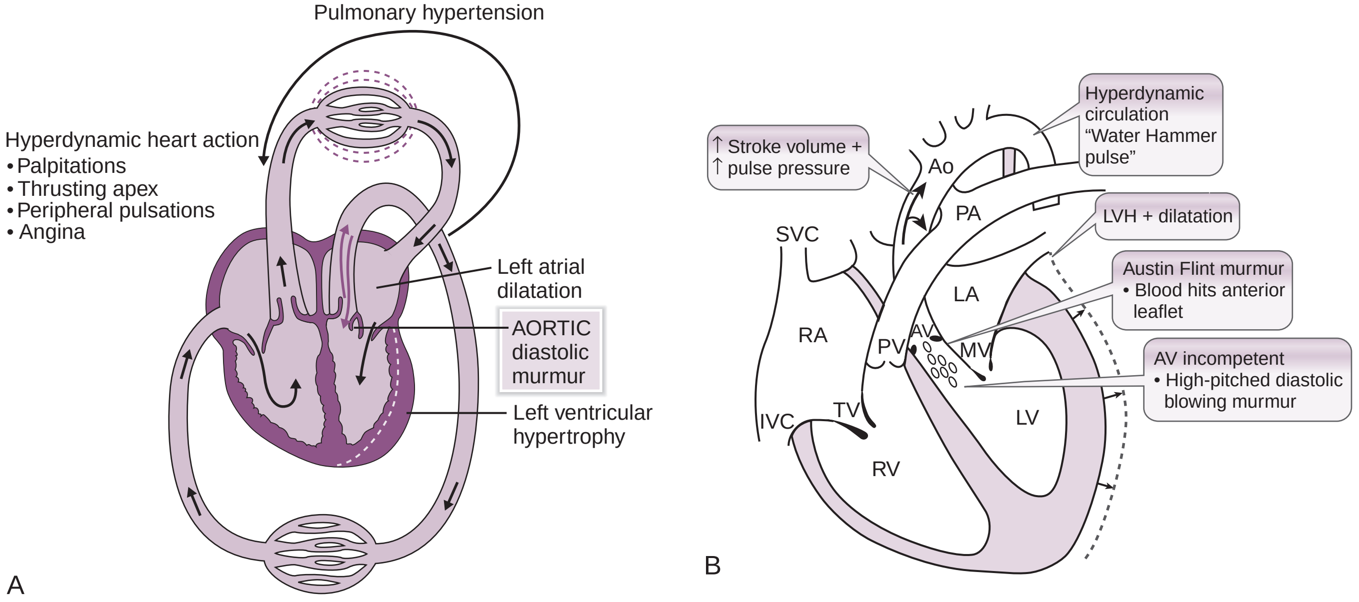
Pathology note: In some individuals, the aortic valve is **congenitally bicuspid.** These bicuspid valves are predisposed to early calcification and stenosis, often causing significant **aortic stenosis** in individuals in their late 40s or early 50s. More commonly, aortic stenosis in elderly people is caused by calcification of the normal tricuspid valve, a condition known as **senile 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).

Aortic regurgitation: ↓ *effective* SV, widened pulse pressure

Aortic regurgitation: increased SV and decreased diastolic pressure → Water Hammer pulse on exam

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).



4-13: **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.

Mitral stenosis: rheumatic fever still most common cause

Mitral stenosis: associated with large diastolic pressure difference between left atrium and ventricle

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.

Mitral stenosis: ↑ left atrial pressures →↑ hydrostatic pressures in pulmonary circulation → pulmonary edema

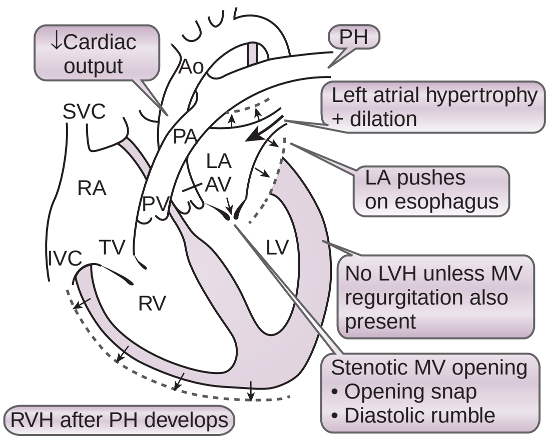
- As left atrial pressures become elevated, the hydrostatic pressures in the pulmonary veins and capillaries also become elevated, causing net **transudation of fluid into the pulmonary interstitium.**
- Initially, the pulmonary lymphatics can reabsorb this fluid and prevent pulmonary edema.
- Once the 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.

Symptoms of pulmonary edema: dyspnea, reduced exercise capacity

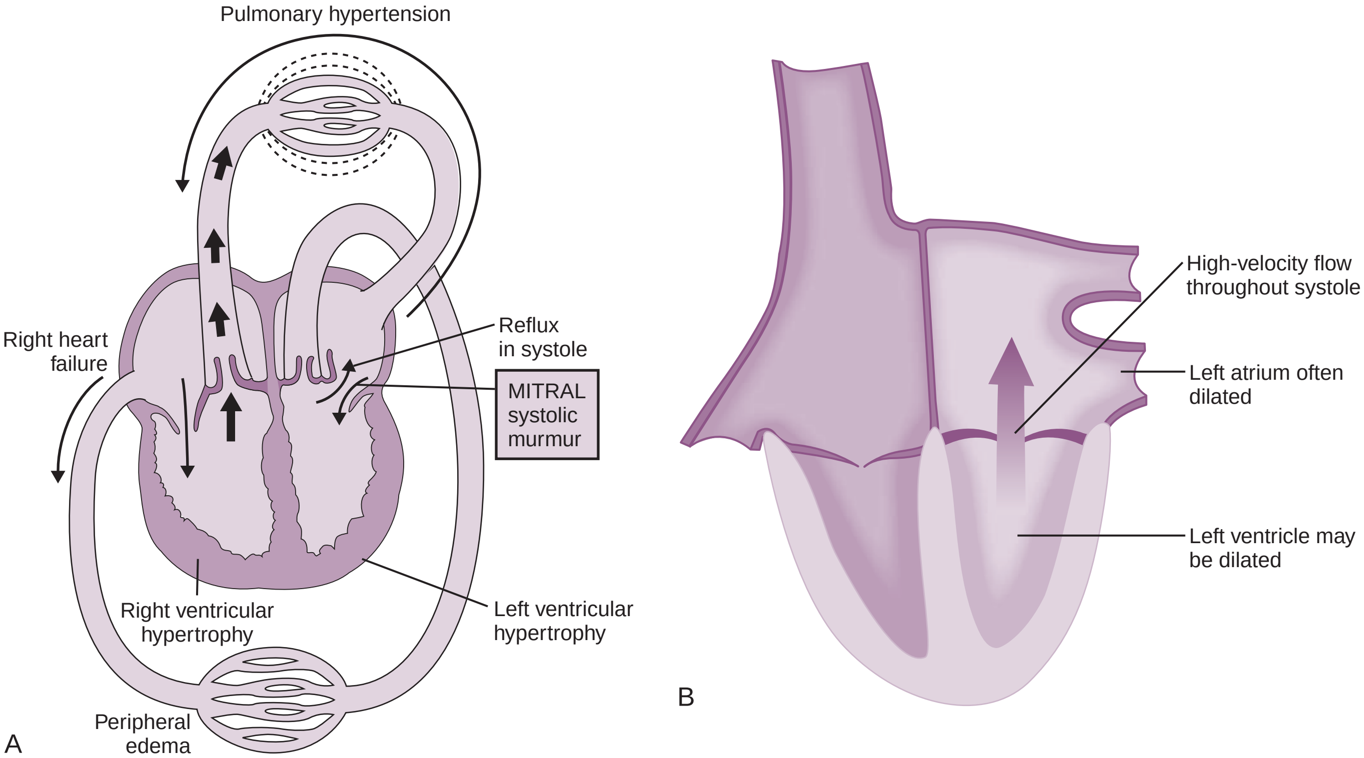
Treatment of severe symptomatic mitral stenosis: mitral valve repair (commissurotomy), balloon valvuloplasty, or valve replacement

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 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; *LVH,* left ventricular hypertrophy; *MV,* mitral valve; *PA,* pulmonary artery; *PH,* pulmonary hypertension; *PV,* pulmonary valve; *RA,* right atrium; *RV,* right ventricle; *RVH,* right ventricular hypertrophy; *SVC,* superior vena cava; *TV,* tricuspid valve. *(From Goljan EF: Rapid Review Pathology, 3rd ed. Philadelphia: Mosby; 2010, Fig. 10-14.)*



4-15: Mitral regurgitation with part **A** showing the pathologic changes associated with mitral regurgitation and part **B** highlighting the high-velocity flow into the left atrium during systole. *(**A,** From Damjanov I: Pathophysiology. Philadelphia: Saunders; 2008, Fig. 4-55; **B,** from Talley N, O'Connor S: Clinical Examination, 5th ed. Philadelphia: Elsevier; 2006, Fig. 3-40.)*

Precise symptoms of mitral regurgitation depend on temporal course of the mitral regurgitation; acute onset → severe symptoms; chronic onset → typically asymptomatic or minor symptoms

- **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.

Murmurs: most likely with high-flow velocity in large vessels

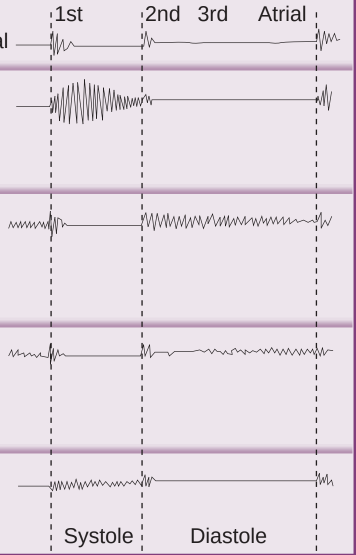
5. **Pathophysiology of murmurs**
   - Blood flow through most of the cardiovascular system is normally **laminar** and silent.
   - In certain circumstances, flow velocity is increased or viscosity is decreased, and nonlaminar **(turbulent) flow** occurs that can produce noise **(murmurs** or **bruits)**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

- Turbulent flow typically occurs when the **Reynolds' number** is elevated, exceeding approximately 2500.
- The Reynolds' number (Re) can be calculated as follows:

$$Re = 2rv\rho/\eta$$

where r = radius of the vessel, v = velocity of flow, ρ = density of the fluid, and η = viscosity of the fluid.

Type of Murmur	Physiologic Basis of Murmur	Timing
Aortic stenosis	Increased velocity of flow across narrowed aortic valve	Throughout systole
Aortic regurgitation	Turbulent flow back into left ventricle from the high-pressure aorta	Early diastole; decreases in intensity throughout diastole
Mitral stenosis	Turbulent flow across stenotic mitral valve during ventricular filling	Diastole
Mitral regurgitation	Turbulent flow into left atrium during ventricular systole	Throughout systole



4-16: Phonocardiograms from a normal heart and hearts with murmurs.

III. Myocardial Oxygen Supply and Demand

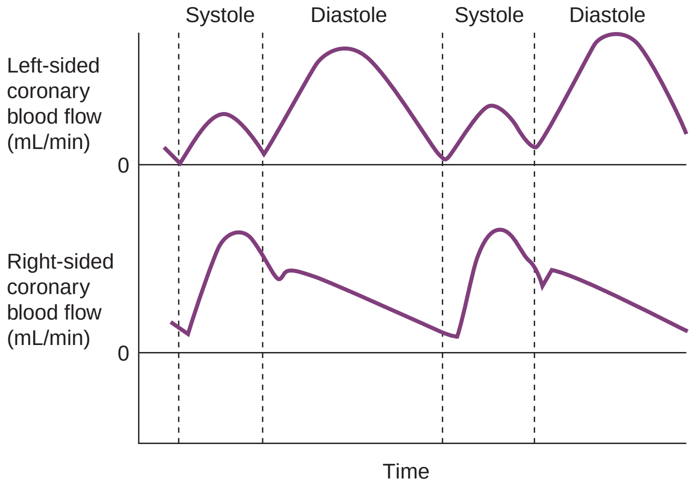
A. Main determinants of myocardial O_2 supply

1. Coronary blood flow

- Myocardial O_2 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.

Coronary blood flow: dependent on length of diastole, diastolic perfusion pressure, coronary vascular resistance

Left ventricular myocardial perfusion largely occurs during diastole.



4-17: Ventricular blood flow.

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: driving force for coronary artery perfusion; equal to diastolic pressure in proximal aorta; augmented with use of intra-aortic balloon pump

- **Diastolic perfusion pressure**
  a. The **driving force for coronary blood flow**
  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 O_2 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 blood flow: left ventricular myocardial perfusion largely occurs during diastole

Vascular resistance: ↑ by atherosclerotic narrowing of coronary vessels

Local vasodilatory substances: adenosine, hydrogen ions, and potassium

- **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.

O_2-carrying capacity of blood dependent on hemoglobin concentration and efficiency of oxygen exchange across the pulmonary membrane

Severe anemia compromises myocardial O_2 supply.

2. **Arterial O_2 content**
   - The arterial O_2 content primarily depends on the **O_2-carrying capacity** of the blood, determined by the **concentration of hemoglobin,** and the **efficiency of gas exchange** by the lungs.
   - Normally, the arterial O_2 content is constant; therefore, it does not regulate myocardial O_2 supply.
   - In severe **anemia,** however, the decreased arterial O_2 content can compromise myocardial O_2 supply, causing myocardial ischemia.

Determinants of myocardial O_2 demand: heart rate most important

B. Determinants of myocardial O_2 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 O_2 demand.
   - Additionally, because less time is spent in diastole, myocardial O_2 supply is simultaneously compromised; this sets the stage for "supply-demand mismatch."

Increased preload, contractility, or afterload → ↑ wall tension → ↑ O_2 demand

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 O_2 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 O_2 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 O_2 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 O_2 demand.** However, cocaine can also compromise myocardial O_2 supply by causing **coronary artery vasospasm.**

C. **Pathophysiology of angina pectoris**

Angina pectoris: occurs when myocardial O_2 demand exceeds O_2 supply

1. **Angina occurs when myocardial O_2 demand exceeds O_2 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.
     b. **Anginal pain** associated with coronary artery disease typically becomes noticeable or more pronounced when myocardial O_2 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

Coronary artery spasm can cause Prinzmetal angina; difficult to diagnose

Pharmacology note: Bearing in mind the determinants of myocardial O_2 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 O_2 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

Concentric hypertrophy → stiff ventricle → predisposes to diastolic congestive heart failure

- Cardiac muscle, much like skeletal muscle, can adapt to increased workloads.

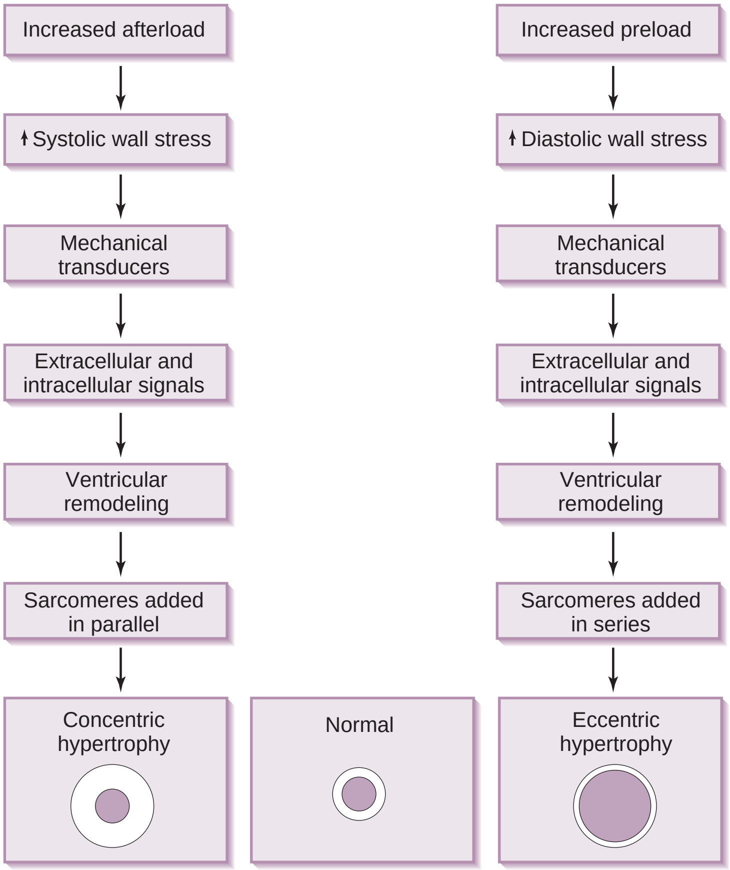
A. **Adaptations to increased afterload** (Fig. 4-18)

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.**

Concentric hypertrophy: sarcomeres added in parallel →↓ wall tension

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).

4-18: Ventricular adaptations to increased preload and increased afterload. Note that both processes may occur simultaneously, for example, in a patient with hypertension (increased afterload) and congestive heart failure (increased preload).



Eccentric hypertrophy: occurs in "volume-overloaded" hearts

Eccentric hypertrophy: sarcomeres are added in series to elongate the ventricle and increase ventricular lumen volume

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.**

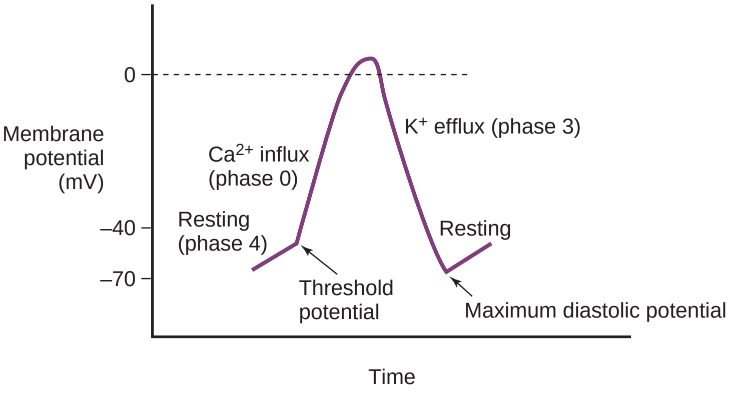
Pathology note: In certain pathologic situations, the heart may dilate *without being volume overloaded*. Most commonly, this happens for unknown reasons and is known as **idiopathic dilated cardiomyopathy.** The most common known cause of dilated cardiomyopathy unrelated to volume overload is **excessive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

V. Electrophysiology of the Heart

A. Overview

Backup nodes will "fire" if the SA node fails to generate an action potential.

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.



4-19: Sinoatrial node depolarization.

B. Electrophysiologic basis of spontaneous depolarization of SA node and other backup nodes (Fig. 4-19**)**

RMP of nodal tissues constantly depolarizing because of Na^+ leak

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^+).

Phase 4: membrane Na^+ permeability → continuous depolarization

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.

Phase 0: when threshold potential is reached Ca^{2+} channels open, 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).

Phase 3: Ca^{2+} channels close, K^+ effluxes, and membrane potential is restored

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.

PNS ↓ maximum diastolic potential → slower heart rate

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.

Slope of phase 4 depolarization: ↑ by SNS, ↓ by PNS

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.**

Threshold for AP generation: ↑ by SNS, ↓ by PNS

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

Overdrive suppression: mechanism by which SA node prevents backup pacemakers from initiating an AP

- "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.**
- 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**)**

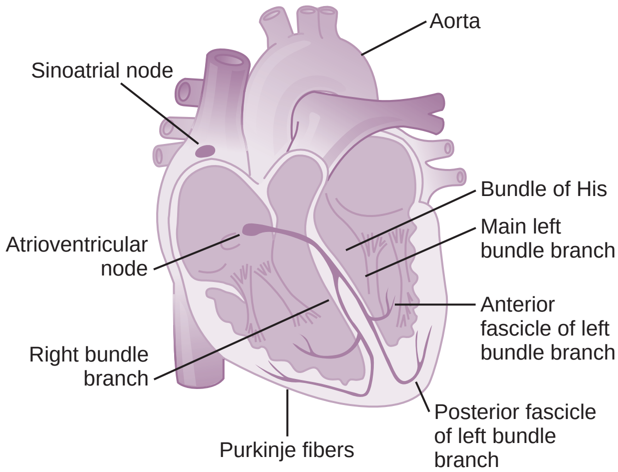
1. After a spontaneous action potential is generated in the SA node, the action potential is distributed throughout the atria and is also rapidly conducted to the AV node through specialized internodal fibers.
2. **Conduction through the AV node** then **occurs very slowly,** which gives the atria sufficient 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

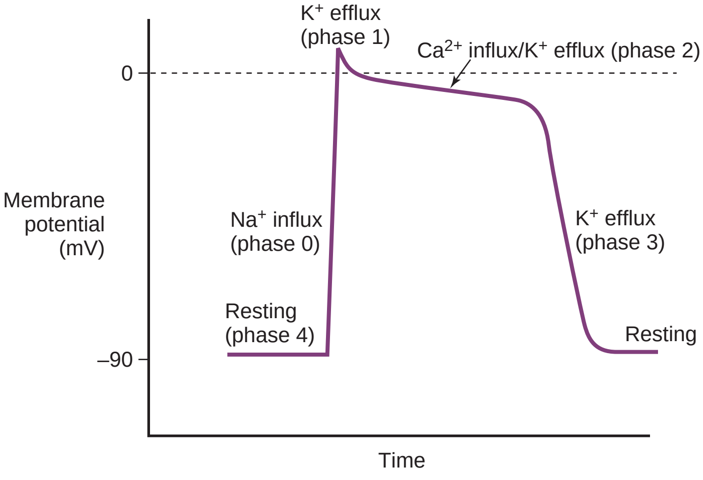
1. **Phases in cardiac myocytes** (Fig. 4-21)
   - **Phase 4: resting membrane potential**

RMP in contractile cardiomyocytes: approximately −90 mV

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.



4-20: Conduction pathways of action potentials. *(From Andreoli T, Carpenter C, Griggs R, Benjamin I: Andreoli and Carpenter's Cecil Essentials of Medicine, 7th ed. Philadelphia: Saunders; 2007, Fig. 3-3.)*



4-21: Action potential in cardiac myocytes.

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.**

Depolarization: opening of fast, voltage-gated Na^+ channels

- **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.

Calcium plateau: balance between K^+ efflux and Ca^{2+} influx

- **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.

Repolarization: simultaneous rapid efflux of K^+ and cessation of Ca^{2+} influx

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^+.

RMP in nodal cells: approximately −70 mV

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.

Refractory period: prevents tetany (sustained systole) and places upper limit on heart rate

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.**

Excitation-contraction coupling: "coupling" of ↑ in membrane potential (excitation) to cell contraction

Force of cardiomyocyte contraction proportional to intracellular $[Ca^{2+}]$

Ventricular relaxation: energy requiring process where Ca^{2+} is pumped into the sarcoplasmic reticulum and extracellular fluid

Sympathetic excitation: + inotropic effect by ↑ influx of extracellular Ca^{2+}

6. For the **ventricles to relax, 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 Ca^{2+}, causing a **greater Ca^{2+}-induced Ca^{2+} release.**
   - It also stimulates reuptake of 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 Ca^{2+} during the cardiac action potential. Such a negative inotropic effect may be beneficial in patients with **chronic heart failure** (by reducing myocardial 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 Ca^{2+}.** It does this indirectly by inhibiting the sodium-potassium adenosine triphosphatase pump (Na^+,K^+-ATPase pump), which increases intracellular Na^+. The increased intracellular Na^+ reduces the Na^+ gradient that drives a Na^+-Ca^{2+} antiport, allowing more 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.

Sympathetic innervation of the heart: innervates *both* atria and ventricles; parasympathetic innervation is only to the atria

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

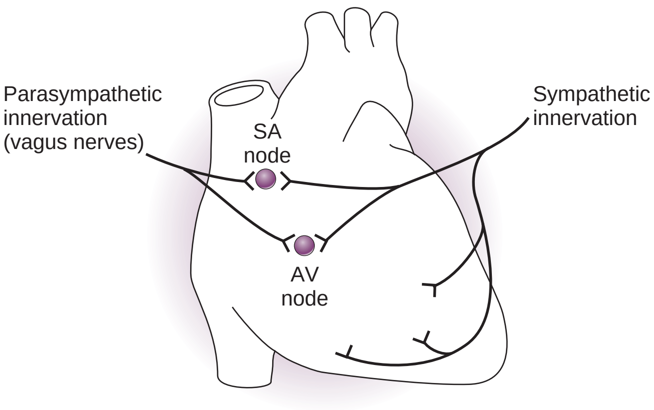
1. **Sympathetic (adrenergic) innervation**
   - **Sympathetic innervation to the heart is extensive,** with innervation to the nodal tissues, atria, and ventricles.
   - **Norepinephrine** released from sympathetic nerves binds to adrenergic receptors in the heart, resulting in **increased heart rate**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

Pharmacology note: The β_1-adrenergic receptor is primarily responsible for mediating sympathetic excitation of HR and contractility. **β-Blocking drugs** such as **metoprolol** antagonize this receptor and slow HR and reduce contractility. However, despite being marketed as β_1-specific antagonists, drugs such as metoprolol also bind to β_2-adrenergic receptors and can occasionally worsen breathing in patients with asthma or chronic obstructive pulmonary disease. At low doses, **nebivolol** is a truly β_1-selective antagonist that can be used in such susceptible patients.

Parasympathetic nervous system: does not innervate the ventricles; allows for *ventricular escape rhythm* to be generated following some forms of syncope

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.**

4-22: Cardiac nerves. *AV,* Atrioventricular; *SA,* sinoatrial.



- **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** (V_1 through V_6).
3. The bipolar and unipolar limb leads detect electrical activity in the **vertical (frontal) plane;** the precordial leads detect current in the **transverse plane.**

ECGs monitor electrical activity in heart by recording electrical changes at the body surface.

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 a V_F, although a simplified approach is discussed below.
3. A normal QRS axis is typically defined as lying between −30 and +90 degrees.

Bipolar leads (I, II, and III) and unipolar leads (aVR, aVL, and aVF) detect current in the vertical (frontal) plane.

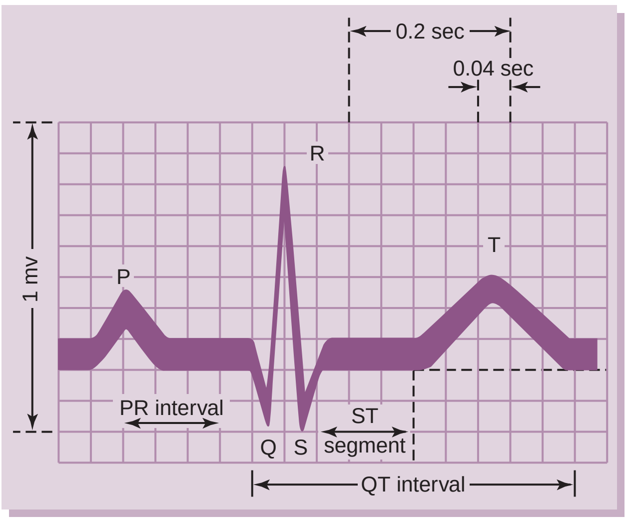
Precordial leads (V_1 through V_6) detect current in the transverse plane.

P wave: atrial depolarization

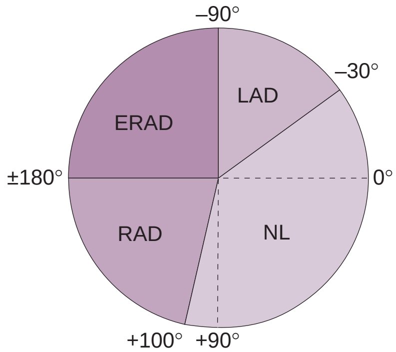
PR interval: time spent during conduction through AV node

QRS complex: ventricular depolarization

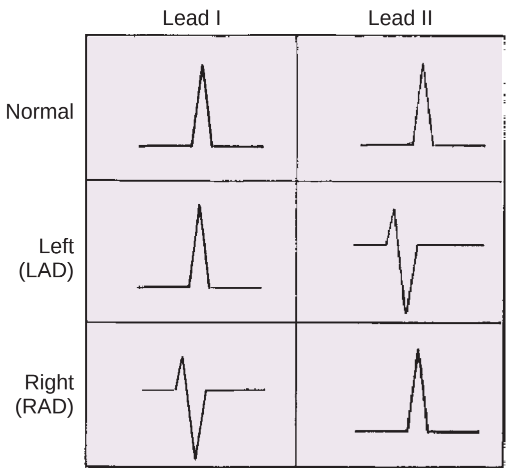
T wave: ventricular repolarization



4-23: The normal electrocardiogram (ECG). All mechanical events are slightly preceded by electrical changes on the ECG: the start of the P wave slightly precedes atrial contraction, the start of the QRS complex precedes ventricular contraction, and so on. *(From Andreoli T, Carpenter C, Griggs R, Benjamin I: Andreoli and Carpenter's Cecil Essentials of Medicine, 7th ed. Philadelphia: Saunders; 2007, Fig. 5-2.)*



4-24: Determination of QRS axis. −30 to +100 degrees is considered normal axis; −30 to −90 degrees is considered left axis deviation (LAD); +100 to +180 degrees is considered right axis deviation (RAD); −90 to +180 degrees is considered extreme right axis deviation (ERAD). *NL,* Normal. *(From Goldman L, Ausiello D: Cecil Medicine, 23rd ed. Philadelphia: Saunders; 2008, Fig. 52-6.)*



4-25: Simplified method of determining QRS axis using leads I and II. *LAD,* Left axis deviation; *RAD,* right axis deviation. *(From Goldberger A: Clinical Electrocardiography, 7th ed. Philadelphia: Mosby; 2006, Fig. 5-12.)*

- 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.
   - If the area under the QRS complex in both lead I and II is positive, the axis must be normal.
   - If the QRS complex is positive in lead I and negative in lead II, LAD is present.
   - If the QRS complex is negative in lead I and positive in lead II, RAD is present.

D. Correlation of ECG with cardiac events

- Table 4-1 correlates ECG abnormalities with cardiac events and their pathophysiology.

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

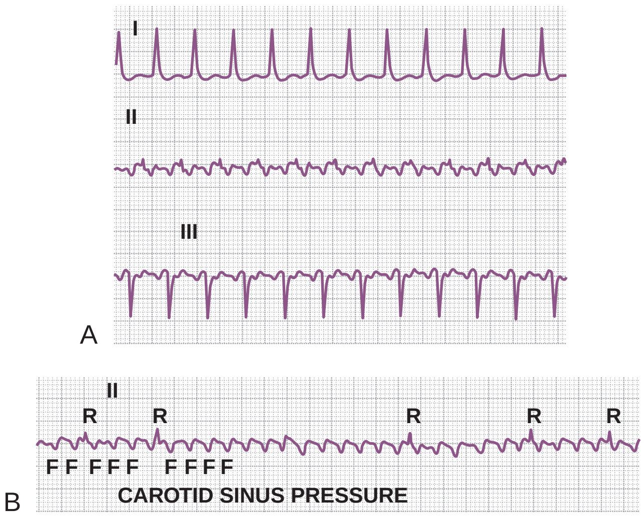
TABLE 4-1. Correlation of Electrocardiogram With Cardiac Events

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

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.)*

Atrial fibrillation: no P waves, irregular ventricular response

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.)*

Atrial flutter: sawtooth F (flutter) waves

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):

$$MAP = CO \times TPR$$

   - 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:**

$$R = 8\eta l/\pi r^4$$

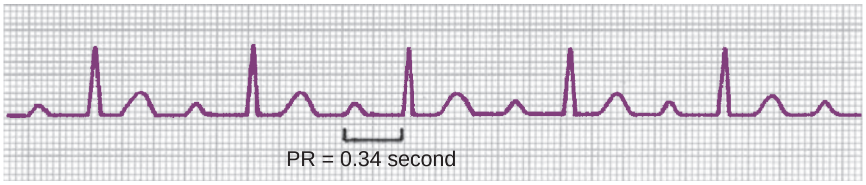
where η = viscosity; l = length of the vessel; and r = radius of the vessel.

$MAP = CO \times TPR$

Poiseuille relationship: $R = 8\eta l/\pi r^4$

Resistance to fluid flow in a vessel is inversely related to the 4th power of the radius.

First-Degree AV block: PR interval uniformly prolonged > 0.2 second

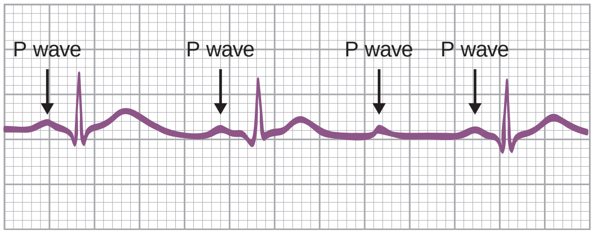


4-29: First-degree atrioventricular block. PR interval prolonged beyond 0.2 second with each beat. *(From Goldberger A: Clinical Electrocardiography, 7th ed. Philadelphia: Mosby; 2006, Fig. 17-1.)*

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

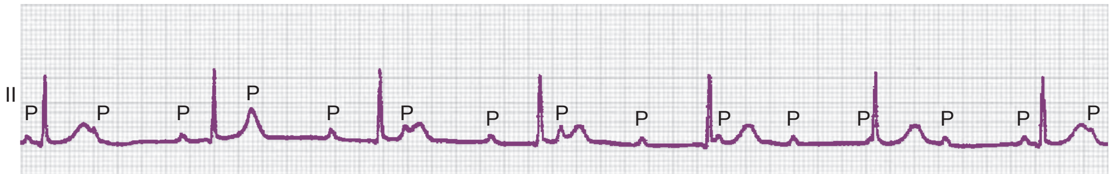
4-30: Mobitz type 1 second-degree AV block. The PR interval lengthens progressively with successive beats until one sinus **P** wave is not conducted at all. Then the cycle repeats itself. Notice that the **PR** interval after the nonconducted **P** wave is shorter than the **PR** interval of the beat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

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



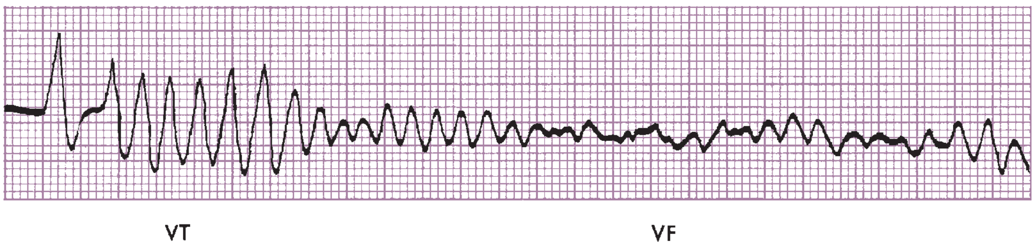
4-31: Second-degree heart block (Mobitz type 2). Note how not all **P** waves are conducted, resulting in a dropped **QRS** complex after the third **P** wave. *(From Lim E, Loke YK, Thompson A: Medicine and Surgery. New York: Churchill Livingstone; 2007, Fig. 1-4C.)*

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



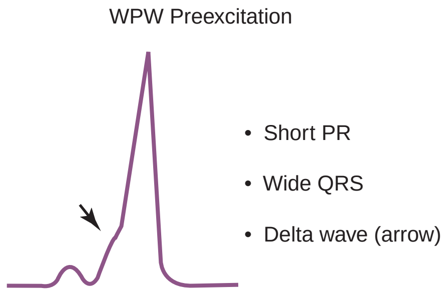
4-32: Complete heart block with underlying sinus rhythm characterized by independent atrial **(P)** and ventricular (QRS complex) activity. The **PR** intervals are completely variable. Some sinus **P** waves fall on the **T** wave, distorting its shape. Others may fall in the **QRS** complex and be "lost." *(From Goldberger A: Clinical Electrocardiography, 7th ed. Philadelphia: Mosby; 2006, Fig. 17-5.)*

Ventricular tachycardia: often a precursor to potentially fatal ventricular fibrillation



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.)*

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



4-34: Wolff-Parkinson-White **(WPW)** syndrome: shortened **PR** interval, widened **QRS** wave with slurred upstroke (delta wave). *(From Goldberger AL, Goldberger E: Clinical Electrocardiography: A Simplified Approach, 5th ed. St. Louis: Mosby; 1994.)*

- 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).

Resistance in circulatory system: determined primarily by diameter of arterioles rather than large arteries

Pharmacology note: Sympathetic stimulation of arteriolar vascular smooth muscle contraction is mediated by α_1-receptors. α_1-Blocking drugs such as prazosin antagonize this receptor and inhibit vasoconstriction, thereby lowering blood pressure.

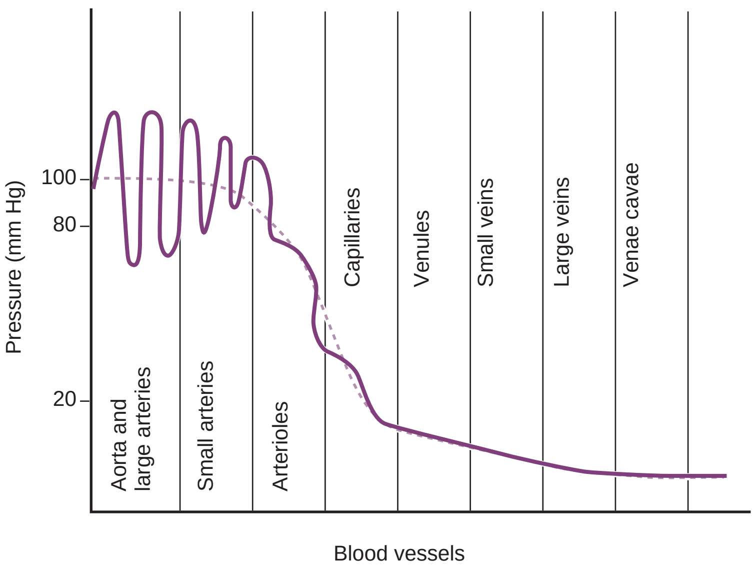
3. **Tonic sympathetic outflow through the medullary vasomotor center**
   - Tonic sympathetic outflow from the medullary vasomotor center **increases TPR** and **maintains vasomotor tone.**
   - When vasomotor tone is normal, most of the body's arterioles are at least partly constricted, helping to 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).

Medullary vasomotor center: tonic sympathetic outflow that maintains vasomotor tone and TPR

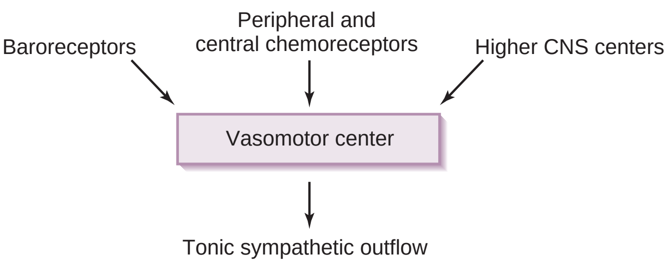
B. Rapid blood pressure control by the autonomic nervous system

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.

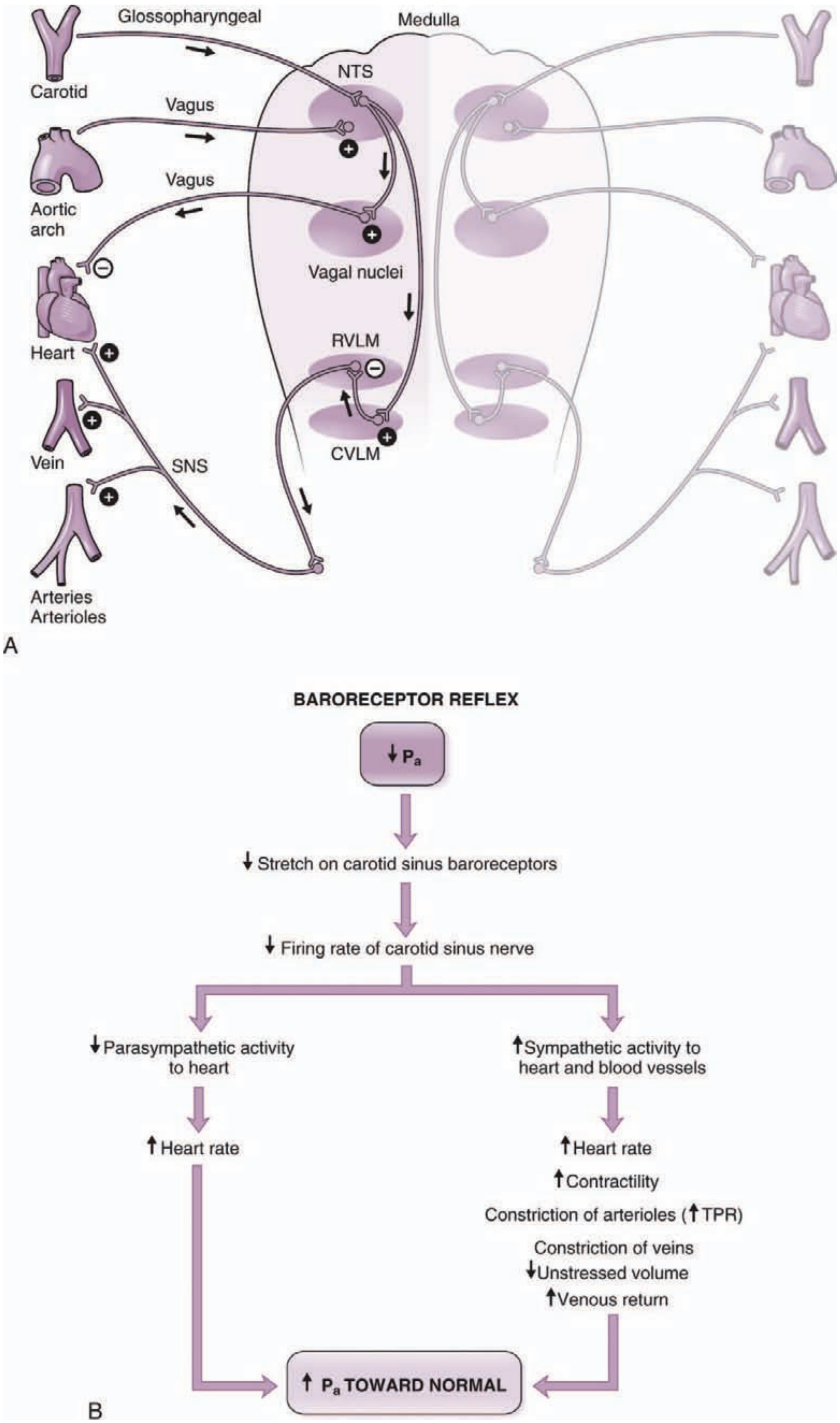
Baroreceptor reflex: dependent on mechanoreceptors in aortic arch and carotid sinuses



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.



4-37: 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 α_1-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.

CNS ischemic response: may be seen in stroke to ↑ cerebral perfusion

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:

$$C = \Delta V / \Delta P$$

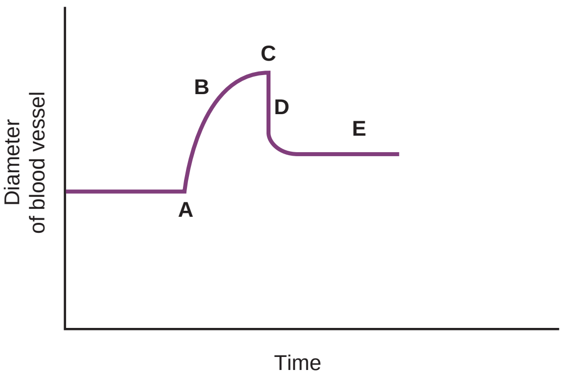
Metabolic mechanism: demand regulates supply by production of vasodilatory substances

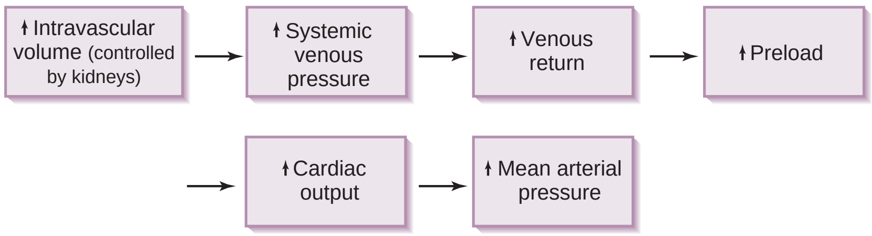
Myogenic mechanism: VSMC contraction dependent on Ca^{2+} permeability

Arteriosclerosis: arteries become noncompliant and contribute to development of hypertension

Compliant vessel: able to withstand ↑ in volume without causing significant ↑ in pressure

4-38: Myogenic mechanism in autoregulation of local blood flow. If the vascular smooth muscle cell is passively stretched (B), which occurs with increased blood flow, Ca^{2+} permeability increases and Ca^{2+} enters the vascular smooth muscle cell (C). This causes contraction of the cell and a compensatory vasoconstriction (D). This action establishes a new blood vessel diameter (E), which is only slightly larger than the initial diameter (A), thereby maintaining a relatively constant blood flow through the capillary bed.





4-39: Long-term control of intravascular volume by the kidneys.

Veins are much more compliant than arteries.

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

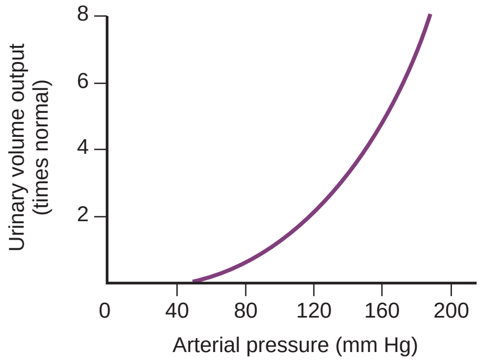
Kidneys control blood pressure by regulating intravascular volume.

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).

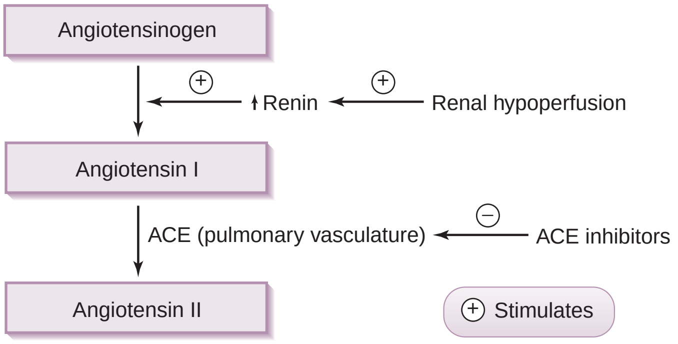
Pressure diuresis: ↑ BP → ↑ GFR → ↑ Na^+/H_2O excretion → ↓ intravascular volume → ↓ BP

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.
   - **Note:** In theory, pressure diuresis by the kidneys can fully compensate for any increase in systemic blood pressure, thus preventing hypertension.
     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.**

RAAS: activated by renal hypoperfusion



4-40: Increased urinary output in response to arterial pressure (pressure diuresis).



4-41: Enzymatic cascade in the renin-angiotensin-aldosterone system. *ACE,* Angiotensin-converting enzyme.

- 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).

Angiotensin II: stimulates renal Na^+ reabsorption, thirst, and systemic vasoconstriction

- **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 renal Na^+ reabsorption and K secretion; ↑ intravascular volume and MAP

Pathology of excess aldosterone: hypokalemic metabolic alkalosis and difficult to treat hypertension

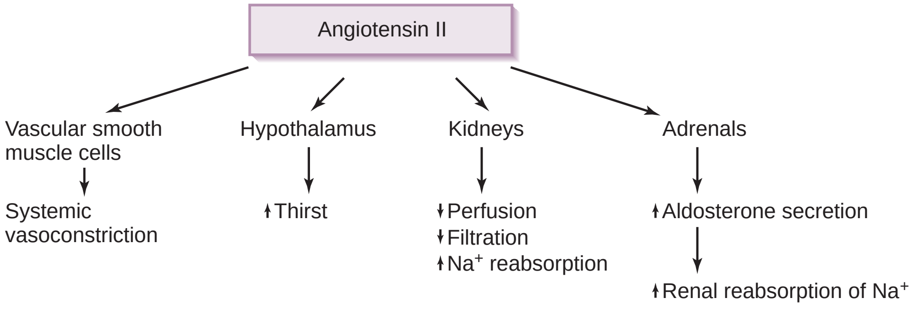
- **Actions of aldosterone**
  a. Stimulates **Na^+ reabsorption** and **K secretion** from the distal nephron
  b. Acts to **increase intravascular volume** and maintain arterial blood pressure
  c. In excess can contribute to the development of hypertension and electrolyte abnormalities such as **hypernatremia, 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.

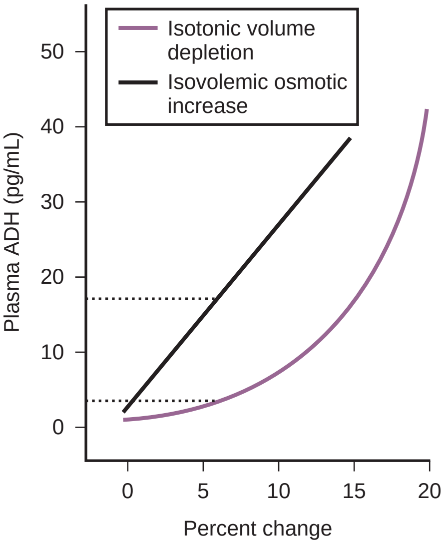
Pharmacology note: Because aldosterone acts to expand plasma volume, aldosterone antagonists such as **spironolactone** are useful in managing congestive heart failure. In patients with dyspnea with minimal exertion or at rest (these patients are referred to as having stage 3 or 4 heart failure per the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

ADH secretion: More sensitive to ↑ plasma osmolarity than ↓ plasma volume

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.

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.

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

ANP: atrial stretching ↑ secretion → 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.

BNP: ventricular stretching ↑ secretion → promotes diuresis

VIII. Fluid Exchange in the Capillaries

A. Overview

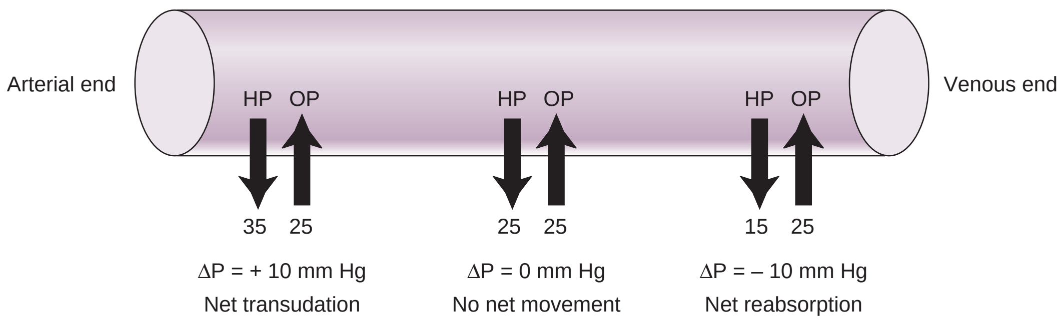
1. Fluid exchange across the capillary membrane is dependent on the permeability characteristics of the capillary bed and the net filtration pressure generated across the capillary bed.
2. The **net filtration pressure** (NFP) depends on the interaction between plasma and interstitial hydrostatic and 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.

↓ Capillary hydrostatic pressures: hemorrhage, hypotension, hypoalbuminemia

B. Starling forces

1. **Hydrostatic pressure of the capillary (P_c)**
   - 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.

↑ Capillary hydrostatic pressure forces fluid into the interstitium, 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).

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.

Plasma oncotic pressure: keeps fluid in the vascular compartment

2. **Plasma oncotic pressure or plasma colloid osmotic pressure (π_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.**

↓ Plasma oncotic pressure leads to fluid accumulation in the interstitium (edema)

Pathology note: Albumin is synthesized from amino acids by the liver. Therefore, malnutrition or liver disease can cause **hypoalbuminemia** and **edema.** Additionally, certain kidney diseases such as **nephrotic syndrome** are characterized by the loss of large quantities of serum protein in the urine, which also may lead to hypoalbuminemia and edema. The fluid that is directed into the interstitium is called a **transudate,** which is a protein-poor (<3 g/dL) and cell-poor fluid. Because of its low viscosity, it obeys the law of gravity and collects in the most dependent portion of the body (e.g., feet in a patient standing up). Gentle pressure on the skin displaces the fluid, producing **pitting edema.**

Interstitial hydrostatic pressure: slightly negative because of constant drainage by the lymphatics

Interstitial oncotic pressure: outward force (typically small) exerted by interstitial proteins

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 (π_{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.

Small NFP able to drive capillary filtration due to high permeability of capillary membrane

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:

$$\begin{aligned} NFP &= (P_c + \pi_{IF}) - (P_{IF} + \pi_c) \\ &= (17.3 + 8) - (-3 + 28) \\ &= 0.3 \text{ mm Hg} \end{aligned}$$

   where NFP = net filtration pressure; P_c = hydrostatic pressure of capillary; P_{IF} = interstitial hydrostatic pressure; π_c = plasma oncotic pressure; and π_{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).

Lymphatic system: returns excess fluid to the vascular compartment through the thoracic duct

Dysfunction of lymphatic system → edema

Edema: excess fluid (transudate, exudate, lymphatic, glycosaminoglycans) in interstitium

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

Systolic heart failure: pump failure (impaired contractility, increased afterload)

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_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

Diastolic heart failure: impaired ventricular filling during diastole due to stiff ventricle or obstruction to ventricular filling (e.g., mitral stenosis)

Examples of obstruction to left ventricular filling: mitral stenosis, cardiac tamponade

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_2 supply. The underlying cause of myocardial ischemia is typically coronary artery disease.

TABLE 4-2. Starling Forces and Edema

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

TABLE 4-3. Compensatory Responses to Reduced Cardiac Output

COMPENSATORY RESPONSE	PRIMARY TRIGGERING STIMULUS	ADVERSE EFFECTS
Frank-Starling relationship	Reduced renal perfusion from reduced cardiac output activates renin-angiotensin-aldosterone system and expands plasma volume	Pulmonary edema Peripheral edema
Myocardial hypertrophy	Increased myocardial wall stress	Increased myocardial oxygen demand Reduced ventricular compliance if concentric hypertrophy develops Impaired contractility if eccentric hypertrophy develops Risk for arrhythmias
Neurohormonal activation	Baroreceptors	Vasoconstriction in skeletal muscles produces weakness

TABLE 4-4. Physiologic Basis for Signs of Shock

SIGNS	PHYSIOLOGIC BASIS
Lactic acidosis	Tissue ischemia, hypoxia → ↑ anaerobic respiration
Pale, cool, moist skin	Sympathetic-mediated peripheral vasoconstriction and sweating
Rapid, weak pulse	Reflex tachycardia in hypotension
Reduced urinary output	↓ Renal blood flow → ↓ glomerular filtration rate
Confusion	Insufficient cerebral perfusion

High-output heart failure: usually precipitated by peripheral conditions in which the body requires a pathologically elevated CO

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.

Compensatory responses in heart failure: Frank-Starling relationship, myocardial hypertrophy, neurohormonal activation

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**

Shock: cold and clammy skin, rapid and weak pulse, confusion, and reduced urinary output

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.

Types of shock: cardiogenic, distributive, hypovolemic

Cardiogenic shock: "pump" failure

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.

TABLE 4-5. Types of Shock

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

- 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**

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

- 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.**

CHAPTER 5
RESPIRATORY PHYSIOLOGY

O_2: 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

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 5-1. **Comparison of Bronchi and Bronchioles**

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

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.**

Mucociliary escalator: impaired by smoking, diseases such as cystic fibrosis, and intubation

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.

Primary ciliary dyskinesia: immotile cilia; absent dynein arm (see clinical note)

Kartagener syndrome: ciliary dyskinesia in a setting of situs inversus, chronic sinusitis, and bronchiectasis (see clinical note)

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.*

Respiratory airways: site of gas exchange

Respiratory airways: ↓ resistance because arranged in parallel

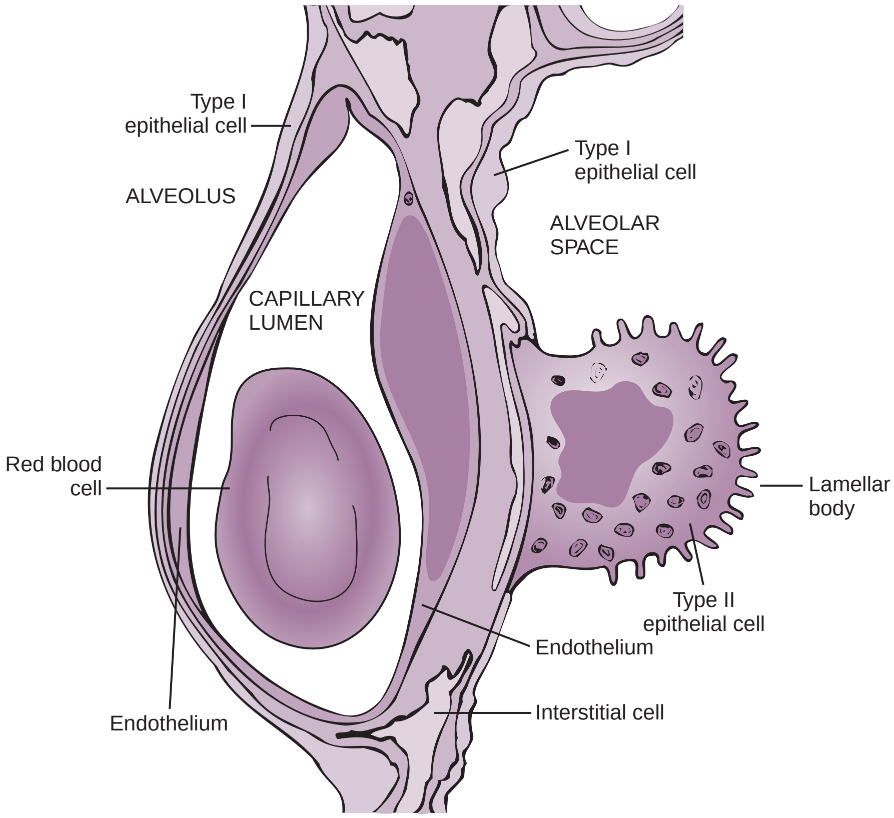
D. Pulmonary membrane: the "air-blood" barrier (Fig. 5-1)

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 **surfactant-containing fluid layer** that lines the alveoli
   - **Alveolar epithelium** composed of pneumocytes (both type I and type II)
   - **Epithelial** and **capillary basement membranes,** separated by a thin interstitial space (fused in areas)
   - **Capillary endothelium**

Type II pneumocytes: synthesize surfactant; repair cell of lung

TABLE 5-2. Comparison of Conducting and Respiratory Airways

PARAMETER	CONDUCTING AIRWAYS	RESPIRATORY AIRWAYS
Histology	Ciliated columnar tissue Goblet cells (mucociliary tract)	Nonciliated cuboidal tissue No goblet cells Lacks smooth muscle
Presence of cartilage	Yes	No
Resistance	Large diameter Arranged in series High resistance	Small diameter Arranged in parallel Low resistance



5-1: Microscopic structure of the alveolar wall. *(From Kumar V, Abbas A, Fausto N: Robbins and Cotran Pathologic Basis of Disease, 7th ed. Philadelphia, Saunders, 2005, Fig. 15-1.)*

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.

Ventilation is the process by which air enters and exits the lungs.

Normal ventilation but impaired gas exchange: anemia, high altitude

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.

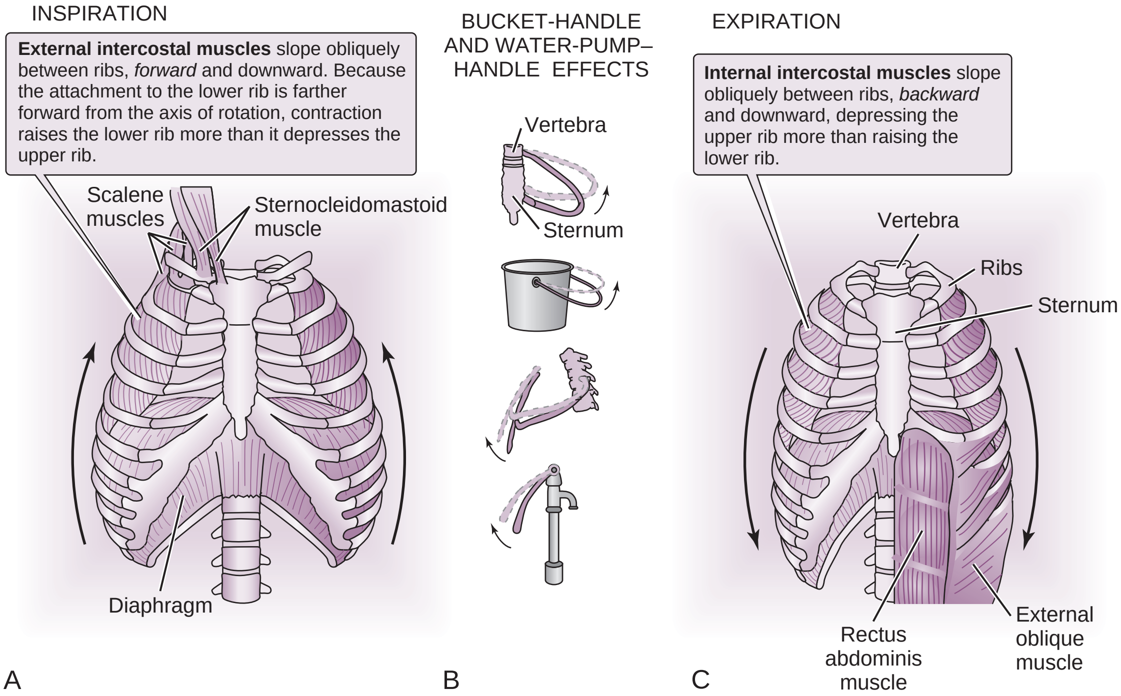
Pathology note: Gas exchange may be impaired in certain conditions in which pulmonary ventilation is nevertheless normal or even increased. Two examples are **anemia** and **high-altitude respiration.**

Diaphragm: most important muscle of respiration

Accessory muscles: sternocleidomastoid, scalenes, pectoralis major; important in forceful breathing

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).



5-2: **A,** Muscles of inspiration. Note how contraction of the diaphragm increases the vertical diameter of the thorax, whereas contraction of the external intercostal muscles results in anteroposterior and lateral expansion of the thorax. **B,** Movement of thoracic wall during breathing. **C,** Muscles of expiration. *(From Boron W, Boulpaep E: Medical Physiology, 2nd ed. Philadelphia, Saunders, 2009, Fig. 27-3.)*

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

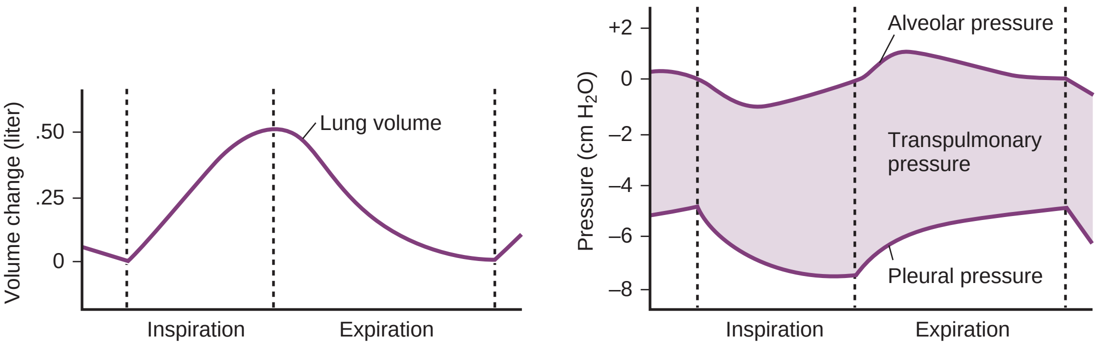
Negative intrapleural pressure: responsible for pressure gradient driving air into lungs

Boyle's law: $V_2 = P_1V_1/P_2$; i.e., as lung volume ↑ during inspiration the intrapleural pressure must ↓

Transpulmonary pressure: difference between pleural and alveolar pressures

Airways resistance: friction between air molecules and airway wall caused by air moving at high velocity

Compliance resistance: resistance to stretching of lungs during inspiration



5-3: Pressure and volume changes during the respiratory cycle. Note that alveolar pressure equals zero at the end of a tidal inspiration (when there is no airflow). In contrast, at the end of a tidal inspiration, the pleural pressure has decreased to its lowest value (approximately −7.5 cm H_2O). The difference between pleural and alveolar pressures is referred to as the *transpulmonary pressure.*

- **Tissue resistance:** friction that occurs when the pleural surfaces glide over each other as the lungs inflate

Tissue resistance: friction generated by pleural surfaces sliding over each other during inspiration

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.

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

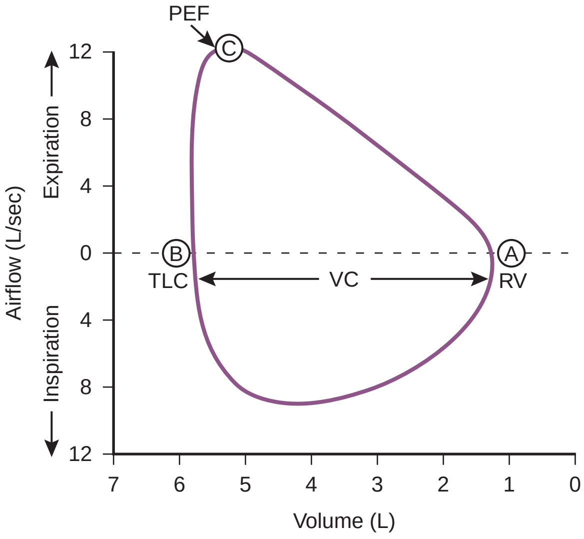
2. **Driving forces for expiration**
   - An **increase in intrapleural pressure** is created by movement of the diaphragm upward and the chest wall inward.
     a. This increase is then transmitted to the terminal air spaces (alveolar ducts and alveoli) and compresses them, causing air to leave the 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.

↑ Intrapleural pressure: caused by movement of diaphragm upward and chest wall inward

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.

Airflow resistance during expiration: primarily due to ↓ airway diameter from ↑ intrathoracic pressures

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.**



5-4: Flow-volume curve recorded during inspiration and expiration in a normal subject. Note the linear decline during most of expiration. *PEF,* Peak expiratory flow; *RV,* residual volume; *TLC,* total lung capacity; *VC,* vital capacity. *(From Goljan EF, Sloka K: Rapid Review Laboratory Testing in Clinical Medicine. Philadelphia, Mosby, 2008, Fig. 3-3.)*

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.

Work of breathing: pressure-volume work performed in moving air into and out of lungs

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 equated to the resistance encountered by a fluid traveling through a rigid tube.
     a. **Poiseuille's equation** relates airflow resistance (R), air viscosity (η), airway length (l), and airway radius (r), assuming laminar rather than turbulent airflow:

$$R = 8\eta l/\pi r^4$$

Air: essentially a low-viscosity fluid, so airflow resistance can be approximated by Poiseuille's equation

Poiseuille's equation: $R = 8\eta l/\pi r^4$

     b. 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.

Airway diameter: small changes can have dramatic impact on airflow resistance because of inverse relationship of resistance to the fourth power of radius

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

$$R_{total} = R_1 + R_2 + R_3 + \ldots + R_n$$

Large airways: contribute most to airway resistance; arranged in series with small total cross-sectional area

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.**

Small airways provide relatively little resistance: arranged in parallel; large total cross-sectional area; slow/laminar flow

Pharmacology note: Many classes of drugs affect large-airway diameter by affecting bronchial smooth muscle tone. For example, **β_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 **lipoxygenase inhibitors.**

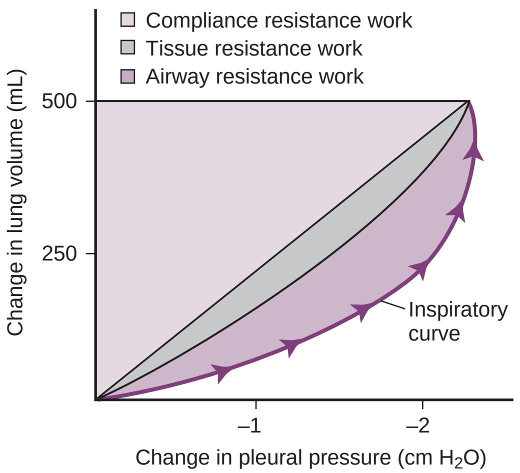
3. **Compliance resistance (work)**
   - As the lungs inflate, work must be performed to overcome the intrinsic **elastic recoil of the lungs.**
   - This work, termed **compliance work,** normally accounts for the largest proportion (~75%) of the total work of breathing (Fig. 5-5).

Compliance work: work required to overcome elastic recoil of lungs; largest component of work of breathing

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.

Tissue resistance: normally small component of work of breathing due to presence of pleural fluid



5-5: Relative contributions of the three resistances to 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):

$$C = \frac{\Delta V}{\Delta P}$$

Lung compliance: compliant lungs are easy to distend

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.

Compliance curve of the lungs: compliance greatest in midportion of curve; demonstrates hysteresis

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.

Lung–chest wall system: at equilibrium at FRC

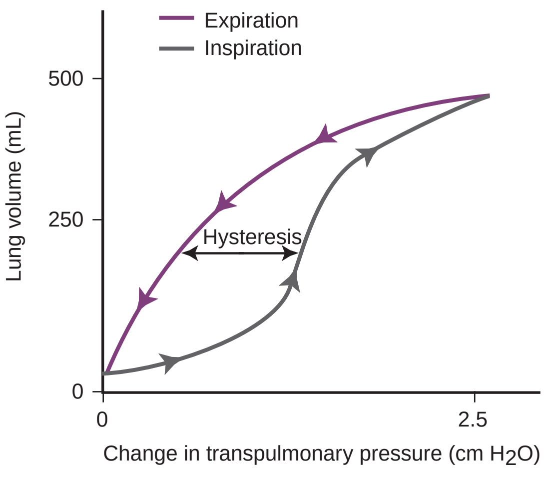
Pathology note: In emphysema, destruction of lung parenchyma results in **increased compliance** and a **reduced elastic recoil** of the lungs because of destruction of elastic tissue by neutrophil-derived elastases. At a given FRC, the tendency is therefore for the lungs to expand because of the unchanged 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

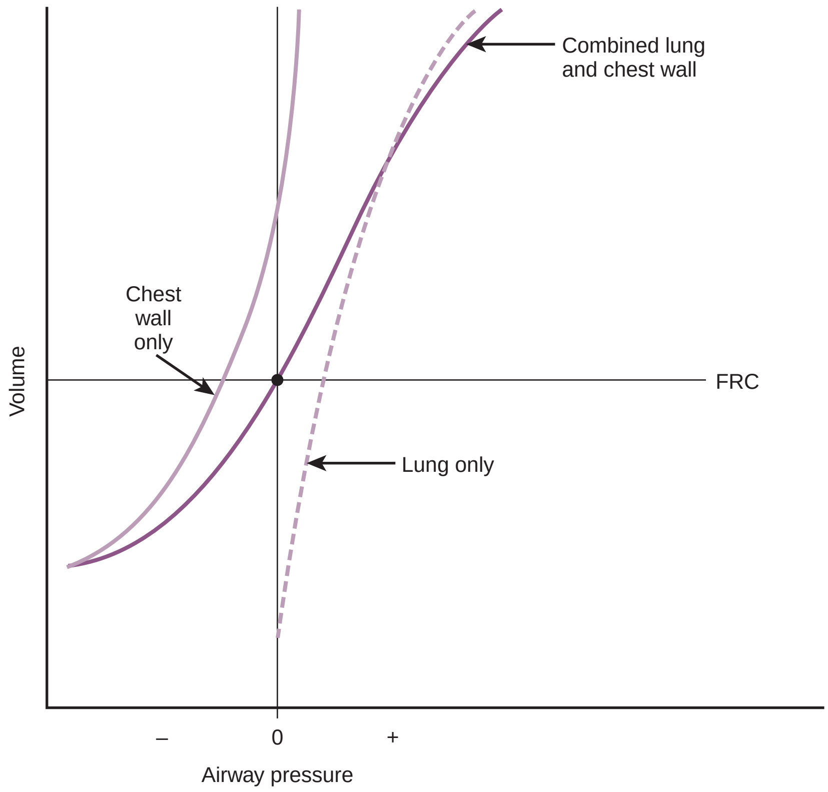
1. Elastance is the property of matter that makes it **resist deformation.**
   - Highly elastic structures are difficult to deform.
2. Pulmonary elastance (E) is the pressure (P) required for a fractional change of lung volume (ΔV):

$$E = \frac{\Delta P}{\Delta V}$$

Elastance: elastic structures are difficult to deform, e.g., fibrotic lungs



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.



5-7: Compliance of the lungs and chest wall separately and together. *FRC,* Functional residual capacity. *(From West JB: Respiratory Physiology: The Essentials, 8th ed. Philadelphia, Lippincott Williams & Wilkins, 2008, Fig. 7-11.)*

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.

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 ↓ in surface tension and alveolar collapsing pressure

Laplace's law: collapsing pressure inversely proportional to alveolar radius; CP = T/R

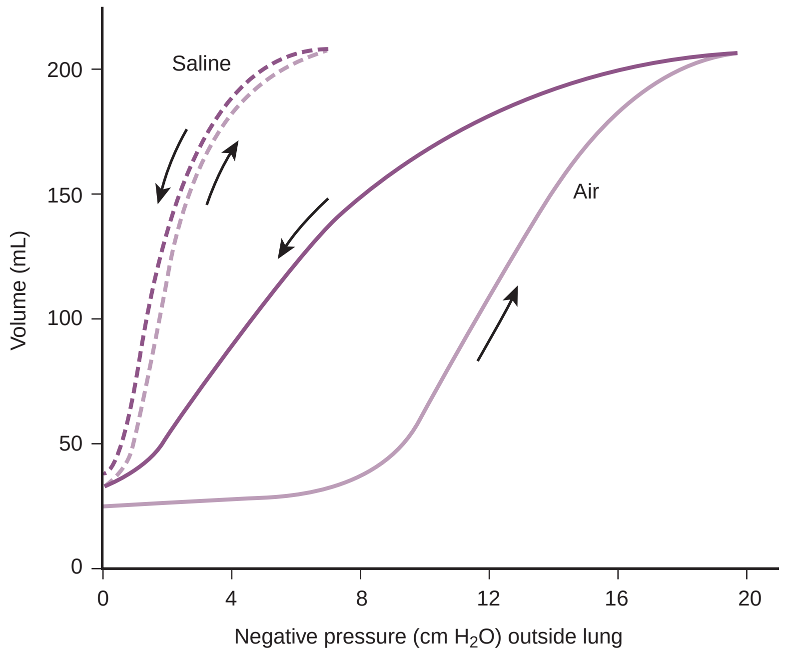
G. Surface tension

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:

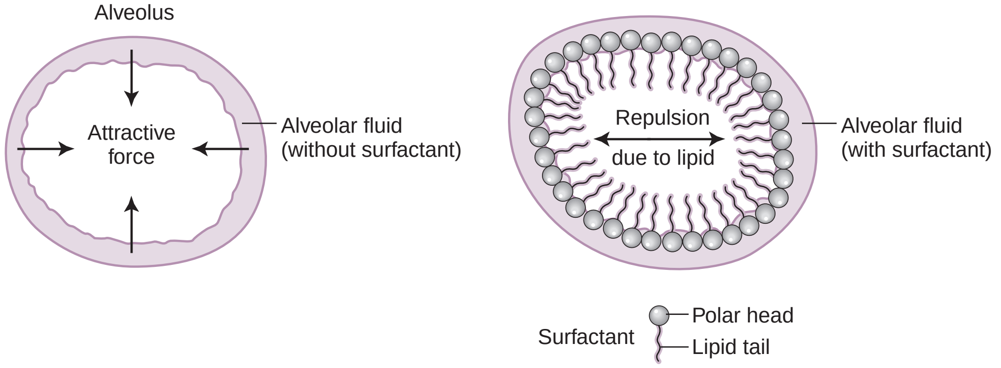
$$CP = T/R$$

where
CP = collapsing pressure
R = alveolar radius
T = surface tension

5. Figure 5-8 demonstrates that saline-inflated lungs are more compliant that air-inflated lungs because of reduced surface tension and collapsing pressures.



5-8: Compliance of air-inflated lungs versus saline-inflated lungs. Note that the saline-inflated lungs are more compliant than air-filled lungs owing to the reduction in surface tension, which reduces the collapsing pressure of alveoli.



5-9: Role of surfactant in reducing alveolar surface tension. Note the orientation of the hydrophilic "head" in the alveolar fluid and the hydrophobic "tail" in the alveolar air.

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.

Surfactant reduces compliance resistance of lungs.

Surfactant: complex phospholipid secreted by type II epithelial cells; ↓ alveolar surface tension to ↓ work of breathing

Alveolar surface tension: *moderate* amount beneficial because generates collapsing pressure that contributes to elastic recoil

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.

Gas exchange across the pulmonary membrane occurs by diffusion.

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

Dalton's law: partial pressure exerted by a gas in a mixture of gases is proportional to the fractional concentration of that gas

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:

$$Px = P_B \times F$$

where
Px = 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 (PO_2) at sea level, which has a fractional concentration of 21%, is calculated as follows:

$$Px = P_B \times F$$

$$PO_2 = 760 \text{ mm Hg} \times 0.21 = 160 \text{ mm Hg}$$

3. The partial pressure of O_2 in **humidified tracheal air** is calculated as follows:

$$Px = (P_B - P_{H_2O}) \times F$$

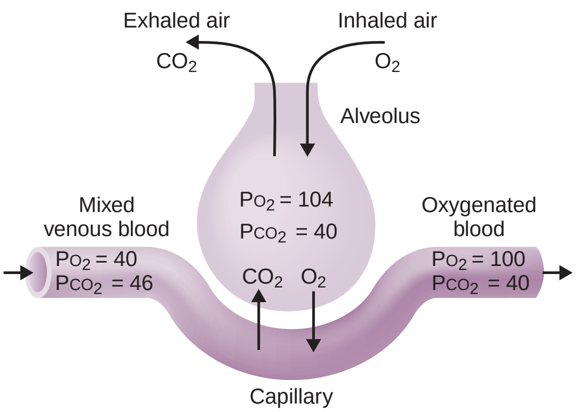
$$PO_2 = (760 - 47) \times 0.21 = 150 \text{ mm Hg}$$

Dilution of inspired air by H_2O vapor: ↓ partial pressure of alveolar O_2; important at high altitude

- 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:



5-10: Schematic illustrating diffusion of O_2 from alveolar gas into pulmonary capillary blood and diffusion of CO_2 from capillary blood into alveolar gas. *(From Damjanov I: Pathophysiology. Philadelphia, Saunders, 2008, Fig. 5-6.)*

$$P_{AO_2} = (P_B - P_{H_2O}) \times F$$
$$P_{AO_2} = (460 - 47) \times 0.21$$
$$P_{AO_2} = 413 \times 0.21 = 86.7 \text{ mm Hg}$$

Note that the value of 86.7 mm Hg is less than the P_{AO_2} 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)

GAS	ATMOSPHERIC	ALVEOLAR	ARTERIAL	VENOUS
O_2	160	100	100	40
CO_2	0.3	40	40	46
N_2	600	573	—	—
H_2O	0	47	—	—

C. Diffusion

1. The **diffusion rate** of oxygen across the pulmonary membrane depends on:
   - The **pressure gradient** (ΔP) 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.

$$D = \frac{\Delta P \times A \times S}{T}$$

Fick's law of diffusion: $D = \Delta P \times A \times S/T$

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**).

Oxygen diffusion: impaired by any process that ↓ O_2 pressure gradient, ↓ surface area of pulmonary membrane, or ↑ diffusion distance

D. Diffusing capacity of the pulmonary membrane

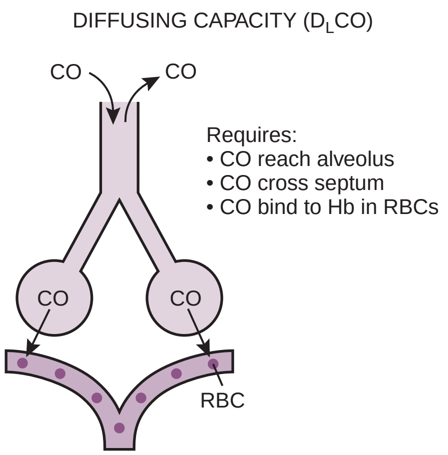
1. This is the *volume of gas* that can diffuse across the pulmonary membrane in 1 minute when the pressure difference across the membrane is 1 mm Hg.
   - It is often measured using **carbon monoxide (Fig. 5-11).**
2. The diffusing capacity of the lungs is normally so great that O_2 exchange is **perfusion 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: volume of gas able to diffuse across pulmonary membrane in 1 minute with pressure gradient across membrane of 1 mm Hg

Diffusing capacity: often measured using CO

O_2 exchange normally so efficient that it is perfusion limited

With lung disease O_2 exchange may become diffusion limited.



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 O_2 (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 O_2 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.

Perfusion-limited gas exchange: diffusion can ↑ only if blood flow ↑; examples: N_2O and O_2 *under normal conditions*

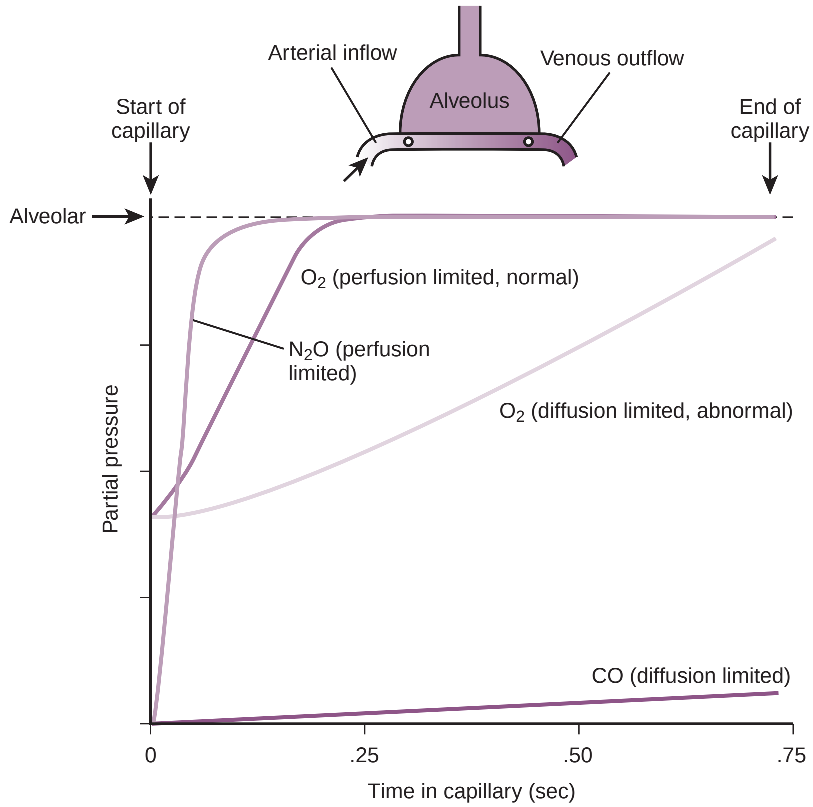
Diffusion-limited gas exchange: diffusion continues as long as pressure gradient exists across pulmonary membrane; examples: O_2 *during vigorous exercise at high altitude* and CO

V. Pulmonary Blood Flow

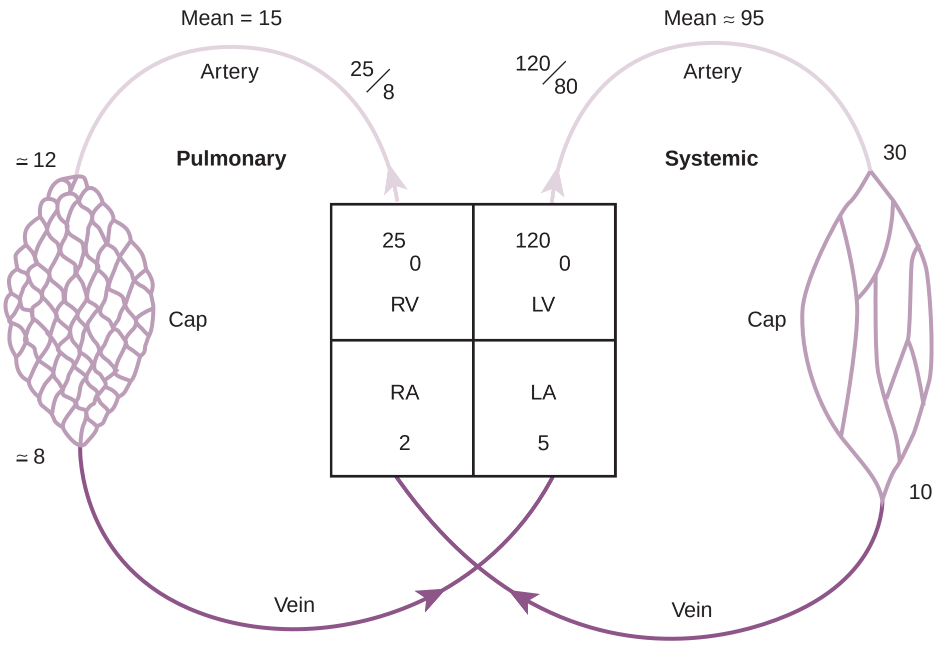
A. Pressures in the Pulmonary Circulation

- Despite receiving the entire cardiac output, pressures in the pulmonary circulation are remarkably low compared with the systemic circulation.

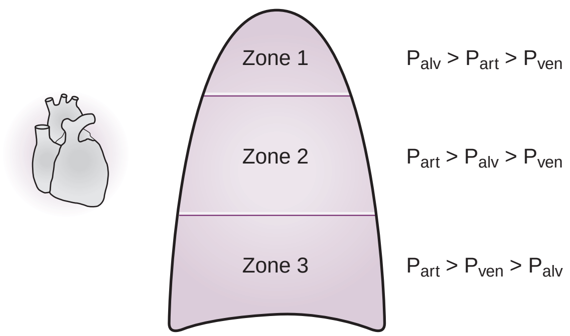
Pulmonary hemodynamics: pulmonary circulation receives entire cardiac output yet has low pressures compared with systemic circulation



5-12: Uptake of N_2O, O_2, and CO across the pulmonary membrane. *(From West JB: Respiratory Physiology: The Essentials, 8th ed. Philadelphia, Lippincott Williams & Wilkins, 2008, Fig. 3-2.)*



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.)*



5-14: Zones of pulmonary blood flow. Note the vertical position of the heart relative to the lung zones. P_{alv}, Alveolar partial pressure; P_{art}, arterial partial pressure; P_{ven}, venous partial pressure.

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.

Lung apices: relatively underperfused in upright position owing to low arterial hydrostatic pressure at lung apices

Zone 1 has *no blood flow* during the cardiac cycle.

Zone 1 blood flow: may be seen with severe hemorrhage and positive-pressure ventilation

Zone 2 has *intermittent blood flow* during the cardiac cycle.

Zone 2 blood flow: no blood flow during diastole because of collapse of pulmonary capillaries; occurs in upper two thirds of lungs

Zone 3 has *continuous blood flow* during the cardiac cycle.

Zone 3 blood flow: primarily occurs in the lung bases

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.

V/Q matching: important for efficient gas exchange

V/Q matching: inefficient to perfuse unventilated alveoli or ventilate nonperfused alveoli

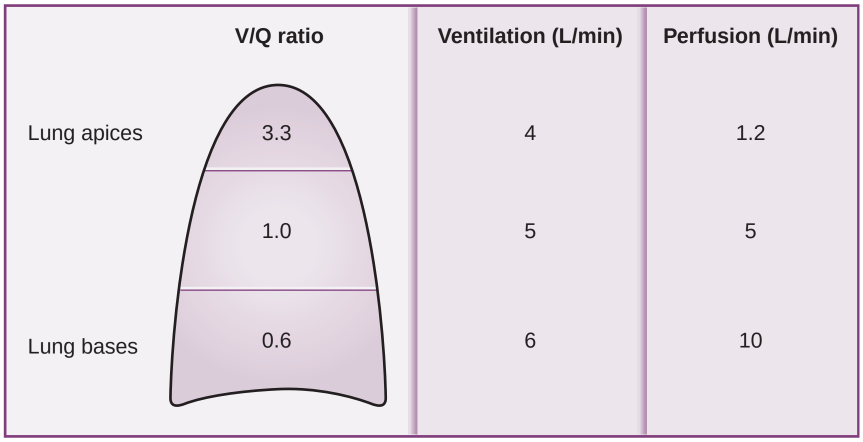
Lung apices relatively overventilated at rest

Lung bases relatively overperfused at rest

Mechanisms of V/Q matching: hypoxia-induced vasoconstriction, pulmonary hemodynamic and ventilatory changes with exercise

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.**



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.

Hypoxemia in pulmonary capillaries stimulates pulmonary arteriolar *vasoconstriction.*

Hypoxia-induced vasoconstriction: mechanism whereby hypoxia-induced vasoconstriction shunts blood to better-ventilated lung segments

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.

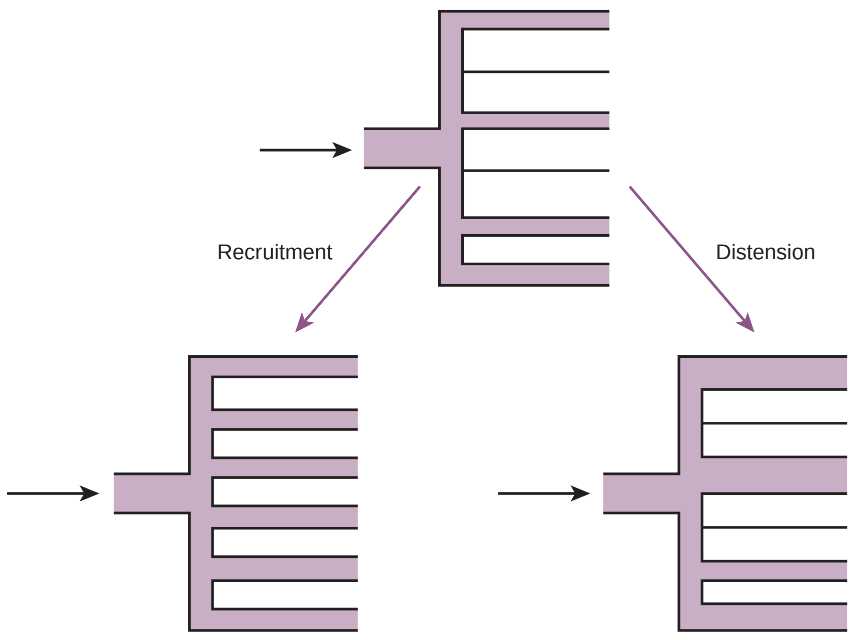
Pathology note: At **high altitudes,** where the alveolar partial pressure of O_2 is low, pulmonary vasoconstriction may become harmful, leading to a **global hypoxia-induced vasoconstriction.** This further inhibits gas exchange and increases pulmonary vascular resistance, contributing to the development 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.

Recruitment: opening of previously closed pulmonary capillaries because of increased pulmonary arterial pressures, as may occur with exercise

Distension: already patent capillaries dilate further to accommodate additional blood

V/Q matching: occurs more efficiently during exercise



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. O_2 saturation takes only approximately 0.3 second. This "safety cushion" of approximately 0.7 second is essential for O_2 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.

Anatomic shunt: blood diverted from lungs; examples: fetal blood flow, right-to-left intracardiac shunting

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.

Physiologic shunt: blood supplying the lungs is not involved in gas exchange; examples: bronchial arterial circulation, pneumonia, pulmonary edema

TABLE 5-4. Types of Shunt

TYPE	CHARACTERISTICS	CLINICAL EXAMPLES
Physiologic	Blood flow to unventilated portions of lungs	Pneumothorax, pneumonia
Anatomic	Blood flow bypasses lungs	Increased perfusion of bronchial arteries in chronic inflammatory lung disease
Left-to-right	Bypasses systemic circulation May cause pulmonary hypertension and eventual right-to-left shunt	Patent ductus arteriosus, ventricular septal defect
Right-to-left	Bypasses pulmonary circulation	Tetralogy of Fallot, truncus arteriosus, transposition of great vessels, atrial septal defect

VI. Lung Volumes

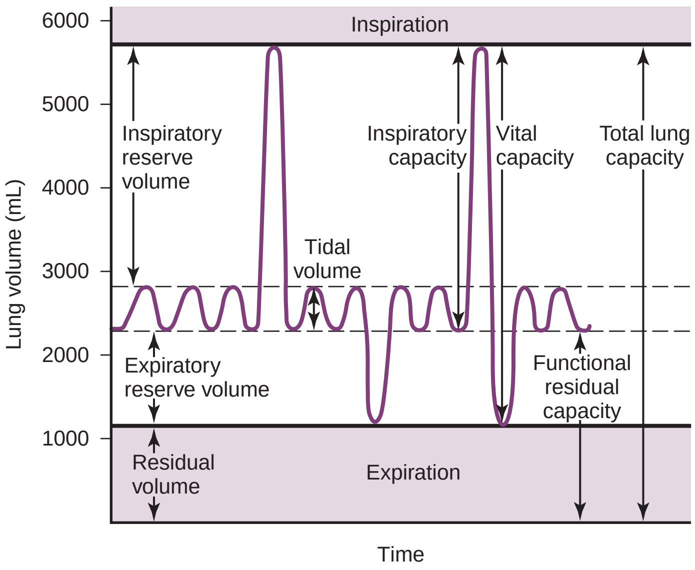
A. Overview

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.

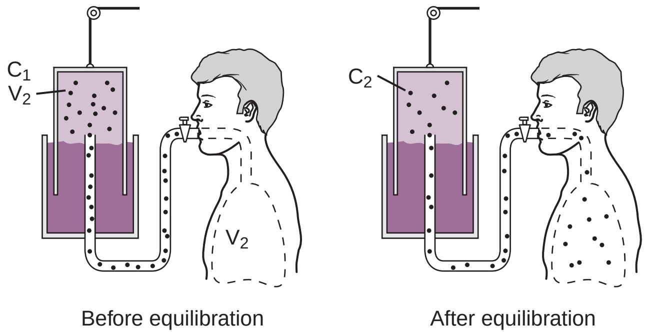
Residual volume: air left in lungs after maximal expiration; cannot be measured with spirometry

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.

Lung volumes: ↓ in restrictive disease; ↑ in obstructive disease



5-17: Spirogram showing changes in lung volume during normal and forceful breathing. Even after maximal expiration, the lungs cannot be completely emptied of air. *(From Guyton A, Hall J: Textbook of Medical Physiology, 11th ed. Philadelphia, Saunders, 2006, Fig. 37-6.)*



5-18: Measurement of residual volume by the helium dilution technique. *(From Berne R, Levy M, Koeppen BM, Stanton BA: Physiology, 5th ed. Philadelphia, Mosby, 2003, Fig. 26-3.)*

B. Tidal volume (V_T)
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).

Tidal volume: volume of air inspired or expired with each breath; approximately 500 mL

Inspiratory reserve volume: volume of air that can be inspired beyond a normal tidal inspiration

Expiratory reserve volume: volume of air that can be exhaled after a normal tidal expiration

Residual volume: can be measured by helium dilution technique

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 ($C_1 \times V_1$) equals the amount after equilibrium [$C_2 \times (V_1 + V_2)$].
d. Rearranging yields the following:

$$C_1 \times V_1 = C_2 \times (V_1 + V_2)$$
$$V_2 = V_1(C_1 - C_2)/C_2$$

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

Helium dilution concept: $C_1 \times V_1 = C_2 \times (V_1 + V_2)$

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).

Air-trapping in COPD: ↑ residual volume → ↑ anteroposterior diameter → "barrel-chested" appearance

Lung capacities: sum of two or more lung volumes

VII. Lung Capacities

A. Overview

1. Lung capacities are the sum of two or more lung volumes.
2. There are four lung capacities: functional residual capacity, inspiratory capacity, vital capacity, and total lung capacity.
3. Typical adult values for these are given in the calculations below.

B. Functional residual capacity (FRC)

1. The amount of air remaining in the lungs after a normal tidal expiration
2. Can also be thought of as the equilibrium point at which the elastic recoil of the lungs is equal and opposite to the outward force of the chest wall
3. Calculated as follows:

$$\begin{aligned} FRC &= RV + ERV \\ &= 1200\text{ mL} + 1100\text{ mL} \\ &= 2300\text{ mL} \end{aligned}$$

4. Mixing of small tidal volumes with this relatively large FRC prevents sudden fluctuations in alveolar oxygen tension with individual breaths.
   - For example, this explains why people do not immediately pass out after holding their breath for a short period.

FRC: equilibrium point at which elastic recoil of the lungs is equal and opposite to outward force of the chest wall

Clinical note: Because of the nature of their disease, patients with COPD "trap" air in their lungs, resulting in an **elevated FRC** at which tidal breaths occur. At a higher FRC, the airways are more patent, which reduces airflow resistance particularly during expiration; this decreases the work of breathing.

C. Inspiratory capacity (IC)

- The maximum volume of air that can be inhaled after a normal tidal expiration:

$$\begin{aligned} IC &= V_T + IRV \\ &= 500\text{ mL} + 3000\text{ mL} \\ &= 3500\text{ mL} \end{aligned}$$

Inspiratory capacity: maximum volume of air that can be inhaled after a normal tidal inspiration

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):**

$$\begin{aligned} VC &= IRV + V_T + ERV = IC + ERV \\ &= 3000\text{ mL} + 500\text{ mL} + 1100\text{ mL} \\ &= 4600\text{ mL} \end{aligned}$$

Vital capacity: maximum volume of air expired after maximal inspiration; synonymous with forced vital capacity

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_1) and FEV_1/FVC ratio**

FEV_1: maximum amount of air that can be exhaled in 1 second following a maximal inspiration

1. FEV_1 is the maximum amount of air that can be exhaled in 1 second after a maximal inspiration.
2. In healthy individuals, the FEV_1 typically constitutes about 80% of FVC; this relationship is usually expressed as a ratio:

$$FEV_1/FVC = 0.8$$

3. The FEV_1/FVC ratio is clinically useful in helping to distinguish between restrictive and obstructive lung disease.
   - The FEV_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.

FEV_1/FVC ratio: ↓ with obstructive lung disease, ↑ with restrictive lung disease

Pathology note: Although FEV_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_1, resulting in an **FEV_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_1 is reduced more than is FVC, and the **FEV_1/FVC ratio** is **reduced.**

F. **Total lung capacity (TLC)**
- The maximum volume of air in the lungs after a maximal inspiration:

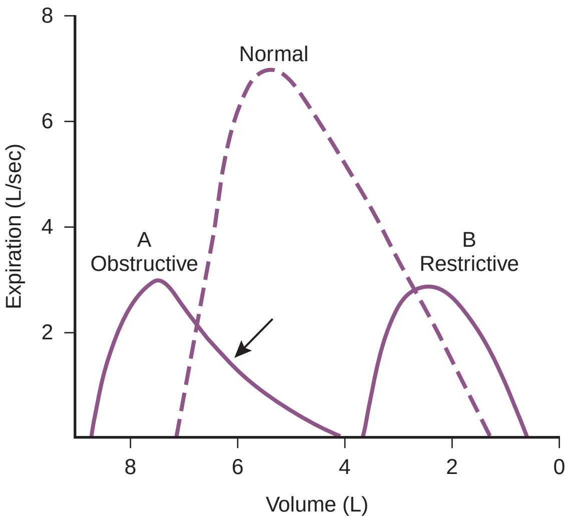
$$\begin{aligned} TLC &= IRV + V_T + ERV + RV \\ &= 3000\ mL + 500\ mL + 1100\ mL + 1200\ mL \\ &= 5800\ mL \end{aligned}$$

Total lung capacity: maximum lung volume; ↑ in obstructive disease, ↓ in restrictive disease

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

Types of dead space: anatomic, alveolar, physiologic



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.

Anatomic dead space: volume of conducting airways not involved in gas exchange

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.

Anatomic dead space: approximately 1 mL per pound of body weight in lean adults; increases considerably in mechanically ventilated patients

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.

Alveolar dead space: ventilated alveoli that are not perfused; negligible volume in healthy young adults

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:

$$V_D = V_T \times (P_{aCO_2} - P_{ECO_2})/P_{aCO_2}$$

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)

Physiologic dead space: sum of the anatomic and alveolar dead spaces

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.

Calculation of physiologic dead space: $V_D = V_T \times (P_{aCO_2} - P_{ECO_2})/P_{aCO_2}$

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):

$$\begin{aligned}\text{Minute ventilation}(\dot{V}) &= \text{respiratory rate} \times \text{tidal volume}\\ &= 12 \text{ breaths/minute} \times 500 \text{ mL/breath}\\ &= 6 \text{ L/minute}\end{aligned}$$

Minute ventilation: respiratory rate × V_T; ~ 6 L/min in healthy adult

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:

$$\begin{aligned}\text{Alveolar ventilation}(\dot{V}A) &= \text{respiratory rate} \times\\ &\quad(\text{tidal volume} - \text{physiologic dead space})\\ &= 12 \text{ breaths/minute} \times (500 \text{ mL/breath} - 150 \text{ mL})\\ &= 4.2 \text{ L/minute}\end{aligned}$$

   - 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:

$$\begin{aligned}\dot{V}_A &= 12 \text{ breaths/minute} \times (500 \text{ mL/breath} - 350 \text{ mL})\\ &= 1.8 \text{ L/minute}\end{aligned}$$

Alveolar ventilation: need to consider volume of physiologic dead space

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_2 is poorly soluble in plasma, it is transported in significant amounts only when bound to hemoglobin.

Oxygen in blood: exists in two forms: hemoglobin-bound and dissolved (unbound)

Oxygen transport: O_2 poorly soluble in blood; ~98% transported 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_2.
2. The pressure this dissolved oxygen exerts in blood is termed the **oxygen tension** or **Pa_{O_2}**, which typically approximates **100 mm Hg** in arterial blood.
3. The amount of dissolved O_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 Pa_{O_2} is directly measured in the clinical laboratory.
   - A decreased Pa_{O_2} (<75 mm Hg) is called **hypoxemia**.

Oxygen tension: pressure exerted by dissolved O_2; ~100 mm Hg in arterial blood

Hypoxemia: refers to ↓ Pa_{O_2} (<75 mm Hg)

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_{AO_2}) and the arterial oxygen tension (Pa_{O_2}):

$$A - a \text{ gradient} = P_{AO_2} - Pa_{O_2}$$

The Pa_{O_2} is determined by an arterial blood gas (ABG) analysis, and the P_{AO_2} is calculated as follows:

$$P_{AO_2}(\text{mm Hg}) = (F_{IO_2} \times [P_{atm} - P_{H_2O}]) - (Pa_{CO_2}/R)$$

where F_{IO_2} = fractional inspired oxygen concentration (0.21 mm Hg for room air), P_{atm} = atmospheric pressure (in mm Hg), P_{H_2O} = partial pressure of water (47 mm Hg at normal body temperature), Pa_{CO_2} = arterial CO_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).

Pa_{O_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.

A-a gradient: gradient > 10 mm Hg implies defective gas exchange across pulmonary membrane

C. Oxygen content of the blood

1. Includes the amount of O_2 bound to hemoglobin *and* dissolved in plasma
2. Most (~ 98%) of this O_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_2.
   - Therefore, a typical man with a hemoglobin concentration of 15 g/dL has an oxygen-carrying capacity of **~20 mL/dL**, or **20%**.

Oxygen-carrying capacity of the blood: approximately 20 mL/dL, sometimes expressed as 20%

TABLE 5-5. Conditions Associated With an Elevated Alveolar-Arterial Gradient

V/Q MISMATCH	SHUNT	DIFFUSION DEFECT
Pulmonary embolism	Intracardiac (e.g., VSD)	Pulmonary fibrosis
Airway obstruction	Intrapulmonary (e.g., pulmonary AVM, pneumonia, CHF)	Emphysema
Interstitial lung disease	Atelectasis	Asbestosis

AVM, Arteriovenous malformation; *CHF*, congestive heart failure; *V/Q*, ventilation-perfusion; *VSD*, ventricular septal defect.

3. To calculate the amount of dissolved O_2 in blood we can invoke **Henry's law,** as shown:

$$Cx = Px \times S$$

where
Cx = concentration of dissolved gas (mL gas/100 mL blood)
Px = partial pressure of the gas (mm Hg) in the liquid phase
S = solubility of gas in the liquid

- Therefore, the calculation for dissolved O_2 in blood is as shown below, assuming O_2 solubility constant of 0.003 mL/100 mL blood is shown as:

$$\text{Dissolved}[O_2] = 100 \text{ mm Hg} \times 0.003 \text{ mL } O_2/100 \text{ mL blood/mm Hg}$$
$$= 0.3 \text{ mL } O_2/100 \text{ mL blood}$$

Reduced oxygen-carrying capacity: anemia, methemoglobinemia

Pathology note: Conditions associated with a reduced oxygen-carrying capacity include anemia and methemoglobinemia.

D. Hemoglobin

1. **Types of hemoglobin**
   - Tetrameric protein with two α-subunits and two β-subunits held by covalent bonds
     a. Each subunit binds one O_2 molecule.
     b. A hemoglobin molecule can therefore carry a maximum of four O_2 molecules at once.
   - **Fetal hemoglobin (Hb F)** comprises **two α- and two γ-subunits.** 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.

Fetal hemoglobin: higher affinity for oxygen, causing right shift of Hb dissociation curve

2. **O_2 binding to hemoglobin**
   - Each of the four hemoglobin subunits contains a **heme group,** which is an iron-containing porphyrin moiety that contains iron in the ferrous state (Fe^{2+}).
   - This **heme group binds O_2** in a **cooperative** manner; that is, within a hemoglobin molecule, the binding of O_2 to one heme group enhances the binding of O_2 to another heme group, and so on.
   - Hemoglobin in the **taut** or deoxyhemoglobin form has a low affinity for O_2.
   - Upon binding of O_2 to deoxyhemoglobin, however, hemoglobin takes on a **relaxed form** that has a much higher affinity for O_2.

Taut form of hemoglobin: low affinity for O_2

Relaxed form of hemoglobin: high affinity for O_2

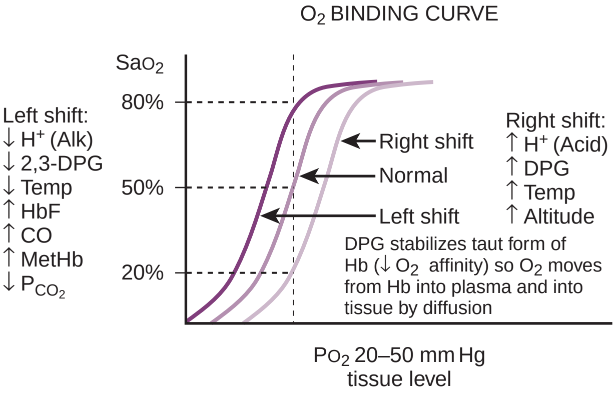
Methemoglobinemia: patients cyanotic (low O_2 saturation) despite normal PaO_2

Clinical note: Methemoglobin is an altered form of hemoglobin in which the **ferrous (Fe^{2+})** irons of **heme** are oxidized to the **ferric (Fe^{3+})** state. Oxidizing agents include nitrates, nitrites, and sulfa compounds. The ferric form of hemoglobin is unable to bind O_2, so patients with methemoglobinemia have functional anemia. Patients present with **cyanosis** (decreased O_2 saturation) despite having a normal 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-O_2 dissociation curve**
   - The hemoglobin-O_2 dissociation curve (Fig. 5-20) has a sigmoidal shape, which represents the increasing affinity of hemoglobin for O_2 with increasing PaO_2 ("loading phase") and the decreasing affinity of hemoglobin for O_2 with decreasing PaO_2 ("unloading phase").

Hemoglobin-O_2 dissociation curve: sigmoidal shape; ↑ affinity of Hb for O_2 at high PaO_2, ↓ at low PaO_2

Clinical note: Carbon monoxide (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 CO (240 times its affinity for O_2). CO avidly binds to hemoglobin to form **carboxyhemoglobin,** which has greatly diminished ability to bind O_2. Nonsmokers may normally have up to 3% carboxyhemoglobin at baseline; this may increase to 10% to 15% in smokers.



5-20: The hemoglobin-O_2 dissociation curve. DPG, Diphosphoglycerate; *Hb*, hemoglobin; *MetHb*, methemoglobin; *Sa_{O_2}*, oxygen saturation. *(From Goljan EF: Rapid Review Pathology, 3rd ed. Philadelphia, Mosby, 2010, Fig. 1-2.)*

When CO binds to hemoglobin, the **conformation** of the hemoglobin molecule is changed in a way that greatly diminishes the ability of the other O_2-binding sites to offload oxygen to tissues. Blood P_{O_2} tends to remain normal because P_{O_2} measurement usually reflects O_2 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 O_2 to dissociate from hemoglobin (myoglobin).

CO toxicity: CO binds Hb → carboxyhemoglobin → Hb unable to offload O_2 to tissues; treated with hyperbaric oxygen

- **O_2 saturation (Sa_{O_2})**
  a. Each hemoglobin molecule contains four Fe^{2+}-containing groups to which oxygen can bind.
  b. The percentage of the available heme groups that are bound to oxygen is termed the O_2 saturation, or the Sa_{O_2} when referring to arterial blood.
  c. In a healthy person, Sa_{O_2} is approximately 98% at a typical O_2 tension (Pa_{O_2}) of 100 mm Hg.
    - An Sa_{O_2} 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. O_2 saturation is measured in arterial, oxygenated blood, usually by using a sensor attached to a finger (pulse oximeter).
  e. The Sa_{O_2} can be calculated or directly measured in the clinical laboratory.

O_2 saturation (Sa_{O_2}): percentage of heme groups bound to oxygen

- **Increased O_2 delivery to the tissues**
  a. **Right shift** of the O_2 dissociation curve (see Fig. 5-20) indicates a decrease in the affinity of hemoglobin for O_2 and a corresponding increased degree of oxygen unloading into the tissues.
    - There is an increase in P_{50}, the pressure of oxygen (P_{O_2}) at which hemoglobin is half saturated (i.e., two O_2 molecules are bound to each hemoglobin molecule), which facilitates the release of O_2 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 CO_2 to hemoglobin, as well as increased body temperature.
    - Note that each of these increases during **exercise.**

Cyanosis: caused by presence of ≥ 5 g/dL deoxygenated Hb

Right shift of O_2 dissociation curve: ↑ 2,3-DPG, ↑ H^+ ions (acidosis), ↑ CO_2 binding to Hb, ↑ body temperature

- **Decreased O_2 delivery to the tissues**
  a. **Left shift** of the O_2 dissociation curve occurs when there is increased affinity of hemoglobin for O_2.
    - The P_{50} decreases, and unloading of oxygen into the tissues is decreased.
  b. Factors that cause a leftward shift of the hemoglobin-O_2 dissociation curve include increased pH, decreased P_{CO_2}, decreased body temperature, decreased 2,3-DPG, fetal hemoglobin, and carbon monoxide.

Left shift of O_2 dissociation curve: ↑ pH, ↓ P_{CO_2}, ↓ body temperature, ↓ 2,3-DPG, ↑ fetal Hb, ↑ CO

X. Carbon Dioxide (CO_2) Transport

A. Overview

1. CO_2 is a byproduct of cellular respiration.
2. It diffuses across cell and capillary membranes into the bloodstream.
3. Most (~70%) of the CO_2 then crosses the RBC membrane.

Most CO_2 travels in the blood in the form of HCO_3^- in RBCs.

4. Once inside the RBC, it is converted to **bicarbonate ion** (HCO_3^-).
5. The rest of the CO_2 travels in the blood as either **carbaminohemoglobin** (~20% of total CO_2), or **dissolved CO_2** (~10%).

Clinical note: Whereas Pa_{O_2} decreases and the A-a gradient widens with normal aging, the P_{CO_2} does **not** change with age.

Chloride shift: Cl^- enters RBCs in exchange for HCO_3^-; HCO_3^- then travels "free" in blood to lungs

Reverse chloride shift: in pulmonary capillaries HCO_3^- enters RBCs in exchange for Cl^- → HCO_3^- converted to CO_2, which is expired

Bohr effect: right-shifting of Hb-O_2 dissociation curve due to binding of CO_2 to Hb

Dissolved CO_2: CO_2 highly soluble in blood relative to O_2; ~10% CO_2 transported in blood in dissolved form

Buffering effect of deoxyhemoglobin: soaks up H^+ ions resulting from HCO_3^- production in RBCs, which minimizes drop in pH along the capillary

B. Bicarbonate ion

1. Approximately **70% of CO_2** is transported in the blood as HCO_3^- (Fig. 5-21).
2. **Carbonic anhydrase,** present in abundance in RBCs, catalyzes the hydration of CO_2 to H_2CO_3.
   - This dissociates to form HCO_3^- and H^+.
     a. The HCO_3^- is exchanged for chloride ions (Cl^-) across the RBC membrane to maintain a balance of charge.
   - This countertransport is termed the *chloride shift.*
     a. 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 CO_2, which is expired.
4. Low P_{ACO_2} and a high solubility coefficient stimulate diffusion of CO_2 from pulmonary capillaries into the alveolar air.
   - The consequent decrease in P_{CO_2} allows hemoglobin to bind oxygen more effectively (left shift; see Fig. 5-20).

C. Carbaminohemoglobin

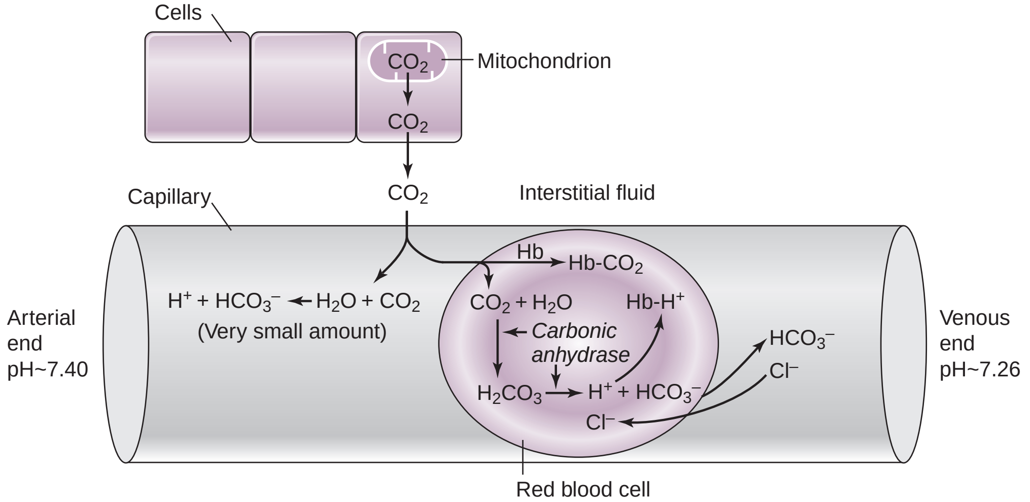
1. Approximately **20% of CO_2** is transported in the blood in a form that is chemically bound to the amino groups of hemoglobin.
2. The binding of CO_2 to hemoglobin decreases the O_2 affinity of hemoglobin, causing a right shift of the hemoglobin-O_2 dissociation curve **(Bohr effect)**, which promotes unloading of O_2 to the tissues.

D. Dissolved CO_2 (P_{CO_2})

1. Approximately **10% of CO_2** is transported as dissolved CO_2 (compared with 0.3% of O_2), because of the high solubility constant of CO_2, which is approximately 20 times greater than that of O_2.
2. The arterial P_{CO_2} is directly measured in the laboratory; a normal value is approximately 40 mm Hg.

E. Buffering effect of deoxyhemoglobin

1. For every HCO_3^- ion produced in the RBCs, one 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 O_2 unloading at the tissues, corresponding to a right shift of the dissociation curve.



5-21: Bicarbonate and the chloride shift. *Hb,* Hemoglobin; *Hb-CO_2,* carbaminohemoglobin.

XI. Control of Respiration

A. Overview

1. Respiration is tightly controlled to maintain optimal Pa_{O_2} and Pa_{CO_2} 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.

Control of respiration: tightly controlled to maintain optimal Pa_{O_2} and Pa_{CO_2}

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.

Basic control of respiratory rhythm originates from dorsal and ventral respiratory groups located within the medulla.

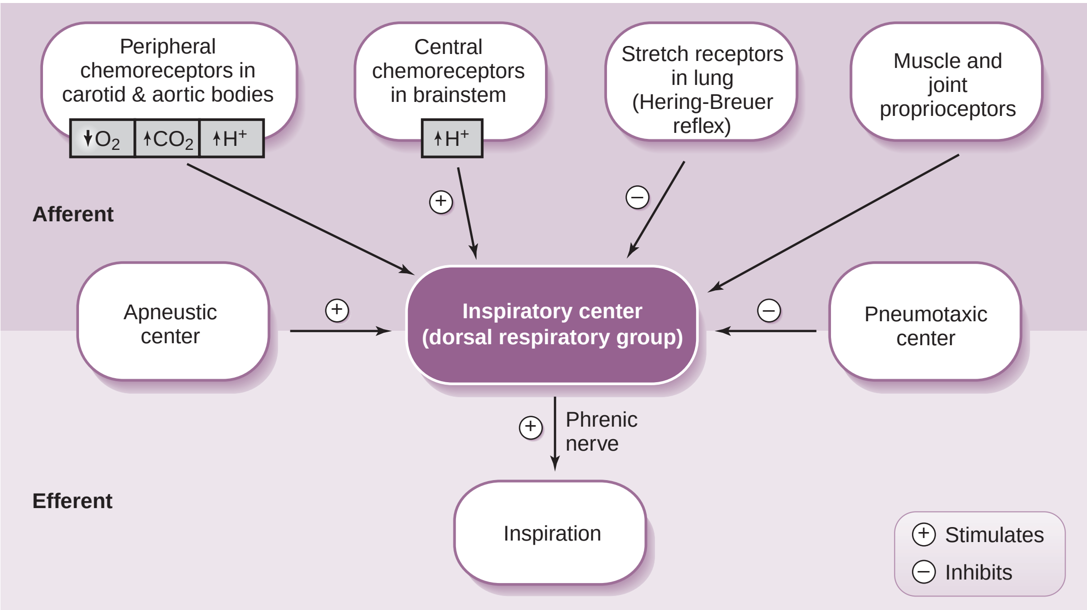
Fine control of respiratory rhythm originates from the pneumotaxic and apneustic centers of the pons.

Cortical influence on respiration: can have a powerful influence; example: hyperventilation during panic attack

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.



5-22: Central (brainstem) control of respiration.

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, Pa_{O_2}, and Pa_{CO_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 Pa_{CO_2} within normal limits, having an indirect response to the amount of CO_2 dissolved in cerebrospinal fluid (CSF) (Fig. 5-23)
       a. Through the central chemoreceptors, high Pa_{CO_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 H^+, because H^+ **does not** cross the blood-brain and blood-CSF barriers.

Ventral respiratory group: stimulates expiratory muscles (normally relaxed); important in forced expiration (e.g., exercise)

Pneumotaxic center: located in pons; inhibits inspiration → ↓ lung filling, ↑ breathing rate

Apneustic center: located in pons; ↑ duration of inspiration → ↑ lung filling, ↓ breathing rate

Chemoreceptors: sensitive to changes in pH, Pa_{O_2}, and Pa_{CO_2}

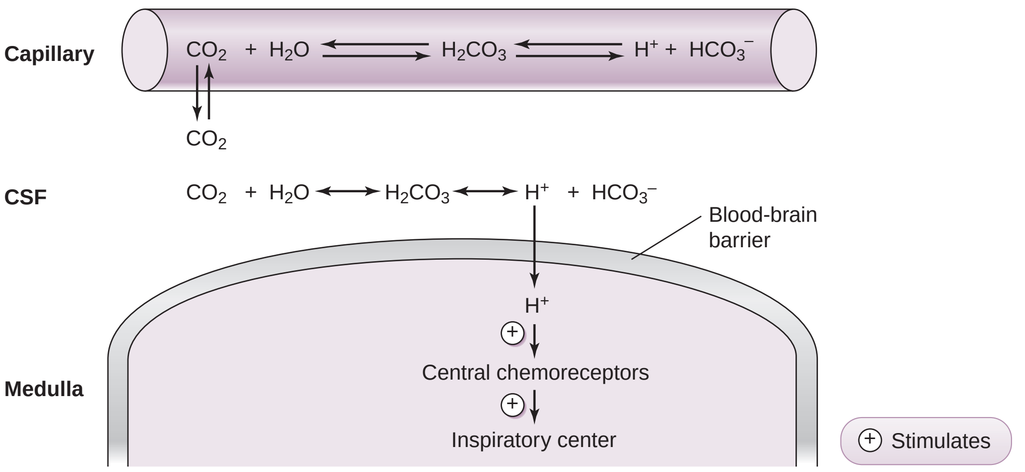
Central chemoreceptors: stimulate hyperventilation in response to ↑ Pa_{CO_2} (rapid response) and ↓ pH (slow response)

Central chemoreceptor response to ↓ pH [↑ H^+]: slow because H^+ ions do not directly cross the blood-brain barrier

Central chemoreceptors: CO_2 crosses blood-brain barrier into CSF → reacts with H_2O (slowly) to form H^+ ions → H^+ ions directly activate chemoreceptors

Respiratory response to high altitude: hyperventilation due to hypoxia-induced stimulation of peripheral chemoreceptors

Clinical note: At **high altitudes,** hypoxia (decreased Pa_{O_2}) stimulates hyperventilation through **peripheral chemoreceptors,** leading rapidly to decreased Pa_{CO_2} and decreased [H^+], both of which antagonize hypoxia-induced hyperventilation. Renal compensation for the respiratory alkalosis involves increased HCO_3^- excretion and decreased 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.



5-23: Central chemoreceptors. CO_2 crosses the blood-brain barrier, diffusing from cerebral capillaries into the cerebrospinal fluid (CSF) bathing the medulla. At a steady but slow rate (slow because of the absence of carbonic anhydrase in the CSF), CO_2 reacts with H_2O to form HCO_3^- and H^+. Only the H^+ directly activates the central chemoreceptors, stimulating hyperventilation.

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.**
   - They respond to pH, Pa_{CO_2}, and Pa_{O_2}.
     a. Although mild hypoxemia does not strongly stimulate them, they are strongly stimulated by a Pa_{O_2} less than 60 mm Hg.
     b. When pH or Pa_{O_2} decreases or when Pa_{CO_2} increases, **breathing rate** is increased.
   - They can also trigger **hyperventilation.**
     a. High Pa_{CO_2} **(hypercapnia)** or acidosis stimulates production of action potentials, which travel along afferents to the dorsal respiratory group, leading to hyperventilation.

Peripheral chemoreceptors: located in carotid and aortic bodies with afferents to the dorsal respiratory group

Peripheral chemoreceptors: respond to pH, Pa_{CO_2}, and Pa_{O_2}

Clinical note: Hypoxia has a limited ability to stimulate hyperventilation, because hyperventilation rapidly decreases Pa_{CO_2} and H^+, thereby inhibiting the process. However, in conditions in which Pa_{CO_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.

Hypoxia-induced hyperventilation: limited effect due to decreasing Pa_{CO_2} and H^+, although with lung disease Pa_{CO_2} and H^+ may not decrease such that hypoxia remains a potent stimulator of ventilation

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.

Irritant receptors: located in large-diameter airways; promote coughing, sneezing, and bronchoconstriction in response to noxious agents

Stretch receptors: located in walls of larger-diameter airways; activated by airway distension and inhibit further inspiration; play protective role

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.

Hyperventilation during exercise: occurs even *before* changes in blood gas levels are detectable

XII. Respiratory Responses to Stress

A. **Hypoxia and hypoxemia**
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 Pa_{O_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.

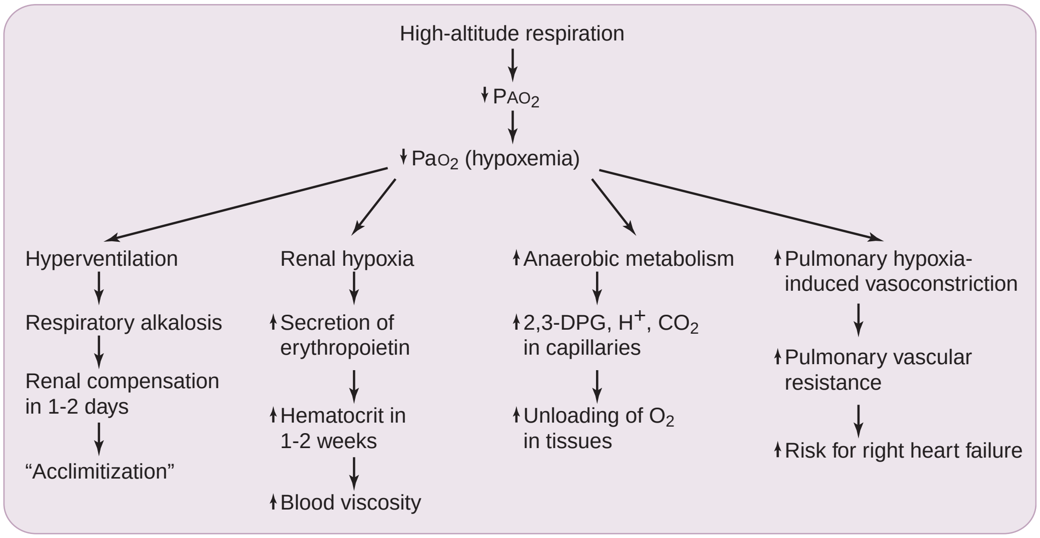
Hypoxemia: inadequate O_2 in the blood

Hypoxia: inadequate O_2 supply to the tissues

Hypoxemic hypoxia is the most common cause of hypoxia.

TABLE 5-6. Types of Hypoxia

TYPE OF HYPOXIA	PATHOPHYSIOLOGY	EXAMPLE
Hypoxic	Decreased oxygenation of blood	Lung disease
Ischemic	Inadequate tissue perfusion	Myocardial infarction
Anemic	Decreased O_2-carrying capacity of blood secondary to low hemoglobin	Iron-deficiency anemia
Histotoxic	Inability of cells to use O_2 effectively	Cyanide poisoning



5-24: Physiologic responses to high-altitude respiration. Note that relatively long-term exposure to high-altitude respiration can produce right-sided heart failure by increasing the work demand placed on the right ventricle in two ways: (1) increased blood viscosity and (2) increased pulmonary vasculature resistance. *2,3-DPG,* 2,3-Diphosphoglycerate.

Treatment of hypoxia: most cases will respond to supplemental O_2; histotoxic hypoxia will not

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_{AO_2} is decreased
   - Several **physiologic responses** enable the body to acclimatize to this change, maintaining adequate oxygenation of tissues; the reduced Pa_{O_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_{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.

TABLE 5-7. Altered Breathing Patterns and Their Causes

TYPE OF BREATHING	DESCRIPTION	EXAMPLES
Apnea	Temporary cessation of breathing	Sleep apnea
Dyspnea	"Air hunger" (sensation of difficulty breathing)	Congestive heart failure or lung disease
Eupnea	Normal breathing	—
Hyperpnea	Increased pulmonary ventilation in response to body's demand for O_2	Exercise
Biot breathing	Several short breaths followed by period of apnea	Increased intracranial pressure
Cheyne-Stokes breathing	Periodic breathing; need higher P_{CO_2} to stimulate breathing	Head trauma
Hyperventilation	Pulmonary ventilation in excess of body's demand for O_2	Pulmonary disease, asthma, metabolic acidosis, anxiety
Hypoventilation	Pulmonary ventilation that does not meet body's demand for O_2	Sedatives, anesthetics
Kussmaul respirations	Rapid deep breathing associated with metabolic acidosis	Diabetic ketoacidosis
Ondine curse	Impaired autonomic control of respiration	Patients need to be on respirator when sleeping

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.

CHAPTER 6

RENAL PHYSIOLOGY

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.**

Excretion of unneeded substances: excess water, electrolytes, potentially toxic end products of metabolism

Reclamation of needed substances: water, electrolytes, glucose, bicarbonate

Renal contribution to homeostasis: regulates ECF volume, osmolality, acid-base status

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.**

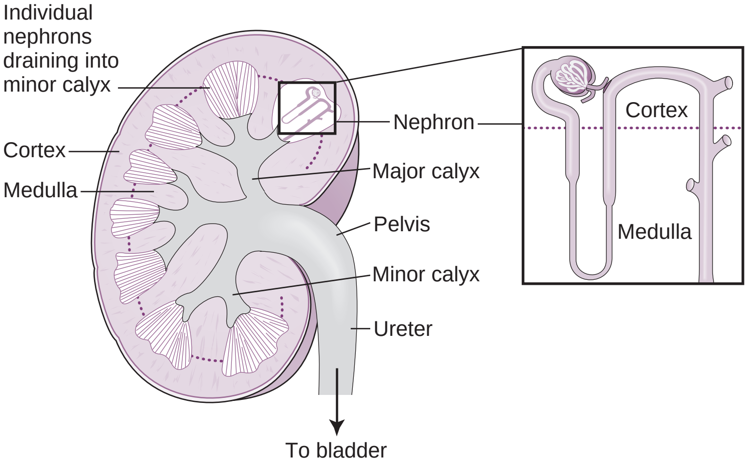
Renal perfusion: highly perfused; receives approximately 25% of cardiac output

Nephron: basic functional unit of kidney; approximately 1 million per kidney

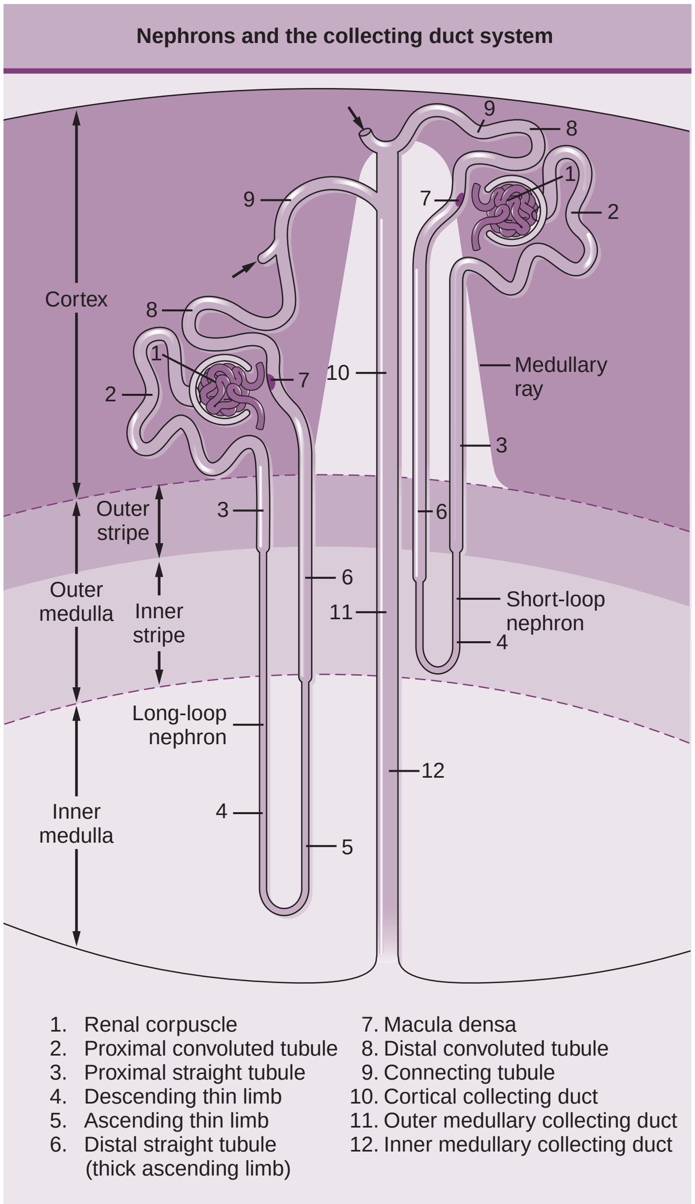
C. Structure of the filtration unit: the nephron (Fig. 6-2)

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.

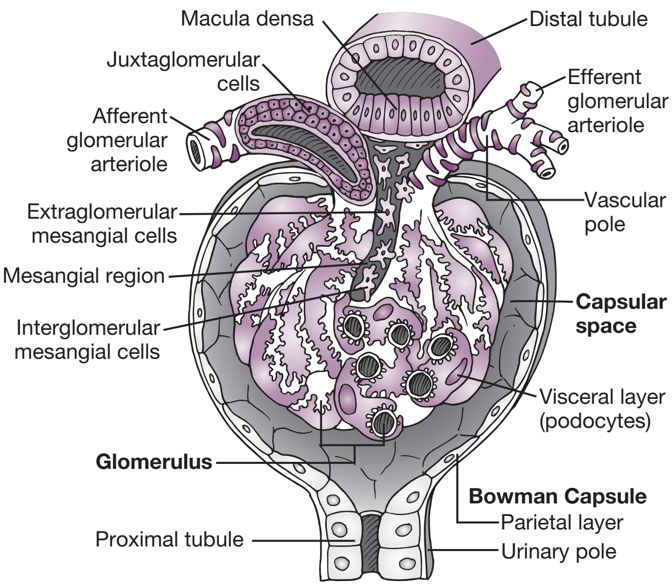
Glomerulus: expansion of afferent arteriole into capillary bed across which filtration occurs



6-1: Structure of the kidney. The *inset* shows the location of the nephron depicted in Fig. 6-2.



6-2: Anatomy of the nephron. *(From Feehally J, Floege J, Johnson RJ: Comprehensive Clinical Nephrology, 3rd ed. Philadelphia, Mosby, 2007, Fig. 1-2.)*



6-3: Anatomy of the glomerulus. *(From Bargmann W: Histologie und Mikronscopische Anatomie des Menschen. Stuttgart, Germany, Georg Thieme, 1977, p 86.)*

Filtration barrier: prevents filtration of cells and large proteins

Layers of filtration barrier: fenestrated endothelium, negatively charged basement membrane, visceral epithelial cells

Fenestrated endothelium: allows for large volume filtration across glomerulus

Negatively charged basement membrane: prevents passage of negatively charged proteins such as albumin

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).

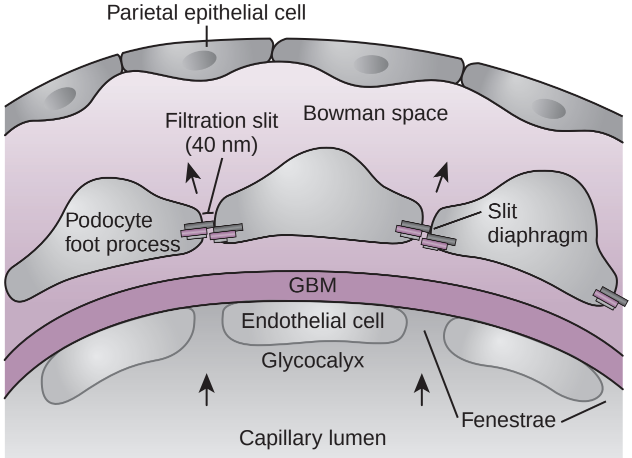
Pathology note: In a condition known as **minimal change disease (lipoid nephrosis),** the negative charges on the glomerular filtration barrier are lost for unknown reasons. Certain proteins are then able to pass through the basement membrane, resulting in proteinuria. This disease is the most common 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.

Starling forces promoting filtration: glomerular hydrostatic pressure (large) and Bowman space oncotic pressure (small)

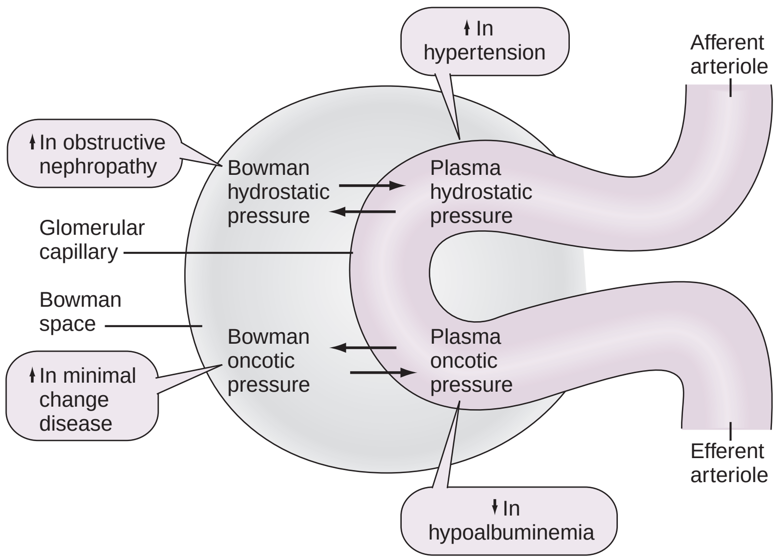
II. Regulation of Glomerular Function

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** (Π_{BS}); however, because most proteins are not readily filtered into Bowman space, the latter is typically negligible.



6-4: Layers of the glomerular filtration barrier. *GBM,* Glomerular basement membrane. *(From Mount DB, Pollak MR: Molecular and Genetic Basis of Renal Disease. Philadelphia, Saunders, 2008, Fig. 21-2B.)*



Afferent end		Efferent end
60 mm Hg	P_{GC}	58 mm Hg
0 mm Hg	π_{BS}	0 mm Hg
–15 mm Hg	P_{BS}	–15 mm Hg
–28 mm Hg	π_{GC}	–35 mm Hg
17 mm Hg	P_{UF}	8 mm Hg

6-5: Filtration forces at the glomerulus. Note how individual forces can be affected in pathologic states. P_{BS}, Hydrostatic pressure in Bowman space; P_{GC}, hydrostatic pressure in glomerular capillary. *(From Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 32-17.)*

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** (Π_{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:

Starling forces opposing filtration: glomerular oncotic pressure and Bowman space hydrostatic pressure

$$\begin{aligned} NFP &= (P_{GC} + \Pi_{BS}) - (P_{BS} + \Pi_{GC}) \\ &= (60 + 0) - (18 + 32) \\ &= 10 \text{ mm Hg} \end{aligned}$$

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** (Lp) and available **surface area** (S) of the glomerular capillaries.
   - In the healthy kidney, the product of these two factors (LpS) is equal to approximately 12.5 mL/minute per mm Hg filtration pressure.

GFR: equivalent to summated filtration volume of all glomeruli each minute

GFR dependent on glomerular filtration forces, glomerular permeability, glomerular surface area

- Because the NFP is equal to approximately 10 mm Hg, GFR can therefore be approximated as follows:

$$\begin{aligned} GFR &= (Lp \times S) \times NFP \\ &= 12.5\ mL/min/mm\ Hg \times 10\ mm\ Hg \\ &= 125\ mL/min \end{aligned}$$

GFR: high filtration rate due to ↑ capillary permeability and ↑ glomerular hydrostatic pressures

- 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**

Glomerular marker: substance that is freely filtered and neither secreted nor reabsorbed along the nephron

Inulin: ideal marker for measuring GFR because it is freely filtered and neither reabsorbed nor secreted along the nephron

- 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)

$$C_{inulin} \sim GFR = U_{inulin} \times V/P_{inulin}$$

where
C_{inulin} = clearance of inulin (mL/minute)
GFR = glomerular filtration rate (mL/minute)
U_{inulin} = urine concentration of inulin (mg/mL)
V = urine flow rate (mL/minute)
P_{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

$$\text{Filtration fraction} = GFR/RPF$$

Filtration fraction = GFR/RPF; typical value 20%

- A typical value is about 20%.

4. **Regulation of GFR**

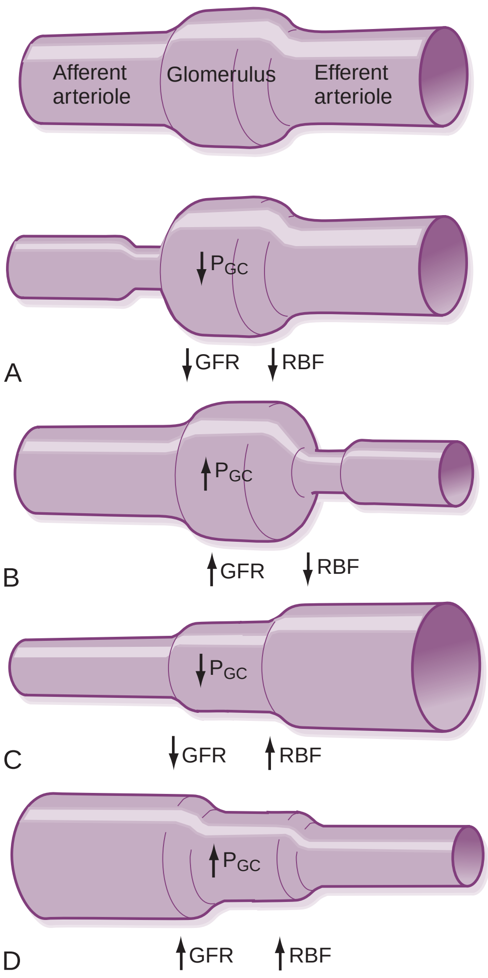
Regulation of GFR: occurs primarily through regulation of glomerular hydrostatic pressure

- **Overview**
  a. 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.**
  b. The glomerular hydrostatic pressure depends on the systemic arterial pressure and afferent and efferent arteriolar resistances, respectively.
  c. 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**
  a. As systemic arterial pressure increases, the increased renal perfusion tends to increase glomerular hydrostatic pressure and GFR.
  b. However, the changes in glomerular hydrostatic pressure are relatively small compared with the often substantial fluctuations in systemic arterial pressure.
  c. 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).
  d. Consequently, the contribution of systemic arterial pressure is typically minor, and the primary determinants of glomerular hydrostatic pressure are afferent and efferent arteriolar resistance.

Glomerular hydrostatic pressure remains relatively constant (despite varying systemic arterial pressures) due to intrinsic autoregulatory mechanisms.

Regulation of glomerular hydrostatic pressure: primarily depends on afferent and efferent arteriolar resistances

- **Afferent arteriolar resistance** (Fig. 6-6; Table 6-1)
  a. Dilation of the afferent arteriole through prostaglandins such as prostaglandin E_2 increases renal blood flow, glomerular hydrostatic pressure, and, hence, GFR.
  b. Vasoconstriction has the opposite effect.



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

EFFECT	RPF	GFR	FILTRATION FRACTION (GFR/RPF)
Constriction of afferent arteriole	↓	↓	NC
Constriction of efferent arteriole	↓	↑	↑
Increased plasma protein concentration	NC	↓	↓
Decreased plasma protein concentration	NC	↑	↑
Constriction of the ureter	NC	↓	↓

GFR, Glomerular filtration rate; *NC*, no change; *RPF*, renal plasma flow.
From Costanzo L: Physiology, 3rd ed. Philadelphia, Saunders, 2006, Table 6-6.

- **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).

Efferent arteriolar vasoconstriction: mild → ↓ RBF, ↑ GFR; marked: ↓ RBF, ↓ GFR

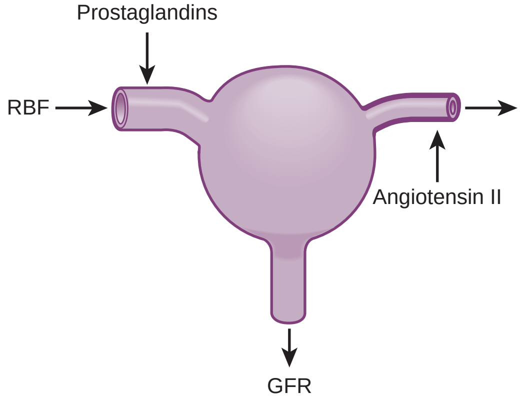
5. **Renal Blood Flow**
- **Overview**
  a. Highly perfused, receiving approximately 25% of cardiac output
  b. Blood supply through the renal arteries
  c. Vasodilatory prostaglandins maintain afferent arteriolar dilatation, whereas the sympathetic nervous system and angiotensin II promote vasoconstriction with preferential vasoconstriction of the efferent arteriole (Fig. 6-7).

Etiology of renal artery stenosis: fibromuscular hyperplasia in young women, atherosclerotic disease in older adults

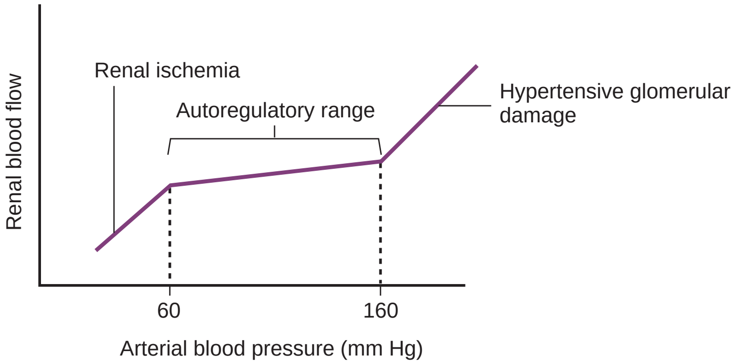
Clinical note: Narrowing of the renal arteries **(renal artery stenosis)** most commonly occurs as a result of **atherosclerosis** or **fibromuscular hyperplasia.** In unilateral renal artery stenosis, hypertension may occur because decreased perfusion of the affected kidney is incorrectly "interpreted" 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.

Autoregulation: ensures relatively constant RPF, GFR, and distal flow in face of widely varying systemic arterial pressures



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.

Autoregulation: occurs through tubuloglomerular feedback and myogenic mechanism

- **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.

Myogenic response to increased renal perfusion: reflexive constriction of afferent arteriole → minimizing ↑ in RPF, GFR, and glomerular damage

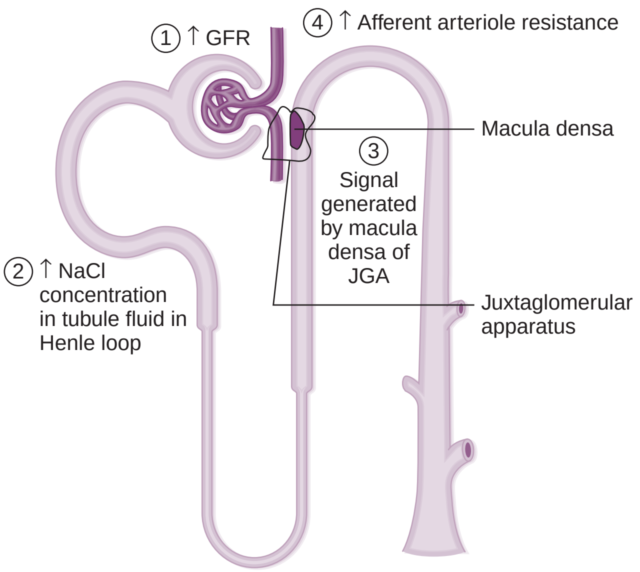
- **Tubuloglomerular feedback**
  a. In this mechanism, the rate of NaCl delivery to the distal nephron significantly influences the glomerular blood flow and therefore the GFR.
    - The rate of NaCl delivery to the distal tubule is dependent on the tubular concentration of NaCl as well as the tubular 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.

Tubuloglomerular feedback: mechanism whereby flow of $NaCl^{-}$ to macula densa influences RPF and GFR

Tubuloglomerular feedback: dependent on signal (NaCl delivery), sensor (macular densa), and effector (VSMCs of afferent arteriole)



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

Renal function: refers to rate at which kidneys *remove toxins from blood*

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

Clearance: volume of plasma from which a substance has been completely cleared by the kidneys per unit of time

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 (Px, in milligrams per milliliter), the quotient reflects the volume of plasma that has been cleared of that substance in 1 minute, called its **clearance** (Cx):

$$\text{Clearance} = \frac{\text{Amount excreted in urine in 1 minute}}{\text{Plasma concentration}}$$

3. This can be expressed in terms of urinary flow rate (V, in mL/minute) and urinary concentration (Ux, in mg/mL):

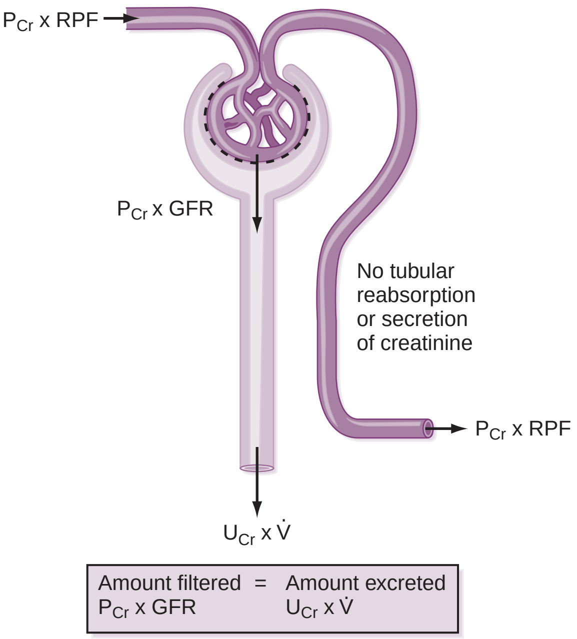
$$Cx = \frac{V \times Ux}{Px}$$

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:

$$C_{urea} = \frac{15}{0.2} = 75 \text{ mL/min}$$

C_{urea} < GFR, indicating net reabsorption of urea

5. Note that the C_{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.



6-10: Renal handling of creatinine. *GFR*, Glomerular filtration rate; *P_{Cr}*, plasma creatinine concentration; *RPF*, renal plasma flow; *U_{Cr}*, urine creatinine concentrate; *V*, volume of urine produced. *(From Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 32-13.)*

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).

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

$$GFR = \frac{V \times Ucr}{Pcr}$$

   - 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.

Creatinine clearance: used as rough approximation of GFR

$GFR = V \times U_{cr}/P_{cr}$

Creatinine clearance: slightly overestimates GFR due to tubular secretion

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.

Inulin clearance: more accurate estimate of GFR, but its use is clinically impractical

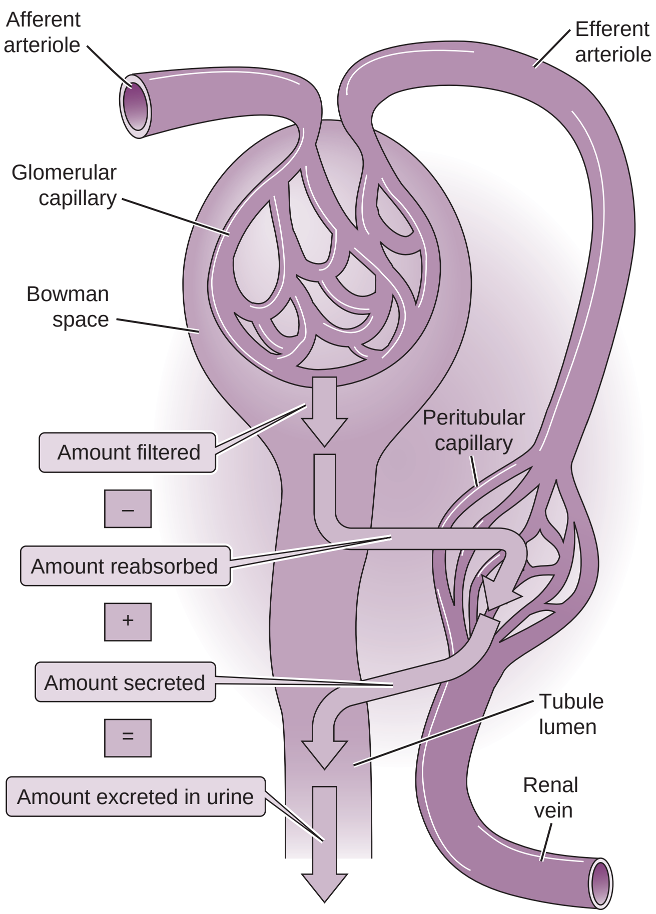
2. **Inulin clearance**
   - Inulin is a nonmetabolized polysaccharide that is freely filtered at the glomerulus.
   - Unlike creatinine, it is neither reabsorbed nor secreted along the tubule, so inulin clearance is a more **accurate measurement of the GFR.**

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.

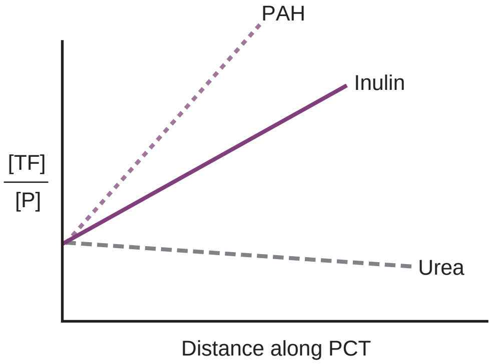
Clearance = GFR if substance freely filtered and neither reabsorbed nor secreted

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**).



6-11: Filtration, reabsorption, and secretion along the nephron. *(From Boron W, Boulpaep E: Medical Physiology, 2nd ed. Philadelphia, Saunders, 2009, Fig. 33-8.)*



6-12: Because of the reabsorption of water, the tubular fluid concentration of inulin increases roughly threefold compared with plasma concentration along the proximal convoluted tubule (PCT). Because inulin is neither secreted nor reabsorbed, substances that become concentrated more than inulin (e.g., PAH) must therefore be secreted, and substances that becomes less concentrated than inulin (e.g., urea) must be reabsorbed. *PAH,* Para-aminohippuric acid; *[P],* plasma concentration; *[TF],* tubular fluid concentration.

TABLE 6-2. Summary of Important Clearance Values

SUBSTANCE	APPROXIMATE CLEARANCE RATE (AS % OF GFR)
Urea	50
Inulin	100
Creatinine	100
Para-aminohippuric acid	>>100
Sodium	1
Potassium	10
Glucose	0
Amino acids	0

GFR, Glomerular filtration rate.

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**).

Clearance < GFR if substance freely filtered but undergoes net reabsorption; example: 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).

Clearance > GFR if substance freely filtered but undergoes net secretion; example: PAH

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.

PAH: clearance approximates RBF because freely filtered and very efficiently secreted

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

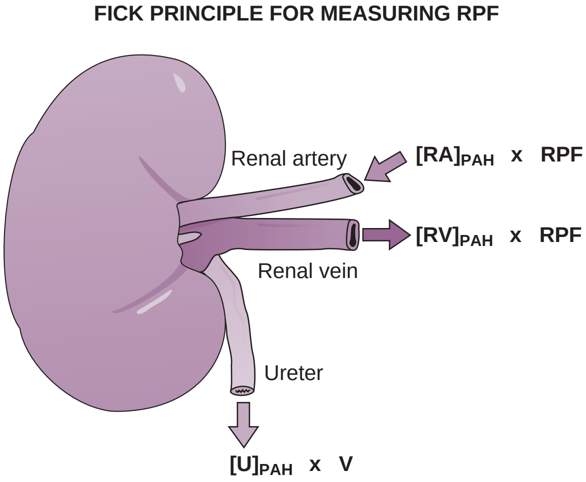
$$C_{PAH} = U_{PAH} \times V/P_{PAH}$$

this becomes

$$RPF \approx C_{PAH}$$

Effective RPF = C_{PAH}

6-13: Fick principle for measuring renal plasma flow (RPF). *PAH,* Para-aminohippuric acid. *(From Costanzo L: Physiology, 3rd ed. Philadelphia, Saunders, 2006, Fig. 6-8.)*



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:

True RPF = C_{PAH} /0.90

$$\text{True RPF} = C_{PAH}/0.90$$

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 = RPF/1 − hematocrit

$$\text{RBF} = \frac{\text{RPF}}{1 - \text{Hematocrit}}$$

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

Life-threatening fluid and electrolyte abnormalities would rapidly occur if most of the filtrate were not reabsorbed.

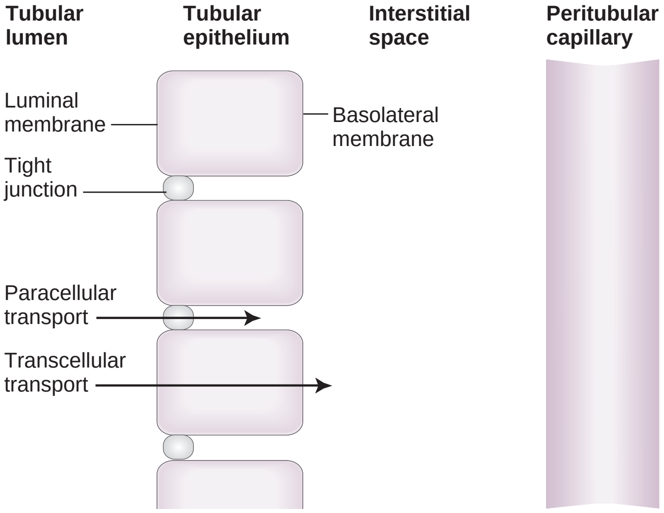
1. A huge amount of glomerular filtrate is delivered into the tubules each day.
2. Potentially life-threatening fluid and electrolyte disturbances would rapidly occur if the tubules did not reclaim most of this filtrate.
3. Therefore, the tubules of the nephron undertake a complex array of activities to excrete unneeded substances (excess electrolytes, toxins, hydrogen ions) while reclaiming the rest.

B. General tubular function

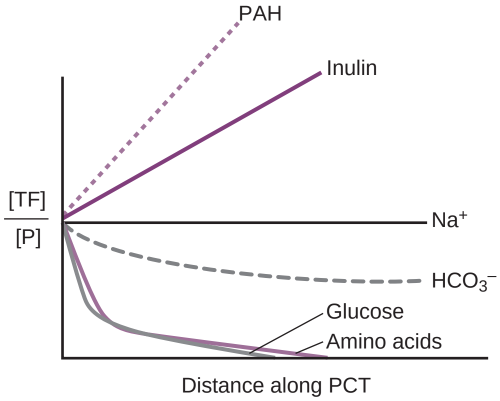
1. As a consequence of *selective* reabsorption and secretion, the solute composition of tubular fluid, which is initially plasmalike, changes dramatically along the course of the nephron.
2. The reabsorption and secretion of fluids and solutes from the tubular fluid is accomplished by a variety of tubular epithelial cell types, which have distinctly different transport capabilities and are located in different segments of the nephron.

Two routes of transport across tubular epithelium: transcellular, paracellular

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**



6-14: Paracellular and transcellular transport from the tubular lumen into the interstitial space and circulation. Substances traversing the transcellular route pass through two distinct portions of the tubular cell membrane, which are separated by the tight junctions: the luminal membrane, which is in contact with the tubular lumen, and the basolateral membrane, which contacts the interstitial space.



6-15: Relative changes in concentration of substances in the tubular fluid (TF) with respect to their concentration in plasma (P) along the proximal convoluted tubule (PCT). Note that the concentration of sodium remains constant along the length of the PCT because water is simultaneously reabsorbed. Filtered substances that are neither reabsorbed nor secreted (e.g., inulin) increase in concentration along the PCT, but not as much as do substances that are secreted but not reabsorbed (e.g., PAH). This graph also reflects the fact that most of the glucose and amino acids are reabsorbed in the early segments of the PCT. *PAH,* Para-aminohippuric acid.

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.

Transcellular transport: transport across tubular epithelial cells to peritubular capillaries; responsible for bulk of transport

- **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.

Paracellular transport: across tight junctions that vary in their permeability throughout the nephron

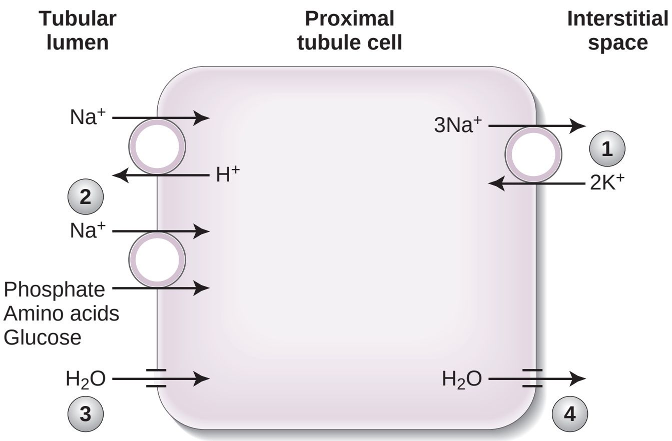
C. Reabsorption of salt and water

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

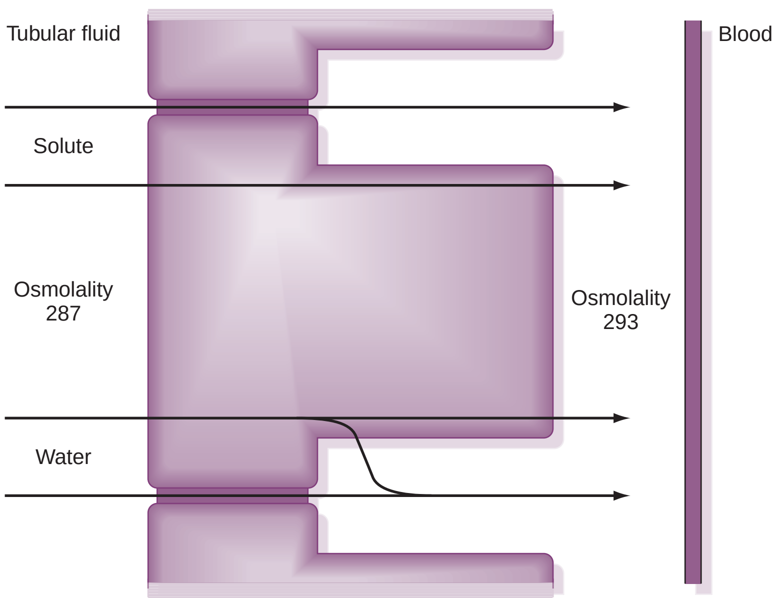
Transcellular transport in proximal tubule: primarily driven by activity of the Na^+,K^+-ATPase pump interstitium through the **Na^+,K^+-ATPase pump** located on the basolateral membrane of the tubular epithelial cell.

- 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 Na^+ ions for two 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., Na^+-glucose, Na^+–amino acid, Na^+-phosphate) and **countertransporters** (Na^+-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 K^+ and Ca^{2+} through **solvent drag** (see figure below).

Na^+,K^+-ATPase pump: maintains low intracellular [Na^+] and negatively charged intracellular environment → Na^+ transcellular transport



6-16: Steps in proximal tubular solute and water reabsorption: (1) the Na^+,K^+-ATPase pump creates a favorable intracellular electrochemical gradient for further entry of 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**.

Isosmotic reabsorption: reabsorption of fluid along the proximal tubule in which there is no change in tubular osmolality

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_H) is low, favoring reabsorption from the interstitium (Fig. 6-18).

High oncotic pressure in peritubular capillaries promotes reabsorption of fluid from interstitium into peritubular capillaries.

Low hydrostatic pressure in peritubular capillaries also promotes fluid reabsorption from interstitium into peritubular capillaries.

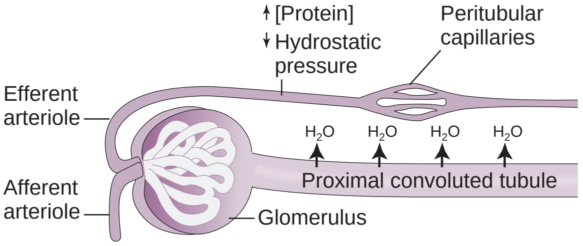
3. **Glomerulotubular balance**
   - Despite a varying GFR, when total body sodium balance is normal, a relatively constant fraction of the filtrate (approximately 67%) is reabsorbed from the proximal tubule.
   - This phenomenon, termed **glomerulotubular balance,** tends to minimize the effects of 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.

Glomerulotubular balance: balance among GFR, peritubular oncotic pressure, and proximal tubular reabsorption

Response to volume-depleted state: ↓ RPF → ↑ filtration fraction to maintain GFR → ↑ peritubular oncotic pressure → ↑ proximal tubular reabsorption → ↑ ECF volume

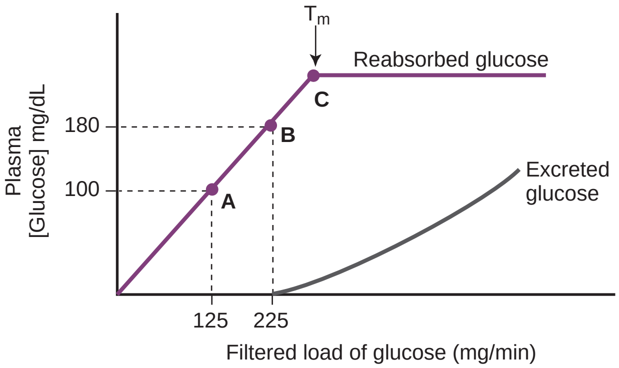
Response to volume-expanded state: ↑ RPF → ↓ filtration fraction to maintain GFR → ↓ peritubular oncotic pressure → ↓ proximal tubular reabsorption → ↑ urinary losses → ↓ ECF volume

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-contracted 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.



6-18: Increased plasma oncotic pressure and reduced hydrostatic pressure in the peritubular capillaries drive salt and water reabsorption from the proximal tubule.

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_m) 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.



D. Transport maximum (T_m)

Transport maximum: maximum rate at which a substance can be reabsorbed from the tubular fluid

Filtered load = plasma concentration of substance × GFR

If renal load > T_m → substance accumulates in urine

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_m 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_m,** 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:

$$\text{Renal load for glucose} = [P_{glucose}] \times GFR$$
$$= 100\ mg/dL \times 125\ mL/minute$$
$$= 125\ mg/min$$

where
$P_{glucose}$ = plasma glucose concentration in mg/dL

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_m 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_m is reached.

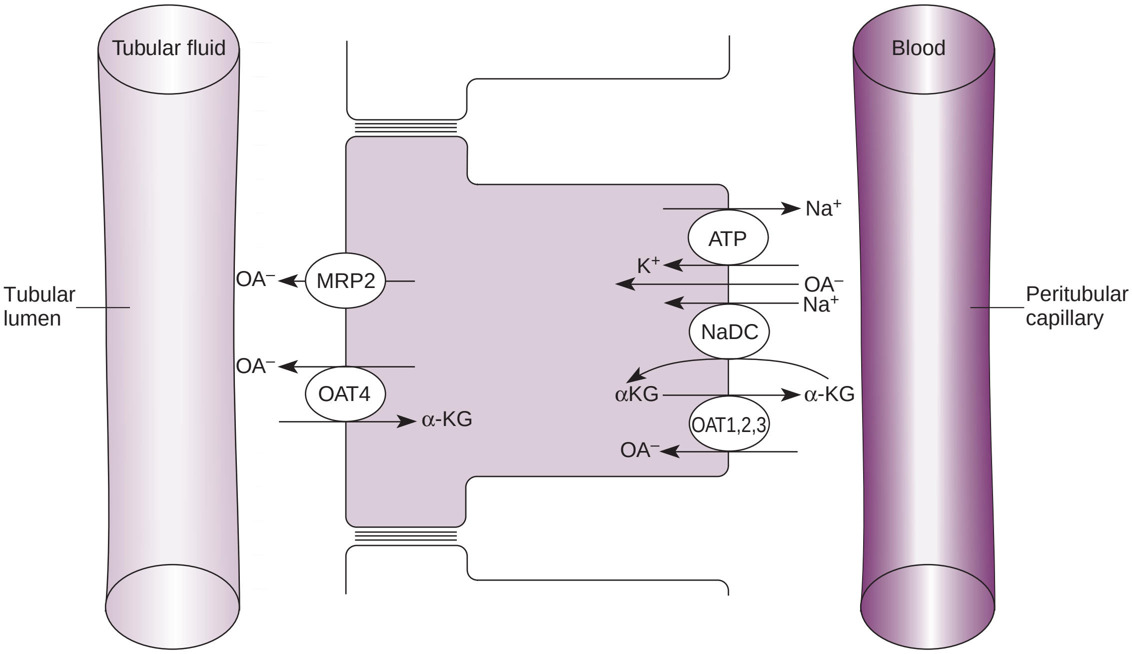
E. Tubular secretion

Route of secretion: peritubular capillaries → tubular epithelial cells → tubular lumen → urine

Secreted substances: uric acid, salicylic acid, bile salts, ketoacids, PAH

Diuretics lose their effectiveness in renal failure as they are less able to enter the tubular lumen (see clinical note).

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).



6-20: Organic anion (OA^-) secretion across the basolateral membrane. *(From Koeppen BM, Stanton BA: Renal Physiology, 4th ed. Philadelphia, Mosby, 2007, Fig. 4-6.)*

TABLE 6-3. Some Organic Cations Secreted by the Proximal Tubule

ENDOGENOUS	DRUGS
Creatinine	Atropine
Dopamine	Isoproterenol
Epinephrine	Cimetidine
Norepinephrine	Morphine
	Quinine
	Amiloride
	Procainamide

From Koeppen BM, Stanton BA: Renal Physiology, 4th ed. Philadelphia, Mosby, 2007, Box 4-2.

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.

Organic transporters: relative lack of specificity; saturable; can be competitively inhibited

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.

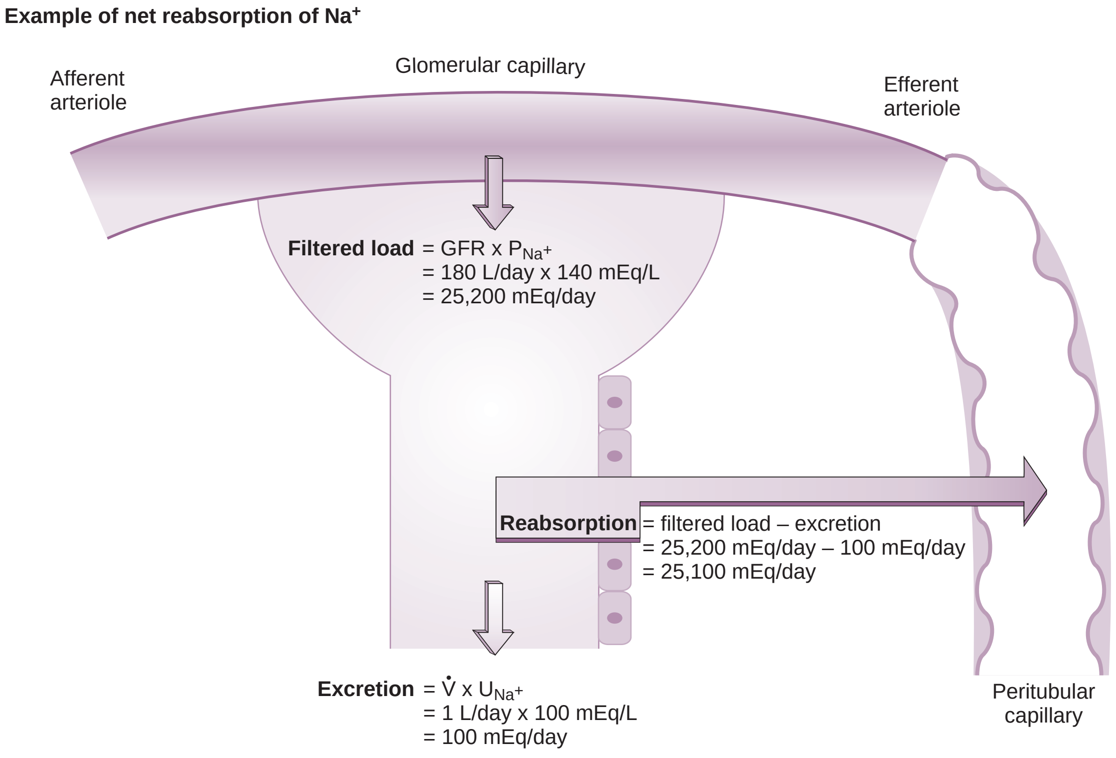
F. Pathophysiology of Renal Transport Mechanisms

- Impaired transport along the various nephron segments result in numerous conditions, as shown in Table 6-4.

TABLE 6-4. Function of Nephron Segments

NEPHRON SEGMENT	PRIMARY FUNCTIONS	HORMONAL REGULATION	ASSOCIATED DISORDERS
Proximal convoluted tubule	Reabsorption and secretion	Ang II, PTH	Fanconi syndrome, carbonic anhydrase deficiency
Loop of Henle	Concentration followed by dilution of tubular fluid	ADH	Nephrogenic diabetes insipidus, volume derangements
Thin ascending limb	Permeable to water		
Thick ascending limb	Impermeable to water, dilution of tubular fluid through activity of Na^+-K^+-$2Cl^-$ channel	Aldosterone and ADH	Diuretic-induced volume depletion, Bartter syndrome (chronic metabolic alkalosis)
Distal tubule	Site of macula densa, tubuloglomerular feedback	ADH, aldosterone, PTH	Gitelman syndrome
Cortical collecting tubules	Baseline permeability to urea		Hyperkalemia secondary to potassium-sparing diuretics
Medullary collecting tubules	Permeability to urea depends on presence or absence of ADH	ADH	Liddle syndrome, pseudohypoaldosteronism

ADH, Antidiuretic hormone; *Ang II,* angiotensin II; *PTH,* parathyroid hormone.



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.)*

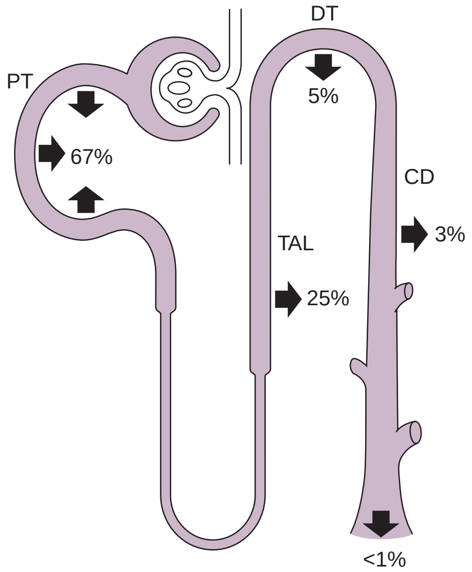
V. Handling of Specific Substances along the Nephron

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).

Kidneys play a critical role in preventing loss of excess NaCl and water.



6-22: Segmental Na^+ reabsorption. *CD,* Collecting duct; *DT,* distal tubule; *PT,* proximal tubule; *TAL,* thick ascending limb.

TABLE 6-5. Sodium Handling Along the Nephron

TUBULAR SEGMENT	FILTERED SODIUM REABSORBED (%)	MECHANISM OF SODIUM ENTRY	REGULATORY FACTORS
Proximal tubule	67	Na^+-H^+ countertransport, Na^+ cotransport with glucose, phosphate, amino acids, and other substances	Angiotensin II, epinephrine GFR
Loop of Henle	25	Na^+-K^+-$2Cl^-$ channel	Flow dependent
Distal tubule	5	Na^+-Cl^- channel	Flow dependent
Collecting tubules	3	Na^+ channels	Aldosterone, atrial natriuretic factor

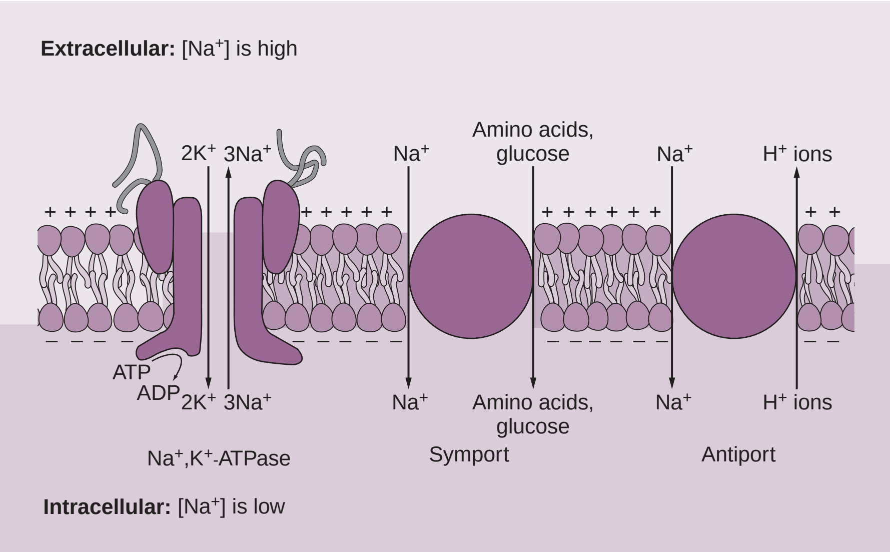
Data from Rennke HG, Denker BM: Renal Pathophysiology: The Essentials, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2006, Table 1-1.

2. **General Mechanisms of Na^+ Reabsorption**
   - As a charged substance, Na^+ is unable to freely diffuse across the lipid bilayer.
   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^+.

Stoichiometry of Na^+,K^+-ATPase pump: generates low intracellular [Na^+] and intracellular electronegative potential, both of which drive Na^+ from tubular lumen into peritubular epithelial cell

Secondary active transport: energy created by Na^+ diffusing down its electrochemical gradient drives transfer of other charged substances into tubular epithelial cell



6-23: Na^+ transport demonstrating secondary active transport across the tubular epithelial cell. *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate. *(From Lamb N, Manson A: Crash Course: Cell Biology and Genetics. Philadelphia, Mosby, 2007, Fig. 3-13.)*

- 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 HCO_3^- reabsorption because the H^+ combines with HCO_3^- to produce carbonic acid, which then dissociates into CO_2 and water, as shown below.

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

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 HCO_3^-), and overdiuresis with diuretics.

- Removal of solutes from the lumen reduces luminal osmolality, creating an osmotic gradient for H_2O 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

Leaky tight junctions in proximal tubular: prevent creation of osmotic and concentration gradients for solutes (and water), which are linked to Na^+ reabsorption

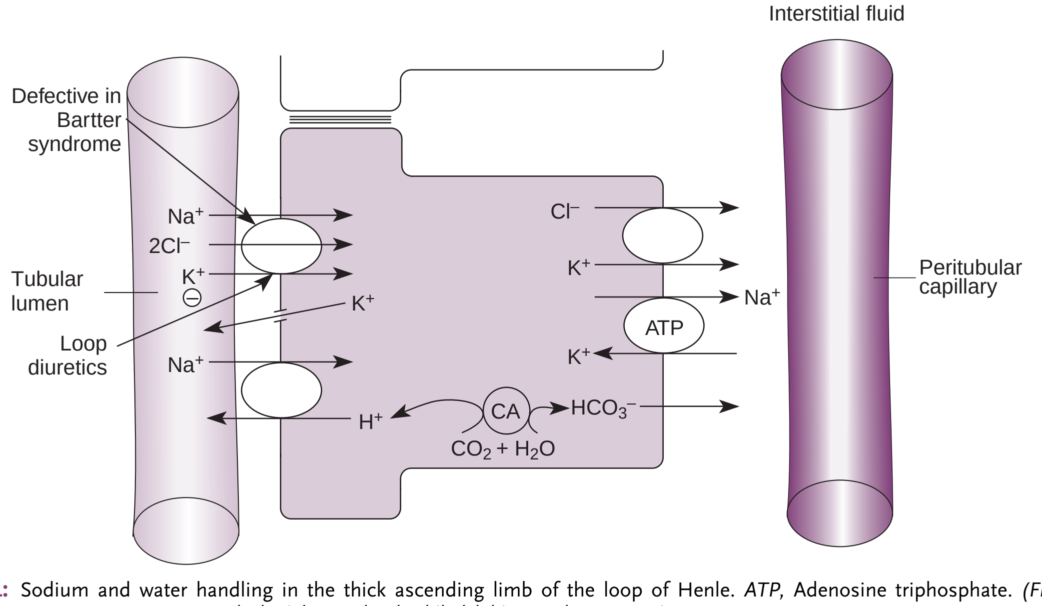
Tight junctions in distal nephron: allow for the excretion of a concentrated urine and a significant acid load

4. **Reabsorption of Na^+ and H_2O 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^+-$2Cl^-$ channel.
   - Na^+ is stimulated to enter these cells because of the low intracellular Na^+ concentration, owing to activity of the Na^+,K^+-ATPase pump and to the electropositive interior of these cells, which is caused by continuous efflux of K^+ ions into the lumen.
     a. This lumen positivity also drives cation (Na^+, Ca^{2+}, Mg^{2+}) transport across the tight junctions in the ascending limb; for example, the thick ascending limb of the LOH is the major site of Mg^{2+} reabsorption in the nephron.

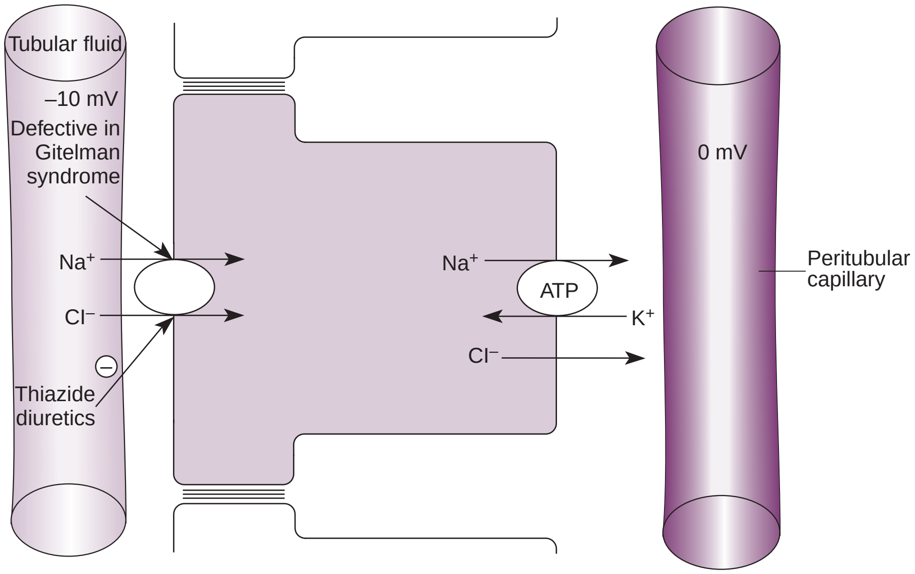
Pharmacology note: Loop diuretics inhibit activity of the Na^+-K^+-$2Cl^-$ channel by binding to the Cl^- binding site on the transporter, thereby promoting a vigorous diuresis. By blocking the Na^+-K^+-$2Cl^-$ channel they may also cause hyponatremia, hypokalemia, and a hypochloremic metabolic alkalosis (through loss of H^+ ions as well as volume depletion).

5. **Reabsorption of Na^+ and H_2O 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).

Na^+ and Cl transport in the distal nephron is *flow dependent.*



6-24: Sodium and water handling in the thick ascending limb of the loop of Henle. *ATP*, Adenosine triphosphate. *(From Koeppen BM, Stanton BA: Renal Physiology, 4th ed. Philadelphia, Mosby, 2007, Fig. 4-8.)*



6-25: Na^+ uptake in the early distal tubule. *ATP*, Adenosine triphosphate. *(From Koeppen BM, Stanton BA: Renal Physiology, 4th ed. Philadelphia, Mosby, 2007, Fig. 4-9.)*

Clinical note: Assume uptake of Na^+ and Cl^- is flow dependent in the LOH and distal tubule. Now imagine a patient is placed on a loop diuretic. This will substantially increase flow to the distal tubule, which will result in increased Na^+ reabsorption occurring before the interstitial Na^+ concentration is high enough to promote significant backflux. This distal response therefore limits the degree to which a loop diuretic can increase Na^+ excretion. Because thiazide diuretics inhibit the ability of the distal tubule to reabsorb Na^+, this may be why they are so synergistic with loop diuretics in promoting diuresis.

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

Kidneys are the body's major route of solute and water excretion.

Urine concentration can vary from 50 mOsm/L to 1200 mOsm/L in healthy young adults.

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

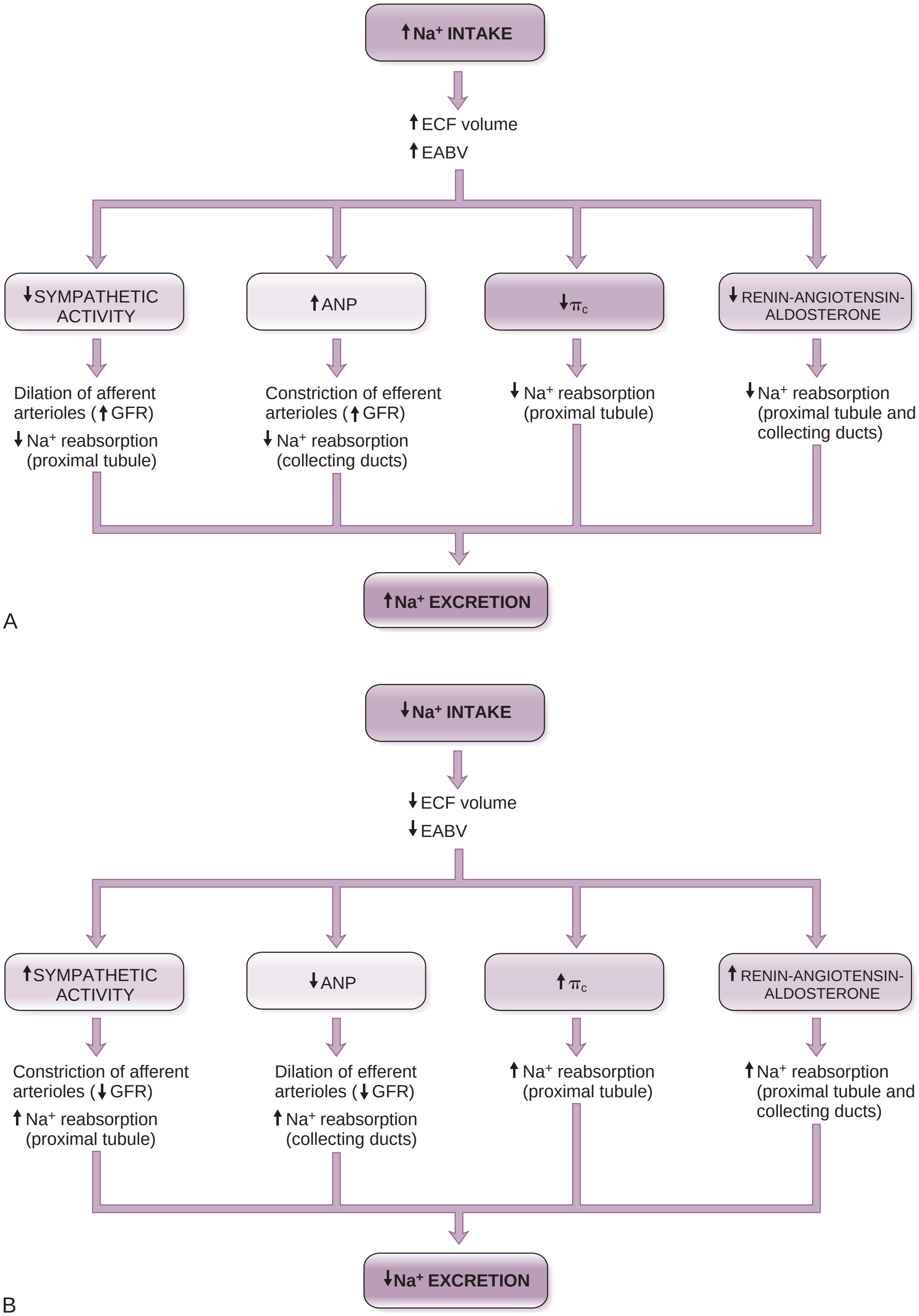
Obligatory urine output: minimum amount of urine needed to be produced daily to excrete metabolic waste products

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

To remove excess water, the kidney must be able to excrete a dilute urine.

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. Π_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.)*

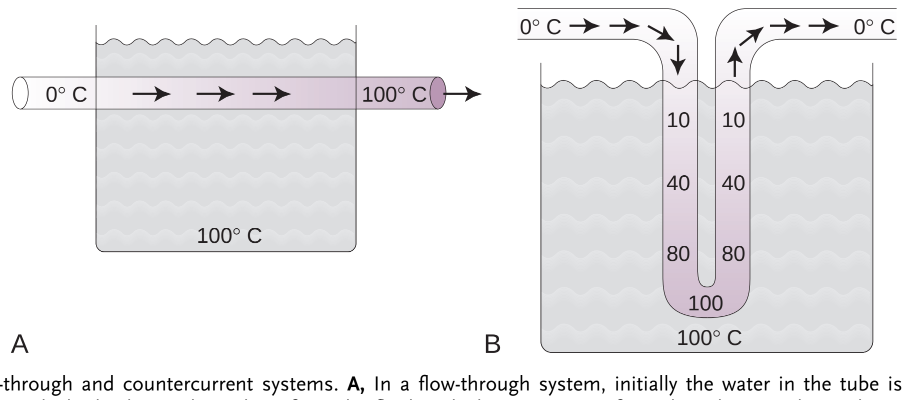
Excretion of excess water: water channels in distal nephron are closed

To remove excess solute, the kidney must be able to excrete a concentrated urine.

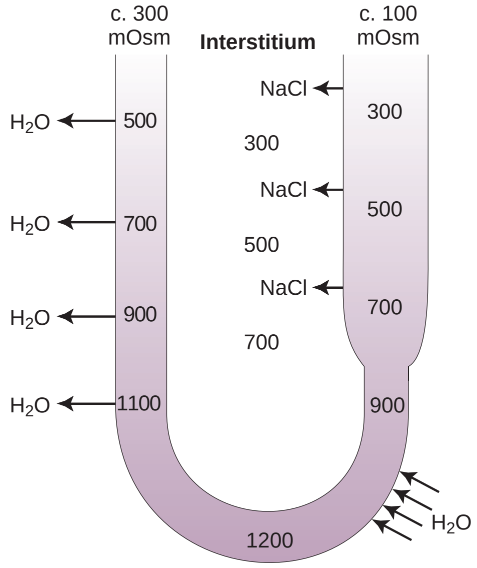
Production of concentrated urine: occurs as a result of the collecting ducts passing through a hyperosmolar region with the aquaporin channels open so water diffuses into the interstitium

Countercurrent mechanism: dependent on hairpin structure of vasa recta and LOH, active NaCl transport from the thick limb of the LOH, and urea trapping within medullary interstitium

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 hyperosmolar 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 in a changed state at 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.



6-28: Schematic of the loop of Henle as a countercurrent system.

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.

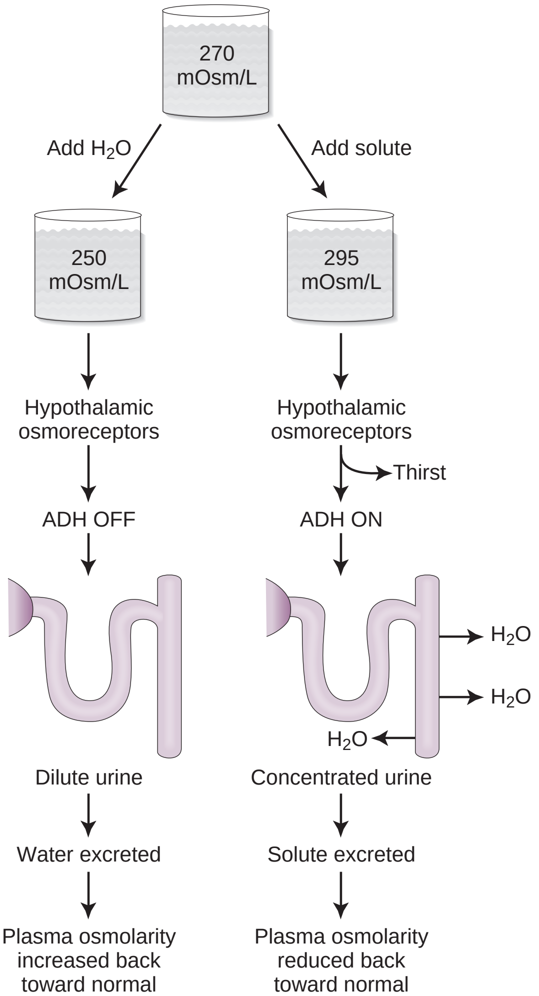
The distal nephron delivers a very dilute tubular fluid to the collecting tubules.

- **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: $P_{osm} = 2 \times [Na^+] + glucose/18 + urea/2.8$

  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).

Permeability of medullary collecting ducts to H_2O: dependent on presence or absence of ADH



6-29: Renal response to water and solute loads. The addition of water decreases plasma osmolality, which triggers the hypothalamic osmoreceptors to turn off production of antidiuretic hormone (ADH), which results in the excretion of the excess water as dilute urine. The addition of solute increases plasma osmolality. This triggers ADH release, which stimulates thirst and the reabsorption of water by the kidney.

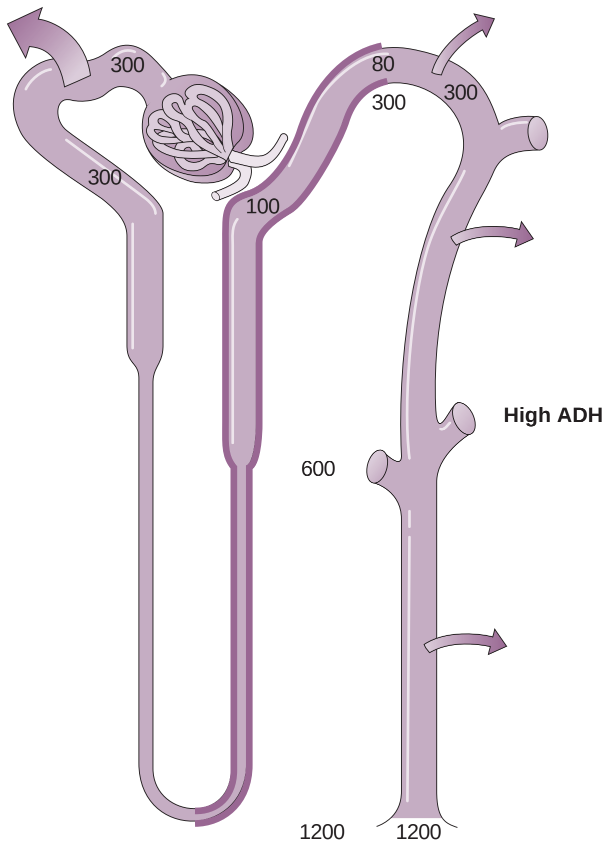
e. Because of this, the excess water is excreted into the urine; the loss of this excess water returns plasma osmolality to normal.
f. In response to **raised plasma osmolality** (addition of solute or loss of water), the osmoreceptors stimulate ADH secretion.
g. As a result, the collecting tubules become 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.

ADH: increases distal nephron permeability to H_2O and stimulates thirst

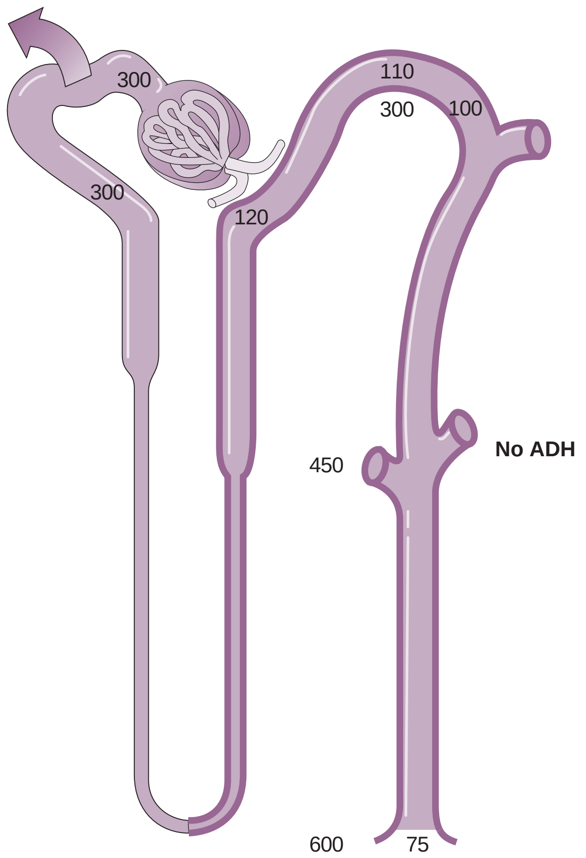
The inner medullary collecting tubules are variably permeable to urea; permeability ↑ in presence of ADH

ADH ↑ urea permeability of inner medullary collecting duct → urea exits tubular lumen to create more hypertonic interstitium → ↑ [urine]

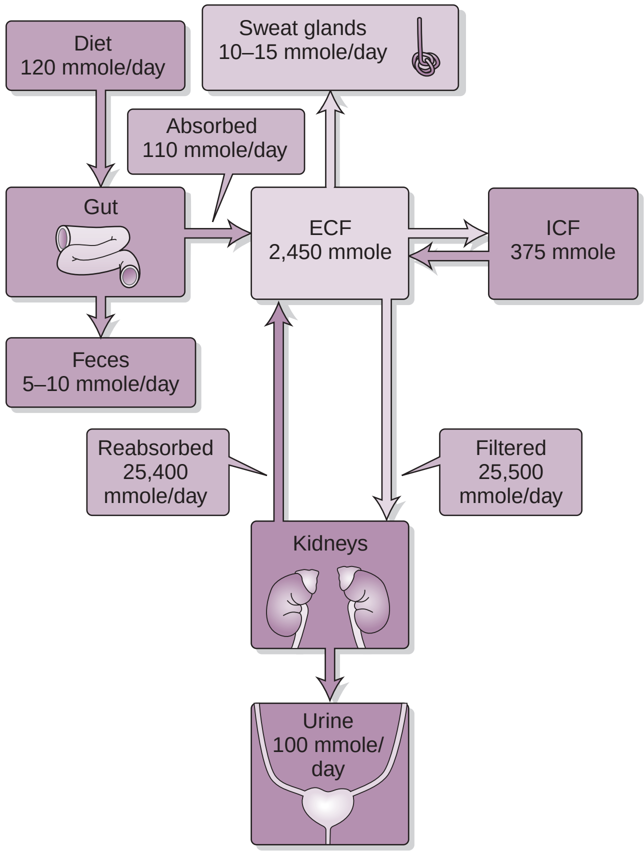
- **Urea trapping** (Fig. 6-32)
  a. Approximately one half of the solute that contributes to the medullary concentrating gradient is urea.
  b. Urea is freely filtered through the glomerulus and only partially reabsorbed in the proximal tubule.
  c. The cortical and outer medullary portions of the collecting 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.)*



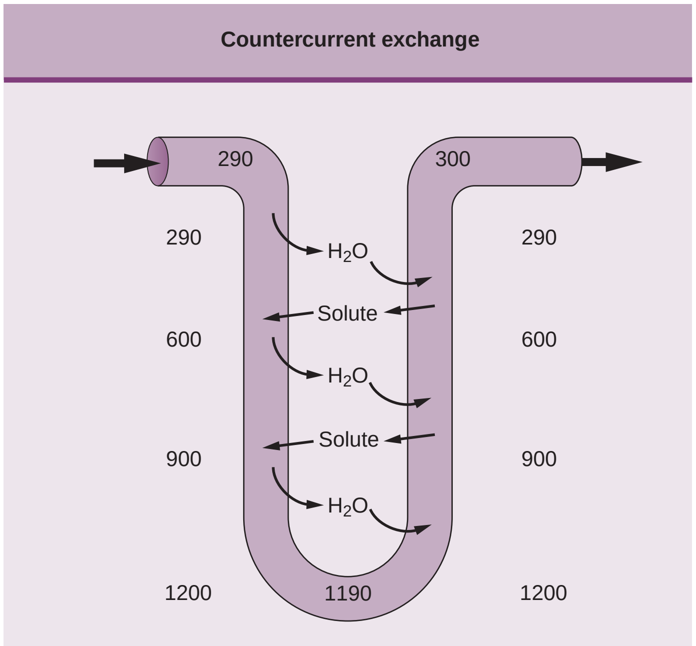
6-32: Urea handling by the kidney. *ECF*, Extracellular fluid; *ICF*, intracellular fluid. *(From Boron W, Boulpaep E: Medical Physiology, 2nd ed. Philadelphia, Saunders, 2009, Fig. 35-1.)*

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: capillary network that supplies the nephron

- **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**.



6-33: Countercurrent exchange by the vasa recta. *(From Feehally J, Floege J, Johnson RJ: Comprehensive Clinical Nephrology, 3rd ed. Philadelphia, Mosby, 2007, Fig. 2-14.)*

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.

Potassium distribution: ~98% of potassium is intracellular

Acute kidney injury: often results in hyperkalemia

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 β_2-adrenergic receptors promotes entry of potassium into cells; α-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.

Na^+,K^+-ATPase pump: regulated by insulin, catecholamines, and K^+

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*.

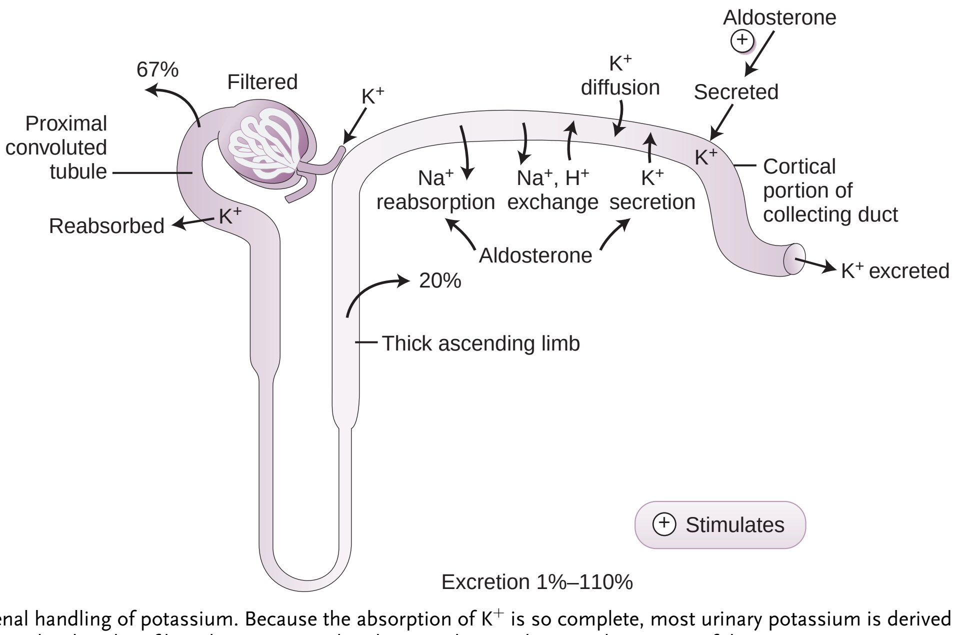
9. H^+ shifts are much less prominent with **metabolic alkalosis,** and K^+ levels typically exhibit only small decreases.

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 β_2-receptor agonist). Because of their ability to shift potassium to the intracellular location, these drugs are used to treat severe hyperkalemia.

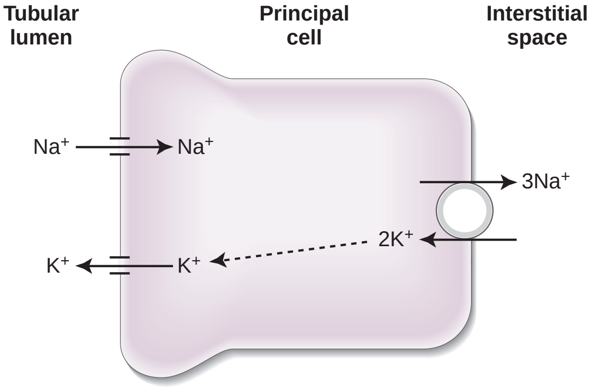
C. Control of potassium homeostasis

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.



6-35: Potassium secretion by the principal cells in the cortical collecting tubule of the distal nephron. Potassium that has entered the tubular cells through the basolateral Na^+,K^+-ATPase diffuses into the tubular lumen through luminal K^+ channels.

- 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).

Lumen negativity (as occurs with Na^+ reabsorption) → ↑ K^+ secretion

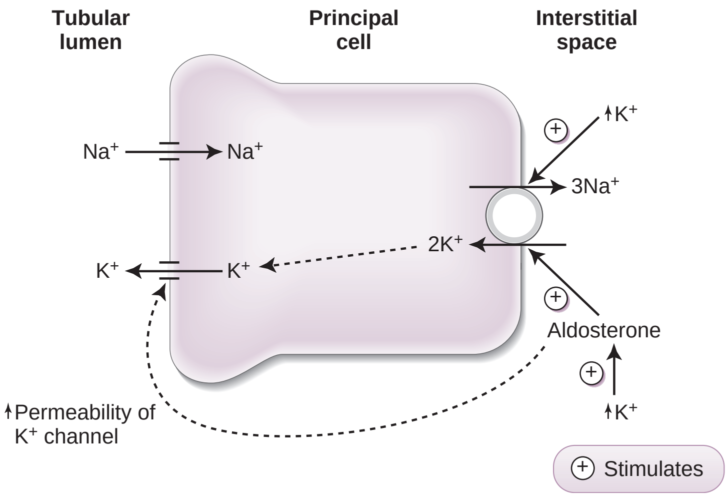
↑ Tubular flow rate → ↑ K^+ secretion

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.

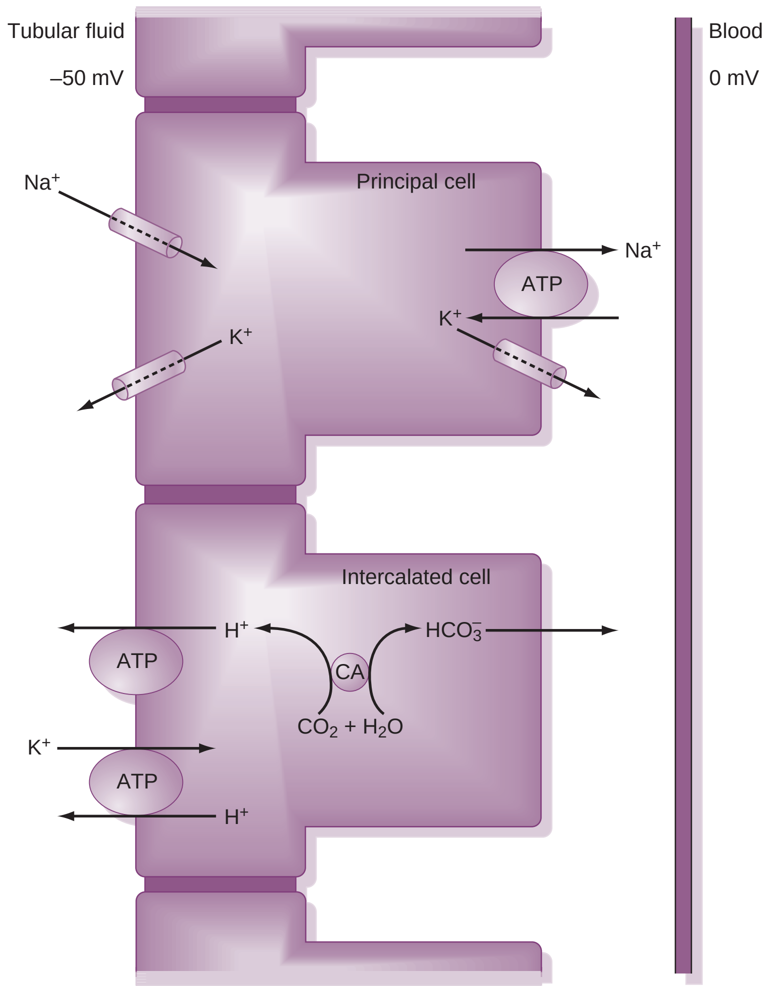
  b. Regulation of renal potassium secretion and reabsorption
    - **Aldosterone** and **plasma K^+ concentration** are the major regulators of K^+ secretion by the kidney.
    - Small increases (0.1 mEq/L) in plasma potassium concentration promote significant increases in aldosterone secretion by the **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.

Aldosterone promotes K^+ secretion by ↑ activity of basolaterally located Na^+, K^+-ATPase pump and by ↑ number of open Na^+ and K^+ channels in luminal membrane

Principal cells: important in Na^+ absorption and K^+ secretion



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.)*

Intercalated cells: secretes H^+ ions; critical role in acid-base balance

- 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.

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

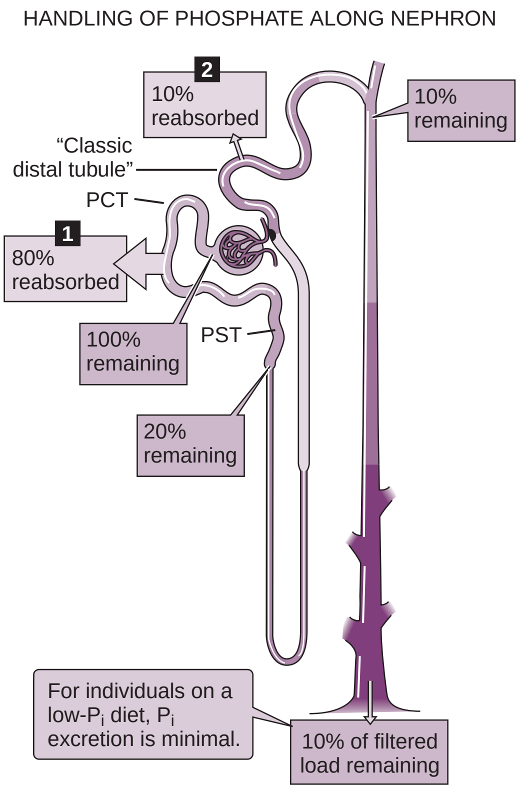
1. The contribution of the kidney to phosphate homeostasis involves a more complex regulatory system than does its contribution to acid-base, bicarbonate, and potassium homeostasis, all of which involve near-complete absorption from the gut with a matching of daily intake to urinary losses.
2. Regulation 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).

Phosphate concentration regulated by PTH, calcium, and calcitriol

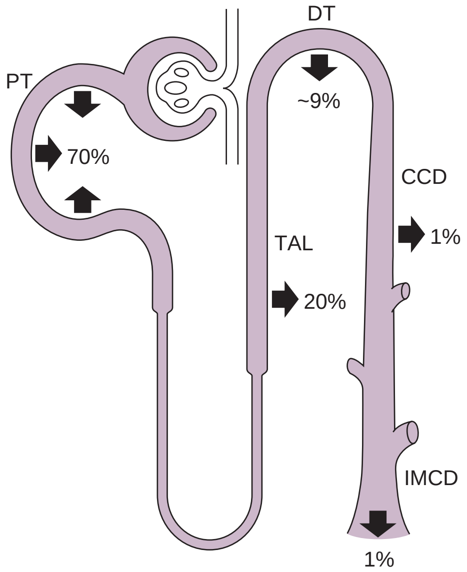
B. Parathyroid hormone

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.

Hypocalcemia → ↑ [PTH] → ↑ release Ca^{2+} and PO_4^- from bone and ↑ reabsorption of renally filtered Ca^{2+}

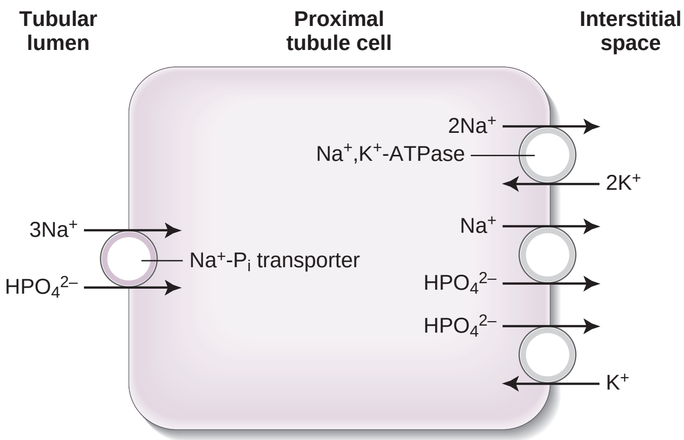


6-38: Phosphate handling in the nephron. *PCT,* Proximal convoluted tubule; *P_i,* inorganic phosphate; *PST,* proximal straight tubule. *(From Boron W, Boulpaep E: Medical Physiology, 2nd ed. Philadelphia, Saunders, 2009, Fig. 36-14A.)*



6-39: Calcium handling in the nephron. *CCD,* Cortical collecting duct; *DT,* distal tubule; *IMCD,* inner medullary collecting duct; *PT,* proximal tubule; *TAL,* thick ascending limb. *(From Koeppen BM, Stanton BA: Renal Physiology, 4th ed. Philadelphia, Mosby, 2007, Fig. 9-3.)*

6-40: Phosphate transport in the proximal tubule. An increase in parathyroid hormone levels decreases the number of Na^+-P_i 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.



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 **sodium phosphate (Na^+-P_i) cotransporters** present on the luminal membrane of epithelial cells of the proximal convoluted tubule, the major site of phosphate reabsorption (Fig. 6-40).
7. **Hyperphosphatemia** also stimulates an increase in PTH, which increases renal phosphate losses by decreasing the number of Na^+-P_i cotransporters.

PTH: prevents hyperphosphatemia by ↑ renal phosphate excretion

Hyperphosphatemia (as in renal failure): stimulates PTH secretion

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:

Calcitriol: most active form of vitamin D; PTH and calcitriol regulate phosphate balance

Hypophosphatemia: ↑ calcitriol synthesis

Hyperphosphatemia: → ↓ calcitriol synthesis 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^+-P_i 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^+-P_i 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^+-P_i cotransporter.
   - Calcitriol levels fall.
   - Increased PTH secretion further lowers Na^+-P_i 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, hyperphosphatemia 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.

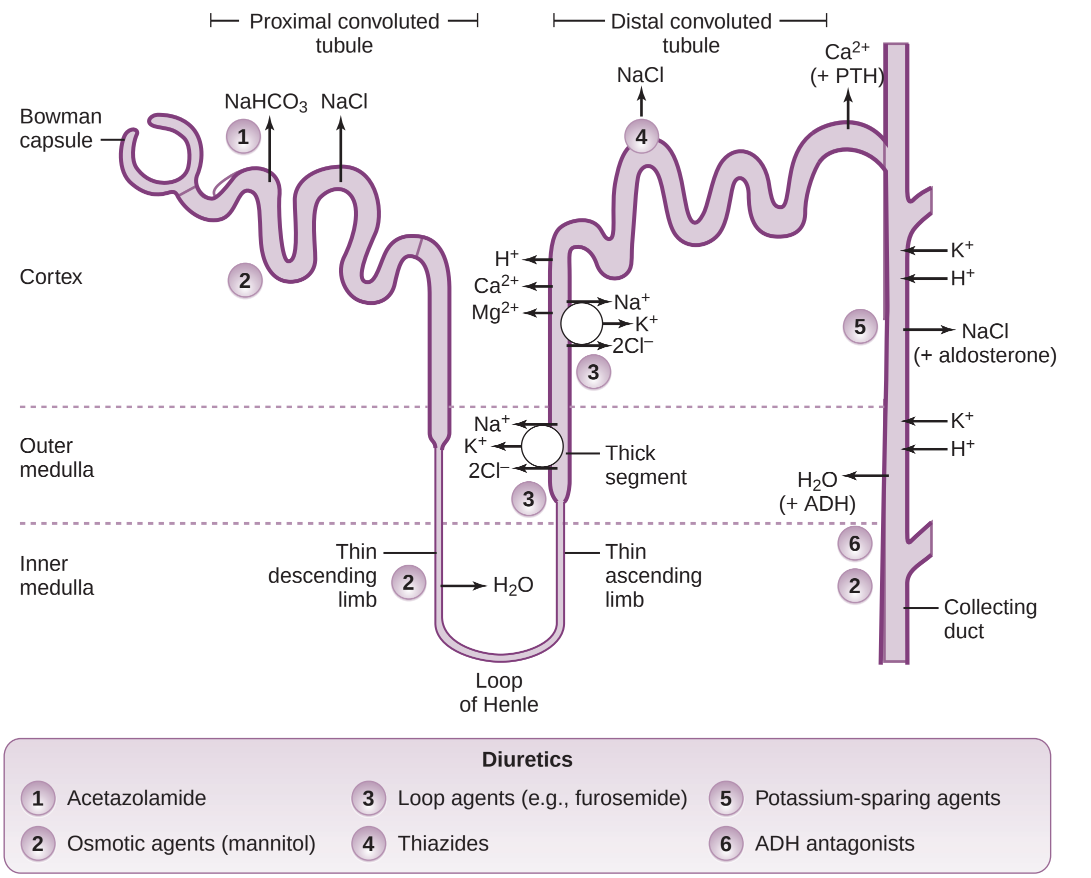
B. Diuretics and sodium

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

CLASS OF DIURETIC	SITE OF ACTION	MECHANISM	POTENCY	CLINICAL USE	SIDE EFFECTS
Carbonic anhydrase inhibitors (acetazolamide)	Proximal convoluted tubule	Promote metabolic acidosis by inhibiting bicarbonate reclamation (i.e., increase bicarbonate excretion), weak diuretic effect by inhibiting Na^+ reabsorption	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	High-altitude sickness, glaucoma	Metabolic acidosis, ↓ K
Thiazide diuretics (HCTZ, metolazone)	Distal convoluted tubule	Inhibit the activity of the Na^+-Cl cotransporter	Relatively weak because act at sites where smaller amounts of sodium (5%-10%) are reabsorbed	Hypertension Diabetes insipidus Only metolazone is useful in chronic renal failure	Hyponatremia, hypercalcemia, ↓ K Inhibits urinary dilution
Potassium-sparing diuretics (spironolactone, triamterene, amiloride)	Collecting tubule	Decreasing the number of open Na^+ channels in principal cells of the tubule	Relatively weak because act at sites where smaller amounts of sodium (3%-5%) are reabsorbed	Cirrhosis Added to thiazides to avoid ↓ K	Hyperkalemia (rarely), gynecomastia (spironolactone)
Loop diuretics (furosemide)	Loop of Henle	Inhibit Na^+-K^+-$2Cl^-$ carrier in thick ascending limb of loop of Henle	More potent because act at a site responsible for reabsorption of approximately 25% of filtered sodium	Pulmonary edema associated with congestive heart failure	Hyponatremia, hearing loss
Osmotic diuretics (mannitol)	—	Osmotic diuresis	—	Cerebral edema	Vascular space expansion with volume overload

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

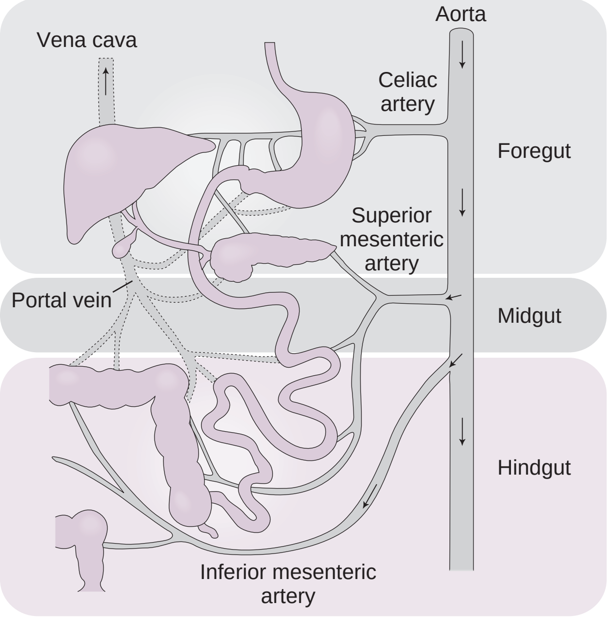
I. Structure and Function of the Gastrointestinal Tract

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.

Vascular supply of intestinal tract: foregut—celiac artery; midgut—SMA; hindgut—IMA

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,** a variety of pathophysiologic changes result in elevated portal vein pressures, termed **portal hypertension.** Because the portal vein has multiple **anastomoses with systemic veins,** 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.



7-1: Splanchnic circulation, which is derived entirely from the celiac artery, the superior mesenteric artery, and the inferior mesenteric artery.

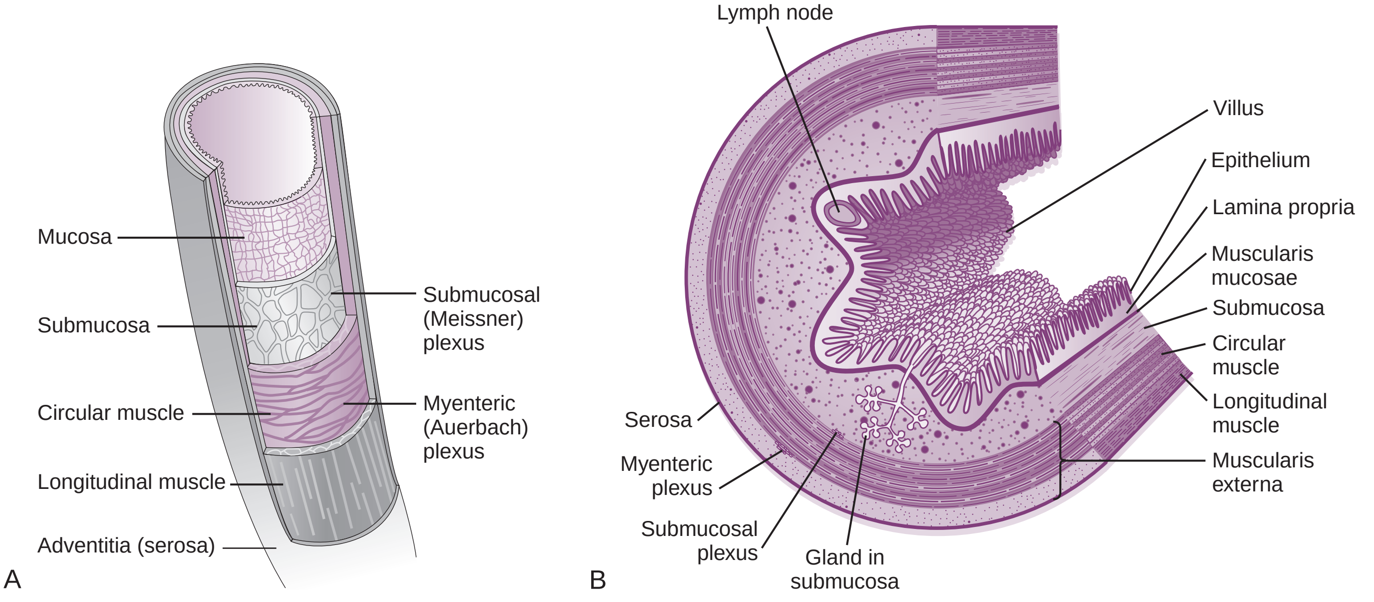
Mucosa: composed of mucosal epithelium, lamina propria, and muscularis mucosae

Epithelial cells: stratified squamous in esophagus, columnar in GI until dentate line, squamous in rectum

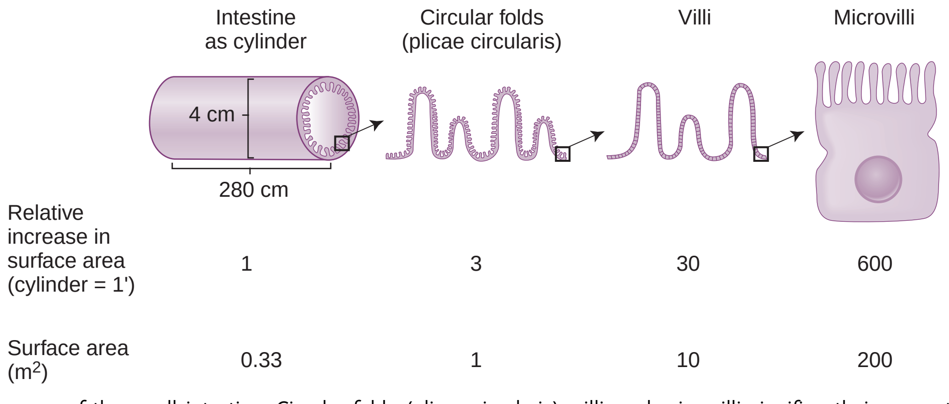
2. **Layers of the gut wall**
   - Throughout most of the GI tract, the gut wall is composed of four layers; from inside to outside, these are the mucosa, submucosa, muscularis propria, and serosa (Fig. 7-2).

   a. **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.
      - 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.
      - In the stomach, the mucosa is folded into **rugae.**
      - 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).
      - In the large intestine, there are **crypts** but no villi.



7-2: Two different views of the layers of the gut wall. *(**B**, From Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 26-2.)*



7-3: Arrangement of mucosa of the small intestine. Circular folds (plicae circularis), villi, and microvilli significantly increase the surface area of the mucosa. Surface areas are shown in square meters.

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.

Metaplasia: transformation of one adult cell type into another

- 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)

Submucosa: contains blood vessels, lymphatic vessels, and nerves (submucosal plexus), which supply the mucosa

c. **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.**

Serosa: absent in certain parts of the intestinal tract, such as the esophagus

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.

Enteric nervous system: composed of submucosal and myenteric plexuses and entirely contained within gut wall

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**

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.

Myenteric plexus: promotes motility of intestinal tract

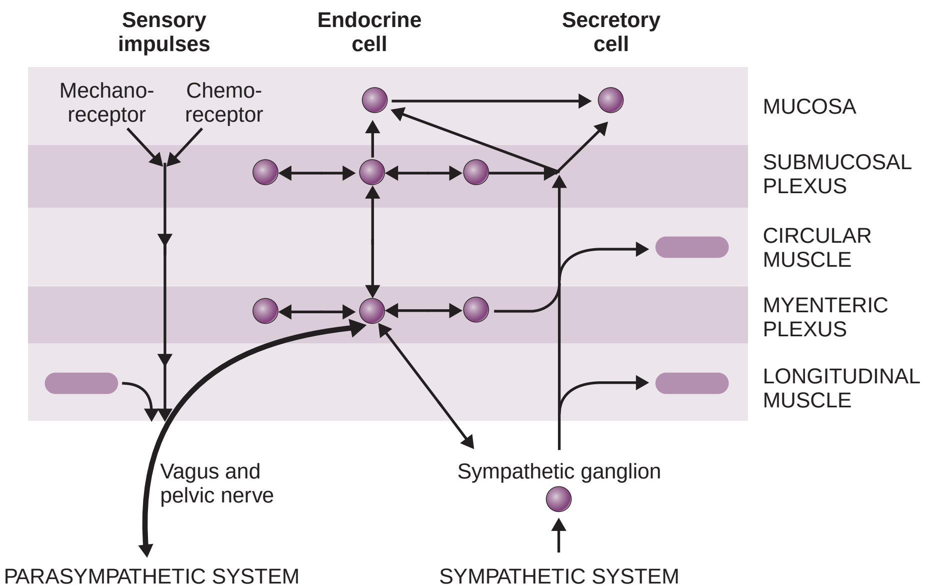
c. **Myenteric (Auerbach) plexus**
- Located between the inner circular and the outer longitudinal muscle layer of the muscularis propria
- **Primary role is coordination of intestinal motility**
- Stimulation of the myenteric plexus increases intestinal motility mainly by **stimulating peristalsis** and also by **inhibiting contraction of sphincter muscles** throughout the intestinal tract.

PNS: promotes digestion and absorption by stimulating secretions and intestinal motility

SNS: inhibits digestion and absorption in part through vasoconstriction of the splanchnic circulation

- 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.



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

EFFECT	PARASYMPATHETIC	SYMPATHETIC
Motility	+	−
Sphincter tone	−	+
Secretion	+	−
Vasoconstriction	No effect	+

- **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.

Gastrocolic reflex: gastric distension promotes bowel movement

Vagovagal reflexes: afferents from stretch receptors, chemoreceptors, and osmoreceptors in the gut travel to and from the central nervous system through the vagus nerve

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.

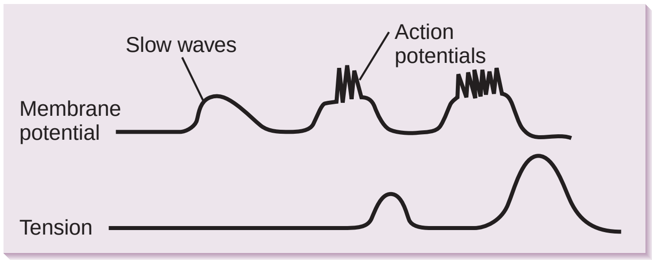
Intestinal SMCs: resting membrane potential unstable and continually depolarizing

Slow waves → threshold potential reached → action potential generated → smooth muscle contraction → propulsion of intestinal contents toward anus

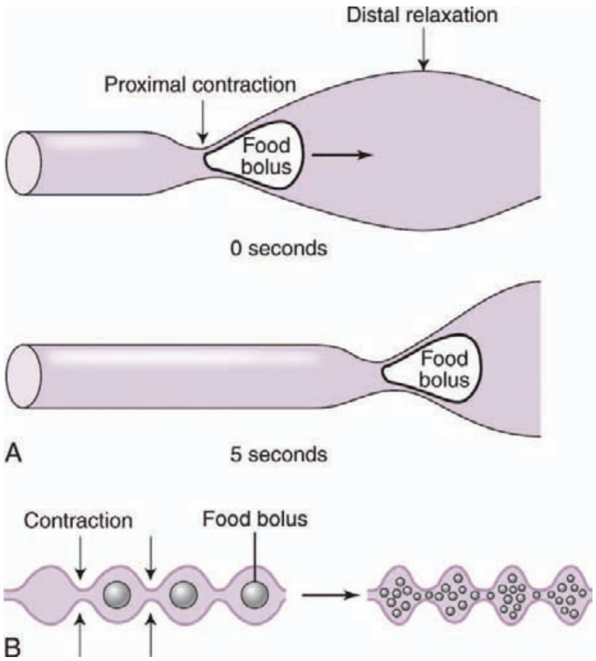
Pharmacology note: Metoclopramide is a D2 receptor antagonist and 5-HT3 antagonist that is a **prokinetic agent** useful in the treatment of nausea and vomiting, particularly in patients who have delayed gastric emptying (gastroparesis).

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.



7-6: Peristalsis **(A)** and segmentation **(B).**

- The myenteric plexus is almost entirely responsible for coordination of peristalsis.
- In its absence, peristaltic contractions may be severely impaired or even absent.

Peristalsis: dependent on functional myenteric plexus

Pathology note: In a condition called **achalasia,** esophageal peristalsis is severely compromised because of damage to the myenteric plexus (see later discussion).

Segmentation: simultaneous contractions proximal and distal to food bolus; promotes digestion; no forward propulsion of food bolus

b. **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 of sphincter muscles prevent premature analward passage of intestinal contents.

c. **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.**

Digestion: enzymatic hydrolysis of macromolecules into absorbable smaller compounds

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.

Efficient absorption: dependent on large surface area of mucosal epithelium

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.

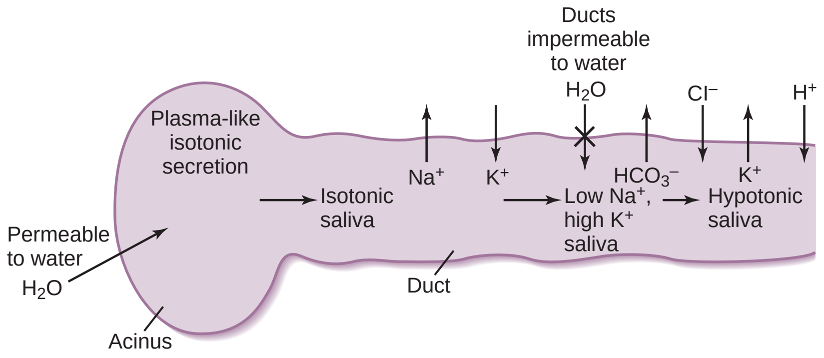
II. Salivation and Mastication

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).

TABLE 7-2. **Composition and Function of Saliva**

COMPONENT	PRIMARY FUNCTION
Potassium bicarbonate	Neutralizes bacterial acid, preventing digestion of tooth enamel and dentine (prevents cavities)
Lingual lipase	Initiates lipid digestion
Salivary amylase	Initiates carbohydrate digestion
Mucins	Lubricate food bolus, are primary determinant of viscosity
Lysozyme	Initiates bacterial lysis
Immunoglobulins	Offer immune protection



7-7: Saliva production.

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).

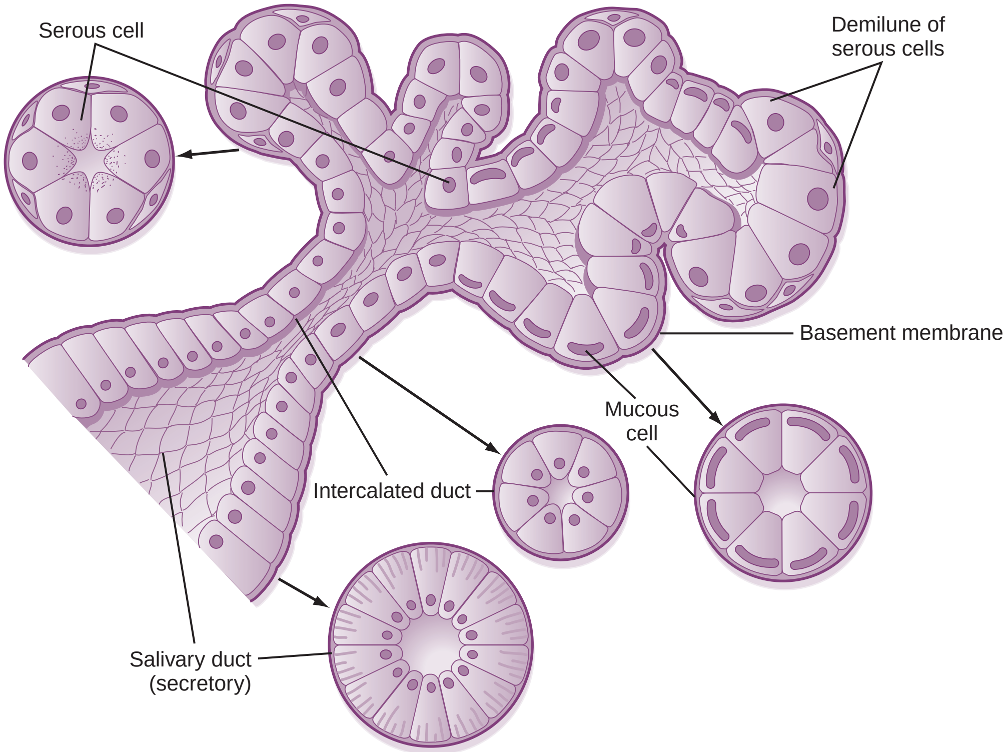
Saliva: usually hypotonic relative to plasma when secreted

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.

Salivary glands: two types—serous and mixed

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.



7-8: Structure of a mixed salivary gland, showing both serous and mucous cells. *(From Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 27-1.)*

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_3).

Muscles of mastication: masseter, temporalis, medial and lateral pterygoids

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

Swallowing: under both voluntary and involuntary control

Upper third of esophagus composed of striated muscle, lower third composed of smooth muscle that is controlled by myenteric plexus

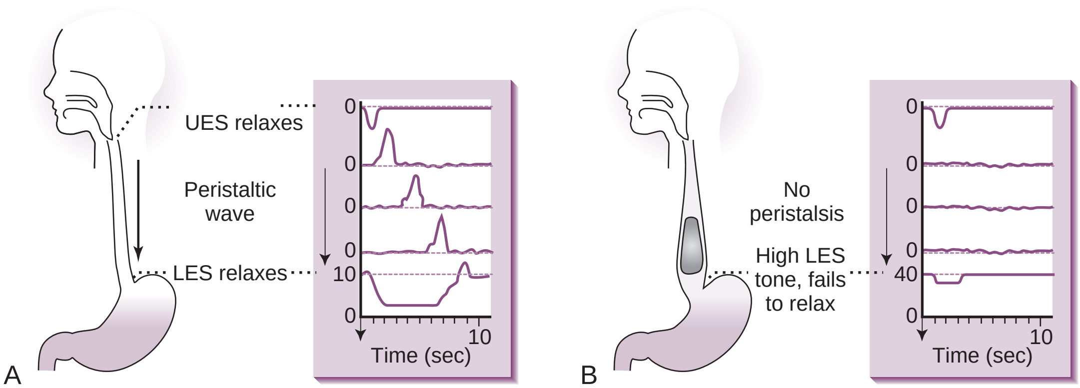
1. Overview
   - Esophageal motility is under both voluntary and involuntary control.
   - This reflects the differential distribution of striated and smooth muscle fiber throughout the esophagus.
   - The upper third of the esophagus is composed of **striated muscle fibers,** whereas the lower third 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).

LES: normally tonically constricted, which helps prevent gastric reflux

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.**



7-9: Pressure changes in the esophagus during swallowing. **A,** Normal pressure changes during peristalsis. There is decreased pressure in the lower esophagus because of relaxation of the lower esophageal sphincter (LES) (receptive relaxation). **B,** Abnormal pressure changes that occur in achalasia. *UES,* Upper esophageal sphincter.

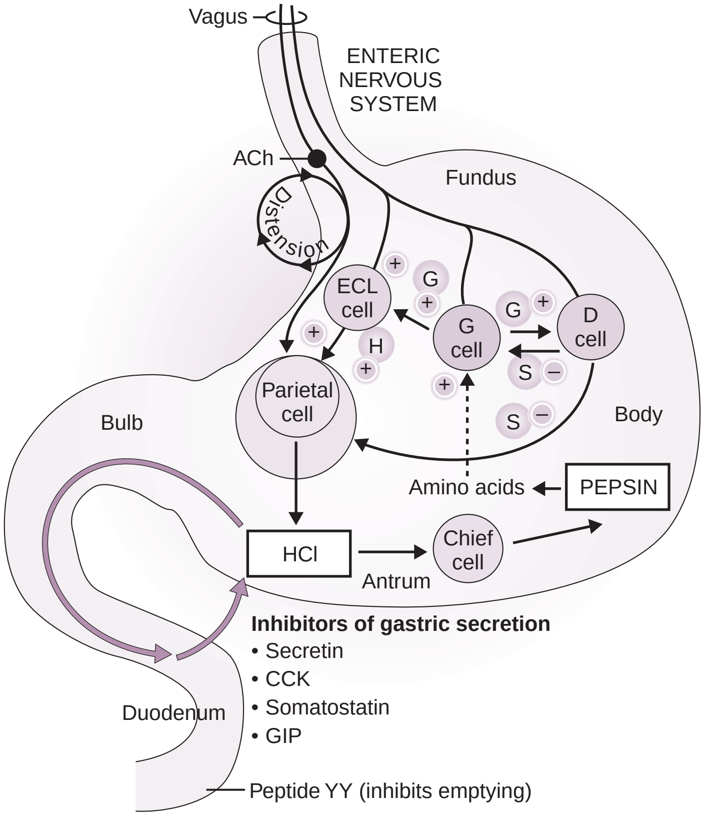
IV. Stomach (Fig. 7-10)

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.

Stomach: holding area for food; converts food to chyme and releases small aliquots to duodenum

7-10: Functional anatomy of the stomach. *ACh,* Acetylcholine; *CCK,* cholecystokinin; *ECL,* enterochromaffin-like; *GIP,* gastric inhibitory peptide. *(Modified from Damjanov I: Pathophysiology. Philadelphia, Saunders, 2008, Fig. 7-9.)*



Cephalic phase: sight, smell, or thought of food stimulates gastric secretions

Gastric phase: abdominal distension from food bolus triggers gastric secretions

Enteric (intestinal) phase: entry of chyme into small bowel stimulates release of factors that slow gastric emptying

Receptive relaxation: reflexive relaxation of stomach in response to food descending through lower esophagus

Gastric accommodation: relaxation of the stomach in response to gastric distension

Low gastric pH: denatures protein, activates proteases, inhibits bacterial growth

Intrinsic factor: binds vitamin B_{12} to prevent its degradation in small bowel

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.

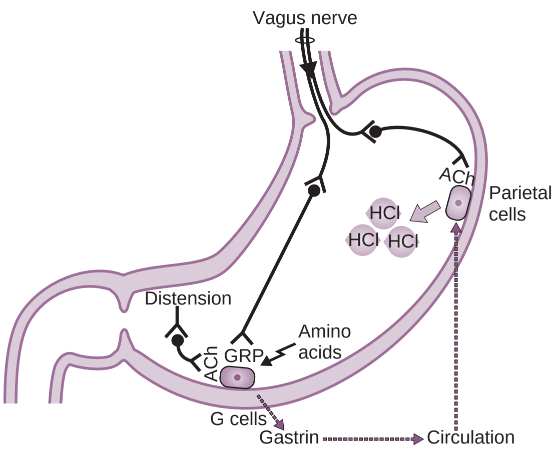
C. Receptive relaxation of the stomach

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

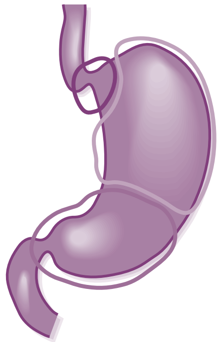
1. **Parietal cells** (Table 7-3)
   - Parietal cells secrete hydrogen ions, which creates a low gastric pH.
   - This low pH serves many functions:
     a. It denatures proteins.
     b. It **activates** protein-digesting enzymes such as **pepsinogen.**
     c. It creates a **harsh environment for bacterial 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 B_{12} in protein-rich foods such as meats to prevent its degradation in the small intestine and to allow absorption in the terminal ileum.

REGULATION OF HCl SECRETION



Phase	% of HCl Secretion	Stimuli	Mechanisms
Cephalic	30%	Smell, taste, conditioning	Vagus → parietal cell Vagus → gastrin → parietal cell
Gastric	60%	Distension	Vagus → parietal cell Vagus → gastrin → parietal cell
		Distension of antrum	Local reflex → gastrin → parietal cell
		Amino acids, small peptides	Gastrin → parietal cell

A



Region	Luminal secretion	Motility
LES* and cardia	Mucus HCO_3^-	Prevention of reflux Entry of food Regulation of belching
*LES is part of the esophagus		
Fundus and body	H^+ Intrinsic factor Mucus HCO_3^- Pepsinogens Lipase	Reservoir Tonic force during emptying
Antrum and pylorus	Mucus HCO_3^-	Mixing Grinding Sieving Regulation of emptying

B

7-11: **A,** Phases of digestion. **B,** Particular physiologic roles of the parts of the stomach. *ACh,* Acetylcholine; *GRP,* gastric-related peptide; *LES,* lower esophageal sphincter. *(**A,** From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 8-19; **B,** from Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 28-1.)*

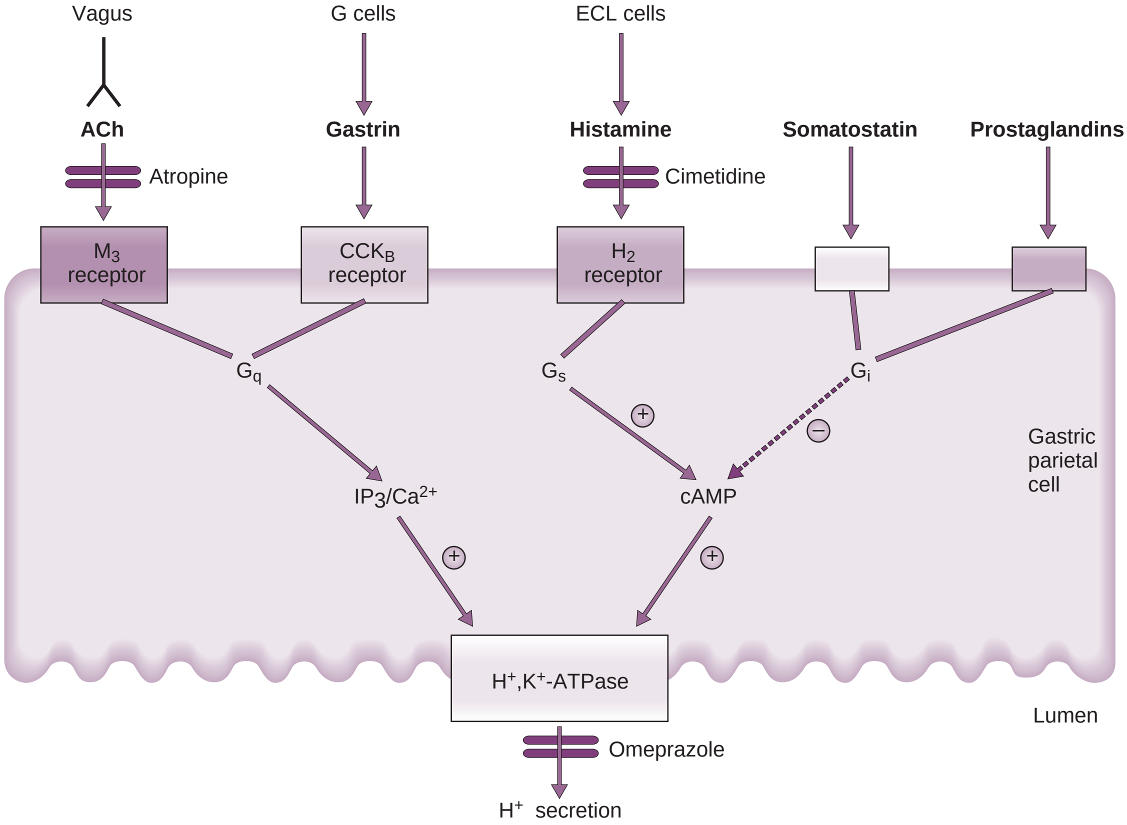
TABLE 7-3. Gastric Secretions

SECRETION	CELL OF ORIGIN	STIMULUS	ACTIONS	PATHOPHYSIOLOGY
Hydrochloric acid	Parietal	Parasympathetic innervation, histamine, gastrin	Converts pepsinogen to pepsin, denatures proteins, kills most bacteria	Excessive secretion due to gastrin-secreting tumor (Zollinger-Ellison syndrome) may lead to peptic ulcer disease Hypochlorhydria from atrophic gastritis → G-cell hyperplasia; ↑ gastrin → ↑ risk for gastrinoma
Intrinsic factor	Parietal	Parasympathetic innervation, histamine, gastrin	Prevents vitamin B_{12} from degradation in small intestines (i.e., necessary for vitamin B_{12} absorption)	Destruction of parietal cells in pernicious anemia (atrophic gastritis) → vitamin B_{12} deficiency → macrocytic anemia
Mucus and HCO_3^-	Mucous	Prostaglandins	Protects gastric mucosa from low pH	NSAIDs → ↓ prostaglandins → ↓ activity of mucous cells → peptic ulcer disease
Pepsinogen	Chief	Ingestion of food	Digests proteins to peptides (major) and amino acids (minor)	
Gastrin	G cell	Food in stomach, particularly protein	Stimulates parietal cell activity, resulting in secretion of hydrochloric acid and intrinsic factor	May be elevated in Zollinger-Ellison syndrome or with prolonged administration of proton pump inhibitors such as omeprazole

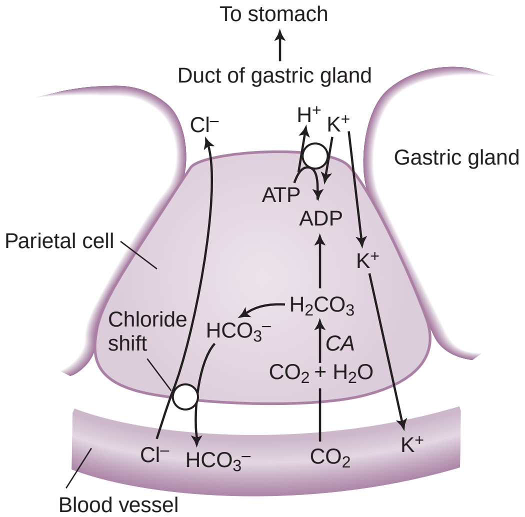
NSAIDs, Nonsteroidal anti-inflammatory drugs.

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 B_{12} (cobalamin). This produces a **macrocytic anemia** (more specifically, a *megaloblastic anemia*), because vitamin B_{12} 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 (H_2-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 CO_2 is generated within the parietal cells or diffuses into parietal cells, where it reacts with water to form HCO_3^- and H^+ ions. H^+ ions are then secreted into the gastric lumen in exchange for K^+ ions, and HCO_3^- 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 HCO_3^- 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).

G cells: secrete gastrin, promote 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.**

Gastrin secretion: stimulated by presence of protein in stomach

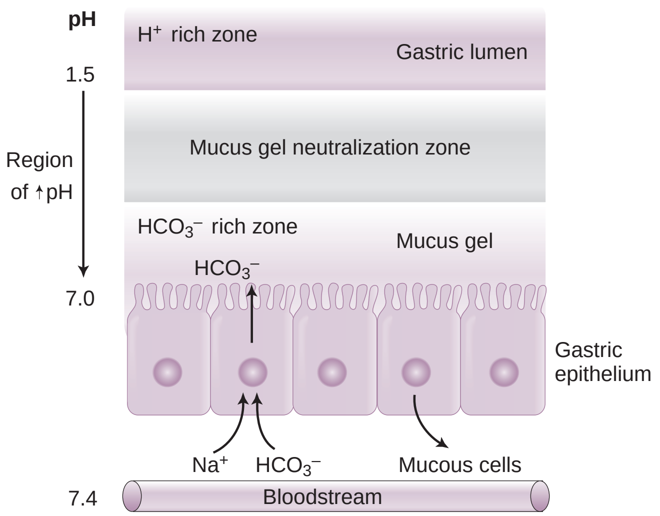
3. **Chief cells**
   - Protein digestion (hydrolysis of proteins to peptides and amino acids) begins in the stomach because of the activity of chief cells (see Table 7-3).
   - These cells secrete the inactive precursor protein, **pepsinogen,** which is activated to the proteolytic enzyme, **pepsin,** in the presence of acid and/or small amounts of active pepsin.
   - Pepsin functions optimally at a pH of approximately 2.

Chief cells secrete pepsinogen, which when cleaved to pepsin initiates protein digestion in stomach.

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.

Mucous cells: secretion of mucus and HCO_3^-, both of which prevent mucosal damage from low gastric pH

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.



7-14: Mucus-bicarbonate layer.

Gastric emptying is delayed by a high-fat meal.

Gastric motility and pyloric sphincter tone: regulated by hormones produced in small intestine

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.

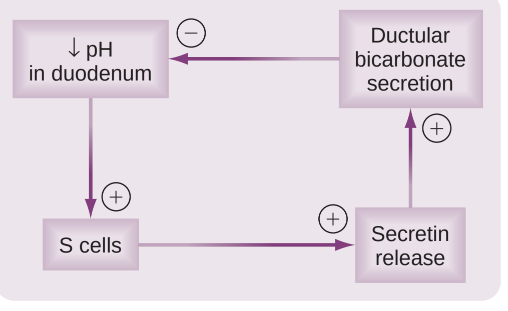
Clinical note: A normally functioning pyloric sphincter is tonically contracted and relaxes only periodically to allow small volumes of chyme to enter the duodenum. If the pyloric sphincter is incompetent, as is often caused by **gastric surgery,** large volumes of hypertonic chyme may enter the duodenum, 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 ↑ HCO_3^--rich 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



7-15: Regulation of secretin secretion. *(From Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 29-3.)*

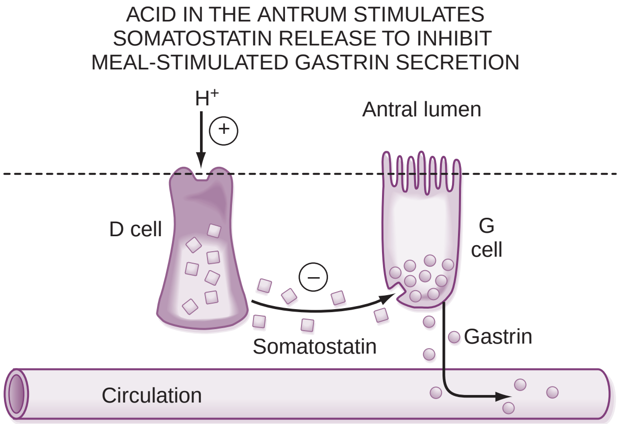
- Secretin then stimulates the release of a **HCO_3^--rich secretion** from the ductal cells of the pancreas to neutralize the acidic chyme and to allow pancreatic digestive enzymes to function close to their pH optima.
- Secretin also stimulates the secretion of HCO_3^- by the duodenum and inhibits 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 δ cells, globally inhibits gastric activity (Fig. 7-16).

Secretin: secretion stimulated by acidic chyme entering duodenum; promotes HCO_3^--rich secretion from pancreas and inhibits further gastric emptying

CCK: secretion stimulated by entry of fatty acids into duodenum; prevents further gastric emptying by inhibiting pyloric sphincter relaxation; stimulates gallbladder contraction

Gastric inhibitory peptide and somatostatin generally inhibit digestion.



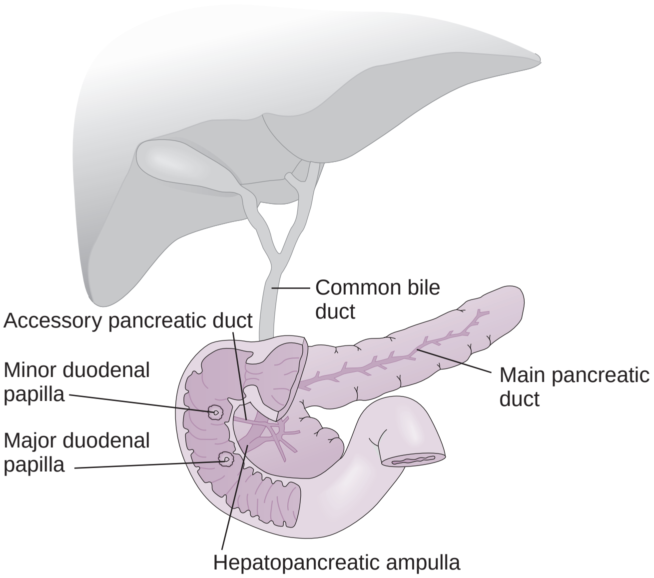
7-16: Regulation of somatostatin secretion. *(From Koeppen BM, Stanton BA: Berne and Levy Physiology, 6th ed. Updated ed. Philadelphia, Mosby, 2010, Fig. 28-8.)*

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.

Pancreas: retroperitoneal organ with important endocrine and exocrine functions



7-17: Functional anatomy of the pancreas.

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_3^--rich and neutralize acidic chyme to allow for proper function of pancreatic enzymes (Fig. 7-18).

Acinar secretions: enzyme-rich secretions critical for digestion

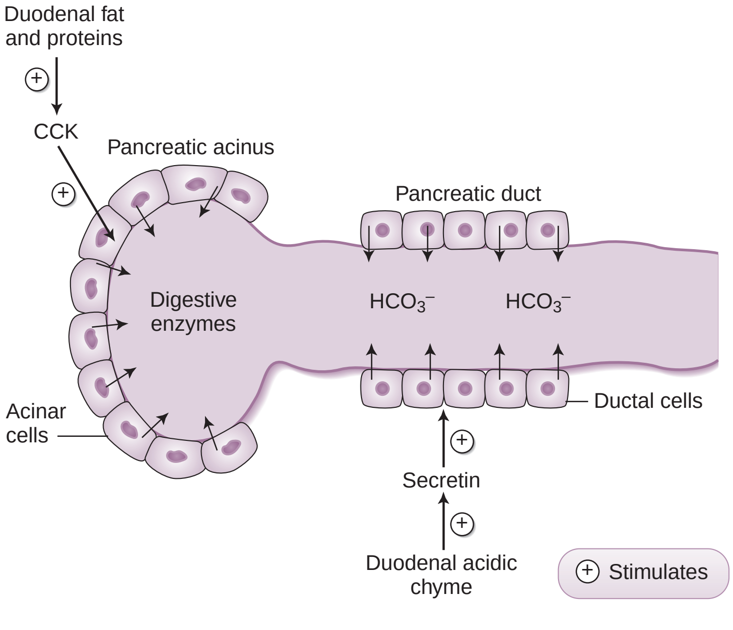
Ductal secretions: HCO_3^--rich secretions that neutralize acidic chyme; allow digestive enzymes to function

Pancreatitis: most common causes are alcohol abuse and obstructing gallstones

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.



7-18: Pancreatic secretions. *CCK,* Cholecystokinin.

VI. Liver and Biliary Tree

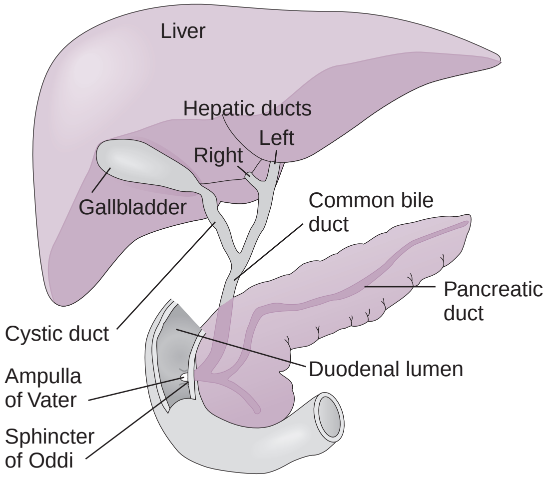
A. Functional anatomy

- 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

Functions of bile: solubilization of cholesterol, dietary fat absorption, excretion of waste products



7-19: Anatomy of the biliary tree.

TABLE 7-5. Composition and Function of Bile

COMPONENT	FUNCTION
Bile acids, bile salts	Emulsify fats to facilitate digestion by lipases Form micelles to deliver fatty acids to mucosal surface for absorption Solubilize cholesterol Cholesterol degradation product for elimination
Lecithin	Solubilizes cholesterol
Bilirubin	Forms waste product from metabolism of heme
Cholesterol	Effects waste elimination

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 imino-diacetic 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.**

Enterohepatic circulation: cycling of substances such as bile acids between liver and intestinal tract

Cholesterol excretion: primarily occurs through the loss of bile acids in feces

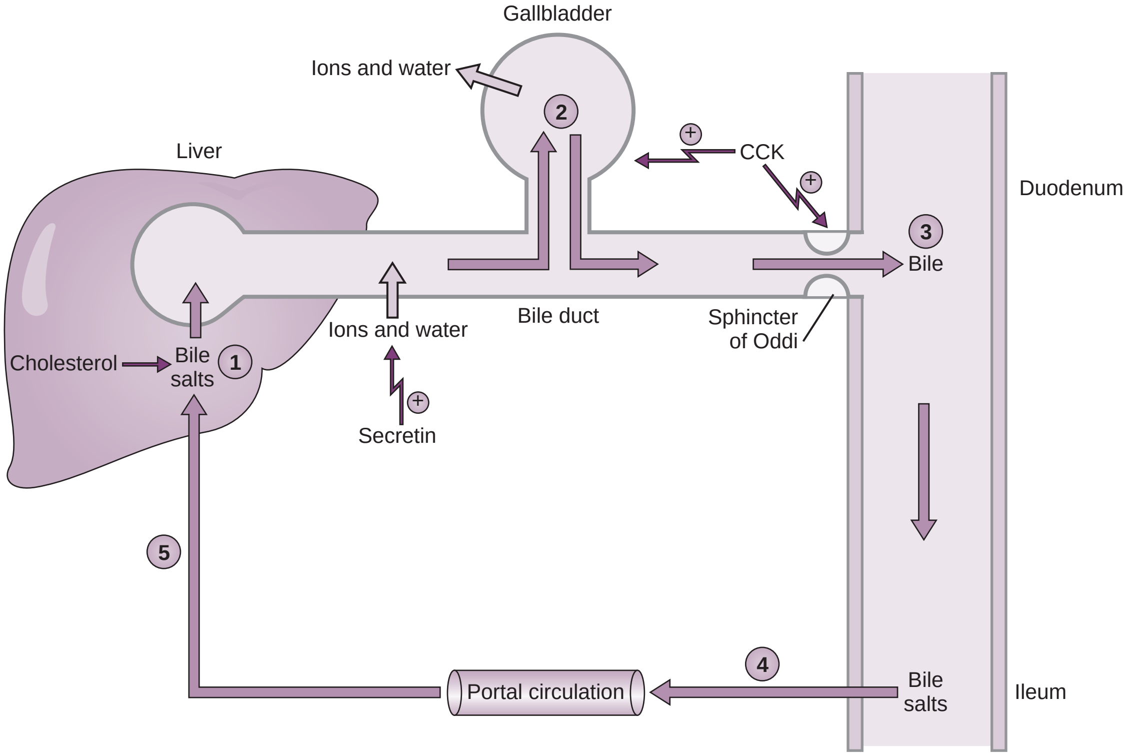
Clinical note: Bile-sequestering agents, such as **cholestyramine,** act by preventing reabsorption of bile in the distal ileum, thereby depleting hepatic stores of bile acids. Because bile acids are synthesized from cholesterol, compensatory hepatic synthesis of new bile acids necessitates increased 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 B_{12} are absorbed in the distal ileum.

Most fat-soluble substances such as vitamins are absorbed in the distal ileum.



7-20: Steps in bile production and recycling. (1) Bile salts produced in the liver. (2) Bile concentrated and stored in gallbladder. (3) Bile secreted into duodenum. (4) Bile reabsorbed in terminal ileum and returned to the liver through the portal circulation. *CCK*, Cholecystokinin. *(From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 8-24.)*

TABLE 7-6. Digestion and Absorption of the Major Fuels

FUEL	ENZYMES USED IN DIGESTION	STRUCTURAL FORM ABSORBED	COMMENTS
Proteins	Pepsin in stomach Protease in pancreas	Amino acids and small peptides	Small peptides broken down into amino acids in enterocytes
Carbohydrates	Amylase in saliva Amylase in pancreas Disaccharidases in intestinal mucosa	Monosaccharides	
Fats	Lipase in saliva and stomach Lipase/colipase in pancreas	Free fatty acids	Bile acids/salts emulsify for digestion and form micelles to facilitate absorption Resynthesized to triglycerides and packed into chylomicrons by enterocytes

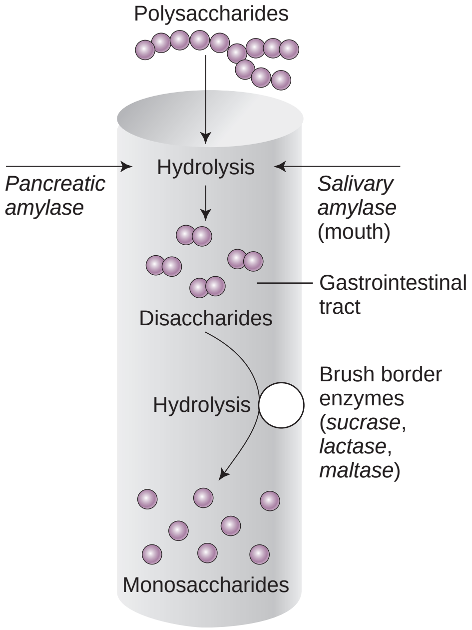
Carbohydrate absorption: requires breakdown to monosaccharides glucose, galactose, and fructose

Pancreatic amylase: primarily responsible for carbohydrate digestion

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.



7-21: Carbohydrate digestion.

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.**

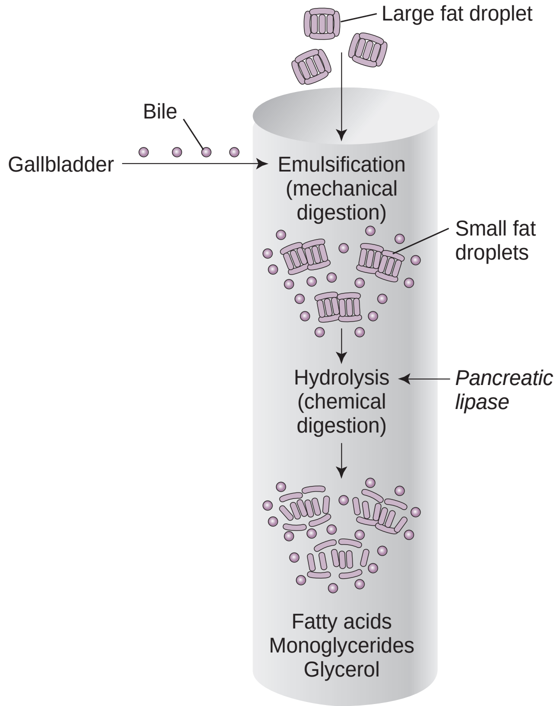
2. **Proteins** (see Table 7-6)
   - Protein digestion begins in the stomach because of the acidic pH and the presence of the enzyme pepsin, but most protein digestion occurs in the small intestine.
   - By neutralizing the acidic chyme, the HCO_3^--rich ductal secretions allow the pancreatic proteases 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.

Protein digestion: begins in stomach, but quantitatively important digestion occurs in small intestines

Peptides and amino acids are cotransported into enterocytes with Na^+.

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.

Triglyceride digestion: primarily occurs in small intestines



7-22: Lipid digestion and absorption.

Large lipid droplets → emulsification via bile and lecithin → small lipid globules → pancreatic lipase → free fatty acids and monoglycerides → bile salts form micelles → absorption

Triglyceride transport: occurs through chylomicrons, which drain from intestinal lymphatics to thoracic duct to the left subclavian vein

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.

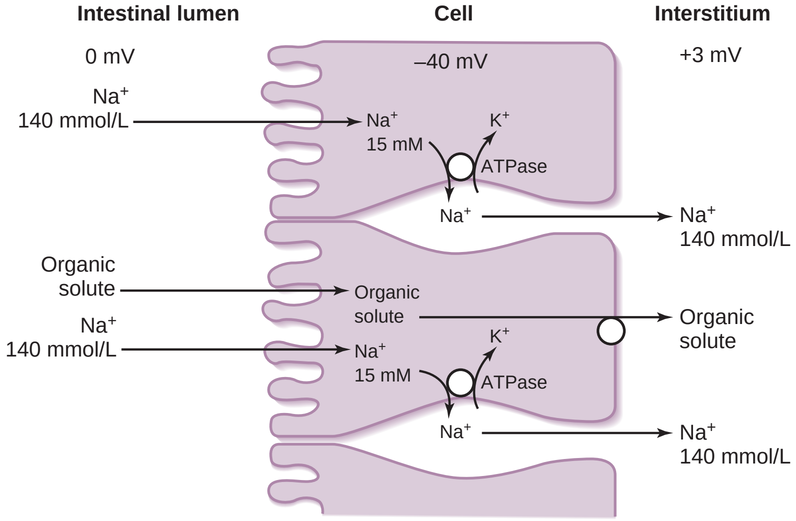
Pathology note: In **celiac sprue** (celiac disease), massive loss of intestinal surface area occurs because of a hypersensitivity reaction to the gliadin component of the protein gluten, found in grains such as wheat. This hypersensitivity reaction results in autoimmune destruction of intestinal villi, 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.**

Lumen-intracellular Na^+ gradient drives much of intestinal absorption, just as it does in the proximal nephron.

Cobalamin is absorbed in the distal ileum; diseases of distal ileum can impair its absorption.

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 B_{12} (cobalamin)**
  a. Vitamin B_{12} 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 B_{12} 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 B_{12}.

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).



7-23: Sodium absorption in the small intestine. The luminal concentration of sodium is much larger than the intracellular concentration because of the continual activity of the basolateral Na^+,K^+-ATPase pumps. Sodium entry can therefore be coupled to entry of a wide variety of organic solutes, including glucose, hexoses, dipeptides, amino acids, and water-soluble vitamins.

- **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.**

Iron: abundant in meats; absorbed in proximal small bowel, transported in blood bound to transferrin; stored intracellularly 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

Migrating myoelectric complex: clears out intestinal tract during interdigestive periods; hormone motilin plays important role

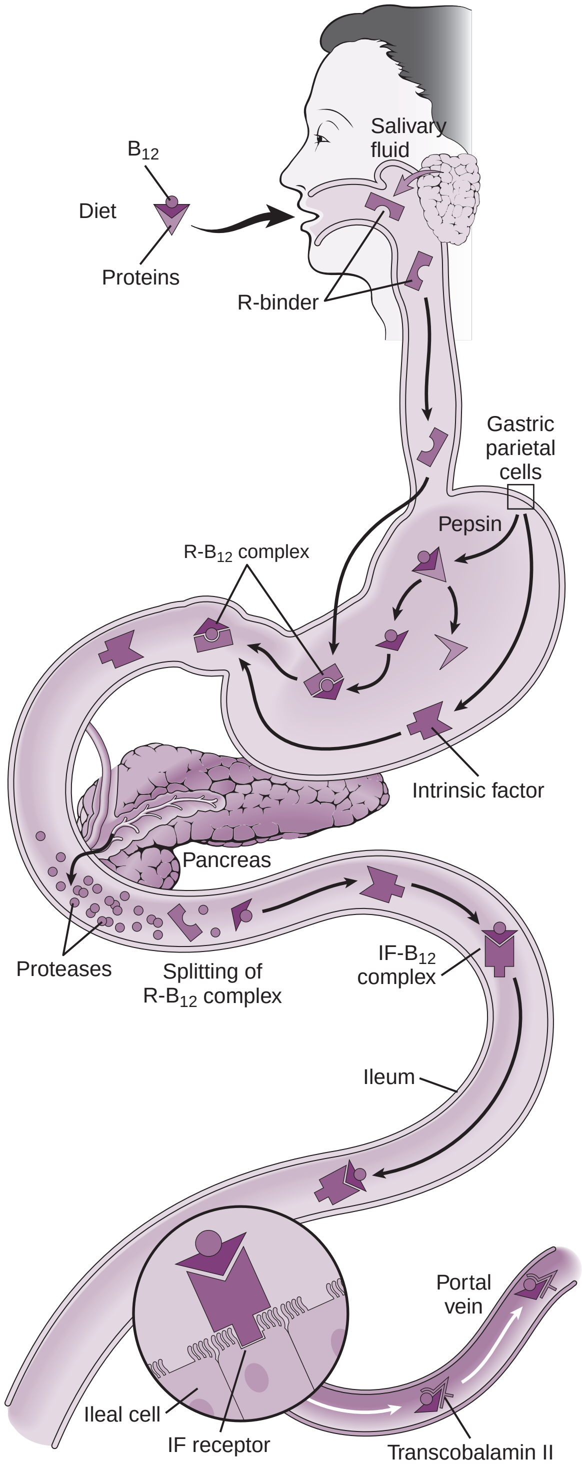
Pharmacology note: The antibiotic **erythromycin,** often referred to as "erythroterrible" because of its common side effects (e.g., nausea, diarrhea) is sometimes used specifically because of these side effects; for example, as a laxative in constipated adults. It is believed to produce these effects 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

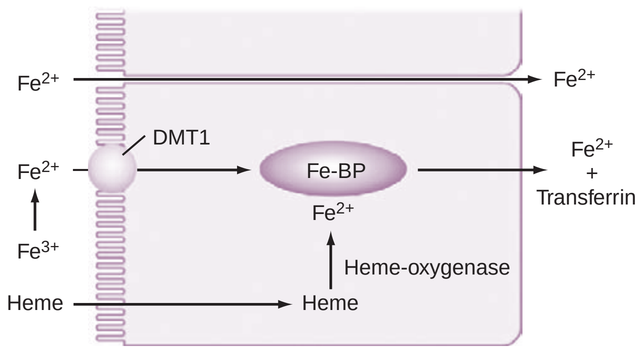
1. Gastric and/or duodenal distension after a meal stimulates various reflexes.
2. These reflexes are controlled entirely by the **enteric nervous system,** as shown by their continuation after **autonomic denervation.**

Intestinal reflexes: entirely contained within the enteric nervous system

7-24: Schematic of vitamin B_{12} absorption. *IF,* Intrinsic factor. *(From Kumar V, Abbas A, Fausto N, Aster J: Robbins and Cotran Pathologic Basis of Disease, 8th ed. Philadelphia, Saunders, 2010, Fig. 14-18.)*



7-25: Mechanism of iron absorption in the intestine. *Fe-BP,* Iron-bonding proteins. *(From Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 8th ed. Philadelphia, Saunders, 2006, Fig. 97-21.)*



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.

Gastrocolic reflex: distension of the stomach promotes a bowel movement

Gastroileal reflex: promotes passage of intestinal contents from the small intestine into the colon

Enterogastric reflex: entry of acidic chyme into 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.

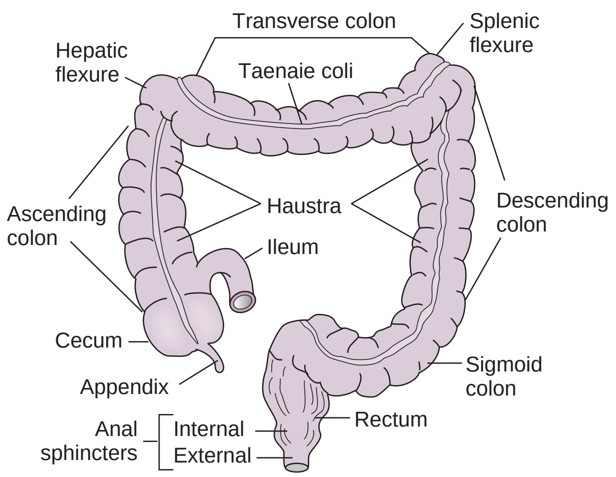
Functions of colon: salt and water reabsorption; elimination of feces

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.



7-26: Anatomy of the large intestine.

TABLE 7-7. Structural Comparison of Small and Large Intestines

	SMALL INTESTINE	LARGE INTESTINE
Plicae circularis	+	–
Villi	+	–
Microvilli	+	Fewer in number
Glycocalyx	+	+
Peyer patches	+ (Ileum)	–
Brunner glands	+ (Duodenum)	–
Outer longitudinal muscle	Continuous sheet	Arranged as taeniae coli

Chapter 8

Acid-Base Balance

I. Acid and Base

A. Overview

pH maintained in tight range to preserve protein function

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.

Tight control of pH: maintained by buffers, removal of CO_2 by lungs, excretion of nonvolatile acids by kidneys

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.

Metabolism of fats and carbohydrates to CO_2 produces an enormous daily acid load; most of this can be removed by the lungs.

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.

Metabolism of proteins to nonvolatile acids produces a modest daily acid load; most of this is excreted by the kidneys.

6. The primary buffer of the extracellular fluid (ECF) compartment is **bicarbonate,** which buffers the daily load of acid generated by metabolism.

Primary buffer of ECF: bicarbonate system

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.

Primary nonvolatile acids removed by kidneys: sulfate, phosphate

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.

Diagnosis of acid-base disorder: often inferred from electrolyte abnormalities alone if clinical story highly suggestive

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.

Acidemia: low plasma pH; acidosis: process in which excess acid is produced

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.

Alkalemia: high plasma pH; alkalosis: process in which excess base is produced

Normal pH does *not* mean an underlying acid-base disturbance is not present.

TABLE 8-1. Normal Concentrations of Cations and Anions in Plasma

CATIONS (mEq/L)	ANIONS (mEq/L)
Na^+ 140	Cl^- 103
K^+ 4	HCO_3^- 25
Ca^{2+} 5 (2.5 mmol/l)	Proteins 16
Mg^{2+} 2 (1 mmol/L)	Organic 4
H^+ 0.000040 (40 nmol/L)	Other inorganics 3

From Halperin M, Goldstein M: Fluid, Electrolyte, and Acid-Base Physiology, 2nd ed. Philadelphia, Saunders, 1994, Table 1-2.

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 (H_2CO_3) is an acid, whereas after it donates a hydrogen ion, it becomes bicarbonate (HCO_3^-), its (conjugate) base.
2. Assuming the reaction $HA \rightarrow H^+ + A^-$, the higher the concentration of a conjugate base (A^-) relative to its acidic form (HA), the higher will be the pH.
3. This relationship is demonstrated by the **Henderson-Hasselbalch equation,** shown below.

$$pH = pKa + \log[A^-]/[HA]$$

$$pH = pKa + \log[\text{base}]/[\text{acid}]$$

which can be rewritten as:

$$pH = pKa + \log[A^-]/[HA]$$

4. Note that the pKa equals the pH at which the acid is half dissociated; in other words, the pH at which [A] = [HA].
   - Buffering systems *typically* work best at a pH near their pKa.
5. In the plasma, the most important buffer is the **bicarbonate/carbon dioxide system.**
6. In this system, carbonic acid (H_2CO_3), a weak acid, rapidly dissociates into either CO_2 or HCO_3^-, as shown here:

$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

7. The bicarbonate buffer system is an effective buffering system *despite* the fact that the pKa 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.

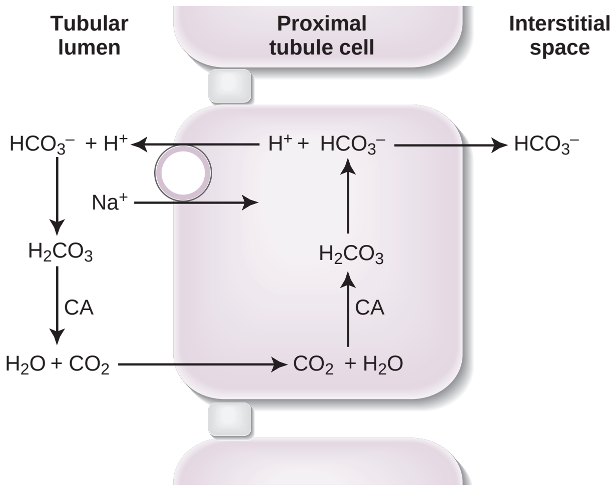
H_2CO_3: weak acid; HCO_3^-: its conjugate base

pKa: pH at which acid is half dissociated

HCO_3^-/CO_2 system most important buffer in the plasma

Buffering systems *typically* work best at a pH near their pKa; the bicarbonate system is an exception because of the ability of CO_2 and HCO_3^- to be rapidly removed by the lungs and kidneys, respectively.

Ammoniagenesis: process whereby HCO_3^- is produced and NH_4^+ is excreted in urine



8-1: Bicarbonate reclamation. *CA*, Carbonic anhydrase.

- The CO_2 and water diffuse across the tubular cell membrane, and inside the cell, the reverse reaction takes place.
  a. The CO_2 and water react to form carbonic acid, which then dissociates into H^+ ions and bicarbonate.
- The resulting bicarbonate is pumped out of the basolateral surface of the cell and returned to the plasma.
- Notice that there is no net acid secretion or generation because the hydrogen ions are continually recycled in this reclamation process.

Bicarbonate reclamation: no net acid secretion or generation (see Fig. 8-1)

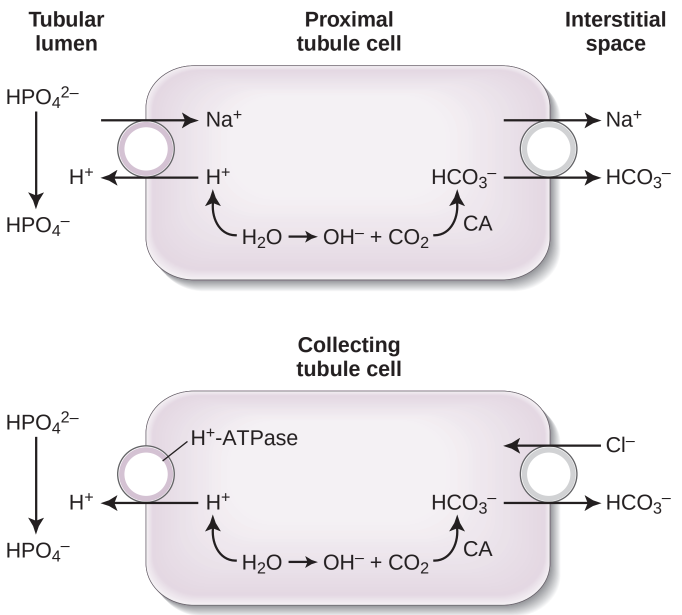
Pharmacology note: Because sodium reabsorption in the proximal tubule is indirectly coupled to bicarbonate reabsorption, carbonic anhydrase inhibitors such as acetazolamide exert a diuretic effect by blunting sodium reabsorption. However, this **diuretic** action is weak because of the capacity of more 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^-.

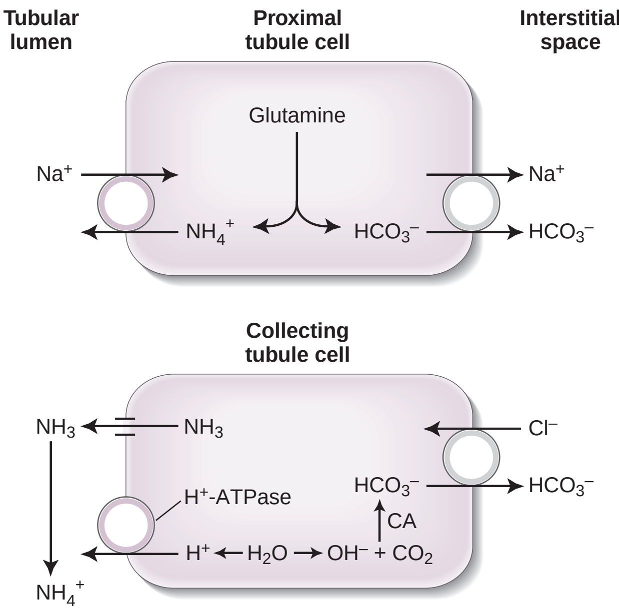
   a. **Titratable acidity**
      - Filtered phosphate (HPO_4^{-2}) is the major contributor to titratable acidity (Fig. 8-2); less abundant acids with less favorable pKa values (e.g., creatinine and uric acid) also contribute.
      - The amount of titratable acidity present in the urine can be determined 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.

Urinary buffers: maximize acid excretory capacity of the kidneys

Filtered phosphate (HPO_4^{-2}): major contributor to titratable acidity



8-2: Titratable acidity.



8-3: Ammoniagenesis.

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.

Deamination of glutamine: produces two NH_4^+ molecules and two HCO_3^- molecules

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.

HCO_3^- reclamation: normally approximates 100%

As systemic pH falls → ↑ H^+ excretion by kidneys

As systemic pH increases → ↓ H^+ excretion by kidneys

Clinical note: Acidosis can develop because of bicarbonate depletion **(metabolic acidosis)** or carbon dioxide accumulation **(respiratory acidosis),** or both. In either situation, the kidneys attempt to compensate by increasing H^+ excretion. Similarly, **alkalosis** can occur because of an increase in bicarbonate or a decrease in CO_2. In this situation, the kidneys decrease H^+ excretion in an effort to bring the pH back toward the normal range (rarely does it bring the pH into the normal range, which implies complete compensation).

D. Metabolic acidosis

1. Overview

Causes of metabolic acidosis: excess acid production, impaired renal acid excretion

Metabolic acidosis: low pH, low $[HCO_3^-]$, low P_{CO_2}

Metabolic acidoses: classified as anion gap or normal anion gap

- Caused by excess acid production or impaired renal acid excretion
- Characterized by low pH, low HCO_3^- (<22 mEq/L) and low P_{CO_2} (from respiratory compensation)
  a. Note that a low 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. See Box 8-1 for a clinical example of normal anion gap metabolic acidosis.
- 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.

Anion gap acidoses: typically clinically serious conditions requiring emergent therapy

Normal gap acidoses: renal and extrarenal etiologies

Renal causes of normal anion gap acidosis: early acute renal failure, renal tubular acidoses

Extrarenal causes of normal anion gap acidosis: diarrhea, dilutional, ureteral-colonic fistulas

- 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 HCO_3^- and Cl^-; the anion gap can be calculated as shown:

$$AG = Na^+ - (Cl^- + HCO_3^-)$$

  which can be rewritten as

$$AG = \text{unmeasured anions} - \text{unmeasured cations}$$

Anion gap: measured by subtracting measured anions from measured cations

$AG = Na^+ - (Cl^- + HCO_3)$; normal anion gap is ~12

Anion gap acidosis: results from consumption of HCO_3^- by buffering H^+ ions and production of unmeasured anions

  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 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 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.)

$$UAG = (U_{NA^+} + U_{K^+} - U_{Cl^-})$$

$$UAG = \text{unmeasured anions} - \text{unmeasured cations}$$

UAG: can help differentiate renal and extrarenal causes of normal AG metabolic acidosis

  b. Note that the primary unmeasured urinary anion is 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.

e. 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.

f. 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_{CO_2} is shown.

$$\text{Expected } P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$$

   - Typically the P_{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).

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: $P_{CO_2} = 1.5 \times [HCO_3^-] + 8 +\pm 2$

Respiratory compensation for metabolic acidosis: P_{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

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_{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_{CO_2} from 40 to approximately 32 (expected $P_{CO_2} = 1.5 \times [16] + 8 \pm 2$). 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

TYPE	PATHOPHYSIOLOGY	URINE pH	DEGREE OF ACIDOSIS	SERUM K^+	EXCRETION OF HCO_3^- (AFTER HCO_3^- LOAD) (%)
Distal RTA (Type I)	Inability to secrete H^+ in distal tubule	>5.3	Severe (serum HCO_3^- often <10)	Decreased	<3
Proximal RTA (Type II)	Inhibition of carbonic anhydrase (e.g., acetazolamide) and/or HCO_3^- reclamation in proximal tubule	<5.3	Modest (serum HCO_3^- 12-16)	Decreased	>15
Hyporeninemic hyperaldosteronism (hyperkalemic) RTA (Type 1V)	Destruction of juxtaglomerular apparatus causes hyporeninemic hypoaldosteronism	<5.3	Mild (serum HCO_3^- 14-20)	Increased	<3

BOX 8-2 SAMPLE CASE: ACUTE RENAL FAILURE

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), HCO_3^- 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.

Lactic acidosis: seen in shock, sepsis, prolonged seizures, prolonged strenuous exercise

DKA: typically occurs in patients with type 1 diabetes, often as their initial presentation

DKA: characterized by hyperglycemia, volume depletion, ketosis, anion gap acidosis

DKA: caused by an absolute deficiency in insulin

Pathogenesis of DKA: runaway lipolysis supplies ketogenic precursors to the liver, resulting in ketogenesis and acidosis

Hyperglycemia in DKA: causes dehydration through osmotic diuresis; reduced GFR further impairs acid excretory ability of kidneys

Hyperkalemia: may be present despite total body potassium wasting

Causes of hyperkalemia in DKA: solvent-drag effect, buffering role, insulin deficiency

Anion gap acidosis + respiratory alkalosis ± tinnitus → think aspirin intoxication

Reye syndrome in children: ingestion of aspirin in setting of viral illness → liver failure, encephalopathy, hypoglycemia

Aspirin toxicity: causes respiratory alkalosis and anion gap metabolic acidosis

Anion gap acidosis + blurry vision → think methanol ingestion

Ethanol and fomepizole: competitively inhibit alcohol dehydrogenase → ↓ formic acid production → minimize toxic effects

b. Tissue hypoperfusion can occur with sepsis, shock, hypovolemic states, prolonged seizure activity, 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 (CH_3OH) 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.

BOX 8-3 SAMPLE CASE: DIABETIC KETOACIDOSIS

A 15-year-old boy misses school for 2 days because of nausea, vomiting, and fatigue. He then begins to complain of abdominal pain, and his mother notices that he is breathing deeply and rapidly. She takes him immediately to the emergency department, where the workup reveals the following:

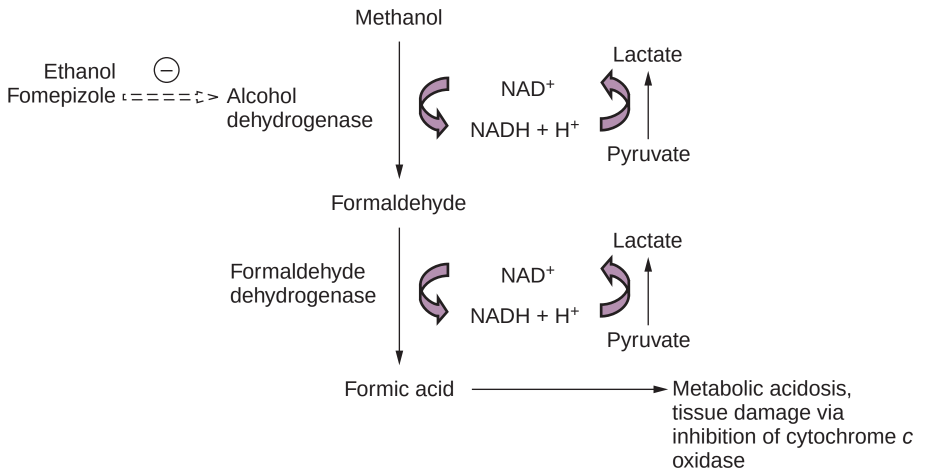
- Vitals: HR 125; RR 24; BP 125/75
- Arterial blood gases: pH 7.20; P_{CO_2} 20; HCO_3^- 8; P_{O_2} 160 (on supplemental O_2)
- Labs: K^+ 6.2 (normal, 3.0-4.5); glucose 422 (normal, 80-110); Na^+ 128 (normal, 135-145); anion gap 28; plasma β-hydroxybutyric acid, markedly elevated

Case Discussion

This is a classic presentation for diabetic ketoacidosis. The patient is exhibiting Kussmaul respirations, a deep and rapid breathing pattern, in an attempt to "blow off" CO_2 to compensate for the underlying metabolic acidosis. His tachycardia suggests that he is volume depleted. His hyperkalemia is expected in DKA, but one should realize that he will need potassium soon because his whole body potassium stores are low. His elevated plasma β-hydroxybutyric acid suggests ongoing hepatic ketogenesis resulting from insulin deficiency. His sodium concentration is low because of the hyperglycemia, which draws water out of cells and dilutes the extracellular sodium; this phenomenon is termed *pseudohyponatremia.* In terms of the above arterial blood gas measurement, this reveals a metabolic acidosis due to the low pH and low HCO_3^-. Expected respiratory compensation for a metabolic acidosis can be calculated by using
Winter's formula:

$$\text{Expected } P_{CO_2} = 1.5 \times HCO_3^- + 8 \pm 2$$

In this case, the expected P_{CO_2} (20 mm Hg) equals the actual P_{CO_2} (20 mm Hg), indicating appropriate respiratory compensation for an anion gap metabolic acidosis. We know that this is a primary anion gap metabolic acidosis without a superimposed normal gap acidosis or metabolic alkalosis because the "delta-delta" ($\Delta AG/\Delta HCO_3$) equals 1. If the delta-delta were less than 1, we would have a superimposed normal gap metabolic acidosis, perhaps from the diarrhea. If the delta-delta were greater than 2, we would have a superimposed metabolic alkalosis, perhaps from the vomiting. However, a full discussion of the concept of the delta-delta is beyond the level of understanding necessary for the USMLE step 1.



8-4: Metabolism of methanol. *(From Brenner BM: Brenner and Rector's The Kidney, 8th ed. Philadelphia, Saunders, 2008, Fig. 62-2.)*

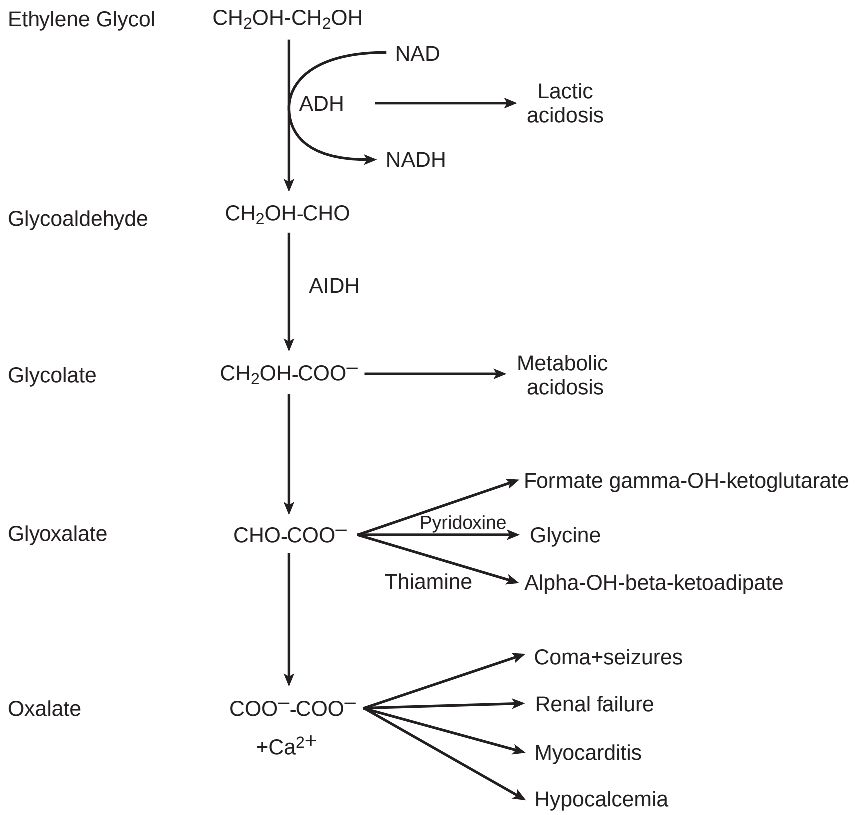
- **Ethylene glycol toxicity**
  a. Ethylene glycol is a sweet-tasting organic compound frequently used in automotive antifreeze.
  b. Children and animals may ingest large amounts of it owing to its sweet taste if they are exposed to antifreeze.
  c. As with methanol, the toxicity from ethylene glycol 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.

Ethylene glycol: sweet-tasting substance present in antifreeze

Anion gap acidosis + urine with oxalate crystals and/or Woods lamp fluorescence → think ethylene glycol ingestion

4. Causes of normal anion gap metabolic acidosis
   - **Diarrhea**
     a. Most common cause of normal anion gap metabolic acidosis

Diarrhea: most common cause of normal anion gap acidosis



8-5: Metabolism of ethylene glycol. *(From Shannon MW, Borron SW, Burns MJ: Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose, 4th ed. Philadelphia, Saunders, 2007, Fig. 32B-1.)*

b. Diarrhea increases intestinal transit time and prevents HCO_3^-/Cl^- exchange, resulting in low HCO_3^- with retention of Cl^-, and causing a hyperchloremic metabolic acidosis.

c. The anion gap is not increased because the fall in HCO_3^- is counterbalanced by a rise in 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.

Chronic diarrhea: may cause a metabolic alkalosis because of volume contraction

- **Renal tubular acidosis**

a. An acidosis resulting from impaired renal excretion of 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 HCO_3^- (>28 mEq/L), high pH, and high PCO_2 as a result of respiratory compensation. See Box 8-4 for a clinical example of metabolic alkalosis.
- Recall that a high 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, diuretics) but can also occur in volume-overloaded states caused by excess renin and/or aldosterone.
- It can also occur with transcellular shifts (e.g., in hypokalemia, K^+ exits the cells in exchange for Na^+ and H^+ ions) and by the administration of 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.

Metabolic alkalosis: high HCO_3^-, high pH, and high PCO_2

Metabolic alkalosis: think volume-depleted states (e.g., vomiting) or hyperreninemic and/or hyperaldosteronemic states

Respiratory compensation for metabolic alkalosis: hypoventilatory capacity limited owing to resulting hypoxemia

2. Specific causes of metabolic alkalosis

- **Vomiting**

a. Characterized by high HCO_3^-, low Cl^-, high 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 increase in pH.
d. Loss of Cl^- ions will additionally inhibit HCO_3^- secretion in the distal nephron because of decreased Cl^-/HCO_3^- exchange by intercalated cells in an attempt to maintain electroneutrality, further increasing plasma HCO_3^- levels.
e. Vomiting will also cause a volume-contracted state, and because Na^+ and HCO_3^- 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.

Vomiting: powerfully stimulates metabolic alkalosis through direct loss of H^+, loss of Cl^-, and volume depletion

- **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 *(real)* 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^+.

Mineralocorticoid excess: think volume expansion, hypertension, hypokalemia, hypernatremia, metabolic alkalosis

Excess mineralocorticoid-like states: Conn syndrome, Cushing syndrome, Bartter syndrome, Gitelman syndrome, Liddle disease, 11β-(OH)-steroid dehydrogenase deficiency, licorice ingestion

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
- P_{CO_2} 51 mm Hg
- HCO_3^- 40 mEq/L
- P_{O_2} 100 mm Hg

Case Discussion

The above patient likely has a *contraction alkalosis* caused by furosemide, a potent loop diuretic. His HCO_3^- is increased 16 mEq/L above normal. Given that the expected respiratory compensation for a metabolic alkalosis is a rise in P_{CO_2} of 0.7 mm Hg for every 1 mEq/L rise in HCO_3^-, we would expect a rise in P_{CO_2} 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

CONDITION	PATHOPHYSIOLOGY
Conn syndrome	The action of aldosterone in the distal tubule results in an increase in H^+ (and K^+) secretion in exchange for Na^+
Cushing disease	Levels of cortisol exert mineralocorticoid effects on the kidney
Bartter syndrome	Defective $Na^+/K^+/Cl^-$ transporter in the loop of Henle (mimics the effect of a loop diuretic)
Gitelman syndrome	Defective Na^+/Cl^- transporter (mimics the effect of a thiazide diuretic)
Liddle disease	A defect in the Na^+ channel in the distal tubule that is normally stimulated by aldosterone results in the channel being permanently activated (mimics mineralocorticoid excess; in this setting spironolactone will not work so one must use triamterene or amiloride instead)
11β-(OH)-steroid dehydrogenase deficiency	Defect of the enzyme that normally breaks down cortisol within aldosterone-responsive cells causes cortisol to build up and activate the mineralocorticoid receptor
Licorice ingestion	Contains a substance that inhibits 11β-OH-SD

Respiratory compensation for metabolic alkalosis: hypoventilation → ↑ P_{CO_2}

Expected rise in P_{CO_2}: 0.7 mm Hg for every 1 mEq/L rise in $[HCO_3^-]$

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**

Respiratory acidosis: almost always caused by alveolar hypoventilation

   - 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.

Respiratory acidosis: may cause CO_2 narcosis, ↑ ICP, cardiac dysrhythmias, impaired cardiac contractility, hypoxemia

Hypoventilation as a compensatory response to metabolic alkalosis will *not* cause hypoxemia.

Therapy for respiratory acidosis: may involve mechanical intubation

   - 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.

$$H_2CO_3 + \text{buffer}^- \rightarrow HCO_3^- + H - \text{buffer}$$

     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}.

Acute compensation for respiratory acidosis: ↑ in $[HCO_3^-]$ by 1 mEq/L for every 10 mm Hg rise in P_{CO_2}

Renal compensation: maximally effective within 3 to 5 days

Chronic compensation: ↑ in $[HCO_3^-]$ by 3.5 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

Respiratory alkalosis: always caused by alveolar hyperventilation

Respiratory alkalosis: occurs in response to hypoxemia and/or central causes (see Table 8-5)

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

CAUSES OF HYPERCAPNIA	EXAMPLE
Lung disease	Chronic bronchitis, bronchiectasis
Central hypoventilation	Sedatives, central nervous system trauma, pickwickian syndrome
Neuromuscular disorders	Myasthenia gravis, Guillain-Barré, amyotrophic lateral sclerosis, muscular dystrophy, poliomyelitis
Upper airway obstruction	Acute airway obstruction, laryngospasm, obstructive sleep apnea
Thoracic cage abnormalities	Pneumothorax, flail chest, scoliosis
O_2 administration	In chronic bronchitis patient with chronic hypercapnia

TABLE 8-5. Compensation for Acute and Chronic Respiratory Acidosis

CONDITION	PRIMARY CHANGE	EXPECTED COMPENSATION
Acute respiratory acidosis	Increased P_{CO_2}	Increased $HCO_3^- = 0.1 \times \Delta P_{CO_2}$
Chronic respiratory acidosis	Increased P_{CO_2}	Increased $HCO_3^- = 0.35 \times \Delta P_{CO_2}$

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

Mechanical ventilation
Pulmonary embolism
High-altitude respiration
Pneumonia
Asthma
Drugs (e.g., aspirin)
Fever
Pregnancy
Pain
Anxiety
Central nervous system disorders (e.g., stroke, subarachnoid hemorrhage)

TABLE 8-7. Compensation for Respiratory Alkalosis

CONDITION	PRIMARY CHANGE	EXPECTED COMPENSATION
Acute respiratory alkalosis	Decreased P_{CO_2}	Decreased $HCO_3^- = 0.2 \times \Delta P_{CO_2}$
Chronic respiratory alkalosis	Decreased P_{CO_2}	Decreased $HCO_3^- = 0.4 \times \Delta P_{CO_2}$

- 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.

Respiratory alkalosis: P_{CO_2}, high pH, and low HCO_3^-

Kidneys better able to compensate for respiratory alkalosis than for respiratory acidosis

2. **Specific causes of respiratory alkalosis** (Table 8-6)
3. **Metabolic compensation** (Table 8-7)
   - Acute compensation
     a. Initial response involves buffering by transcellular 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}.

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}

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:

- pH 7.48
- P_{CO_2} 20 mm Hg
- 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 HCO_3^- would be 0.2 times the change in P_{CO_2}. Because P_{CO_2} has dropped by 20 mm Hg, we would expect a drop in 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 HCO_3^- urinary excretion and decrease urinary ammonium (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 [HCO_3^-] by approximately 4 mEq/L for every 10 mm Hg decrease in the P_{CO_2}.

Chronic compensation for respiratory alkalosis: ↓ [HCO_3^-] by 4 mEq/L for every 10 mm Hg ↓ in P_{CO_2}

Chapter 9

Sodium and Water Balance, Fluid Compartments

I. Body Fluids

A. Distribution of body fluids

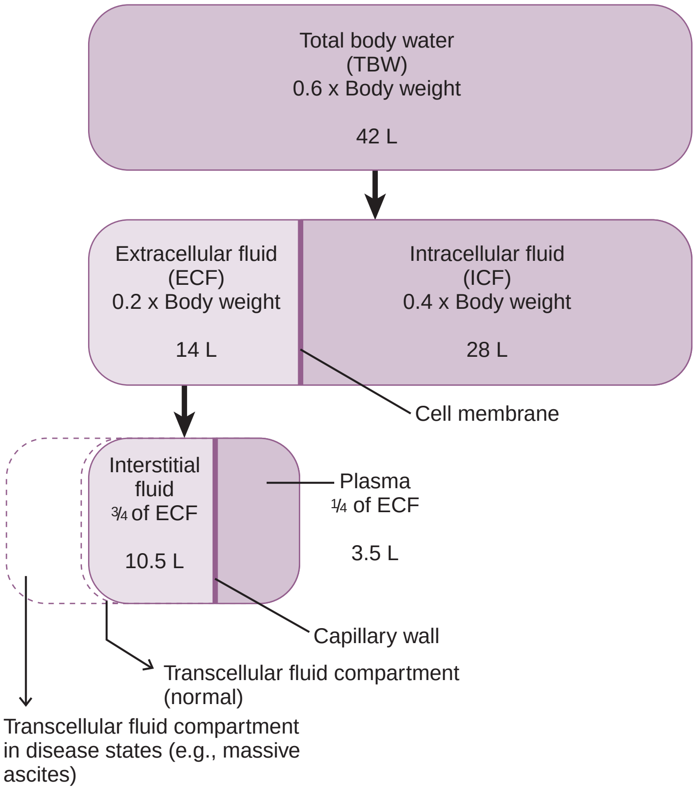
1. Fluid compartments (Fig. 9-1)
   - Approximately 50% to 60% of total body weight consists of water (approximately 50% in women, 60% in men, and 70% in infants).
   - Roughly two thirds of total body water (TBW) is located within cells (intracellular fluid, ICF), with the remainder located in the extracellular 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.

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



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.)*

- 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.

2. **Composition of fluid compartments**
   - Intracellular fluid

ICF rich in protein, potassium, calcium, and phosphate

K^+: major ICF cation

Intracellular phosphate: important in ATP synthesis and intracellular buffering

ECF rich in sodium, chloride; low in potassium and phosphate

     a. Relative to ECF, the ICF has large amounts of protein, potassium, calcium, and phosphate and low levels of sodium and chloride.
     b. Approximately 98% of total body potassium is located within cells; this potassium can play an important role in buffering of a metabolic acidosis.
     c. Most total body phosphate is also located within cells; this phosphate is important in adenosine triphosphate (ATP) generation as well as in intracellular buffering.
     d. The large amounts of proteins are necessary for cellular function and also play an important buffering and osmotic role.
     e. The low $[Na^+]$ and $[Cl^-]$ are due to activity of the Na^+,K^+-ATPase pump, which maintains the electrochemical gradient across the cell membrane.
   - Extracellular fluid

IF protein poor; excess fluid and proteins returned to vascular compartment through lymphatics

Dysfunction or obstruction of lymphatic drainage may result in interstitial edema.

     a. 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.
     b. **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).

Indicator substance: diffusion-restricted to specific fluid compartment

Deuterium and tritiated water: measure TBW volume

Inulin and mannitol: measure ECF volume

Radiolabeled albumin: measure plasma volume

B. 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}I-albumin) is diffusion restricted to the vascular compartment; it can therefore be used to measure plasma volume.

Volume: regulated through *sodium* balance

Osmolarity and sodium concentration: regulated through *water balance*

II. Regulation of Sodium and Water Balance

A. 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.

Kidneys regulate ECF volume by adjusting Na^+ excretion.

ECV osmolarity and Na^+ concentration regulated through water balance via ADH secretion

Hyponatremia (in presence of normal ECV) inhibits ADH secretion.

Hypernatremia stimulates ADH secretion.

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 osmolarity. 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 ECF 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-aldosterone-angiotensin system is possibly the most important of these mechanisms.

ECV: portion of intravascular compartment perfusing organs

ECV: varies with ECF volume and total body sodium

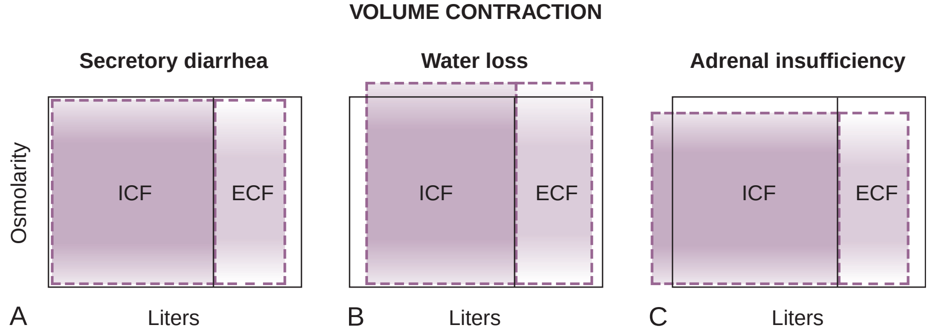
Pressure and volume detectors monitor ECF volume.

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 ECF volume).

ECV: sensed by stretch receptors in carotid sinus, aortic arch, and glomerular afferent artery

Sympathetic outflow with ↓ ECV: multiple actions to ↑ plasma volume, retain sodium, and ↑ arterial perfusion pressure



9-2: Volume contracted states. **A,** Secretory diarrhea causing isosmotic volume contraction. **B,** Water loss causing hyperosmotic volume contraction. **C,** Adrenal insufficiency causing hyposmotic volume contraction. *ECF,* Extracellular fluid; *ICF,* intracellular fluid. *(From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 6-5.)*

- 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.

Diarrhea: isosmotic volume contraction

- 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.

Water deprivation: hyperosmotic volume contraction

- 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.

Adrenal insufficiency: hyposmotic volume contraction

- **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.

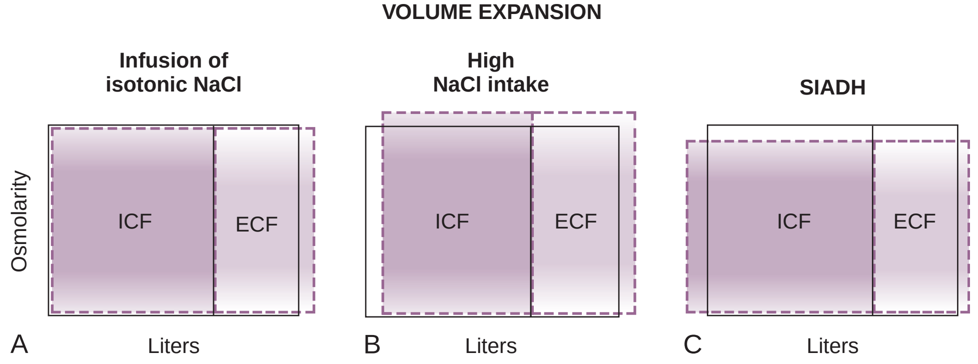
Response to ↑ ECV: ↑ baroreceptor stretch → ↓ sympathetic outflow → ↓ CO and blood pressure

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*).

Saline infusion: isosmotic volume expansion

- High NaCl intake
  (1) Increased NaCl intake, in the absence of excess water, increases ECF volume and osmolarity (*hyperosmotic volume expansion*).



9-3: Volume expanded states. **A,** Isotonic NaCl infusion causing isosmotic volume expansion. **B,** High NaCl intake causing hyperosmotic volume expansion. **C,** SIADH causing hyposmotic volume expansion. *ECF,* Extracellular fluid; *ICF,* intracellular fluid; *SIADH,* syndrome of inappropriate antidiuretic hormone. *(From Costanzo L: Physiology, 4th ed. Philadelphia, Saunders, 2010, Fig. 6-5.)*

(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.

↑ NaCl intake: hyperosmolar volume expansion

- 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.

SIADH: hyposmotic volume expansion

This page intentionally left blank

Common Laboratory Values

TEST	CONVENTIONAL UNITS	SI UNITS
Blood, Plasma, Serum		
Alanine aminotransferase (ALT, GPT at 30°C)	8–20 U/L	8–20 U/L
Amylase, serum	25–125 U/L	25–125 U/L
Aspartate aminotransferase (AST, GOT at 30°C)	8–20 U/L	8–20 U/L
Bilirubin, serum (adult): total; direct	0.1–1.0 mg/dL; 0.0–0.3 mg/dL	2–17 µmol/L; 0–5 µmol/L
Calcium, serum (Ca^{2+})	8.4–10.2 mg/dL	2.1–2.8 mmol/L
Cholesterol, serum	Rec: <200 mg/dL	<5.2 mmol/L
Cortisol, serum	8:00 AM: 6–23 µg/dL; 4:00 PM: 3–15 µg/dL	170–630 nmol/L; 80–410 nmol/L
	8:00 PM: ≤50% of 8:00 AM	Fraction of 8:00 AM: ≤0.50
Creatine kinase, serum	Male: 25–90 U/L	25–90 U/L
	Female: 10–70 U/L	10–70 U/L
Creatinine, serum	0.6–1.2 mg/dL	53–106 µmol/L
Electrolytes, serum		
Sodium (Na^{+})	136–145 mEq/L	135–145 mmol/L
Chloride (Cl^{-})	95–105 mEq/L	95–105 mmol/L
Potassium (K^{+})	3.5–5.0 mEq/L	3.5–5.0 mmol/L
Bicarbonate (HCO_3^{-})	22–28 mEq/L	22–28 mmol/L
Magnesium (Mg^{2+})	1.5–2.0 mEq/L	1.5–2.0 mmol/L
Estriol, total, serum (in pregnancy)		
24–28 wk; 32–36 wk	30–170 ng/mL; 60–280 ng/mL	104–590 nmol/L; 208–970 nmol/L
28–32 wk; 36–40 wk	40–220 ng/mL; 80–350 ng/mL	140–760 nmol/L; 280–1210 nmol/L
Ferritin, serum	Male: 15–200 ng/mL	15–200 µg/L
	Female: 12–150 ng/mL	12–150 µg/L
Follicle-stimulating hormone, serum/plasma (FSH)	Male: 4–25 mIU/mL	4–25 U/L
	Female:	
	Premenopause, 4–30 mIU/mL	4–30 U/L
	Midcycle peak, 10–90 mIU/mL	10–90 U/L
	Postmenopause, 40–250 mIU/mL	40–250 U/L
Gases, arterial blood (room air)		
pH	7.35–7.45	$[H^{+}]$ 36–44 nmol/L
P_{CO_2}	33–45 mm Hg	4.4–5.9 kPa
P_{O_2}	75–105 mm Hg	10.0–14.0 kPa
Glucose, serum	Fasting: 70–110 mg/dL	3.8–6.1 mmol/L
	2 hr postprandial: <120 mg/dL	<6.6 mmol/L
Growth hormone–arginine stimulation	Fasting: <5 ng/mL	<5 µg/L
	Provocative stimuli: >7 ng/mL	>7 µg/L
Immunoglobulins, serum		
IgA	76–390 mg/dL	0.76–3.90 g/L
IgE	0–380 IU/mL	0–380 kIU/L

Continued

TEST	CONVENTIONAL UNITS	SI UNITS
IgG	650–1500 mg/dL	6.5–15 g/L
IgM	40–345 mg/dL	0.4–3.45 g/L
Iron	50–170 µg/dL	9–30 µmol/L
Lactate dehydrogenase, serum	45–90 U/L	45–90 U/L
Luteinizing hormone, serum/plasma (LH)	Male: 6–23 mIU/mL	6–23 U/L
	Female:	
	Follicular phase, 5–30 mIU/mL	5–30 U/L
	Midcycle, 75–150 mIU/mL	75–150 U/L
	Postmenopause, 30–200 mIU/mL	30–200 U/L
Osmolality, serum	275–295 mOsm/kg	275–295 mOsm/kg
Parathyroid hormone, serum, N-terminal	230–630 pg/mL	230–630 ng/L
Phosphatase (alkaline), serum (p-NPP at 30°C)	20–70 U/L	20–70 U/L
Phosphorus (inorganic), serum	3.0–4.5 mg/dL	1.0–1.5 mmol/L
Prolactin, serum (hPRL)	<20 ng/mL	<20 µg/L
Proteins, serum		
Total (recumbent)	6.0–8.0 g/dL	60–80 g/L
Albumin	3.5–5.5 g/dL	35–55 g/L
Globulin	2.3–3.5 g/dL	23–35 g/L
Thyroid-stimulating hormone, serum or plasma (TSH)	0.5–5.0 µU/mL	0.5–5.0 mU/L
Thyroidal iodine (^{123}I) uptake	8–30% of administered dose/24 hr	0.08–0.30/24 hr
Thyroxine (T_4), serum	4.5–12 µg/dL	58–154 nmol/L
Triglycerides, serum	35–160 mg/dL	0.4–1.81 mmol/L
Triiodothyronine (T_3), serum (RIA)	115–190 ng/dL	1.8–2.9 nmol/L
Triiodothyronine (T_3) resin uptake	25–38%	0.25–0.38
Urea nitrogen, serum (BUN)	7–18 mg/dL	1.2–3.0 mmol urea/L
Uric acid, serum	3.0–8.2 mg/dL	0.18–0.48 mmol/L
Cerebrospinal fluid		
Cell count	0–5 cells/mm^3	0–5 $\times 10^6$/L
Chloride	118–132 mEq/L	118–132 mmol/L
Gamma globulin	3–12% total proteins	0.03–0.12
Glucose	50–75 mg/dL	2.8–4.2 mmol/L
Pressure	70–180 mm H_2O	70–180 mm H_2O
Proteins, total	<40 mg/dL	<0.40 g/L
Hematology		
Bleeding time (template)	2–7 min	2–7 min
Erythrocyte count	Male: 4.3–5.9 million/mm^3	4.3–5.9 $\times 10^{12}$/L
	Female: 3.5–5.5 million/mm^3	3.5–5.5 $\times 10^{12}$/L
Erythrocyte sedimentation rate (Westergren)	Male: 0–15 mm/hr	0–15 mm/hr
	Female: 0–20 mm/hr	0–20 mm/hr
Hematocrit (Hct)	Male: 40–54%	0.40–0.54
	Female: 37–47%	0.37–0.47
Hemoglobin A_{IC}	≤6%	≤0.06%
Hemoglobin, blood (Hb)	Male: 13.5–17.5 g/dL	2.09–2.71 mmol/L
	Female: 12.0–16.0 g/dL	1.86–2.48 mmol/L
Hemoglobin, plasma	1–4 mg/dL	0.16–0.62 mmol/L
Leukocyte count and differential		
Leukocyte count	4500–11,000/mm^3	4.5–11.0 $\times 10^9$/L
Segmented neutrophils	54–62%	0.54–0.62
Bands	3–5%	0.03–0.05
Eosinophils	1–3%	0.01–0.03
Basophils	0–0.75%	0–0.0075
Lymphocytes	25–33%	0.25–0.33
Monocytes	3–7%	0.03–0.07
Mean corpuscular hemoglobin (MCH)	25.4–34.6 pg/cell	0.39–0.54 fmol/cell

TEST	CONVENTIONAL UNITS	SI UNITS
Mean corpuscular hemoglobin concentration (MCHC)	31–37% Hb/cell	4.81–5.74 mmol Hb/L
Mean corpuscular volume (MCV)	80–100 μm^3	80–100 fl
Partial thromboplastin time (activated) (aPTT)	25–40 sec	25–40 sec
Platelet count	150,000–400,000/mm^3	150–400 $\times 10^9$/L
Prothrombin time (PT)	12–14 sec	12–14 sec
Reticulocyte count	0.5–1.5% of red cells	0.005–0.015
Thrombin time	$<$2 sec deviation from control	$<$2 sec deviation from control
Volume		
Plasma	Male: 25–43 mL/kg	0.025–0.043 L/kg
	Female: 28–45 mL/kg	0.028–0.045 L/kg
Red cell	Male: 20–36 mL/kg	0.020–0.036 L/kg
	Female: 19–31 mL/kg	0.019–0.031 L/kg
Sweat		
Chloride	0–35 mmol/L	0–35 mmol/L
Urine		
Calcium	100–300 mg/24 hr	2.5–7.5 mmol/24 hr
Creatinine clearance	Male: 97–137 mL/min	
	Female: 88–128 mL/min	
Estriol, total (in pregnancy)		
30 wk	6–18 mg/24 hr	21–62 µmol/24 hr
35 wk	9–28 mg/24 hr	31–97 µmol/24 hr
40 wk	13–42 mg/24 hr	45–146 µmol/24 hr
17-Hydroxycorticosteroids	Male: 3.0–9.0 mg/24 hr	8.2–25.0 µmol/24 hr
	Female: 2.0–8.0 mg/24 hr	5.5–22.0 µmol/24 hr
17-Ketosteroids, total	Male: 8–22 mg/24 hr	28–76 µmol/24 hr
	Female: 6–15 mg/24 hr	21–52 µmol/24 hr
Osmolality	50–1400 mOsm/kg	
Oxalate	8–40 µg/mL	90–445 µmol/L
Proteins, total	$<$150 mg/24 hr	$<$0.15 g/24 hr

This page intentionally left blank

INDEX

Note: Page numbers followed by *f* indicate figure(s); those followed by *t* indicate table(s).

A

A band, 20
A-a gradient, 159
Abdominal trauma, 220
Abnormal gait, 215
Absolute refractory period, 13, 13*f*
Absorption (digestive)
  of carbohydrates, 222, 222*t*
  of fats, 222*t*, 223, 224
  process of, 210
  of proteins, 222*t*, 223
Acalculous cholecystitis, 221
Accessory oculomotor nucleus, 50
Accommodation reflex, 50, 52, 52*f*
Acetylcholine (ACh)
  autonomic nervous system and, 30, 33*f*
  function of, 15
  parasympathetic innervation of the heart and, 123
  parietal cell activity and, 214
Acetylcholine receptor, 33*t*
Acetylsalicylic toxicity, 234
Achalasia, 210, 213, 213*f*
Achlorhydria, 217
Acid, 228
Acid-base balance and kidneys, 229
Acid-base disorder, 228
Acidemia, 228
Acidic pH of lysosomes, 3
Acidosis
  causes of, 232
  defined, 228
  DKA and, 94–95
  hyperventilation and, 165
  ionized calcium and, 98
  Kussmaul respiration and, 167
  metabolic
    overview of, 232
    in renal failure, 231
    treatment of, 230
Acinar cells, 220
Acinar secretion, 220
Acne and testosterone, 84
Acoustic neuroma, 54
Acromegaly, 89, 90
Action potential
  accommodation of, 14
  all or none phenomenon of, 13
  in cardiac muscle, 120
  changes during generation of, 12*f*
  conductance without decrement and, 14
  conduction pathway of, 120, 120*f*
  electrophysiology of the heart and, 118
  generation of
    in sensory system, 42, 42*f*
    in skeletal muscle cells, 13
  GI tract and, 209
  nodal cell vs. myocyte generation of, 121
  overview of, 13
  properties of, 13
  transmission of between cells, 14, 14*f*
Active carrier-mediated transport
  characteristics of, 9
  example of, 8*t*, 9*f*
Acute renal failure
  acute tubular necrosis and, 176
  causes of, 196
  hyperkalemia and, 197
  potassium excretion and, 197
  sample case, 234
Acute respiratory distress syndrome (ARDS), 242
Acute tubular necrosis (ATN), 176, 196
Addison disease
  chronic adrenal insufficiency and, 76
  clinical features of, 77*t*
  ECV decrease and, 244
  See also Adrenal insufficiency
Adenohypophysis, 69
Adenosine, 116
Adenosine triphosphate (ATP), 138
Adenylate cyclase, 59
Adrenal androgen synthesis, 76
Adrenal catecholamine
  overview of, 96
  physiologic actions of, 96, 97*f*
Adrenal cortex hormone, 66*t*
Adrenal corticosteroid, 72*f*
  biosynthetic pathway of, 72
Adrenal Cushing, 75
Adrenal disorder, 77, 77*t*
Adrenal gland
  aldosterone and, 199
  steroid hormones and, 73
  tumor of, 71
Adrenal insufficiency
  clinical features of, 77*t*
  ECV decrease and, 244
  overview of, 75
  steroid therapy and, 76
  See also Addison disease
Adrenal medulla
  chromaffin cell tumors of, 97
  function of, 28, 96
Adrenal medulla hormone, 66*t*
Adrenal mineralocorticoid, 96
Adrenal steroid
  list of, 65
  synthesis of, 72
Adrenal steroidogenesis, 72*f*, 76*f*
Adrenergic innervation of the heart, 122
Adrenergic receptor
  features of, 32*t*
  overview of, 32
Adrenergic transmission
  function of, 17
  norepinephrine pathway of, 17*f*
Adrenocorticotropic hormone (ACTH)
  diurnal secretion of, 72, 72*f*
  features and function of, 70
Adventitia, 207
Afferent arteriolar resistance, 172, 173*f*, 173*t*
Afferent fibers, 209
Afferent loop, 25
Afterload
  adaptations to increased, 117
  myocardial adaptations to increased, 118*f*
  stroke volume and, 107
Aganglionic megacolon, 208
Air-blood barrier, 139, 140*f*
Airflow pattern, 157, 157*f*
Airway obstruction, 159*t*
Airway resistance
  breathing and, 143, 144*f*
  contribution of airways to, 143
  defined, 141
Albuterol, 198
Alcohol abuse, 220
Aldosterone
  function of, 132
  physiologic actions of, 96
  potassium excretion and, 200*f*
  potassium ion secretion and, 199
  regulation of secretion of, 96
  sodium absorption and, 227
  synthesis of, 73
Aldosterone antagonist, 132
Alkalemia, 228
Alkalosis
  causes of, 232
  defined, 228
  ionized calcium and, 98
All or none phenomenon of action potentials, 13
Allergen, 137
All-*trans*-retinal, 48
Alpha motor neuron, 33
Alpha wave
  example of, 61*f*
  features of, 61
  sleep and, 62*f*
Alveolar air, 138
Alveolar dead space, 158
Alveolar duct, 139
Alveolar epithelium, 139, 140
Alveolar hyperventilation, 238
Alveolar hypoventilation, 238
Alveolar surface tension, 147
Alveolar ventilation
  overview of, 158
  respiratory acidosis and, 238
Alveolar wall, 140*f*
Alveolar-arterial gradient, 159, 159*t*
Alveoli, 139
Alzheimer disease, 16
Amacrine cell, 49
Ambiguous genitalia, 71, 76, 77
Amenorrhea, 87
Amino acid
  function of, 16
  glucagon and, 96
Amino acid hormone, 65
Ammoniagenesis, 229, 231*f*
Ammonium
  production of, 231
  renal handling of, 231
Amygdala, 59

Amyotrophic lateral sclerosis (ALS), 38
Anaphylactic shock, 137, 137*t*
Anatomic dead space, 138, 158
Androgen
  ACTH secretion and, 70
  adrenal steroidogenesis pathways and, 72*f*, 76*f*
  CRH secretion and, 71, 76
  synthesis of, 72
Androgen insensitivity syndrome, 83–84, 88*t*
Anemia
  arterial oxygen content and, 116
  gas exchange impairment and, 140
  heart failure and, 136
  iron absorption and, 225
  parietal cells and, 215
  reduced oxygen-carrying capacity and, 160
Anemic hypoxia, 166*t*
Angina pectoris, 117
Angiotensin II
  ACE inhibitors and, 131
  GFR regulation and, 172
  physiologic actions of, 131, 132*f*
  production of, 131
  renal blood flow and, 174, 174*f*
Angiotensin-converting enzyme (ACE) inhibitor, 131
Anion
  intracellular fixed, 12
  in plasma, 228*t*
  transport across membranes and, 6
Anion gap acidosis
  causes of, 233
  overview of, 232
  renal failure and, 233
Anion gap (AG), 232
Ankyrin, 5
Ankyrin gene, 5
Annular pancreas, 220
Anorexia, 81
Anosmia, 59
Anovulation, 87
Anovulatory infertility, 87
Anterior cerebral artery (ACA), 63
Anterior funiculus, 37
Anterior horn, 34, 37
Anterior pituitary
  effect of hormones on, 70*t*
  hormonal control systems of, 70
  hormone secretion and, 69
Anterior pituitary hormone, 66*t*, 67*f*
Anterograde action potential transport, 15
Anterolateral system, 44, 45*f*
Anticholinergic, 144
Antidiuretic hormone (ADH)
  CNS osmoreceptors and, 132, 132*f*
  ECF osmolarity and, 243
  lack of secretion of, 193, 195*f*
  physiologic actions of, 91
  secretion of, 91, 193, 195*f*
  urea concentration and, 194
  urine concentration and, 193
Antiport, 9
Aortic body, 165
Aortic insufficiency
  defined, 112
  diastolic pressure and, 116
  with impaired contractility, 135
  increased preload and, 118
  pathologic and clinical findings with, 112
  pulse pressure and, 102
Aortic regurgitation
  defined, 112
  diastolic pressure and, 116
  with impaired contractility, 135
  increased preload and, 118
  pathologic and clinical findings with, 112*f*
  pulse pressure and, 102
Aortic stenosis
  afterload and, 135
  hypertrophied heart and, 116
  pathophysiology of, 111
  pressure-volume changes in, 111*f*
  pulse pressure and, 102
Aortic valve
  congenitally bicuspid, 112
  function of, 102
  stenotic, 112
Aphasia. *See specific types*
Apnea, 167*t*
Apneustic center, 164
Aquaporin, 193
Arachidonic acid, 74
Archicerebellum, 40
Arginine vasopressin. *See* Antidiuretic hormone (ADH)
Argyll Robertson pupil, 50
Arterial oxygen content, 116
Arterial pressure
  maintenance of, 125
  oncotic, 242
  systemic, 172
Arteriolar pressure, 175
Arteriosclerosis, 129, 130
Arteriovenous fistula, 136
Artificial tears, 211
Asbestosis, 146, 159*t*
Ascites, 242, 243
Aspirin toxicity, 234
Asthma, 139, 142, 143
Astrocyte, 25
Ataxia, 40, 41*t*
Ataxic gait, 57
Atelectasis, 147, 150
Atherosclerosis
  angina pectoris and, 117
  renal artery stenosis and, 174
ATP hydrolysis, 9
Atresia, 86
Atrial fibrillation, 125
Atrial flutter, 125, 125*f*
Atrial gallop, 104
Atrial natriuretic peptide (ANP), 133
Atrial pressure, 111
Atrial pressure in cardiac cycle, 111*f*
Atrial systole, 102
Atrioventricular block
  first-degree, 126, 126*f*
  Mobitz type 1 second-degree, 126
  third-degree, 126
Atrioventricular valve
  function of, 102
  sounds of closure of, 102, 104
Atrophic gastritis, 217
Atropine, 123
Audition (hearing), 52
Auditory radiation, 54
Auditory testing, 56*t*
Auditory transduction, 54, 55*f*
Auerbach plexus
  function of, 208
  overview of, 30
Auscultation, 143
Autoimmune thyroiditis, 82*t*
Autonomic denervation, 225
Autonomic innervation of the heart, 122, 122*f*
Autonomic nervous system (ANS)
  blood pressure and, 127
  effects of on target organs, 28*t*
  enteric nervous system and, 30
  features of, 25
  function of, 27
  GI tract and, 208, 208*f*, 208*t*
  neurons in, 30*t*
  neurotransmitters of, 30
  nitric oxide and, 31
  organization of, 27
  salivation and, 211
Avascular necrosis, 74
Axial muscle, 37
Axon, 15

B

β_2-adrenergic agonist, 144
Babinski response, 37, 37*f*
Backup pacemaker, 119
Bacterial meningitis, 27
Bainbridge reflex, 133
Bare zone, 20
Baroreceptor, 129
Baroreceptor reflex, 127, 128*f*
Barrett esophagus, 207
Bartter syndrome, 186*t*, 237, 237*t*
Basal ganglia
  anatomy of, 38*f*, 38*t*
  movement and, 38, 39*f*
Basal ganglia movement influence, 39
Basal metabolic rate (BMR), 78
Base, 228
Basement membrane
  damaged, 171
  defined, 139
  in the glomerular filtration barrier, 170, 170*f*
Basilar membrane
  auditory transduction and, 54
  sound frequency and, 54, 55*f*
  structure of, 53
β-cell dysfunction with impaired insulin secretion, 95
Bence-Jones protein, 170
Benign prostatic hyperplasia, 83
Beta blocking drug, 122
Beta wave
  example of, 61*f*
  features of, 61
  sleep and, 62*f*
Bicarbonate
  acid-base balance and, 228
  large intestine absorption of, 227
Bicarbonate ion, 162, 162*f*
Bicarbonate reclamation, 229, 229*f*
Bicarbonate/carbon dioxide system, 228
Bicuspid valve, 102
Bilateral pupil constriction, 50
Bile, 220, 221*t*, 222*f*
Bile acids, 221, 221*t*
Bile salts
  distal ileum disease and, 224
  enterohepatic circulation and, 221
  function of, 221*t*
  production of, 222*f*
Bile-sequestering agent, 221
Biliary dyskinesia, 221
Biliary obstruction, 221
Biliary tree, 220, 221*f*
Bilirubin, 221*t*
Binasal hemianopia, 51*f*
Biot breathing, 167*t*
Bipolar cell
  balance and, 56
  hearing and, 54
  vision and, 49
Bitemporal hemianopia, 49, 51*f*
Bladder and ANS, 28*t*
Blind spot, 48
Blood, oxygen content of, 159
Blood flow
  autoregulation of local, 129
  cardiovascular, 114
  in coronary arteries, 115
  myogenic mechanism of regulation of, 130*f*
  pulmonary
    pressures in, 150
    zones of, 151, 151*f*
Blood pressure
  autonomic nervous system and, 127
  cortisol and, 74
  diastolic, 102
  drugs for lowering, 127, 131
  oscillations of, 127, 127*f*
  pulmonary artery occlusion, 152
  systolic, 102
Blood-brain barrier (BBB)
  features of, 25
  function of, 26*f*
Blood-CSF barrier, 27
Body fluid distribution, 241
Bohr effect, 162
Bone
  cortisol and, 74
  phosphate and, 202
Bone disease, 203
Bony labyrinth, 52
Botulinum toxin, 19*t*
Bowman gland, 59

Bowman space, 170, 171*f*
Boyle's law, 141, 142
Bradycardia, 81
Brain
  blood supply to, 63*f*
  hemisphere control in, 61
  protection of, 25
Brain wave
  example of, 61*f*
  features of, 61
  sleep and, 62*f*
Brainstem
  breathing and, 163, 163*f*
  ischemia of, 129
Breathing
  control of, 163
  disorders of, 167, 167*t*
  forceful, 140
  mechanics of, 140
  paradoxical, 141
  work of
    airway resistance and, 143, 144*f*
    compliance resistance and, 144, 144*f*
    overview of, 143
    tissue resistance and, 144
  See also Respiration
Broca area, 61
Bronchi, 138, 138*t*, 147
Bronchial arterial circulation, 154
Bronchiectasis, 139
Bronchiole
  ANS effects on, 28*t*
  conducting, 138, 139
  defined, 138*t*
  respiratory, 139
Bronchoconstriction, 139, 142, 144
Bronchodilation, 144
Bruit, 102–137
  See also Heart murmur
Buffering system, 228

C

C fiber and slow pain, 46
C peptide
  diabetes mellitus and, 94, 95
  hypoglycemia, 95
Ca^{2+}-induced Ca^{2+} release, 121
Calcidiol, 99, 202
Calcitonin
  calcium homeostasis and, 98
  secretion of, 77
Calcitriol, 202
  bones and, 100
  calcium homeostasis and, 98, 99
  hypocalcemia and, 101
  organ effects of, 99*f*
  phosphate and, 100
  PTH and, 98
  RANKL and, 99
  synthesis of, 100*f*
Calcium
  exocytosis and, 11
  phosphate homeostasis and, 97
  renal contribution to control of, 201
Calcium channel blocker, 23
Calcium homeostasis, 97
Calcium plateau, 121
Caloric nystagmus, 58, 58*f*
Calyceal system, 168
Cancer. *See specific types*
Capillary
  fluid exchange in, 133
  hydrostatic pressure of, 133, 133*f*
Capillary endothelium, 139
Capillary-lipoprotein lipase (CPL), 94
Caput medusae, 205
Carbaminohemoglobin, 162
Carbohydrate
  acid-base balance and, 228
  digestion of, 222*t*, 223*f*
Carbon dioxide (CO_2)
  dissolved, 162
  transport of, 161
Carbon monoxide (CO), 160
Carbon monoxide poisoning, 161
Carbonic anhydrase, 162
Carbonic anhydrase deficiency, 186*t*
Carboxyhemoglobin, 160
Cardiac arrhythmia and potassium, 197
Cardiac condition treatment, 23
Cardiac cycle
  atrial pressure changes during, 111, 111*f*
  components of, 102
  ventricular pressure changes during, 104, 105*f*
Cardiac disease, 104
Cardiac glycosides, 9
Cardiac mechanics, 102
Cardiac muscle
  mechanism of, 23
    regulation of, 23
  features of, 24*t*
  structure of, 23
Cardiac myocyte
  action potential phases in, 120, 120*f*
  membrane potential and, 119
Cardiac nerves, 122*f*
Cardiac output (CO)
  compensatory responses to reduced, 136*t*
  defined, 105
  MAP and, 125
  venous return and, 109*f*
Cardiac performance, 105
Cardiac tamponade, 135
Cardiac-output state, 103
Cardiogenic shock, 136, 137*t*
Cardiomyocyte, 23
Carotid body, 165
Carotid sinus pressure, 129
Carrier binding sites, 7
Carrier-mediated transport
  characteristics of, 7
  examples of, 8*t*
  vs. simple diffusion, 8*f*
Cartilage ring, 138
Catecholamine
  cortisol and, 73
  heart rate and, 119
  potassium and, 197
  thyroid hormones and action of, 79
Catechol-O-methyl transferase (COMT), 16
Cation
  intracellular fixed anions and, 12
  in plasma, 228*t*
  transport across membranes and, 6
Caudal medulla, 37
Celiac artery, 205
Celiac disease, 224
Celiac sprue, 224
Cell
  composition of, 1*f*
  depolarization of, defined, 13
  DNA in, 2
  junctions between, 5
  morphology of, 2
  structure and function of, 1
Cell division
  centrioles and, 5
  cytoskeleton and, 4
  nucleus and, 2
Cell membrane
  composition of, 1*f*
  as fluid mosaic, 1
  folding of, 2
  proteins in, 1, 2*t*
  structure of, 1
Cellular receptor, 65
Cellular respiration, 138
Central chemoreceptor, 164
Central diabetes insipidus, 91, 92
Central hypoventilation, 238*t*
Central nervous system (CNS)
  breathing and, 163, 163*f*
  components of, 25, 26*f*
  cortisol and, 73
  insulin and, 93
  ischemic response of, 129
  osmoreceptors of, 132
Central vision, 49
Centriole, 5
Centrosome
  centrioles in, 5
  defined, 5
Cephalic phase of digestion, 214
Cerebellar disease, 41
Cerebellar lesion, 41*t*
Cerebellopontine angle, 54
Cerebellopontine angle tumor, 54
Cerebellum
  equilibrium and, 41
  functional components of, 40*f*
  movement and, 39
Cerebral blood supply, 63, 63*f*
Cerebral cortex
  higher functions of, 60
  movement and, 34
  respiration and, 163
Cerebrocerebellum, 39
Cerebrospinal fluid (CSF), 27
Cerebrovascular accident, 212
Chagas disease, 23, 213
Chemoreceptor, 164, 164*f*
Chemoreceptor trigger zone, 26
Chemosensitive area, 164
Chest wall compliance, 146*f*
Chewing, 212
Cheyne-Stokes breathing, 167*t*
Chief cells, 217
Chloride shift, 162, 162*f*
Cholecalciferol. *See* Vitamin D
Cholecystokinin (CCK), 218*t*, 219, 221
Cholera, 244
Cholesterol, 93, 221, 221*t*
Cholestyramine, 221
Cholinergic innervation of the heart, 122, 122*f*
Cholinergic receptor, 32, 33*f*, 33*t*
Cholinergic transmission
  characteristics of, 15
  pathophysiology of, 16
Cholinoceptor, 33*t*
Cholinomimetics, 32
Chorda tympani, 59
Choroid plexus, 27
Chromaffin cell
  defined, 28
  function of, 97
  tumor of, 97
Chromatin, 2
Chronic bronchitis, 143
Chronic granulomatous disease (CGD), 10
Chronic heart failure, 122
Chronic kidney disease and hyperparathyroidism, 203
Chronic metabolic alkalosis, 186*t*
Chronic obstructive pulmonary disease (COPD), 156
Chronic renal failure, 101
Chronic sinusitis, 139
Chronotropy
  defined, 23
  heart and, 122
Chylomicron, 224
Chyme, 218
Cilia, 5
Ciliary dyskinesia, 139
Ciliary ganglion, 50
Ciliary muscle, 52
Circadian, 62
Circle of Willis, 63, 64
Circulatory insufficiency. *See* Shock
Circulatory system
  ECV decrease and, 243
  resistance governance of, 127, 127*f*
Circumvallate papillae, 59
Cirrhosis, 205, 243
11-*cis*-retinal, 48
Clathrin, 9, 10
Clearance
  and reabsorption/secretion, 178, 178*f*
  in renal function, 176, 177
Clearance value
  defined, 178, 179*f*
  renal plasma flow and, 179
  summary of important, 179*t*
CN I (olfactory), 59

CN II (optic), 49
CN III (oculomotor), 50, 51*f*
CN IX (glossopharyngeal), 60
CN VII (facial), 59, 60
CN VIII (vestibulocochlear)
  balance and, 56
  hearing and, 54
CN X (vagus), 60
Cobalamin
  absorption of, 224, 226*f*
  deficiency of, 43
Cobalamin deficiency, 215
Cocaine
  anginal chest pain and, 117
  as norepinephrine reuptake inhibitor, 17
Cochlea, 52, 53, 53*f*
Cochlear ganglion, 54
Cochlear microphonic potential, 54
Cochlear nerve, 53, 54
Cochlear nuclei, 54
Collecting tubule, 186*t*, 187*t*
Colon, potassium excretion and, 198
Columnar mucosal epithelium, 206
Compensatory hyperparathyroidism, 101
Compensatory vasoconstriction, 129
Competitive inhibition, 185
Compliance resistance
  defined, 144, 144*f*
  during inspiration, 141
  surfactant and, 147
Compliant vessel, 129
Concentration gradient (DC), 6
Concentric hypertrophy, 117
Conductance without decrement, 14
Conducting airway
  compared to respiratory airways, 139*t*
  overview of, 138
  resistance and, 143
Conduction deafness
  causes of, 54
  Rinne test and, 54–55
  test interpretation for, 56*t*
  Weber test and, 55
Conduction velocity, 15
Cone (optic), 48
Congenital adrenal hyperplasia (CAH)
  21-hydroxylase deficiency and, 77
  enzyme blocks and, 71
  pathophysiology of, 76
Congenital aganglionic megacolon, 30
Congestive heart failure (CHF)
  aldosterone antagonists and, 132
  ECV and, 243
  RAAS and, 131
  ventricular gallop and, 104
Conn syndrome, 132, 237, 237*t*
Connexon, 6
Contraceptive, 85, 87
Contractility
  myocardial oxygen demand and, 117
  stroke volume and, 107, 107*f*
Contraction
  heart, mechanical characterization of, 107
  intestinal, 209
Contraction alkalosis, 188, 237
Contralateral LGN, 49
Convection as transport, 11
Cor pulmonale, 153
Cornea, 46
Corneal ulceration, 211
Coronary artery disease, 94
Coronary artery vasospasm, 117
Coronary blood flow, 115, 115*f*, 116
Coronary vascular resistance, 116
Corpus luteum, 86, 87
Corticotropin-releasing hormone (CRH), 71
Cortisol
  anti-inflammatory action of, 74, 74*f*
  blood pressure and, 74
  bone and, 74
  diurnal secretion of, 72, 72*f*
  hypothalamic-pituitary-adrenal axis and, 71
  inflammatory and immune responses and, 74
  kidneys and, 74
  mechanism of action of, 73
  metabolic actions of, 73, 73*f*
  physiologic actions of, 73
  production of, 70
  synthesis of, 72
Corticospinal tract, 37
Cotransmission, 18
Cotransport, 8*t*, 9
Countercurrent system
  function of, 192, 192*f*
  loop of Henle as, 192, 193*f*
Countertransport, 9
C-peptide and diabetes mellitus, 95
Cranial nerve nuclei, 29
Cranial nerve V3, 212
Craniotabes, 100
Creatinine, 177, 177*f*, 178
Cretinism, 81, 82*t*
CRH-ACTH-cortisol axis, 74
Cribriform plate, 59
Crohn disease, 224
Cross-bridging and skeletal muscle contraction, 20
Crypt, 206
Cryptorchidism, 84
Cupula, 56
Curare (toxin), 19*t*
Cushing sign, 129
Cushing syndrome
  defined, 74
  metabolic alkalosis and, 237, 237*t*
  physical features of, 75*f*
  pregnancy and, 68
  See also Pituitary Cushing
Cyanide poisoning as type of hypoxia, 166*t*
Cyanosis, 160
Cyclic adenosine monophosphate (cAMP), 59
Cyst, 98
Cystic fibrosis, 139, 220
Cytochrome oxidase, 138
Cytokine, 74
Cytoplasm
  composition of, 1
  structure and function of, 2
Cytoplasmic calcium ($Ca2^+$), 106
Cytoplasmic receptor
  cortisol and, 73
  steroid hormones and, 68*f*
Cytoskeleton, 4
Cytosol
  cell structure and, 1
  composition of, 2

D

Dalton's law, 148
De novo bicarbonate synthesis
  acid-base balance and, 230
  process of, 229
  regulation of, 231
de Quervain thyroiditis, 82*t*
Decerebrate posturing, 37, 37*f*
Decomposition of movement and lateral cerebellar lesions, 40
Decorticate posturing, 37, 37*f*
Decreased plasma LDL, 221
Deep pressure receptor, 42
Defecation reflex, 227
Deglutition, 213
Dehydration
  ADH secretion and, 91
  RAAS and, 131
  shock and, 137
Dehydroepiandrosterone (DHEA), 71
Delayed gastric emptying, 209
Delta wave, 62
  example of, 61*f*
  features of, 61
  sleep and, 62*f*
Dense bodies in smooth muscle cells, 22
Deoxyhemoglobin, 160, 162
Depolarization and action potential, 13, 121
Depolarizing neuromuscular blocking drugs, 19*t*
Depression and monoamines, 17
Dermatome, 46, 47*f*, 47*t*
Dermopathy, 81
Desmosome
  intermediate filaments and, 5
  structure and function of, 6
Deuterium, 242
Dexamethasone suppression test, 75
Diabetes insipidus (DI)
  commonality of, 91
  pathophysiology of, 91
Diabetes mellitus
  carbohydrate digestion and, 223
  cortisol and, 73
  Cushing syndrome and, 74
  gastroparesis and, 209
  growth hormone and, 90
  type I
    clinical presentation of, 94
    diabetic ketoacidosis and, 94
    pathophysiology of, 94
  type II
    C peptide and, 95
    insulin resistance in, 2*t*
    pathophysiology of, 95
  unintentional weight loss and, 81
Diabetic ketoacidosis (DKA)
  diabetes mellitus and, 95
  features of, 94–95
  hyperkalemia and, 198
  hypokalemia and, 198
  initial presentation of, 94
  Kussmaul respiration and, 167
  overview of, 234
  sample case, 235
Diabetic neuropathy, 41
Diabetogenic hormone, 90
Diaphragm, 140
Diaphragmatic paralysis, 147
Diarrhea
  and normal anion gap acidosis, 235
  secretory, 244, 244*f*
Diastole
  coronary blood flow and, 115
  defined, 102
Diastolic blood pressure (DBP), 102
Diastolic heart failure, 106, 135
Diastolic perfusion pressure, 116
Diastolic potential, 119
Diffuse toxic goiter, 80
Diffusion
  of charged substances, 6
  facilitated
    characteristics of, 8
    example of, 8*t*
  of gases, 6
  of nonpolar substances, 6
  of oxygen across the pulmonary membrane, 149
  of polar substances, 6
  pulmonary membrane capacity of, 149, 149*f*
  respiratory, 148, 148*f*
  simple, 6, 8*f*
  of uncharged substances, 6
Diffusion limited gas exchange, 149, 150
Diffusion rate of a gas (Vg), 7
Diffusivity coefficient (d), 7
Digestion
  of carbohydrates, 222, 222*t*, 223*f*
  of fats, 222*t*, 223
  phases of, 214, 215*f*
  process of, 210
  of proteins, 222*t*, 223
  submucosal plexus and, 207
Digitalis
  function of, 122
  hyperkalemia and, 198
Dihydrotestosterone (DHT)
  conversion of, 76
  physiologic actions of, 83
1,25-Dihydroxyvitamin D3. *See* Calcitriol
Dilated cardiomyopathy, 135
Dilutional hyponatremia, 92
Disaccharidase, 222
Disinhibition, 16
Distal ileum disease, 224
Distal muscle, 37
Distal RTA (Type I), 233*t*

Distal tubule
function of, 186*t*
sodium handling and, 187*t*
sodium reabsorption in, 189, 190*f*
Distension and pulmonary perfusion, 153
Distributive shock, 137, 137*t*
Diuretic
classification of, 203
function of, 203
nephron function and, 204*f*
Diuretic classes, 204*t*
Diuretic-induced volume depletion, 186*t*
DNA, 2
Dominant follicle, 86
Dopamine
autonomic nervous system and, 30
function of, 17
overview of, 96
Parkinson disease and, 31
physiologic actions of, 96
synthesis of, 18*f*
Dopaminergic transmission
function of, 17
pathways of, 18
Dorsal column system (DCS), 43, 45*f*
Dorsal horn, 44
Dorsal respiratory group, 163, 163*f*
Dorsal root ganglia, 42
Dorsiflexion and Babinski sign, 37, 37*f*
Dromotropy, 23
Duchenne muscular dystrophy, 2*t*, 24
Ductal cells, 220
Ductal secretion, 220
Dumping syndrome, 218
Duodenal obstruction, 220
Dwarfism, pituitary, 89
Dysarthria, 41*t*
Dysdiadochokinesia, 41*t*
Dysmetria, 40, 41*t*
Dysphagia, 211, 213
Dyspnea, 113, 132, 167*t*
Dystrophin, 24

E

Ear
function of, 53
structure of, 52, 53*f*
Eccentric hypertrophy, 118
Ectopic Cushing, 75
Edema
causes of, 134, 242
hypoalbuminemia and, 134
inflammation and, 134
interstitial, 242
pathophysiology of, 135
Starling forces and, 135, 135*t*
Edinger-Westphal nucleus, 50, 52
Effective circulating volume (ECV)
overview of, 243
regulation of, 243
response to decrease in, 243, 244*f*
response to increase in, 244
volume contracted states of, 244, 245*f*
Effector organ, 29
parasympathetic nerves and, 30
Efferent arteriolar resistance, 173, 173*f*
Efferent autonomic signal, 27
Efferent loop, 25
Ehlers-Danlos syndrome, 113
Ejection fraction (EF), 106
Ejection murmur, 112
Ejection period, 110
Elastance, 145
Electrocardiogram (ECG)
abnormal
atrial flutter, 125*f*
complete heart block, 126*f*
digitalis toxicity and, 125*f*
elongated PR interval, 126*f*
first-degree atrioventricular block, 126*f*
hyperthyroidism and, 125*f*
Mobitz type 2 second-degree heart block, 126*f*
ventricular fibrillation (VF), 126*f*
ventricular tachycardia (VT), 126*f*
Wolff-Parkinson-White syndrome, 126*f*
correlation of with cardiac events, 124, 124*t*
determination of QRS axis of, 123, 124*f*
leads used with, 123
normal, 123, 123*f*
Electroencephalogram (EEG)
example of, 61*f*
function of, 61
Electrolyte abnormalities, 74
Emphysema
a-a gradient and, 159*t*
compliance work and, 144
hypoxia and, 165
lung compliance and, 145
lung volumes and, 154, 156
oxygen diffusion and, 149
pulmonary membrane diffusing capacity and, 150
Empyema, 145
Emulsification, 223
Endocarditis, 113
Endocrine disease
causes of, 65
classification of, 70
Endocrine gland, 69
Endocrine organ defects, 70
Endocrine pancreas, 92
Endocytosis
function of, 9
lysosomes and, 3
receptor-mediated, 9
Endolymph, 52
Endoplasmic reticulum (ER), 3
Endothelial cell, 170, 170*f*
End-plate potential, 18
Endurance training, 22
Engulfing as vesicular transport, 10
Enteric nervous system (ENS)
features of, 30
function of, 27
GI tract and, 207, 209*f*
small intestine and, 225
Enteric phase of digestion, 214
Enterogastric reflex, 227
Enterohepatic circulation, 221
Enzyme, 2*t*
Epilepsy, 61
Epinephrine
adrenergic receptors and, 32
effects of, 28
overview of, 96
physiologic actions of, 96
regulation of secretion of, 97
secretion of, 28
Epiphyseal plate, 85
Epithelial cell types, 140
Equilibrium potential
examples of, 12*f*
ionic, 11
RMP calculation and, 12
Erectile dysfunction, 32
Erythromycin, 225
Erythropoiesis, 225
Esophageal adenocarcinoma, 207
Esophageal cancer, 207
Esophageal distension, 213
Esophageal hiatus, 213
Esophageal manometry, 213
Esophageal motility, 212
Esophageal varices, 205
Esophagus
functional anatomy of, 212
motility of, 212
swallowing and, 213*f*
Estrogen
physiologic actions of, 85
regulation of secretion of, 86
Ethylene glycol
metabolism of, 236*f*
toxicity of, 235
Eupnea, 167*t*
Euthyroid sick syndrome, 82
Excessive postsynaptic stimulation, 15
Excitation-contraction coupling, 121
Excitatory postsynaptic potential (EPSP), 15
Exercise
hyperventilation and, 165
pulmonary blood flow and, 153, 154
respiration control and, 165
Exocytosis
characteristics of, 10
phagocytosis and, 10
Exophthalmos, 81
Expiration (respirational)
driving forces for, 142
forced, 142
muscles of, 141*f*
overview of, 142
sources of resistance during, 142
Expiratory muscle, 164
Expiratory reserve volume (ERV), 155
Expiratory wheezing, 139
Expression down-regulated in virally infected cells, 2*t*
Expressive aphasia, 61
Extensor antigravity muscle, 36
External respiration, 138
Extracellular fluid
composition of, 242
distribution of, 241, 241*f*
vs. intracellular fluid, 2, 3*t*
kidneys and, 168
measurement of, 242
sodium and, 190
Extracellular pH, 197
Extrafusal muscle fiber, 34
Extrapyramidal tract, 34, 35*t*
Exudate, 134
Eye
ANS effects on, 28*t*
structure and function of, 46, 49*f*

F

Fabry disease, 4*t*
Facial nerve (CN VII), 59, 60
Facilitated carrier-mediated transport. *See* Diffusion
Familial hypercholesterolemia, 10
Familial hypocalciuric hypercalcemia, 98
Fanconi syndrome, 186*t*
Fast pain, 45
Fastigial nucleus, 40
Fast-twitch skeletal muscle fiber, 21, 22*t*
Fat
absorption of, 224*f*
acid-base balance and, 228
digestion of, 222*t*, 224*f*
insulin and, 93
malabsorption of, 224
Fat-soluble substance and cell membrane, 1
Female pseudohermaphroditism, 88*t*
Female reproductive axis, 85, 85*f*
Fenestration, 170
Ferric form of hemoglobin, 160
Ferritin, 225
Fetal blood flow, 154
Fetal hemoglobin (Hb F), 160
FEV1/FVC ratio, 157, 157*f*
Fibric acid derivative, 94
Fibromuscular hyperplasia, 174
Fick principle, 105, 180*f*
Fick's law of diffusion, 149
Fight-or-flight system, 96
See also Sympathetic nervous system
Filament, intermediate
overview of, 4*t*
structure and function of, 5
Filtration fraction, 172, 173*t*
Finasteride, 83
First-order neuron
olfaction and, 59
sensory pathways and, 42
smell and, 59
Flagella, 5
Flocculonodular lobe, 56
Flow-through system, 192*f*
Flow-volume curve, 142, 143*f*

Fluid compartment
composition of, 242
measurement of, 242
overview of, 241
typical makeup of, 241*f*
Fluid mosaic model of cell membrane, 2
Foliate papillae, 59
Follicle-stimulating hormone (FSH)
in females, 86
in males, 84
Follicular cell, 77, 78*f*, 86
Follicular lumen, 77
Follicular phase of menstruation, 86, 86*f*
Forced expiration, 142
Forced expiratory volume (FEV1), 157
Forced vital capacity (FVC)
defined, 156
lung diseases and, 157
restrictive lung disease and, 157
Forceful breathing, 140, 142
Foregut, 205
Fourth-order neuron
anterolateral system and, 44
sensory pathways and, 43
somatosensory system and, 43
spinothalamic tract and, 44
Frank-Starling relationship
heart failure and, 136, 136*t*
stroke volume and, 106
venous return and, 109
Fuel metabolism, 73
Functional residual capacity (FRC)
COPD and, 156
defined, 156
emphysema and, 145
lung-chest wall system and, 145
Fungiform papillae, 59

G

G actin, 4
G cells, 217
G protein signal transduction, 68, 69*f*
Galactorrhea, 86, 89
Gallbladder, 220, 222*f*
Gallbladder contraction, 219
Gallstone, 220, 221
Gamma aminobutyric acid (GABA)
function of, 16
pathophysiology of, 16
Gamma motor neuron, 33
Ganglion cell, 49
Gap cellular junctions, 6
Gap junction, 14, 22
Gas exchange
across the pulmonary membrane, 148
diffusion-limited, 150
perfusion-limited, 150
V/Q matching and, 152
Gas pressure, 148, 149*t*
Gastric accommodation, 214
Gastric cell types and secretions, 214, 215*t*
Gastric emptying, 218
Gastric inhibitory peptide, 218*t*, 219
Gastric lipase, 223
Gastric motility, 218
See also Intestinal motility
Gastric motility dysfunction, 209
Gastric mucosa. *See* Mucosa
Gastric pacemaker, 209
Gastric phase of digestion, 214
Gastrin, 214, 217
Gastritis, 217
Gastrocolic reflex, 209, 227
Gastroenteric reflex, 227
Gastroesophageal reflux disease (GERD), 207
Gastroileal reflex, 227
Gastrointestinal (GI) tract
ANS effects on, 28*t*
function of, 209
functional anatomy of
autonomic nervous system and, 208*f*, 208*t*
gut wall layers in, 205
neural regulation of, 207
overview of, 205
response to meal in, 214
Gastroparesis
diabetes mellitus and, 209
impaired gastric emptying and, 218
metoclopramide and, 209
Gaucher disease, 4*t*
Geniculocalcarine tract, 49
Gestational hyperthyroidism, 68
Gibbs-Donnan equation, 12
Gigantism, 89, 90
Gitelman syndrome, 186*t*, 237, 237*t*
Gliadin, 224
Glomerular capillaries, 170, 171*f*
Glomerular filtration barrier, 168, 170*f*
Glomerular filtration rate (GFR)
calculation of, 172
DKA and, 94
measurement of, 177
overview of, 171
pressure diuresis and, 130
regulation of, 172
renal clearance and, 176
sodium and water handling and, 186, 186*f*
Starling force changes and, 173*t*
vasoconstriction and, 173*f*
Glomerular function, 170
Glomerular marker, 172
Glomerulotubular balance
peritubular capillaries and, 183
salt and water reabsorption and, 183
tubuloglomerular feedback and, 183
Glomerulus
anatomy of, 169*f*
filtration forces at, 170, 171*f*
functional anatomy of, 168
Glossopharyngeal nerve (CN IX), 60
Glucagon, 73
first-pass effect and, 96
function of, 95
physiologic actions of, 92*t*, 96
regulation of secretion of, 96
source of, 92
Glucagonoma, 96
Glucocorticoid
ACTH and, 71
adrenal steroidogenesis pathways and, 72*f*, 76*f*
sodium absorption and, 227
Gluconeogenesis
cortisol and, 73
epinephrine and, 97
Glucose intolerance, 73
Glucose transporter (GLUT4), 92
Glucose utilization, 96
Glucosuria, 94
Glutamate
function of, 16
pathophysiology of, 16
Glutamatergic transmission, 16
Glyburide, 95
Glycine, 16
Glycogen, 93
Glycogenesis, 93
Glycogenolysis, 97
Glycolysis, 93
Goiter
Graves disease and, 81
hyperthyroidism and, 80
hypothyroidism and, 82*t*
Golgi apparatus, 3
Golgi tendon organ, 40
Gonad, 73
Gonadotropin-releasing hormone (GnRH)
in females, 86
in males, 84
GPIIb/IIIa, 6
Graded muscle contraction, 20
Granulomatous disease, 98
Graves disease, 80, 80*t*, 81
Group III fiber and fast pain, 45
Growth factor-1 (IGF-1), 89
Growth hormone (GH)
anabolic actions of, 89
metabolic actions of, 89
physiologic actions of, 90*f*
regulation of secretion of, 90
Growth hormone suppression test, 90
Growth hormone-releasing hormone (GHRH), 90
Guillain-Barré syndrome, 15, 238
Gut wall, 206*f*
layers of, 205

H

H zone, 20
Hair cell (auditory)
auditory transduction and, 54
structure and function of, 53
Hair cell (vestibular), 56
Hashimoto thyroiditis, 81, 82*t*
Head injury and CNS ischemic response, 129
Hearing, 52
Heart, 118
ANS effects on, 28*t*
autonomic innervation of, 122, 122*f*
blood flow pattern in, 103*f*
electrophysiology of, 118
hypertrophied, 116, 117
inotropic state of, 107
principal sounds of, 102
sympathetic excitation of, 122
volume-overloaded, 104
wall tension in, 107
Heart block, 123
complete, 126*f*
Mobitz type 2 second-degree, 126, 126*f*
Heart failure
aldosterone antagonists and, 132
ANP and, 133
chronic, 122
compensatory mechanisms in, 136, 136*t*
defined, 135
diastolic, 106, 135
digitalis and, 122
high-output, 136
systolic, 106, 135
Heart murmur
pathophysiology of, 114
types of, 115*f*
Heart rate
autonomic influence of SA node on, 119
myocardial oxygen demand and, 116
Heart valve
function of, 102, 103*f*
See also specific types
Helium dilution, 155, 155*f*
Heme group, 160
Hemidesmosome
intermediate filaments and, 5
structure and function of, 6
Hemiretina, 49
Hemoglobin, types of, 160
Hemoglobin-O_2 dissociation curve, 160, 161*f*
Hemolytic anemia, 5
Hemorrhage
ADH secretion and, 91
baroreceptor reflex and, 128*f*
hydrostatic pressure and, 134
shock and, 137
Henderson-Hasselbalch equation, 229
Hepatic gluconeogenesis, 89
Hereditary spherocytosis, 2*t*, 5
Hering-Breuer reflex, 165
Hermaphroditism, 88*t*
Hiatal hernia, 213
High-altitude respiration, 140, 166, 166*f*
Hindgut, 205
Hippocampus and memory, 60
Hirschsprung disease, 30, 208
Histamine, 214
Histotoxic hypoxia, 166, 166*t*
Horizontal cell, 49
Horizontal nystagmus, 58
Hormonal control systems independent of pituitary regulation, 92
Hormone
duodenal production of, 218, 218*t*
effect on anterior pituitary, 70*t*

function of, 65
hierarchical control of secretion of, 69, 70*f*
master list of, 66*t*
mechanism of action of, 65
types of, 65, 66*t*
See also specific types
Hormone-binding protein, 68, 69*t*
Hormone-receptor complex
cortisol and, 73
steroid hormones and, 65, 68*f*
Human chorionic gonadotropin (hCG), 87
Humidified tracheal air, 148
Hunter syndrome, 4*t*
Huntington disease, 16
Hurler syndrome, 4*t*
Hyaline membrane disease, 148
Hydrogen ion, 116
Hydrolysis, 217
Hydrophilic substance and cell membrane, 1
Hydrophobic substance and cell membrane, 1
Hydrostatic pressure, glomerular, 170, 171*f*, 172
11-Hydroxylase deficiency, 77
21-Hydroxylase deficiency, 76, 76*f*, 77
Hyperaldosteronism, 96
Hypercalcemia
calcium homeostasis and, 98
calcium-phosphate and, 100
causes of, 98
hyperparathyroidism and, 203
pancreatitis and, 220
primary hyperparathyroidism and, 98
Hypercapnia
causes of, 238*t*
chemoreceptors and, 164
hypoxia and, 165
peripheral chemoreceptors and, 165
Hypercortisolism
adrenal gland tumors and, 71
clinical features of, 77*t*
mineralocorticoid excess and, 237, 237*t*
pathophysiology of, 74
Hypergastrinemia, 217
Hyperglycemia
acidosis and, 94
DKA and, 94
glucagon and, 96
growth hormone and, 90, 91
insulin deficiency and, 94
type II diabetes and, 95
Hyperglycemic diuresis, 95
Hyperinsulinemia, 95
Hyperkalemia
acute kidney failure and, 197
albuterol and, 198
defined, 14
digitalis and, 198
DKA and, 94–95, 198, 234
insulin and, 94
nephron function and, 186*t*
potassium excretion and, 200*f*
renal dysfunction and, 199
Hyperkalemic RTA (Type 1V), 233*t*
Hypernatremia, 132, 243
Hyperosmolar hyperglycemic nonketotic coma (HHNC), 95
Hyperosmolar hypertonic syndrome (HHS), 95
Hyperosmotic volume contraction, 244, 244*f*
Hyperosmotic volume expansion, 244, 245*f*
Hyperparathyroidism
compensatory
chronic kidney disease and, 203
defined, 101
primary
causes of, 98
health issues associated with, 98
problem of, 203
secondary
chronic kidney disease and, 203
PTH and, 101
Hyperphosphatemia
calcitriol and, 202
metastatic calcification and, 100
physiologic responses to, 203
PTH and, 98, 202, 203
Hyperpigmentation, 76
Hyperpnea, 167*t*
Hyperpolarization, 13
Hyperprolactinemia
causes of, 88
effects of estrogen and progesterone on, 86
in males, 88, 89
in nonpregnant females, 89
treatment of, 89
Hypertension
adaptations to, 117
afterload and, 135
CAH and, 71
cortisol and, 74
hypercortisolic states and, 74
hypertrophied heart and, 116
isolated systolic, 130
Non-dihydropyridine calcium channel blocking drugs and, 122
renal artery stenosis and, 132
in unilateral renal artery stenosis, 174
Hyperthyroidism
amiodarone and, 78
BMR and, 78, 80
catecholamines and, 79
differential diagnosis of, 80, 81*t*
laboratory evaluation of, 80, 80*t*
pulse pressure and, 102
symptoms of, 80
thionamides and, 78
unintentional weight loss and, 81
Hypertonic solution, 7, 7*f*
Hypertriglyceridemia, 220
Hypertrophic cardiomyopathy, 117, 135
Hypertrophic pyloric stenosis, 225
Hyperventilation
causes of, 167*t*
causing, 163
chemoreceptors and, 164
exercise and, 165
high altitudes and, 164
metabolic acidosis and, 233
peripheral chemoreceptors and, 165
Hypoalbuminemia
causes of, 134
edema and, 134, 242
total plasma calcium levels and, 98
Hypocalcemia
chronic renal failure and, 101
enhanced membrane excitability and, 98
ethylene glycol and, 236*f*
primary hyperparathyroidism and, 203
PTH and, 100, 101
total plasma calcium levels and, 98
Hypochloremic metabolic alkalosis, 189, 215
Hypocortisolism, 75
Hypoglycemia
C peptide and, 95
cortisol secretion and, 71
epinephrine and, 97
growth hormone and, 90, 91
sulfonylurea drugs and, 95
Hypokalemia
aldosterone and, 132
cortisol and, 74
DKA and, 198
loop diuretics and, 189
metabolic acidosis and, 236
potassium secretion and, 201, 227
Hyponatremia, 189, 243
Hypophosphatemia
calcitriol and, 202
hyperparathyroidism and, 203
physiologic responses to, 203
Hyporeninemic hyperaldosteronism RTA (Type 1V), 233*t*
Hyposmia, 59
Hyposmotic fluid, 244
Hyposmotic volume
contraction of, 244, 244*f*
expansion of, 245, 245*f*
Hypotension
acute renal failure and, 176
adrenal insufficiency and, 76
CAH and, 71, 76, 77
defined, 129
diastolic perfusion pressure and, 116
orthostatic, 129
in tubular epithelial cells, 196
Hypothalamic growth hormone-releasing hormone (GHRH), 90
Hypothalamic hormones, 66*t*
Hypothalamic nuclei, 91
Hypothalamic osmoreceptor, 132
Hypothalamic tumor, 80, 80*t*
Hypothalamic-hypophyseal portal system, 69, 70*f*, 70*t*
Hypothalamic-pituitary-adrenal axis
determinants of, 71*f*
overview of, 70
regulation of, 71
Hypothalamic-pituitary-endocrine organ axis, 67*f*
Hypothalamic-pituitary-gonadal axis, 82
Hypothalamic-pituitary-thyroid axis, 77
Hypothalamus
autonomic nervous system and, 27
defects in, 70
hormone secretion and, 67*f*, 69
Hypothyroidism
amiodarone and, 78
classification of, 70
etiology and differential diagnosis of, 82*t*
laboratory values associated with, 82*t*
signs and symptoms of, 81
treatment of, 80
Hypotonic solution, 7, 7*f*
Hypoventilation
defined, 167*t*
hypoxemia and, 238
Hypovolemia
ADH and, 243
dumping syndrome and, 218
ECV decrease and, 244
Hypovolemic shock, 137, 137*t*
Hypoxemia
ATN and, 176
defined, 159
metabolic alkalosis and, 238
overview of, 165
Hypoxia
at high altitudes, 164
hyperventilation and, 165
overview of, 165
physiologic responses to, 165
right-to-left shunts and, 154
treatment of, 166
in tubular epithelial cells, 196
types of, 166*t*
Hypoxia-induced polycythemia, 166
Hypoxia-induced vasoconstriction
in fetal lungs, 153
high altitudes and, 153
overview of, 153
V/Q matching and, 152
Hypoxic hypoxia, 166, 166*t*
Hysteresis, 145

I

I band, 20
I cells, 218*t*
Iatrogenic hypercortisolism, 75
Iatrogenic hypocortisolism, 75
Iatrogenic thyroiditis, 82*t*
I-cell disease, 3
Idiopathic dilated cardiomyopathy, 118
Idiopathic pulmonary fibrosis, 150
Immotile cilia syndrome, 5
Immunoglobulin G (IgG) autoantibody, 80
Immunoglobulin light chain, 170
Implantable cardioverter-defibrillator (ICD), 117
Impotence, 88
Indicator substance, 242
Inferior colliculus, 54
Inferior mesenteric artery, 205
Inferior pons, 164
Inflammation
bronchial muscles and, 144
vascular permeability and, 134
Inhibin, 84, 85
Inhibitory postsynaptic potential (IPSP), 15

Inner ear, 52
Inotropy
  defined, 23
  heart and, 122
Inspiration (respirational)
  driving force for, 141
  muscles of, 141*f*
  overview of, 140
  sources of resistance during, 141
Inspiratory capacity (IC), 156
Inspiratory reserve volume (IRV), 155
Insulin
  diabetes mellitus and, 95
  hyperkalemia and, 94, 198
  mechanism of action of, 92
  metabolic actions of, 93, 93*t*
  Na^+,K^+-ATPase pump and, 197
  physiologic actions of, 92*t*, 93*f*
  regulation of secretion of, 93*f*
  source of, 92
Insulin resistance, 2*t*, 95
Insulin-dependent diabetes mellitus (IDDM). *See* Diabetes mellitus, type I
Insulinoma, 95
Intention tremor, 41*t*
Intercalated cell and potassium reabsorption, 199, 200*f*
Intercostal muscle, 140, 141*f*
Interdigestive period, 225
Intermediolateral horn of the spinal cord
  parasympathetic nerves and, 29
  sympathetic nerves and, 28
Internal carotid system, 63
Internal respiration, 138
Interposed nuclei lesions, 40
Interstitial fluid
  composition of, 242
  distribution of, 241*f*
  in ECF, 241
Interstitial hydrostatic pressure, 134
Interstitial lung disease, 159*t*
Interstitial oncotic pressure, 134
Interstitial osmotic gradient, 190, 192
Intestinal contraction, 209
Intestinal motility
  electrical basis for, 209
  migrating myoelectric complex and, 225
  muscularis propria (externa) and, 207
  myenteric plexus and, 208
  parasympathetic nerves and, 208, 208*t*
Intestinal obstruction, 208
Intestinal phase of digestion, 214
Intestinal smooth muscle cells (SMCs), 209
Intra-aortic balloon pump, 116
Intracardiac shunting, 154
Intracellular fluid
  composition of, 242
  distribution of, 241, 241*f*
  vs. extracellular fluid, 2, 3*t*
Intrafusal muscle fiber, 34
Intrapleural pressure, 142
Intravascular volume, 130
Intrinsic factor, 214, 215, 224
Inulin, 178, 242
Involuntary movement, 33
Iodide pump, 77
Ion, permeant, 11
Ipsilateral blindness, 49
Ipsilateral hemianopia, 51*f*
Ipsilateral LGN, 49
Iris, 52
Iron (Fe) absorption, 225, 226*f*
Iron-deficiency anemia, 166*t*
Irritant receptor, 165
Ischemia, 176
Ischemic cardiomyopathy, 114
Ischemic hypoxia, 166*t*
Islets of Langerhans, 92
Isolated systolic hypertension, 130
Isometric muscle contraction, 20
Isosmotic reabsorption, 183
Isosmotic volume contraction, 244, 244*f*
Isosmotic volume expansion, 244, 245*f*
Isotonic, 7
Isotonic muscle contraction, 20
Isotonic NaCl infusion, 244, 245*f*
Isovolumic contraction, 110
Isovolumic relaxation, 110

J

Jugular venous distention, 111
Juxtaglomerular apparatus, 131, 175, 175*f*

K

K complex, 62
Kartagener syndrome, 5, 139
Keratoconjunctivitis sicca, 211
Kidney
  acid-base balance and, 228, 229
  aldosterone and, 96
  ANS effects on, 28*t*
  autoregulatory mechanisms in, 172
  cortisol and, 74
  diabetes insipidus (DI) and, 91
  ECF volume and, 243
  function of, 168
  functional anatomy of, 168, 168*f*
  intravascular volume control by, 130
  potassium excretion and, 197, 198
  potassium handling by, 198, 198*f*
  urine excretion and, 190
Kinetic energy work and stroke volume, 108
Kinocilium, 56
Klinefelter syndrome, 88*t*
Krabbe disease, 4*t*
Kussmaul respiration, 167, 167*t*

L

Lactase deficiency, 222
Lactation, 88
Lactic acid accumulation, 117
Lactic acidosis, 233, 236*f*
Lactogenesis, 87
Lambert-Eaton syndrome, 15
Lamina propria, 207
Laminar air flow, 144
Laminar blood flow, 114
Language, 61
Laplace equation, 107
Laplace's law, 146, 148
Large intestine
  electrolyte movements in, 227
  functional anatomy of, 227, 227*f*
  structural comparison of, with small intestine, 227, 227*t*
Lateral cerebellar lesion and decomposition of movement and, 40
Lateral corticospinal tract
  lesions on, 37
  movement and, 37
Lateral geniculate nucleus (LGN), 49
Lateral lemniscus, 54
Lateral olfactory stria, 59
Lateral pterygoid, 212
Lateral vestibulospinal tract, 56
Learning, 60
Leber hereditary optic neuropathy (LHON), 4
Lecithin, 221*t*
Left bundle branch block (LBBB), 103, 104*f*
Left ventricular dysfunction, 137
Left ventricular end-diastolic pressure (LVEDP), 152
Left ventricular hypertrophy, 135
Left-to-right shunt, 154, 154*t*
Length-tension relationship, 21, 21*f*
Length-tension relationship of the heart theory, 106
Lens (optic), 46
Lenticulostriate vessel, 63
Leukotriene, 74
Leukotriene-receptor antagonist, 144
Leuprolide, 84
Libido, loss of, 88, 89
Lichtheim's disease, 43
Licorice ingestion, 237, 237*t*
Liddle syndrome, 186*t*, 237, 237*t*
Ligand-gated receptor, 15
Light touch receptor, 42
Lingual lipase, 223
Lingual nerve, 59
Lipase, 223
Lipid. *See* Fat
Lipid bilayer
  as cell membrane structure, 1
  in nuclei, 2
Lipogenesis and insulin, 93
Lipoid nephrosis, 170
Lipolysis
  cortisol and, 73
  epinephrine and, 97
  glucagon and, 96
  growth hormone and, 89
  insulin and, 94
Lipoxygenase inhibitor, 144
Liver, 220
Liver disease, 134, 205
Locked-in syndrome, 64
Long-term memory, 60
Loop diuretic
  aldosterone secretion and, 201
  features of, 204*t*
  function of, 176, 190, 193
  Na^+,K^+-ATPase channel and, 189
  renal failure and, 185
Loop of Henle
  as countercurrent system, 192, 192*f*, 193*f*
  function of, 186*t*
  osmotic gradient and kidney and, 192
  reabsorption of salt and water along, 186, 189
  sodium and water handling in, 189, 189*f*
  sodium handling and, 187*t*
  vasa recta and, 196
Lower esophageal sphincter (LES), 213, 213*f*
Lower motor neuron
  lesions of, 38, 38*t*
  upper motor neurons and, 37
Lung
  acid-base balance and, 228
  compliance of, 146
    air-inflated vs. saline-inflated, 147*f*
    chest wall and, 146*f*
    emphysema and, 145
    hysteresis and, 145, 145*f*
  compliance resistance of, 147
  See also Pulmonary *entries*
Lung capacities, 156
Lung disease
  diffusion limitation and, 149
  FEV_1/FVC ratio and, 157
  lung volumes and, 154
  respiratory acidosis and, 238*t*
  as type of hypoxia, 166*t*
Lung distensibility, 145
Lung volume
  lung diseases and, 154
  measurement of, 154, 155*f*
Lung–chest wall system, 145, 146*f*
Lusitropy, 23
Luteal phase of menstruation, 86*f*, 87
Luteinizing hormone (LH)
  in females, 86
  in males, 84
Lymphatic system, 135
Lymphoma, 98
Lysosomal storage diseases, 3, 4*t*
Lysosome, 3

M

M line, 20
Macrocytic anemia, 215
Macula adherens, 6
Macula densa, 175, 175*f*
Macular input, 49
Malabsorption syndrome, 81
Male hermaphroditism, 83–84
Male pattern baldness, 83
Male pseudohermaphroditism, 88*t*
Male reproductive axis, 82, 83*f*

Malnutrition, 134
Mannitol, 242
Mannose-6-phosphate (M6P) tags, 3
Marfan syndrome, 112*f*, 113
Masseter, 212
Massive blood loss, 109
Mast cell stabilizer, 144
Mastication, 212
Mean arterial pressure (MAP) determinants, 125
Mechanoreceptor, 165
Medial descending system (MDS)
  lesions on, 35
  movement and, 34
Medial geniculate body, 54
Medial lemniscal pathway, 43
Medial lemnisci, 43
Medial longitudinal fasciculus (MLF), 56, 58*f*
Medial pterygoid, 212
Medial recti, 52
Medulla
  respiration and, 163
  respiration and dorsal, 163, 165
Medullary reticulospinal tract and movement, 36
Medullary vasomotor center, 127, 127*f*
Megaloblastic anemia, 215
Meissner corpuscle, 42
Meissner plexus
  function of, 207
  location of, 207
  overview of, 30
Melanin, 47
Melanocyte-stimulating hormone (MSH), 76
Membrane, transport across, 6
Membrane invagination, 9
Membrane permeability (P)
  proportionality of, 6
  RMP and, 11
  selective, equilibrium potential and, 11
Membrane potential, resting
  overview of, 11
  SMCs and, 209
Membrane-spanning receptor and hormones, 68
Membranous labyrinth, 52
Membranous nephropathy, 171
Memory, 60
Memory tract, 60
Meningitis, 27
Menses, 86, 87
Menstrual cycle, 86, 86*f*
Mesolimbic pathway, 18
Messenger RNA synthesis, 2
Metabolic acidosis
  acute diarrhea and, 227
  causes of, 232
  ethylene glycol and, 236*f*
  extracellular pH and, 197
  Kussmaul respiration and, 167
  methanol and, 235*f*
  overview of, 232
  in renal failure, 231
  respiratory compensation and, 233
Metabolic alkalosis
  aldosterone and, 132
  carbonic anhydrase inhibitors and, 230
  causes of, 236
  hydrogen and, 198
  mineralocorticoid excess states resulting in, 237*t*
  overview of, 236
  sample case, 237
Metabolic compensation for respiratory acidosis, 238
Metabolism
  acid-base balance and, 228
  local blood flow regulation and, 129
Metaplasia, 207
Metastatic calcification, 100
metastatic cancer, 76
Methanol
  ingestion of, 234
  metabolism of, 235*f*
Methemoglobin, 160
Methemoglobinemia, 160
Methimazole, 77
Metoclopramide, 209
Metoprolol, 122
Micelle, 223
Microcytic anemia, 225
Microfilament, 4, 4*t*
Microtubule, 4, 4*t*
Microvilli
  in the small intestine, 206
  structure and function of, 5
Middle cerebral artery (MCA), 63
Middle ear, 52
Midgut, 205
Midsystolic "click,"114
Migrating myoelectric complex, 225
Milk-alkali syndrome, 98
Mineralocorticoid
  adrenal steroidogenesis pathways and, 72*f*, 76*f*
  impaired synthesis of, 76
  synthesis of, 72
Mineralocorticoid action, 74
Mineralocorticoid excess, 237, 237*t*
Minimal change disease, 170
Minute ventilation rate, 158
Mitochondria, 3
Mitochondrial DNA
  function of, 3
  inheritance of, 4
Mitochondrial dysfunction, 4
Mitochondrial energy production, 4
Mitral commissurotomy, 113
Mitral insufficiency
  hemodynamic changes in, 114*f*
  increased preload and, 118
  pathophysiology of, 113
Mitral regurgitation
  hemodynamic changes in, 114*f*
  increased preload and, 118
  pathophysiology of, 113
  ventricular gallop and, 104
Mitral stenosis
  AV valve closure and, 103
  diastolic heart failure and, 135
  pathophysiology of, 113
  schematic of, 113*f*
Mitral valve
  function of, 102
  prolapse of, 114
  replacement of, 113
Mixed acid-base disorder, 228
Mixed gland, 211, 212*f*
Molecule, permeability of small hydrophobic, 6
Monoamine, 16
Monoamine deficiency theory of depression, 17
Monoamine oxidase (MAO), 16
5'-Monodeiodinase, 80
Motilin, 225
Motility. *See* Intestinal motility
Motor end plate. *See* Neuromuscular junction (NMJ)
Motor nerve fiber, 34*t*
Motor neuron
  features of, 33, 34*t*
  upper and lower
    lesions of, 38, 38*t*
    relationship of, 37
Motor thalamus
  basal ganglia and, 39
  movement and, 38, 39
Motor unit of skeletal muscle, 21
Movement
  basal ganglia and, 38
  cerebellum and, 39
  cerebral cortex and, 34
  classification of, 33
  control of, 33
  involuntary, 33
  spinal cord tracts and, 34
  See also Voluntary movement
Mucociliary escalator, 139
Mucociliary tract, 139
Mucosa
  functional anatomy of, 206
  hormones produced in, 218*t*
  mucous cells and, 217
  in the small intestine, 206*f*
Mucosal blood flow, 217
Mucosal epithelium, 206
Mucous cells, 217, 217*f*
Mucus-bicarbonate layer, 217, 217*f*
MUDPILES, 232
Multiple myeloma, 170
Multiple sclerosis, 14, 27
Multiunit smooth muscle, 22
Murmur. *See* Heart murmur
Muscarinic acetylcholine receptor, 211
Muscarinic receptor, 32, 123
Muscle, 93*t*
  See also specific types
Muscle fiber
  extrafusal, 34
  intrafusal, 34
Muscle spindle, 40
Muscle wasting, 74
Muscular dystrophy, 24
Muscularis mucosa, 207
Muscularis propria (externa), 207
Myasthenia crisis, 238
Myasthenia gravis, 2*t*, 16
Myelin and action potential, 14
Myenteric plexus
  function of, 208
  overview of, 30
  peristalsis and, 209
Myocardial adaptation
  to increased afterload, 117, 118*f*
  to increased preload, 118, 118*f*
Myocardial hypertrophy, 136, 136*t*
Myocardial infarction, 135
  atrial gallop and, 104
  rupture of papillary muscle in, 114
  as type of hypoxia, 166*t*
Myocardial ischemia
  cause of, 135
  diastolic heart failure and, 135
  predisposition to, 116
  systolic heart failure and, 135
Myocardial oxygen demand
  angina pectoris and, 117
  determinants of, 116
Myocardial oxygen supply, 115
Myocardial wall tension, 116
Myocarditis, 137, 236*f*
Myocyte disk, 118
Myocyte gap junction, 120
Myoelectric complex, 225
Myogenic mechanism
  arteriolar pressure and, 175
  pathophysiology of, 175
Myogenicity, 129, 130*f*
Myxedema coma, 82

N

Na^+,K^+-ATPase pump
  aldosterone and, 199
  membrane potential and, 12
  potassium distribution and, 197
  potassium secretion and, 199
  proximal tubular reabsorption and, 181
  sodium distribution and, 197
  sodium reabsorption and, 187
  stoichiometry of, 182, 187
NaCl intake, 244, 245*f*
Nasal hemiretina, 49
Nebivolol, 122
Negative intrapleural pressure, 141
Neocerebellum and movement, 39
Neonatal respiratory distress syndrome, 148
Nephrogenic diabetes insipidus
  diagnosing, 92
  Loop of Henle and, 186*t*
  pathophysiology of, 91
  renal tubules and, 133
Nephron
  anatomy of, 169*f*
  calcium handling in, 202*f*
  distal
    potassium handling and, 198, 199*f*
    reabsorption of salt and water in, 190*f*
    urine concentration and, 193
  filtration, reabsorption, and secretion along, 178, 178*f*

Nephron (*Continued*)
  function of, 168
  phosphate handling in, 201*f*
  reabsorption of salt and water in distal, 189
  segmental functions, 186*t*, 187*f*
  sodium and water handling along, 186
  sodium handling along, 186*f*, 187*t*
  structure of, 168, 168*f*
Nephrotic syndrome, 170, 242
Nerve fiber, sensory, 41*t*
Nerve transmission, 11
Nervous system
  functional anatomy of, 25
  organization of, 25
  overview of, 25
  See also specific types
Net filtration pressure (NFP)
  glomerular function regulation and, 170
  overview of, 133
  Starling forces and, 134
Neurogenic shock, 137, 137*t*
Neurohormonal activation, 136, 136*t*
Neurohypophysis and hormone secretion, 69
Neuromuscular disorders, 238*t*
Neuromuscular junction (NMJ)
  drugs and toxins acting at, 19*t*
  structure of, 18
  synaptic transmissions and, 19*t*
Neuromuscular transmission, 18, 19*t*
Neuron
  comparison of in nervous systems, 30*t*
  See also specific types
Neuron-to-neuron junction, 19*t*
Neuropeptide, 18
Neurosecretory granule, 69
Neurotransmitter receptor types, 32
Neurotransmitter types, 15
Nicotinic receptor, 32
Niemann-Pick disease, 4*t*
Nigrostriatal pathway and dopaminergic transmission, 18
Nitrate and angina pectoris, 117
Nitric oxide (NO) and autonomic nervous system, 31
Nociception, 45
Nodes of Ranvier
  action potential and, 14
  conduction velocity and, 15
Nondepolarizing neuromuscular blocking drugs, 19*t*
Non–insulin-dependent diabetes mellitus (NIDDM). *See* Diabetes mellitus, type II
Nonlaminar blood flow, 114
Non–rapid eye movement (NREM) sleep, 62
Nonsteroidal anti-inflammatory drugs (NSAIDs), 217
Norepinephrine (NE)
  adrenergic receptors and, 32
  autonomic nervous system and, 30, 33*f*
  function of, 17
  overview of, 96
  pathway and adrenergic transmission, 17*f*
  physiologic actions of, 96
  sympathetic innervation of the heart and, 122
  sympathetic nerves and, 28
Normal anion gap acidosis
  causes of, 232, 235
  renal failure and, 233
  sample case, 233
NSAID, 217
Nuclear envelope, 2
Nucleolus, 2
Nucleoplasm, 2
Nucleus
  cellular, 1
  composition of, 2*f*
  roles of, 2
  structure and function, 2
Nucleus cuneatus, 43
Nucleus gracilis, 43
Nystagmus
  defined, 41*t*, 57
  pendular, 40
  spontaneous, 57
  See also specific types

O

O_2 saturation (SaO_2), 161
Octreotide, 91
Ocular reflex, 49
Oculomotor nerve (CN III), 50, 51*f*
11β-(OH)-steroid dehydrogenase deficiency, 237, 237*t*
Olfaction, 58
Olfactory apparatus, 58
Olfactory bulb, 58*f*, 59
Olfactory epithelium, 58, 58*f*
Olfactory gland, 59
Olfactory nerve (CN I), 59
Olfactory receptor cell, 58
Olfactory tract, 59
Olfactory transduction, 59
Oncotic pressure, 170, 171*f*
Ondine curse, 163, 167*t*
Ophthalmopathy, 81
Optic chiasm, 49
Optic disc, 48
Optic nerve (CN II), 49
Optic radiation, 49
Optic tract lesion, 49, 51*f*
Organ of Corti
  auditory transduction and, 54
  structure and function of, 53
Organelle
  membrane-enclosed, 3
  non-membrane enclosed, 5
Organic anion transport, 185, 185*f*
Organophosphates and neuromuscular junction, 19*t*
Orthostatic hypotension, 129
Osmolarity
  ADH and, 243
  increased ECV and, 245
  regulation of, 242, 243
Osmoreceptor, 91
Osmosis, 7, 7*f*
Osmotic diuresis, 94
Osmotic pressure, 7
Ossicle, 52
Osteitis fibrosa cystica, 98, 101, 203
Osteoblast, 74
Osteoclast, 74, 99
Osteoclastogenic molecule, 99
Osteomalacia, 100
Osteoporosis, 74, 98
Outer ear, 52
Ovarian hormone, 66*t*
Ovaries and steroid hormones, 73
Overdrive suppression, 119
Overshoot potential, 13
Ovulation, 86
Oxidative burst, 10
Oxygen
  administration of and respiratory acidosis, 238*t*
  binding to hemoglobin, 160
  diffusion rate of, 149
  increased delivery to tissues of, 161
  partial pressure of, 148, 149*t*
  stages of delivery of, 138
  transport of, 159
Oxygen tension (PaO_2), 159
Oxytocin, 92

P

P wave (ECG), 123
Pacemaker, 119
Pacinian corpuscle, 42
Pain fiber, 45
Pain perception, 45
Pain receptor, 45
Paleocerebellum and movement, 40
Pancreas
  embryologic development of, 220
  functional anatomy of, 219, 219*f*
  pathophysiology of, 220
  secretions of, 220, 220*f*
Pancreatic amylase, 222
Pancreatic dysfunction, 224
Pancreatic hormone
  physiologic actions of, 66*t*, 92*t*
  sources of, 92
Pancreatic insufficiency, 220
Pancreatic lipase, 223
Pancreatitis
  annular pancreas and, 220
  digestion and, 220
  triglycerides and, 94
  vitamin B12 absorption and, 224
Papillae, 59, 60*f*
Papillary muscle, 114
Para-aminohippuric acid (PAH), 179, 180*f*
Paracellular transport
  defined, 11, 11*f*
  renal, 181, 181*f*
Paradoxical breathing, 141
Paraesophageal hiatal hernia, 213
Parafollicular cell, 77
Paraneoplastic syndrome, 98
Paraproteinemia, 170
Parasympathetic innervation of the heart, 122, 122*f*
Parasympathetic nervous system (PNS)
  function of, 27
  functional anatomy of, 29, 31*f*
  GI tract and, 208, 208*f*
  overview of, 28
Parasympathetic stimulation of cardiac muscle, 23
Parasympathomimetics, 32
Parathyroid gland, 202*f*
  function of, 201
Parathyroid hormone (PTH)
  calcitriol and, 99, 203
  calcium homeostasis and, 97
  hypocalcemia and, 101
  organ effects of, 99*t*
  osteoclast formation and, 99
  overview of, 98, 99*f*
  phosphate and, 100
  plasma phosphate and, 201, 201*f*
Parietal cells
  mechanism of secretion by, 216*f*
  pernicious anemia and, 215
  pharmacologic regulation of, 216*f*
  secretions from, 214
Parkinson disease
  basal ganglia and, 39*f*
  dopamine agonists and, 18
  features of, 39
  L-DOPA and, 31
Parotid gland, 211
Patent ductus arteriosus, 154
Pedicel, 25
Pendular reflex, 40
Penis, ANS effects on, 28*t*
Pepsin, 217
Pepsinogen, 214, 217
Peptic ulcer disease, 9, 217
Peptide hormone, 65
Percutaneous balloon valvuloplasty, 113
Perfusion limited gas exchange, 149, 150, 150*f*
Perfusion of unventilated alveoli, 154
Perilymph, 52
Perimacular input, 49
Peripheral chemoreceptor, 165
Peripheral nervous system (PNS) components, 25
Peripheral neuropathy, 215
Peripheral vision, 49
Peristalsis
  esophagus and, 213, 213*f*
  migrating myoelectric complex and, 225
  muscularis propria (externa) and, 207
  myenteric plexus and, 208
  process of, 209, 210*f*
Peritonitis, 208
Peritubular capillaries, 183, 183*f*
Pernicious anemia, 215
Peroxidase, 77
pH of human body, 228
Phagocytosis
  characteristics of, 10
  lysosomes and, 3
Phagosome, 10
Phasic receptor, 42

Pheochromocytoma, 97
Phosphate, renal contribution to control of, 201, 201*f*
Phosphate homeostasis, 100
Phospholipase, 74
Phospholipids and cell membrane, 1
Physiologic dead space, 158
Pilocarpine, 211
Pineal gland and blood-brain barrier, 26
Pinocytosis, 9
Pituitary adenoma, 80*t*, 90
Pituitary Cushing, 75
Pituitary dwarfism, 89
Pituitary gland
  defects in, 70
  posterior
    hormonal control systems of, 91
    hormones of, 91
  tumor of, 75
Pituitary tumor, 80
Plantar flexion and Babinski sign, 37, 37*f*
Plasma
  cations and anions in, 228, 228*t*
  composition of, 242
  distribution of, 241, 241*f*
  measurement of, 242
Plasma albumin concentration, 134
Plasma calcium, 74
Plasma colloid osmotic pressure, 134
Plasma glucose
  insulin and, 93, 93*f*
  threshold value for, 184
Plasma K^+ concentration and potassium, 199
Plasma membrane
  maintenance of, 3
  See also Cell membrane
Plasma oncotic pressure, 134
Plasma osmolality
  defined, 193
  renal responses to changes in, 193, 194*f*
Plasma potassium
  renal control of, 197
  renal potassium excretion and, 199
  See also Potassium
Plasma protein, 69*t*
Plasma volume
  ADH secretion and, 91
  expansion of, 74
  reduction of, 92, 94
Pleural effusion, 147
Pleural fluid, 144, 144*f*
Pleuritic condition, 145
Pneumocyte, 139
Pneumonia
  achalasia and, 213
  gas exchange and, 7
  hypoxia and, 165
  physiologic shunts and, 154
Pneumotaxic center, 164
Podocyte, 170, 170*f*
Poiseuille equation, 125
Poiseuille's equation, 143
Polycythemia, 166
Polycythemia vera, 166
Polydipsia, 94
Polyphagia, 94
Polyuria, 94
Pons
  inferior, 164
  respiration and, 163, 163*f*
  superior, 164
Pontine reticulospinal tract and movement, 36
Pontocerebellum and movement, 39
Portal hypertension, 205
Portal vein, 205
Posterior cerebral artery (PCA)
  circulatory compromise of, 64
  features and function of, 64
Posterior pituitary, 69
Posterior pituitary hormone, 66*t*, 67*f*
Postganglionic neuron
  parasympathetic nerves and, 29, 30
  physiology of, 28
  sympathetic nerves and, 28
Postmenopause, 85
Postpartum hemorrhage, 92
Postrotatory nystagmus, 58
Potassium
  aldosterone and excretion of, 200*f*
  coronary vascular resistance and, 116
  distal nephron secretion of, 199, 199*f*
  distribution of, 197
  large intestine absorption of, 227
  regulation of secretion and reabsorption of, 199
  renal control of plasma, 197
  renal handling of, 198, 198*f*
  response to depletion of, 199
Potassium homeostasis, 198
Potassium ion concentration, 197
Potassium-sparing diuretic, 201
PR interval (ECG), 103, 123, 126*f*
Precocious puberty
  CAH and, 71, 76, 77
  pathophysiology of, 88*t*
Preganglionic nerve fiber, 29
Preganglionic neuron
  parasympathetic nerves and, 29
  sympathetic nerves and, 28
Pregnancy hormone, 68
Pregnenolone, 72
Preload
  myocardial adaptations to increased, 118, 118*f*
  stroke volume and, 106, 106*f*, 108*f*
Presbycusis, 54
Pressure diuresis, 130
Pressure natriuresis, 130, 131*f*
Pressure-volume work, 108
Pretectal area of the midbrain, 50
Pretibial myxedema, 81
Primary active transport, 9, 9*f*
Primary auditory cortex, 54
Primary hyperaldosteronism, 132, 237
Primary hyperparathyroidism, 98
Primary olfactory cortex, 59
Primary polycythemia, 166
Principal cell and potassium secretion, 199, 200*f*
Prinzmetal angina, 117
Progesterone
  physiologic actions of, 86
  regulation of secretion of, 86
Pro-insulin, 95
Prolactin
  pathophysiology of, 89
  physiologic actions of, 87, 89*f*
  secretion of, 88
Prolactinoma, 18
Proliferative phase of menstruation, 86, 86*f*
Propylthiouracil (PTU), 77
Prostaglandin, 74, 174
Protein
  acid-base balance and, 228
  anchor, 2*t*
  carrier
    function and pathophysiology of, 2*t*
    saturation of, 7
    stereospecificity of, 7
  channel, 2*t*
  cytoskeletal, 4*t*
  digestion of, 217, 222*t*, 223
  identifier, 2*t*
  insulin and, 93
  integrin cell adhesion, 6
  post-translational modification of, 3
  receptor, 2*t*
  See also specific types
Protein hormone, 65
Protein-digesting enzyme, 214
Proteinuria, 170, 171
Proteoglycan hormone, 65
Proton pump inhibitors, 9
Proximal muscle, 37
Proximal renal tubular acidosis, 2*t*
Proximal RTA (Type II), 233*t*
Proximal tubule
  ATN and, 176
  function of, 186*t*
  glomerulotubular balance and, 183
  organic cations secreted by, 184, 185*t*
  paracellular transport and, 181
  phosphate transport in, 202, 202*f*
  reabsorption of salt and water from
    changes in substance concentration along, 181*f*
    pressures driving, 183*f*
    process of, 181, 187
    segmental functions, 186, 187*f*
    solvent drag and, 182*f*
    steps in, 182*f*
  sodium handling along, 187*t*
Pseudohypoaldosteronism, 186*t*
Pseudohyponatremia, 235
Pseudopodia, 10
Puberty in males, 84
Pulmonary airway disease, 158
Pulmonary arterial hypertension, 32
Pulmonary artery catheter, 152
Pulmonary artery occlusion pressure, 152
Pulmonary blood flow
  exercise and, 153, 154
  pressures in, 150
  zones of, 151, 151*f*
Pulmonary circulation, 150, 151*f*
Pulmonary compliance (C), 145, 147*f*
Pulmonary dead space, 157
Pulmonary edema
  mitral regurgitation and, 114
  physiologic shunts and, 154
  stiff ventricle and, 117
Pulmonary elastance (E), 145, 146
Pulmonary embolism, 159*t*
Pulmonary fibrosis
  a-a gradient and, 159*t*
  compliance resistance and, 144
  lung volumes and, 154
  oxygen diffusion and, 149
Pulmonary hemodynamics, 150
Pulmonary hypertension, 104*f*, 108, 112*f*
Pulmonary membrane
  diffusing capacity of, 149, 149*f*
  physiology of, 139, 140*f*
Pulmonary perfusion, 153, 153*f*
Pulmonary reflex, 165
Pulmonary venous congestion, 117
Pulmonary wedge device, 111
Pulmonic valve, 102
Pulse pressure, 102
Pulsus parvus et tardus, 112
Pump failure, 135, 136
Pupil (optic), 46
Pupillary light reflex, 49, 50, 51*f*
Purkinje fibers, 119, 120
Purkinje system, 118
Pursed-lip breathing, 146
Pyloric sphincter, 218, 219
Pyramidal tract and movement, 34, 35*t*

Q

QRS complex (ECG), 123

R

R protein, 224
Rachitic rosary, 100
Radiolabeled albumin, 242
RANKL (receptor for activation of nuclear factor kappa B), 99
Rapid eye movement (REM) sleep, 62
Rapidly adapting receptor, 42
Rate of diffusion (J)
  of charged substances, 6
  of a gas, 7
  of uncharged substances, 6
Receptive aphasia, 61
Receptive field, 41
Receptive relaxation, 209
Receptor cell, 56
Receptor potential, 41, 42*f*
Recruitment and pulmonary perfusion, 153, 153*f*
Red nucleus, 40
5α-Reductase deficiency, 88*t*
Referred pain, 46, 48*f*, 48*t*
Reflex, 33

Reflex (digestive), 225
Reflex loops, 209
Reflexive movement, 34
Refractive power, 52
Refractory period of action potentials, 13, 13*f*, 121
Relative refractory period, 13, 13*f*
Relaxed form of hemoglobin, 160
Renal artery stenosis, 131, 132, 174
Renal blood flow
  autoregulation of, 174, 174*f*
  overview of, 174, 174*f*
Renal blood flow (RBF), 180
Renal calculi, 98
Renal clearance. *See* Clearance
Renal failure
  acute
    acute tubular necrosis and, 176
    causes of, 196
    hyperkalemia and, 197
    sample case, 234
  anion gap acidosis and, 233
  causes of, 233
  diuretics and, 185
  ethylene glycol and, 236*f*
  GFR and, 199
  hyperphosphatemia and, 203
  hypocalcemia and, 101
  metabolic acidosis and, 231
Renal function
  defined, 176
  measurement of, 176, 178
Renal osteodystrophy, 101, 203
Renal papillary necrosis, 196
Renal plasma flow (RPF)
  clearance values and, 179
  Fick principle for measuring, 179, 180*f*
  filtration fraction and, 172
  Starling force changes and, 173*t*
Renal transport mechanism
  general tubular function and, 180, 181*f*
  overview of, 180
  pathophysiology of, 185, 186*t*
  reabsorption of salt and water in, 176, 181
Renal tubular acidosis (RTA)
  defined, 233, 236
  determining types of, 233
  metabolic acidosis and, 233
  types of, 233*t*
Renin-angiotensin-aldosterone neurohormonal cascade, 243
Renin-angiotensin-aldosterone system (RAAS), 130, 131, 131*f*
Repolarization and action potential, 13, 121
Reproductive disorders, 87, 88*t*
Residual volume (RV), 155, 155*f*
Respiration
  central control of, 163
  overview of control of, 163
  physiologic responses to high-altitude, 166*f*
  See also Breathing
Respiratory acidosis
  acidosis and, 232
  causes of, 238*t*
  compensation for, 238*t*
  overview of, 238
  sample case, 239
Respiratory airway
  compared to conducting airways, 139*t*
  function of, 138, 139
Respiratory alkalosis
  causes of, 239*t*
  compensation for, 239, 239*t*
  overview of, 238
  sample case, 240
Respiratory compensation
  metabolic acidosis and, 233
  metabolic alkalosis and, 236, 238
Respiratory cycle, 141, 142*f*
Respiratory failure in premature babies, 148
Respiratory pump, 109
Respiratory system
  functional anatomy of, 138
  overview of, 138
Rest and digest system. *See* Parasympathetic nervous system (PNS)
Resting membrane potential (RMP)
  action potential and, 120
  calculating, 12
  equilibrium potential, 11
  function of, 121
  overview of, 11
  selective permeability and, 11
  SMCs and, 209
Restrictive cardiomyopathy, 135
Restrictive pericarditis, 135
Reticulospinal tract and movement, 36
Retina
  structure of, 47, 50*f*
  vision and, 46
Retinal, 48
Reverse chloride shift, 162
Reye syndrome, 234
Reynolds number, 115
Rheumatic fever, 112, 113
Rhodopsin, 48
Rhythmic movement, 34
Ribosomal RNA (rRNA), 2
Ribosome, 5
Rickets, 100
Riedel thyroiditis, 82*t*
Right hemianopia, 51*f*
Right hemianopia with macular sparing, 51*f*
Right lower quadrantanopia, 51*f*
Right upper quadrantanopia, 51*f*
Right-sided heart failure, 153
Right-to-left shunt, 154, 154*t*
Rigor mortis, 20
Rinne test, 54–55
Rod (optic), 48
Rolling hiatal hernia, 213
Romberg test, 41
Rough ER (rER), 3
Rugae, 206

S

S cells, 218, 218*t*
S1 (AV valve closure)
  accentuation of, 103
  causes of, 104
  defined, 102
S2 (semilunar valve closure)
  cardiac auscultation and, 110
  causes of, 104
  defined, 103
  reversed splitting of, 103, 104*f*
  splitting and respiration, 104*f*
S3 (ventricular gallop), 103
S4 (atrial gallop), 104
Saccule, 56
Salicylic acid toxicity, 234
Saliva
  composition and functions of, 210, 211*f*, 211*t*
  production of, 211
Salivary gland, 211, 212*f*
Salivation, 210
Salt retention (hypertension), 71
Salt wasting (hypotension)
  adrenal insufficiency and, 76
  CAH and, 71, 76, 77
Saltatory conduction, 14
Sarcoidosis, 98
Sarcolemma
  defined, 18
  skeletal muscle and, 19
Sarcomere
  skeletal muscle and, 19
  structure of, 19*f*
Sarcoplasmic reticulum, 19
Sarcoplasmic reticulum (ER), 19
Saturable transporter, 185
Scala media, 52
Scala tympani, 52
Scala vestibuli, 52
Schizophrenia, 18
Scotopsin, 48
Secondary active transport
  characteristics of, 9
  example of, 9*f*
  sodium reabsorption and, 187, 188*f*
Secondary hyperparathyroidism, 101
Secondary polycythemia, 166
Second-order neuron
  anterolateral system and, 44
  sensory pathways and, 42
  somatosensory system and, 43
  spinothalamic tract and, 44
  taste and, 60
Secretin, 218, 218*f*, 218*t*
Secretory diarrhea, 244, 244*f*
Secretory phase of menstruation, 86*f*, 87
Segmentation (digestive), 210, 210*f*
Selective membrane permeability of membranes, 11
Semicircular canal, 56
Semilunar valve
  function of, 102
  sounds of closure of
    cardiac auscultation and, 110
    causes of, 104
    defined, 103
    respiration and, 104*f*
Seminiferous tubule, 84
Senile calcific aortic stenosis, 112
Sensorineural deafness
  causes of, 54
  Rinne test and, 54–55, 56*t*
  vestibular neuromas and, 54
  Weber test and, 55, 56*t*
Sensory deficit, 41
Sensory homunculus, 43, 44*f*
Sensory nerve fiber classification, 41*t*
Sensory pathway, 42, 43*f*
Sensory receptor, 41, 42
Sensory system, 41
Sensory transduction, 41
Septic shock, 137, 137*t*
Serosa, 207
Serotonin (5-HT)
  function of, 17
  synthesis of, 17*f*
Serous gland, 211
Sertoli cell, 84
Sex steroid, 65
Shock
  pathophysiologic basis for classification of, 136
  signs and symptoms of, 136, 136*t*
  types of, 137*t*
Short-term memory, 60
Shunt
  anatomic, 154, 154*t*
  physiologic, 154, 154*t*
Sildenafil, 32
Silicosis, 146, 150
Single-unit smooth muscle, 22
Sinoatrial (SA) node
  depolarization of, 119, 119*f*
  heart electrophysiology and, 118
  rate of action potential generation by, 119
  rate of depolarization of, 119
Situs inversus, 139
Sjögren syndrome, 211
Skeletal muscle
  contraction of
    mechanism of, 20
    regulation of, 21
    types of, 20, 21*f*
  features of, 24*t*
  functional unit of, 21
  relaxation of, 20
  structure of, 19
  types of fiber, 21, 22*t*
Skeletal muscle pump, 109
Sleep
  EEG of, 62*f*
  stages of, 62
Sleep spindle, 62
Sliding hiatal hernia, 213
Sliding-filament theory, 20
Slow pain, 45
Slow wave
  GI tract and, 209, 209*f*
  smooth muscles and, 22

Slowly adapting receptor, 42
Slow-twitch skeletal muscle fiber, 21, 22*t*
Small cell lung cancer and Cushing syndrome, 75
Small intestine
  digestion and absorption in, 222
  functional anatomy of, 221
  motility of, 225
  reflexes in, 225
  structural comparison of, with large intestine, 227, 227*t*
Smell, 58
Smooth ER (sER), 3
Smooth muscle
  contraction of
    mechanism of, 23
    regulation of, 23
  features of, 24*t*
  relaxation of, 23
  structure of, 22
  types of, 22
Sodium
  concentration regulation of, 243
  diuretics and, 203
  large intestine absorption of, 227
  potassium secretion and, 199
  reabsorption of
    blunting, 230
    general mechanisms of, 187, 188*f*
  small intestine absorption of, 224, 225*f*
  water balance and, 242
Sodium ion balance regulation, 190, 191*f*
Sodium pump, 12
Solvent drag, 182, 182*f*
Somatic nervous system
  features of, 25
  neurons in, 30*t*
  skeletal muscle contraction and, 21
Somatosensory system
  pathways of, 43
  special aspects of, 44
Somatostatin
  function of, 219
  functional anatomy of, 218*t*
  GH secretion and, 90
  physiologic actions of, 92*t*
  regulation of, 219*f*
  source of, 92
Somatotroph, 90
Sound
  encoding, 54, 55*f*
  frequency of, 54, 55*f*
  localization of, 54
  perception of, 53
Spastic paralysis, 16
Spatial summation, 42
Special senses, 46
Spectrin, 5
Spermatogenesis, 84
Sphincter muscle
  contraction inhibition of, 208
  sympathetic nerves and, 208*t*
Sphincter pupillae, 52
Spike potential. *See* Action potential
Spinal cord
  dermatomes and injury of, 47*t*
  intermediolateral horn of
    parasympathetic nerves and, 29
    sympathetic nerves and, 28
  subacute combined degeneration of, 43, 215
Spinal cord tract
  location of, 36*f*
  movement and, 34, 35*t*
Spinal shock, 137, 137*t*
Spinocerebellar lesion, 40
Spinocerebellum and movement, 40
Spinothalamic system, 45*f*
Spinothalamic tract, 44
Spiral ganglion, 54
Spirometry, 154, 155*f*
Spironolactone, 132
Splanchnic circulation, 205, 205*f*, 208
Starling equation, 134
Starling forces
  in capillaries, 133, 133*f*
  defined, 133
  edema and, 135, 135*t*
  GFR regulation and, 173*t*
  at the glomerulus, 170
  interstitial pressure and, 134
  plasma pressure and, 134
  renal fluid reabsorption and, 183
  Starling equation and, 134
Steatorrhea
  bile inhibition and, 221
  cystic fibrosis and, 220
  distal ileum disease and, 224
Stenotic aortic valve, 112
Stereocilia, 56
Steroid, 144
Steroid hormone, 65, 68*f*
Stomach
  functional anatomy of, 214*f*
  overview of, 213
  physiologic roles of, 215*f*
  receptive relaxation of, 209, 214
  response to meal in, 214
Stratified squamous mucosal epithelium, 206
Strength training, 22
Stress, respiratory responses to, 165
Stress hormone, 71
Stretch receptor, 165, 243
Striatum, 38
Stricture from scarring, 207
Stroke, 63, 129
Stroke volume (SV)
  calculating, 106
  contractility and, 107, 107*f*
  determinants of, 106, 107*f*
  preload and, 106*f*, 108*f*
Stroke work, 107
Subacute combined degeneration of spinal cord, 43, 215
Subacute granulomatous thyroiditis, 82*t*
Sublingual gland, 211
Submandibular gland, 211
Submucosa, 207
Submucosal plexus
  function of, 207
  location of, 207
  overview of, 30
Substance P, 30
Sulfonylurea drug, 95
Summation (muscular), 20
Superior colliculus, 37
Superior mesenteric artery, 205
Superior olivary nucleus, 54
Superior pons, 164
Surface tension (T)
  breathing and, 146
  lung compliance and, 147*f*
  neonatal respiratory problems and, 148
  surfactant and, 147, 147*f*
Surfactant and breathing, 147, 147*f*
Swan-Ganz catheter, 111, 152
Sweat gland, ANS effects on, 28*t*
Sympathetic excitation of the heart, 122
Sympathetic innervation of the heart, 122
Sympathetic nervous system
  fight-or-flight response and, 27
  function of, 27
  functional anatomy of, 28, 29*f*
  GFR regulation and, 172
  GI tract and, 208, 208*f*
  renal blood flow and, 174
Sympathetic outflow, 243, 244
Sympathetic stimulation of cardiac muscle, 23
Sympathomimetics, 32
Symport, 9
Symptomatic bradycardia, 123
Synaptic delay, 18
Synaptic transmission, 19*t*
Syncope, 117, 129
Syncytium, 14
Syndrome of inappropriate antidiuretic hormone (SIADH)
  hypo-osmotic volume expansion and, 245, 245*f*
  pathophysiology of, 92
Syphilitic aortitis, 113
Systemic arterial pressure, 172
Systemic circulation, 151*f*
Systole, 102
Systolic blood pressure (SBP), 102
Systolic ejection murmur, 112
Systolic heart failure, 106, 135

T

T wave (ECG), 123
Tabes dorsalis, 43
Tachycardia, 103
Tachypnea, 159, 167
Taeniae coli, 207
Taste, 59
Taste bud, 59, 59*f*
Taste receptor cell, 59
Taste transduction, 60
Taut form of hemoglobin, 160
Tay-Sachs disease, 4*t*
Tectorial membrane, 53
Tectospinal tract and movement, 37
Temporal hemiretina, 49
Temporal summation, 42
Temporalis, 212
Terminal tremor, 40
Testes and steroid hormones, 73
Testicular cancer, 84
Testicular feminization, 83–84
Testicular hormone, 66*t*
Testosterone
  conversion of, 76
  mechanism of action of, 82
  physiologic actions of, 83
  regulation of secretion of, 84
Tetanus (muscular), 20
Tetanus toxin, 16
Tetany, 98, 121
Thalamic ischemia, 42
Thalamic syndrome, 42, 45
Thalamus
  anatomy of, 46*f*
  balance and, 56
  respiration and, 163
  sensory pathways and, 42
  somatosensory system and, 43, 44
  taste and, 60
  vision and, 49
Theta wave
  example of, 61*f*
  features of, 61
  sleep and, 62*f*
Third-order neuron
  anterolateral system and, 44
  sensory pathways and, 42
  somatosensory system and, 43
  spinothalamic tract and, 44
Thoracic cage abnormalities, 238*t*
Threshold value of action potentials, 13
Thrombosis, 196
Thyroglobulin, 77
Thyroid gland, 77
Thyroid hormone
  catecholamine action and, 79
  features and function of, 65
  physiologic actions of, 66*t*, 78, 79*f*
  synthesis of, 77, 78*f*
  See also specific types
Thyroiditis, 80
Thyroid-stimulating hormone (TSH), 77
Thyrotoxicosis
  CO demand and, 136
  etiology of, 81*t*
  Graves disease and, 81
  thyroiditis and, 81
Thyrotroph, 77
Thyrotropin-releasing hormone (TRH), 77
Thyroxine (T4)
  production of, 77
  T3 and, 80
Tidal breathing, 159
Tidal volume (VT), 155
Tight cellular junctions
  renal transport and, 181
  structure and function of, 5

Tight cellular junctions (*Continued*)
water transport an, 188
Tissue resistance, 142, 144, 144*f*
Titratable acidity, 230, 230*f*
Tolbutamide, 95
Tongue, 59, 60*f*
Tonic contraction of sphincter muscles, 210
Tonic receptor, 42
Total body water (TBW)
distribution of, 241*f*
loss of, 244, 244*f*
measurement of, 242
sodium balance and, 242
typical makeup of, 241
volume contracted states of, 244, 244*f*
Total lung capacity (TLC), 154, 157
Total peripheral resistance (TPR)
arterial pressure maintenance and, 127
MAP and, 125
Toxic adenoma, 80
Toxic megacolon, 23, 213
Tracheal air, 148
Transcellular electrical potential, 199
Transcellular fluid, 241
Transcellular transport
defined, 11, 11*f*
renal, 180, 181*f*
Transcytosis, 11
Transfer RNA (tRNA), 3
Transferrin, 225
Transient repolarization, 121
Transmembrane transport molecules, 8*t*
Transport maximum (Tm), 7, 184, 184*f*
Transpulmonary pressure, 141, 142*f*
Transudate, 134
Transverse tubules (T tubules), 19
Traveler's diarrhea, 244
Tricuspid valve, 102
Trigeminal nerve, 212
Triglyceride
absorption of, 224
digestion of, 223
synthesis of, 94
Triiodothyronine (T3)
production of, 77
T4 and, 80
Tritiated water, 242
Trypanosoma cruzi, 23
Trypanosoma cruzi, 213
Tuberculosis, 76, 98
Tuberoinfundibular pathway, 18
Tubular lumen
potassium secretion and, 199
reabsorption of salt and water and, 181, 182*f*
substance transport from, 181, 181*f*
tubular secretion and, 184
Tubular secretion, 184, 185*f*, 185*t*
Tubulin, cytoskeletal, 4
Tubuloglomerular feedback
glomerulotubular balance and, 183
renal blood flow and, 175, 175*f*
Turbulent air flow, 144
Turbulent blood flow, 114
Turner syndrome, 88*t*
Twitch, 20
Tympanic membrane, 53
Tyrosine kinase receptor, 92

U

Ulcer, 217
Undescended testes, 84
Unitary smooth muscle, 22
Upper airway obstruction and respiratory acidosis, 238*t*
Upper esophageal sphincter, 213, 213*f*
Upper motor neuron
lesions of, 38, 38*t*
lower motor neurons and, 37
Urea trapping, 192, 194, 196*f*
Urinary anion gap (UAG), 232
Urinary buffers, 230
Urine
concentration and dilution of, 190
defined, 168
foamy or frothy, 171
Urine osmolarity, 92
Urine output, 190
Uterine endometrium, 87
Utricle, 56

V

Vagal stimulation
LES relaxation and, 213
parietal cell activity and, 214
Vagovagal reflex, 209
Vagus nerve (CN X)
parasympathetic innervation of the heart and, 123
taste and, 60
Valvular disease
pathophysiology of major, 111
shock and, 137
van't Hoff's law, 7
Vasa recta, 180, 196, 197*f*
Vascular compliance, 129
Vascular disease, 158
Vasoactive inhibitory peptide (VIP), 30
Vasoactive substance, 116
Vasoconstriction
compensatory, 129
hypoxia-induced
in fetal lungs, 153
at high altitudes, 153
overview of, 153
V/Q matching and, 152
sympathetic nerves and, 208*t*
Vasogenic edema, 27
Vasopressin. *See* Antidiuretic hormone (ADH)
Vasovagal syncope, 123
Venous pooling, 109
Venous return
effect of on cardiac output, 108, 108*f*, 109*f*
low-pressure receptors and, 133
other determinants of, 109
Ventilation, 140
Ventilation-associated pneumonia, 139
Ventilation-perfusion (V/Q)
matching, 152, 152*f*
mismatching, 159*t*
Ventral corticospinal tract and movement, 37
Ventral horn and movement, 34
Ventral respiratory group, 164
Ventricular blood flow, 115, 115*f*, 116
Ventricular escape rhythm, 123
Ventricular fibrillation (VF), 126*f*
Ventricular filling, 110
Ventricular gallop, 103
Ventricular pressure in cardiac cycle, 104, 105*f*
Ventricular pressure-volume loop phases, 110, 110*f*
Ventricular systole, 102
Ventricular tachycardia (VT), 126, 126*f*
Vertebrobasilar system, 64
Vesicular transport, 9, 10*f*
Vestibular apparatus, 40
Vestibular disease, 41
Vestibular ganglion, 56
Vestibular neuroma, 54
Vestibular nuclei, 40, 56
Vestibular nystagmus, 58
Vestibular organ, 56
Vestibular system, 56, 56*f*
Vestibular transduction, 56
Vestibular-ocular reflex, 57
Vestibulitis, 41
Vestibulocerebellar pathway, 57
Vestibulocerebellum and movement, 40
Vestibulocochlear nerve (CN VIII)
balance and, 56
hearing and, 54
Vestibulospinal lesion, 40
Vestibulospinal tract
movement and, 35
pathways of, 36*f*
Viagra, 32
Villi, 206
Visceral epithelial cell, 170, 170*f*
Visceral reflex
ANS and, 27
response to cold, 27
Visceral smooth muscle, 22
Vision, 46
Visual cortex, 49
Visual pathway, 49, 51*f*
Vital capacity (VC), 156
See also Forced vital capacity (FVC)
Vitamin A deficiency, 48
Vitamin B_{12}
absorption of, 224, 226*f*
deficiency of, 43
Vitamin D
plasma phosphate and, 201, 202
synthesis of, 100*f*
toxicity, 98
See also Calcitriol
Volatile acid load, 228
Volume derangement, 186*t*
Volume-overloaded heart, 104, 118
Voluntary movement
basal ganglia and, 38, 39*f*
control of, 34
defined, 33
Vomiting and metabolic alkalosis, 236

W

Warm shock, 137
Water. *See* Total body water (TBW)
Water Hammer pulse, 112, 112*f*
Water-soluble substance and cell membrane, 1
Weber test, 55
Wedge pressure, 152
Wernicke area, 61
Winter's formula, 235
Wolff-Parkinson-White (WPW) syndrome, 126*f*
Women's Health Initiative trial, 85

X

Xerostomia, 211

Z

Z disk, 20
Zollinger-Ellison syndrome, 217
Zona fasciculata
adrenal steroidogenesis pathways and, 72*f*, 76*f*
cortisol synthesis and, 72
Zona glomerulosa
adrenal steroidogenesis pathways and, 72*f*, 76*f*
mineralocorticoid synthesis and, 72
Zona occludens, 5
Zona reticularis
adrenal steroidogenesis pathways and, 72*f*, 76*f*
androgen synthesis and, 72