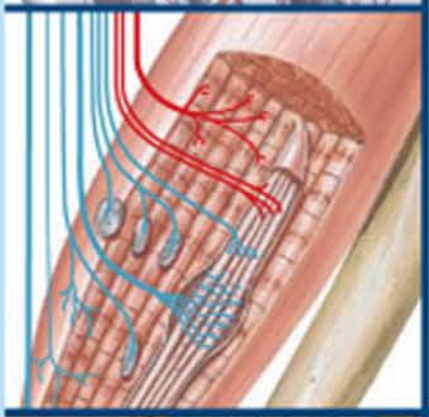
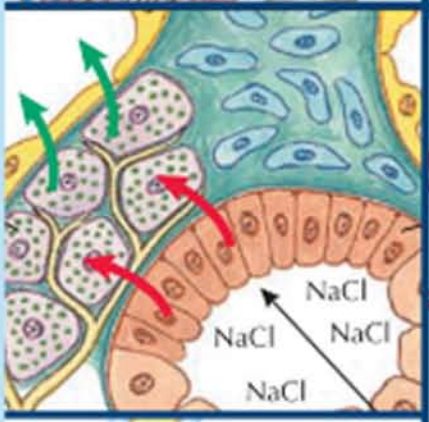
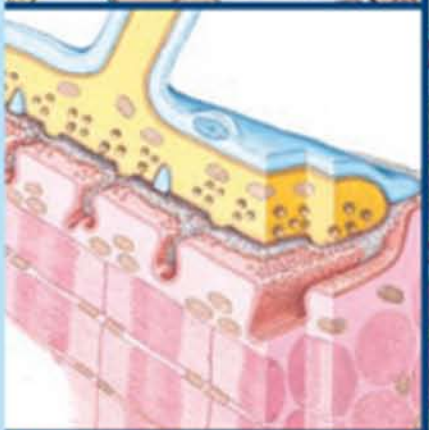
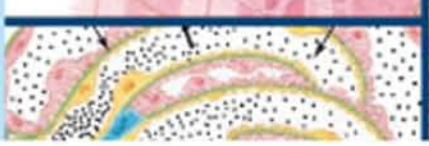
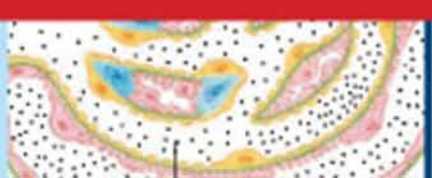






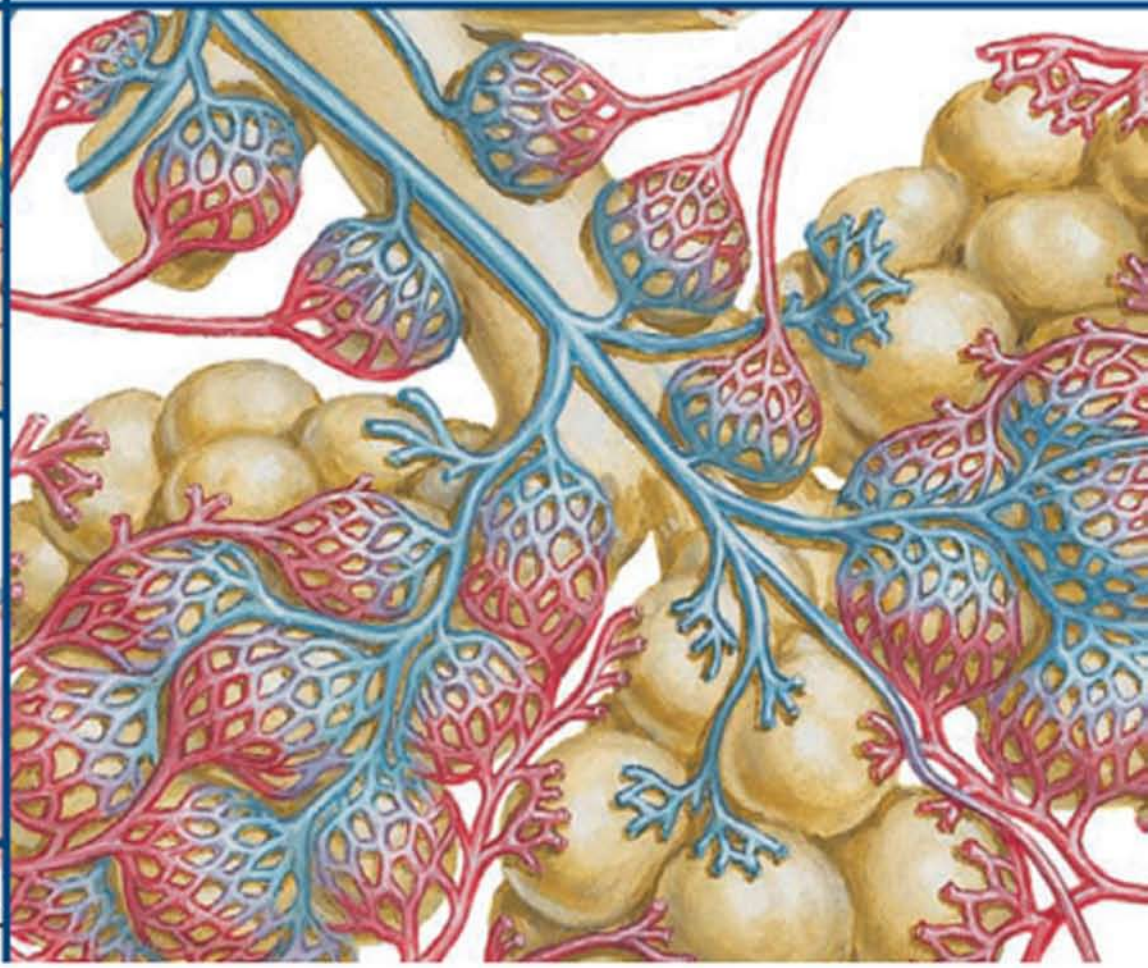






NETTER'S ESSENTIAL PHYSIOLOGY

SUSAN MULRONEY • ADAM MYERS



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F. Netter M.D.

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NETTER'S ESSENTIAL PHYSIOLOGY

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NETTER'S ESSENTIAL PHYSIOLOGY ISBN: 978-1-4160-4196-2
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The Publisher

Library of Congress Cataloging-in-Publication Data
Mulroney, Susan E.
Netter's essential physiology / Susan E. Mulroney, Adam K. Myers ; illustrations by Frank H. Netter ; contributing illustrators, Carlos A.G. Machado, John A. Craig, James A. Perkins.—1st ed.
p. ; cm.
ISBN 978-1-4160-4196-2
1. Human physiology. I. Myers, Adam K. II. Netter, Frank H. (Frank Henry), 1906-1991. III. Title. IV. Title: Essential physiology.
[DNLM: 1. Cell Physiology—Atlases. QU 17 M961n 2009]
QP34.5.M85 2009
612—dc22

2008027016

Editor: Elyse O'Grady
Developmental Editor: Marybeth Thiel
Project Manager: David Saltzberg
Design Direction: Lou Forgione
Illustrations Manager: Karen Giacomucci
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We dedicate this book to our families, for their love and support and for their patience during the preparation of this book. We dedicate it also to the students of Georgetown University, who are exceptional in their character and their love of learning.

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PREFACE

Human physiology is the study of the functions of our bodies at all levels: whole organism, systems, organs, tissues, cells, and physical and chemical processes. Physiology is a complex science, incorporating concepts and principles from biology, chemistry, biochemistry, and physics; and often, a true appreciation of physiological concepts requires multiple learning modalities, beyond standard texts or lectures. This book, *Netter's Essential Physiology,* has been prepared with this in mind. Its generous illustrations and concise, bulleted, and highlighted text are designed to draw the student in, to focus the student's efforts on understanding the essential aspects of difficult concepts. It is intended not to be a detailed reference book, but rather a guide to learning the essentials of the field, in conjunction with classroom work and other texts when necessary.

This book is organized in the classical order in which subdisciplines of physiology are taught. Beginning with fluid compartments, transport mechanisms, and cell physiology, it progresses through neurophysiology, cardiovascular physiology, the respiratory system, renal physiology, the gastrointestinal system, and endocrinology. It is ideal for the visual learner. Each section is thoroughly illustrated with the great drawings of the late Frank Netter as well as the more recent, beautiful work of Carlos Machado, John Craig, and James Perkins.

Recognizing that physiology, cell biology, and anatomy go hand in hand in the modern, integrated curriculum of many institutions, we have included more than the usual number of illustrations relevant to anatomy and histology. By reading the text, studying the illustrations, and taking advantage of the review questions, the student will become familiar with the important concepts in each subdiscipline and gain the essential knowledge required in medical, dental, upper level undergraduate, or nursing courses in human physiology.

Too many textbooks, although very useful reference works, go for the most part unread by students. It is our hope that students will find this book enriching and stimulating and that it will inspire them to thoroughly learn this fascinating field.

Susan E. Mulroney, PhD
Adam K. Myers, PhD

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Acknowledgments

The preparation of this textbook has benefited from the efforts of numerous colleagues and students who reviewed various sections of the work and offered valuable criticisms and suggestions. We especially wish to thank Charles Read, Henry Prange, Stefano Vicini, Jagmeet Kanwal, Peter Kot, Edward Inscho, Jennifer Rogers, Adam Mitchell, Milica Simpson, Lawrence Bellmore, and Joseph Garman for their critical reviews. In addition, we express our appreciation to Adriane Fugh-Berman, whose insights and advice helped us avert many potential nightmares; Amy Richards, for her constant good humor and willingness to help; and all our colleagues and coworkers for their friendship, collegiality, and encouragement during this project.

Our special thanks go to the dedicated team at Elsevier, particularly Marybeth Thiel and Elyse O'Grady. We also acknowledge Jim Perkins for his talented work on the new illustrations in this volume, which gracefully complement the original drawings of the master illustrator, Frank Netter.

Finally, we acknowledge the role of our students in this project, for their encouragement and for their enthusiasm in learning, which is the greatest inspiration for our work.

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SUSAN E. MULRONEY, PhD, is an award-winning teacher and researcher at Georgetown University Medical Center, where she is Professor of Physiology and Biophysics and Director of the highly acclaimed Physiology Special Master's Program. Dr. Mulroney directed the Medical Human Physiology course for the first-year medical students at the School of Medicine and now is Director of the Medical Gastrointestinal module in the new systems-based medical curriculum. She also directs the Medical Physiology course for the Georgetown Summer Medical Institute. Dr. Mulroney lectures to medical and graduate students in multiple areas of human physiology, including renal, gastrointestinal, and endocrine physiology, and is recognized for her expertise in curricular innovation in medical education. Dr. Mulroney is a well-known researcher in renal and endocrine physiology, has published extensively in these areas, and was director of the Physiology PhD program for 12 years. She is also coeditor of *RNA Binding Proteins: New Concepts in Gene Regulation.*

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About the Artists

FRANK H. NETTER, MD, was born in 1906 in New York City. He studied art at the Art Student's League and the National Academy of Design before entering medical school at New York University, where he received his MD degree in 1931. During his student years, Dr. Netter's notebook sketches attracted the attention of the medical faculty and other physicians, allowing him to augment his income by illustrating articles and textbooks. He continued illustrating as a sideline after establishing a surgical practice in 1933, but he ultimately opted to give up his practice in favor of a full-time commitment to art. After service in the United States Army during World War II, Dr. Netter began his long collaboration with the CIBA Pharmaceutical Company (now Novartis Pharmaceuticals). This 45-year partnership resulted in the production of the extraordinary collection of medical art so familiar to physicians and other medical professionals worldwide.

In 2005, Elsevier Inc. purchased the Netter Collection and all publications from Icon Learning Systems. There are now more than 50 publications featuring the art of Dr. Netter available through Elsevier Inc. (in the United States: www.us.elsevierhealth.com/Netter and outside the United States: www.elsevierhealth.com).

Dr. Netter's works are among the finest examples of the use of illustration in the teaching of medical concepts. The 13-book *Netter Collection of Medical Illustrations,* which includes the greater part of the more than 20,000 paintings created by Dr. Netter, became and remains one of the most famous medical works ever published. *The Netter Atlas of Human Anatomy,* first published in 1989, presents the anatomical paintings from the Netter Collection. Now translated into 16 languages, it is the anatomy atlas of choice among medical and health professions students the world over.

The Netter illustrations are appreciated not only for their aesthetic qualities but, more importantly, for their intellectual content. As Dr. Netter wrote in 1949, ". . . clarification of a subject is the aim and goal of illustration. No matter how beautifully painted, how delicately and subtly rendered a subject may be, it is of little value as a *medical illustration* if it does not serve to make clear some medical point." Dr. Netter's planning, conception, point of view, and approach are what informs his paintings and what makes them so intellectually valuable.

Frank H. Netter, MD, physician and artist, died in 1991.

Learn more about the physician-artist whose work has inspired the Netter Reference collection: http://www.netterimages.com/artist/netter.htm.

CARLOS A.G. MACHADO, MD, was chosen by Novartis to be Dr. Netter's successor. He continues to be the main artist who contributes to the Netter collection of medical illustrations.

Self-taught in medical illustration, cardiologist Carlos Machado has contributed meticulous updates to some of Dr. Netter's original plates and has created many paintings of his own in the style of Netter as an extension of the Netter collection. Dr. Machado's photorealistic expertise and his keen insight into the physician/patient relationship informs his vivid and unforgettable visual style. His dedication to researching each topic and subject he paints places him among the premier medical illustrators at work today.

Learn more about his background and see more of his art at http://www.netterimages.com/artist/machado.htm.

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Section 1

CELL PHYSIOLOGY, FLUID HOMEOSTASIS, AND MEMBRANE TRANSPORT

Physiology *is the study of how the systems of the body work, not only on an individual basis, but also in concert to support the entire organism. Medicine is the application of physiologic principles, and understanding these principles gives us insight into the development of disease. The terms* regulation *and* integration *will keep surfacing as you learn more about how each system functions. Because of these building interactions, the field of physiology is always expanding. As we discover more about the genes, molecules, and proteins that regulate other factors, we see that the discipline of physiology is far from static. Each new discovery gives us more insight into how our impossibly complex organism exists, and how we might intercede when pathophysiology occurs. This text will explore essential elements in each of the body's systems; it is not intended to be comprehensive, but focuses, rather, on ensuring a solid understanding of these principles related to the regulation and integration of the systems.*

Chapter 1 **The Cell and Fluid Homeostasis**

Chapter 2 **Membrane Transport**

Review Questions

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Chapter 1 The Cell and Fluid Homeostasis

CELL STRUCTURE AND ORGANIZATION

Organisms evolved from single cells floating in the primordial sea (Fig. 1.1). A key to appreciating how multicellular organisms exist is through understanding how the single cells maintained their internal fluid environment when exposed directly to the outside environment with the only barrier being a semipermeable membrane. Nutrients from the "sea" entered the cell, diffusing down their concentration gradients through channels or pores, and waste was transported out through exocytosis. In this simple system, if the external environment changed (e.g., if salinity increased due to excess heat and evaporation of sea water or water temperature changed), the cell adapted or perished. To evolve to multicellular organisms, cells developed additional barriers to the outside environment to allow better regulation of the intracellular environment.

In multicellular organisms, cells undergo differentiation, developing discrete intracellular proteins, metabolic systems, and products. The cells with similar properties aggregate and become tissues and organ systems [cells → tissues → organs → systems].

Various tissues serve to support and produce movement (muscle tissue), initiate and conduct electrical impulses (nervous tissue), secrete and absorb substances (epithelial tissue), and join other cells together (connective tissue). These tissues combine and support organ systems that control other cells (nervous and endocrine systems), provide nutrient input and continual excretion of waste (respiratory and gastrointestinal systems), circulate the nutrients (cardiovascular system), filter and monitor fluid and electrolyte needs and rid the body of waste (renal system), provide structural support (skeletal system), and provide a barrier to protect the whole structure (integumentary system [skin]) (Fig. 1.2).

THE CELL MEMBRANE

The human body is composed of eukaryotic cells (those that have a true nucleus) containing various organelles (mitochondria, smooth and rough endoplasmic reticulum, Golgi apparatus, etc.) that perform specific functions. The nucleus and organelles are surrounded by a **plasma membrane** consisting of a lipid bilayer primarily made of phospholipids, with varying amounts of glycolipids, cholesterol, and proteins. The lipid bilayer is positioned with the hydrophobic fatty acid tails of phospholipids oriented toward the middle of the membrane, and the hydrophilic polar head groups oriented toward the extracellular or intracellular space. The fluidity of the membrane is maintained in large part by the amount of short-chain and unsaturated fatty acids incorporated within the phospholipids; incorporation of cholesterol into the lipid bilayer reduces fluidity (Fig. 1.3). The oily, hydrophobic interior region makes the bilayer an effective barrier to fluid (on either side), with permeability only to some small hydrophobic solutes, such as ethanol, that can diffuse through the lipids.

To accommodate multiple cellular functions, the membranes are actually **semipermeable** because of a variety of proteins inserted in the lipid bilayer. These proteins are in the form of ion channels, ligand receptors, adhesion molecules, and cell recognition markers. Transport across the membrane can involve passive or active mechanisms and is dictated by the membrane composition, concentration gradient of the solute, and availability of transport proteins (see Chapter 2). If the integrity of the membrane is disrupted by changing fluidity, protein concentration, or thickness, transport processes will be impaired.

FLUID COMPARTMENTS: SIZE AND CONSTITUTIVE ELEMENTS

Fluid Compartments and Size

The typical adult body is approximately 60% water; in a 70-kilogram (kg) person, this equals 42 liters (L) (Fig. 1.4). The actual size of all fluid compartments is dependent on a variety of factors including size and body mass index. In the normal 70-kg adult:

- **Intracellular fluid** (**ICF**) constitutes $^2/_3$ of the **total body water** (28 L), and the **extracellular fluid** (**ECF**) accounts for the other $^1/_3$ of total body water (14 L).
- The **extracellular fluid** compartment is composed of the *plasma* (blood without red blood cells) and the **interstitial**

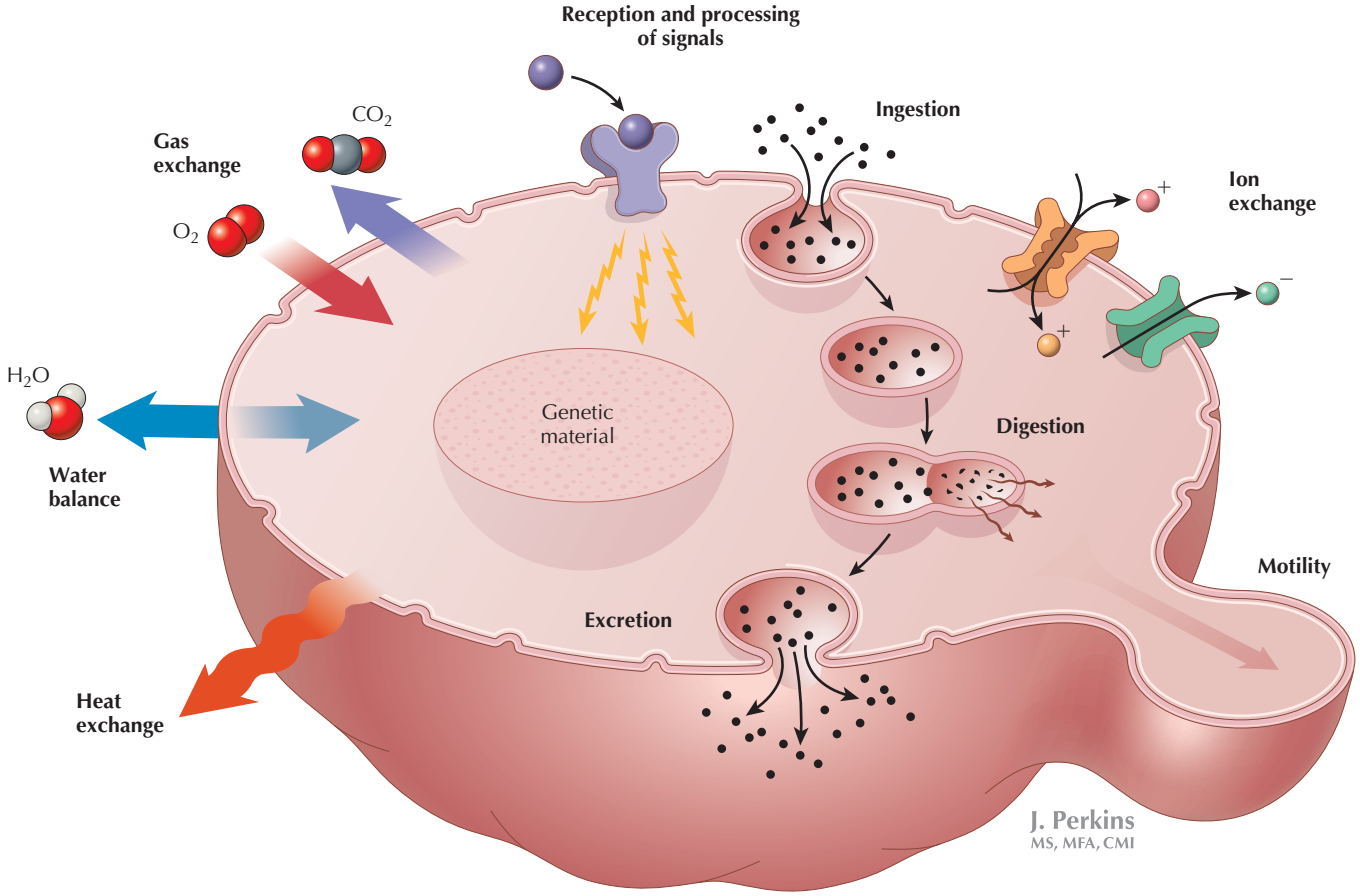


Figure 1.1 Cell in the Primordial Sea The first single-celled organisms had to perform basic functions and be able to adapt to changes in their immediate external environment. The semipermeable cell membrane facilitated the processes that provided nutrients to the cell, using diffusion, endocytosis and exocytosis, and protein transporters to maintain homeostasis.

fluid (ISF), which is the fluid bathing cells (outside of the vascular system) as well as the fluid in bone and connective tissue. Plasma constitutes $^1/_4$ of ECF (3.5 L), and ISF constitutes the other $^3/_4$ of ECF (10.5 L).

The amount of **total body water (TBW)** differs with age and general body type. TBW in rapidly growing infants is ~75% of body weight, whereas older adults have a lower percentage. In addition, body fat plays a role: obese individuals have lower TBW than age-matched individuals, and, in general, women have less TBW than age-matched men. This is especially relevant for drug dosages. Because fat solubility varies with the type of drug, body water composition (relative to body fat) can affect the effective concentration of the drug (Fig. 1.5).

Intracellular and Extracellular Compartments

The intracellular and extracellular compartments are separated by the cell membrane. Within the ECF, the plasma and interstitial fluid are separated by the endothelium and basement membranes of the capillaries. The ISF surrounds the cells and is in close contact with both the cells and the plasma.

The ICF has different solute concentrations than the ECF, primarily due to the Na^+ pump, which maintains an ECF high in Na^+, and an ICF high in K^+ (Fig. 1.6). The maintenance of different solute concentrations is also highly dependent on the selective permeability of cell membranes separating the extracellular and intracellular spaces. The cations and anions in our body are in balance, with the number of positive charges in each compartment equaling the number of negative charges (see Fig. 1.6). Because the ion flow across the membrane is responsive to both the electrical charge and the solute gradient, the overall environment is controlled by maintenance of this **electrochemical equilibrium.**

The osmolarity (total concentration of solutes) of fluids in our bodies is ~290 milliosmoles (mosm)/L (generally rounded to 300 mosm/L for calculations). This is true for all of the fluid compartments (see Fig. 1.6). The basolateral sodium ATPase pumps (seen on cell membranes) are instrumental in establishing and maintaining the intracellular and extracellular

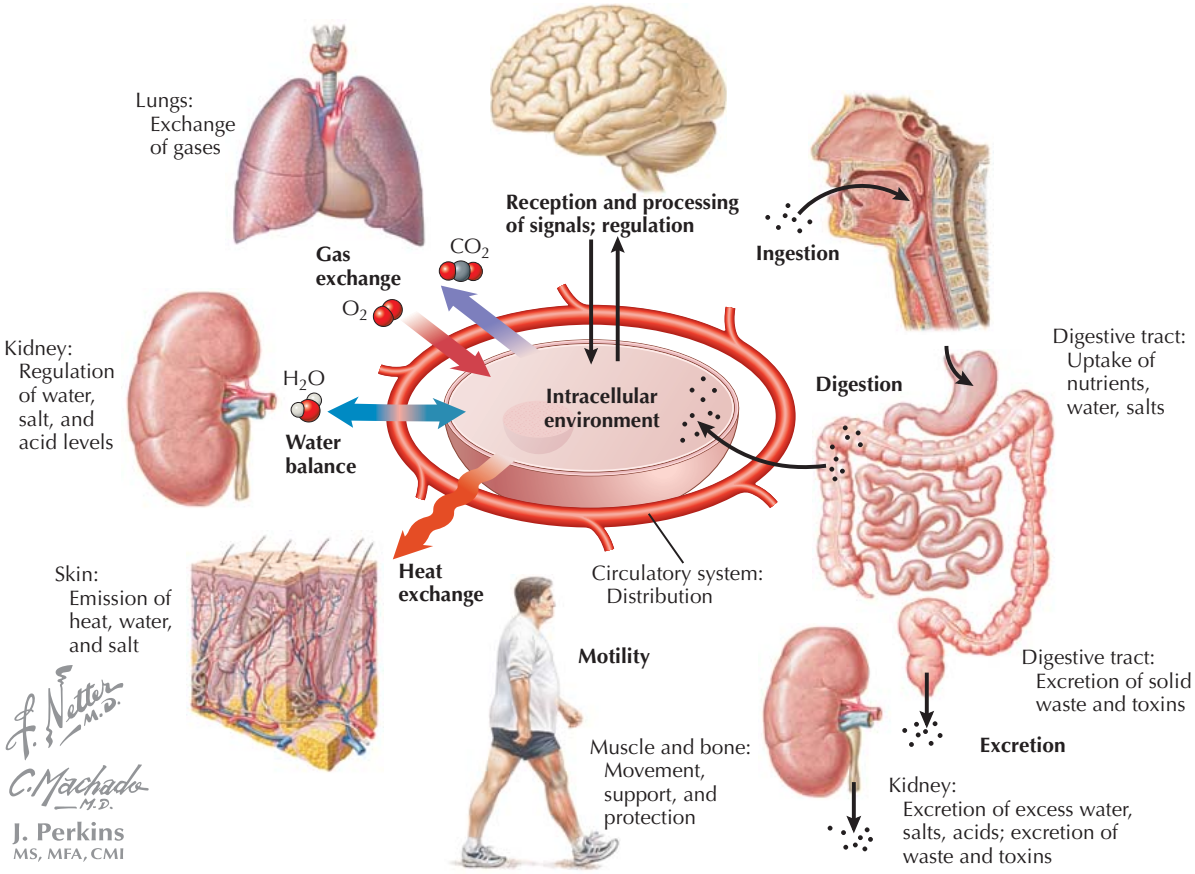


Figure 1.2 Buffering the External Environment In multicellular organisms, the basic homeostatic mechanisms of single-celled organisms are mirrored by integration of specialized organ systems to create a stable environment for the cells. This allows specialization of cellular functions and a layer of protection for the systems.

environments. Intracellular Na^+ is maintained at a low concentration (which drives the Na^+-dependent transport into the cells) compared with the high Na^+ in ECF. The **extracellular sodium** (and the small amount of other positive ions) is balanced by chloride and bicarbonate anions and anionic proteins. For the most part, the concentration of solutes between plasma and ISF is similar, with the exception of proteins (indicated as A^-), which remain in the vascular space (under normal conditions, they cannot pass through the capillary membranes). The high ECF Na^+ concentration drives Na^+ leakage into cells, as well as many other transport processes.

The primary intracellular cation is *potassium ion,* which is balanced by phosphates, proteins, and small amounts of other miscellaneous anions. Because of the high concentration gradients for sodium, potassium, and chloride, there is passive leakage of these ions down their gradients. The leakage of potassium out of the cell through specific K^+ channels is the key factor contributing to the resting membrane potential. The differential sodium, potassium, and chloride concentrations across the cell membrane are crucial for the generation of electrical potentials (see Chapter 3).

OSMOSIS, STARLING FORCES, AND FLUID HOMEOSTASIS

Osmosis

Membranes are **selectively permeable** (**semipermeable**), meaning they allow some, but not all, molecules to pass through. Membranes of tissues vary in their permeability to specific solutes. This tissue specificity is critical to function, as seen in the variation in cell solute permeability through a renal nephron (see Chapters 17 and 18). On either side of the membrane, there are factors that oppose and facilitate movement of water and solutes out of the compartments. These factors include:

- Concentration of specific solutes. Higher concentration of a solute on one side of the membrane will favor movement of that solute to the other by diffusion.
- Overall concentration of solutes. Higher osmolarity on one side provides osmotic pressure "pulling" water into that space (diffusion of water).
- Concentration of proteins. Because the membrane is impermeable to proteins, protein concentration

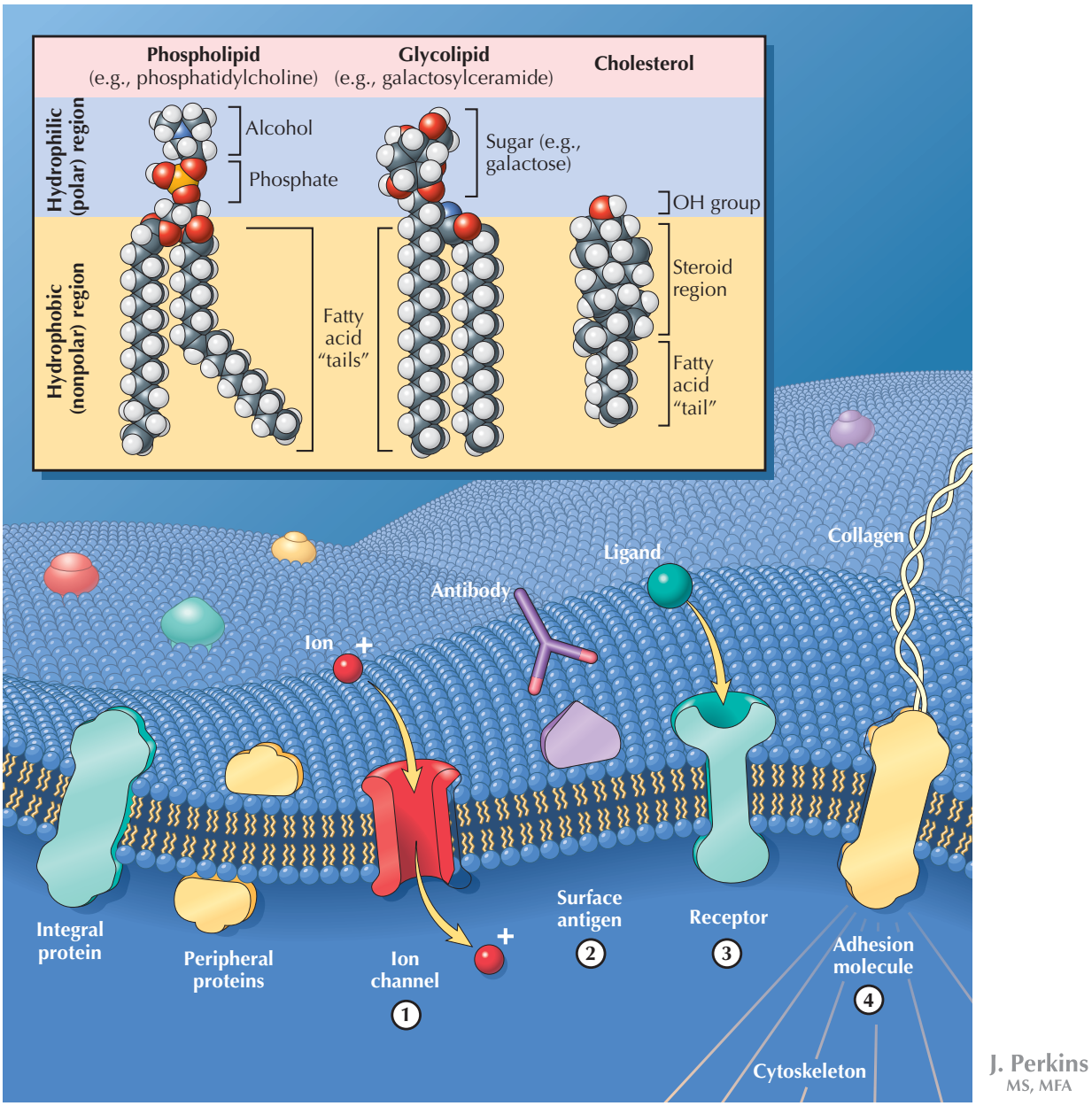


Figure 1.3 The Eukaryotic Plasma Membrane The plasma membrane is a lipid bilayer, with hydrophobic ends oriented inward and hydrophilic ends oriented outward. Primary constituents of the membrane are phospholipids, glycolipids, and cholesterol. There are a wide variety of proteins associated with the membrane, including *(1)* ion channels, *(2)* surface antigens, *(3)* receptors, and *(4)* adhesion molecules.

establishes an oncotic pressure "pulling" water into the space with higher concentration.

- Hydrostatic pressure, which is the force "pushing" water out of the space, for example, from capillaries to ISF (when capillary hydrostatic pressure exceeds ISF hydrostatic pressure).

If the membrane is permeable to a solute, **diffusion** of the solute will occur down the concentration gradient (see Chapter 2). However, if the membrane is not permeable to the solute, the solvent (in this case water) will be "pulled" across the membrane toward the compartment with higher solute concentration, until the concentration reaches equilibrium across the membrane. The movement of water across the membrane by diffusion is termed **osmosis,** and the permeability of the membrane determines whether diffusion of solute or osmosis (water movement) occurs. The concentration of the impermeable solute will determine how much water will move through the membrane to achieve **osmolar equilibration** between ECF and ICF.

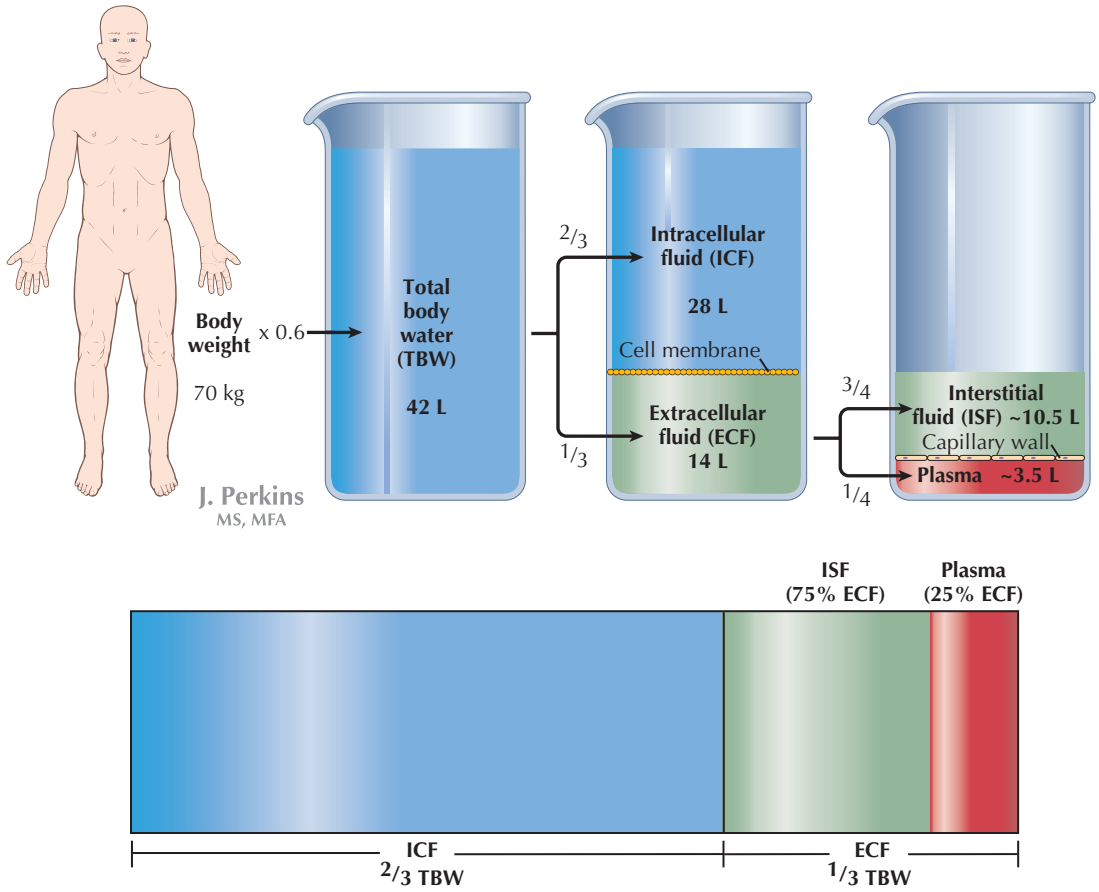


Figure 1.4 Body Fluid Compartments Under normal conditions the total volume of water in the human body (TBW) is about 60% of the body weight. Of TBW, most ($^2/_3$) is intracellular fluid (ICF), and $^1/_3$ is extracellular fluid (ECF). The extracellular fluid is made up of plasma and interstitial fluid (ISF).

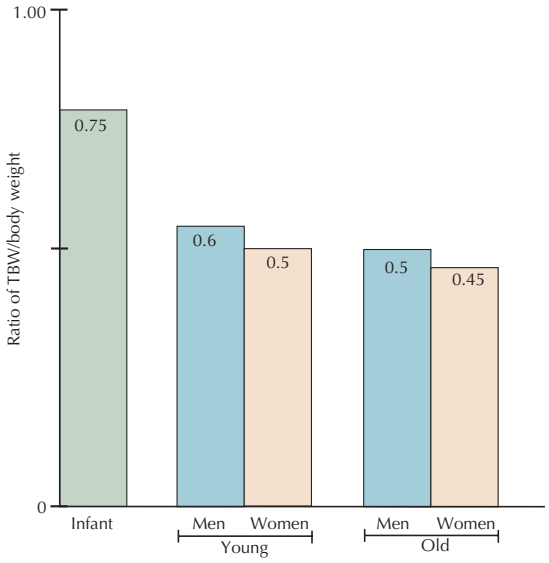


Figure 1.5 Total Body Water as Function of Body Weight Under normal conditions, total body water is most affected by the amount of body fat, and there is more body water as a percentage of body weight in infants and women (because of estrogens). Aging also decreases the ratio because of reduced muscle mass.

Osmosis occurs when **osmotic pressure** is present. This is equivalent to the hydrostatic pressure necessary to prevent movement of fluid through a semipermeable membrane by osmosis. The idea can be illustrated using a U-shaped tube with different concentrations of solute on either side of an **ideal semipermeable membrane** (where the membrane is permeable to water but is impermeable to solute) (Fig. 1.7*A*).

Because of the unequal solute concentrations, fluid will move to the side with the higher solute concentration (right side of tube), against the gravitational force (hydrostatic pressure) that opposes it, until the **hydrostatic pressure** generated is equal to the **osmotic pressure.** In the example, at equilibrium, solute concentration is nearly equal and water level is unequal, and the displacement of water is due to osmotic pressure (Fig. 1.7*B*).

In the plasma, the presence of proteins also produces a significant **oncotic pressure,** which opposes hydrostatic pressure (filtration out of the compartment) and is considered the **effective osmotic pressure of the capillary.**

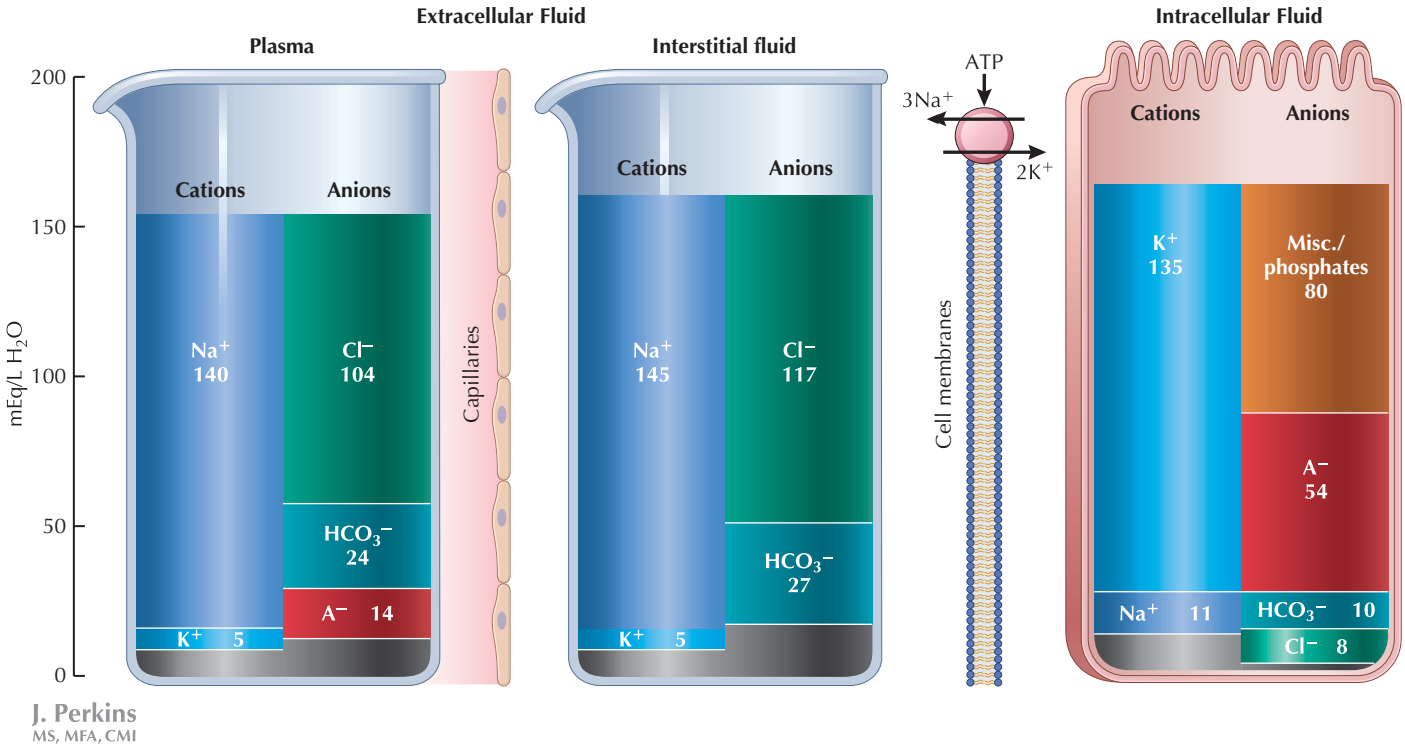


Figure 1.6 Electrolyte Concentration in Extracellular and Intracellular Fluid The primary extracellular fluid (ECF) cation is sodium, and the primary interstitial fluid (ICF) cation is potassium. This difference is maintained by the basolateral Na^+/K^+ ATPases, which transport three Na^+ molecules out of the cell in exchange for two K^+ molecules transported into the cell. A balance of positive and negative charges is maintained in each compartment, but by different ions. (Values are approximate.)

Starling Forces

The oncotic and hydrostatic pressures are key components of the **Starling forces.** Starling forces are the pressures that control fluid movement across the capillary wall. Net movement of water out of the capillaries is **filtration,** and net movement into the capillaries is **absorption.** As seen in Figure 1.8, there are four forces controlling fluid movement:

- HP_c, the **capillary hydrostatic pressure,** favors movement out of the capillaries and is dependent on both arterial and venous blood pressures (generated by the heart).
- π_c, the **capillary oncotic pressure,** opposes filtration out of the capillaries and is dependent on the protein concentration in the blood. The only effective oncotic agent in capillaries is protein, which is ordinarily impermeable across the vascular wall.
- P_i, the **interstitial hydrostatic pressure,** opposes filtration out of capillaries, but normally this pressure is low.
- π_i, the **interstitial oncotic pressure,** favors movement out of the capillaries, but under normal conditions, there is little loss of protein out of the capillaries, and this value is near zero.

Movement of fluid through capillary beds can differ due to physical factors particular to the capillary wall (e.g., pore size, fenestration) and its relative permeability to protein, but in general these factors are considered constant for most tissues.

These forces are used to describe net filtration using the ***Starling Equation***,

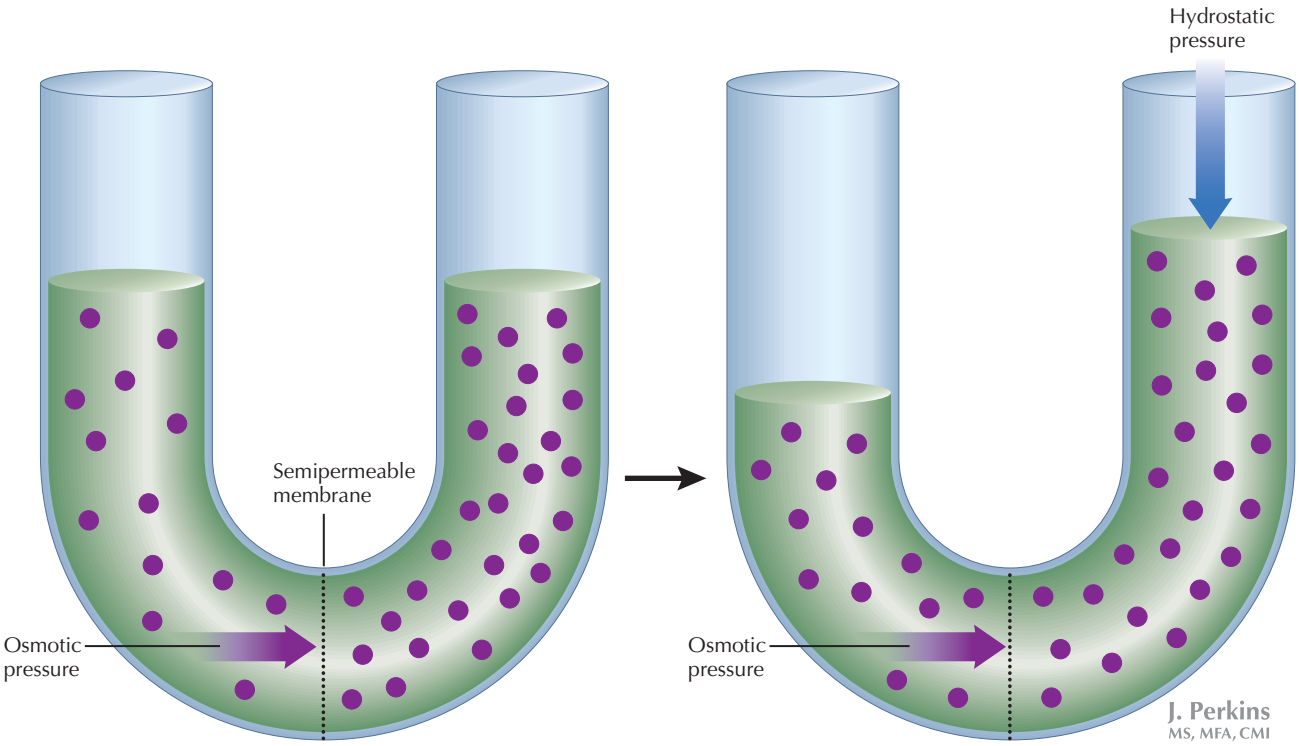
$$\text{Net filtration} = K_f\left[(HP_c - P_i) - \sigma(\pi_c - \pi_i)\right]$$

in which the constant, K_f, accounts for the physical factors affecting permeability of the capillary wall, and σ describes the permeability of the membrane to proteins (where $0 < \sigma < 1$). The liver capillaries (sinusoids) are highly permeable to proteins, and $\sigma = 0$. Thus, bulk movement in the liver sinusoids is controlled by hydrostatic pressure. In contrast, capillaries in most tissues have low permeability to proteins, and $\sigma = \sim 1$, so the Starling equation can easily be viewed as the pressures governing filtration minus those favoring absorption:

$$(\text{Filtration}) - (\text{Absorption})$$

$$\textbf{Net Filtration} = K_f\left[(HP_c + \pi_i) - (P_i + \pi_c)\right]$$

Although K_f is a "constant," it differs between systemic, cerebral, and renal glomerular capillaries, with cerebral



A. Initial state of unopposed osmotic pressure.

B. Equilibrium state in which remaining osmotic pressure is opposed by equal and opposite hydrostatic pressure.

Figure 1.7 Osmosis and Osmotic Pressure When a semipermeable membrane separates two compartments in a "V tube," fluid will move through the membrane toward the higher solute concentration *(A),* until near equilibrium of solutes is reached and the remaining osmotic pressure is opposed by the hydrostatic pressure difference between the two sides of the tube *(B).* In blood vessels, hydrostatic pressure is generated by gravity and the pumping of the heart, and the osmotic pressure is measured as the force needed to oppose the hydrostatic pressure. Osmotic pressure works toward equalization of solute concentrations on either side of the membrane. Oncotic pressure (π) is the osmotic pressure produced by impermeable proteins. In the plasma, oncotic pressure is considered the effective osmotic pressure of the capillary.

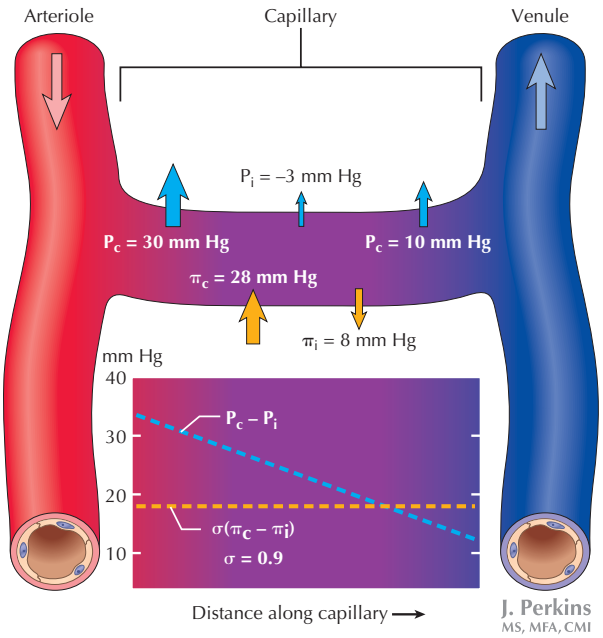
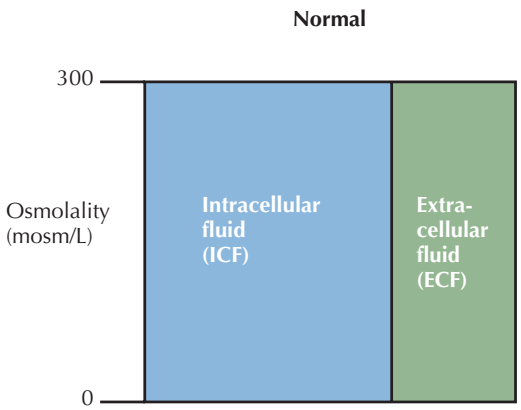
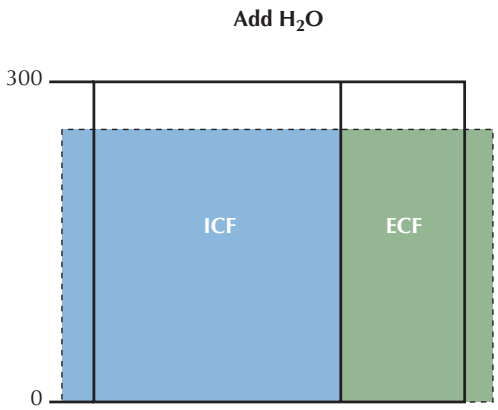


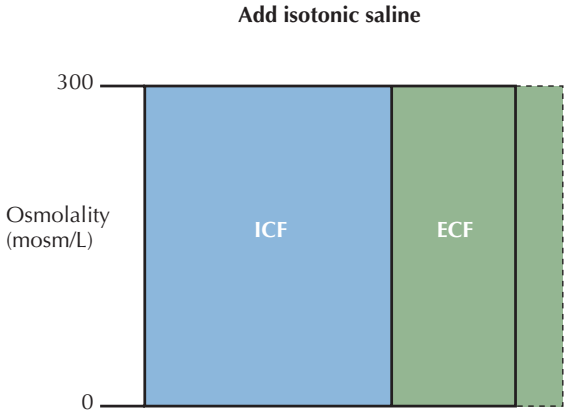
Figure 1.8 Starling Forces across the Capillary The Starling forces (hydrostatic and oncotic pressures) allow for bulk flow of fluid and nutrients across the capillary wall. The permeability of the membranes of the capillary wall to proteins is usually very low in most tissues and is reflected by a protein reflection coefficient (σ) of ~1. The inset panel illustrates that as fluid moves though the capillaries and diffusion into tissues occurs, the Starling forces change, and the forces favoring net filtration (especially P_c [HP_c, capillary hydrostatic pressure]) decrease *(dotted blue line).*



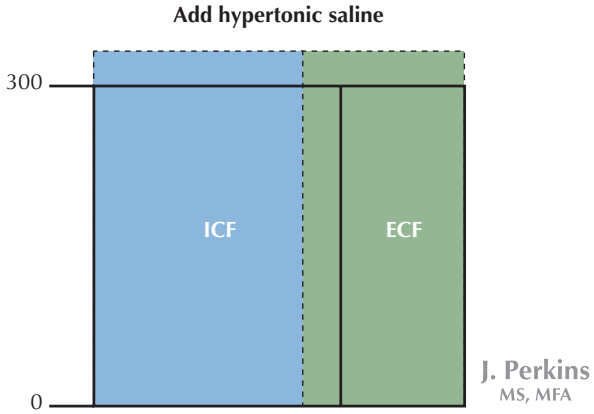
A. Under normal conditions, ICF is 2/3 and ECF is 1/3 of TBW. The osmolality of both compartments is ~300 mosm/L.



B. If **water** was added to the plasma (thus, ECF), ECF osmolality would be diluted initially (become **hypotonic**) compared to ICF. Water would then enter the ICF space (cells would swell) to equilibrate the osmolality between compartments. The overall effect would be to reduce the osmolality of ICF and ECF and expand the compartment size.



C. If **isotonic saline** (solution with NaCl concentration of ~300 mosm/L) was added to the plasma (ECF), the fluid will stay in the ECF because it is isotonic, expanding that compartment.



D. If **hypertonic saline** was added to the plasma, ECF osmolality would increase greatly initially and fluid would be drawn out of the cells and into the ECF to lower the tonicity of the ECF. This would contract the volume of the ICF compartment (cells would shrink) and increase the volume of the ECF compartment, as well as increase overall osmolality.

Figure 1.9 Effect of Adding Solutes to the Extracellular Fluid on Compartment Size If there were not compensatory mechanisms in place to sense and regulate plasma volume and osmolarity, addition of water and hypertonic solutions would have a profound effect on ICF volume and tonicity. *A* illustrates the intracellular fluid (ICF) and extracellular fluid (ECF) compartment sizes under normal osmolar conditions (300 mosm/L). *B* through *D* illustrate the effect of changing the tonicity (the osmolarity relative to plasma) of the extracellular fluid on cells. *B,* Addition of pure water to the ECF will increase both ECF and ICF volume, and reduce overall osmolarity. *C,* Addition of isotonic (same osmolarity as plasma) saline (NaCl) to the ECF will expand only the ECF compartment size, because NaCl is mainly ECF electrolytes. *D,* Addition of pure NaCl will increase overall osmolarity of both compartments to a new level. ICF will shrink, as water is drawn into the ECF toward the higher osmolar concentration, and the volume of the ECF will expand by addition of the ICF fluid.

capillaries having a lower K_f (limiting filtration), and glomerular capillaries having a greater K_f (promoting filtration) compared with systemic capillaries. Thus, filtration will be determined by the difference in hydrostatic pressure between the capillary and interstitium, minus the difference between capillary and interstitial oncotic pressure (corrected for the protein reflection coefficient). It should be clear that under normal conditions, the forces that are most variable are the HP_c and the π_c, because those can reflect changes in plasma volume.

Examples of the effects of Starling forces on fluid shifts can be illustrated by changes in fluid volume as well as changes in physical factors. A severely dehydrated person will have a decreased blood volume, which would potentially lower blood pressure (e.g., HP_c) and increase π_c. Looking at the Starling equation, those changes will decrease filtration force and increase the absorptive force, causing an overall decrease in net filtration. This will keep fluid in the vascular space.

When physical attributes of the membrane change, Starling forces are also affected: K_f can change if the capillary membrane is damaged, such as by toxins or disease. If the clefts between endothelial cells or fenestrations expand (as seen in diseased renal glomeruli), plasma proteins may pass into the interstitial space and alter the Starling forces by increasing π_i: In peripheral capillaries, this causes **edema.** Starling forces are also affected in congestive heart failure (CHF), cirrhosis, and sepsis.

Homeostasis

French physiologist Claude Bernard first articulated the concept that maintaining a constant internal environment, or **milieu intérieur,** was essential to good health. In multicellular organisms, the balance between internal and external environments is critical, and the ability to maintain a constant internal function during changes in the external environment is termed **homeostasis.** This is accomplished through integrated regulation of the internal environment by the multiple organ systems (see Fig. 1.2).

On the cellular level, homeostasis is possible due to expandable semipermeable membranes, which can accommodate small changes in osmolarity via osmosis. However, for proper cellular function, the intracellular fluid, and thus osmolarity, must be kept under tight control.

The plasma is the interface between the internal and the external environment; therefore, maintaining plasma osmolarity is an important key to cell homeostasis. Because of this, many systems play a role in controlling plasma osmolarity. Both **thirst** and the **salt appetite** are behavioral responses that can be stimulated by dehydration and/or blood loss. These serve to stimulate specific ingestive behaviors (drinking, or eating salty foods that will also stimulate drinking) that will increase the input of fluid and salt to the system. On a minute-to-minute basis, the endocrine and sympathetic nervous systems work to regulate the amount of sodium and water retained by the kidneys, thus controlling plasma osmolarity (Fig. 1.9).

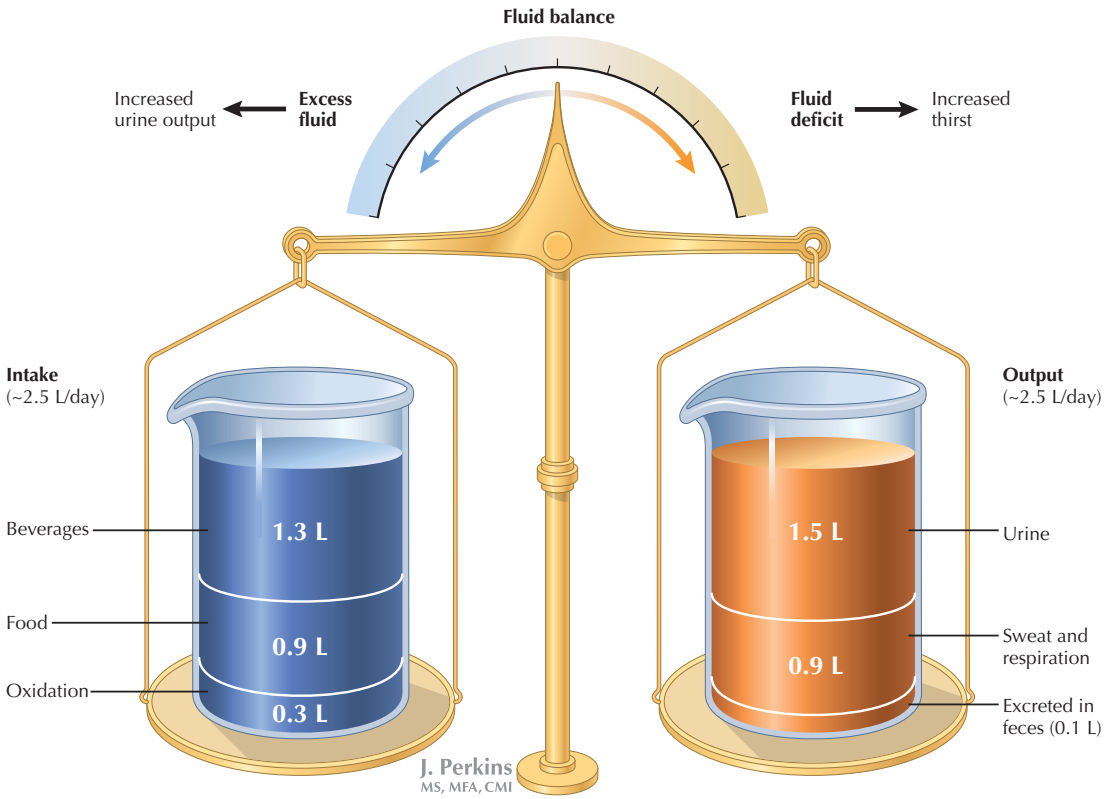


Figure 1.10 Net Fluid Balance To maintain fluid balance, fluid input needs to match fluid output. If intake (from food and beverages) exceeds output (urine, fluid in feces, insensible losses), the organism is in positive balance, and urine volume will increase to eliminate excess fluid. Negative fluid balance occurs when intake is less than output. In this case, integrated responses will increase thirst and decrease additional fluid losses, until homeostasis is restored.

Normally, changes in plasma osmolarity are well controlled and homeostasis is maintained as a result of hypothalamic osmoreceptors and the kidneys sensing fluid composition; carotid and aortic baroreceptors sensing pressure; release of hormones in response to altered pressure and osmolarity; and the actions of the kidney to regulate sodium and water reabsorption. This integrated control is the key to fluid homeostasis. Control of renal fluid and electrolyte handling will be covered in Section 5.

Fluid intake and output must be in balance (Fig. 1.10). If water intake (through food and fluids) is greater than the output (urine and insensible losses from sweat, breathing, and feces), the organism has a surplus of fluid, which will decrease plasma osmolarity, and the kidneys will excrete the excess fluid (see Section 5). Conversely, if the intake is less than output, the organism has a deficit of fluid, and plasma osmolarity will increase. In this situation, the thirst response will be activated and the kidneys will conserve fluid, producing less urine. This idea of balance is expanded on in the following sections, and the integration of the endocrine, cardiovascular, and renal systems in regulation of fluid and electrolyte homeostasis is discussed more fully.

CLINICAL CORRELATE
Measurement of Fluid Compartment Size

The indicator-dilution method is used to determine the volume of fluid in the different fluid compartments. This is done using indicators specific to each compartment. A known quantity of the substance is infused into the bloodstream of the subject and allowed to disperse. A plasma sample is then obtained, and the amount of indicator determined. The compartment volume is then calculated by the formula:

$$\text{Volume (in liters)} = \frac{\text{amount of indicator injected (mg)}}{\text{final concentration of indicator (mg/L)}}$$

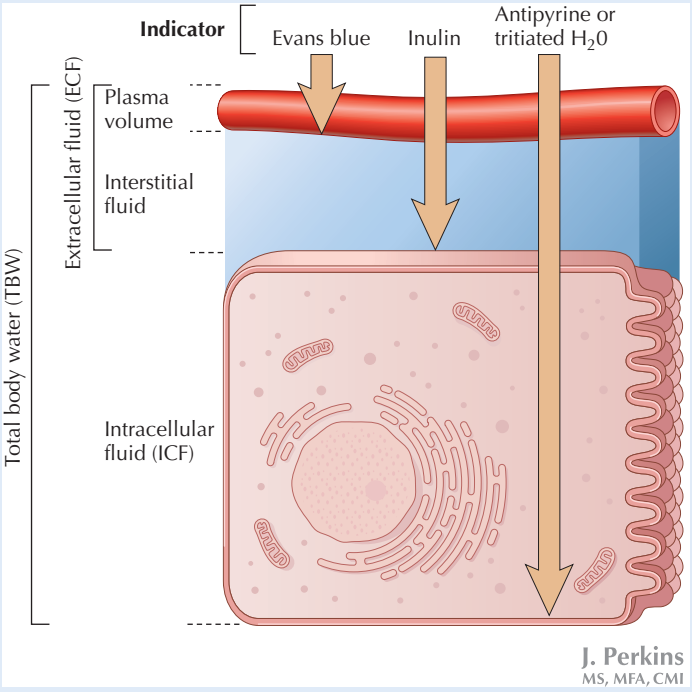
Compartment	Indicator
TBW	Antipyrine or tritiated water, because both of these substances will diffuse through *all* compartments.
ECF	Inulin, which will diffuse throughout plasma and ISF. Inulin is a large sugar (MW 500) that cannot cross cell membranes and is not metabolized.
Plasma volume	Evans blue dye, which binds to plasma proteins. The total blood volume is comprised of the plasma and red blood cells, and the hematocrit is the percentage of red blood cells (RBC) in the whole blood. Hematocrit is ~0.42 (42% RBC) in normal adult men, and ~0.38 in women.

By extrapolation, the other compartments can be determined:

$$\text{Since TBW} = \text{ECF} + \text{ICF},$$
$$ICF = \text{TBW} - \text{ECF}$$
$$ISF = (\text{ECF} - \text{Plasma Volume})$$

Because blood volume = plasma volume + red blood cell volume (see earlier), it can be calculated by the formula:

$$Blood\ Volume = (\text{Plasma Volume} \div [1 - \text{hematocrit}])$$



Substances Used to Determine Fluid Compartment Size

Chapter 2
Membrane Transport

CELLULAR TRANSPORT: PASSIVE AND ACTIVE MECHANISMS

Ions and solutes move through several different types of carrier proteins and channels that allow solute movement through the plasma membrane in several different ways. The carriers and channels include:

- **Ion channels** and **pores** that allow diffusion of solutes between compartments.
- **Uniporters,** which are membrane transport proteins that recognize specific molecules, such as fructose.
- **Symporters** that transport a cation (or cations) down its concentration gradient with another molecule (either another ion or a sugar, amino acid, or oligopeptide).
- **Antiporters** that transport an ion down its concentration gradient while another substance is transported in the opposite direction. This type of transport is often associated with Na^+ transport, or may be dependent on gradients of other ions, as in the case of the HCO_3^-/Cl^- exchanger.

Transporters (or carrier proteins) can be energy dependent or independent. Movement through channels and uniporters follows the concentration gradient of the molecule or the electrochemical gradient established by movement of other ions. However, most movement in nonexcitable cells occurs though some expenditure of energy, either by primary or secondary active transport.

Passive Transport

Regardless of the type of carrier or channel involved, if no energy is expended in the transport process, it is considered **passive transport**. Passive transport can occur via **simple** or **facilitated diffusion**.

Simple Diffusion

If a substance is lipid soluble (a property of gases, some hormones, and cholesterol), it will move down its concentration gradient through the cell membrane by **simple diffusion** (Fig. 2.1). This movement is described by ***Fick's law***.

Fick's Law

$$J_i = D_i \times A(1/X) \times (C_1 - C_2)$$

Where:

- J_i represents net flux
- D_i is the coefficient of diffusion
- A is the area
- X is the distance through the membrane
- $(C_1 - C_2)$ is the difference in concentration across the membrane

Thus, passive diffusion of a molecule across a membrane will be directly proportional to the surface area of the membrane and the difference in concentration of the molecule, and inversely proportional to the thickness of the membrane.

Facilitated Diffusion

Facilitated diffusion can occur through either **gated channels** or carrier proteins in the membrane. Gated channels are pores that have "doors" that can open or close in response to external elements, regulating the flow of the solute (Fig. 2.2*A*). Examples include Ca^{2+}, K^+, and Na^+. This type of gated transport into and out of the cell is critical to most membrane potentials, except the resting potential (see Chapter 3). When facilitated diffusion of a substance involves a carrier protein, binding of the substance to the carrier results in a conformational change in the protein and translocation of the substance to the other side of the membrane.

Simple and facilitated diffusion do not require expenditure of energy, but do depend on the size and composition of the membrane and the concentration gradient for the solute. Key differences between these two types of diffusion include:

- **Simple diffusion** occurs over all concentration ranges at a rate linearly related to the concentration gradient—as the concentration gradient increases, the rate of diffusion from the compartment with high concentration to the compartment with low concentration will increase.
- **Facilitated diffusion** is subject to a maximal rate of uptake (V_{max}). The rate of facilitated diffusion is greater than that of passive diffusion at lower solute concentrations. However, at higher solute concentrations the rate of facilitated uptake reaches its V_{max} (carrier is

saturated), while the rate of passive diffusion is not rate-limited by a carrier. Another characteristic of facilitated diffusion is that the V_{max} can be increased by adding transport proteins to the membrane—this is a key regulatory aspect of the transport process.

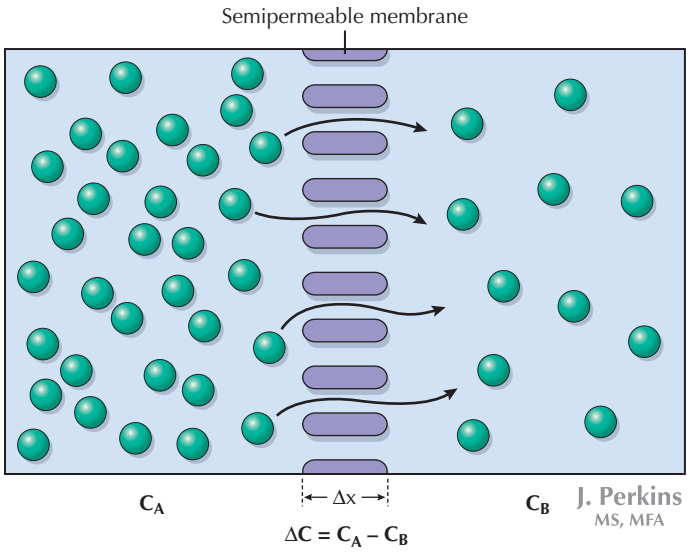


Figure 2.1 Diffusion through a Semipermeable Membrane If the membrane is permeable to a solute, diffusion can occur down the solute's concentration gradient. The rate of diffusion is contingent upon the solute gradient (ΔC) and the distance through the membrane (Δx).

Active Transport

Primary Active Transport

Primary (1°) active transport involves the direct expenditure of energy in the form of **adenosine triphosphate (ATP)** to transport an ion into or out of the cell (Fig. 2.3). Although the elements depicted in Figure 2.3 are important in many cells, the most ubiquitous is the *Na^+ pump (Na^+/K^+ ATPase)*. The Na^+ pump uses ATP to drive Na^+ out of the cells and K^+ into the cells, which establishes the essential intracellular and extracellular ion environments (Fig. 2.4). Because three molecules of Na^+ are transported out of the cell in exchange for two molecules of K^+ transported into the cell, this helps establish an electrical gradient (slightly negative inside the cell), in addition to the effects of ion diffusion due to concentration gradients (discussed in Chapter 3). The ability of the Na^+ pump to maintain the internal and external cell Na^+ and K^+ milieu is essential to cell function. If the Na^+ pump is blocked (for example, by the drug ouabain), intracellular and extracellular Na^+ and K^+ would equilibrate, affecting membrane transport and electrical potentials (see Chapter 3).

Secondary Active Transport

Many substances are transported into or out of the cell via **secondary active transport (2° AT**, also known as **cotransport**) with Na^+. The Na^+ concentration gradient is maintained by the active Na^+/K^+ pump, which results in diffusion of Na^+ into the cell down its concentration gradient through a specific symporter or antiporter (as described earlier), allowing simultaneous transport of another molecule into or out of the

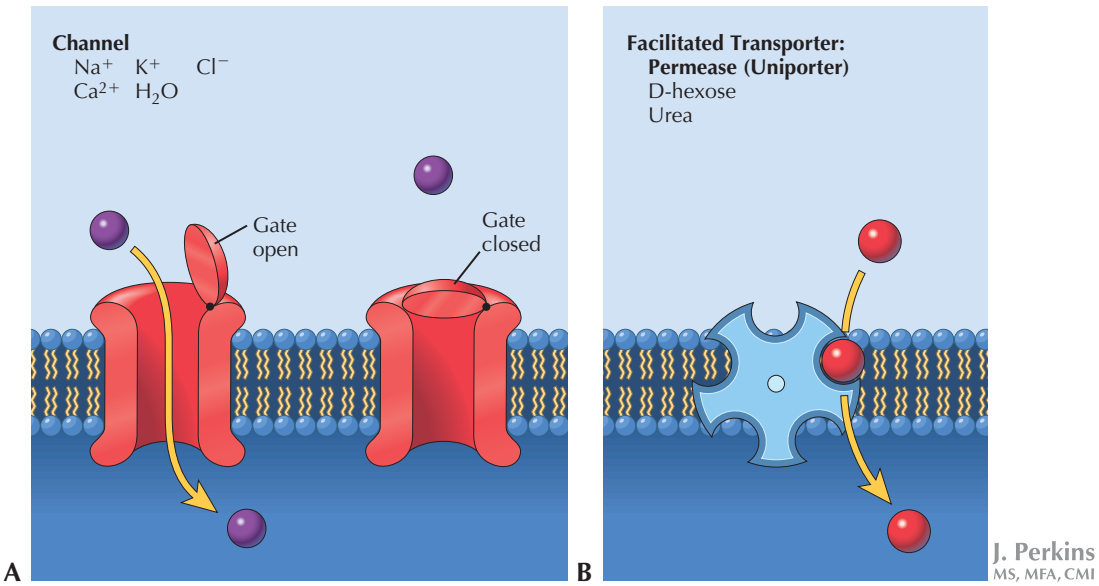


Figure 2.2 Passive Membrane Transport Passive transport of substances through the membrane can occur via specific channels or transport proteins. Channels *(A)* can be opened or closed depending on the position of the "gate." The conformational change to open and close gates can be stimulated by ligand binding or changes in voltage. Specific transport proteins *(B)* bind substances, undergo conformational change, and release the substance on the other side of the membrane.

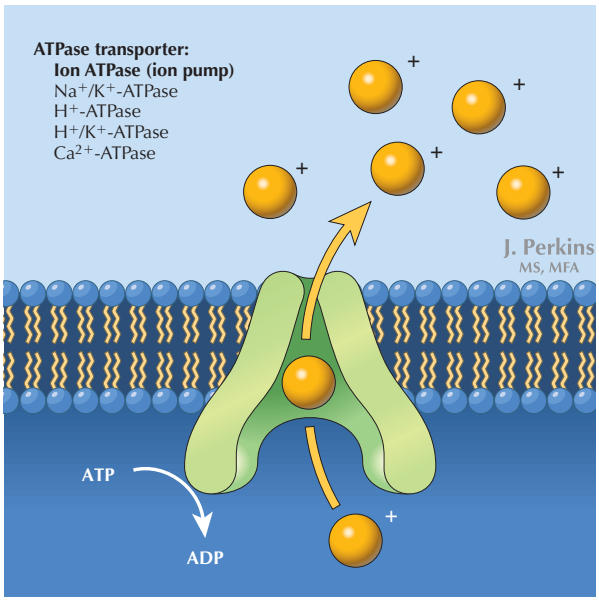


Figure 2.3 Primary (1°) Active Transport The proteins involved in primary active transport require energy in the form of ATP to transport substances against their concentration gradients.

Ouabain (or digoxin) is a cardiac glycoside derived from leaves of the foxglove plant, and the plant extract has been used in a variety of ways for hundreds of years. It is an irreversible blocker of the Na^+/K^+ ATPase pump, which will allow equilibration of sodium and potassium across the membrane, effectively stopping Na^+-dependent transport, and depolarizing the resting membrane potential. Digoxin is used in low doses to correct cardiac arrhythmias and in congestive heart failure. The effective dose of digoxin is near the lethal dose, and excess amounts can lead to death because of the wide-ranging effects. Thus, its use is closely monitored.

cell (see Fig. 2.4). The *active* portion of this process is the original transport of Na^+ against its gradient by the Na^+/K^+ pump; the subsequent events are *secondary*. A typical example of 2° AT by symport is Na^+-glucose and Na^+-galactose transport across the intestinal epithelium. An example of antiport is Na^+/H^+ exchange that occurs in many cells, including renal and intestinal cells, in which Na^+ enters the cells along its concentration gradient through the antiporter while H^+ leaves the cells. The Na^+ pump also results in *passive movement* of ions through channels: Na^+ (down its concentration gradient), Cl^- (following Na^+ to preserve electroneutrality), and H_2O (following the osmotic pressure gradient) (see Fig. 2.4*C*).

ION CHANNELS

Movement of ions occurs through channels in addition to membrane carrier-mediated processes. **Ion channels** show high selectivity and allow specific ions to pass down their concentration gradient (e.g., Na^+, Cl^-, K^+, Ca^{2+}) (see Fig. 2.2*A*). Selectivity depends on the size of the ion, as well as its charge. Gated channels can open or close in response to different stimuli. Stimuli such as sound, light, mechanical stretch, chemicals, and voltage changes can affect control of the ion flux by controlling the gating systems.

Types of channels include the following:

- **Ligand-gated channels** are opened by the binding of a ligand specific for that channel, such as acetylcholine (ACh). Binding of the ligand to its receptor causes the channel to open, allowing ion movement. These are tetrameric or pentameric (four or five protein subunit) channels.
- **Voltage-gated channels** open in response to a change in membrane voltage. These channels are ion-specific and are composed of several subunits, with transmembrane domains forming a pathway for ion flux across the membrane.
- **Gap junction channels** (also called hemichannels) are formed between two adjacent cells and open to allow passage of ions and small molecules between the cells. The hemichannels are generally hexameric (six subunits, or connexins).

Vesicular Membrane Transport

In addition to movement through channels and transporters, certain substances can enter or be expelled from the cell through **exocytosis**, **endocytosis**, or **transcytosis**. These types of movement through the cell membrane require ATP and involve packaging of the substances into lipid membrane vesicles for transport (Fig. 2.5).

- Exocytosis involves fusion of vesicles to the cell membrane for extrusion of substances contained in the vesicles.
- Endocytosis is the process whereby a substance or particle outside the cell is engulfed by the cell membrane, forming a vesicle within the cell. Phagocytosis is endocytosis of large particles; pinocytosis ("cell-drinking") is endocytosis of fluid and small particles associated with the engulfed fluid.
- Transcytosis occurs in capillary endothelial cells and intestinal epithelial cells to move material across the cell via endocytosis and exocytosis.

Vesicular packaging and transport is especially important when the material needs to be isolated from the intracellular environment because of toxicity (antigens, waste, iron) or potential for altering signaling pathways (e.g., Ca^{2+}).

Aquaporins

In addition to ion channels, there are specific water channels or **aquaporins** that allow water to pass through the hydrophobic cell membrane, following the osmotic pressure gradient

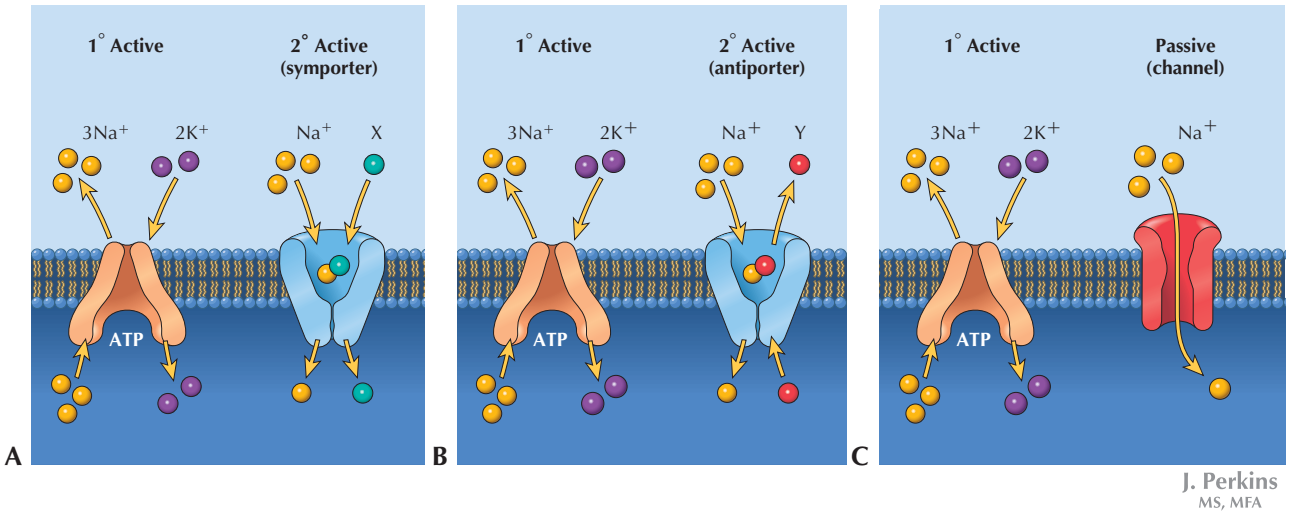


Figure 2.4 Secondary (2°) Active Transport While energy is not directly expended, secondary active transporters use a concentration gradient (usually for Na^+) established by 1° active transporters to move another substance in the same direction (symport, *A*), the opposite direction (antiport, *B*), or down the concentration gradient of the ion *(C)*.

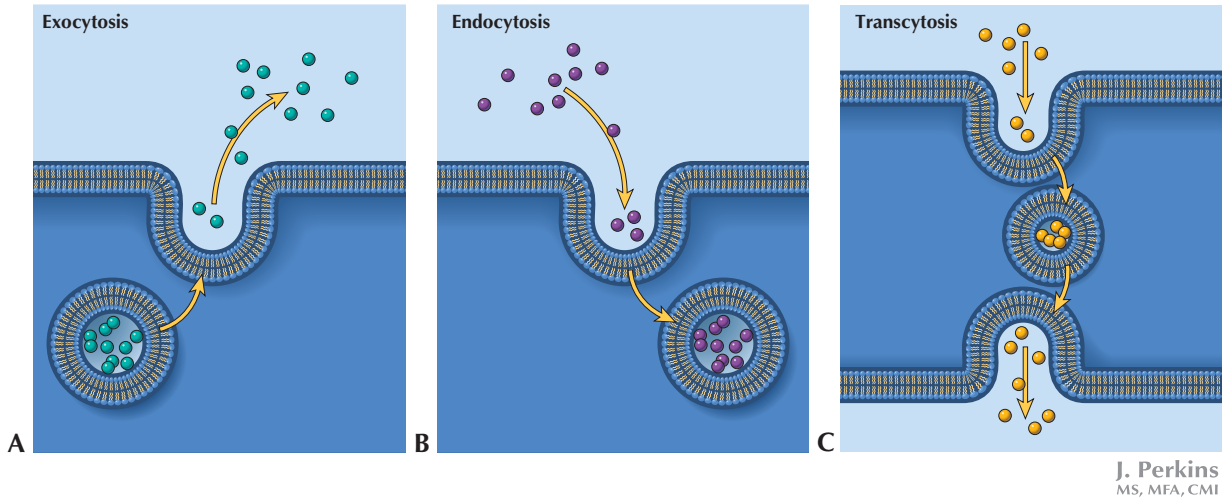


Figure 2.5 Vesicular Transport through the Membrane *A*, Exocytosis; *B*, endocytosis; *C*, transcytosis.

(Fig. 2.6). Many types of aquaporins (AQP) have been identified; the channels can be constitutively expressed in the membranes, or their insertion into the membrane can be regulated (for example, by antidiuretic hormone [ADH]; see Chapter 18). As exemplified in the renal cortical collecting ducts, whereas AQP-3 is always present in the basolateral membranes of principal cells, regulation of water flux is through insertion of AQP-2 into the apical (lumenal) membranes.

SIGNAL TRANSDUCTION MECHANISMS

Much of the basic regulation of cellular processes (e.g., secretion of substances, contraction, relaxation, production of enzymes, cell growth, etc.) occurs by the binding of a regulatory substance to its receptor and the coupling of the receptor to effector proteins within the cell.

Agonists, such as neurotransmitters, steroids, or peptide hormones, stimulate different transduction pathways. The pathways frequently include activation of **second messenger systems** such as cAMP, cGMP, Ca^{2+}, and IP_3 (inositol trisphosphate). The second messengers can activate protein kinases, or in the case of Ca^{2+}, calmodulin. The pathways can end in the secretion of substances, release of ions, contraction or relaxation of muscle, or regulation of transcription of specific genes, as well as other processes.

Examples of some G protein–coupled ligands using these pathways are given in Table 2.1, and some common signal transduction pathways are outlined in Table 2.2.

Protein Kinases

Many transduction pathways work through the phosphorylation of proteins by protein kinases. Protein kinase C (PK-C) can be activated by Ca^{2+}, diacylglycerol (DAG), and certain membrane phospholipids. Protein kinases, such as PK-A, can be activated by the second messenger cAMP, and are designated "cAMP-dependent kinases." There are also "cGMP-dependent kinases."

Another critical pathway occurs via influx of Ca^{2+} through ligand-gated channels (Fig. 2.7), which results in activation of Ca^{2+}-calmodulin–dependent kinases. These kinases are important in smooth muscle contraction, hormone secretion, and neurotransmitter release.

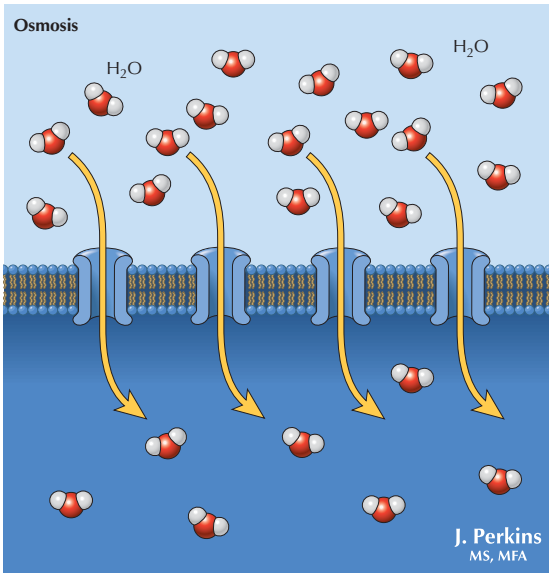


Figure 2.6 **Water Channels** Water flux follows the osmotic pressure gradient, and takes place through specific water channels, or aquaporins. Water movement through aquaporins can be regulated by insertion or removal of the proteins from the cell membrane.

G Proteins (Heterotrimeric GTP-Binding Proteins)

Most membrane receptors are associated with G proteins (heterotrimeric GTP-binding proteins). Ligand binding to the membrane-bound receptor-G-protein complex will cause phosphorylation of GDP → GTP, allowing specific subunits of the G protein to interact with different effector proteins (Fig. 2.8). The activated G proteins also have GTPase activity, which serves to inactivate the complex and end the process. Many hormones and peptides act through this general mechanism, and examples of several G protein–coupled receptors are given in Table 2.1.

Nuclear Receptors

Several ligands, such as steroid hormones and thyroid hormone (T_3), bind directly to their **nuclear receptors**, interact with the DNA, and increase or decrease transcription of mRNA from target genes (Fig. 2.9). When this pathway is stimulated to increase protein synthesis, there is a delay in

Table 2.1 **G Proteins**

G Protein	Activated by Receptors for	Effectors	Signaling Pathways
G_s	Epinephrine, norepinephrine, histamine, glucagon, ACTH, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, others	Adenylyl cyclase Ca^{2+} channels	↑ Cyclic AMP ↑ Ca^{2+} influx
G_{olf}	Odorants	Adenylyl cyclase	↑ AMP (olfaction)
G_{r1} (rods)	Photons	Cyclic GMP phosphodiesterase	↓ Cyclic GMP (vision)
G_{r2} (cones)	Photons	Cyclic GMP phosphodiesterase	↓ Cyclic GMP (color vision)
G_{i1}, G_{i2}, G_{i3}	Norepinephrine, prostaglandins, opiates, angiotensin, many peptides	Adenylyl cyclase Phospholipase C Phospholipase A_2 K^+ channels	↓ Cyclic AMP ↑ Inositol 1,4,5-trisphosphate, diacylglycerol, Ca^{2+} Membrane polarization
G_q	Acetylcholine, epinephrine	Phospholipase Cβ	↑ Inositol 1,4,5-trisphosphate, diacylglycerol, Ca^{2+}

Note: There is more than one isoform of each class of a subunit. More than 20 distinct α subunits have been identified.
ACTH, Adrenocorticotropic hormone.
(Reprinted with permission from Hansen J: Netter's Atlas of Human Physiology, Philadelphia, Elsevier, 2002.)

Table 2.2 Signal Transduction Pathways

Adenylyl Cyclase (cAMP)	Phospholipase C (IP_3 – Ca^{2+})	Cytoplasmic/Nuclear Receptor	Tyrosine Kinase	Guanylate Cyclase (cGMP)
ACTH	GnRH*	Cortisol	Insulin	ANP
LH	TRH*	Estradiol	IGFs	Nitric oxide
FSH	GHRH*	Progesterone	GH	
ADH (V_2 receptor)	CRH*	Testosterone		
PTH	Angiotensin II	Aldosterone		
Calcitonin	ADH (V_1 receptor)	Calcitriol		
Glucagon	Oxytocin	Thyroid hormones		
β-Adrenergic agonists	α-Adrenergic agonists			

Summary of some hormones, neurotransmitters, and drugs and the signal transduction pathways involved in their actions on cells.
*Also increase intracellular cAMP.
ACTH, Adrenocorticotropic hormone; ADH, antidiuretic hormone (vasopressin); ANP, atrial natriuretic peptide; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; PTH, parathyroid hormone; TRH, thyrotropin-releasing hormone.
(Reprinted with permission from Hansen J: Netter's Atlas of Human Physiology, Philadelphia, Elsevier, 2002.)

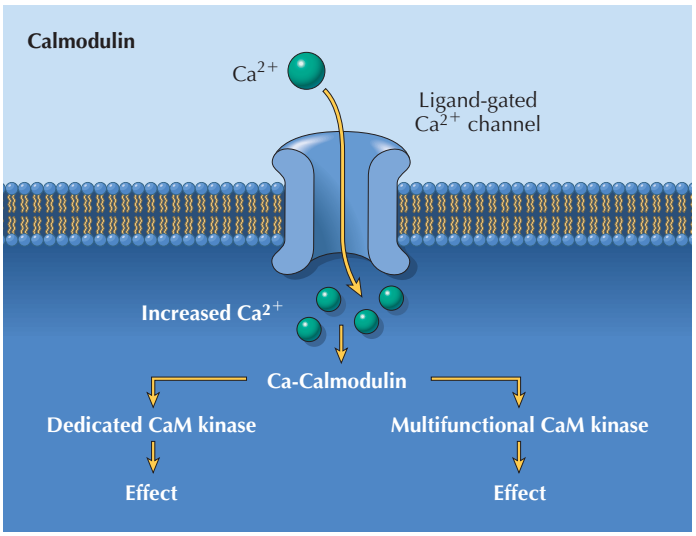


Figure 2.7 Ca^{2+}-Calmodulin Signal Transduction A good example of this mechanism is in stimulation of smooth muscle contraction, in which release of a neurotransmitter (such as tachykinin in gut smooth muscle) will act on its receptors to open Ca^{2+} channels. The increased Ca^{2+} in the cytosol binds to calmodulin, which activates specific myosin kinases. In this case, phosphorylation of myosin results in binding to actin, causing crossbridge formation and contraction of the muscle.

presentation of the end protein because the process involves gene transcription and translation. This delayed action is in contrast to that of other hormones and ligands that release proteins from storage vesicles and thus can have a rapid effect.

Simple vs. Complex Pathways

Transduction pathways can be relatively simple and fast-acting, as is usually the case for the guanylate cyclase system (cGMP). This type of rapid effect is illustrated in the smooth muscle relaxation response to nitric oxide (NO) released by vascular endothelial cells (Fig. 2.10). This is in contrast to the complex, slower transduction system observed in the multiple steps involved in growth factor signal transduction, where ligand binding initiates a multistep process ending in nuclear transcription and protein synthesis (see Fig. 2.10).

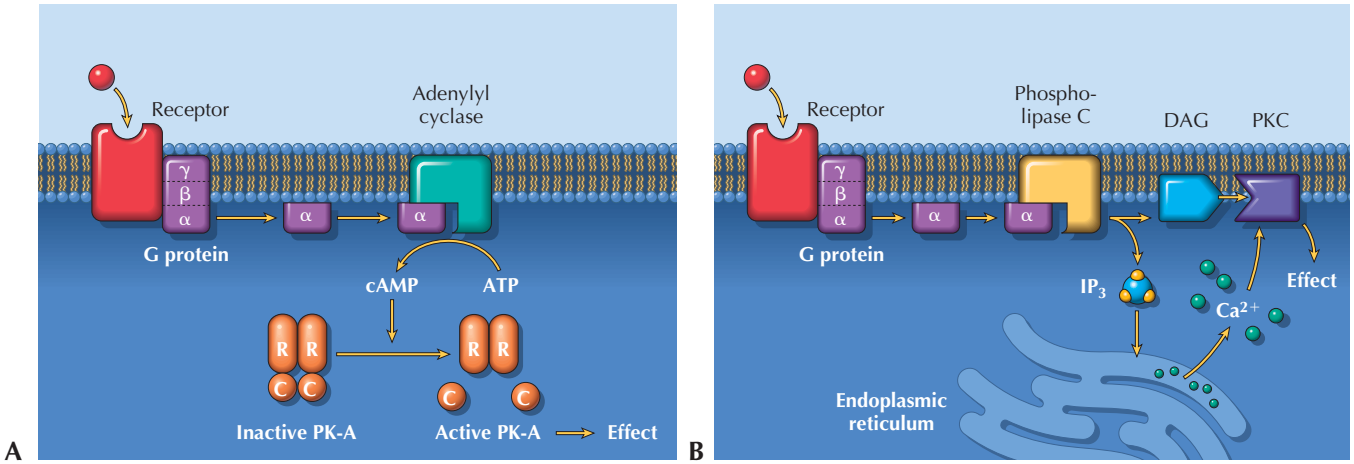


Figure 2.8 **G Protein–Coupled Receptors** Many ligands bind to receptors associated with membrane-bound G proteins to initiate transduction pathways. These G proteins interact with other membrane-bound proteins that activate second messenger systems. The second messengers represented (cAMP and IP_3) activate the effector proteins PK-A *(A)* and PK-C *(B),* respectively.

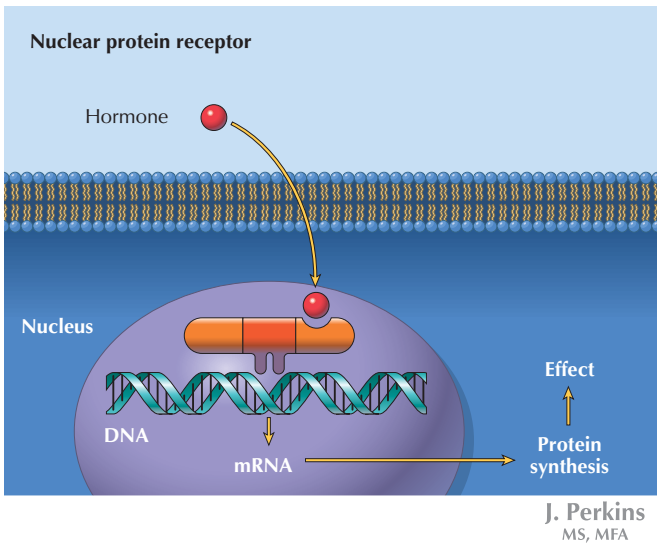


Figure 2.9 **Nuclear Protein Receptors** Several lipophilic hormones do not bind to the cell membrane, but instead diffuse through the membrane and are translocated through the cytosol to the nucleus. In the nucleus, they bind to receptors associated with the DNA and regulate RNA synthesis. Because this involves transcription and translation of proteins, the process takes time to produce the end effect.

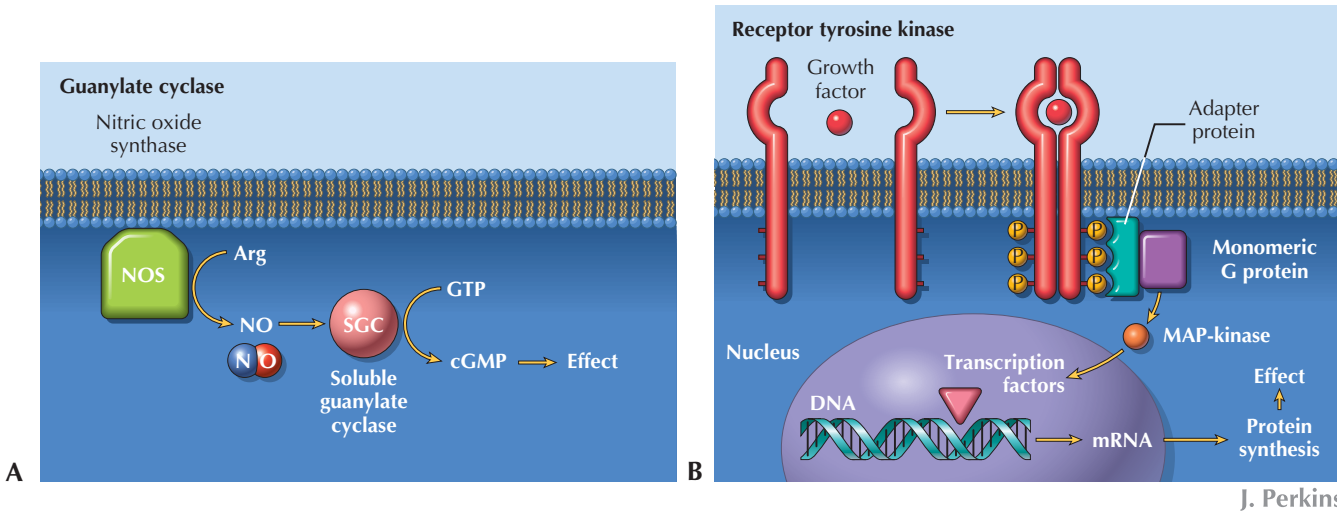


Figure 2.10 **Simple and Complex Transduction Systems** *A,* Some transduction pathways have immediate effects, such as those observed with guanylate cyclase activation of cGMP. *B,* Other pathways are far more complex, involving multiple effectors and nuclear transcription, which prolongs the time for the final effect.

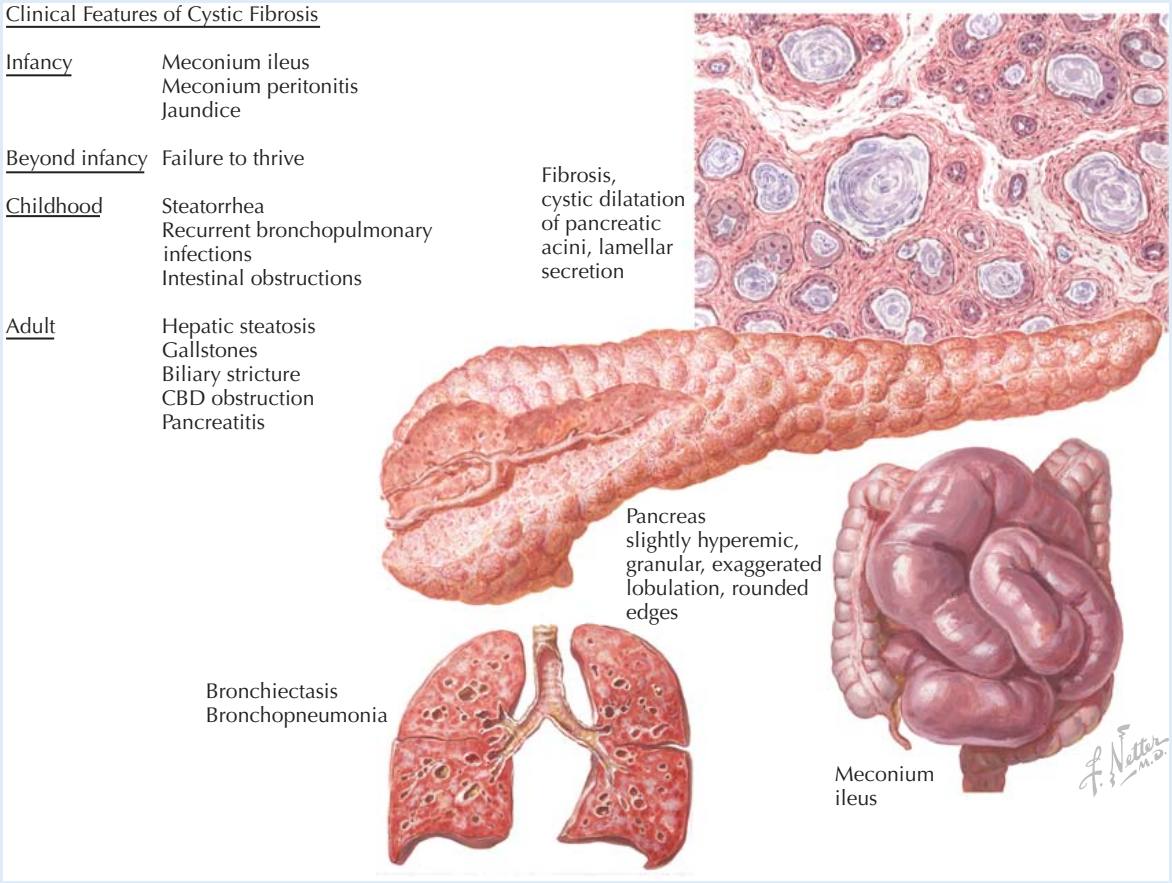
CLINICAL CORRELATE
Cystic Fibrosis

The importance of **membrane transporters** can be illustrated in cystic fibrosis, the most common lethal genetic disease affecting Caucasians (1 in ~2000 live births). Cystic fibrosis is caused by a defect in the *cystic fibrosis transmembrane regulator* (CFTR) gene that regulates specific apical (luminal) electrogenic chloride channels (see Fig. 2.2*A*). The defect has profound effects on ion and fluid transport, primarily in the lungs and pancreas. In these tissues, it is critical for Cl^- to be secreted into the lumen of the conducting airways and pancreatic acini and ducts, drawing Na^+ and water. In cystic fibrosis, the CFTR proteins are significantly reduced, decreasing Cl^- secretion and resulting in thick secretions. In the lungs, the thick, dry mucus layer contributes to increased infections; in the pancreas, the ducts from the acini are clogged with mucus and unable to secrete proper amounts of the buffers and enzymes necessary for proper digestion. The pancreatic insufficiency can result in GI complications such as meconium ileus in newborns and maldigestion, malabsorption, and weight loss as the child grows older.

Cystic fibrosis is usually diagnosed by age 2, and recently the mean age of survival was determined to be 37 years (as cited by the Cystic Fibrosis Foundation). Though antibiotics are used to treat the frequent lung infections, there is currently no cure for the disease. Treatment includes physical therapy in which the patient's chest and back are pounded to loosen and expel the mucus. There are new methods to simulate the percussive action on the mucus, such as the intrapulmonary percussive ventilator and biphasic cuirass ventilation. As lung disease worsens, patients may need to use bilevel positive airway pressure (BiPAP) to assist in the ventilation of clogged airways.

In addition to the lung pathology, the effects on the GI tract caused by pancreatic dysfunction can necessitate surgical removal of areas of the small intestine that are amotile and usually requires supplementation of pancreatic enzymes that are reduced. In addition, reduction in endocrine pancreas function (insulin, glucagon, somatostatin) can increase the incidence of diabetes in patients with cystic fibrosis.

In all, morbidity is high and lifespan is considerably shortened. If the patient does not succumb to lung infection, the progressive decrease in lung function and exercise intolerance usually leads to lung transplant.



Congenital Cystic Fibrosis CBD, common bile duct.

Review Questions

CHAPTER 1: THE CELL AND FLUID HOMEOSTASIS

1. Antipyrine and inulin are injected into a 60-kg man. After equilibrium, blood is drawn, and the concentrations of the substances are determined.

	Amount of indicator injected	Concentration in blood
Antipyrine	50 mg	1.39 mg/L
Inulin	20 mg	1.67 mg/L

Using the values above, select the best answer:

A. The intracellular fluid volume is 28 L.
B. The interstitial fluid volume is 8 L.
C. The plasma volume is 5 L.
D. The total body water is 42 L.
E. The extracellular fluid volume is 28 L.

2. Determine the pressure and direction of fluid movement (in or out of capillary) given the following Starling forces in a capillary bed where σ is approximately 1:

$HP_c = 30$ mm Hg $\quad HP_i = 3$ mm Hg
$\pi_c = 28$ mm Hg $\quad \pi_i = 8$ mm Hg

A. 3 mm Hg, into capillary
B. 3 mm Hg, out of capillary
C. 7 mm Hg, into capillary
D. 7 mm Hg, out of capillary
E. 19 mm Hg, out of capillary

3. Addition of pure water to the extracellular fluid (ECF) will have what effect on intracellular fluid (ICF) and ECF compartment volume and osmolarity after steady state is achieved? Assume no excretion of water, and an original plasma osmolarity of 300 mosm/L.

A. ICF volume decreases, ECF volume increases
B. ICF osmolarity decreases, ECF osmolarity increases
C. ICF osmolarity increases, ECF osmolarity increases
D. ICF volume increases, ECF volume increases
E. ICF volume and osmolarity decrease

CHAPTER 2: MEMBRANE TRANSPORT

4. Select the **TRUE** statement about cell transport processes:

A. Simple (passive) diffusion of a molecule is not dependent on the thickness of the cell membrane.
B. Ion channels are relatively nonselective and allow movement of multiple electrolytes through a single channel.
C. Voltage-gated channels are ion-specific and open in response to a change in membrane voltage.
D. Secondary active transport directly uses ATP to move substances in and out of cells.
E. Facilitated diffusion requires energy to move substances in and out of cells.

5. The membrane transporter directly responsible for maintenance of low intracellular sodium concentration is the:

A. basolateral Na^+/H^+ antiporter.
B. basolateral Na^+/Ca^{2+} antiporter.
C. apical Na^+/H^+ antiporter.
D. basolateral Na^+/K^+ ATPase.
E. apical Na^+/K^+ ATPase.

6. Ouabain (digoxin) works by:

A. stimulating cGMP.
B. blocking Na^+/K^+ ATPase.
C. stimulating Na^+/K^+ ATPase.
D. blocking cGMP.
E. stimulating H^+/K^+ ATPase.

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Section 2

THE NERVOUS SYSTEM AND MUSCLE

In complex organisms such as humans, homeostasis requires communication between distant parts of the body; continuous monitoring of changing internal and external conditions; and coordinated, often complex, responses to these conditions. This is accomplished in an integrated manner by highly differentiated tissues, organs, and systems. This demanding set of tasks is orchestrated in large part by the nervous system, along with various motor systems that receive its input.

Chapter 3 **Nerve and Muscle Physiology**

Chapter 4 **Organization and General Functions of the Nervous System**

Chapter 5 **Sensory Physiology**

Chapter 6 **The Somatic Motor System**

Chapter 7 **The Autonomic Nervous System**

Review Questions

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Chapter 3
Nerve and Muscle Physiology

To understand the physiology of the nervous system and muscle, it is necessary to examine function in terms of relatively simple cellular processes, as well as more complicated interactions between parts of the central nervous system, peripheral nerves and receptors, and muscle. In this chapter, basic principles of neuronal and muscular function are discussed. The role of the central nervous system in integrating neural and muscular function is considered in Chapter 4.

RESTING MEMBRANE POTENTIALS

Communication through the nervous system requires generation and transmission of electrical impulses, which in turn are dependent upon the ability of cells to maintain resting membrane potentials. The term **resting membrane potential** is synonymous with **steady state potential.** A resting membrane potential is created by passive diffusion of ions through a selectively permeable membrane, producing charge separation. An example using a hypothetical cell is illustrated in Figure 3.1.

In the simplest theoretical case, if a cell membrane is permeable to only one ion and that ion is present in higher concentration inside the cell compared with outside, that ion will diffuse out of the cell until sufficient membrane potential is established to oppose further net flux of the ion. For example, if the membrane is permeable only to K^+, and intracellular K^+ concentration is higher than extracellular concentration, then outward net flux of K^+ will occur, resulting in a negative membrane potential, in which the intracellular compartment is electrically negative relative to the outside of the cell. Only a minute fraction of the ions will diffuse out of the cell, with no appreciable change in ion concentration in the compartments, before the established electrical gradient will be sufficient to oppose further outward net flux of the ion. At this point, a resting membrane potential will be established. Due to the difference in potential between the two compartments (inside vs. outside), the excess positive charges remain close to the membrane in the extracellular compartment, while negative charges line up along the inside of the membrane.

Nernst Equation

The electrical potential difference between the inside and the outside of a cell (E_X) can be predicted if the membrane is permeable to only one ion, using the **Nernst equation** (see Fig. 3.1):

$$E_X = (RT/ZF)\ln([X]_o/[X]_i)$$

Where:

- E_x is the Nernst potential or equilibrium potential
- $\ln([X]_o/[X]_i)$ is the natural log of the ratio of the concentration of ion X outside compartment ($[X]_o$) to the concentration of the ion inside the compartment ($[X]_i$)
- R is the ideal gas constant
- T is absolute temperature
- Z is the charge of the ion
- F is Faraday's number

In biological systems at 37°C, this equation can be simplified to:

$$E_X = (61\text{mV}/Z)\log([X]_o/[X]_i)$$

Thus, in a simple hypothetical situation in which a single, monovalent cation is permeable and its concentration inside the cell is 10-fold higher than outside (see Fig. 3.1), this equation becomes:

$$E_{K^+} = (61\text{mV})\log(0.1) = -61\text{mV}$$

$$E_{K^+} = (61\,\text{mV}/+1)\log(0.1\,\text{M}/1.0\,\text{M}), \text{ or } 61\,\text{mV}$$

The electrochemical equilibrium will be greatly changed by altering the concentration of the permeable ion inside or outside of the cell. For a system in which only one ion is permeable, the Nernst potential for the permeable ion is equal to the resting membrane potential. In actual cells, more than one ion is permeable, and thus the resting membrane potential is a result of different permeabilities (conductances) of the ions present and the concentration differences of those ions across the cell membrane. The Nernst potential (equilibrium potential) represents the *theoretical* membrane potential that would occur if the cell membrane were to be selectively permeable to only a specific ion. Given the normal values for concentrations of various ions inside cells and in the interstitial fluid, the approximate Nernst potentials for the major permeable ions are listed in Table 3.1.

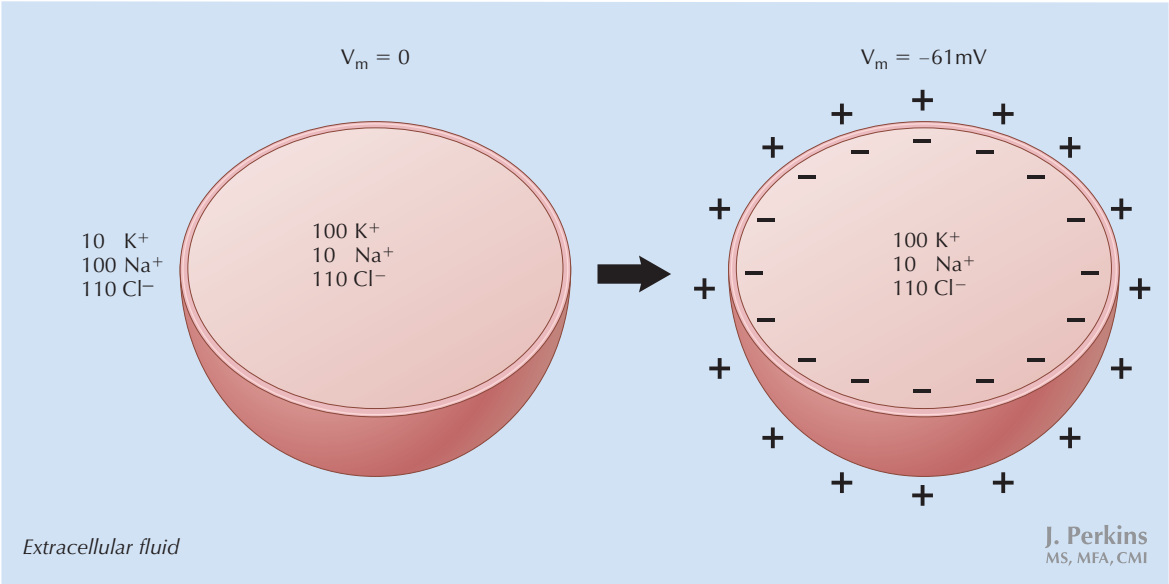


Figure 3.1 Membrane Potential of a Hypothetical Cell When the cell with the indicated intracellular ion concentrations (mEq/L) is placed into a solution with different ion concentrations, there is a gradient for diffusion of ions. In this example, the membrane separating inside and outside compartments is selectively permeable; it is permeable only to K^+. Because the cell is selectively permeable to K^+, diffusion of K^+ from inside to outside the cell immediately begins, resulting in negative charge on the inside of the membrane and positive charge outside the membrane. An electrochemical equilibrium is established, in which the gradient for diffusion of K^+ is opposed by the electrical gradient, and the membrane is negatively charged. In a simple system with only one permeable ion, V_m (the membrane potential) can be calculated by the Nernst equation.

Table 3.1 Approximate Concentrations and Nernst Potentials for Major Ions in Cytosol and Interstitial Fluid

	CONCENTRATION (mM)		
Ion	**Cytosolic**	**Interstitial**	**Nernst Potential (mV)**
Na^+	14	140	61
K^+	140	4	–94
Cl^-	8	108	–68

mM, millimolar; mV, millivolts.

Goldman-Hodgkin-Katz Equation

The actual resting membrane potential (V_m) for a system involving more than one permeable ion is calculated by the **Goldman-Hodgkin-Katz equation (G-H-K equation)**, which takes into account the permeabilities and concentrations of the multiple ions:

$$V_m = \frac{RT}{ZF} \ln \frac{P_{K^+}[K^+_o] + P_{Na^+}[Na^+_o] + P_{Cl^-}[Cl^-_i]}{P_{K^+}[K^+_i] + P_{Na^+}[Na^+_i] + P_{Cl^-}[Cl^-_o]}$$

Where:

- P_X is the membrane permeability to ion x
- $[X]_i$ is the concentration of x inside the cell
- $[X]_o$ is the concentration of x outside the cell
- R is the ideal gas constant
- T is absolute temperature
- Z is the charge of the ion
- F is Faraday's number

Although cells contain many ions, this simplified G-H-K equation omits ions that are much less permeable to the cell membrane than K^+, Na^+, and Cl^-, because their contribution to resting membrane potential is usually negligible. The concentration of Cl^- inside appears in the top of the right-hand term and the concentration of Cl^- outside appears in the bottom, whereas the situation for $[K^+]$ and $[Na^+]$ is opposite that of $[Cl^-]$, because of the difference in charge of these ions (negative vs. positive).

The resting membrane potential for most cells is approximately –70 mV; in nerve cells it is approximately –90 mV. K^+ contributes most to the resting membrane potential, because cytosolic K^+ concentration is high and extracellular K^+ concentration is low, and permeability of the plasma membrane to K^+ is high relative to other ions. Therefore, while the resting membrane potential is *similar* to the Nernst potential for K^+, other ions contribute to the resting membrane potential. Specifically, leaking of Na^+ through Na^+ channels along its electrochemical gradient contributes to the fact that the resting membrane potential of cells is less negative (more positive) than the Nernst potential for K^+. The gradients of Na^+ and K^+ are maintained in living cells by active transport via the

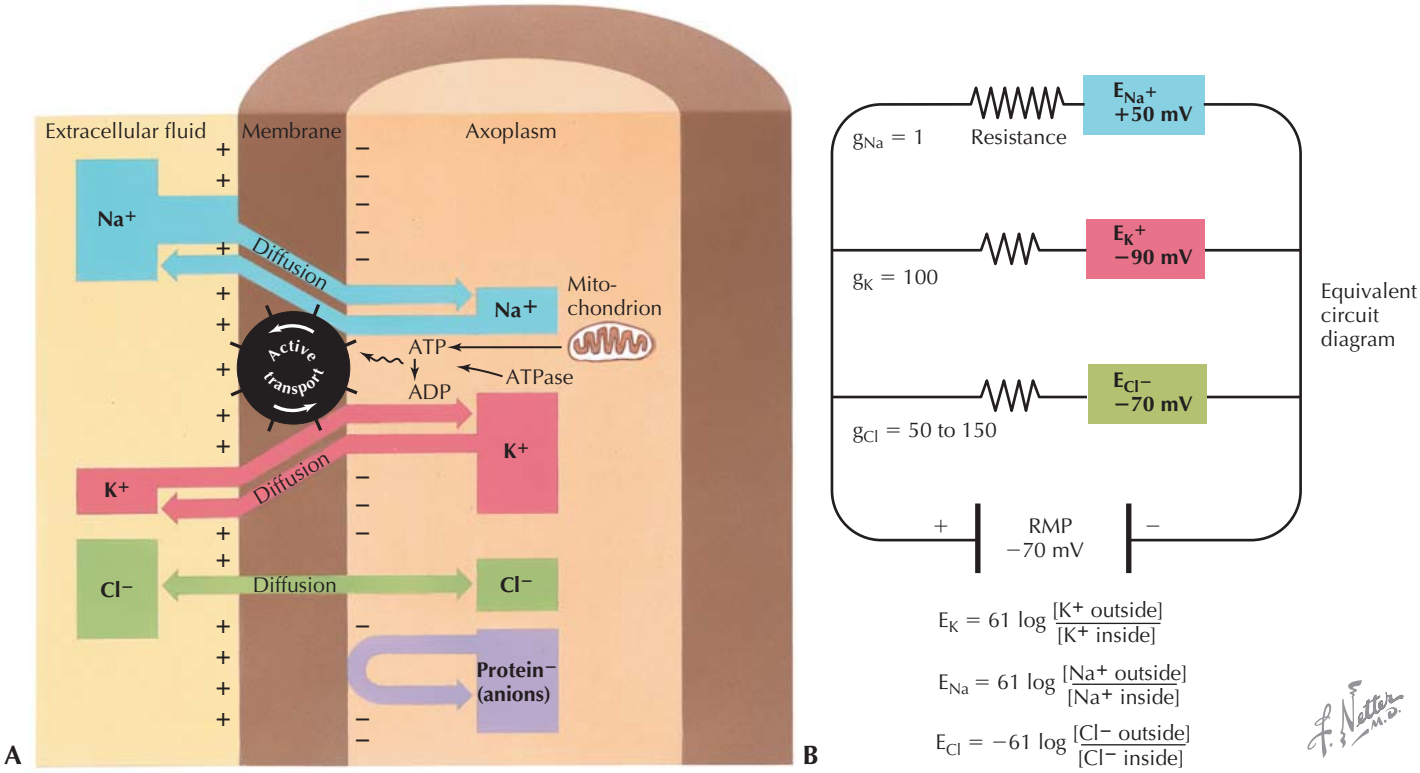


Figure 3.2 The Resting Membrane Potential Ion concentration differences between cytosol (in this example, axoplasm) and interstitial fluid are produced by the activity of transporters, mainly the Na^+/K^+ ATPase, which pumps Na^+ out of the cell in exchange for K^+, which is pumped into the cell *(A)*. (Size of rectangles indicates relative concentration of ions.) The cell membrane has differential permeabilities to the ions, resulting in leak across the membrane at different rates. The membrane is not permeable to proteins, which are negatively charged and are mainly intracellular. Leakage of K^+ out of the cell is the major factor in setting the resting membrane potential, because it is the most permeable ion. This situation can be modeled as an electrical circuit *(B)*, in which potential differences for the ions are expressed (in mV), based on the values obtained from the Nernst equation, and the permeability of the ions is expressed in terms of conductance (g).

Na^+/K^+ ATPase, counteracting the constant leak of Na^+ (and thus K^+) (Fig. 3.2).

A cell is said to be hyperpolarized when its membrane potential is more negative than the normal resting membrane potential for the cell; a cell at membrane potential less negative than its usual resting membrane potential is said to be **depolarized**. The membrane potential is a function of the individual concentration gradients for ions across the cell membrane and the permeabilities of the membrane to those ions.

ELECTROPHYSICAL PRINCIPLES

Some key electrophysical principles apply to movement of ions in cellular systems, and also to conduction of electrical impulses in the nervous system. According to **Ohm's law**:

$$V = IR$$

Where:

- V is the voltage of potential difference, measured in volts (V) or mV
- I is the current, measured in amperes (A), nanoamperes (10^{-9}A), or picoamperes (10^{-12}A)
- R is resistance, measured in ohms or megaohms (10^6 ohms)

In any electrical system, including movement of permeable ions across a cell membrane, current will occur (that is, charged particles will flow) driven by the potential difference in the system and impeded by the resistance of the system. Conductance (G) is the inverse of resistance and is measured in Siemens (S), nanoSiemens, or picoSiemens:

$$G = 1/R$$

In cells, conductance for various ions is a function of "leakiness" of the cell membrane to the ions (related to permeability, or presence of open channels). Ohm's law can be restated

to predict a specific ion current based on membrane potential and conductance of the ion:

$$I_X = G(Vm - E_x)$$

In other words, an ion current across a cell membrane will equal the product of the conductance for the ion and the difference between the membrane potential and the equilibrium (Nernst) potential for the ion. Thus, the positive ion K^+ continues to leak out of the cell (along its concentration gradient) at resting membrane potential, because the V_m (approximately −70 mV in most cells) is less negative than E_{K+} (−94 mV); Na^+ will continually leak into a cell, because its equilibrium potential is 61 mV compared with its resting membrane potential of −70 mV. By convention, the current associated with this outward flux of K^+, I_{K+}, is a positive current, whereas the inward Na^+ current, I_{Na+}, is a negative current. Again, the concentration gradients of these ions are maintained in the face of this constant but slow leak by active transport by the Na^+/K^+ ATPase.

ACTION POTENTIALS

An **action potential** is a rapid depolarization that occurs in an excitable cell (neurons and muscle cells) initiated by an electrical event or chemical stimulation that causes increased ion permeability in the cell membrane (Fig. 3.3). Some important characteristics of action potentials are as follows:

- A **threshold potential**, which is the potential at which an action potential will be initiated by increased conductance of ions (Na^+ in many cases). For example, a cell with a resting membrane potential of −70 mV might have a threshold potential of −50 mV; if the cell is depolarized to that threshold, an action potential will occur.
- **"All-or-none"** response, with a fixed amplitude (voltage change) and stereotypic shape of the action potential for a given cell type.
- **Nondecremental propagation**, in which an action potential at one point on a cell surface will be conducted to adjacent sites along the membrane.
- A **refractory period** beginning with the initiation of the action potential, when it is impossible to elicit a second action potential.
- A **relative refractory period** following the absolute refractory period, when a second potential can be evoked but requires a larger than normal stimulus.

The threshold potential results from the balance between outward K^+ leakage and inward Na^+ current through voltage-gated Na^+ channels. When a stimulus produces depolarization that reaches this threshold, voltage-gated Na^+ channels open, and the inward flux of Na^+ now exceeds the ability of K^+ leakage to maintain a steady state. The further depolarization of the membrane opens more voltage-gated Na^+ channels, and this positive feedback continues until all voltage-gated Na^+ channels are open, producing the rapid, all-or-none depolarization characteristic of an action potential. These "fast channels" are rapidly inactivated as well.

Along with these changes in Na^+ conductance, there is a delayed, slower, and smaller increase in conductance of K^+ during the action potential (see Fig. 3.3). This is caused by opening of voltage-gated K^+ channels, and along with the fall in Na^+ conductance, is responsible for the repolarization of the membrane. These K^+ channels remain open until the membrane finally returns to the equilibrium potential and are therefore responsible for the hyperpolarization or "undershoot" phase of the action potential, during which the membrane is at a more negative potential than the resting potential. This "undershoot" contributes to the relative refractoriness of the membrane to generation of another action potential, because a greater stimulus will be required to displace this hyperpolarized membrane potential to the threshold potential. A second factor contributing to refractoriness, earlier in the relative refractory period, is that some Na^+ channels still remain inactivated.

Extracellular Ca^{2+} concentration affects threshold potential by altering the sensitivity of voltage-gated Na^+ channels. At high Ca^{2+} concentrations, greater membrane depolarization is required to activate the channels, and thus the excitability of cells is reduced at high Ca^{2+} concentrations.



An **action potential** is initiated in a cell when the membrane potential is sufficiently depolarized to reach the **threshold potential**. When this occurs, opening of specific voltage-gated channels results in increased conductance of one or more ions, resulting in a rapid depolarization of the cell. In many excitable cells, the upstroke of the action potential is a result of opening of voltage-gated Na^+ channels. When the cell reaches threshold potential, a sufficient number of **activation gates** of the Na^+ channels are opened to allow Na^+ flux through the membrane, which causes the upstroke of the action potential. Shortly thereafter, **inactivation gates** close the channels, terminating the upstroke. These inactivation gates remain open until the cell returns to the resting membrane potential. Influx of K^+ is responsible for repolarization of the membrane.

ACTION POTENTIAL CONDUCTION

In excitable cells, an action potential is rapidly propagated over the cell membrane. In a neuron, when **threshold potential** is reached, an action potential is generated at the axon hillock, spreads to the axon, and is conducted to the axon terminal (Fig. 3.4) (conduction *between* cells is discussed later). As depolarization occurs at a point on the membrane, Na^+ flows through the membrane from the extracellular fluid. Loss of positive charge at the point of depolarization causes **local currents**, in which positive charges flow from adjacent regions along the membrane to the area of depolarization (Fig. 3.5*A*). Local current results in depolarization of the adjacent regions;

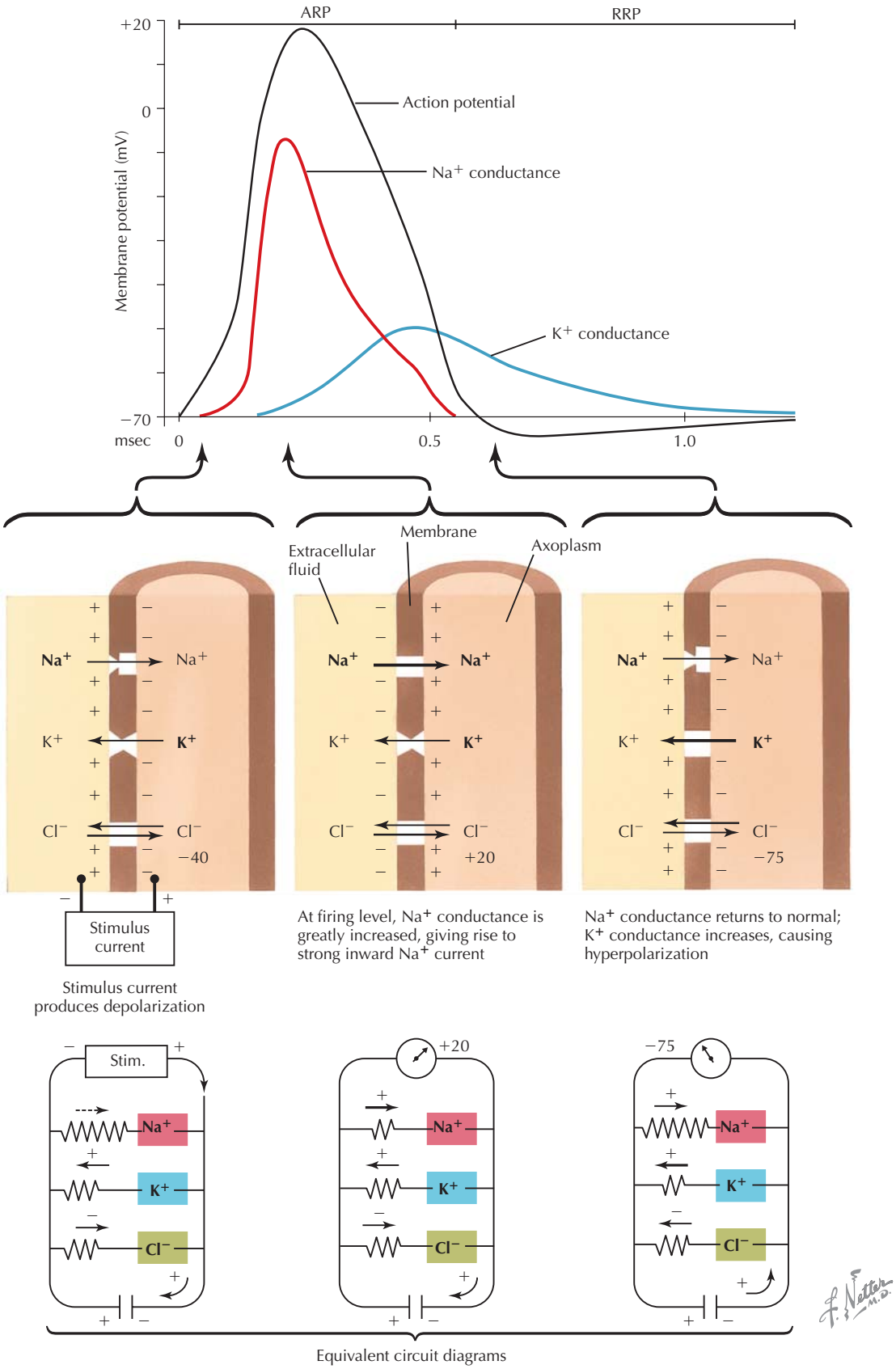


Figure 3.3 **Action Potential** The action potential in most excitable cells is initiated when a local potential on a cell reaches a threshold at which voltage-gated Na^+ channels open, greatly increasing Na^+ conductance. Changes in Na^+ and K^+ conductance during the action potential are illustrated, along with the equivalent circuit diagrams.

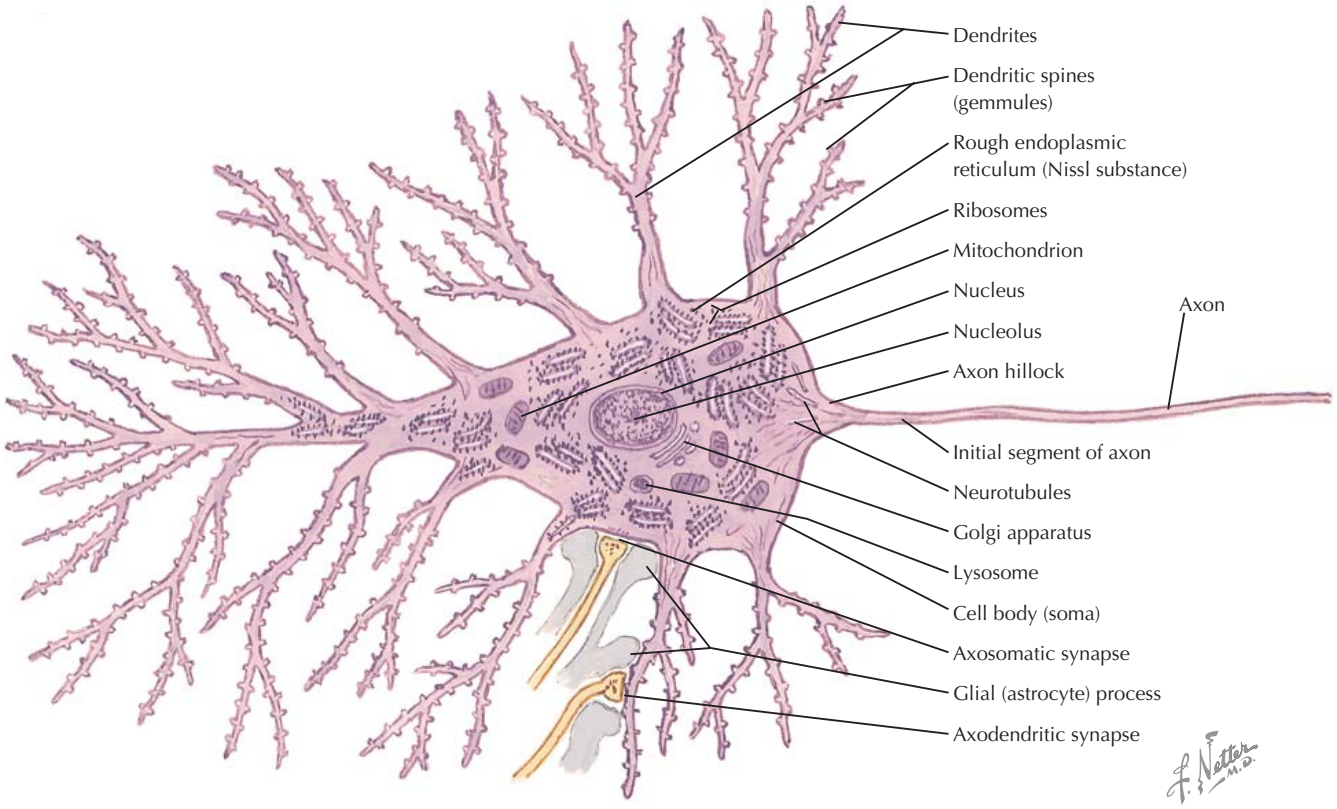


Figure 3.4 Neurons Neurons consist of the soma (cell body), multiple dendrites, and an axon. Neurons receive signals from other neurons at synapses, resulting in changes in local membrane potential. When the membrane potential is sufficiently depolarized, an action potential is initiated at the axon hillock and is propagated down the length of the axon to synapses with other neurons or muscle cells.

when threshold is reached, the action potential is propagated. An important characteristic of **action potential propagation** is that it occurs away from the point of initiation; it cannot travel back toward its origin. As the action potential is conducted, the area of the membrane directly behind the action potential is still in the absolute refractory state due to Na^+ channel inactivation, preventing retrograde conduction.

An essential property of neurons is the ability to rapidly propagate an action potential, analogous to an electrical cable. Conduction velocity is a function of:

- **Internal resistance** (R_i), the impedance to current flow within the cytoplasm (for example, resistance within the axon).
- **Membrane resistance** (R_m), the impedance to current flow through the membrane.
- **Capacitance** (C_m), the ability of the membrane to store charge.

The relationships between these variables result in the **cable properties** of cells: the **space constant** (λ) and the **time constant** (τ), which are useful in describing conduction of electrical activity in an axon. The time it takes for membrane potential to change to 63% of its final value when a current is applied is τ ($\tau = R_m \times C_m$). It is a measure of how slowly or quickly the membrane depolarizes or repolarizes, and is therefore inversely related to action potential conduction velocity. Because τ is inversely related to conduction velocity, low membrane resistance and low membrane capacitance favor faster conduction.

The space constant (λ, also known as the length constant) is the distance along the membrane over which a potential change will fall to 63% of its value, and therefore describes how far a depolarizing current will spread. With greater λ, depolarizing currents will spread further, resulting in greater conduction velocity. λ is proportional to the ratio of R_m to R_i:

$$\lambda = \sqrt{(R_m / R_i)}$$



The importance of internal resistance (R_i) in action potential conduction velocity can be inferred from the anatomy of axons of large invertebrates. The giant axon of the squid has a diameter of 500 μm; with this increased diameter, λ is high because R_i is low, resulting in the rapid conduction necessary in a large animal.

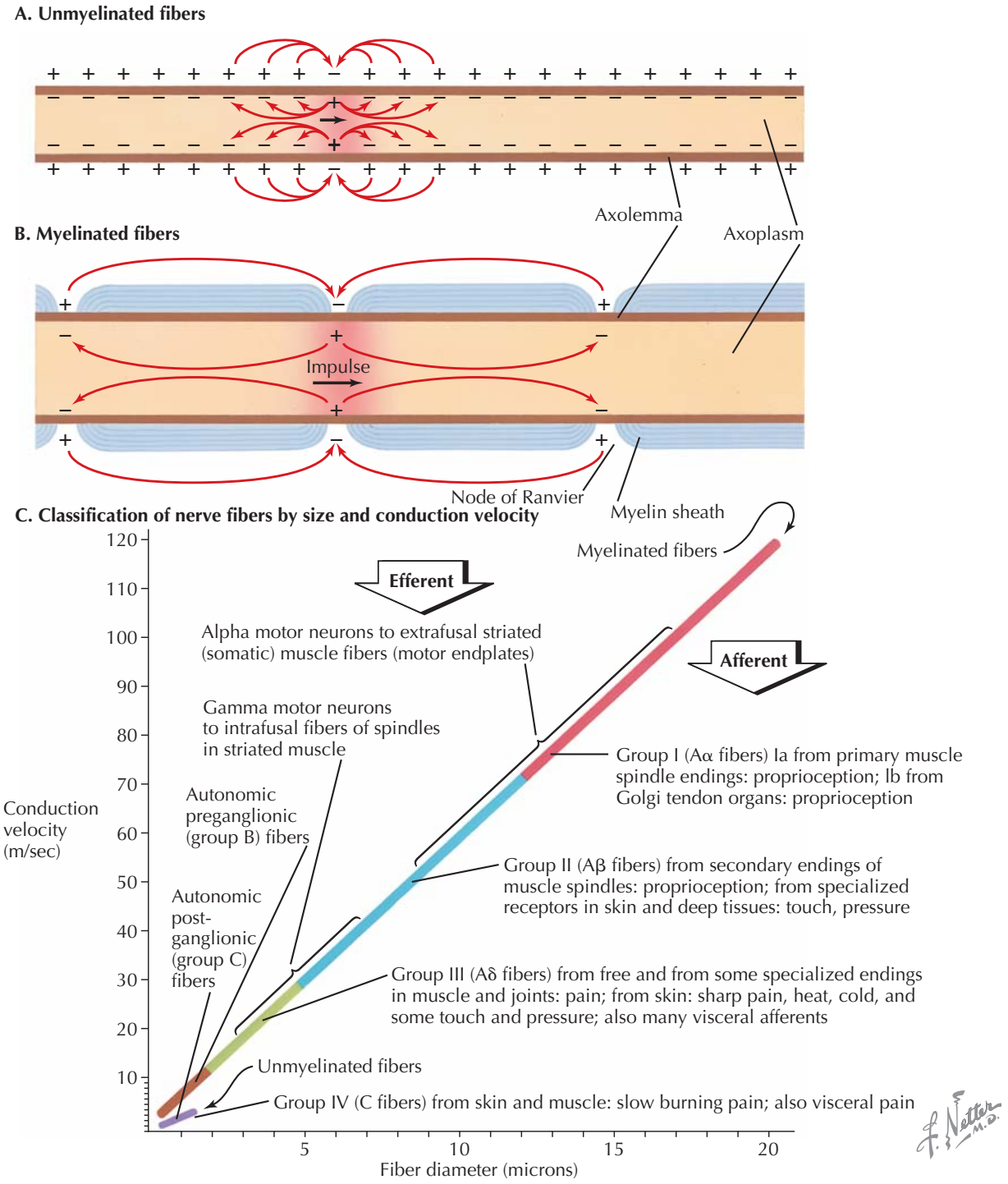
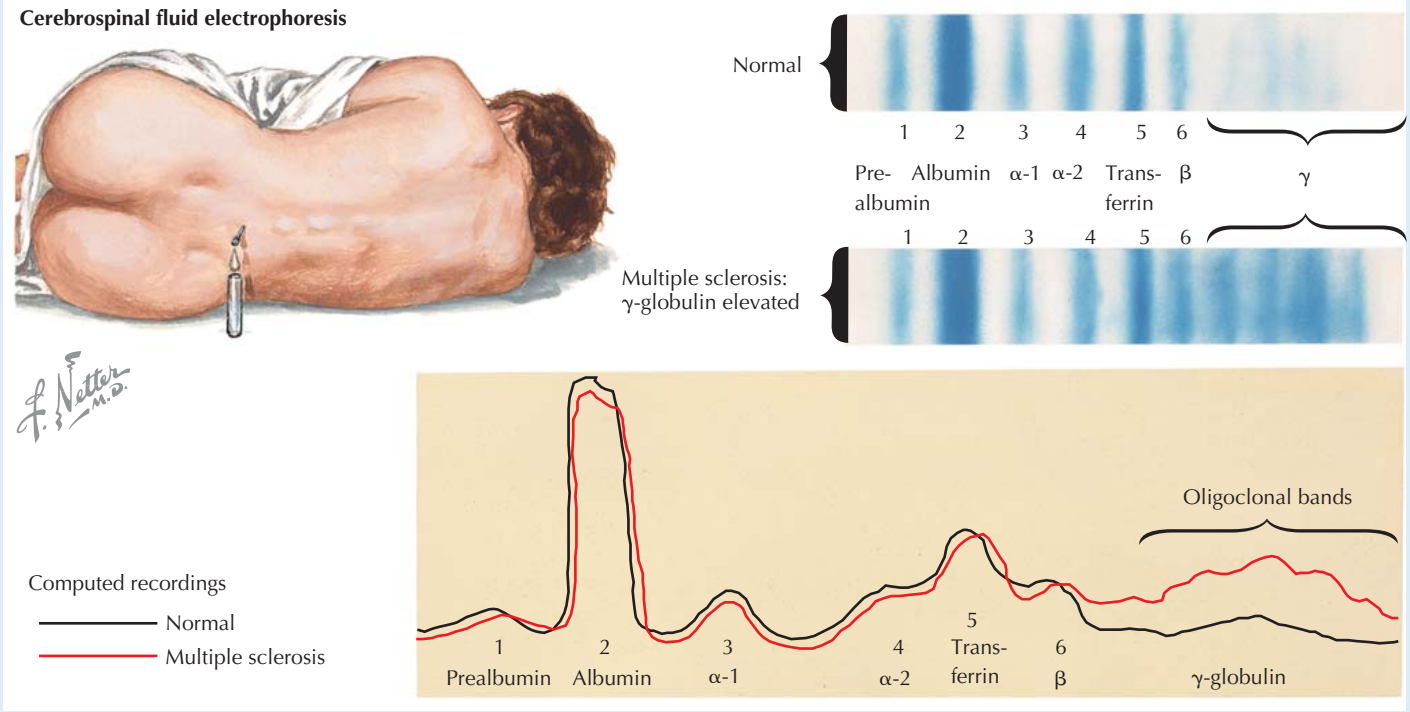


Figure 3.5 **Axonal Conduction** *A*, An action potential is propagated and conducted along an axon as adjacent portions of the membrane are depolarized by local currents. *B*, In myelinated axons, the action potential "jumps" between nodes of Ranvier. This process, called saltatory conduction, greatly increases conduction velocity. *C*, Myelination and axonal diameter are associated with higher conduction velocity.

The nervous system of vertebrates is much more complex and composed of a much larger number of neurons than that of invertebrates. Many nerve cells in the vertebrate nervous system are **myelinated** (Fig. 3.5*B*). They are covered by multiple layers of an insulating sheath of phospholipid membrane, formed by Schwann cells in the peripheral nervous system and oligodendrocytes in the central nervous system. This insulation greatly decreases capacitance and also increases membrane resistance, such that current travels through the interior of the axon, but not across the membrane. To allow propagation of the action potential, there are breaks in the myelin sheath called **nodes of Ranvier**. They are present at 1 to 2 mm intervals along the axon, and the action potential thus "jumps" rapidly from node to node, bypassing the myelinated areas. Essentially, the nodes of Ranvier represent multiple capacitors in series. This process of conduction whereby the action potential "jumps" between nodes is known as **saltatory conduction** and allows very rapid propagation of the action potential, despite small axon diameter. Local currents generated at one node during depolarization result in depolarization at the next node, and the action potential skips along the axon, bypassing the highly insulated segments. Fibers throughout the nervous system vary in terms of diameter and conduction velocity and may be classified into various types on this basis (Fig. 3.5*C*). In contrast to saltatory conduction, in unmyelinated axons, action potentials are conducted as slower waves of depolarization as they are propagated along the axon.

CLINICAL CORRELATE
Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory neurodegenerative disease, believed to be of autoimmune etiology. It is more common in women than men, and the usual age of onset is between 20 and 40 years of age. The inflammatory process of MS results in the gradual destruction of myelin sheaths around myelinated axons of the brain and spinal cord. A wide variety of symptoms may occur, including muscle weakness and paralysis; impaired coordination and poor balance; depression; impaired speech; memory problems; visual problems; altered sensory perception; pain; fatigue; and bowel, bladder, and sexual dysfunctions, resulting from the deficits in neural conduction caused by damage to myelin sheaths and underlying axons in the central nervous system. Diagnosis is based on clinical findings, MRI evidence of demyelinating lesions of the brain and spinal cord, and characteristic oligoclonal bands of γ-globulins in cerebrospinal fluid (CSF).



Multiple Sclerosis: Diagnostic Tests—Spinal Fluid CSF samples obtained by lumbar puncture display characteristic elevation of γ-globulins (oligoclonal bands) upon gel electrophoresis in approximately 90% of patients.

SYNAPTIC TRANSMISSION

A **synapse** is a site at which an electrical response in one cell is transmitted to another cell. This can occur between some cell types through **electrical synapses**, when electrical current passes directly from one cell to another through **gap junctions**. Cardiac myocytes and some types of smooth muscle communicate through this mechanism (some neurons communicate both through electrical and chemical transmission). At electrical synapses between cells, intramembrane proteins called **connexons** form channels that allow flow of ions between cells, thus allowing current transmission.

At a **chemical synapse**, release of a neurotransmitter by a neuron results in electrical stimulation of the presynaptic cell. A wide variety of neurotransmitters are found in various regions of the central and peripheral nervous system (Table 3.2). The morphology of a chemical synapse is illustrated in Figure 3.6. The sequence of events in transmission at this type of synapse is:

1. Depolarization of the neuron reaches the **synaptic bouton** (axon terminal), where it causes opening of Ca^{2+} channels.
2. The influx of Ca^{2+} results in the release of neurotransmitter, stored in presynaptic vesicles, into the **synaptic cleft** (the gap between the cells).
3. The transmitter diffuses across the synaptic cleft and binds to specific membrane receptors on the postsynaptic membrane.
4. Binding of the neurotransmitter produces a change in the membrane potential of the postsynaptic membrane.

Depending on the presynaptic neuron involved (and thus, the specific neurotransmitter released), the chemical transmission may result in either an **excitatory postsynaptic potential** (**EPSP**; depolarization) or an **inhibitory postsynaptic potential** (**IPSP**; hyperpolarization), as a result of Na^+ or Cl^- influx at the postsynaptic membrane, respectively (Fig. 3.7). Chemical transmission of this type is **unidirectional** between a presynaptic fiber and a postsynaptic cell. A given neuron typically receives synaptic input from multiple inhibitory and excitatory neurons; therefore, generation of an action potential depends on summation of these multiple inputs. An action potential may occur as a result of **temporal summation** when a series of impulses is generated by an excitatory presynaptic fiber, or as a result of **spatial summation** of local potentials generated by multiple excitatory fibers in the postsynaptic cell (Fig. 3.8). Synaptic inhibition may be either presynaptic or postsynaptic; some inhibitory fibers act directly on an excitatory fiber (**presynaptic inhibition**), while others produce **postsynaptic inhibition** (Fig. 3.9). Summation of local potentials in the postsynaptic membrane is dependent on the space constant and time constant of the membrane.

NEUROMUSCULAR JUNCTION

Motor neurons (motoneurons) are efferent nerves that originate in the central nervous system and communicate with

Table 3.2 Summary of Some Neurotransmitters and Where within the Central and Peripheral Nervous System They Are Found

Transmitter	Location	Transmitter	Location
Acetylcholine	Neuromuscular junction, autonomic endings and ganglia, CNS	Gas Nitric oxide	 CNS, GI tract
Biogenic amines		Peptides	
Norepinephrine	Sympathetic endings, CNS	β-Endorphins	CNS, GI tract
Dopamine	CNS	Enkephalins	CNS
Serotonin	CNS, GI tract	Antidiuretic hormone	CNS (hypothalamus/posterior pituitary)
Amino acids		Pituitary-releasing hormones	CNS (hypothalamus/anterior pituitary)
γ-Aminobutyric acid (GABA)	CNS	Somatostatin	CNS, GI tract
Glutamate	CNS	Neuropeptide Y	CNS
Purines		Vasoactive intestinal peptide	CNS, GI tract
Adenosine	CNS		
Adenosine triphosphate (ATP)	CNS		

CNS, Central nervous system; GI, gastrointestinal.
(Reprinted with permission from Hansen J: Netter's Atlas of Human Physiology, Philadelphia, Elsevier, 2002.)

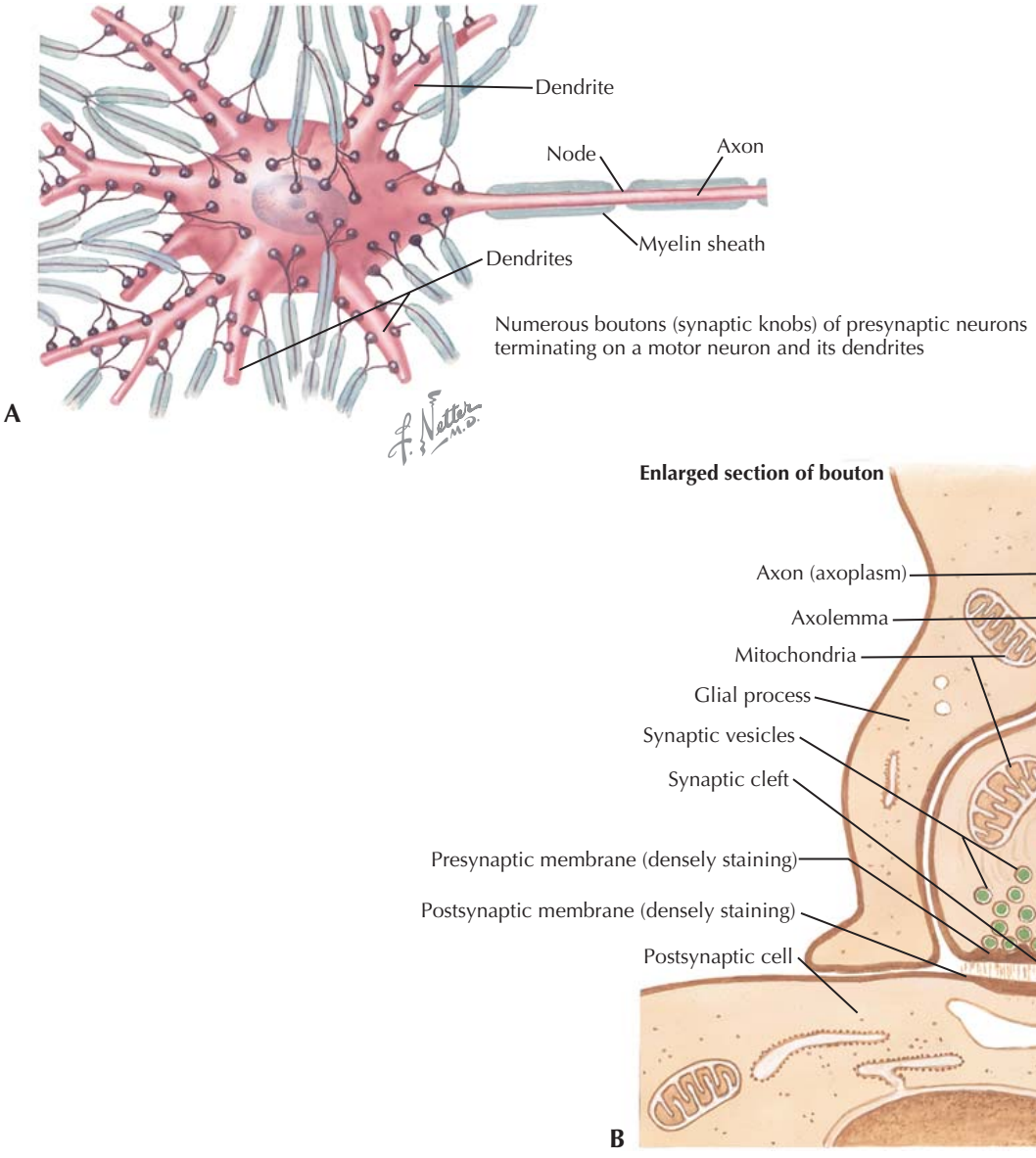
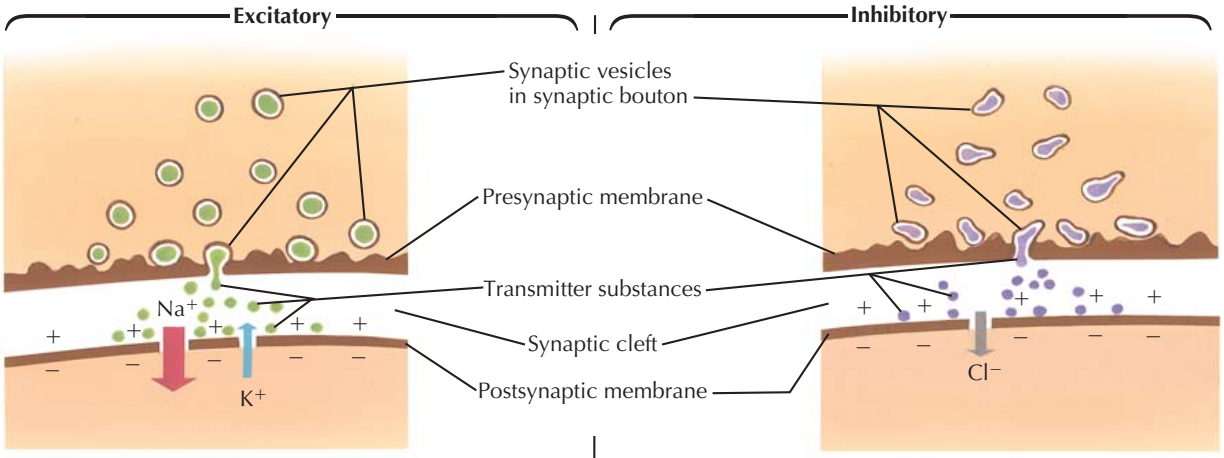


Figure 3.6 Morphology of Synapses An action potential in one neuron is transmitted to another neuron or an effector tissue at the synapses. The terminal regions of axons branch and form synaptic boutons. The myelination is lost where the bouton is in close contact with a dendrite or cell body of another neuron *(A)*. Neurotransmitters are released into the synaptic cleft when vesicles of the synaptic bouton fuse with the presynaptic membrane *(B)*. The released neurotransmitters diffuse and bind to receptors on the postsynaptic membrane, resulting in excitatory or inhibitory effects at the postsynaptic membrane.

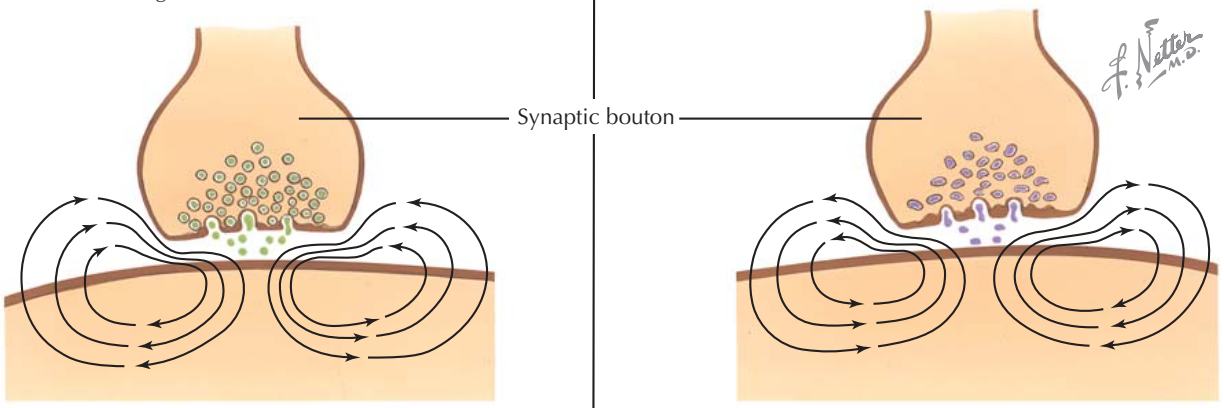
skeletal muscle fibers at specialized synapses known as **motor endplates** or **neuromuscular junctions** (Fig. 3.10). Among the several types of motor neurons, the most common is the α-motor neuron. Branches of an α-motor neuron may form multiple neuromuscular junctions in depressions in the **sarcolemmae** (muscle cell membranes) of muscle fibers; each α-motor neuron may thus innervate multiple muscle fibers, although each fiber is innervated by only one α-motor neuron. An α-motor neuron and the fibers it innervates is called a **motor unit**. All the motor neurons innervating a muscle are collectively known as a **motor neuron pool**.

The synaptic boutons of α-motor neurons are rich in vesicles containing the neurotransmitter acetylcholine. As is the case for other neurons, an action potential in an α-motor neuron produces Ca^{2+} influx at the synaptic bouton, which results in release of neurotransmitter from vesicles of the synaptic bouton. Vesicular release of neurotransmitter is **quantal** in nature, and is conceptualized as the release of packets (quanta) of neurotransmitter, the quanta being defined by the response to the neurotransmitter contained in a single vesicle. At the postsynaptic membrane of a neuromuscular junction, acetylcholine binds to a specific subtype of acetylcholine receptor known as the nicotinic



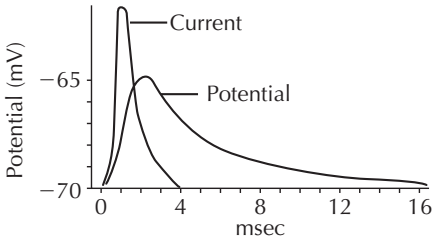
When impulse reaches the excitatory synaptic bouton, it causes release of a transmitter substance into the synaptic cleft. This increases permeability of the postsynaptic membrane to Na^+ and K^+. More Na^+ moves into the postsynaptic cell than K^+ moves out, due to greater electrochemical gradient.

At the inhibitory synapse, transmitter substance released by an impulse increases permeability of the postsynaptic membrane to Cl^-.

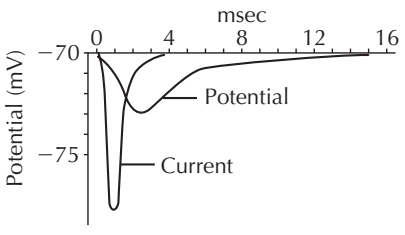


Resultant net ionic current flow is in a direction that tends to depolarize the postsynaptic cell. If depolarization reaches firing threshold, an impulse is generated in the postsynaptic cell.

Resultant ionic current flow is in the direction that tends to hyperpolarize the postsynaptic cell. This makes depolarization by excitatory synapses more difficult—more depolarization is required to reach the threshold.

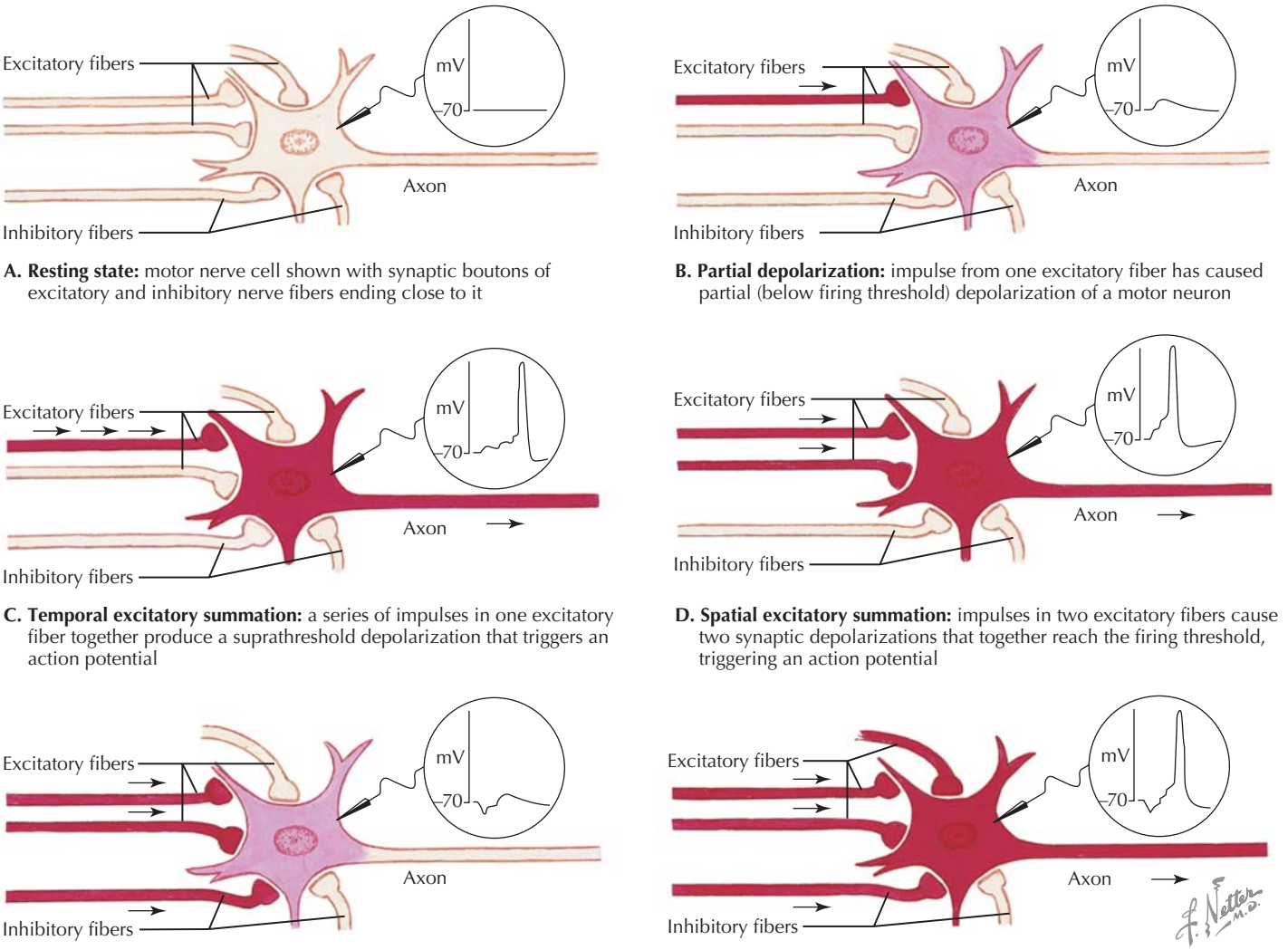


Current flow and potential change



Current flow and potential change

Figure 3.7 Chemical Synaptic Transmission Synaptic transmission may result in either excitatory or inhibitory effects at the postsynaptic membrane. In excitatory transmission *(left)*, a depolarizing change in local potential (excitatory postsynaptic potential; EPSP) is produced. In inhibitory transmission *(right)*, a hyperpolarizing change in local potential (inhibitory postsynaptic potential; IPSP) is produced. An action potential occurs when the temporal and spatial summation of local potentials reaches the threshold for action potential generation (see Fig. 3.8).



A. Resting state: motor nerve cell shown with synaptic boutons of excitatory and inhibitory nerve fibers ending close to it

B. Partial depolarization: impulse from one excitatory fiber has caused partial (below firing threshold) depolarization of a motor neuron

C. Temporal excitatory summation: a series of impulses in one excitatory fiber together produce a suprathreshold depolarization that triggers an action potential

D. Spatial excitatory summation: impulses in two excitatory fibers cause two synaptic depolarizations that together reach the firing threshold, triggering an action potential

E. Spatial excitatory summation with inhibition: impulses from two excitatory fibers reach a motor neuron, but impulses from inhibitory fiber prevent depolarization from reaching the threshold

E. (continued): the motor neuron now receives additional excitatory impulses and reaches firing threshold despite a simultaneous inhibitory impulse; additional inhibitory impulses might still prevent firing

Figure 3.8 Temporal and Spatial Summation In the resting state *(A)*, the nerve cell is at its resting membrane potential. Neurons are subject to multiple inhibitory and stimulatory signals that produce local potential changes, which are subject to both temporal and spatial summation. The sum of these influences determines whether an action potential is produced *(B–E)*.

receptor. The action of acetylcholine is rapid; it is also short-lived because acetylcholine diffuses out of the synaptic cleft or is rapidly broken down by acetylcholinesterase localized on the basement membrane of the muscle fiber.

Binding of postsynaptic nicotinic receptors by acetylcholine causes the opening of ligand-gated channels. Influx of Na^+ and K^+ through these channels produces an excitatory postsynaptic potential (endplate potential). When this endplate potential reaches threshold, an action potential is generated, ultimately producing contraction of the muscle fiber. Pharmacologically, the actions of acetylcholine can be blocked by **curare**, a competitive antagonist that binds reversibly to the nicotinic receptor, thereby blocking acetylcholine binding, or by **cobra venom** (**α-bungarotoxin**), a noncompetitive antagonist that binds irreversibly to the receptor.

Endplate potentials differ from neuronal action potentials in several important ways:

- Endplate potentials are produced by a ligand-gated channel; neuronal action potentials are caused by voltage-gated channels. In both cases, the action potential is generated in the postsynaptic cell when a threshold is reached.
- Rapid depolarization, to a potential of 0 mV, compared with rapid depolarization to +40 mV during a neuronal action potential.

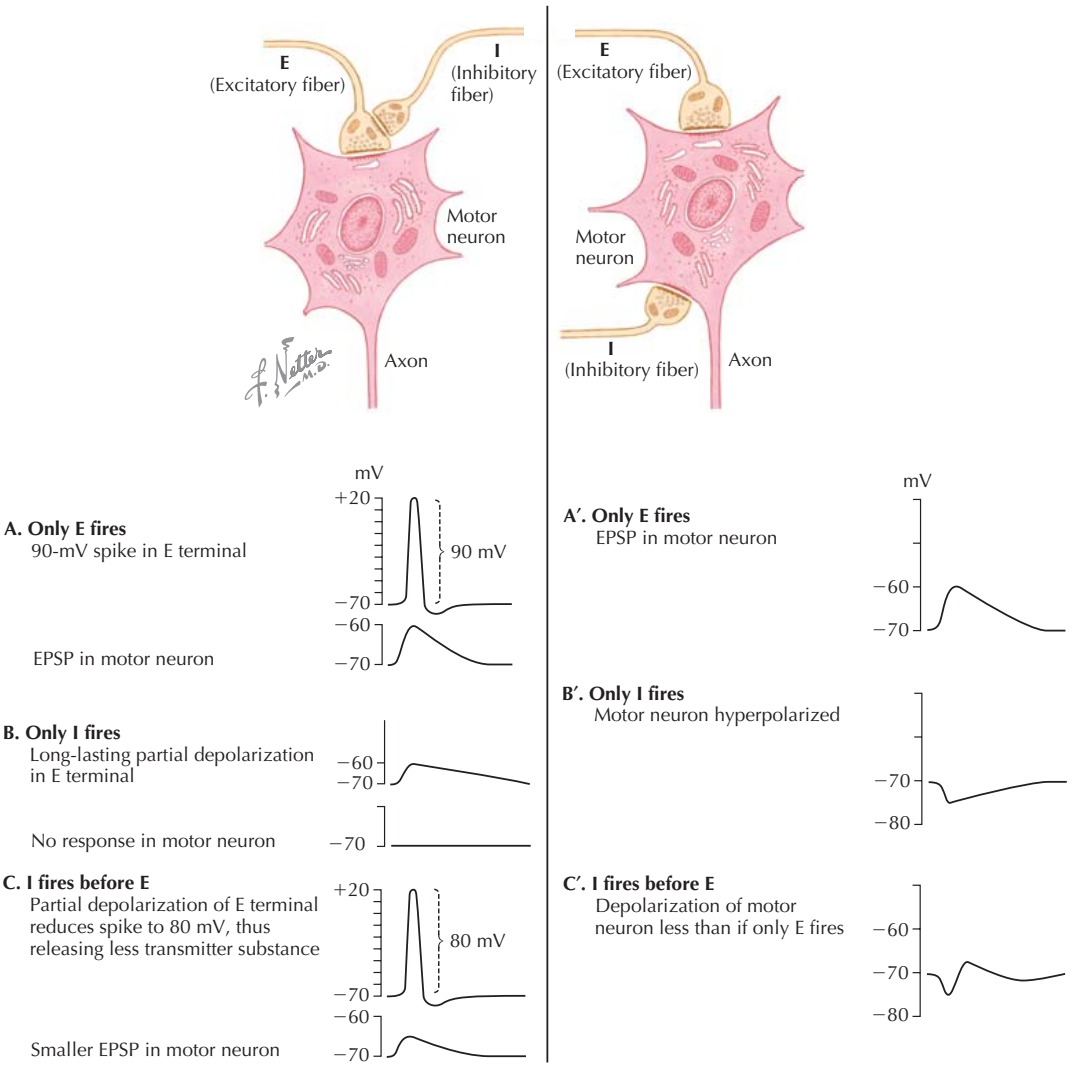


Figure 3.9 Synaptic Inhibitory Mechanisms Inhibition can occur through either presynaptic or postsynaptic mechanisms. In presynaptic inhibition, illustrated *(top left)* for a motor neuron, an inhibitory fiber of one nerve cell has a synapse on an excitatory axon of another neuron before the latter communicates with the motor neuron; in postsynaptic inhibition *(top left),* the inhibitory and excitatory fibers both synapse directly with the target neuron. *A, B,* and *C* illustrate the changes in potential at the excitatory terminal and in the motor neuron when only the excitatory, only the inhibitory, or both inhibitory and excitatory fibers fire. *A′, B′,* and *C′* illustrate membrane potential changes in the motor neuron when only excitatory, only inhibitory, or both excitatory and inhibitory fibers fire.

- A single, large channel for Na^+ and K^+ carries the charge during an endplate potential. Multiple ion channels are involved in a neuronal action potential, which is mainly produced by Na^+ influx.
- Repolarization of the endplate is passive, whereas increased K^+ conductance is responsible for repolarization during a neuronal action potential.

SKELETAL MUSCLE ORGANIZATION

Skeletal muscle contraction is the basis for voluntary muscle movement. Multinucleated cells contain **sarcomeres**, specialized structures that produce contraction upon stimulation of the muscle. Sarcomeres are contained within **myofibrils**, which are further organized as **muscle fibers**; groups of muscle fibers form **muscle fascicles** (Fig. 3.11). Microscopically, the arrangement of sarcomeres and myofibrils results in the striated appearance of skeletal muscle. Contraction is based on sliding of the thin and thick filaments of sarcomeres (see "Excitation-Contraction Coupling").

Within the skeletal muscle cell, the **sarcoplasmic reticulum** composes a complex network surrounding the myofibrils (Fig. 3.12). This specialized form of smooth endoplasmic reticulum is the site for the storage of high concentrations of intracellular Ca^{2+} and contains Ca^{2+}-ATPase and calsequestrin (a low-affinity Ca^{2+}-binding protein) for sequestration of this ion, as

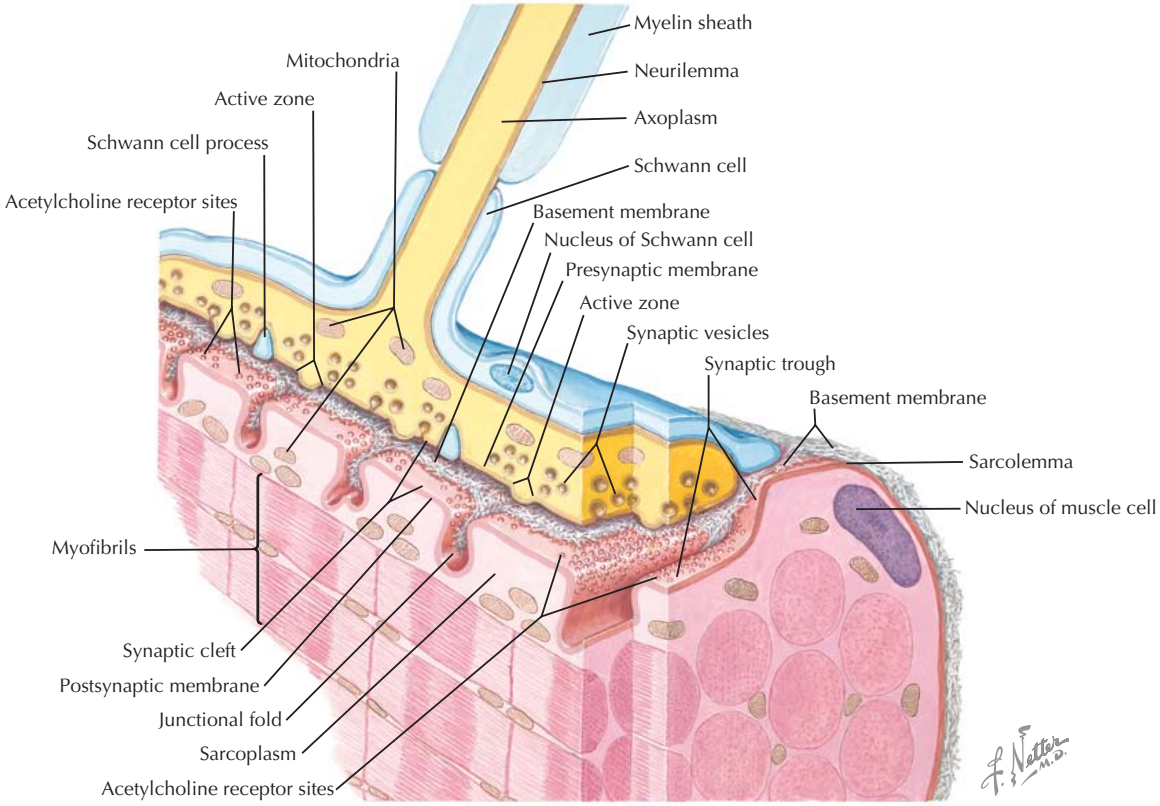


Figure 3.10 Structure of the Neuromuscular Junction At the neuromuscular junction, the axon of a motor nerve synapses with skeletal muscle at a site known as the motor endplate. Stimulation of a motor nerve results in the release of acetylcholine from vesicles at the presynaptic membrane; acetylcholine diffuses and binds to postsynaptic receptors, producing depolarization of the sarcolemma and leading to an action potential.

well as L-type (ligand-gated) Ca^{2+} channels. The **transverse tubules** (**T-tubules**) are deep invaginations of the muscle cell membrane (sarcolemma). They form **triads** with two terminal cisternae of the sarcoplasmic reticulum; these triads are arranged perpendicularly to the muscle fiber. The T-tubules extend into the muscle fiber from the surface, allowing close communication between the interior of the cell and the extracellular fluid. They are responsible for conducting the action potential to the cisternae of the sarcoplasmic reticulum.

EXCITATION-CONTRACTION COUPLING

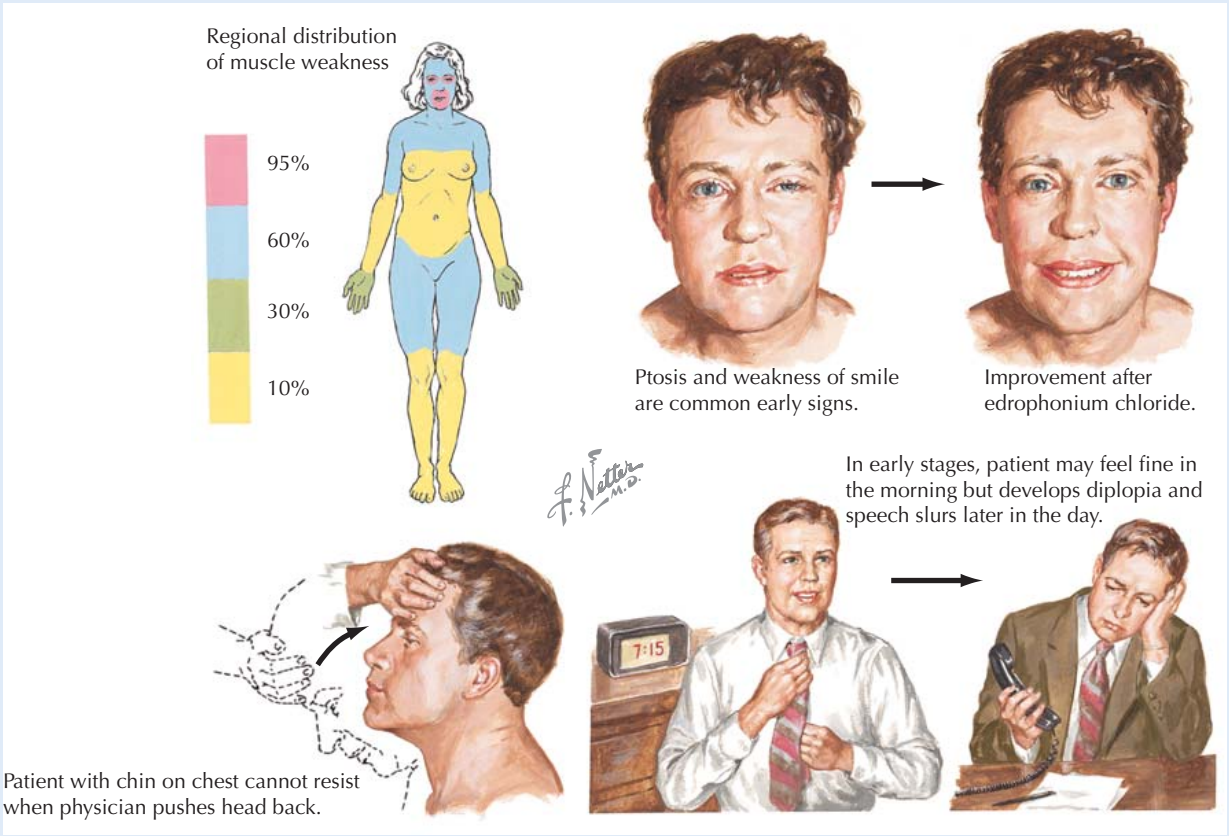
As depolarization spreads across the sarcoplasmic reticulum, it is conducted into the transverse tubules (Fig. 3.13). The T-tubule membrane contains voltage-gated Ca^{2+} channels, also known as **dihydropyridine receptors**. Although the dihydropyridine receptor is a voltage-gated Ca^{2+} channel, ion flux through this channel is not required for contraction of skeletal muscle. Rather, a conformational change in the dihydropyridine receptor, caused by depolarization of the T-tubule, is required. These receptors are in close apposition to calcium channel proteins known as **ryanodine receptors**, which are large proteins of the sarcoplasmic reticulum that extend into the gap between the cisternae of the sarcoplasmic reticulum and the T-tubules. Conformational change of the dihydropyridine receptors is believed to produce a subsequent conformational change in the ryanodine receptors, allowing stored Ca^{2+} to be released from the sarcoplasmic reticulum, initiating the contraction process. The term **excitation-contraction coupling** refers to this linking of depolarization to Ca^{2+} release.

To summarize these events:

- Depolarization of the motor neuron terminal results in Ca^{2+} influx.
- Vesicles of the axon terminal release acetylcholine.
- Binding of acetylcholine by nicotinic receptors results in an endplate potential.
- An action potential is initiated and is propagated along the sarcolemma and down the T-tubules.
- A conformational change in the dihydropyridine receptor of the T-tubule is transduced to a conformational change in the ryanodine receptor of the sarcoplasmic reticulum.
- Ca^{2+} is released from the sarcoplasmic reticulum, initiating contraction.

CLINICAL CORRELATE
Myasthenia Gravis

Myasthenia gravis is an autoimmune, neuromuscular disease that affects the acetylcholine receptors of the neuromuscular junction. In this disease, autoantibodies are produced that block or damage the **acetylcholine receptor** of the motor endplate, inhibiting the normal effects of acetylcholine at these receptors and thus producing muscle weakness. Muscles of the eye and face and muscles involved in swallowing, talking, and chewing are most commonly affected, although weakness of other muscles may also occur. Episodes of myasthenia gravis may occur suddenly, often after a period of high physical activity, and may abate after a period of rest. A myasthenic crisis is a medical emergency that may be caused by an infectious disease or adverse drug reaction. In a crisis, muscles of respiration are weakened, making breathing difficult. Such cases require assisted ventilation, such as positive airway pressure ventilation. In myasthenia gravis, the appearance of symptoms is usually episodic, and treatment often involves an immunosuppressive drug such as corticosteroids, as well as a **cholinesterase inhibitor** (for example, neostigmine). Cholinesterase inhibitors inhibit acetylcholinesterase, prolonging the half-life of acetylcholine in the neuromuscular junction. In some cases, plasmapheresis may be used to remove autoantibodies or thymectomy may be performed.



Clinical Manifestations of Myasthenia Gravis In myasthenia gravis, an autoimmune disease, antibodies block or reduce the number of nicotinic acetylcholine receptors at the neuromuscular junction, resulting in muscle fatigability. Diagnostic tests include the edrophonium test. Edrophonium chloride is a cholinesterase inhibitor and thus increases acetylcholine at the neuromuscular junction. Administered intravenously, it will temporarily relieve symptoms of muscle weakness, including diplopia (double vision), in myasthenia gravis.

THE SLIDING FILAMENT THEORY

The sliding filament theory describes the processes that take place in the sarcomeres that account for skeletal muscle contraction. The sliding of the interdigitated, anchored thick and thin filaments is the basis of contraction (Fig. 3.14). The thick filaments of the sarcomeres are composed of the protein **myosin** and are anchored to the **M line**; the thin filaments are composed of **actin**, **tropomyosin**, and **troponin** and are anchored to the **Z line** (Fig. 3.15). Within the thin filament, globular G-actin is polymerized to form an α-helical filament (F-actin). Actin has binding sites for myosin along the groove of its helix; these sites are covered by the protein **tropomyosin**. Three forms of **troponin** are also incorporated at regular intervals (troponin C, troponin I, and troponin T).

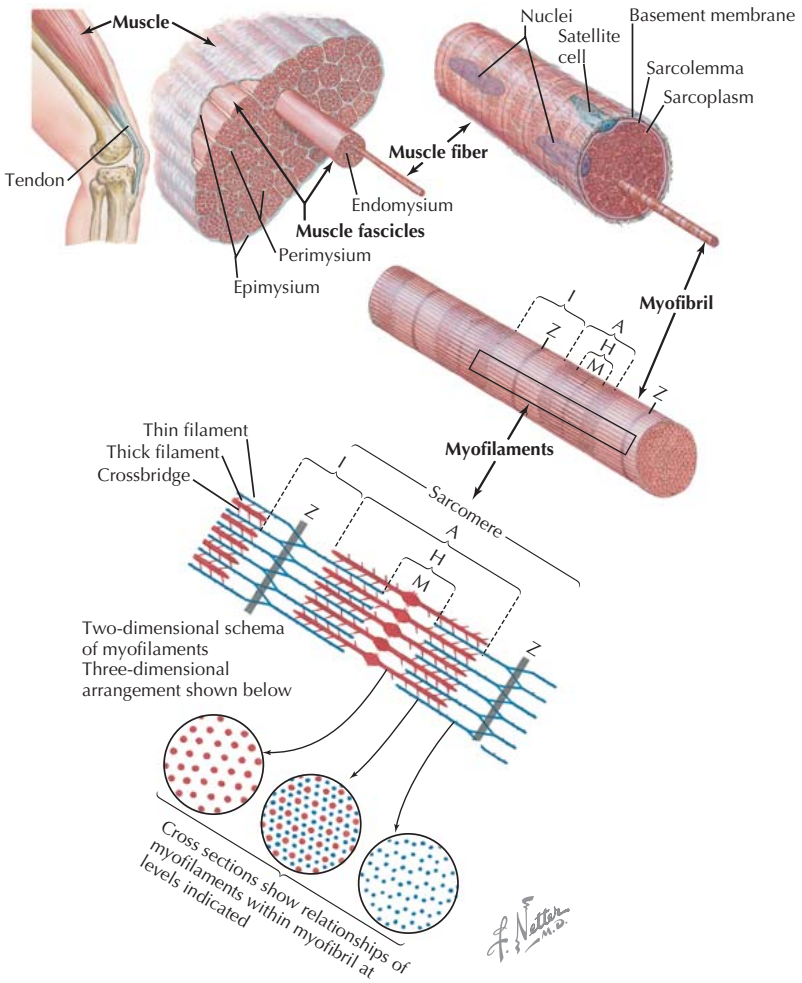


Figure 3.11 Organization of Skeletal Muscle Skeletal muscle is composed of fascicles that are in turn comprised of multinucleated muscle fibers. These fibers are composed of smaller myofibrils, which contain sarcomeres, the site at which sliding of actin and myosin filaments produces contraction. The organization of sarcomeres within the skeletal muscle produces its striated appearance. The Z line marks the boundary between two sarcomeres. The I band contains only the actin thin filaments, which extend from the Z line toward the center of the sarcomere. Myosin thick filaments are found in the dark A band. At the H zone, there is no overlap between actin and myosin. The M line is at the center of the sarcomere and is the site at which the thick filaments are linked with each other.

In the relaxed state, in which cytosolic Ca^{2+} concentration is extremely low (10^{-7} M), binding of myosin to actin is blocked because myosin binding sites on actin are covered by tropomyosin. Partially hydrolyzed ATP (ADP) is bound to the myosin head groups (see Fig. 3.15). When an action potential causes release of Ca^{2+} from the sarcoplasmic reticulum, binding of Ca^{2+} to troponin causes troponin to move into the groove of the actin α-helix. This results in exposure of the myosin binding sites, thus promoting the binding of the myosin head group to actin, forming a **crossbridge**. This binding is followed by a ratcheting action of the myosin head group, shortening the sarcomere as the actin and myosin slide past each other. ADP and inorganic phosphate (P_i) are released. Next, binding of ATP to the myosin head group causes detachment of actin and myosin, after which ATP is partially hydrolyzed



Skeletal muscle fibers can be categorized as **fast twitch** and **slow twitch** fibers, also known as white muscle and red muscle, respectively. Most muscles in the body are composed of a mixture of the two types, but individual motor units contain only one fiber type. The oxygen-binding protein **myoglobin** is found only in slow twitch fibers and is responsible for its red color. Fast twitch (white muscle) fibers utilize anaerobic glycolysis as an energy source and therefore are high in glycogen content. This type of muscle is utilized for rapid, powerful movements; ATPase activity is high and contraction speed is high, and resistance to fatigue is low. Slow twitch (red muscle) fibers utilize oxidative phosphorylation, and thus glycogen content is low. Slow twitch fibers are used for activities requiring endurance. ATPase activity and contraction speed are low, and resistance to fatigue is high.

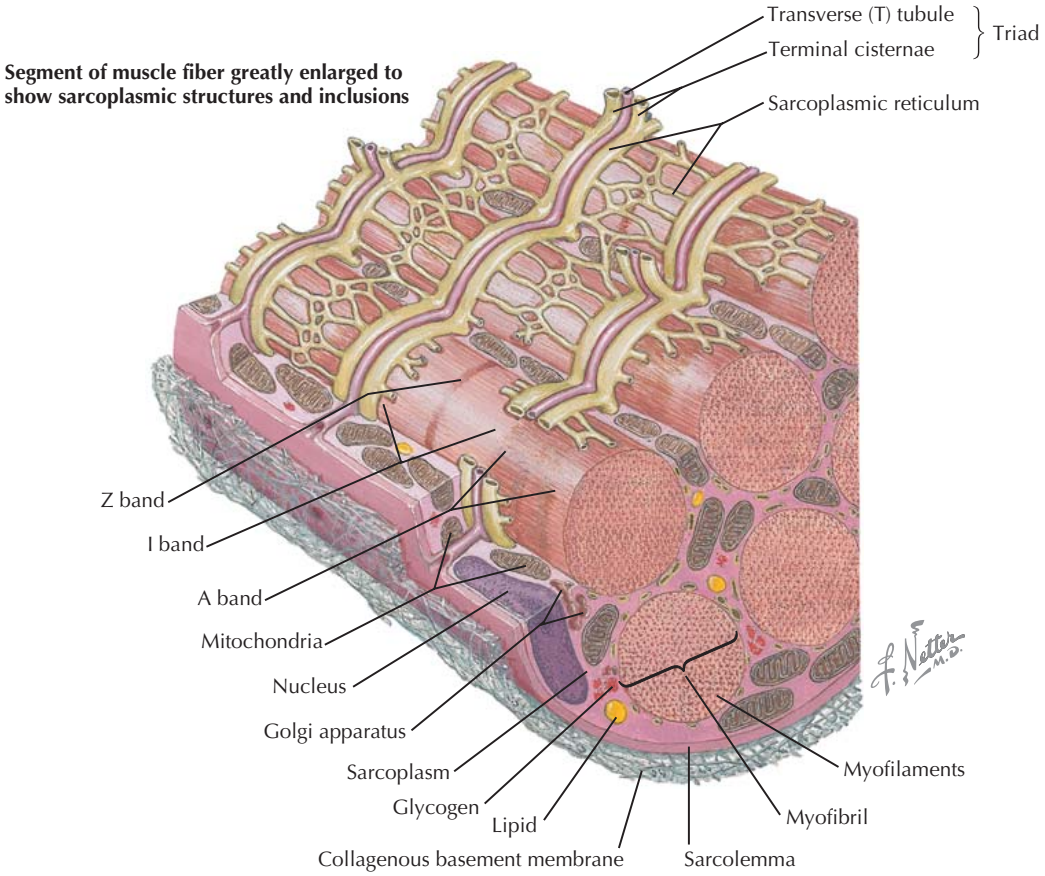


Figure 3.12 Sarcoplasmic Reticulum The sarcoplasmic reticulum is a complex network surrounding the myofibrils and storing high concentrations of Ca^{2+}, sequestered from the sarcoplasm. The membrane of the sarcoplasmic reticulum contains Ca^{2+}-ATPase, which is essential for this sequestration. The transverse tubules are deep invaginations of the sarcolemma and form triads with the terminal cisternae of the sarcoplasmic reticulum. These transverse tubules conduct the action potential from the sarcolemma to the cisternae, causing release of Ca^{2+}.

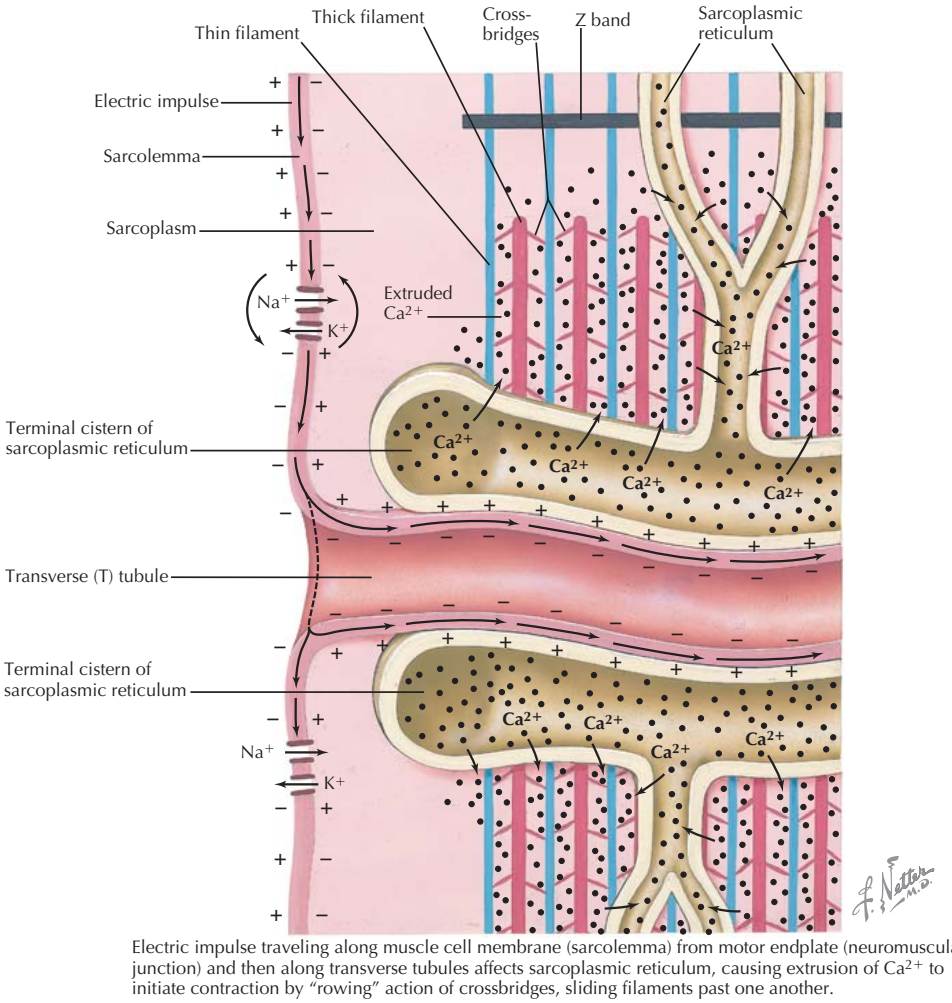
by ATPase; this causes "recocking" of the head group. If cytosolic Ca^{2+} is still elevated, myosin rapidly binds to actin, and crossbridge cycling in this manner causes the contraction to continue. Crossbridge cycling occurs simultaneously at multiple sites, producing the shortening of the sarcomere. When Ca^{2+} is resequestered into the sarcoplasmic reticulum, muscle relaxes due to low cytosolic Ca^{2+} concentration.

During crossbridge cycling, each cycle requires one ATP molecule to dissociate each myosin head group. Furthermore, relaxation requires ATP, for sequestration of Ca^{2+} into the sarcoplasmic reticulum. In **rigor mortis**, because ATP is depleted, myosin remains bound to actin, causing stiffness of the muscles.

MECHANICAL CONSIDERATIONS IN SKELETAL MUSCLE CONTRACTION

Generation of force by skeletal muscle is controlled by a number of factors (Fig. 3.16). For example, variation in the size of motor units is consistent with the function of the motor units. Small motor units are effective in performing fine movements, as in movements of the fingers and eyes, whereas large motor units perform coarser movements (see Fig. 3.16*A*). The force of contraction of skeletal muscles can be increased by **recruitment** of motor units and **summation of twitches.** As noted earlier, all of the muscle fibers associated with a single motor unit will contract simultaneously. Greater contraction can be achieved by recruiting more motor units (**spatial summation**). With repeated stimulation of a muscle, **temporal summation** may occur. In this case, individual twitches of the muscle occur without full relaxation between twitches, with greater force of contraction resulting as Ca^{2+} is released from the sarcoplasmic reticulum at a higher rate than it can be resequestered between the twitches (see Fig. 3.16*B*). In **tetanus** (tetany), there is a sustained, forceful contraction due to high frequency stimulation.

Finally, the muscle tension generated during contraction is dependent on the resting tension or the degree of stretch of the muscle at rest. In other words, there is a **length–tension**



Electric impulse traveling along muscle cell membrane (sarcolemma) from motor endplate (neuromuscular junction) and then along transverse tubules affects sarcoplasmic reticulum, causing extrusion of Ca^{2+} to initiate contraction by "rowing" action of crossbridges, sliding filaments past one another.

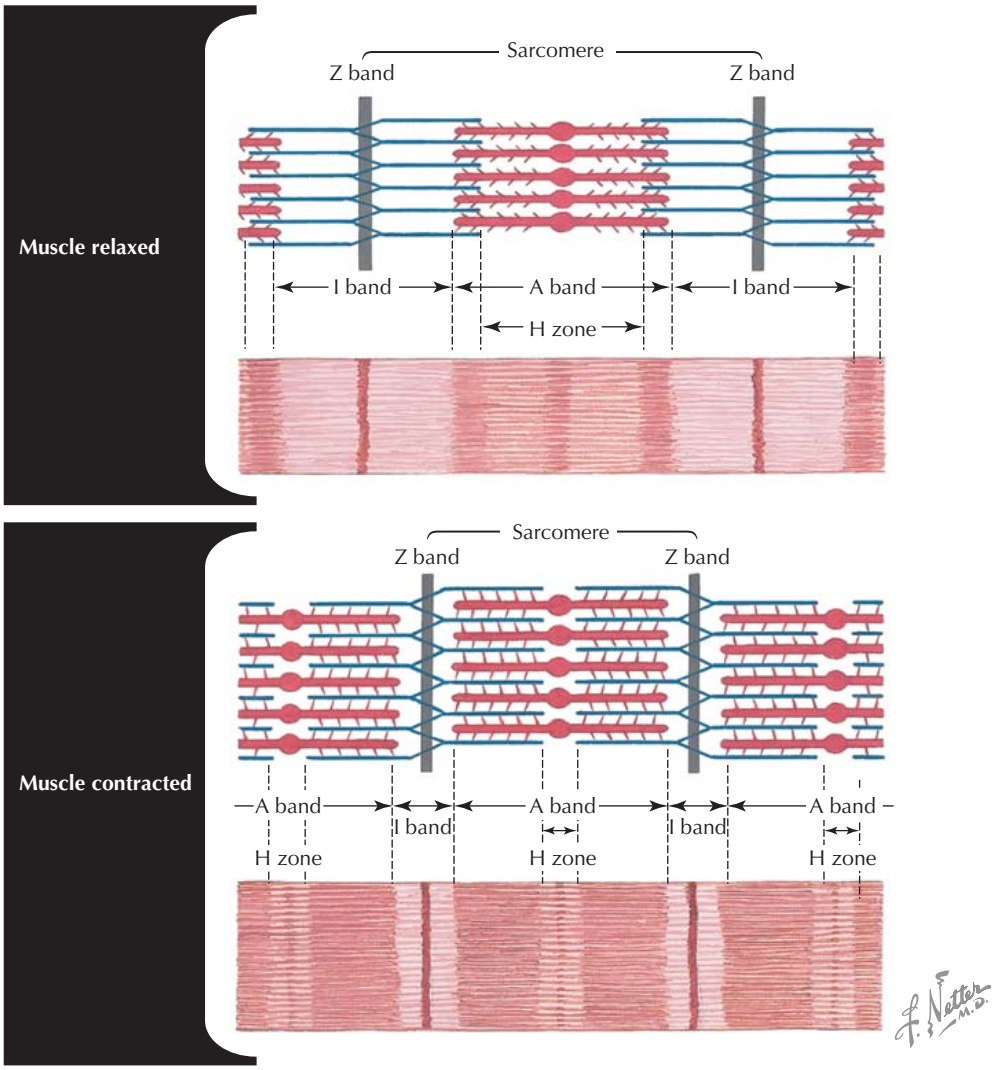
Figure 3.13 Excitation-Contraction Coupling When an action potential in a motor neuron results in the release of acetylcholine at the neuromuscular junction, binding of acetylcholine on the sarcolemma opens a cation channel, permitting influx of Na^+. An action potential is produced and spreads into the transverse tubules, resulting in the release of Ca^{2+} stored in the sarcoplasmic reticulum, initiating crossbridge formation and muscle contraction. Ca^{2+} is resequestered into the sarcoplasmic reticulum by Ca^{2+}-ATPase to terminate the contraction.

relationship for skeletal muscle (see Fig. 3.16*C*). The extent of overlap of the thin and thick filaments of the sarcomeres affects the number of crossbridges formed during contraction. With greater stretch before stimulation, more force is generated, up to an optimal sarcomere length.

Muscle contractions can also be characterized as isometric or isotonic. In **isometric contraction,** muscle length is constant but a change in tone is observed. An example is the contraction that occurs when we exert force against an immovable object. Force is generated, but length remains unchanged. Sarcomere shortening is accompanied by stretch of connective tissue and cytoskeletal components of the muscle (**series elastic elements**). During **isotonic contraction,** muscle tone remains constant while the muscle shortens. An example is the contraction associated with lifting a book. In reality, all muscle movements are a combination of isometric and isotonic contractions. Pressing of heavy free weights involves a large isometric component, but it also involves an isotonic component. In general, isometric exercises like weightlifting are useful for body-building. With repeated isometric exercise, **hypertrophy** of muscle occurs, in which the number of sarcomeres is increased (**hyperplasia,** or increased number of muscle cells, does not normally occur). Muscle **atrophy** or wasting (decreased number of sarcomeres) occurs with disuse, for example during prolonged bed rest.

SMOOTH MUSCLE

Smooth muscle is a type of nonstriated muscle found within organs. Contractile proteins are not organized as sarcomeres in smooth muscle; rather, actin is anchored to the cell membrane and to dense bodies within the cell. As in other types of



During muscle contraction, thin filaments of each myofibril slide deeply between thick filaments, bringing Z bands closer together and shortening sarcomeres. A bands remain the same width, but I bands narrow. H zones also narrow or disappear as thin filaments encroach upon them. Myofibrils and, consequently, muscle fibers (muscle cells), fascicles, and muscle as a whole grow thicker. During relaxation, the reverse occurs.

Figure 3.14 Muscle Contraction and Relaxation During skeletal muscle contraction, cyclical crossbridge formation between interdigitated actin and myosin filaments produces shortening of the sarcomere.

muscle, actin–myosin interactions are the basis of contraction (Fig. 3.17). A comparison of skeletal, smooth, and cardiac muscle is shown in Table 3.3.

Types of Smooth Muscle

Smooth muscle is further classified as unitary or multiunit types. Of these types, **unitary smooth muscle** is far more abundant and is found in the walls of blood vessels, the bladder and the gut, among other organs. This type of smooth muscle is capable of sustained and often powerful contractions. The cells have gap junctions between them, allowing rapid and direct spread of action potentials, as electrical potentials are directly conducted between cells through ion fluxes. Because of this, many smooth muscle cells act as a single unit, producing a synchronous contraction. In contrast, **multiunit smooth muscle** is organized into motor units similar to those in skeletal muscle. Cells are electrically isolated from each other (there are no gap junctions), allowing for fine motor control. This type of muscle is found in a few specific regions such as the ciliary body of the eye, the vas deferens, and the piloerector muscles in the skin.

Contraction of Smooth Muscle

Smooth muscle contraction is controlled by multiple neurotransmitters and other chemical ligands that affect cytosolic

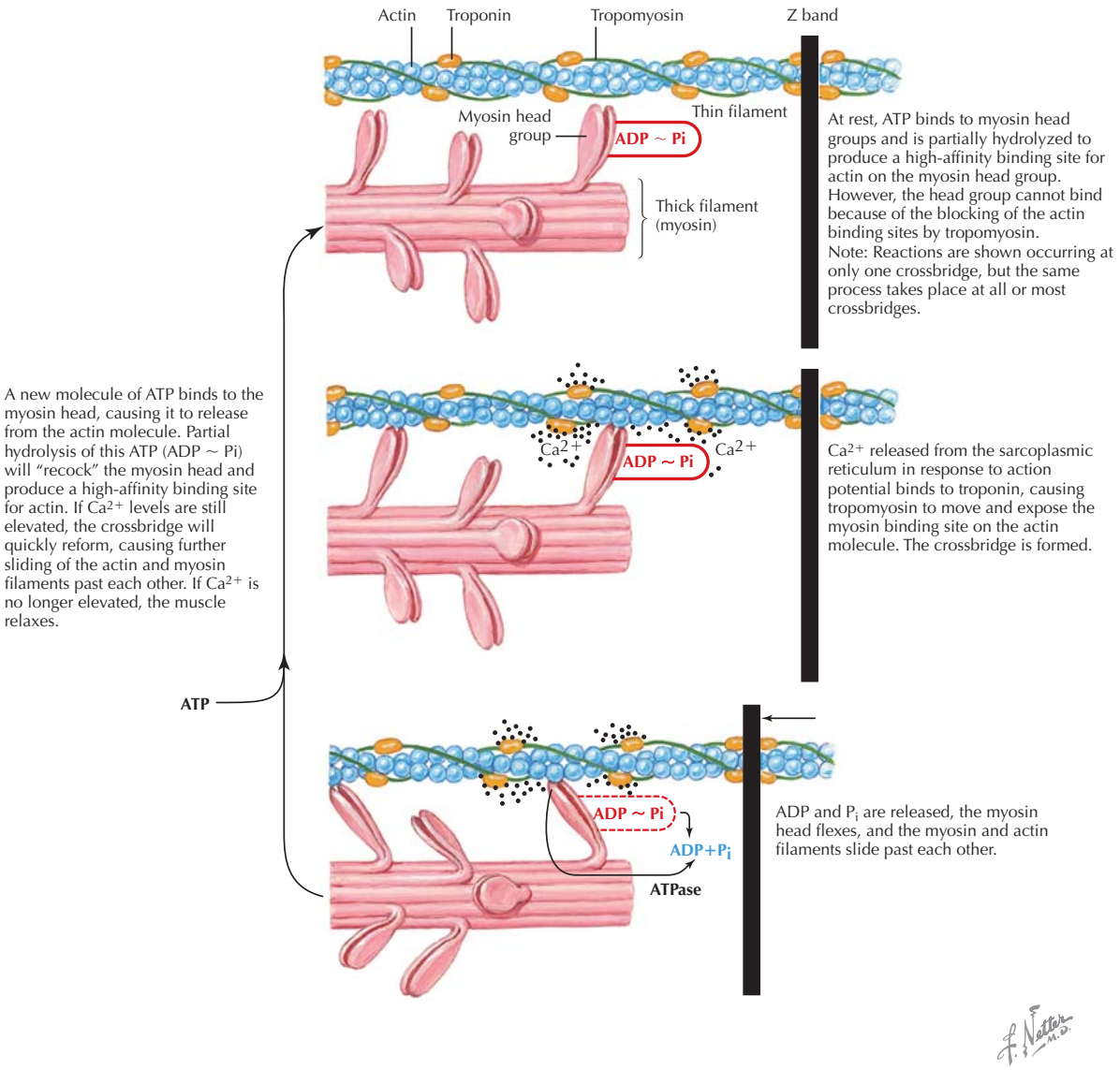


Figure 3.15 Biochemical Mechanics of Muscle Contraction Muscle contraction is produced when actin and myosin form and recycle crossbridges. The process is dependent on the presence of free intracellular Ca^{2+} and the availability of ATP.

Ca^{2+} concentration. Some of these substances produce depolarization of the cell membrane, resulting in opening of voltage-gated membrane Ca^{2+} channels and release of Ca^{2+} from intracellular stores, in a process similar to that in skeletal muscle. In **pharmacomechanical coupling,** binding of a ligand to a membrane receptor produces an increase in intracellular Ca^{2+} concentration, and thus smooth muscle contraction, without altering membrane potential. An example is contraction of vascular smooth muscle by binding of norepinephrine or epinephrine to α-adrenergic receptors.



In **phasic smooth muscle,** contractions are short in duration, as in skeletal muscle. In **tonic smooth muscle,** tension may be maintained for long periods of time with little ATP utilization. In this case, myosin is dephosphorylated while attached to actin, forming the **"latch state"** (see Fig. 3.18). In this state, crossbridge recycling is very slow and ATP utilization is reduced. This latch state is important in maintaining tension in blood vessels and sphincters.

Depolarization or pharmacomechanical coupling leads to elevation of intracellular Ca^{2+}, the common signal in smooth muscle contraction (Fig. 3.18). In the latter case, ligand binding activates membrane phospholipase C, which cleaves inositol bisphosphate, thereby producing IP_3, which releases Ca^{2+} from intracellular stores. Whether elevated by membrane depolarization or activation of the inositol pathway, Ca^{2+} binds to the protein **calmodulin**, and the Ca^{2+}-calmodulin

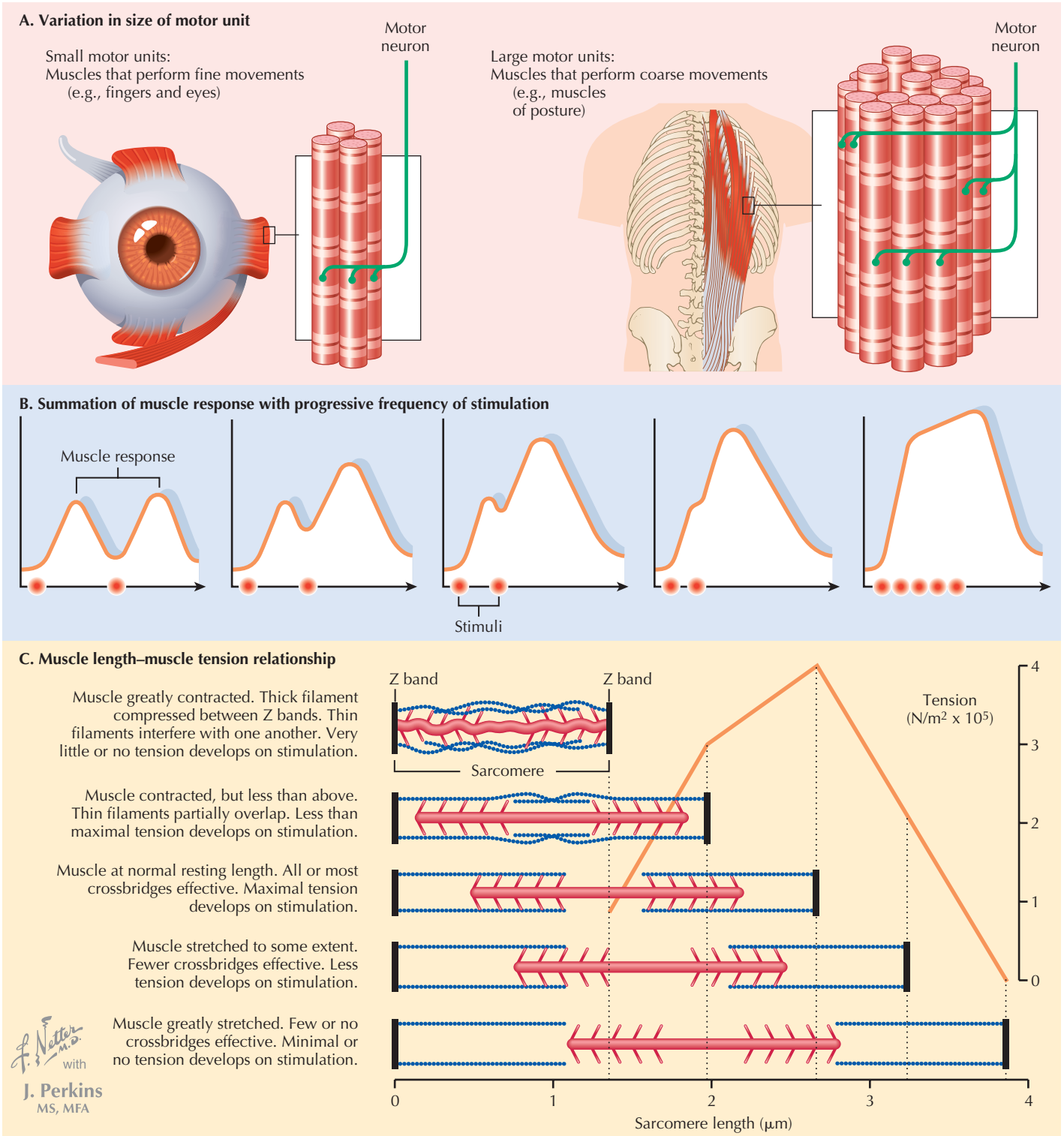


Figure 3.16 Grading of Muscle Tension and Length–Tension Relationship The force generated when skeletal muscle is stimulated is related to the size of the motor units stimulated *(A)*, the number of motor units activated and the frequency of stimulation of the muscle fibers *(B)*, and the resting length of muscle fibers *(C)*. Small motor units are involved in fine motor control, for example in fingers and eyes, while larger motor units are involved in coarser movements *(A)*. Skeletal muscles also produce more force when more motor units are recruited. With repeated stimulation of a muscle fiber, summation occurs, in which individual twitches occur without complete relaxation between twitches *(B)*. There is also a length–tension relationship, whereby greater resting sarcomere length (stretch of the muscle before contraction) is associated with greater force of contraction, up to an optimal resting length *(C)*.

Table 3.3 Comparison of Muscle Structure and Function

	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
STRUCTURE			
Morphology	Long; cylindrical	Branched	Spindle or fusiform
Nuclei	Multiple; located peripherally	One (sometimes two); located centrally	One; located centrally
Sarcomere	Yes; striated pattern	Yes; striated pattern	No
T tubules	Yes; forms triad with sarcoplasmic reticulum	Yes; forms dyad with sarcoplasmic reticulum	No; caveolae
Electrical coupling of cells	No	Yes; intercalated discs contain gap junctions	Yes; gap junctions
Regeneration	Yes; via satellite cells	No	Yes
Mitosis	No	No	Yes
PHYSIOLOGY			
Extracellular Ca^{2+} required for contraction	No	Yes	Yes
Regulation of crossbridge formation	Ca^{2+} binding to troponin	Ca^{2+} binding to troponin	Ca^{2+}-calmodulin activation of myosin kinase and phosphorylation of myosin
Control of contraction	Motor neurons	Autonomic nerves; β-adrenergic agonists	Autonomic nerves; hormones
Summation of twitches by increased stimulus frequency	Yes	No*	Yes
Tension varies with filament overlap	Yes	Yes	Yes

Major differences in structure and function of skeletal, cardiac, and smooth muscle are indicated.
*Cardiac muscle cannot be tetanized, but the force of contraction will increase at high stimulus frequency because of an increase in intracellular [Ca^{2+}], a phenomenon termed "Treppe."
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complex activates the enzyme **myosin kinase,** allowing interaction between myosin and actin, producing contraction as these proteins slide past each other. The contraction cycle continues as long as intracellular Ca^{2+} is elevated.

Relaxation of Smooth Muscle

Smooth muscle *relaxation* may also be induced by pharmacomechanical coupling, in which case various substances stimulate a rise in intracellular cAMP or cGMP. Ultimately, intracellular Ca^{2+} is reduced, causing relaxation. An example is relaxation produced by binding of epinephrine or norepinephrine to β-adrenergic receptors on vascular smooth muscle.

CARDIAC MUSCLE

Cardiac muscle is similar to skeletal muscle or smooth muscle in some respects, and dissimilar in others (Fig. 3.19 and Table 3.3). Contraction of skeletal muscle is under the voluntary control of the central nervous system, whereas contraction of cardiac and smooth muscle is involuntary. Both unitary smooth muscle and cardiac muscle have the capability for spontaneous electrical activity; cardiac contraction is normally under control of cardiac pacemakers cells in the sinoatrial (SA) node. Gap junctions in cardiac muscle, as in unitary smooth muscle, allow synchronous contraction. These gap junctions in cardiac muscle are found in the **intercalated disks** between cells. Cardiac and skeletal muscles have highly organized sarcomeres, leading to a striated appearance.

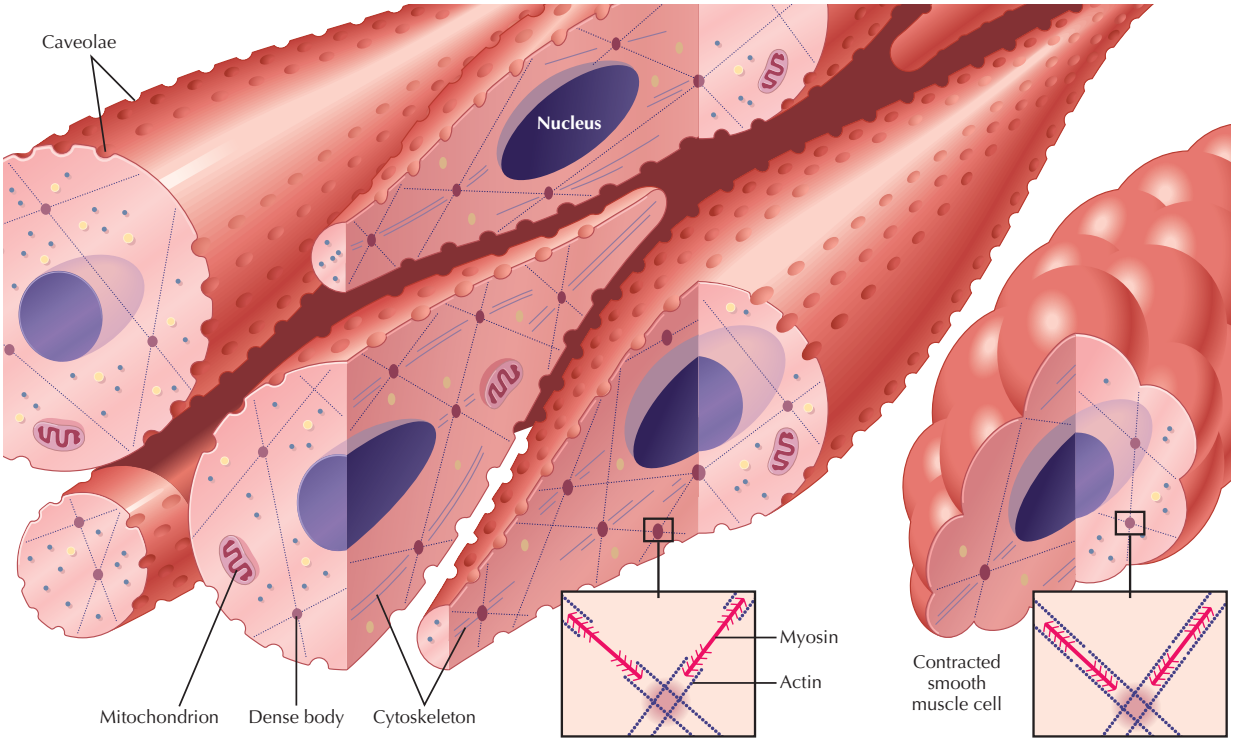


Figure 3.17 **Smooth Muscle Structure** Actin and myosin filaments of spindle-shaped smooth muscle cells are arranged quite differently than contractile proteins in skeletal muscle. Actin is anchored to dense bodies within the muscle cell and to the plasma membrane, and the sliding of myosin and actin filaments produces contraction when intracellular Ca^{2+} is elevated, either by release from intracellular stores or flux through Ca^{2+} channels. Caveolae are invaginations in the cell membrane and are a site of Ca^{2+} flux.

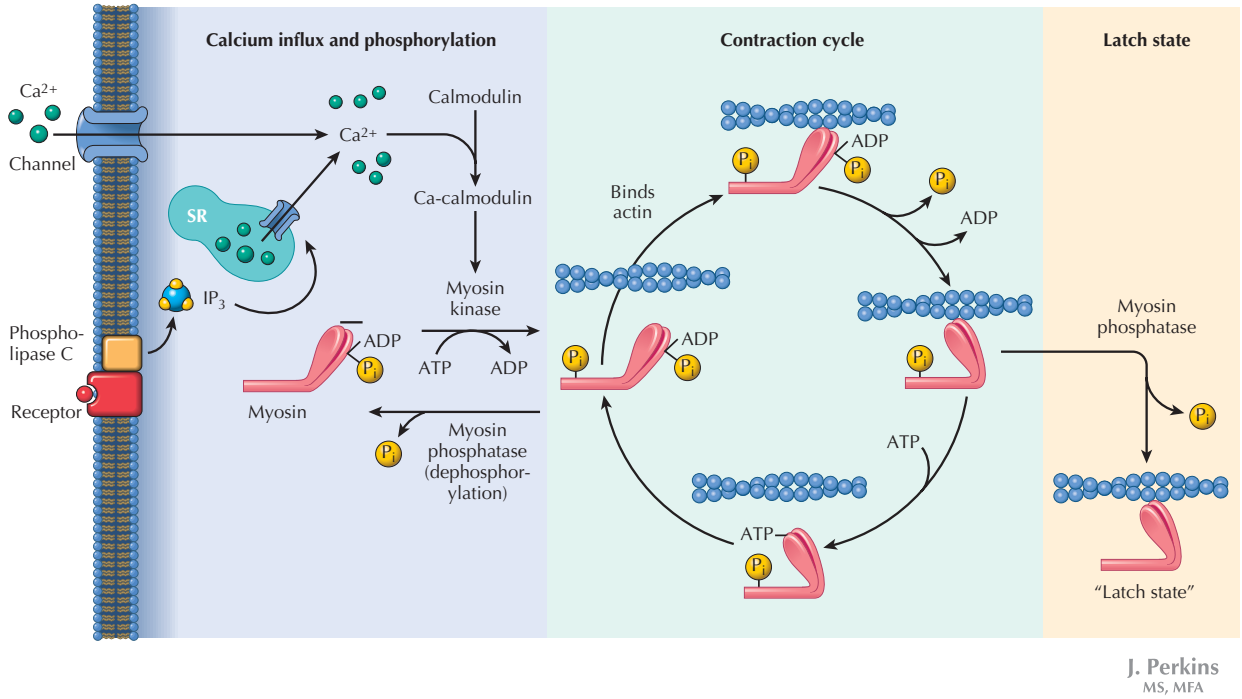


Figure 3.18 **Excitation-Contraction Coupling of Smooth Muscle** Binding of a ligand to the sarcolemma results in elevation of free intracellular Ca^{2+}, through either depolarization of the cell membrane and opening of Ca^{2+} channels, or activation of the enzyme phospholipase C. In the latter case, cleavage of inositol trisphosphate by phospholipase C produces IP_3, which binds to sites on the sarcoplasmic reticulum, causing release of stored Ca^{2+}. In either case, Ca^{2+} binds to the protein calmodulin, which activates myosin kinase, initiating actin–myosin interaction. The contraction cycle continues as long as Ca^{2+} is elevated. The latch state occurs when myosin is dephosphorylated by myosin phosphatase. In this state, contraction can be maintained without further ATP hydrolysis.

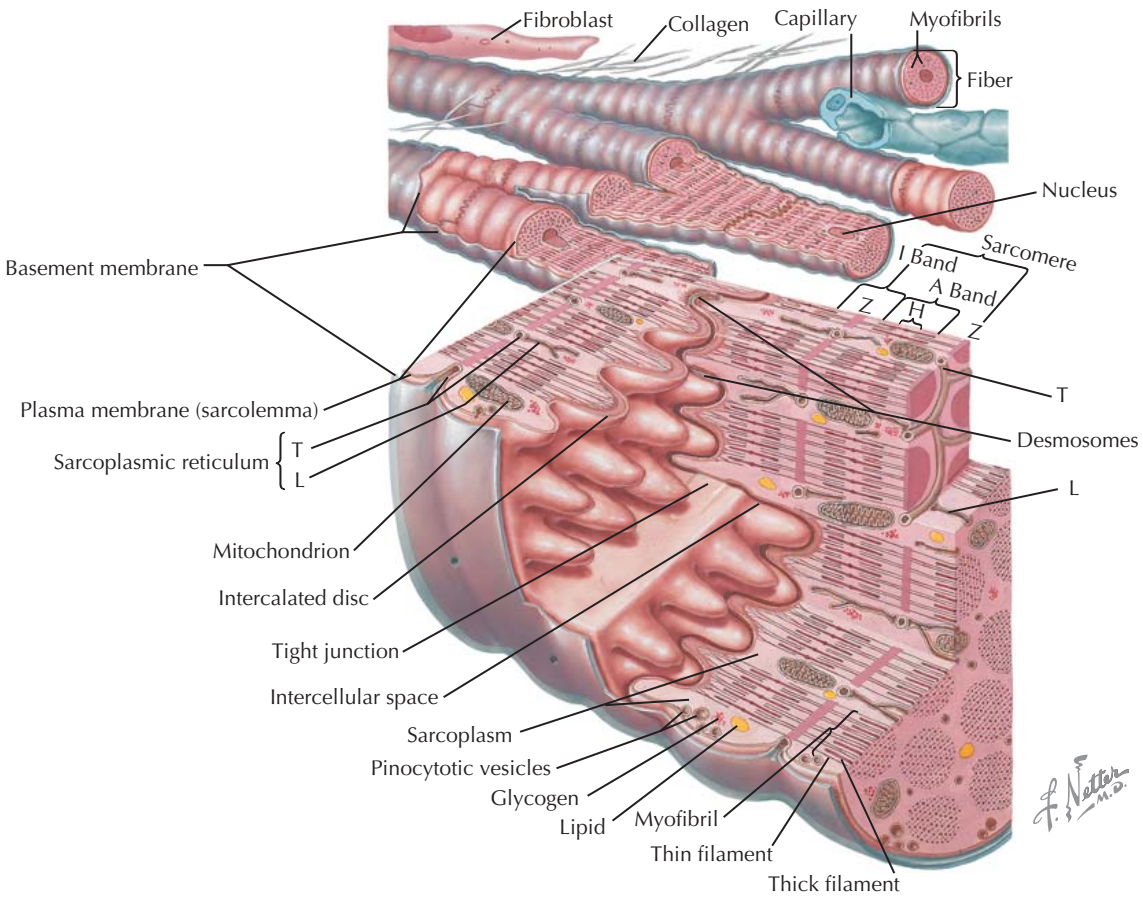


Figure 3.19 Schema of Structure of Cardiac Muscle The striated appearance of cardiac muscle is associated with the arrangement of the contractile proteins actin and myosin into sarcomeres, as in skeletal muscle. A notable difference between these types of muscles is that cardiac muscle utilizes extracellular Ca^{2+} as well as intracellular stores to initiate contraction. Another difference is that transverse tubules of cardiac muscle form dyads with the terminal cisternae of the sarcoplasmic reticulum, as opposed to the triads found in skeletal muscle. In addition, unlike skeletal muscle, cardiac muscle fibers are connected by gap junctions at intercalated disks between the cells, allowing the spread of depolarization from cell to cell, producing synchronous contraction of muscle.

Calcium channel blockers are drugs that block voltage-dependent Ca^{2+} channels (L-type Ca^{2+} channels). These drugs are often used in antihypertensive therapy, based on their effects on vascular smooth muscle. However, because they also block voltage-dependent Ca^{2+} channels of the heart, they slow conduction in the heart and reduce myocardial contractility. Calcium channel blockers may belong to several classes of chemicals, including dihydropyridines. Nifedipine and amlodipine are examples of the dihydropyridine class. Voltage-gated Ca^{2+} channels of T-tubules in cardiac and skeletal muscle are also referred to as dihydropyridine receptors, based on their ability to bind these drugs. Note, however, that while cardiac muscle contractility is reduced by calcium blockers, skeletal muscle contractility is unaffected. Skeletal muscle is not dependent on extracellular Ca^{2+} for contraction.

The velocity of contraction of skeletal muscle is dependent on muscle fiber type (fast twitch vs. slow twitch fibers); cardiac muscle contraction is slower than that of skeletal muscle, but more rapid than contraction in smooth muscle. Cardiac and smooth muscle utilize both intracellular and extracellular sources of Ca^{2+}, whereas the only Ca^{2+} source for contraction of skeletal muscle is intracellular (from the sarcoplasmic reticulum). As in skeletal muscle, Ca^{2+} in cardiac muscle binds to troponin to initiate crossbridge formation.

Other aspects of cardiac muscle function, including mechanical function and regulation of pacemaker activity, are considered in Section 3.

CHAPTER 4
Organization and General Functions of the Nervous System

The nervous system consists of the **central nervous system (CNS)** and the **peripheral nervous system (PNS).** The CNS includes the brain and spinal cord. The peripheral nervous system includes nerves, ganglia, and sensory receptors outside the CNS. The peripheral nervous system can also be subdivided into **sensory** and **motor** divisions. Sensory nerves transmit information from various sensory receptors to the CNS; motor nerves transmit information from the CNS to muscles and glands, thereby controlling their activity.

THE CENTRAL NERVOUS SYSTEM

The general structure of the central nervous system and brain is illustrated in Figure 4.1.

Brain

The brain can be subdivided into the **telencephalon** (also known as the cerebrum or cerebral hemispheres), **diencephalon** (thalamus, hypothalamus), **cerebellum,** and **brainstem** (midbrain, pons, and medulla).

Blood-Brain Barrier

The environment of neurons within the CNS is maintained in part by the **blood-brain barrier.** Endothelial cells of capillaries within the CNS are joined by tight junctions, preventing the movement of water-soluble substances, highly charged molecules, and cells between blood and brain. Astrocytes (nonneuronal cells of the CNS) are also involved in maintaining the integrity of the blood-brain barrier.

Cerebrospinal Fluid

The formation, circulation, and regulation of the composition of **cerebrospinal fluid (CSF)** compose a second important factor in the homeostasis of the environment within the CNS. CSF, which is secreted by ependymal (epithelial) cells of the choroid plexus, differs from blood plasma somewhat in composition and circulates through the ventricles of the brain and the subarachnoid space around the brain and spinal cord (Table 4.1 and Figs. 4.2 and 4.3). Specifically, the CSF has a lower concentration of bicarbonate anion than plasma, resulting in lower pH. This difference makes the CSF sensitive to changes in P_{CO_2} of the blood, an important factor in regulation of respiration by the brain. Substances within the CSF are freely exchanged with the interstitial fluid of the brain, in contrast to substances within blood plasma. Because CSF is secreted at a rate of approximately 500 mL/day and the total volume of CSF is approximately 150 mL, it turns over at a rate of three to four times per day.

Telencephalon

In the telencephalon, the right and left cerebral hemispheres consist of the outer cerebral cortex (gray matter) and inner white matter. (Gray matter contains unmyelinated axons, and white matter contains myelinated axons). The hemispheres are linked anatomically and functionally by bundles of nerves known as commissures: the large corpus callosum and smaller **anterior, posterior,** and **hippocampal commissures** (Fig. 4.4).

The cerebral cortex consists of five major areas, based on gross anatomical features: the frontal, parietal, temporal, and occipital lobes and the insula (Fig. 4.5). It has afferent and efferent connections to the thalamus and basal ganglia (two sets of nuclei deep in the cerebral hemispheres, connecting with the cerebrum, thalamus, and brainstem) and many other regions of the brain. Regions within the cerebral cortex receive and integrate sensory information, integrate motor function, and perform other high-level functions such as learning and reasoning (see Fig. 4.4). Much of the sensory information is received indirectly, passing through the thalamus, except in



The term neocortex refers to the outermost layer of the cerebral hemispheres. This area is the most recently evolved part of the cerebral cortex and is only a few millimeters thick. The neocortex is considered the highest center in the brain, where the most complex functions ascribed to the cerebral cortex are performed, including sensory perception, initiation of motor function, language skills, and conscious thought.

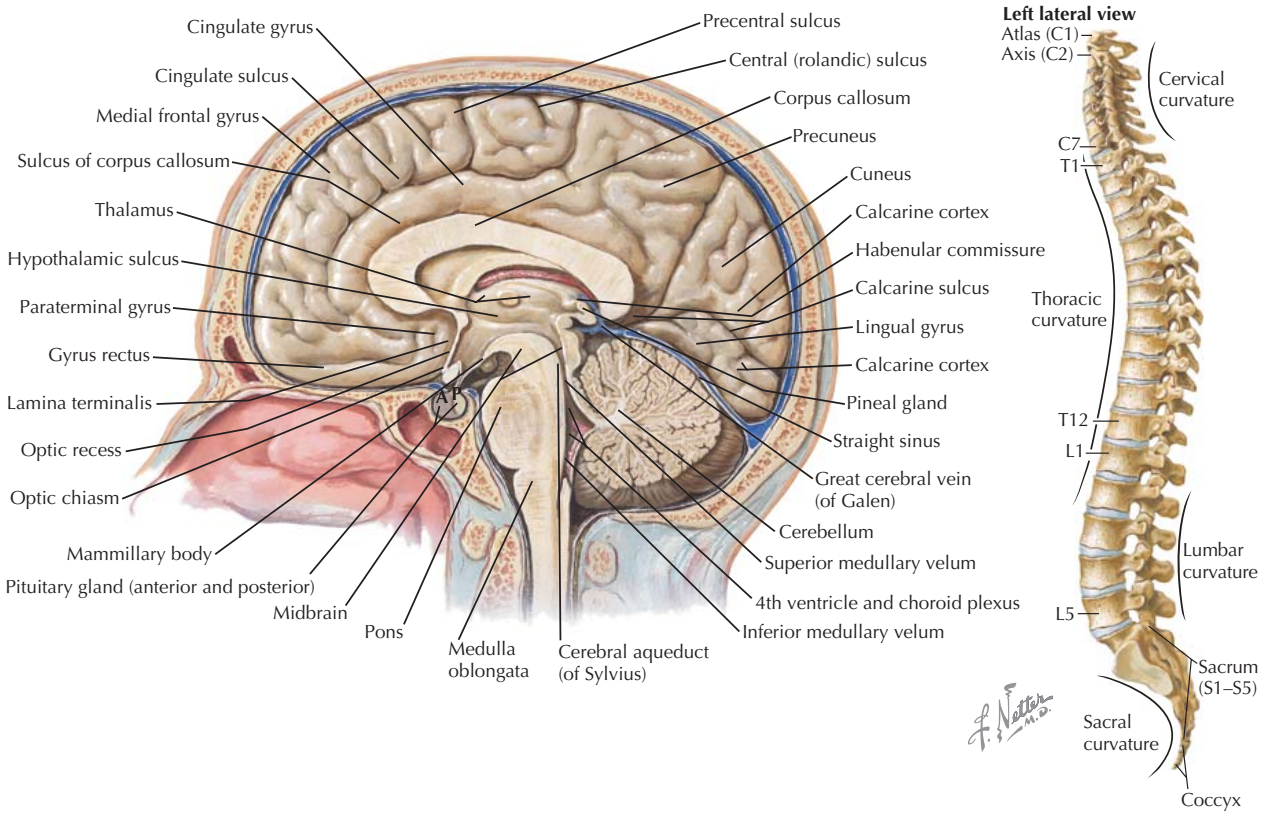


Figure 4.1 **Major Parts of the Central Nervous System and the Vertebral Column** The brain is illustrated as a midsagittal section, with the frontal, parietal, and occipital lobes of the cerebral cortex (outer layer of the cerebral hemispheres) labeled (the temporal lobes are not seen in this section), as well as other major divisions of the brain. The vertebral column consists of cervical, thoracic, lumbar, and sacral vertebrae. It houses the spinal cord, which extends from the medulla oblongata to lumbar level L1–L2.

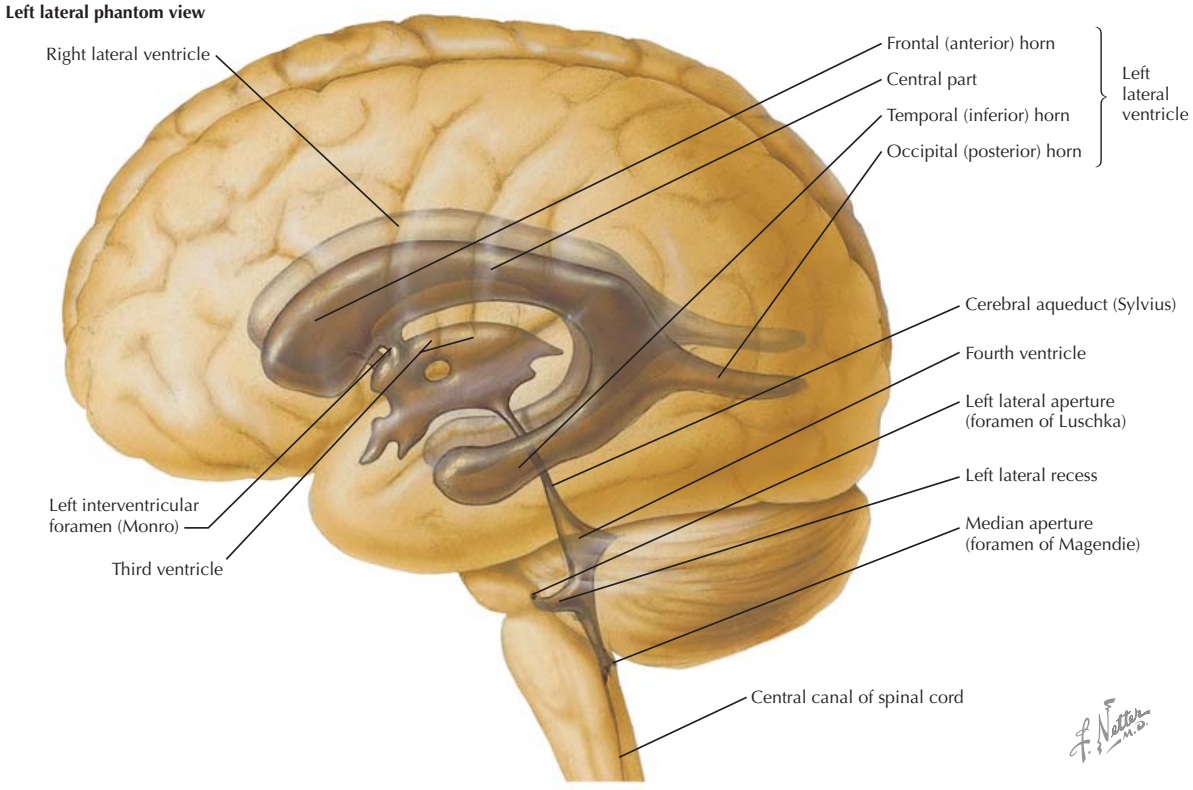


Figure 4.2 **Brain Ventricles and CSF Composition** Circulation of CSF through the four ventricles of the brain and in the subarachnoid space is essential for maintaining the environment of the brain and spinal cord. The composition of CSF, which is secreted by the choroid plexus, differs from that of plasma (see Table 4.1).

the case of olfactory signals. Generally, the right and left cerebral hemispheres receive input from the contralateral side of the body.

The basal ganglia consist of two sets of nuclei (in the right and left hemispheres) located deep within the cerebral hemispheres. With connections to the various lobes of the cerebral cortex, thalamus, and brainstem, the basal ganglia are involved in regulation of movement, among other functions. Two additional deep formations, the **hippocampus** and **amygdala,** are located within the medial temporal lobes. Both are part of the broader limbic system, involved in emotion and long-term memory and affecting the endocrine and autonomic nervous systems (Fig. 4.6). The hippocampus has an important role in memory and spatial navigation; the amygdala is involved in emotion. Through its connections to the hypothalamus, the hippocampus also affects sympathetic nervous system function.

Table 4.1 Comparison of CSF and Blood Composition

Parameter	CSF	Blood Plasma
Na^+ (mEq/L)	140-145	135-147
K^+ (mEq/L)	3	3.5-5.0
Cl^- (mEq/L)	115-120	95-105
HCO_3^- (mEq/L)	20	22-28
Glucose (mg/dL)	50-75	70-110
Protein (g/dL)	0.05-0.07	6.0-7.8
pH	7.3	7.35-7.45

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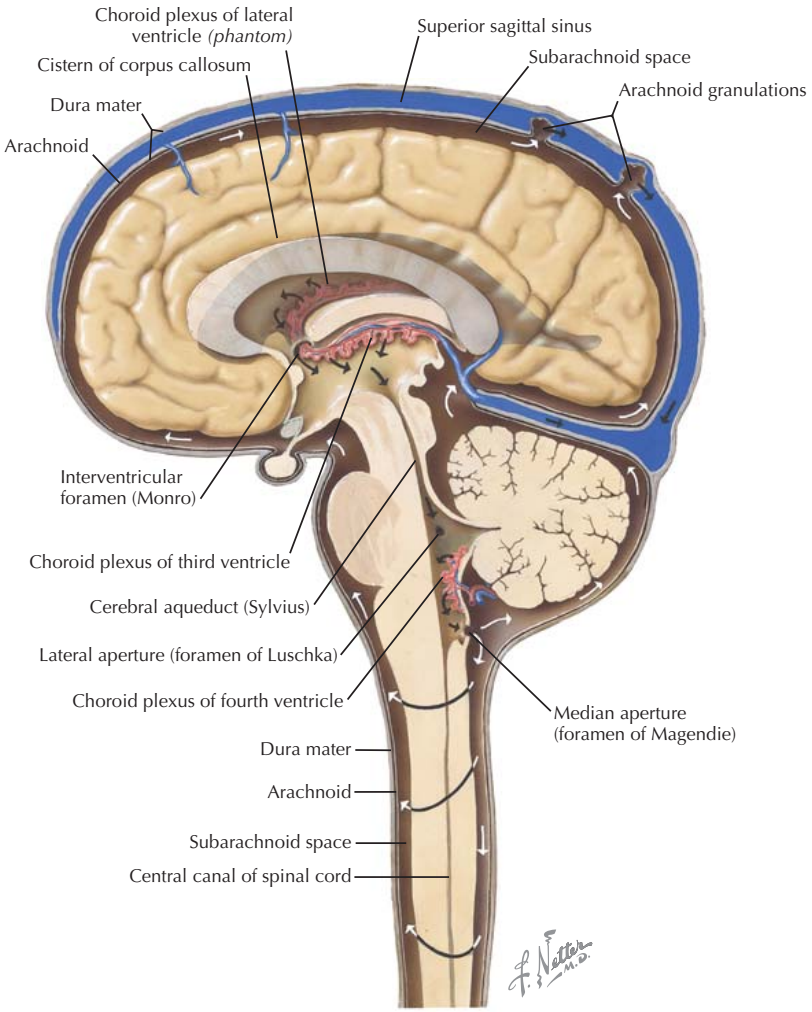


Figure 4.3 Circulation of CSF CSF, produced by the choroid plexus, circulates through the two lateral ventricles and third and fourth ventricles, leaving the fourth ventricle through the lateral and medial apertures and entering the subarachnoid space. Much of the fluid is reabsorbed at the arachnoid granulations, into the venous system, as well as into the capillaries of the CNS and pia mater.

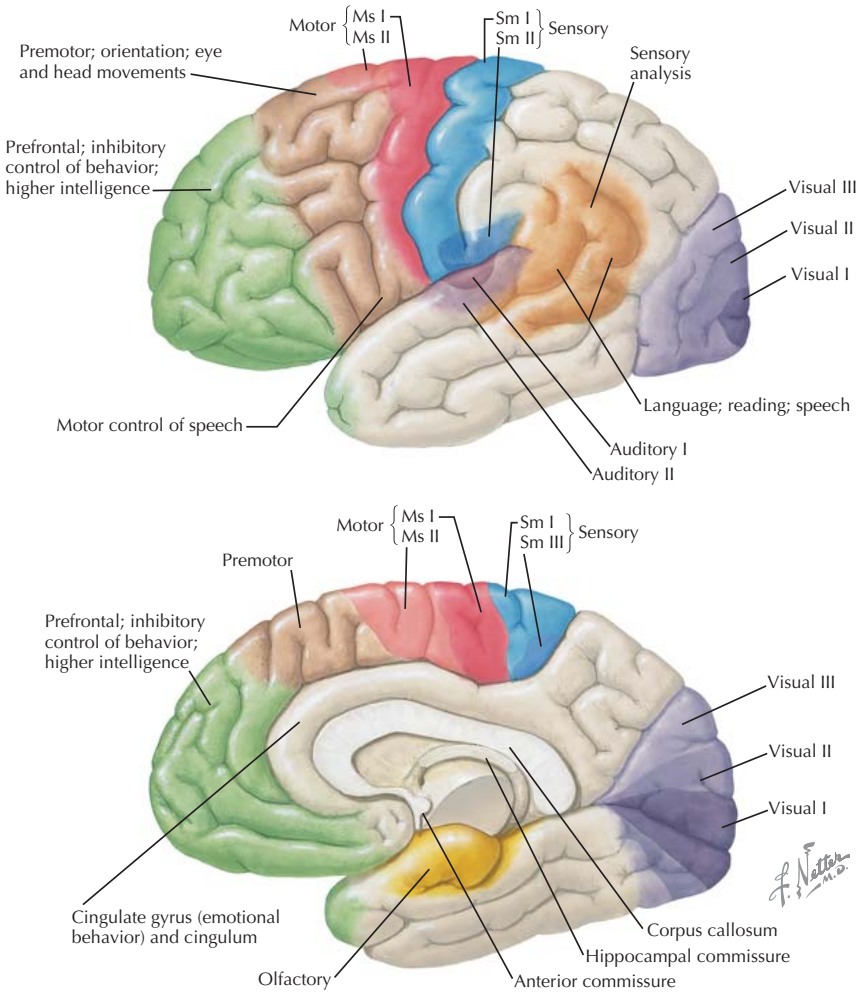


Figure 4.4 Cerebral Cortex: Association Pathways and Localization of Function The two cerebral hemispheres are linked functionally and anatomically by the corpus callosum and anterior, posterior, and hippocampal commissures. In the cerebral cortex, functional regions involved in sensory and motor activity as well as integration of information from various sources have been identified. The cortex is essential for high-level intellectual functions including learning, reasoning, memory and language skills, and conscious thought and is involved in planning and execution of fine motor activity.

Table 4.2 Major Functions of the Hypothalamus

Hypothalamic Area	Major Functions*
Preoptic and anterior	Heat loss center: cutaneous vasodilation and sweating
Posterior	Heat conservation center: cutaneous vasoconstriction and shivering
Lateral	Feeding center: eating behavior
Ventromedial	Satiety center: inhibits eating behavior
Supraoptic (subfornical organ and organum vasculosum)	ADH and oxytocin secretion (sensation of thirst)
Paraventricular	ADH and oxytocin secretion
Periventricular	Releasing hormones for the anterior pituitary

*Stimulation of the center causes the responses listed.
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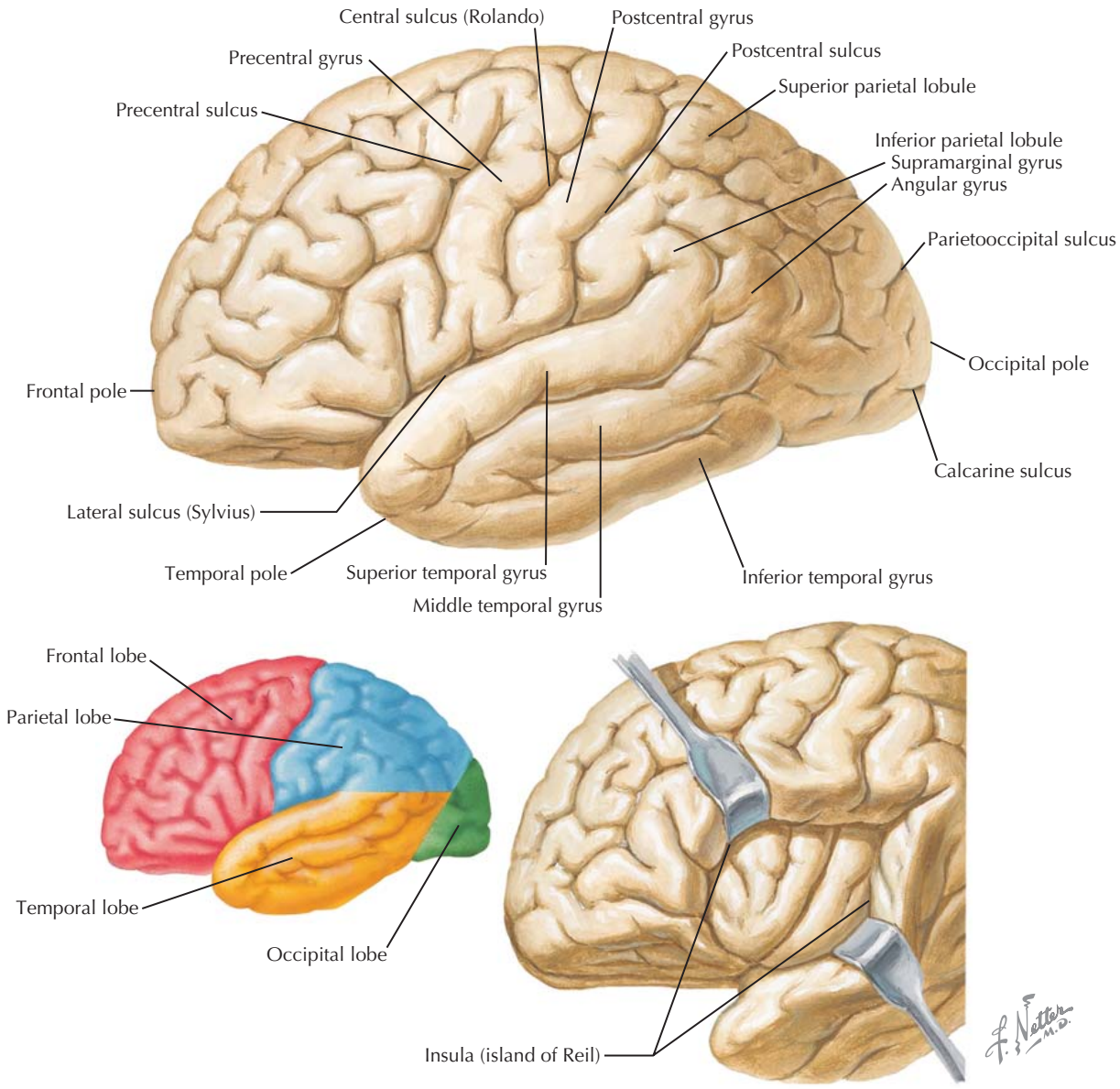


Figure 4.5 Organization of the Brain: Surface Anatomy of the Cerebral Cortex The outer layers of the cerebrum (telencephalon) are the gray matter, containing neurons with unmyelinated fibers. The cerebral cortex is only 2 to 4 mm thick, but is highly convoluted in primates, such that most of the cortex is actually buried in sulci (grooves). Four lobes are discernable from the surface; the fifth lobe, the insula, can be viewed by retracting the outer cortex at the lateral fissure. The cerebral cortex is the highest center of the brain and is involved in learning, memory, and reasoning, as well as motor and sensory control and integration.

Diencephalon

The **diencephalon,** consisting of the thalamus and hypothalamus, is located between the cerebral hemispheres and the brainstem and is part of the limbic system (see Fig. 4.6). The thalamus processes sensory input and relays it to the cerebral cortex and processes motor signals leaving the cerebral cortex. The hypothalamus has a central role in the regulation of body temperature, the reproductive system, hunger and thirst, salt and water balance, circadian rhythms, the autonomic nervous system, and endocrine function (Table 4.2).

Cerebellum

The **cerebellum** is located between the cerebral cortex and the spinal cord and in close proximity to the brainstem (see Fig. 4.1). It integrates sensory and motor information as well as information from the inner ear and has an important role in **proprioception** (unconscious perception of posture, spatial

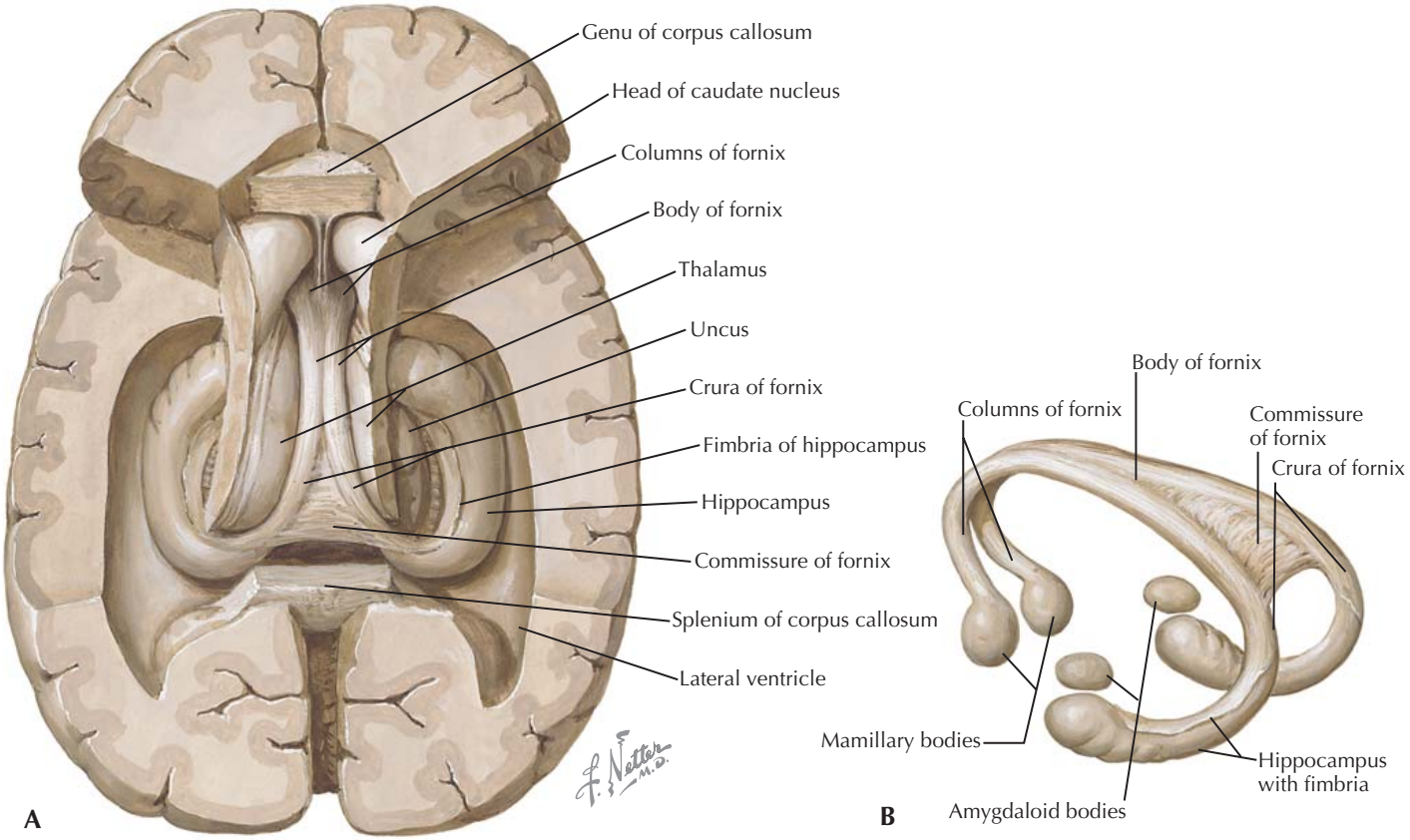


Figure 4.6 The Limbic System The limbic system consists of the hypothalamus and several structures forming a border or ring (limbus) around the diencephalon. It includes the cingulate, parahippocampal, and subcallosal gyri, and the amygdala, hypothalamus, hippocampi, and mamillary bodies. *A*, Cerebral cortical and white matter have been removed, as well as the corpus callosum and part of the thalamus and caudate nucleus. *B,* The fornix consists of curved bundles of fibers connecting the mamillary bodies and hippocampi. The limbic system has an important role in emotion and the linking of emotion with memory, as well as endocrine and autonomic function.

orientation, and movement). Proprioception is based on input from proprioceptors within muscles, joints, tendons, and the inner ear.

Brainstem

The **brainstem** is the lowest portion of the brain, consisting of the midbrain, pons, and medulla oblongata (medulla). The medulla, which is anatomically continuous with the spinal cord, contains centers that regulate autonomic functions. This includes centers involved in the regulation and integration of cardiovascular and respiratory functions, and swallowing, vomiting, and coughing reflexes. The pons, situated above (rostral to) the medulla, is also involved in regulation of breathing, and relays sensory information from the cerebrum to the cerebellum. The midbrain, also known as the **mesencephalon,** is the most rostral portion of the brainstem. It is involved in eye movement and transmission of visual and auditory information. It is also the location of the **substantia nigra,** which, in association with the basal ganglia, has a role in regulation of motor activity. **Cranial nerves III-XII (CN III-XII)** originate from the brainstem.

The Spinal Cord

The spinal cord originates at the medulla at the base of the skull and extends within the vertebral column from the medulla oblongata to the lumbar region (Fig. 4.7). It consists of neural tissues covered by three meninges (membranes) that are continuous with those of the brain:

- the inner pia mater
- the middle arachnoid membrane
- the outer dura mater

Cerebrospinal fluid is found between the arachnoid membrane and pia mater. The spinal cord gives rise to 31 pairs of spinal nerves, organized into three plexuses:

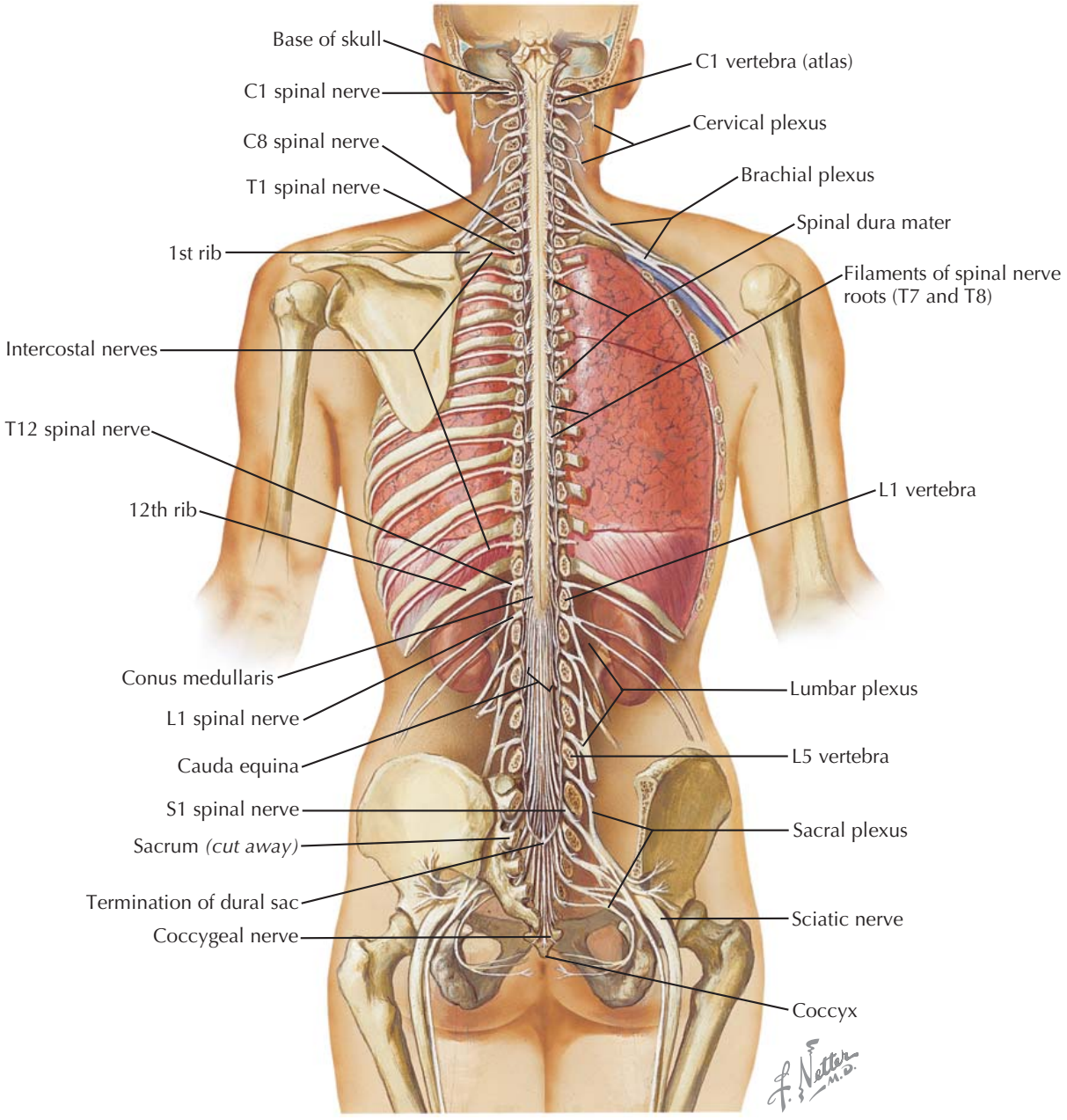


Figure 4.7 Spinal Cord and Ventral Rami In Situ The 31 pairs of spinal nerves originating from the spinal cord are organized into the cervical, brachial, and lumbosacral plexuses. Fibers from the plexuses are distributed, respectively, to the neck, upper limbs, and pelvis and lower limbs. Efferent fibers innervate skeletal muscle, whereas afferent fibers carry sensory information from the skin, muscle, and joints to the CNS.

- The **cervical plexus,** which forms nerves distributed to the back of the head and the neck.
- The **brachial plexus,** which forms nerves distributed to the upper limbs.
- The **lumbosacral plexus,** which forms nerves distributed to the pelvis and lower limbs.

The anatomy of spinal membranes and nerve roots is illustrated in Figure 4.8.

THE PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system is the portion of the nervous system that lies beyond the brain and spinal cord. It consists of:

- Motor neurons that convey impulses from the CNS to effector tissues or organs.
- Sensory neurons that convey impulses from peripheral sensory receptors to the CNS.

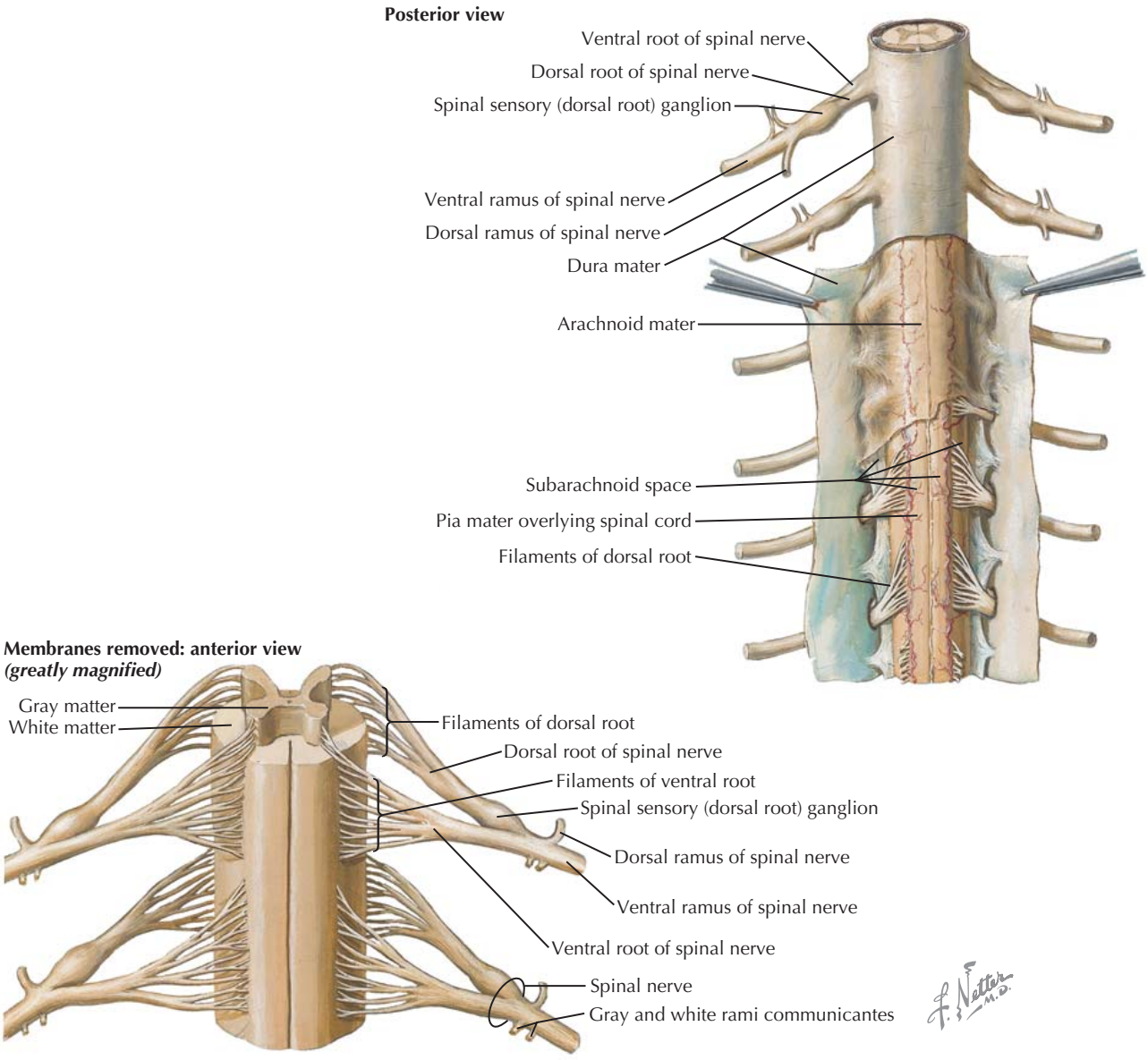


Figure 4.8 Spinal Membranes and Nerve Roots Motor fibers and sensory fibers pass through 31 pairs of spinal nerves. The outer dura mater, arachnoid mater, and inner pia mater are the three coverings of the spinal cord, with CSF circulating in the subarachnoid space.

The peripheral nervous system is subdivided into somatic and autonomic components. In the somatic portion of the peripheral nervous system, motor fibers of the spinal nerves innervate skeletal muscles; sensory information from receptors in the skeletal muscles, joints, and skin is transmitted through sensory fibers to the CNS (Fig. 4.9). The autonomic component of the peripheral nervous system is composed of motor and sensory fibers involved in the involuntary control of homeostatic mechanisms through actions on visceral organs. The autonomic nervous system and its sympathetic and parasympathetic divisions are discussed further in Chapter 7.

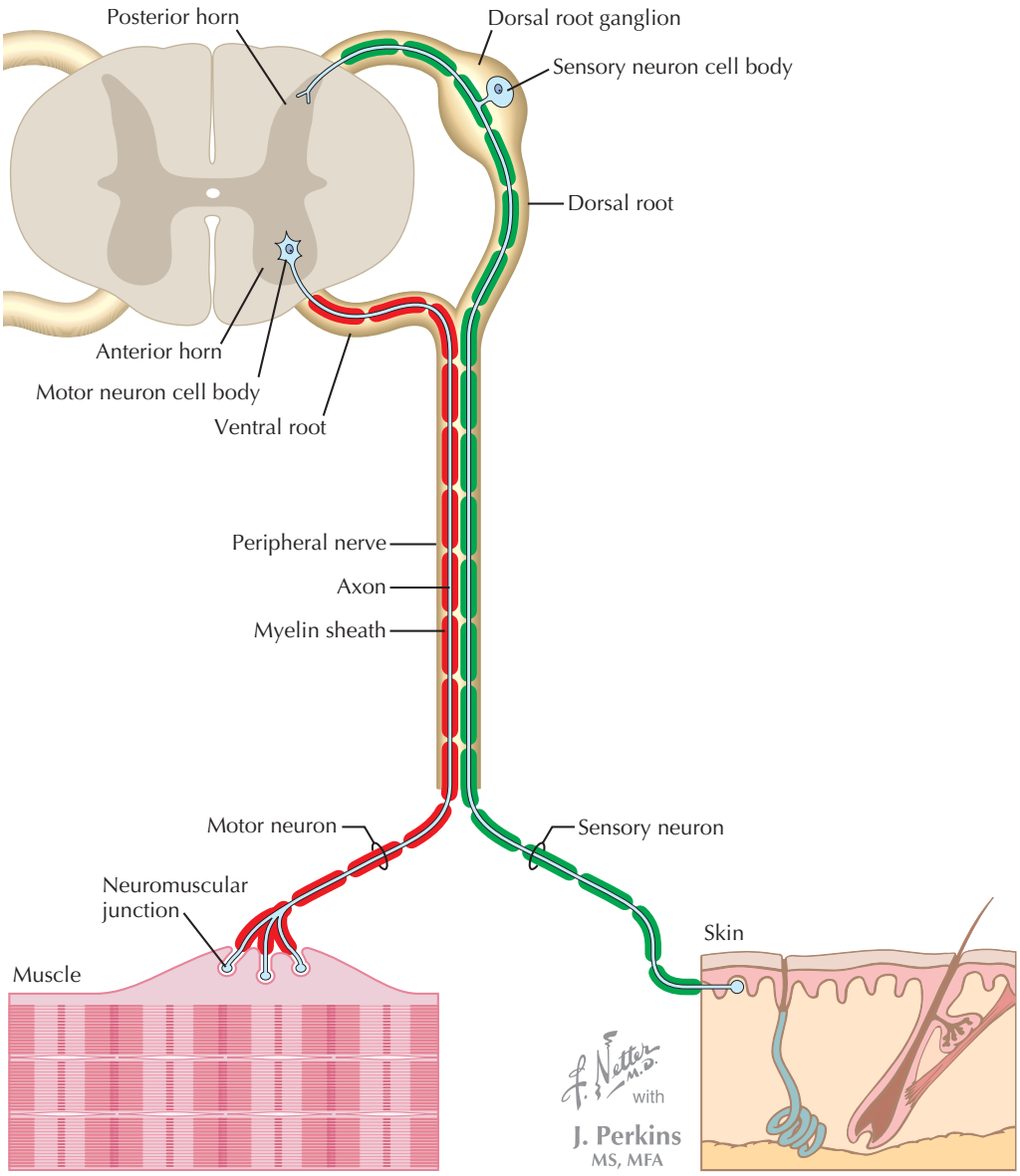
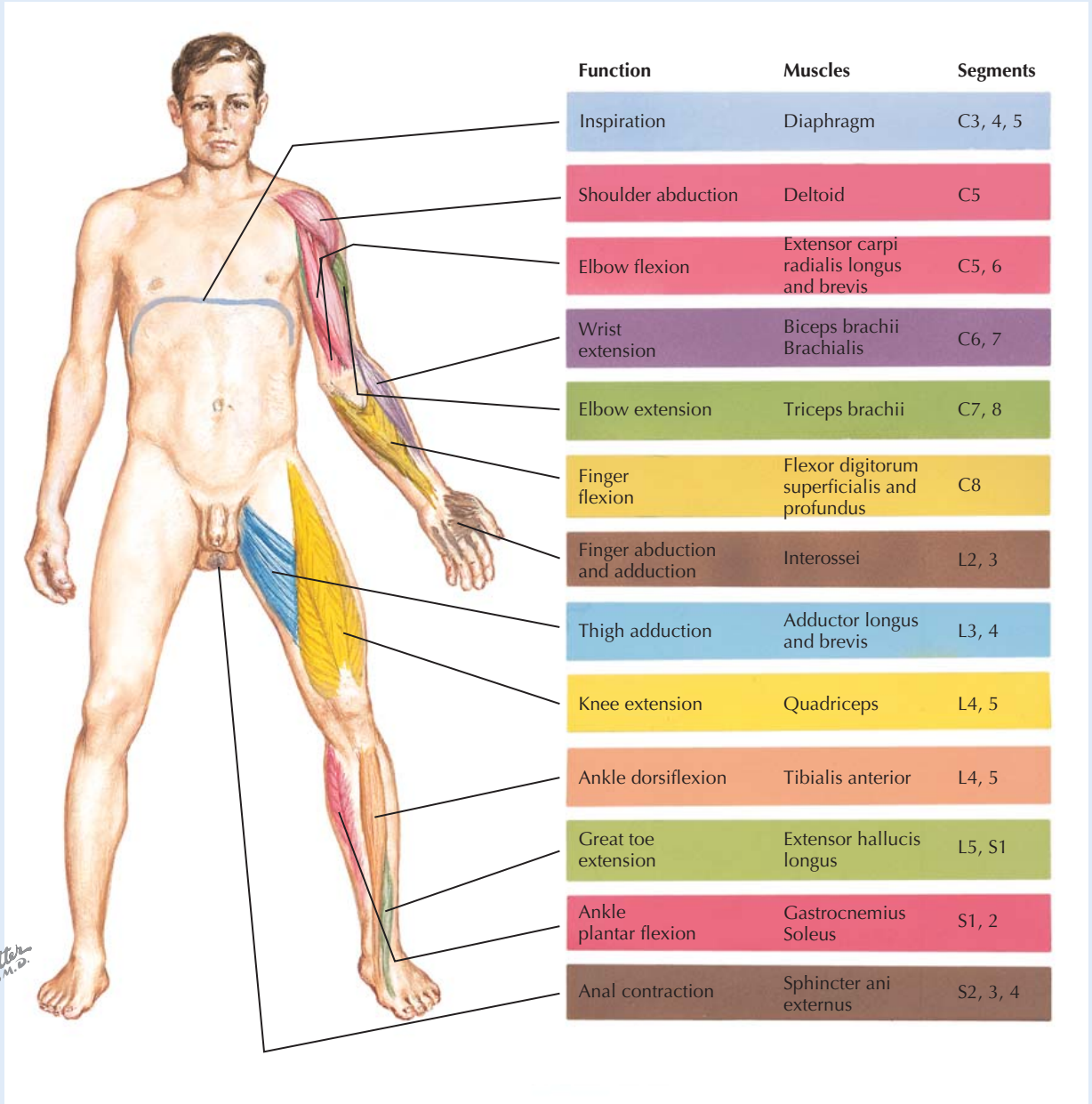


Figure 4.9 **Somatic Component of the Peripheral Nervous System** The peripheral nervous system can be subdivided into somatic and autonomic components. The somatic nervous system contains motor nerves and sensory nerves innervating skin and muscle. The soma (cell bodies) of motor nerves and sensory nerves are located in the gray matter of the anterior horn of the spinal cord and in the dorsal root ganglia, respectively.

CLINICAL CORRELATE
Spinal Cord Injury

Injury to the spinal cord results in deficits in motor and sensory function below the point of injury. The most common cause of spinal cord injury is trauma; other causes include neurodegenerative diseases as well as tumors and vascular diseases affecting the spine. Spinal cord injury is classified as complete, when no neurological function is retained beyond the point of damage, or incomplete, when some sensory or motor function remains. Effects of spinal cord damage correspond to the level of injury, with increasing severity at higher levels:

- Sacral and lumbar injuries are associated with problems in sexual, bladder, and bowel function, as well as motor and sensory deficits in the lower limbs.
- Thoracic injuries are associated with paraplegia (paralysis of the lower body).
- Cervical injuries result in some degree of quadriplegia (paralysis below the neck), depending on the level of injury. Patients with injuries at spinal cord level C3 or above require mechanical ventilation.



Motor Impairment Related to Level of Spinal Injury

CHAPTER 5 Sensory Physiology

Sensory systems allow us to maintain homeostasis and respond to the external environment in an adaptive manner. Much of the awake brain is devoted to transducing, encoding, sensing, and eventually perceiving and reacting to or trying to make sense of both our external and internal environments. An important task of the brain is to filter out the large amounts of incoming information to prevent information overload. During sleep, the incoming sensory information is drastically reduced as the brain continues to try to make sense of the stored information and "reset" itself for the next day's influx of sensory inputs.

SENSORY RECEPTORS

Specialized receptors detect stimuli of various types, including visual, olfactory, gustatory (taste), auditory, and somatosensory (mechanical, thermal, and painful) stimuli. Stimulation of sensory receptors results in the opening or closing of ion channels and generation of a **receptor or generator potential** (a membrane potential change in the receptor). When threshold is reached, the stimulus has been transduced into an electrical signal, and information is transmitted via afferent pathways to the central nervous system (CNS), which integrates such information and transmits signals back to effector systems. The **somatosensory system** includes **mechanoreceptors**, **thermal receptors,** and **nociceptors** (pain receptors) that respond to stimuli in the skin or at the body surface. The term **somatovisceral sensory system** is also used, because such receptors are also located in visceral organs, muscle, and joints.

Several types of sensory receptors are found in the skin (and other tissues); these can be differentiated by the stimuli to which they respond, as well as by the degree of adaptation they exhibit to intensity, duration, and change in stimulus (Fig. 5.1):

- **Meissner's corpuscles** are mechanoreceptors located in the dermal papillae, especially in fingertips, palms, soles, lips, face, tongue, and genital skin (nonhairy skin). These are rapidly adapting receptors with small receptive fields that allow point discrimination and detection of low-frequency stimuli such as flutter.
- **Pacinian corpuscles** are rapidly adapting mechanoreceptors that detect pressure and vibration. The lamellated capsule of these receptors allows them to respond specifically to rapid changes in pressure as well as vibration, as opposed to continual pressure or slow changes in pressure (Fig. 5.2).
- **Merkel's disks** are slowly adapting mechanoreceptors that respond through small receptive fields to pressure and touch, particularly to indentation of the skin.
- **Hair follicle receptors** consist of nerve endings wrapped around the base of hair follicles. These rapidly adapting mechanoreceptors detect movement across the surface of the skin.
- **Ruffini's corpuscles** are mechanoreceptors found in the dermis and in joints; they respond to stretch and are slowly adapting.
- **Thermal receptors** are sensory nerves with endings in the skin that respond to temperature. They are subdivided into warm and cold receptors. Both are slowly adapting.
- **Nociceptors** are sensory nerves with endings in skin, cornea, muscle, joints, and visceral endings. Various types of nociceptors respond to temperature and mechanical and chemical stimuli.
- **Muscle and joint receptors** include muscle spindles and Golgi tendon organs. These receptors are important in proprioception and coordination of motor activity and are considered in more detail later (see "The Motor System").



The receptive field of a sensory neuron is the area over which a stimulus will trigger firing of the neuron. A rapidly adapting receptor is one that responds quickly to a stimulus but adapts rapidly to a constant stimulus, returning to its normal firing rate.

Transduction of Somatosensory Signals

Somatosensory (pain, touch, pressure, temperature) signals originating below the head and in the head are ultimately conveyed to the primary somatosensory area, located in the postcentral gyrus of the parietal lobe of the cerebral cortex. The

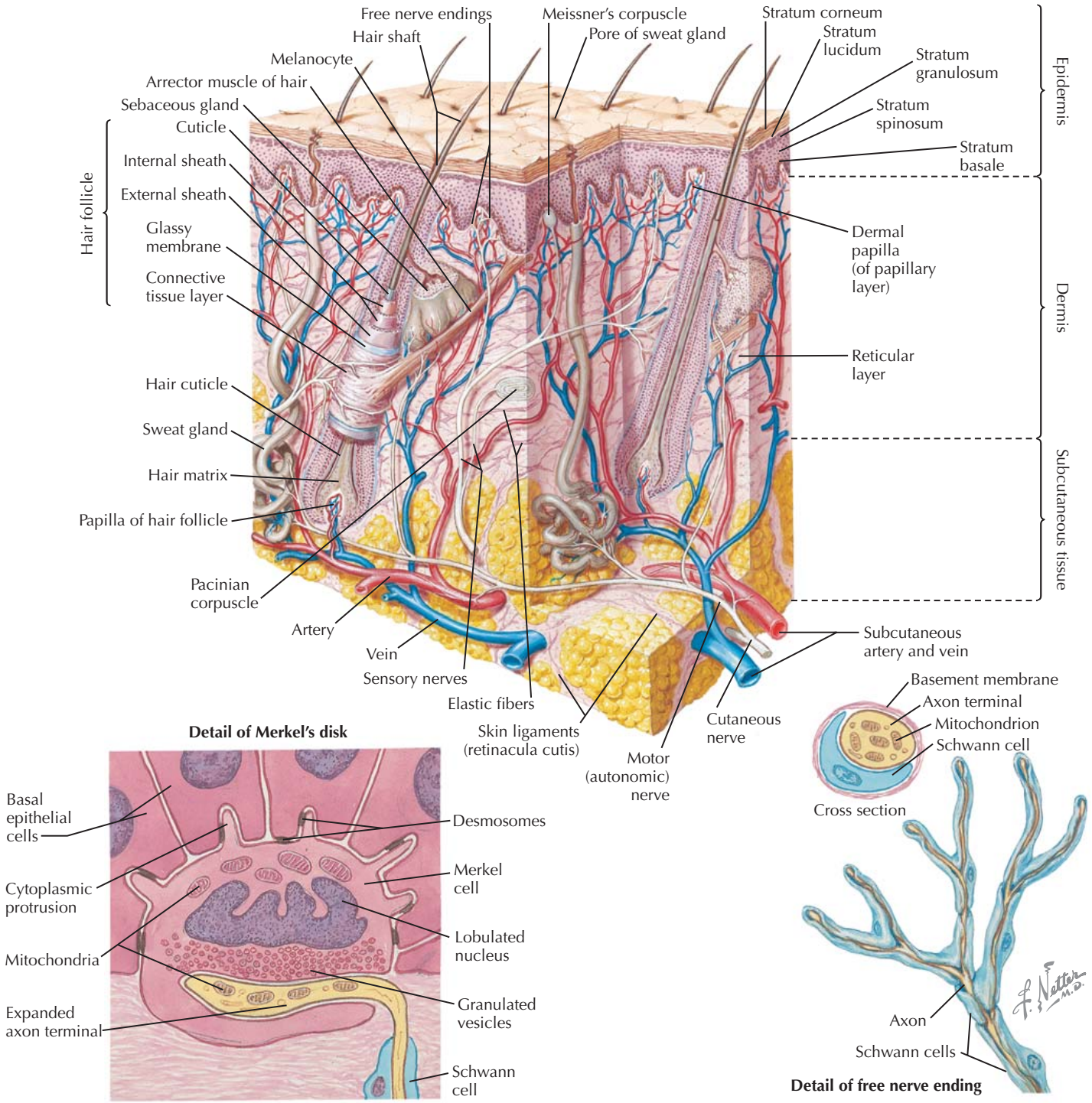
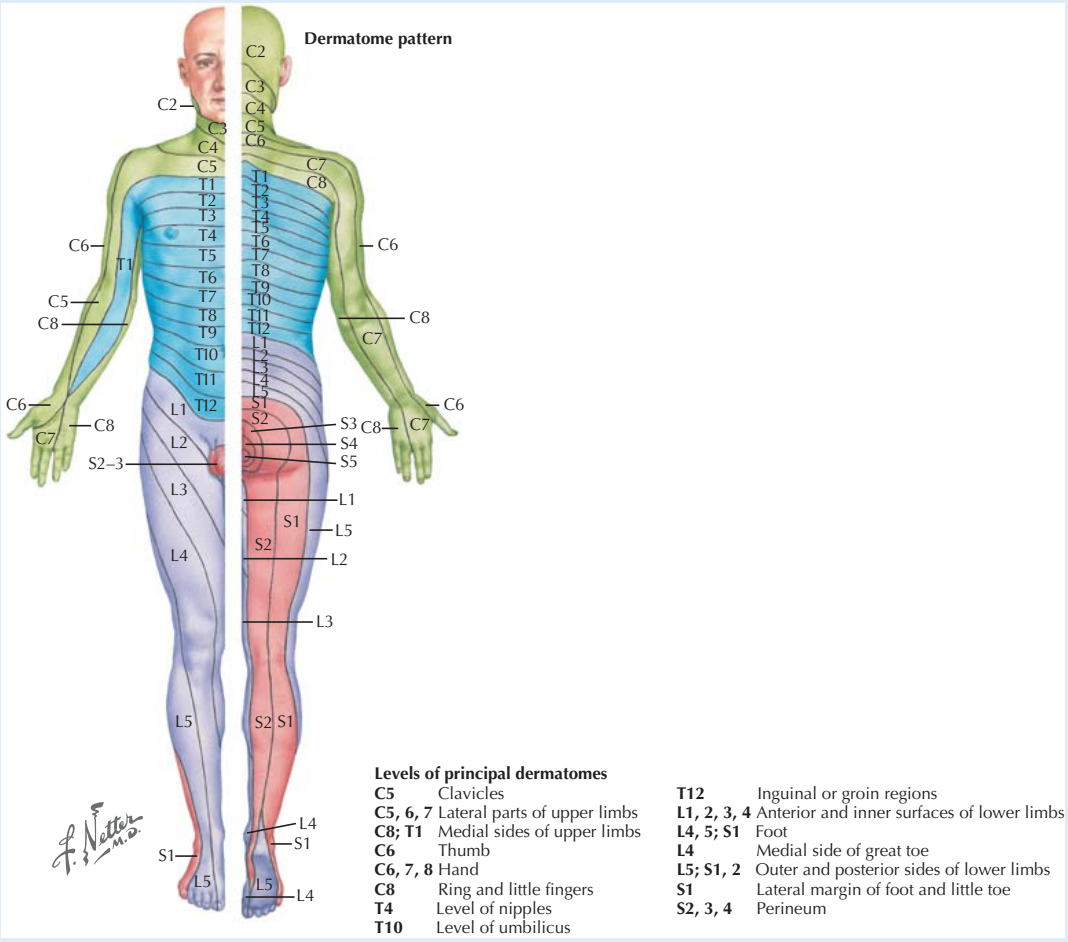


Figure 5.1 Skin and Cutaneous Receptors Mechanoreceptors, thermoreceptors, and nociceptors transduce the effects of touch, temperature, and painful stimuli into neural signals. Within the skin, mechanoreceptors known as Meissner's corpuscles, pacinian corpuscles, and Merkel's disks respond to various types of mechanical stimulation. Temperature and painful stimuli are detected by free nerve endings.

CLINICAL CORRELATE
Dermatomes

Dermatomes are areas of the skin associated with a specific pair of dorsal nerve roots. In other words, sensory signals originating in the skin within a dermatome are largely transmitted to the spinal cord through one of a specific pair of afferent sensory nerve roots, although there is significant overlap between adjacent dermatomes. Clinically, dermatomes are useful in identifying the site of spinal nerve damage, based on the region of skin in which sensation is affected. For example, sensations in the feet are conveyed to the spinal cord through nerve roots at L4, L5, or S1, depending on the area of the foot, with some overlap in regions. In shingles (herpes zoster), the herpes virus usually resides dormant in nerve cell bodies of the dorsal root ganglia, but when active, will specifically affect the skin in the corresponding dermatome on one or both sides (depending which ganglia are infected).



Levels of principal dermatomes

C5	Clavicles	**T12**	Inguinal or groin regions
C5, 6, 7	Lateral parts of upper limbs	**L1, 2, 3, 4**	Anterior and inner surfaces of lower limbs
C8; T1	Medial sides of upper limbs	**L4, 5; S1**	Foot
C6	Thumb	**L4**	Medial side of great toe
C6, 7, 8	Hand	**L5; S1, 2**	Outer and posterior sides of lower limbs
C8	Ring and little fingers	**S1**	Lateral margin of foot and little toe
T4	Level of nipples	**S2, 3, 4**	Perineum
T10	Level of umbilicus		

afferent somatosensory signals originating below the head are conveyed to the dorsal root ganglia and subsequently through the spinothalamic and spinoreticular tracts of the anterolateral system, ultimately reaching the primary somatosensory cortex (Fig. 5.3). Signals involved in proprioception, as well as signals generated by vibratory and tactile stimuli, are carried through the fasciculus gracilis and fasciculus cuneatus to the ventral posterolateral nucleus (VPN) of the thalamus. The lateral cervical system carries some proprioceptive, vibratory, and tactile signals as well. These pathways reach synapses in the thalamus and before extending to the cerebral cortex.

In the head, touch, pressure, pain, and temperature result in afferent nerve traffic to nerve cell bodies in the trigeminal (semilunar) ganglia of the trigeminal nerve. Signals involved in proprioception are carried to neuronal cell bodies in the mesencephalic nucleus of the trigeminal nerve (CN V). Projections in this system are mainly to the contralateral ventral posterolateral nucleus (VPN) of the thalamus, subsequently reaching the primary somatosensory cortex (postcentral gyrus) (Fig. 5.4).

THE VISUAL SYSTEM

The **visual system** performs the remarkable task of detecting light stimuli between 400 and 700 nanometers in wavelength, transducing the stimuli into electrical signals, and transmitting

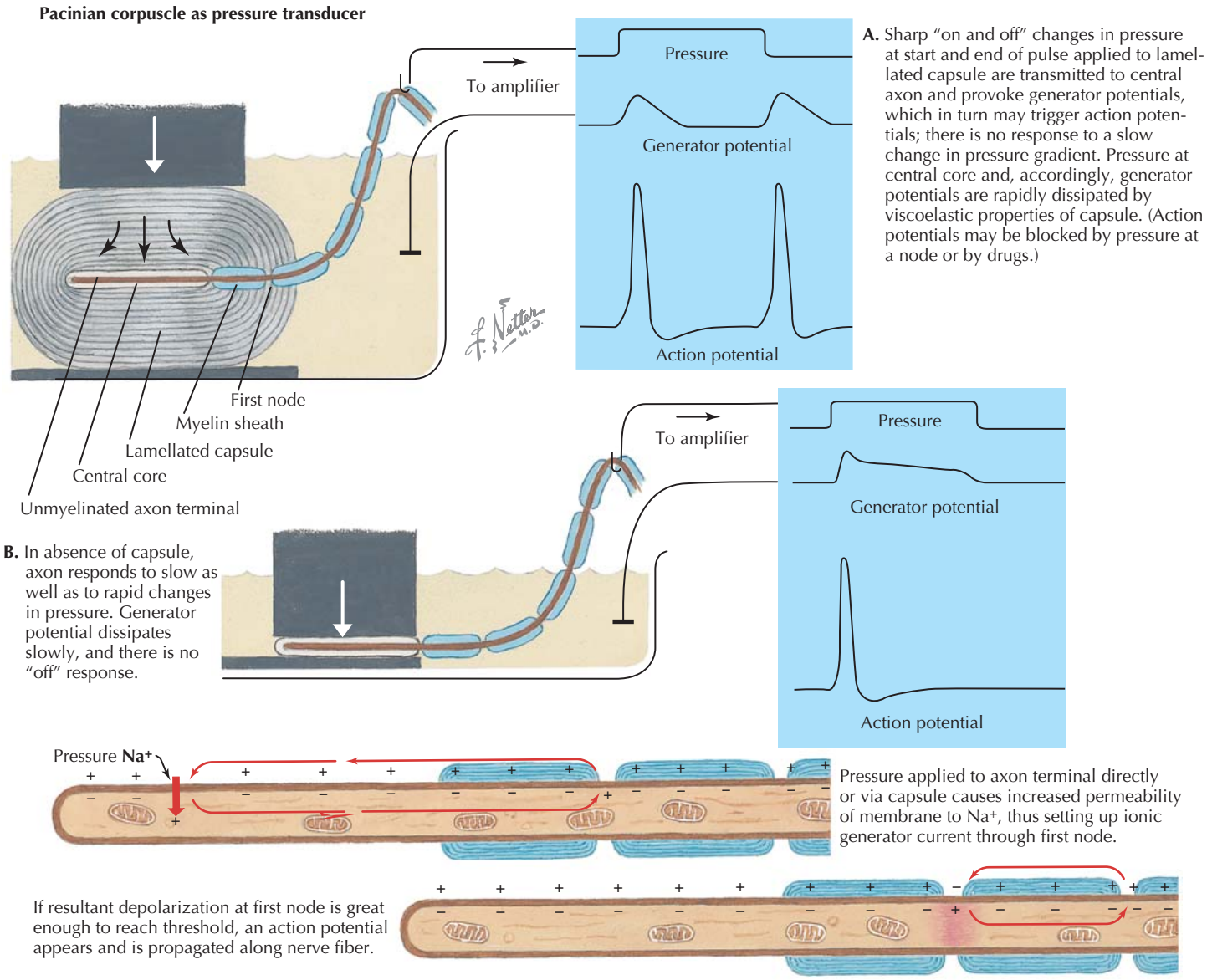


Figure 5.2 Pacinian Corpuscle Pressure and vibration are transduced into electrical potential changes by pacinian corpuscles, which are rapidly adapting mechanoreceptors. The lamellated capsule surrounding the axon terminal dissipates slow pressure changes, and thus, the axon responds only to rapid changes in pressure *(A)*, in contrast to an axon lacking a capsule *(B)*. The action potentials produced are carried through afferent fibers to the dorsal root ganglia (see Fig. 4.9).

these signals to the CNS, where they are used to construct a three-dimensional representation of objects in the visual field that includes color and brightness and detects motion.

Light passes through the cornea of the eye, through the pupil (the circular opening of the iris), and is then focused by the lens onto the retina (Fig. 5.5). Within the retina, photoreceptors known as rods and cones contain the pigment **rhodopsin,** which absorbs photons. Color perception is mainly mediated by cones, whereas rods are sensitive photoreceptors adapted to perceive light at low intensity. The visual fields of the two eyes overlap, with the center being projected, upside-down, on the sensitive macular zone of the retina (Fig. 5.6). Within the macula, the **fovea** is the region of greatest visual acuity; it contains only cones.

Reception of light by the photoreceptors initiates a sequence of events that results in reduced Na^+ permeability and hyperpolarization of the photoreceptor cell membrane. This results in inhibition of the release of either inhibitory or excitatory neurotransmitters at synapses between photoreceptors and **bipolar** and **horizontal cells.** Ultimately, the generated signals are transmitted by the **ganglion cells,** whose axons form the **optic nerves.** Nerve fibers originating in the nasal hemiretina (nasal half of the retina) of each eye cross at the **optic chiasm** (the site of partial crossing of the two optic nerves), while

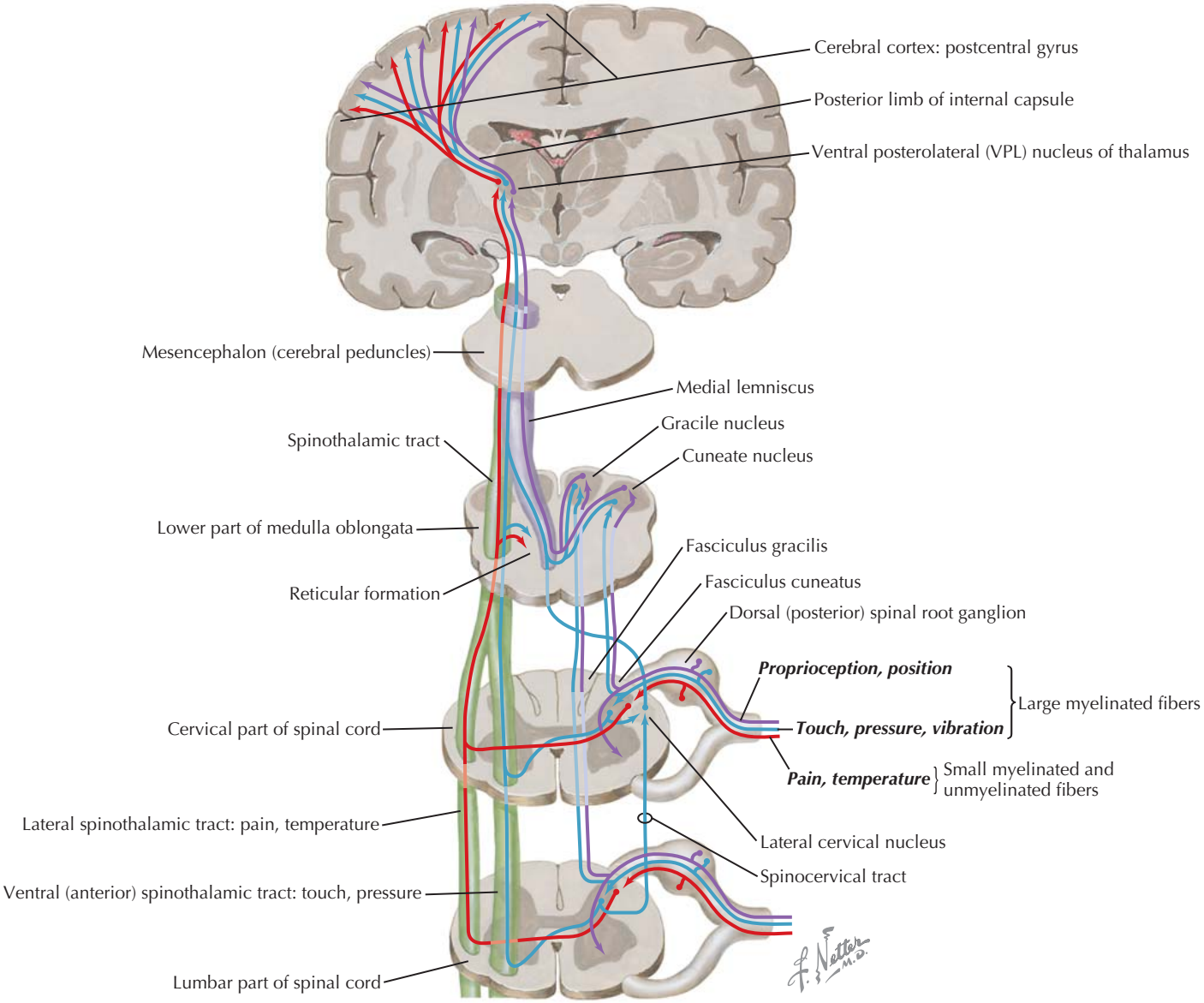


Figure 5.3 Somesthetic System of the Body The primary somatosensory cortex (postcentral gyrus) receives information regarding proprioception, touch, pressure, vibration, pain, and temperature originating at receptors below the head through the illustrated tracts by way of the thalamus. Pain-, temperature-, and pressure-related signals are conducted through the spinothalamic and spinoreticular tracts of the anterolateral system *(red* and *blue lines).* The fasciculus gracilis and fasciculus cuneatus, as well as the lateral cervical system, convey proprioception-, touch-, and vibration-related signals *(blue* and *purple lines).*

fibers from the temporal hemiretina remain in the ipsilateral tract (same side). The optic tracts carry the signals to synapses at the **lateral geniculate nuclei,** from which signals are transmitted to the visual cortex in the occipital lobe of the cerebral cortex.

THE AUDITORY SYSTEM

The **auditory system** detects sound, transduces it into electrical signals, and transmits it to the brain, where the complex task of interpretation of sound, for example as speech, takes place. The process begins at the external ear, which directs sound to the tympanic membrane (eardrum) (Fig. 5.7). This membrane separates the external ear from the air-filled middle ear, where sound is amplified. Vibration of the tympanic membrane is conducted to the maleus, incus, and stapes, the small bones of the middle ear known collectively as the **ossicles.** The stapes is connected to the **oval window,** one of two membranous "windows" between the middle ear and inner ear. Thus, vibration of the ossicles is transmitted to the inner ear by the stapes.

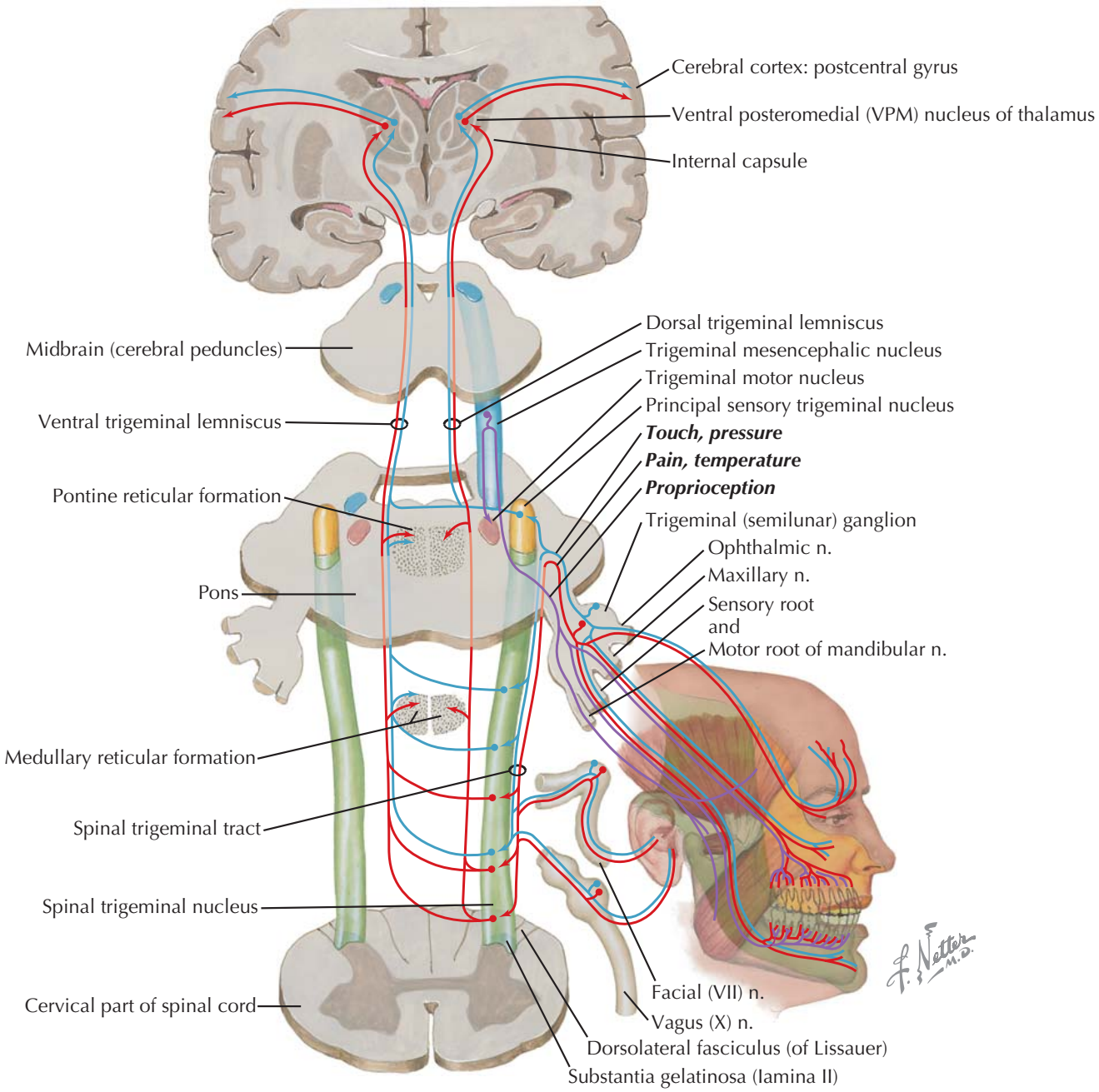


Figure 5.4 Somesthetic System of the Head The primary somatosensory cortex (postcentral gyrus) receives information regarding proprioception, touch, pressure, pain, and temperature originating at receptors in the head through the illustrated tracts by way of the thalamus. Proprioceptive signals are carried by nerve fibers *(purple lines)* originating in cell bodies in the mesencephalic nucleus of the trigeminal nerve (CN V), whereas touch, pressure, pain, and temperature produce signals carried by nerve fibers *(blue* and *red lines)* to cell bodies in the trigeminal ganglion of CN V.

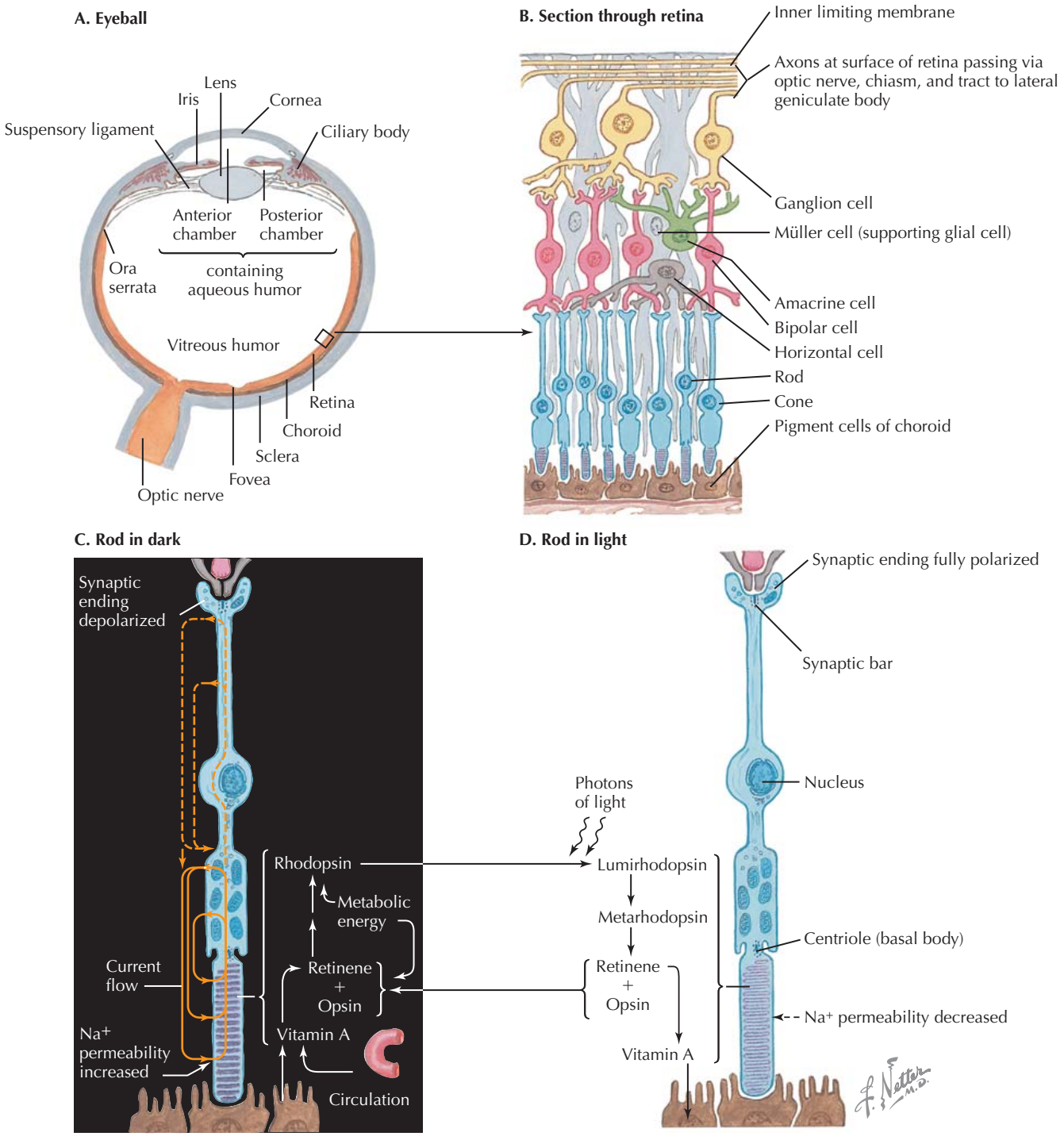


Figure 5.5 **Visual Receptors** Light enters the eye through the cornea and lens *(A)*. Light focused onto the retina by the lens is absorbed by rhodopsin in photoreceptors (rods and cones, *B*). In light, the cGMP second messenger system is activated, resulting in closure of membrane Na^+ channels, hyperpolarizing the cell (illustrated for rod cells in *D*). Subsequent inhibition of neurotransmitter release at synapses with bipolar and horizontal cells is the next step in the transmission of light-generated signals to the optic nerve. In dark, the rod or cone is depolarized *(C)*.

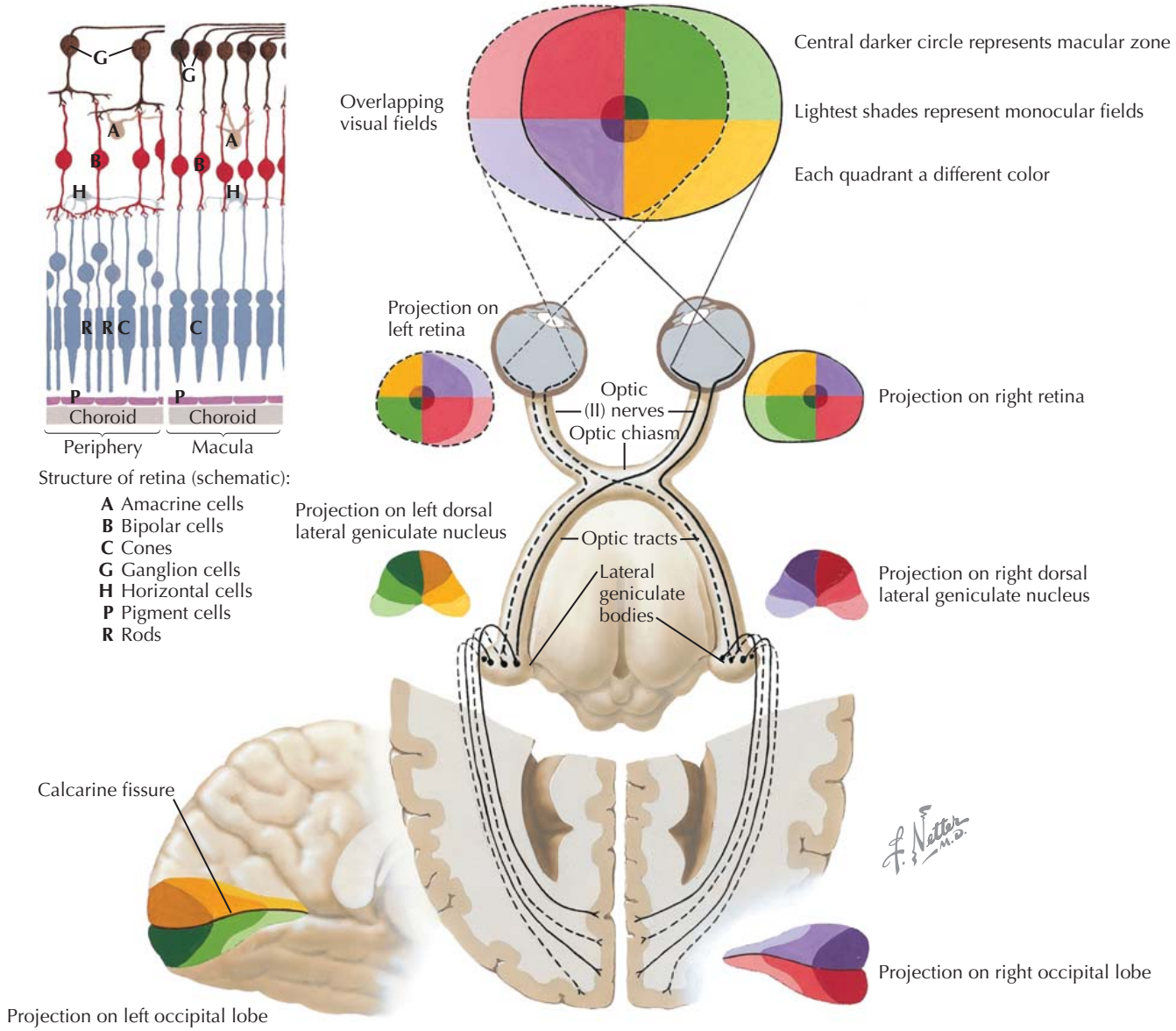


Figure 5.6 Retinogeniculostriate Visual Pathway Rods and cones detect light in the retina, with cones specifically mediating color perception and rods detecting light. In the central macular zone of the retina, only cones are found; this is the region with greatest acuity *(top left).* Axons of ganglion cells carry afferent signals through the optic nerve. At the optic chiasm, fibers originating in the nasal half of the retina cross to the contralateral tract, whereas fibers from the temporal half remain in the ipsilateral tract. Fibers project to synapses in the lateral geniculate nucleus (visual fields are inverted at this point). Signals are conveyed from the lateral geniculate nucleus to the primary visual cortex.

The fluid-filled inner ear is a complex structure that includes the vestibule, the cochlea, and the semicircular canals. The vestibule and cochlea consist of a **membranous labyrinth** within a **bony labyrinth** (Fig. 5.8). The membranous labyrinth of the cochlea includes three ducts known as the scala vestibuli, scala tympani, and scala media (cochlear duct). The fluid of the scala media, the **endolymph,** resembles intracellular fluid in its composition, whereas the **periplymph** of the other two ducts is similar to other extracellular fluids.

Transduction of Sound into Electrical Signals

The **spiral organ of Corti** is the site of transduction of sound into electrical signals. Mechanoreceptors known as **hair cells**

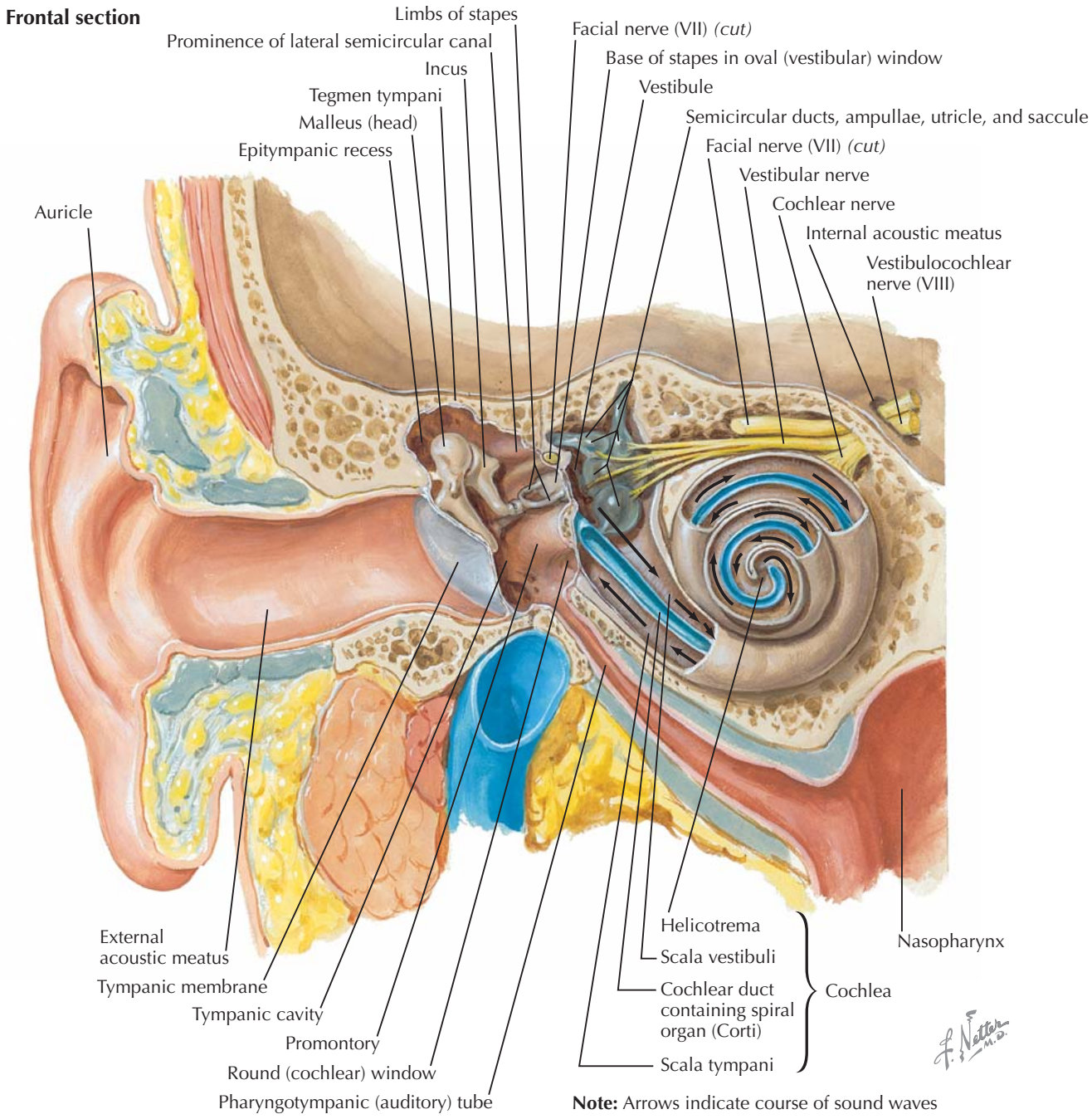


Figure 5.7 **Peripheral Pathways for Sound Reception** The process of auditory perception begins when sound reaches the auricle (external ear) and is directed through the external acoustic meatus to the tympanic membrane, causing it to vibrate. The vibration is transmitted by the bones of the air-filled middle ear (maleus, incus, and stapes) to the fluid-filled inner ear via the oval window. Within the inner ear, the organ of Corti of the cochlea contains auditory receptors (see Fig. 5.8).

have **stereocilia** with their distal ends extending to and embedded in the **tectorial membrane** (see Fig. 5.8). When sound is conducted into the fluid of the inner ear, vibration of the basilar membrane results in bending of these stereocilia. The endolymph is unusual in terms of its electrical potential (approximately +80 mV relative to the perilymph), resulting in a charge difference across the apical membrane of approximately 170 mV. Bending of the stereocilia results in changes in cation conductance of the apical cell membrane of hair cells; bending in one direction produces hyperpolarization, and bending in the other direction causes depolarization. As a result, there is an oscillatory release of neurotransmitter at

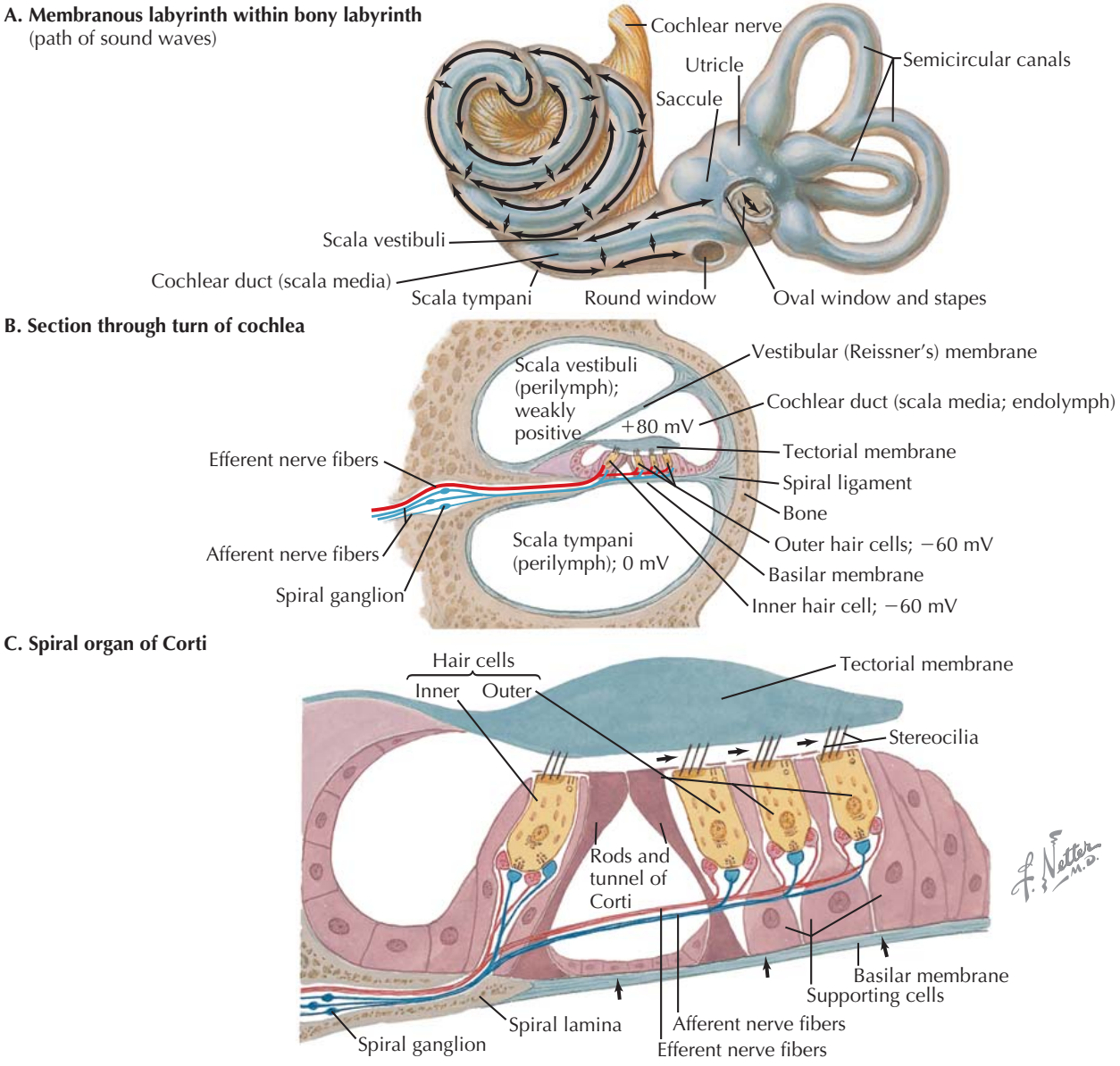


Figure 5.8 Cochlear Receptors Sound waves reaching the inner ear travel through the membranous labyrinth of the cochlea *(A)*, which consists of three ducts *(B)*. When vibration caused by sound reaches the cochlea of the inner ear, periodic displacement of the basilar membrane relative to the tectorial membrane causes bending of stereocilia and depolarizes hair cells within the spiral organ of Corti, resulting in transduction of sound into neural signals *(C)*.

the synapses between hair cells and afferent nerve fibers, with depolarization of hair cells producing increased neurotransmitter release and hyperpolarization causing reduced release. When threshold is reached in the afferent nerve fibers (during depolarizations of the hair cells), action potentials are produced. Within regions of the organ of Corti, the amplitude by which the basilar membrane is repeatedly displaced as it vibrates is dependent on sound frequency. Thus, the organ of Corti is tonotopically organized, with high-frequency sounds causing the largest displacement in the basal region of the cochlea, and low-frequency sounds causing the largest displacement in the apical region (Fig. 5.9). As a result, cochlear nerve fibers respond to different frequencies of sound, according to the **characteristic frequency** of the fiber (the sound frequency of lowest intensity that produces a response in the fiber).

Impulses pass through the **auditory nerve** to the brainstem, where neurons compute various sound parameters (see Fig. 5.9). For example, the **superior olivary complex** detects differences in timing and intensity of sound signals originating from the two ears, allowing us to detect the location of a

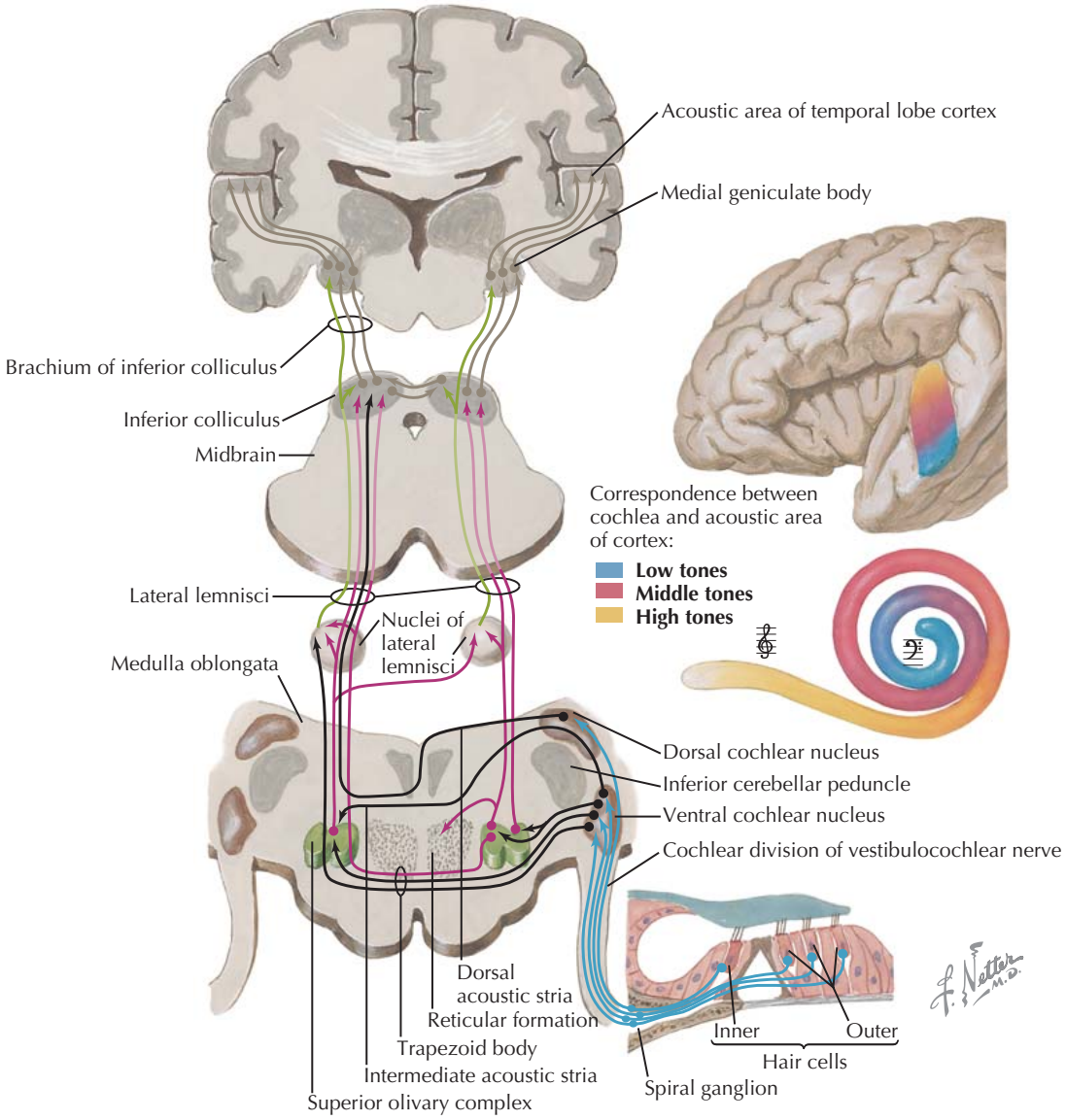


Figure 5.9 Auditory Pathways Electrical signals generated by hair cells in the organ of Corti are conveyed to the dorsal and ventral cochlear nuclei of the medulla, which project to the lateral lemniscus. After further relays, the pathway leads to the medial geniculate bodies of the thalamus, which sends projections to the primary auditory cortex.

sound source. Once the information reaches the thalamus (**medial geniculate body**), it is further processed and relayed to the amygdala and **auditory areas** of the temporal lobe. Within these areas, there is correspondence of tonotopic organization to that within the cochlea. Other parameters, such as amplitude and pitch of a sound, are also mapped there.

THE VESTIBULAR SYSTEM

In addition to its role in audition, the inner ear has an important role in balance and equilibrium through its **vestibular apparatus,** which consist of the **semicircular canals** and the **otolithic organs** (the **utricle** and the **saccule**) (Fig. 5.10). These structures detect angular and linear acceleration of the head, and thus play an important role in proprioception. Specifically, the three semicircular canals are oriented perpendicularly to each other and are therefore able to detect angular acceleration in any plane; the otolithic organs detect linear acceleration.

The sensory tissues of the semicircular canals are found in the **ampullary crest** (**crista ampullaris**). Hair cells in this structure, like those of the organ of Corti, have apical stereocilia, but in this case, each hair cell also has a single large

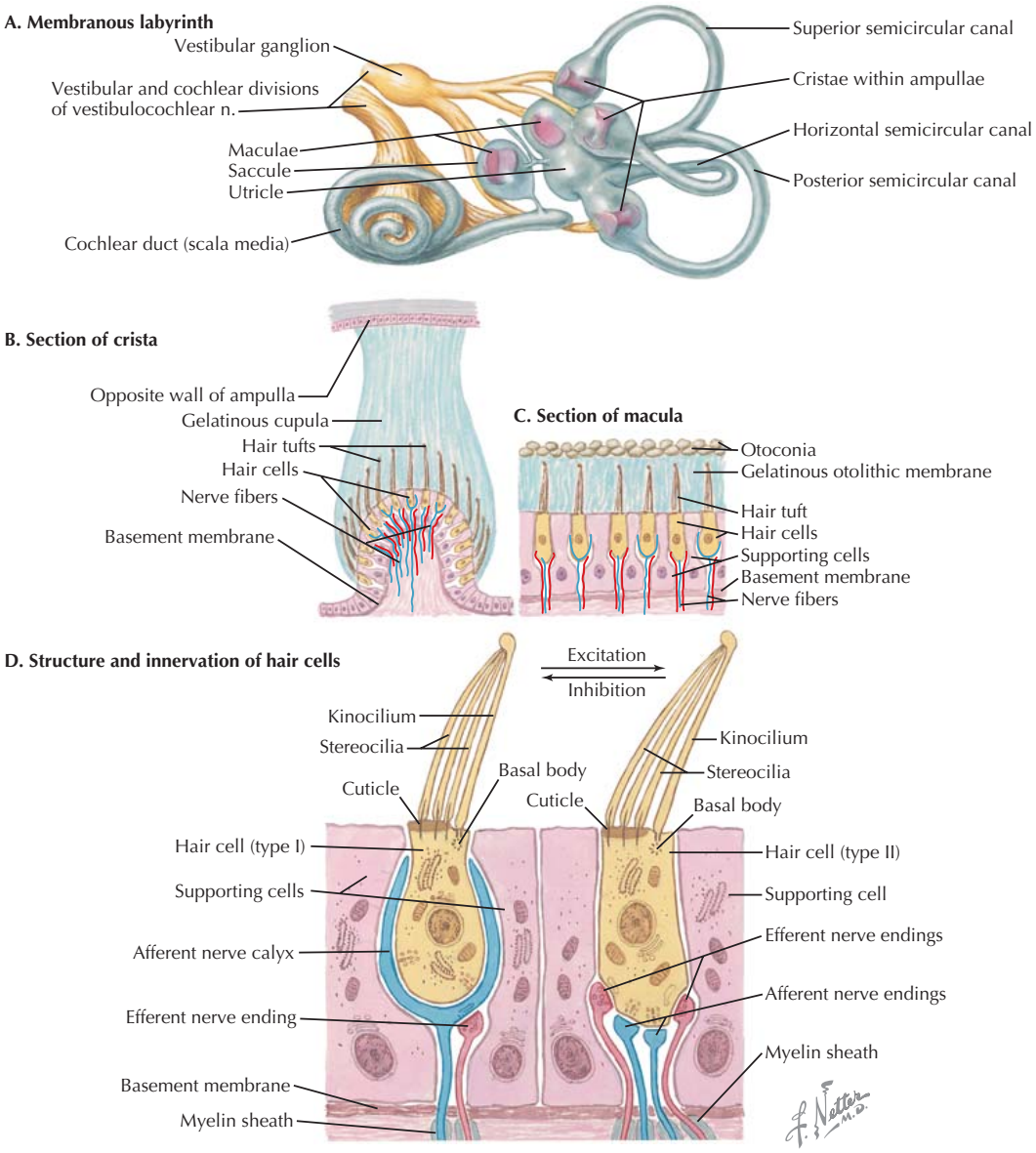


Figure 5.10 **Vestibular Receptors** The semicircular canals and the otolithic organs (the utricle and saccule) constitute the vestibular apparatus of the inner ear, which has a critical role in balance and equilibrium *(A)*. The otolithic organs detect linear acceleration of the head, whereas the three perpendicular semicircular canals respond to angular acceleration. Sensory hair cells in the crista of the semicircular canals *(B)* and macula of the otolithic organs *(C)* respond to fluid (endolymph) movement during linear and angular acceleration *(D)*.

cilium known as the **kinocilium.** A gelatinous mass, the **cupula,** spans and occludes the ampulla at the ampullary crest. The semicircular canals are filled with endolymph, and during angular acceleration of the head, pressure against the cupula causes bending of the cilia. Due to the perpendicular orientation of the three semicircular canals, the pattern of pressure changes in the canals is dependent on the direction of movement of the head. When cilia bend toward the kinocilium, the membrane potential becomes depolarized (due to increased conductance to cations); bending in the opposite direction causes hyperpolarization. Depolarization results in release of neurotransmitter, whereas hyperpolarization reduces neurotransmitter release by the hair cells. Changes in neurotransmitter release alter the firing rate of afferent nerve fibers ending on the hair cells. Impulses are carried by axons of these primary afferent nerves through cranial nerve VIII to the vestibular nuclei of the pons (Fig. 5.11). Subsequent processing involves both ascending and descending pathways that carry the information through secondary axons to the spinal cord, cerebellum, reticular formation, extraocular muscles, and cortex (by way of the thalamus).

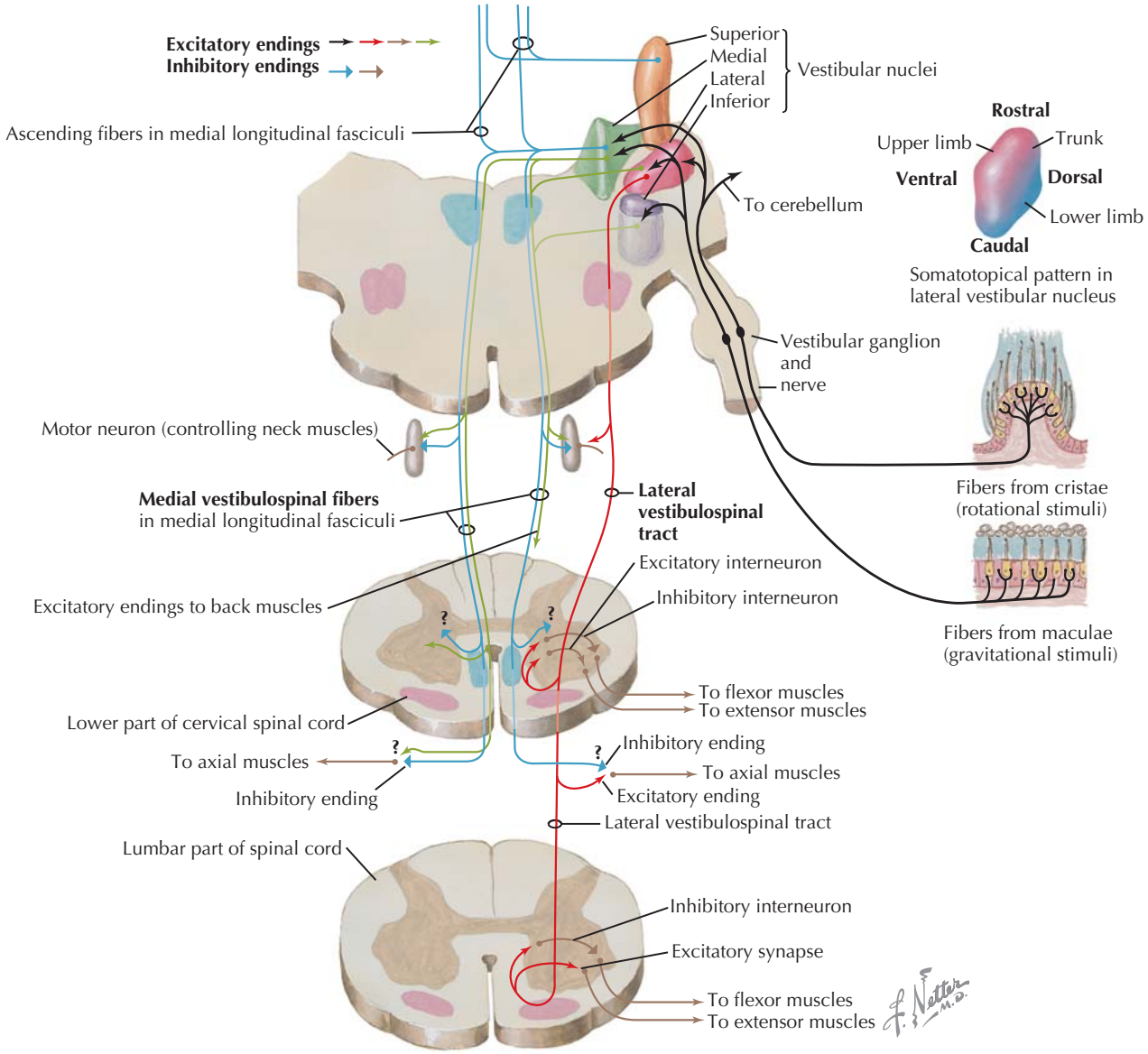


Figure 5.11 **Vestibulospinal Tracts** Sensory signals from the vestibular apparatus are conveyed to the pontine vestibular nucleus, and subsequently, through secondary axons, to the spinal cord, cerebellar vermis, reticular formation of the brainstem, extraocular muscles, and the cerebral cortex (by way of the thalamus). Vestibular sensory input is utilized to maintain balance and posture and in positioning of the head.

In the standing position, the utricle senses horizontal acceleration, whereas the saccule is sensitive to vertical acceleration. This is a result of the orientation of the sensory tissues of the otolithic organs, the **maculae** (see Fig. 5.10). The macula is oriented horizontally in the utricle and vertically in the saccule and contains hair cells like those in the crista of the semicircular canals. A gelatinous **otolithic membrane** lies above the macula. Linear acceleration produces pressure changes in endolymph-filled otolithic organs, shifting the macula and bending hair cells. Again, depolarization or hyperpolarization results, affecting transmitter release, afferent nerve firing, and

Umami (Japanese for "savory") has long been recognized as a basic taste classification in Japan. It is used to describe the savory taste of protein-rich dishes such as those containing meat. The recent discovery of a specific taste receptor that binds glutamates, which are prevalent in protein-rich food, has led to the recognition of the "umami taste receptor," along with the traditional sweet, bitter, salty, and sour receptors on taste buds. The flavor-enhancing quality of monosodium glutamate (MSG) can be ascribed to stimulation of the umami receptor.

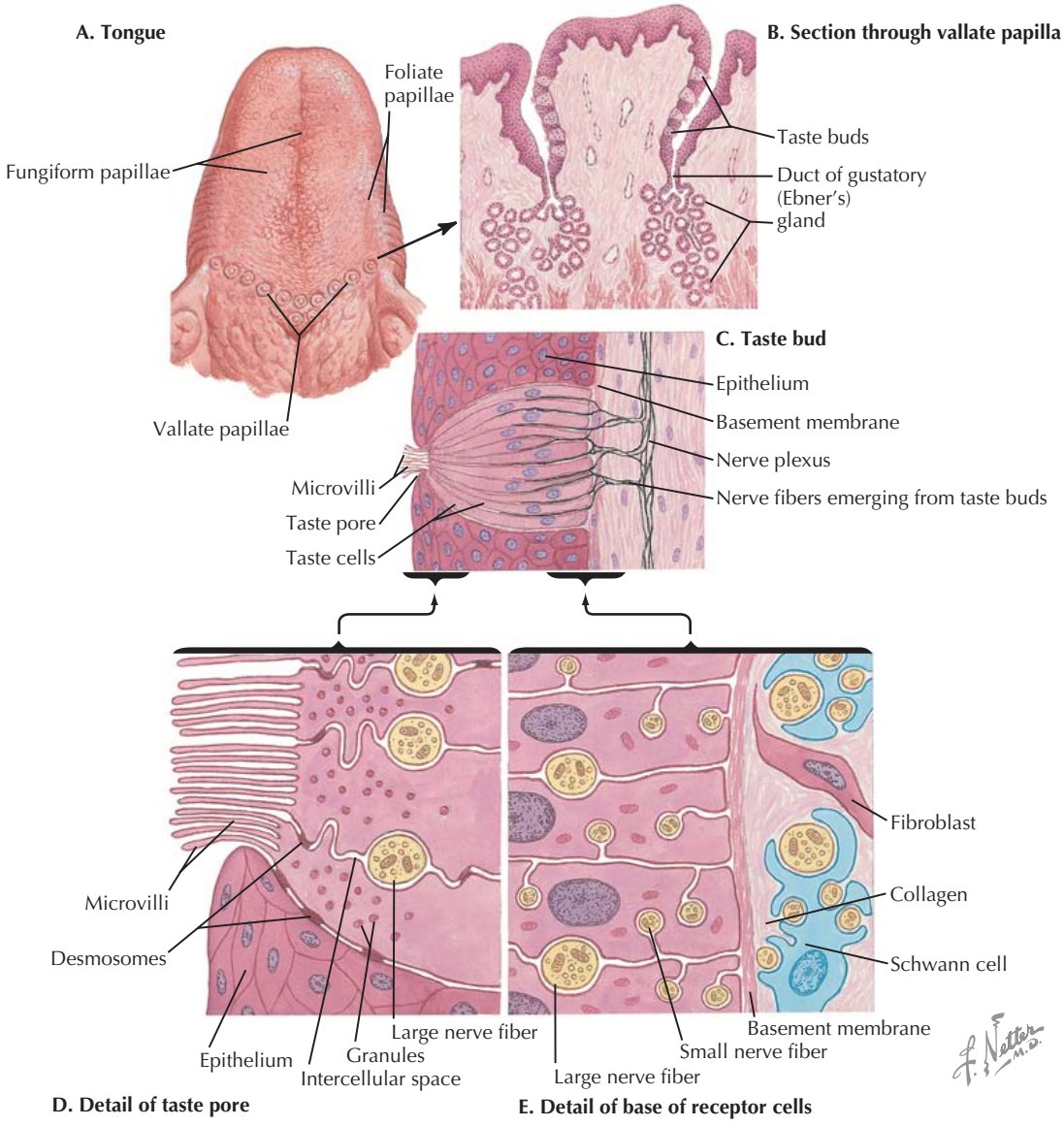


Figure 5.12 Taste Receptors Taste receptors are found mainly in the taste buds of the three types of papillae of the tongue *(A* and *B),* but also in taste buds on the palate, larynx, and pharynx. Goblet-shaped taste buds *(C)* comprise taste cells with microvilli protruding through the taste pore *(D)*. Nerve fibers are found in close association with hair cells *(D* and *E)*. Taste cells, through receptors, respond to chemical signals (taste), ultimately producing depolarization and action potentials in afferent nerve fibers. At least five types of taste receptors exist: sweet, salty, sour, bitter, and umami (savory).

transmission of signals to the brainstem (see Fig. 5.11). By virtue of the orientation of the maculae of the two otolithic organs, linear acceleration in any direction can be detected.

CHEMICAL SENSES

Taste Cells

Gustation (taste) and **olfaction** (smell) are two **chemical senses** involved in detecting chemical stimuli in the environment and the substances we ingest. Traditionally, tastes have been classified as sweet, bitter, salty, and sour. More recently, a fifth classification, **umami** (savory) has become widely accepted (see preceding box). **Taste cells** (also called taste receptor cells or gustatory receptor cells) are found mainly in the **taste buds** of the papillae of the tongue, but also in taste buds of the palate, larynx, and pharynx. Three types of papillae are recognized, based on anatomical structure: the fungiform, foliate, and circumvallate papillae (Fig. 5.12). Taste buds within the papillae consist of groups of taste cells, along with supporting cells and basal cells; the latter differentiate to continuously replace taste cells. Individual taste cells respond

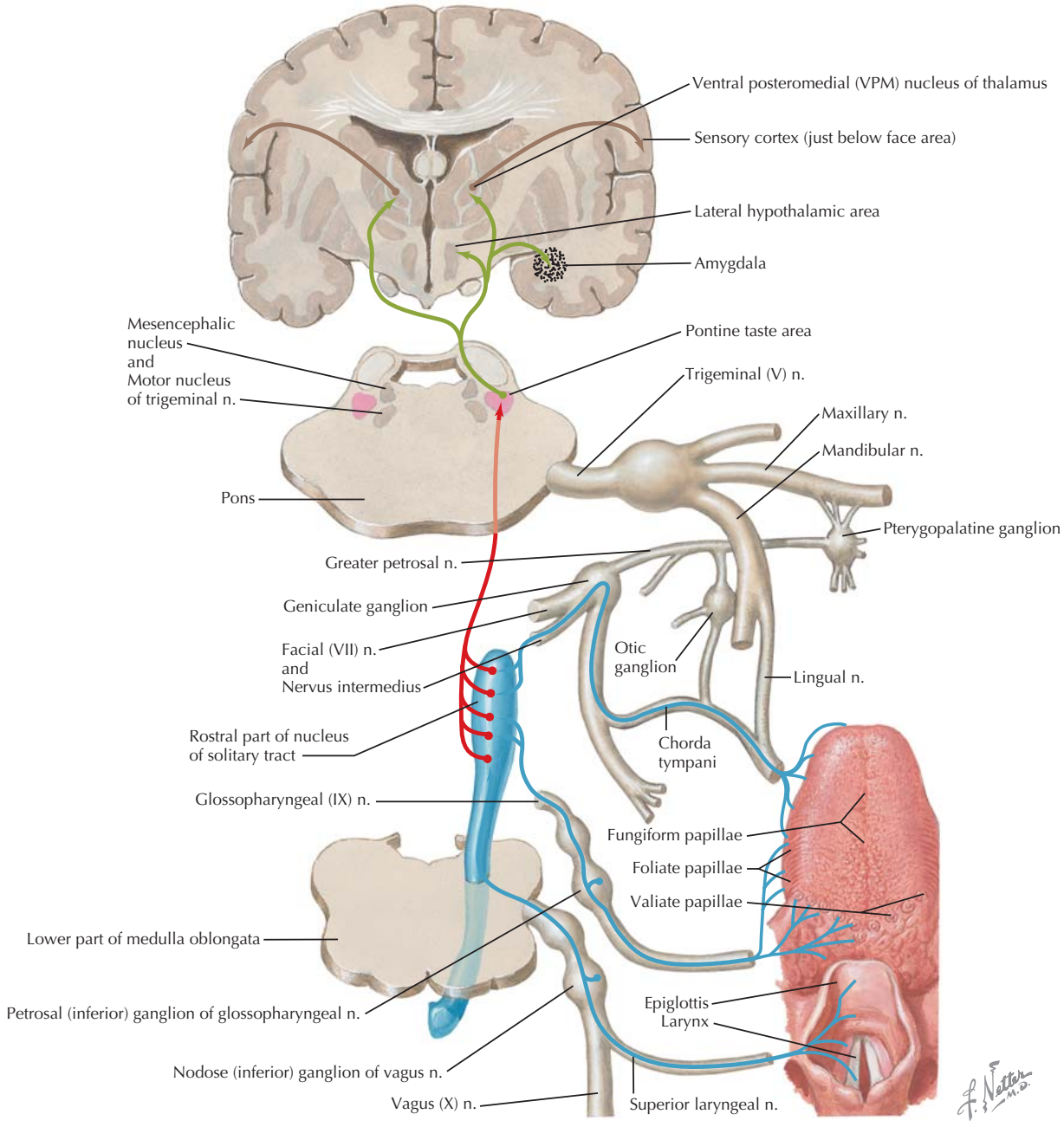


Figure 5.13 Taste Pathways Regions of the tongue are innervated by cranial nerves VII, IX, and X. These pathways transmit afferent signals to the medulla (specifically, the nucleus tractus solitarius), from which they are conveyed to other brain regions, eventually reaching the sensory cortex.

through receptors to all of the fundamental taste types, although they may respond best to one type. Microvilli of taste cells recognize chemical signals in saliva, resulting in activation of G protein–coupled signal transduction mechanisms or changes in ion conductance, ultimately resulting in depolarization and action potentials in primary afferent nerve fibers. Various regions of the tongue are innervated by cranial nerves VII, IX, and X, which carry the signal to the medulla, from which it is transmitted to other regions of the brain, ultimately to the sensory cortex (Fig. 5.13).

Many people will recall seeing a diagram of the tongue, depicting localization of perception for sweet, salty, bitter, and sour tastes to various regions on its surface. Although it was thought for many years that different areas of the tongue are responsible for detection of various tastes, it is now believed that taste perception is not exclusively differentiated in this manner. In other words, the "taste map" seen in many texts is not well defined.

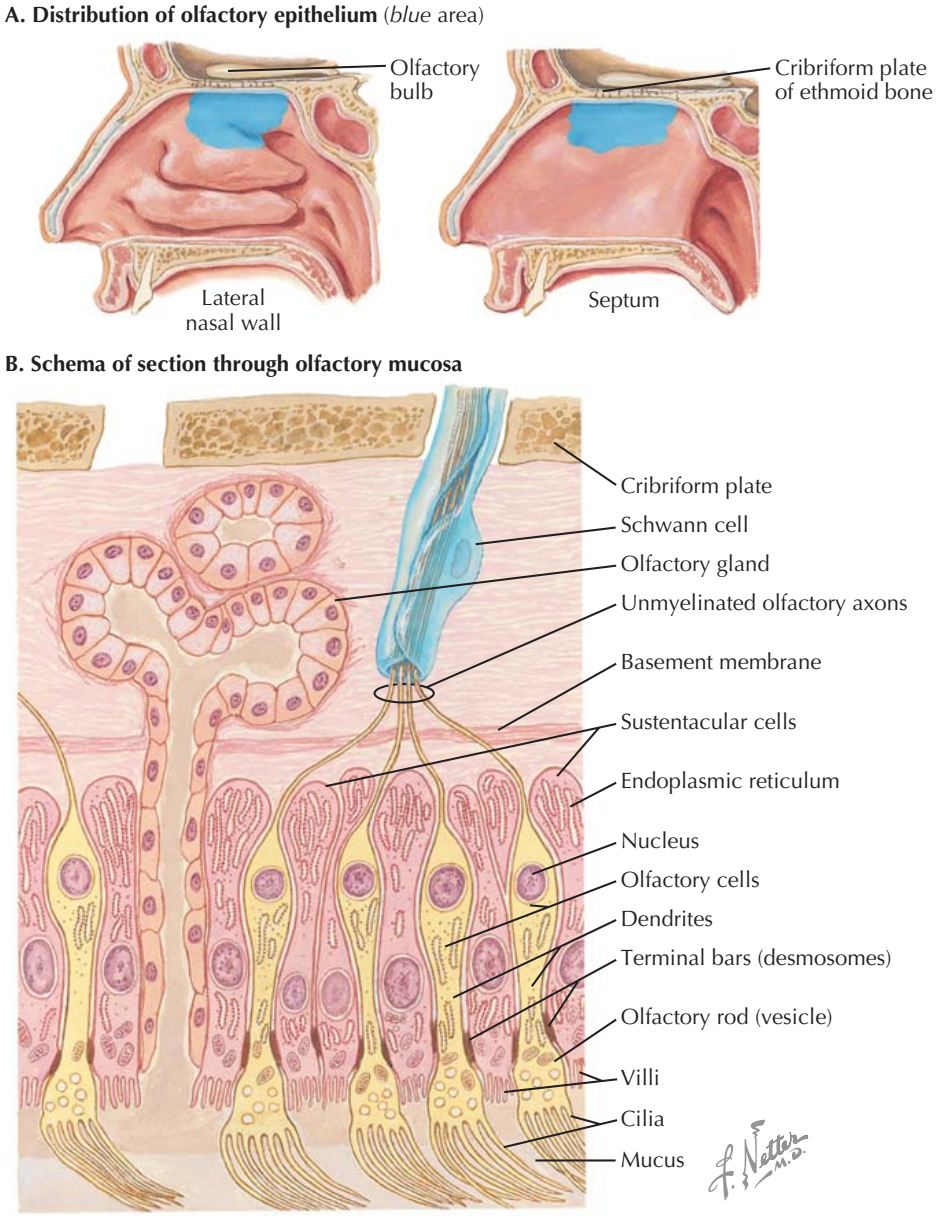


Figure 5.14 Olfactory Receptors Chemical stimuli in the form of odorants result in depolarization of sensory olfactory cells of the olfactory epithelium, located in the upper nasal cavity *(A)*. An olfactory cell, through G protein–coupled receptors, is capable of responding to more than one odor type. Odorants are trapped and also removed by secretions of olfactory glands *(B)*.

Olfactory Cells

The sense of smell has an important role in appetite in humans, but this sense is poorly developed compared with that of other mammals, in which olfaction can play a major role in reproductive and territorial behavior. The six basic types of odors we sense are camphor, floral, ethereal, musky, putrid, and pungent. The sensory **olfactory cells** are found in the **olfactory epithelium** of the nasal cavity, along with supporting (sustentacular) and basal cells. As is the case with basal cells in taste buds, these basal cells differentiate to continuously replace sensory cells. The cilia of olfactory cells extend into the nasal mucosa, where they bind odorant molecules on specific G protein–coupled receptors (Fig. 5.14). Binding of an odorant activates signal transduction mechanisms within the olfactory cells, resulting in opening of ion channels and depolarization. Olfactory cells are primary afferent neurons, and action potentials are carried by their axons to the **olfactory bulb,** where they synapse with **mitral cells** (Fig. 5.15). Projections from the mitral cells form the olfactory tract, which carries signals to higher centers, such as the piriform and orbitofrontal cortices, as well as the amygdala.

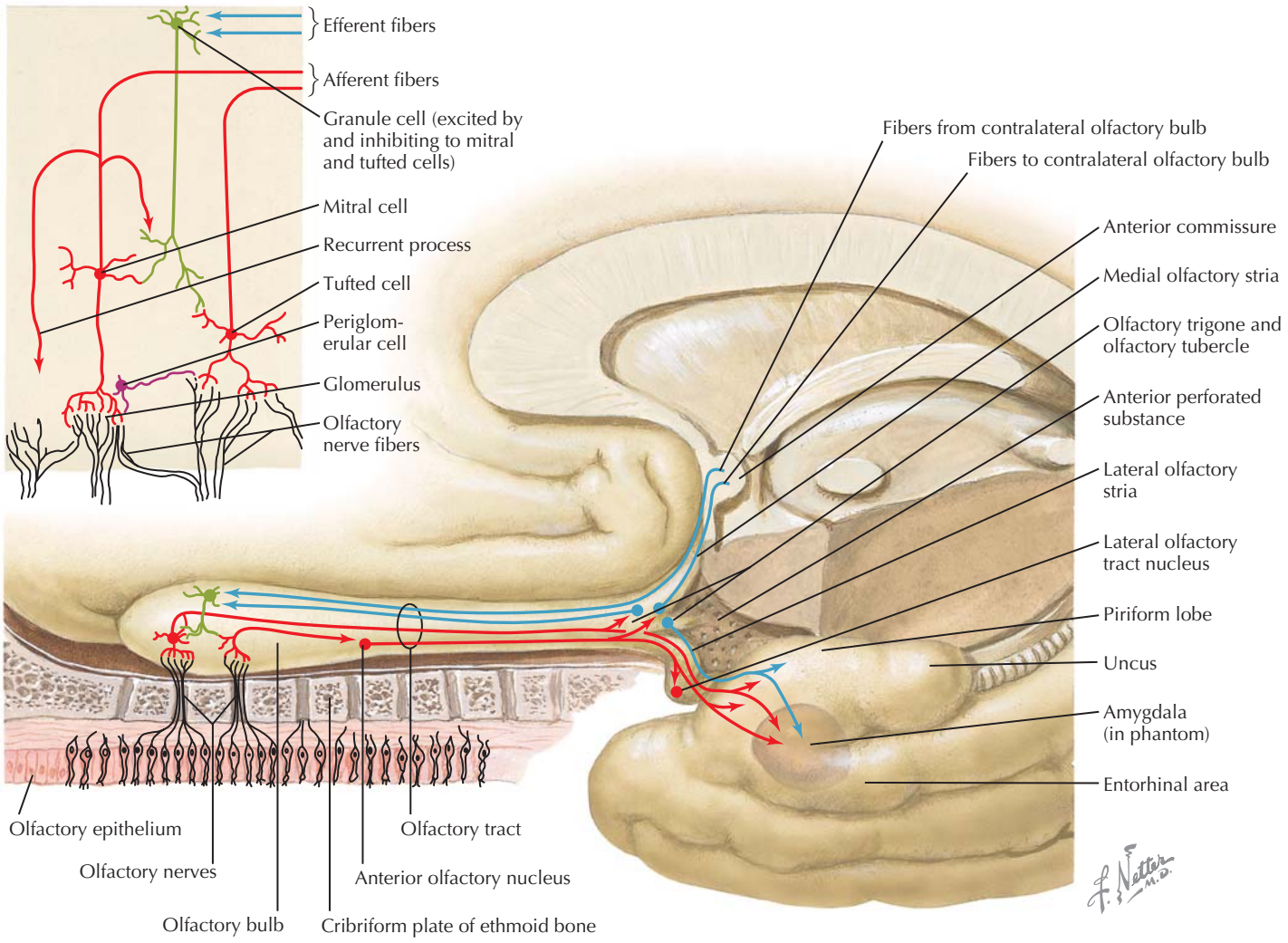


Figure 5.15 **Olfactory Pathway** Axons of bipolar olfactory nerves synapse with tufted and mitral cell dendrites in glomeruli of the olfactory bulb (detail, including modulatory interneurons, in *inset diagram*). Mitral cell axons form the olfactory tract, which extends to the anterior commissure (where fibers project back to the contralateral olfactory bulb), and the olfactory trigone, ultimately projecting to the primary olfactory cortex, lateral entorhinal cortex, and amygdala.

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CHAPTER 6 The Somatic Motor System

The motor system consists of two subdivisions, the **somatic motor system** and the **autonomic motor system.** The somatic nervous system controls **voluntary muscle activity** through motor neurons and skeletal muscle. The autonomic nervous system is responsible for the **involuntary muscle activity** involved in visceral organ function and maintenance of the internal environment.

MUSCLE SPINDLES

The somatic motor system, through the actions of skeletal muscle, motor neurons, the spinal cord, and the brain, is responsible for the complex task of controlling movement and posture. This task is accomplished through involuntary spinal reflexes and voluntary muscle activity, and is dependent on coordinated contraction and relaxation of muscle. Most skeletal muscle fibers are the **extrafusal fibers** that are innervated by α-motor neurons and contract to generate force necessary for movement and postural adjustment.

Intrafusal fibers are a second category of muscle fibers found specifically within **muscle spindles;** these spindles are distributed in parallel with extrafusal fibers and function as sensory organs that detect length changes in muscle (Fig. 6.1). The sensitivity of intrafusal fibers is regulated by the γ-motor neurons that innervate them. Muscle spindles are abundant in muscles that control fine movements, for example in the eye. They have important roles in coordinating fine movements, in the return of muscles to their normal resting length, and in proprioception. Intrafusal fibers are further classified as **nuclear bag fibers** and **nuclear chain fibers.** Two types of sensory (afferent) nerves innervate intrafusal fibers:

- **Group Ia** afferent nerves innervate both nuclear bag fibers and nuclear chain fibers and transmit information regarding the rate of change in muscle length (contraction). Group Ia fibers form spiral endings around intrafusal fibers.
- **Group II** afferent nerves mainly innervate nuclear chain fibers and detect the length of muscle fibers; they form spraylike endings on the fibers.

Golgi tendon organs, like muscle spindles, are stretch receptors and are found at the insertion of skeletal muscles to tendons. They are innervated by group Ib afferent nerves. Excessive stretch or contraction of muscle will cause activation of Golgi tendon organs and their afferent nerves, producing a reflexive relaxation of the muscle. Golgi tendon organs are also important in proprioception; their role in this process, along with the role of muscle spindles and other receptors, is illustrated in Figures 6.2 and 6.3.

SPINAL REFLEXES

Stereotypic motor responses to sensory signals integrated completely within the spinal cord are called **spinal reflexes.** These are the simplest motor responses, but they may be modified by the central nervous system (CNS) during more complex motor activity. The **reflex arc** of a spinal reflex begins with stimulation of sensory receptors; the signal is carried to the spinal cord through sensory afferent nerves, is integrated within the spinal cord, is conducted to the muscle through motor neurons, and finally produces contraction or relaxation. There are three basic types of spinal cord reflexes (Fig. 6.4):

- The **stretch reflex** is the most basic, in which sensory afferent nerves synapse directly with α-motor neurons in the spinal cord. Stretch reflexes are therefore referred to as **monosynaptic reflexes**. In the **knee jerk reflex,** a type of stretch reflex, a tap on the patellar tendon of the knee stretches muscle spindles within the quadriceps muscle. This initiates the reflex arc, in which type Ia afferent nerves depolarize and conduct the signal to the spinal cord, where they synapse directly with α-motor neurons. The α-motor neurons conduct the signal back to the quadriceps, producing contraction (the "knee jerk" response). Simultaneously, activation of interneurons results in relaxation of opposing muscles (see Fig. 6.4*A*).
- The **Golgi tendon reflex** (also known as the **inverse myotactic reflex**), is a **bisynaptic reflex.** It is a mechanism for prevention of muscle damage when muscle tension is excessive. Stretch of Golgi tendon organs activates type Ib afferent sensory nerves that synapse in the spinal cord with interneurons that subsequently inhibit α-motor neurons to the muscle, causing relaxation. The reflex also causes antagonistic muscles to contract, coordinating the response (see Fig. 6.4*B*).

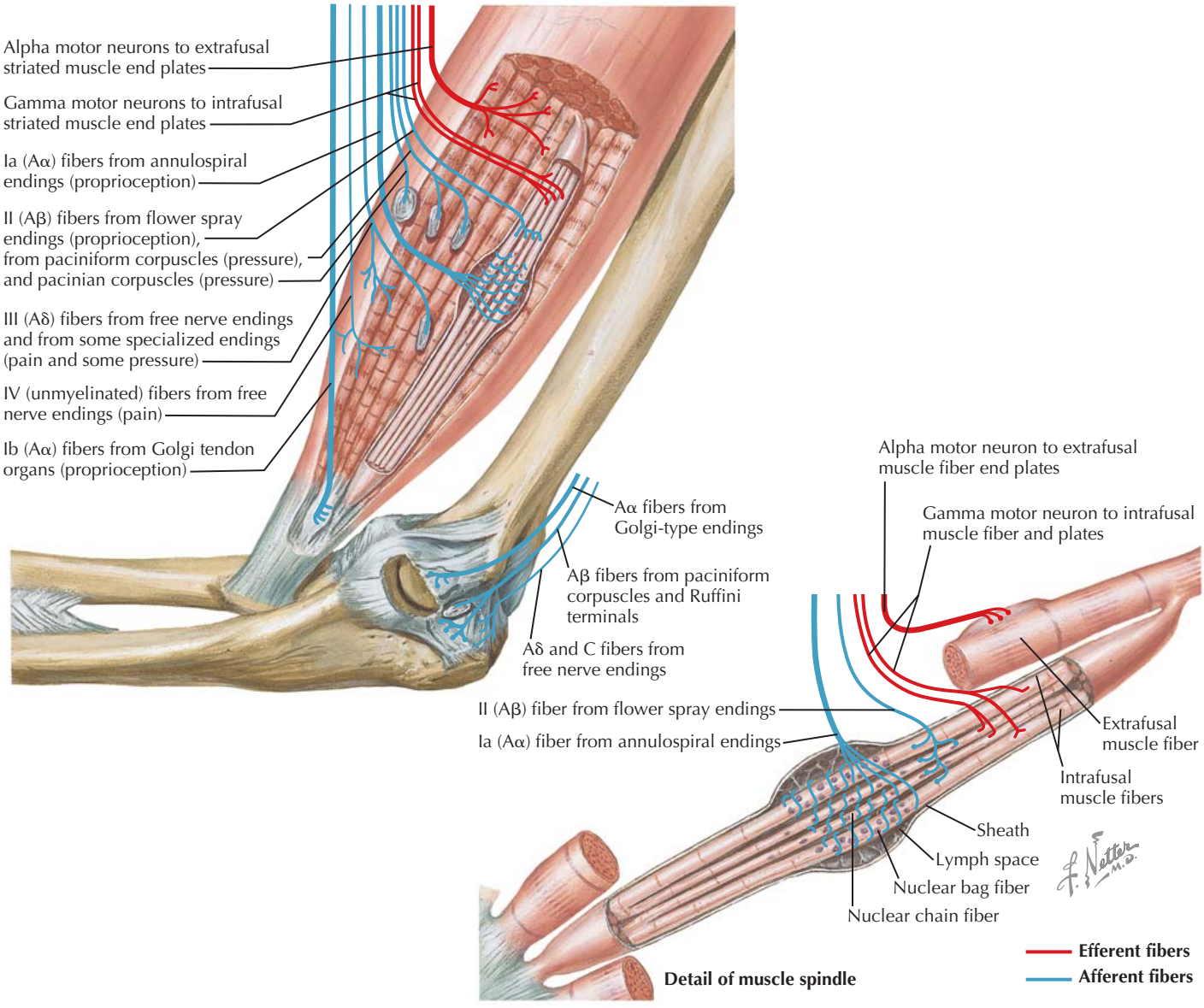


Figure 6.1 Muscle and Joint Receptors Muscle spindles are specialized sensory receptors composed of intrafusal fibers of two types, the nuclear chain fiber and the nuclear bag fiber. They function in coordinating fine movements, returning muscles to normal resting length, and proprioception. Intrafusal fibers are innervated by γ-motor neurons that regulate their sensitivity. Information about rate of change in muscle length is conveyed by group Ia afferent sensory nerves innervating both nuclear chain fibers and nuclear bag fibers. These group Ia nerves form spiral endings around intrafusal fibers. Group II sensory afferent nerves convey information on the length of muscle. Golgi tendon organs are located at the insertion of skeletal muscles of tendons; when stretched, they produce a reflexive relaxation of the skeletal muscle. A number of other joint receptors are also illustrated.

- The **Flexor withdrawal reflex** occurs in response to painful or otherwise noxious stimuli. When cutaneous pain receptors are stimulated, for example by touching a hot object, afferent signals are conducted through sensory nerve fibers to the spinal cord, where activation of multiple interneurons produces simultaneous flexion and relaxation of the appropriate muscles to withdraw the limb. This is a **polysynaptic reflex** (see Fig. 6.4*C*).

ROLE OF HIGHER CENTERS IN MOTOR CONTROL

CNS areas involved in motor system control of balance, posture, and movement include the spinal cord, brainstem, cerebellum, basal ganglia, and cerebral motor cortex. For many types of voluntary movement, lower centers regulate patterns of skeletal muscle activity when they are activated by the motor cortex. In the case of fine motor movements, par-

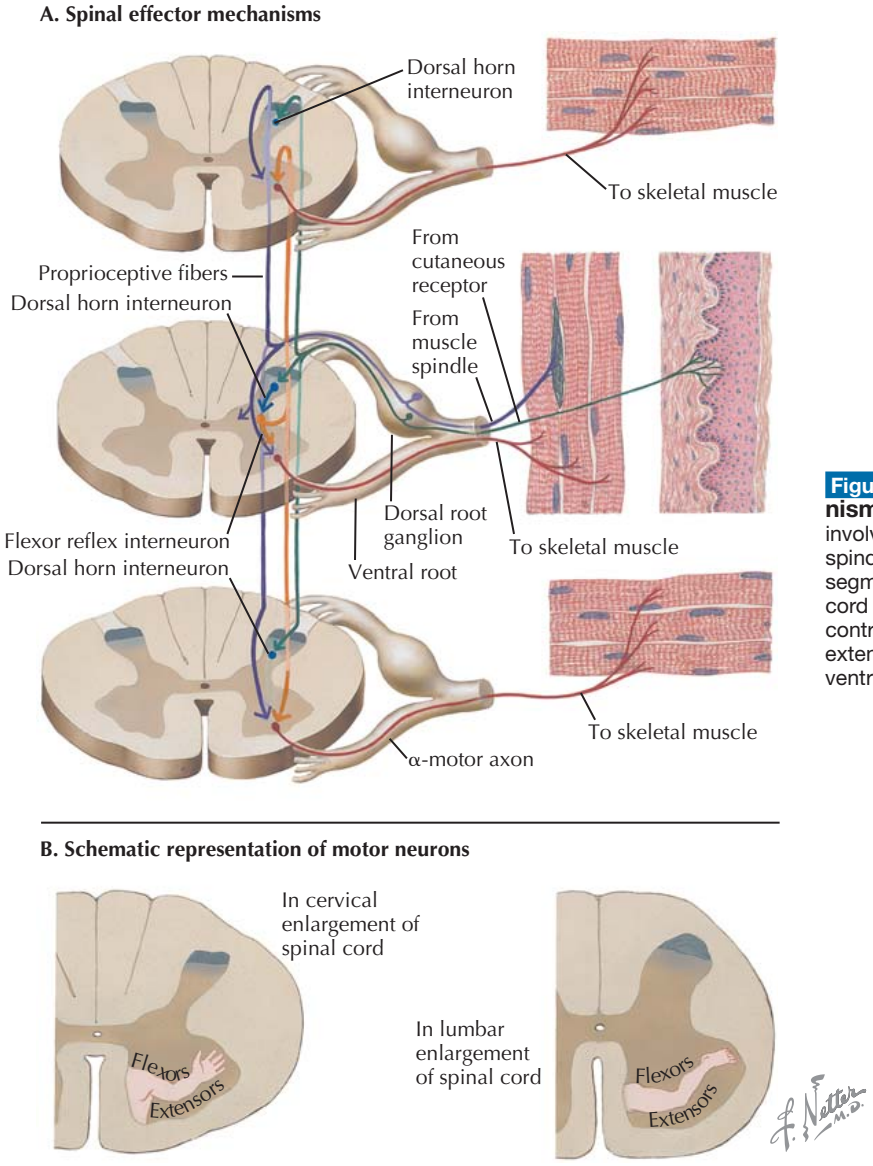


Figure 6.2 Proprioception: Spinal Effector Mechanisms *A*, Spinal effector mechanisms for proprioception involve afferent input from cutaneous receptors and muscle spindles. Monosynaptic reflex pathways at one spinal cord segment and polysynaptic reflex pathways at multiple spinal cord segments activate α-motor neurons, producing muscle contraction. *B*, Motor neuron cell bodies producing flexion and extension of limb muscles are distributed somatopically in the ventral horn.

ticularly of the distal muscles of the limbs (for example, in the fingers and hands), the cerebral cortex regulates muscle activity more directly.

Corticospinal Tract

The **corticospinal tract,** also known as the **pyramidal tract** (because it passes through the medullary pyramids), is the most important descending pathway for control of fine motor activity originating in the cortex (Fig. 6.5). Nerve fibers in this tract originate in the **primary motor cortex,** as well as in the adjacent **premotor** and **supplementary motor areas** and somatosensory areas posterior to the motor cortex. Most of the fibers cross in the lower medulla to form the **lateral corticospinal tract;** others descend through the **anterior corticospinal tract.** At various levels of the spinal cord, some fibers from these tracts synapse directly with second order motor neurons (anterior horn cells). Secondary motor neurons innervated by axons of the lateral corticospinal tract are mainly those controlling distal limb muscles, whereas those innervated by the anterior corticospinal tract are mainly those controlling axial muscles. The **motor homunculus** is a graphic representation of the location and approximate relative size of areas of the motor cortex controlling motor activity of various regions of the body (see Fig. 6.5).

Brainstem

The brainstem (medulla, pons, and mesencephalon) has an important role in the motor system, especially in the control of balance and posture:

- **Pontine reticular nuclei** send projections through the **pontine reticulospinal tract** of the anterior column of

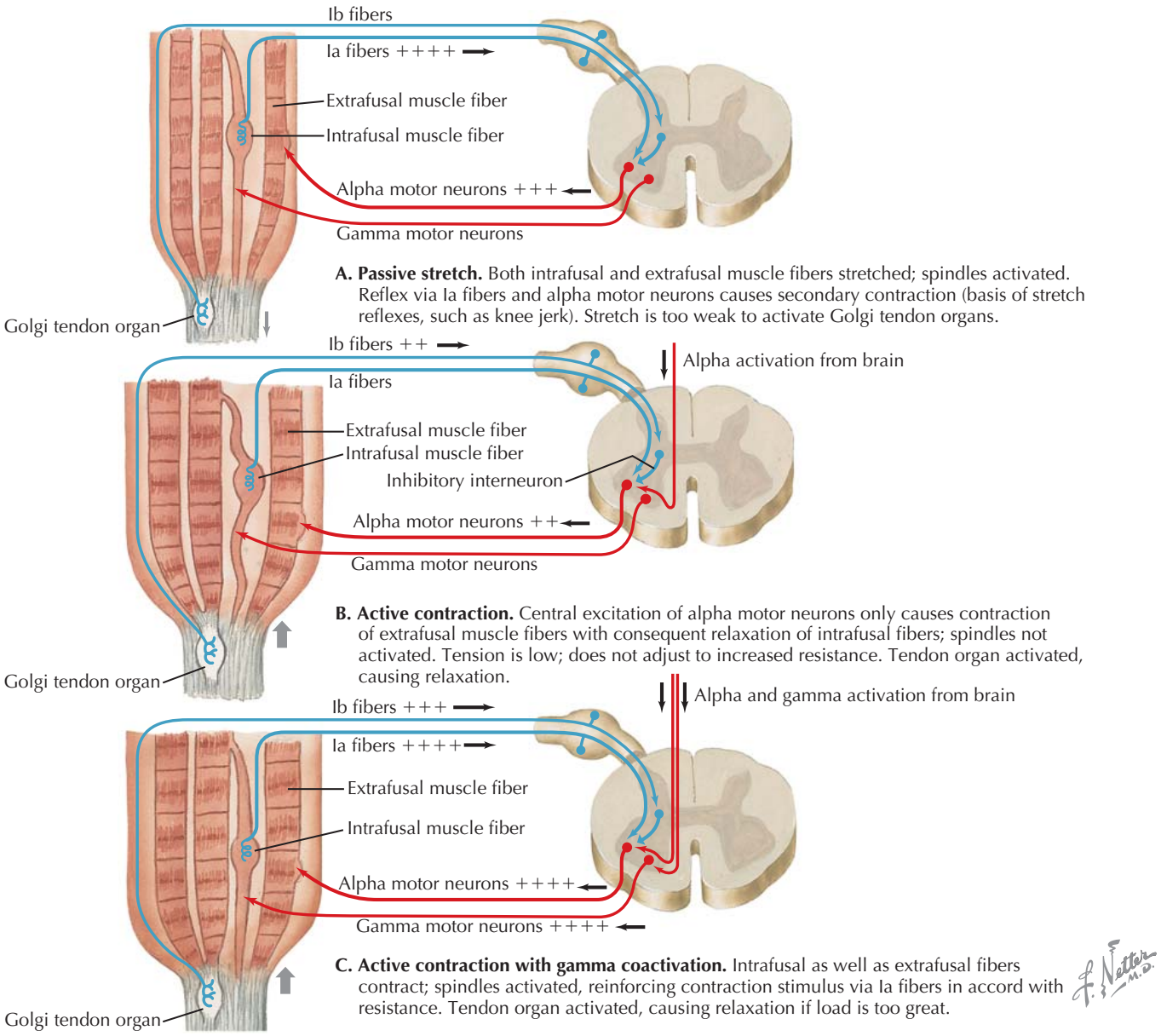


Figure 6.3 Proprioceptive Reflex Control of Muscle Tension *A*, During passive stretch of skeletal muscle, both intrafusal (as well as extrafusal) fibers are stretched, producing reflex contraction via Ia fibers and α-motor neurons, for example, during a knee jerk reflex. *B* and *C*, Reflex control of skeletal muscle tension in response to active contraction varies depending on state of activation of γ-motor neurons (and its effects on muscle spindles) and degree of stretch of Golgi tendon organs.

the spinal cord, with excitatory synapses on motor neurons innervating axial muscles involved in posture and support of the body against gravity.

- **Medullary reticular nuclei,** through projections descending in the **medullary reticulospinal tract** of the lateral column of the spinal cord, inhibit motor neurons that innervate axial muscles.
- **Vestibular nuclei** on the floor of the fourth ventricle have projections that descend by way of the anterior columns of the spinal cord in the **lateral** and **medial vestibulospinal tracts.** These nuclei receive input from the vestibular apparatus and have an important role in controlling muscles to maintain equilibrium, working in conjunction with the pontine reticular nuclei to regulate axial muscles.
- The **superior colliculus** of the mesencephalon receives input from visual nuclei; through the **tectospinal tract,** it is involved in control of head, neck, and eye muscles.
- The **red nucleus** of the mesencephalon receives input from the motor cortex. It sends projections in the **rubrospinal tract** through the lateral columns of the spinal

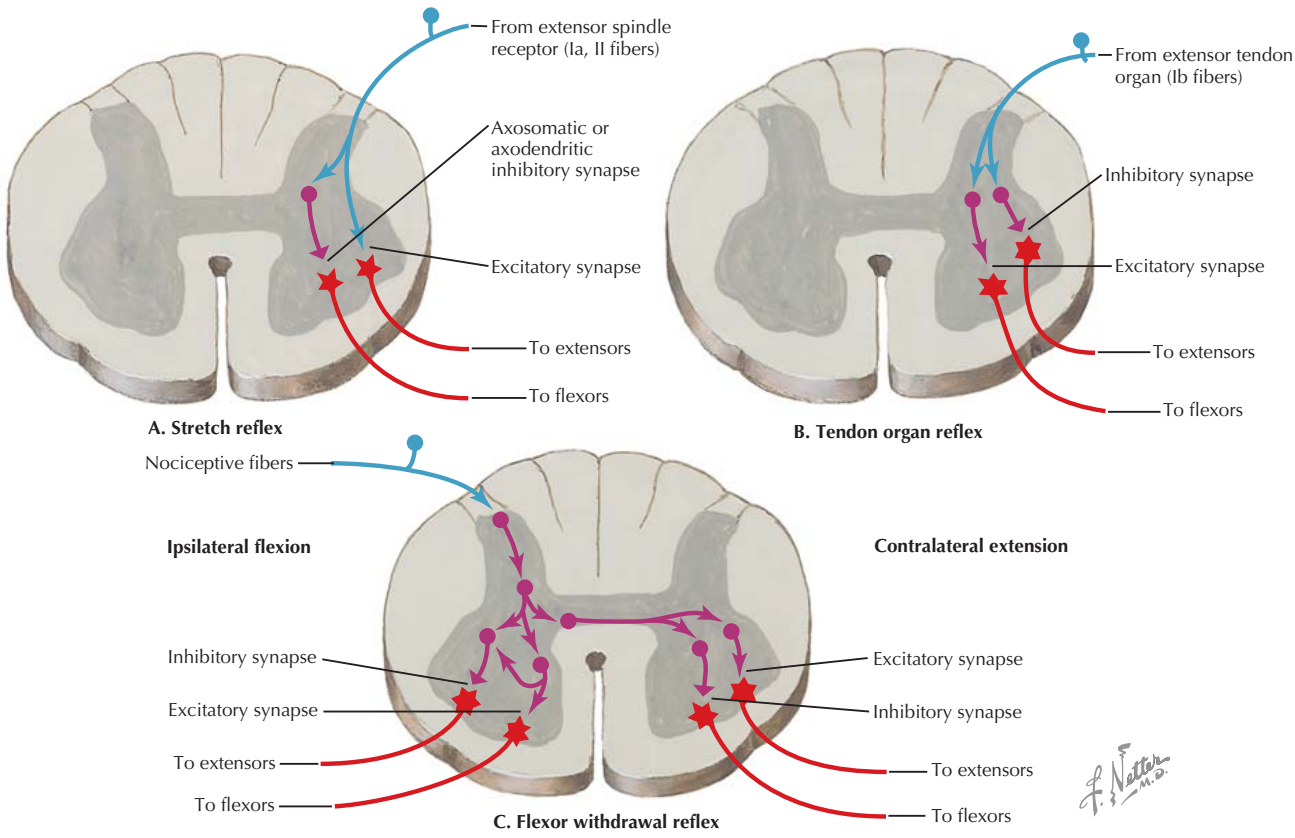


Figure 6.4 Spinal Reflex Pathways for Stretch, Tendon Organ, and Flexor Withdrawal Reflexes Reflexes elicited by stretch of muscle spindle receptor *(A)* or Golgi tendon organs *(B)* associated with an extensor muscle are illustrated. Opposite effects on flexors and extensors occur for reflexes initiated by stretch of a flexor muscle or tendon organ. In the flexor withdrawal reflex, nociceptive stimuli produce ipsilateral flexion and contralateral extension through the pathways illustrated *(C)*.

cord and is involved in voluntary control of large muscles, particularly in the limbs. It can be considered in some ways as an alternative pathway to the corticospinal tract for controlling voluntary muscle movement. This is ordinarily a relatively minor pathway in humans, compared with other mammals, but may gradually assume an expanded role when the corticospinal tract is injured.

Cerebellum

The **cerebellum** ("little brain" in Latin) has an important accessory role to the motor cortex, in coordination and control of posture, balance and movement, and in planning and initiation of motion. These effects are accomplished through the activity of its three lobes (Fig. 6.6):

- The **archicerebellum** (also known as the vestibulocerebellum) is involved in the regulation of posture and balance, and in control of eye and head movement. It receives afferent signals from the vestibular apparatus and sends efferent signals through the relevant descending efferent pathways (Fig. 6.7).
- The **paleocerebellum** (also called the **spinocerebellum**) has an important role in the regulation of proximal limb movement. Afferent sensory signals regarding the position and movement of limbs are utilized to "fine-tune" limb motion through the relevant descending pathways (see Fig. 6.7).
- The **neocerebellum** (also known as the **pontocerebellum**) has a coordinating role in the regulation of distal limb movement, based on input from the cerebral cortex (via the pontine nuclei). It aids in the planning and initiation of motor activity through its efferent fibers (see Fig. 6.7).

Alternatively, the lobes of the cerebellum can be conceptualized as anterior, middle, and flocculonodular lobes (see Fig. 6.6).

The cerebellum's role in muscle control involves coordination and fine-tuning of motion. Deficits in cerebellar function are expressed as deficiency in fine motor activity, coordination, and equilibrium.

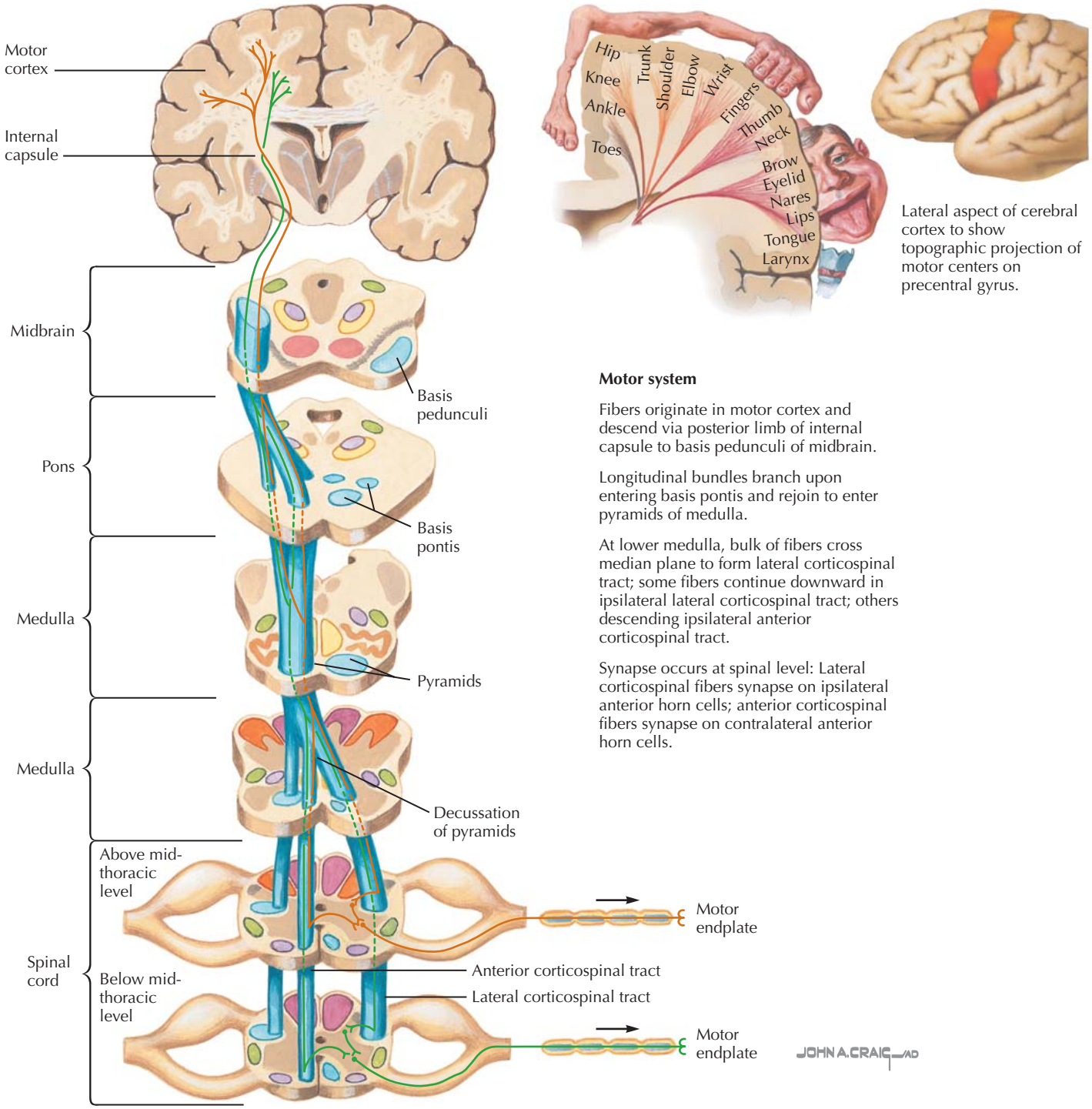


Figure 6.5 Corticospinal Tract The corticospinal tract, also called the pyramidal tract, is the major descending pathway in voluntary motor activity and is particularly important in fine motor activity. The motor homunculus *(top center panel)* illustrates the location and approximate relative size of areas in the motor cortex controlling muscle activity in various regions of the body.

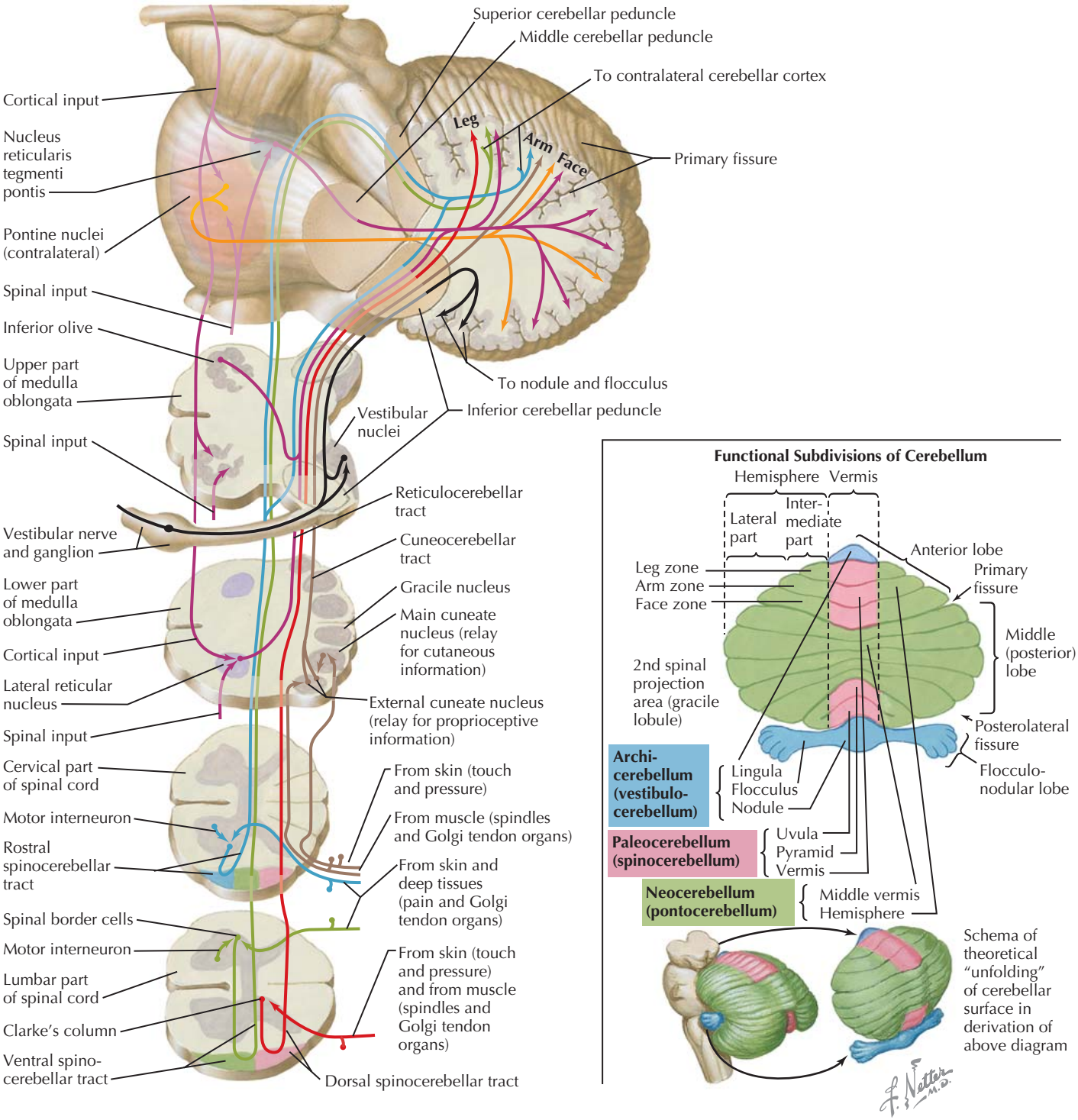


Figure 6.6 **Cerebellar Afferent Pathways and Functional Subdivisions of Cerebellum** The cerebellum acts as an accessory to the motor cortex in regulation of posture, balance, movement, and planning and initiation of motion, based on afferent sensory signals and cortical input. Specific functions ascribed to subdivisions of the cerebellum are illustrated in the right panel or discussed in the text.

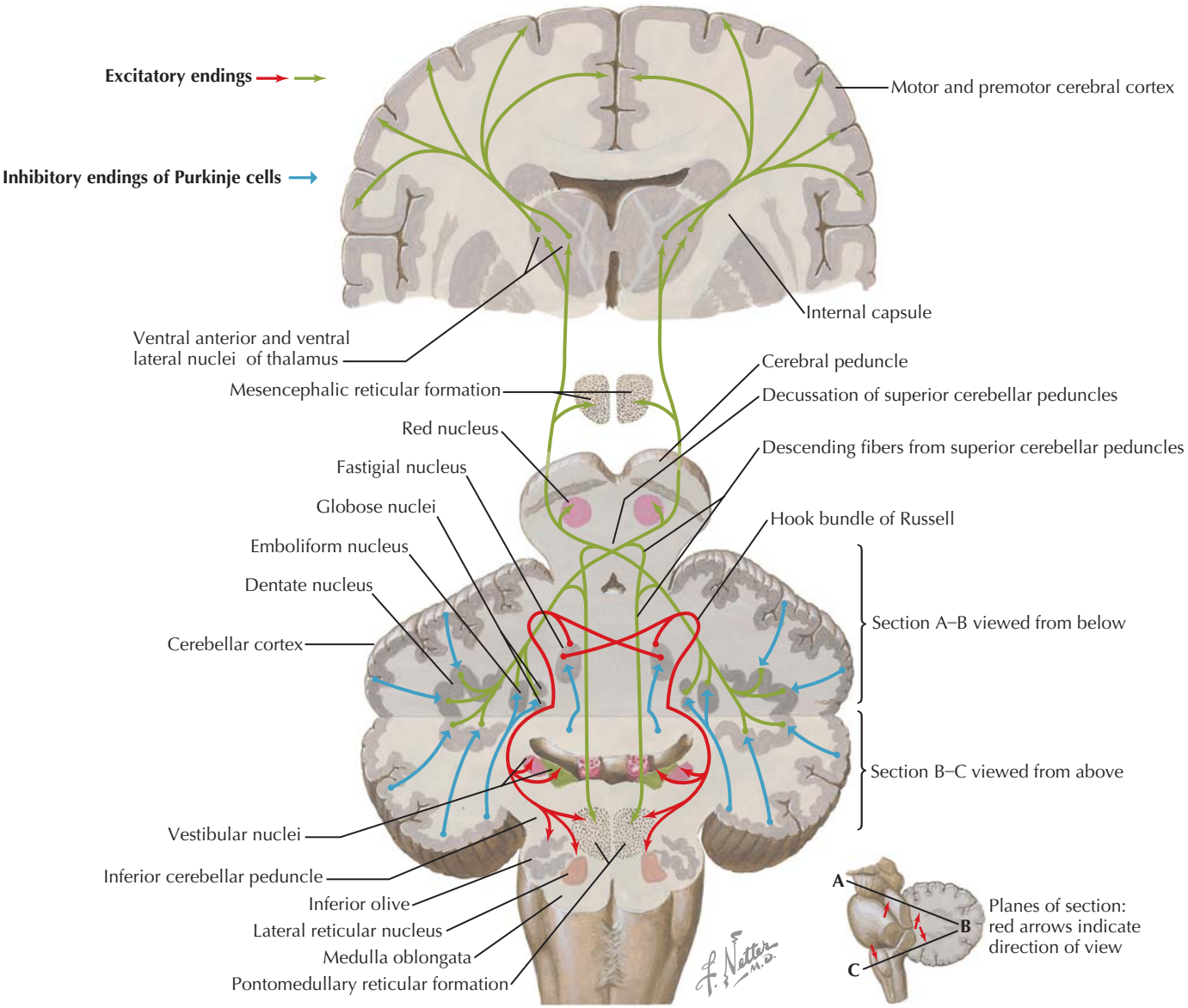


Figure 6.7 Cerebellar Efferent Pathways The cerebellar efferent pathways originate from its deep nuclei, which receive inhibitory input from Purkinje cells of the cerebellar cortex. Axons project from the deep fastigial, globose, emboliform, and dentate nuclei to various nuclei in the brainstem, midbrain, and thalamus, and modulate activity of descending motor pathways, resulting in coordination and fine-tuning of motion.

Cerebellar Cortex

All efferent signals of the cerebellar cortex are inhibitory and emanate from **Purkinje cells** residing in the middle of three layers of the cortex. Signals from Purkinje cells are conducted to deep cerebellar nuclei (see Fig. 6.7). The three layers of the cortex contain various cell types that, through complex interactions between each other and with fibers projecting from other sites, regulate the inhibitory efferent output of Purkinje cells (Fig. 6.8):

- The inner **granular layer,** containing **granule cells, Golgi cells,** and **glomeruli**. Granule cells within this layer are the most numerous type of neuron in the CNS. The glomeruli are the sites of synapses between axons of **mossy fibers** from the spinocerebellar, vestibulocerebellar, and pontocerebellar tracts with the dendrites of the granule and Golgi cells. Granule cells, which receive excitatory input from the mossy fibers, send axons through the Purkinje cell layer to the outer molecular layer (discussed later). They provide excitatory signals to Purkinje cell dendrites and dendrites of cells of the molecular layer. Golgi cells are inhibitory interneurons that inhibit the granule cells' effects on Purkinje cells.

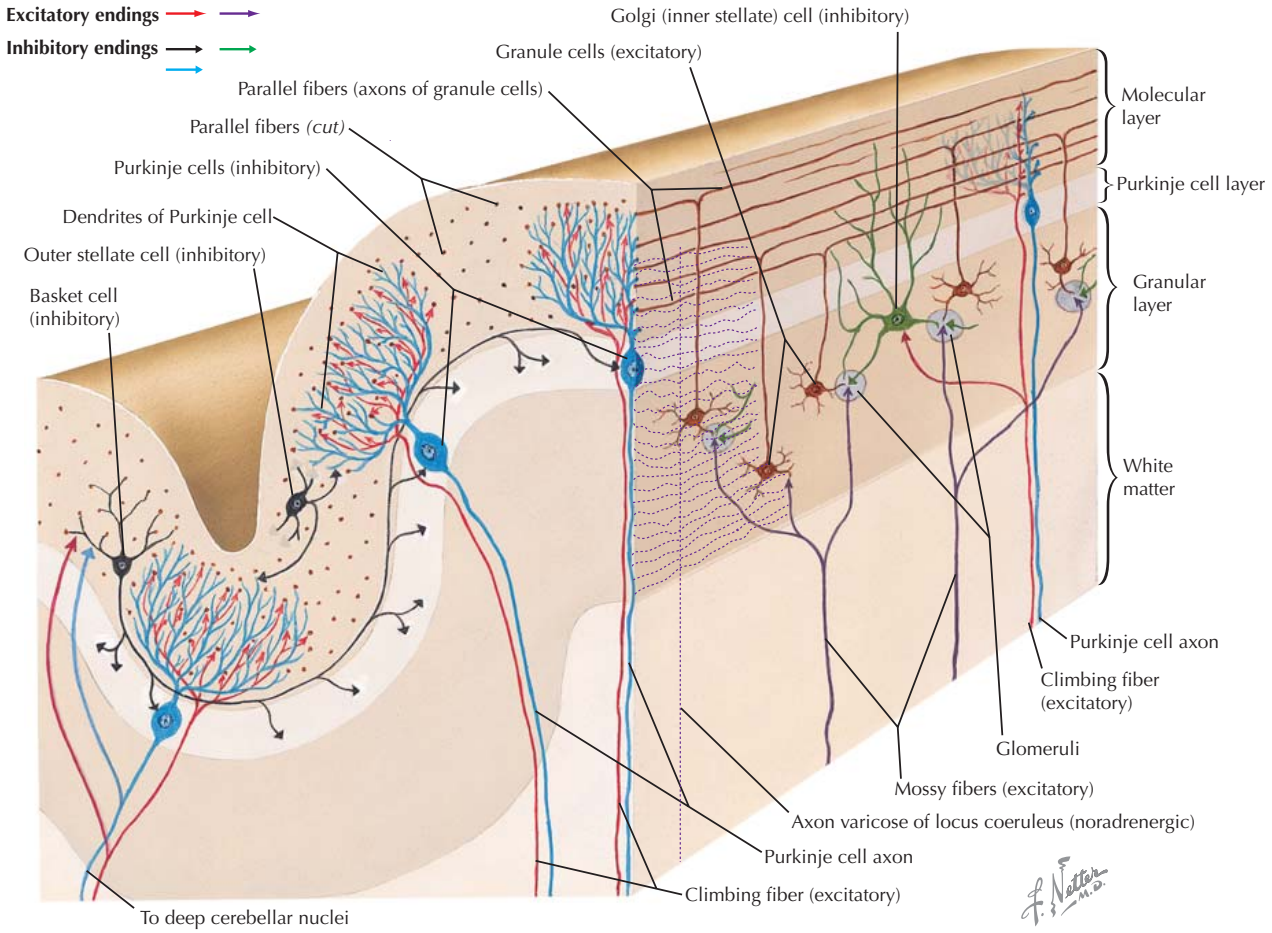


Figure 6.8 Cerebellar Neuronal Circuitry The cerebellar cortex is composed of three layers. All output of the cortex is carried by inhibitory axons of the Purkinje cells. Their cell bodies are located in the Purkinje cell layer, and their dendritic arbors are in the outer molecular layer. The cortex receives input through climbing fibers, which project from the medullary inferior olive, and mossy fibers, which project from the spinocerebellar, vestibulocerebellar, and pontocerebellar tracts. Mossy fibers form excitatory synapses with dendrites of granule cells in the granular layer. The excitatory axons of granule cells reach the molecular layer, where they form parallel fibers that course through and synapse with dendritic arbors of many Purkinje cells. Climbing fibers form excitatory synapses directly with dendrites of Purkinje cells in the molecular layer. Various other interneurons and their actions are illustrated above and discussed in the text.

- The middle **Purkinje cell layer.** Purkinje cells are GABA-ergic (utilize the neurotransmitter gamma amino butyric acid) and are the only efferent output of the cerebellar cortex. They receive input from various axons in the molecular layer and send inhibitory signals to the deep cerebellar nuclei and lateral vestibular nuclei.
- The outer **molecular layer,** which contains **basket cells** and **stellate cells,** and the dendritic arbors of Purkinje cells (extending from the Purkinje cell layer). **Parallel fibers,** containing axons from the granule cells of the granular cell layer, form excitatory synapses with dendrites of Purkinje, basket, and stellate cells. Basket cells and stellate cells are interneurons that inhibit Purkinje cells through the parallel fibers. **Climbing fibers,** projecting from the medullary inferior olive, form excitatory synapses with dendrites of Purkinje cells.

Thus, the inhibitory cerebellar cortical output of the Purkinje cells is regulated by excitatory input from climbing fibers and mossy fibers (via the granule cells) and inhibitory input from various interneurons of the cortex.

Purkinje cells in the cerebellar cortex are stimulated by granule cells and climbing fibers; their activity is modulated by various cerebellar interneurons. When stimulated, Purkinje cells release the inhibitory neurotransmitter GABA at synapses within deep cerebellar nuclei, regulating motion and posture.

Basal Ganglia

The **basal ganglia** are deep nuclei of the cerebral hemispheres, and like the cerebellum, have an accessory role to the motor cortex, regulating motor activity to produce smooth movement and maintain posture. They consist of the:

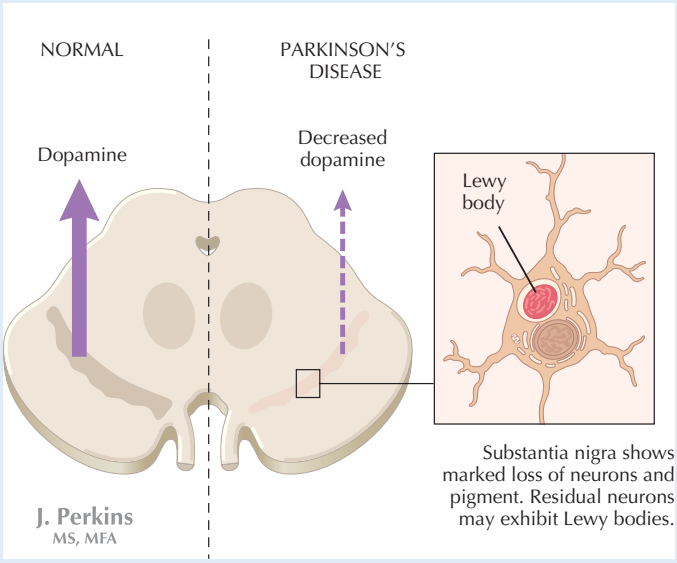
- **caudate nucleus**
- **putamen**
- **globus pallidus**

The caudate nucleus and putamen are referred to as the **striatum,** based on their striated appearance. The **substantia nigra** of the midbrain and **subthalamic nucleus** of the diencephalon are functionally associated with, and sometimes classified as, components of the basal ganglia.

The input to the basal ganglia is from the motor cortex; the output to the cortex is through the thalamus. A complex series of interactions between components of the basal ganglia and associated structures leads to this output, which then regulates the level of excitation in the motor cortex. These interactions form an **indirect pathway** that inhibits cortical excitation and a **direct pathway** that is excitatory. The balance of these opposing pathways is responsible for coordinating smooth movement and maintenance of posture.

CLINICAL CORRELATE
Parkinson's Disease

Diseases of the basal ganglia produce a variety of deficits in motor activity and control of posture. Parkinson's disease is a progressive neurodegenerative disorder characterized by tremor of the hands and arms, rigidity, shuffling gait, and bradykinesia (slow movement). This disorder is caused by loss of dopaminergic cells of the substantia nigra normally projecting to the striatum (caudate nucleus and putamen), affecting both the direct and indirect pathways of the basal ganglia. L-dopa, a dopamine precursor, is effective in treating some but not all Parkinsonian patients.



The Substantia Nigra in Parkinson's Disease Dopamine production by the substantia nigra is reduced in Parkinson's disease as a result of degeneration of dopaminergic neurons. Lewy bodies are observed in the remaining neurons of the substantia nigra of some Parkinson's disease patients. These inclusions are caused by cellular accumulation of the protein alpha-synuclein.

CHAPTER 7
The Autonomic Nervous System

Knowledge of the role of the autonomic nervous system is critical for understanding the function of any of the major organ systems. It is the primary mechanism for the involuntary control and coordinated activity of smooth muscle of visceral organs, cardiac muscle, and glands and is essential for most homeostatic processes. Within the brain, sensory information is integrated and activity of the autonomic nervous system is modulated to orchestrate this involuntary control of physiological processes.



The fight-or-flight response was originally described in 1915 by Walter Canon, who also invented the term "homeostasis." The fight-or-flight response can be characterized as the physiological response to acute stress, in which generalized sympathetic activation occurs, resulting in effects such as tachycardia, bronchial dilation, mydriasis (dilation of the pupils), vasoconstriction in much of the body, piloerection, and inhibition of gastrointestinal motility. It has long been appreciated that the acute stress responses also involves activation of the hypothalamic-pituitary-adrenocortical endocrine axis (Section 7).

ORGANIZATION AND GENERAL FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM

The two divisions of the autonomic nervous system are the **sympathetic nervous system (SNS)** and the **parasympathetic nervous system (PNS)** (the enteric nervous system of the gastrointestinal tract is sometimes considered part of the autonomic nervous system as well; it is discussed in Chapter 21). In many cases, the SNS and PNS have opposing actions on various organs and processes, and regulation of bodily functions often involves reciprocal actions of the two divisions. For example, heart rate is elevated by SNS activity and decreased by PNS activity.

As a generalization, the SNS is said to mediate **stress responses,** such as the classic *fight-or-flight* response, and the PNS mediates "vegetative" responses, such as digestion. The fight-or-flight response is a generalized reaction to extreme fear, stress, or physical activity and results in a patterned response in many organ systems. The response includes elevated heart rate, cardiac output, and blood pressure, as well as bronchial dilation, mydriasis (dilation of pupils), and sweating. Although the sympathetic nervous system often responds in such patterned manners, the parasympathetic may produce more selective effects, for example during the sexual response.

The autonomic nervous system has as its central components the hypothalamus, the brainstem, and the spinal cord; peripherally, it consists of sympathetic and parasympathetic nerves. Areas within the hypothalamus and brainstem regulate and coordinate various processes through the autonomic nervous system, including, for example, temperature regulation, responses to thirst and hunger, micturition, respiration, and cardiovascular function. This regulation is in response to sensory input and occurs through the reciprocal regulation of the SNS and PNS.

Peripherally, axons of **preganglionic neurons** of the SNS and the PNS emerge from the spinal cord and synapse with **postganglionic neurons** at sympathetic and parasympathetic ganglia, respectively, where in both cases, **acetylcholine** is the neurotransmitter, acting at **nicotinic receptors** on postganglionic neurons (Fig. 7.1). Postganglionic neurons then send motor axons to effector organs and tissues. The catecholamine **norepinephrine** is released by postganglionic sympathetic axons and acts at **adrenergic receptors** of effector organs. One exception is the postganglionic axons innervating sweat glands, which release acetylcholine. Furthermore, the adrenal medulla functions as part of the SNS. Preganglionic axons of the SNS extend to the adrenal gland, where they stimulate chromaffin cells of the adrenal medulla to release **epinephrine** (and to a lesser degree norepinephrine) into the bloodstream. Notably, in addition to the catecholamines (norepinephrine and epinephrine), a number of adrenergic **cotransmitters** are released by some sympathetic postganglionic nerves, including **neuropeptide Y, ATP** (adenosine triphosphate), and **substance P,** among others. In the PNS, acetylcholine, acting at **muscarinic receptors,** is the postganglionic neurotransmitter. These and other aspects of the two divisions of the autonomic nervous system are compared in Table 7.1 and illustrated in Figures 7.2 and 7.3. Actions of the autonomic nervous system in various organ systems and tissues are listed in Table 7.2, along with the receptor types involved.

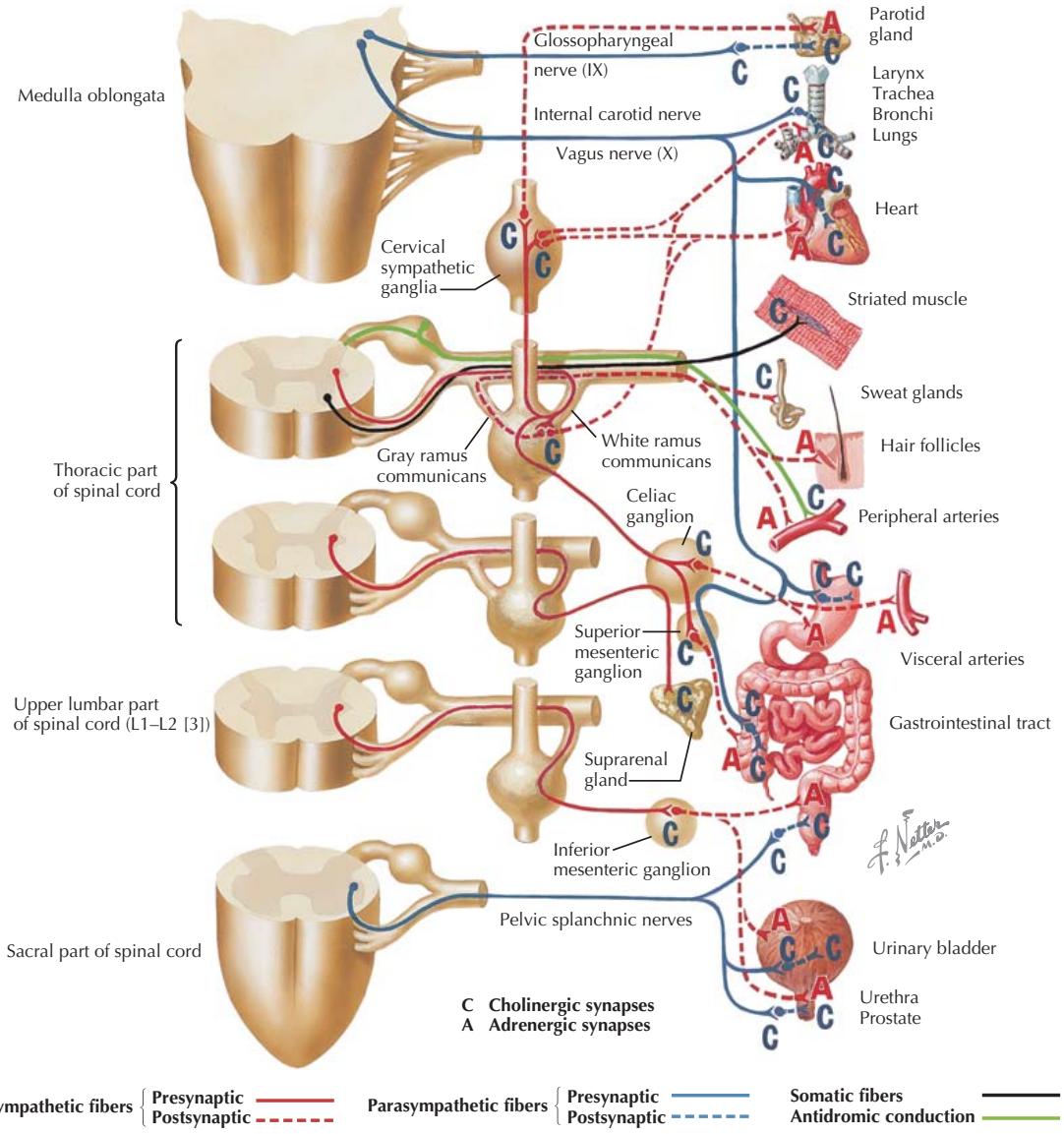


Figure 7.1 **Cholinergic and Adrenergic Synapses: Schema** Preganglionic neurons of the autonomic nervous system emerge from the spinal cord and synapse at autonomic ganglia. For both parasympathetic and sympathetic divisions, acetylcholine is the ganglionic neurotransmitter. Postganglionic fibers from parasympathetic ganglia release acetylcholine, which binds to muscarinic receptors at the effector organs. Sympathetic postganglionic axons release mainly norepinephrine, although acetylcholine is released at sweat glands. The adrenal gland (not illustrated) functions as part of the SNS. Chromaffin cells of the adrenal medulla act as postganglionic cells of the SNS, releasing epinephrine (and to some extent, norepinephrine) directly into the blood stream. Sympathetic postganglionic nerves, in addition to releasing catecholamines (norepinephrine and epinephrine), release several cotransmitters, including neuropeptide Y, ATP, and substance P.

Table 7.1 **General Characteristics of the Parasympathetic and Sympathetic Nervous Systems**

Characteristic	Parasympathetic Nervous System	Sympathetic Nervous System
Location of preganglionic nerve cell bodies	Brainstem (nuclei of cranial nerves II, VII, IX, and X) or sacral spinal cord (S2–S4; sacral parasympathetic nucleus)	Intermediolateral and intermediomedial cell columns of the thoracolumbar spinal cord (T1–L3)
Location of ganglia	In or adjacent to target organs	Paravertebral and prevertebral
Neurotransmitter of preganglionic neurons	Acetylcholine (acts at nicotinic receptors)	Acetylcholine (acts at nicotinic receptors)
Major neurotransmitter released by postganglionic neuron	Acetylcholine (acts at muscarinic receptors)	Norepinephrine (acts at α and β adrenergic receptors)

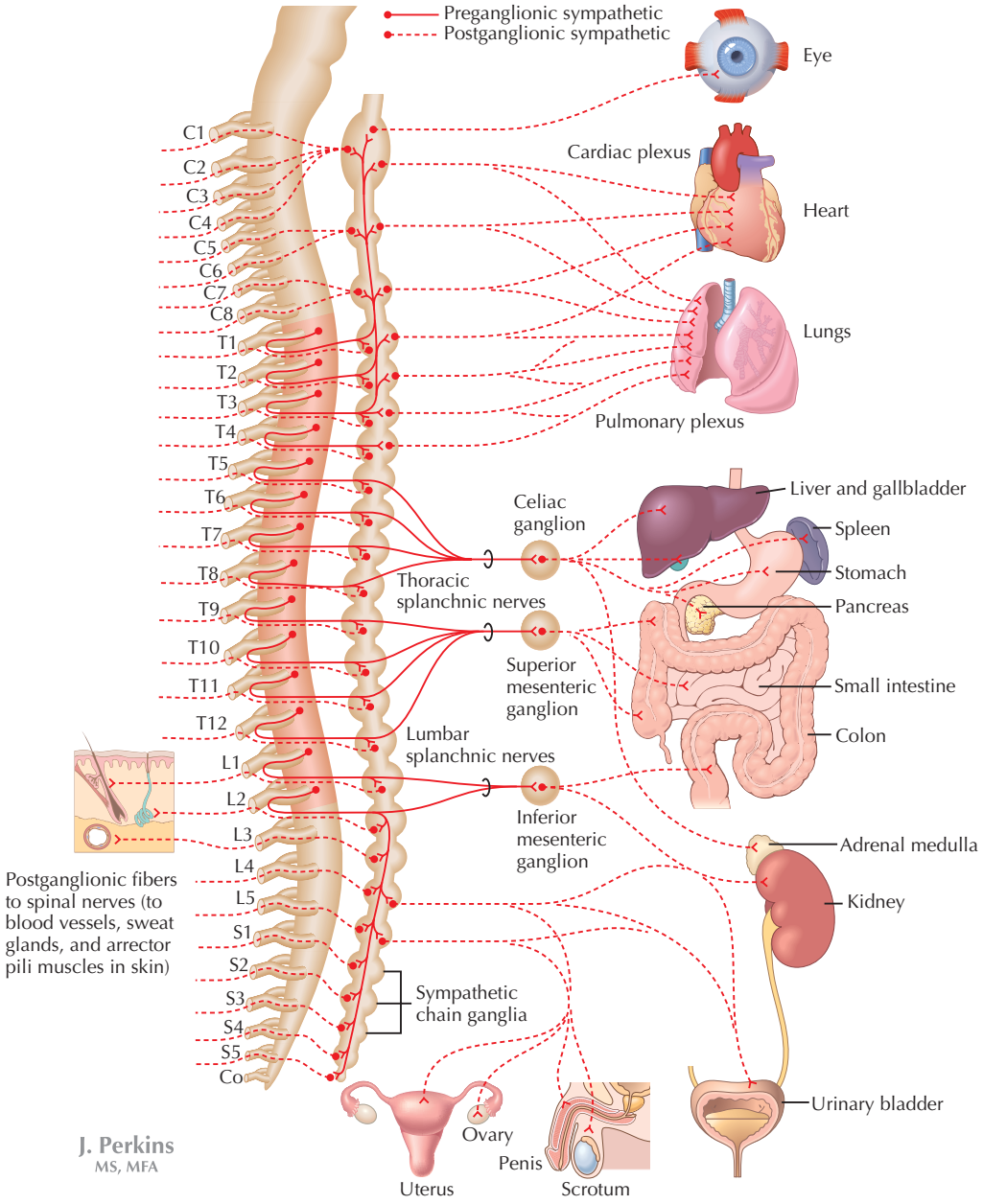


Figure 7.2 **Autonomic Nervous System: Sympathetic Division** The two divisions of the autonomic nervous system are the sympathetic nervous system and the parasympathetic nervous system. Preganglionic fibers of the SNS emerge from the spinal cord at levels T1–T2. The SNS is involved in "fight-or-flight" responses, as well as responses to exercise, hemorrhage, and other challenges to homeostasis. Both SNS and PNS innervate smooth and cardiac muscle and glands; in general, they work together in reciprocal fashion to regulate bodily function.

Sweat gland secretion is stimulated by activation of the sympathetic nervous system. Most of the postganglionic sympathetic neurons innervating these glands are atypical, releasing the neurotransmitter acetylcholine instead of norepinephrine. Acetylcholine acts on muscarinic receptors, inducing sweat secretion. However, in some specific areas, such as the palms of the hands, adrenergic nerves stimulate sweat glands through the release of norepinephrine, which acts at α_1 receptors to stimulate secretion.

AUTONOMIC RECEPTORS

Autonomic receptors are coupled to specific G proteins within the cell membrane and produce their effects through various signal transduction systems in the effector cells. Acetylcholine receptors are classified as nicotinic or cholinergic, based on their pharmacology. Nicotinic receptors are activated by the drug **nicotine** and are blocked by **curare,** the active agent in South American dart poison. Muscarinic receptors, on the other hand, are activated by the mushroom toxin **muscarine**

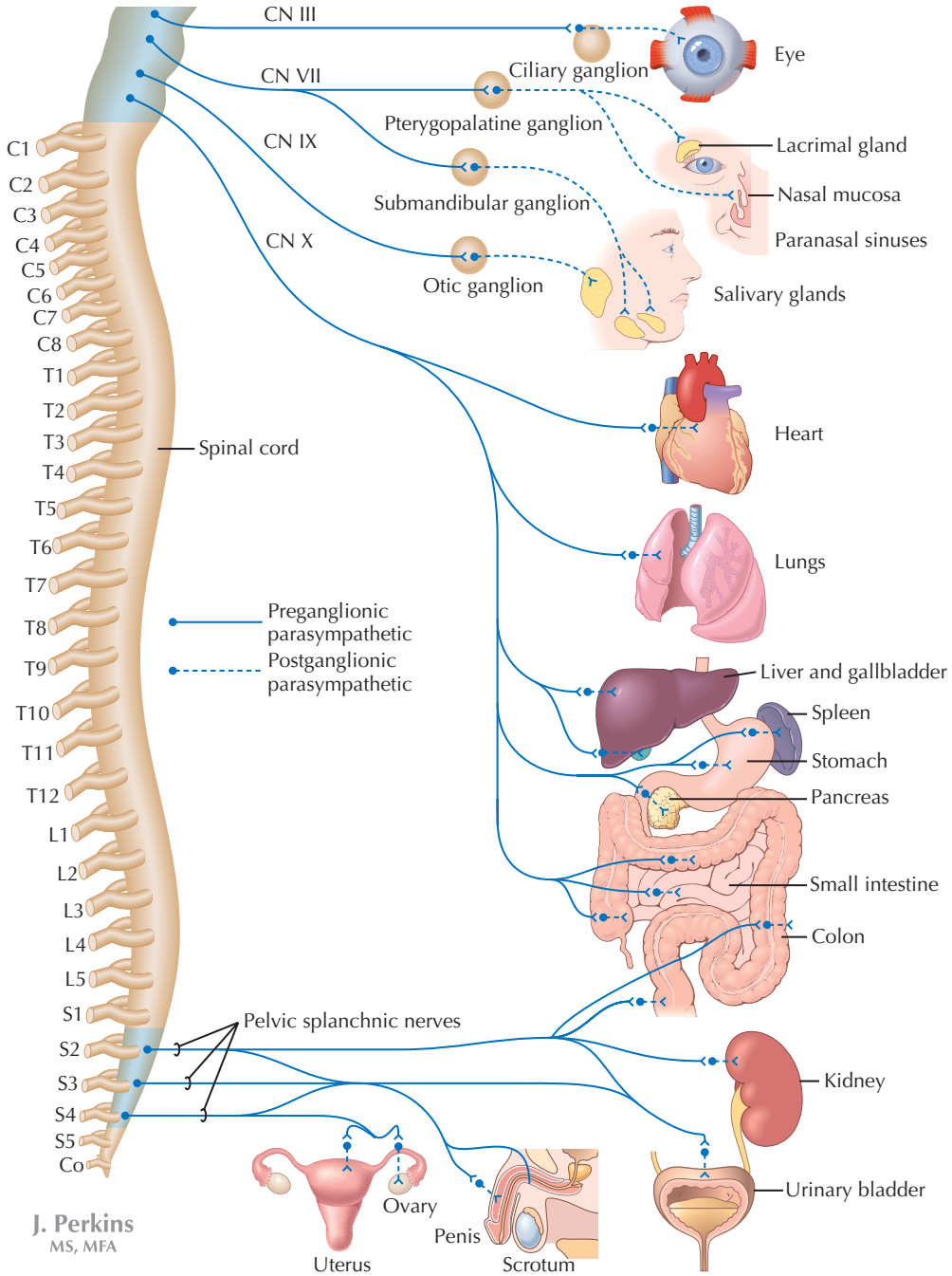


Figure 7.3 Autonomic Nervous System: Parasympathetic Division Preganglionic fibers of the PNS are associated with cranial nerves III, VII, IX, and X and also emerge from the sacral spinal cord at levels S2–S4. The PNS is involved in "vegetative" processes such as digestion as well as homeostatic functions. In general, the SNS and PNS work together in reciprocal fashion to regulate bodily function.

Table 7.2 Actions of the Autonomic Nervous System

	PARASYMPATHETIC NERVOUS SYSTEM		SYMPATHETIC NERVOUS SYSTEM	
Site of Action	**Action**	**Receptor type**	**Action**	**Receptor type**
Cardiac pacemaker	Decreases heart rate	Muscarinic	Increases heart rate	β_1
Cardiac muscle	Decreases contractility of atria; limited effects on ventricles	Muscarinic	Increased contractility	β_1
Cardiac AV node	Decreases conduction velocity	Muscarinic	Increased conduction velocity	β_1
Vascular smooth muscle	Indirect vasodilation (genital organs and lower GI tract only) by nitric oxide released from endothelium	Muscarinic	Constriction (predominant effect in most vascular beds) Vasodilation	α_1 β_2
Gastrointestinal smooth muscle	Increases motility	Muscarinic	Reduces motility	α_2, β_2
	Relaxes sphincters	Muscarinic	Constricts sphincters	α_1
Gastric parietal cells	Acid secretion	Muscarinic		
Pancreas	Exocrine secretion	Muscarinic		
Lung, bronchial smooth muscle	Constricts	Muscarinic	Dilates	β_2
Sweat glands			Secretion (generalized) Secretion (specific areas such as palms)	Muscarinic* α_1
Male reproductive system	Erection	Muscarinic	Emission during orgasm	α
Female reproductive system	Vasocongestion, vaginal lubrication	Muscarinic	Orgasmic smooth muscle constriction	α
Pupil	Miosis (constriction)	Muscarinic	Mydriasis (dilation)	α_1

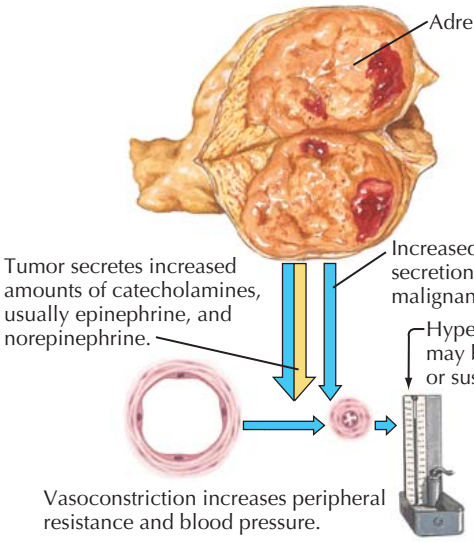
AV, atrioventricular.
*Atypical sympathetic cholinergic nerve fibers secrete acetylcholine.

and are blocked by the drug **atropine,** the deadly nightshade toxin. Nicotinic receptors are membrane channels that conduct Na^+ and K^+ when acetylcholine is bound. There are several subtypes of muscarinic receptors; the most common are coupled to G proteins that activate phospholipase C and produce elevation of IP_3 and free intracellular Ca^{2+}.

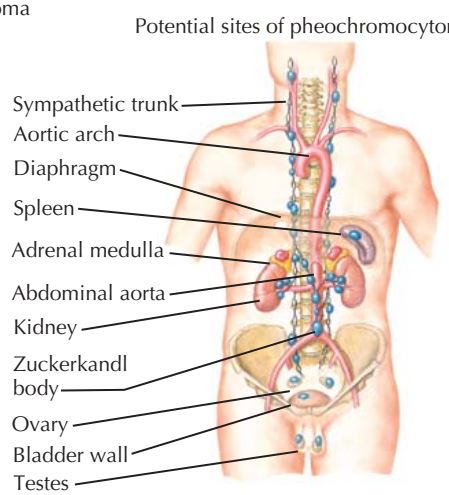
Receptors for catecholamines are classified as α-adrenergic or β-adrenergic on the basis of their responses to specific pharmacologic agents (drugs). β-receptors are blocked by the drug **propranolol,** and α-receptors are blocked by **phentolamine.** Adrenergic receptors may be further subclassified as α_1, α_2, β_1, β_2, and β_3 subtypes on the basis of effects of more specific drugs. At α_1-receptors, binding of an agonist produces elevation of free intracellular Ca^{2+}; binding of an agonist at α_2-receptors produces inhibition of adenyl cyclase and reduction of the levels of the second messenger cAMP. Activation of β-receptors results in activation of adenyl cyclase and elevation of cAMP. How an organ or tissue responds to sympathetic stimulation is largely a function of the type of adrenergic receptors present in the tissue (see Table 7.2).

CLINICAL CORRELATE
Pheochromocytoma

Tumors of the adrenal medulla that secrete epinephrine and norepinephrine are known as pheochromocytomas; catecholamine-secreting tumors in extraadrenal tissue may also occur. In either case, signs and symptoms are consistent with increased sympathetic activity. Catecholamines in plasma and 24-hour urine collections are elevated, and unlike catecholamines released by normal adrenal medulla, are not suppressed by clonidine administration (clonidine acts centrally to suppress sympathetic activity). Treatment is by surgical resection of the tumor. Pheochromocytoma is a rare disorder.



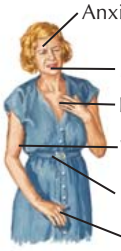
Pheochromocytoma is a chromaffin cell tumor secreting excessive catecholamines resulting in increased peripheral vascular resistance and hypertension.



Most pheochromocytomas are adrenal in origin, but can occur in various sites and may be associated with multiple endocrine neoplasia (MEN) syndromes. Most are sporadic, but some are hereditary.

Clinical features of pheochromocytoma



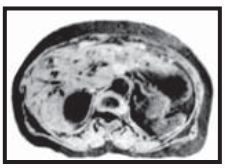




Symptoms are secondary to excessive catecholamine secretion and are usually paroxysmal. More than 90% of patients with pheochromocytoma have headaches, palpitations, and sweating alone or in combination.



Random urine assay for creatine and metanephrine or 24-hour urine assay of metanephrine and free catecholamines used in diagnosis.



CT scan or MRI may reveal presence of tumor.

Catecholamines secreted by tumors of the adrenal medulla or other sites produce excess sympathetic-like activity.

Review Questions

CHAPTER 3: NERVE AND MUSCLE PHYSIOLOGY

1. The resting membrane potential of a cell is measured to be –70 mV in a solution with ion concentrations resembling extracellular fluid. Which of the following manipulations would result in a hyperpolarization of the cell?

A. Reduction in the membrane permeability to sodium ion
B. Reduction in the membrane permeability to potassium ion
C. Influx of calcium ion through the cell membrane
D. Increase in the extracellular sodium ion concentration
E. Increase in the extracellular potassium ion concentration

2. The rapid depolarization during phase 0 upstroke of the action potential in neurons is caused by opening of:

A. ligand-gated Ca^{2+} channels.
B. voltage-gated Ca^{2+} channels.
C. voltage-gated Na^{+} channels.
D. voltage-gated K^{+} channels.
E. voltage-gated Cl^{-} channels.

3. In the myelinated regions of an axon,

A. internal resistance is reduced.
B. membrane resistance is reduced.
C. the space constant is reduced.
D. membrane capacitance is reduced.
E. conduction velocity is reduced.

4. When depolarization of an axon reaches the synaptic bouton, release of neurotransmitter stored in presynaptic vesicles is most closely associated with:

A. influx of Ca^{2+}.
B. influx of Na^{+}.
C. efflux of Na^{+}.
D. influx of K^{+}.
E. efflux of K^{+}.

5. Which of the following is primarily a characteristic of end-plate potentials at the neuromuscular junction, but not of neuronal action potentials?

A. Depolarization is rapid
B. Depolarization to a potential of +40 mV
C. Upstroke caused by opening of voltage-gated channels
D. Charge is carried by a single, large channel for Na^{+} and K^{+}
E. Repolarization is associated with increased K^{+} conductance

CHAPTER 4: ORGANIZATION AND GENERAL FUNCTIONS OF THE NERVOUS SYSTEM

6. The outermost tissue of the spinal cord is:

A. white matter.
B. gray matter.
C. pia mater.
D. the arachnoid membrane.
E. dura mater.

7. Cerebrospinal fluid circulating through the lateral ventricles, third and fourth ventricles, and the subarachnoid space is produced by:

A. the arachnoid membrane.
B. the choroid plexus.
C. the lymphatic system.
D. arachnoid granulations.
E. the pia mater.

8. Association pathways linking the two cerebral hemispheres are found in the:

A. corpus callosum.
B. anterior commissure.
C. posterior commissure.
D. hippocampal commissure.
E. All of the above.

9. Centers involved in integration of cardiovascular and respiratory functions are mainly found in what region of the brainstem?

A. Midbrain
B. Pons
C. Medulla oblongata
D. Thalamus
E. Hypothalamus

CHAPTER 5: SENSORY PHYSIOLOGY

10. Which type of mechanoreceptor responds best to low frequency stimuli such as flutter?

A. Meissner's corpuscles
B. Pacinian corpuscles
C. Merkel's disks
D. Hair follicle receptors
E. Ruffini's corpuscles

11. Light reception by photoreceptors results in reduction of permeability of what ion?

A. K^+
B. Na^+
C. Cl^-
D. HCO_3^-
E. Ca^{2+}

12. The endolymph of the scala media resembles which body fluid in its composition?

A. Interstitial fluid
B. Plasma
C. CSF
D. Lachrymal gland secretions
E. Intracellular fluid

13. During angular acceleration of the head, neurotransmitter release by hair cells within the ampullary crest of the semicircular canal alters the firing rate of afferent nerve fiber axons through cranial nerve:

A. IV.
B. V.
C. VI.
D. VII.
E. VIII.

CHAPTER 6: THE SOMATIC MOTOR SYSTEM

14. The knee jerk reflex is an example of a:

A. stretch reflex.
B. Golgi tendon reflex.
C. flexor withdrawal reflex.
D. bisynaptic reflex.
E. polysynaptic reflex.

15. The most important descending pathway(s) for control of fine motor movements originating in the cortex is (are) the:

A. pontine reticulospinal tract.
B. medullary reticulospinal tract.
C. lateral and medial vestibulospinal tracts.
D. tectospinal and rubrospinal tracts.
E. corticospinal (pyramidal) tract.

16. The inhibitory efferent output of the cerebellar cortex emanates from which type of cell?

A. Granule cells
B. Golgi cells
C. Purkinje cells
D. Basket cells
E. Stellate cells

17. Which of the following structures has as a primary function the regulation of the level of excitation in the motor cortex, resulting in smooth movement and maintenance of posture?

A. Limbic system
B. Basal ganglia
C. The medulla oblongata
D. Hypothalamus
E. The pons

CHAPTER 7: THE AUTONOMIC NERVOUS SYSTEM

18. Preganglionic nerve cell bodies in the sympathetic nervous system are located in the:

A. cervical spinal cord.
B. thoracolumbar spinal cord.
C. sacral spinal cord.
D. sympathetic chain ganglia.
E. brainstem.

19. Release of acetylcholine and subsequent binding to muscarinic receptors is the major mode of neurotransmission at:

A. parasympathetic ganglia.
B. neuroeffector junctions of the SNS.
C. sympathetic ganglia.
D. neuroeffector junctions of the PNS.
E. All of the above.

20. β_2-adrenergic receptors mediate which of the following effects of the sympathetic nervous system?

A. Constriction of vascular smooth muscle
B. Increased cardiac contractility
C. Dilation of bronchial smooth muscle
D. Dilation of the pupil (mydriasis)
E. Sweat gland secretion

Section 3

CARDIOVASCULAR PHYSIOLOGY

The main function of the cardiovascular system is transport of gases, nutrients, and wastes. It transports oxygen from the lungs to the rest of the body; carbon dioxide to the lungs from tissues throughout the body; nutrients between sites of absorption, utilization, and storage; and metabolic waste products from throughout the body to sites at which they are eliminated or recycled. The cardiovascular system also has important roles in thermoregulation, defense mechanisms, endocrine system function, and embryonic development. All of these roles are served by the continuous flow of blood, pumped by the heart, to capillary beds, where exchange between tissues and blood takes place. Nearly all living cells in our body are located no more than a few cell thicknesses from a capillary. In the following chapters, key concepts of cardiovascular physiology are presented, from basic electrophysiological and biophysical principles, to integrated mechanisms for control of cardiovascular system function.

Chapter 8 **Overview of the Heart and Circulation**

Chapter 9 **Cardiac Electrophysiology**

Chapter 10 **Flow, Pressure, and Resistance**

Chapter 11 **The Cardiac Pump**

Chapter 12 **The Peripheral Circulation**

Review Questions

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CHAPTER 8
Overview of the Heart and Circulation

The main functions of the cardiovascular system are gas transport, nutrient delivery, and waste removal. These functions are dependent on circulation of blood, which requires structural integrity of the heart and vessels. In this chapter, the major structural features of the human heart and circulation are presented.

GENERAL SCHEME OF THE CIRCULATION

The cardiovascular system consists of the heart, blood vessels, and blood. The overall circulation can be characterized as a series circuit (Fig. 8.1), in which:

- oxygenated blood is pumped by the left ventricle into the systemic arterial circulation,
- deoxygenated blood returns to the right atrium through the systemic veins,
- the right ventricle pumps this blood into the pulmonary circulation, and
- reoxygenated blood subsequently returns to the left atrium through the pulmonary veins.

Thus, all of the oxygenated blood returning to the left side of the heart from the lungs flows through the systemic circulation, and all of the deoxygenated blood returning to the right side of the heart is pumped to the pulmonary circulation for reoxygenation. Within these circulations, the regional circulations are parallel to each other. For example, skeletal muscle vascular beds lie in parallel to the renal vasculature. In both the systemic and pulmonary circulations, arteries are the *distributing* vessels, supplying blood to capillary beds of the body and lungs, respectively. The veins can be considered *collecting* vessels for return of capillary blood to the heart; they also serve a reservoir function, whereby generalized venous constriction produces an overall rise in blood pressure, for example during compensation for dehydration or blood loss. Of the total blood volume of 5 liters (L), more than 60% is found in the systemic veins (see Fig. 8.1).

STRUCTURE OF THE HEART

The human heart consists of four chambers: the two muscular ventricles and the two atria. High-pressure ejection of blood into the systemic circulation is accomplished by the action of the muscular left ventricle (Fig. 8.2). The interventricular septum functions as part of the left ventricle in this pumping action. The right ventricle ejects blood at lower pressures into the pulmonary circulation. The contraction of the left ventricle consists of constriction of the chamber and shortening of the heart from base to apex; the less forceful contraction of the right ventricle consists of a lateral to medial bellows-like motion, with some shortening from base to apex. In the left heart, backflow of blood into the atria is prevented by the **mitral valve** between the left ventricle and atrium. The right ventricle and atrium are separated by the **tricuspid valve.** The **chordae tendinae** are tendons connecting the **papillary muscles** to the mitral and tricuspid valves. The chordae tendinae and papillary muscles function to prevent eversion of the mitral and tricuspid valves into the atria during ventricular ejection, thereby preventing "regurgitation" of blood back into the atria. During ejection of blood, the aortic and pulmonic valves are open; they prevent backflow to the ventricles during cardiac filling. Valvular opening and closing are accomplished by passive responses of the valves to pressure gradients.



The four-chambered heart of mammals and birds is an evolutionary adaptation to prevent mixing of oxygenated blood returning to the heart from the lungs with deoxygenated blood returning from the systemic circulation. The efficiency of the series circulation created by this adaptation is consistent with the high metabolic rate and warm-blooded nature of these species. Some reptiles also have four-chambered hearts. Amphibians have a dual circulation with a three-chambered heart; the muscular ventricle is not separated into two pumps. In contrast to the dual circulation made possible by four chambers, fish have a single circulation and a two-chambered heart.

CONDUCTION SYSTEM OF THE HEART

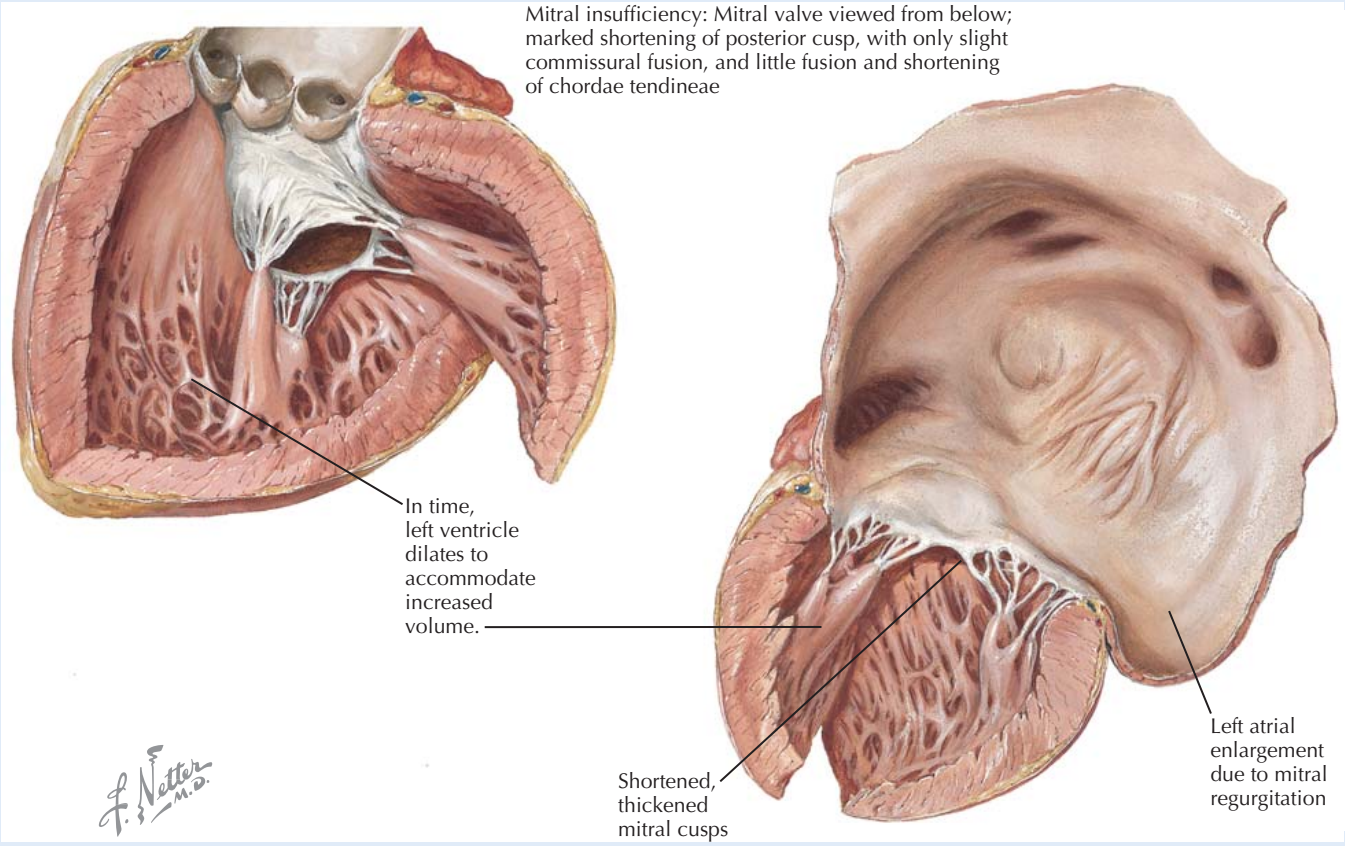
Effective ejection of blood from the heart requires coordinated contraction and relaxation of the chambers. At rest, this cycle occurs approximately 70 times per minute, and to accomplish this, the sinoatrial (SA) node acts as the pacemaker, initiating the depolarization of the heart.

Depolarization spreads from the SA node across the atria, depolarizing atrial muscle and initiating atrial contraction (Fig. 8.3). The atrioventricular (AV) node is the only pathway for spread of the depolarization to the ventricle. Electrical conduction through the AV node is slow, allowing atrial contraction to accomplish the final filling of the ventricles. Next, depolarization reaches the bundle of His, and depolarization proceeds rapidly through the left and right bundle branches to the Purkinje fibers and ventricular muscle, producing ventricular contraction.

CLINICAL CORRELATE
Cardiac Structural Changes in Disease

The normal structure of the heart may be altered in valvular disease, systemic or pulmonary hypertension, heart failure, and other diseases. Common pathologies affecting cardiac structure include the following:

- Pulmonary hypertension: Right ventricular hypertrophy may occur in response to the chronically increased work of the right ventricle.
- Aortic stenosis (narrowing of the aortic valve): Left ventricular hypertrophy occurs in response to the greater work performed by the ventricle.
- Mitral incompetence: Left atrial dilation may develop as a result of the elevation of left atrial pressure and volume caused by mitral regurgitation (leakage of blood back into the atrium from the left ventricle).



Cardiac Structural Changes in Mitral Regurgitation Incompetence of the mitral valve results in regurgitation of blood into the left atrium during systole. Chronic mitral regurgitation results in left atrial enlargement and left ventricular dilation.

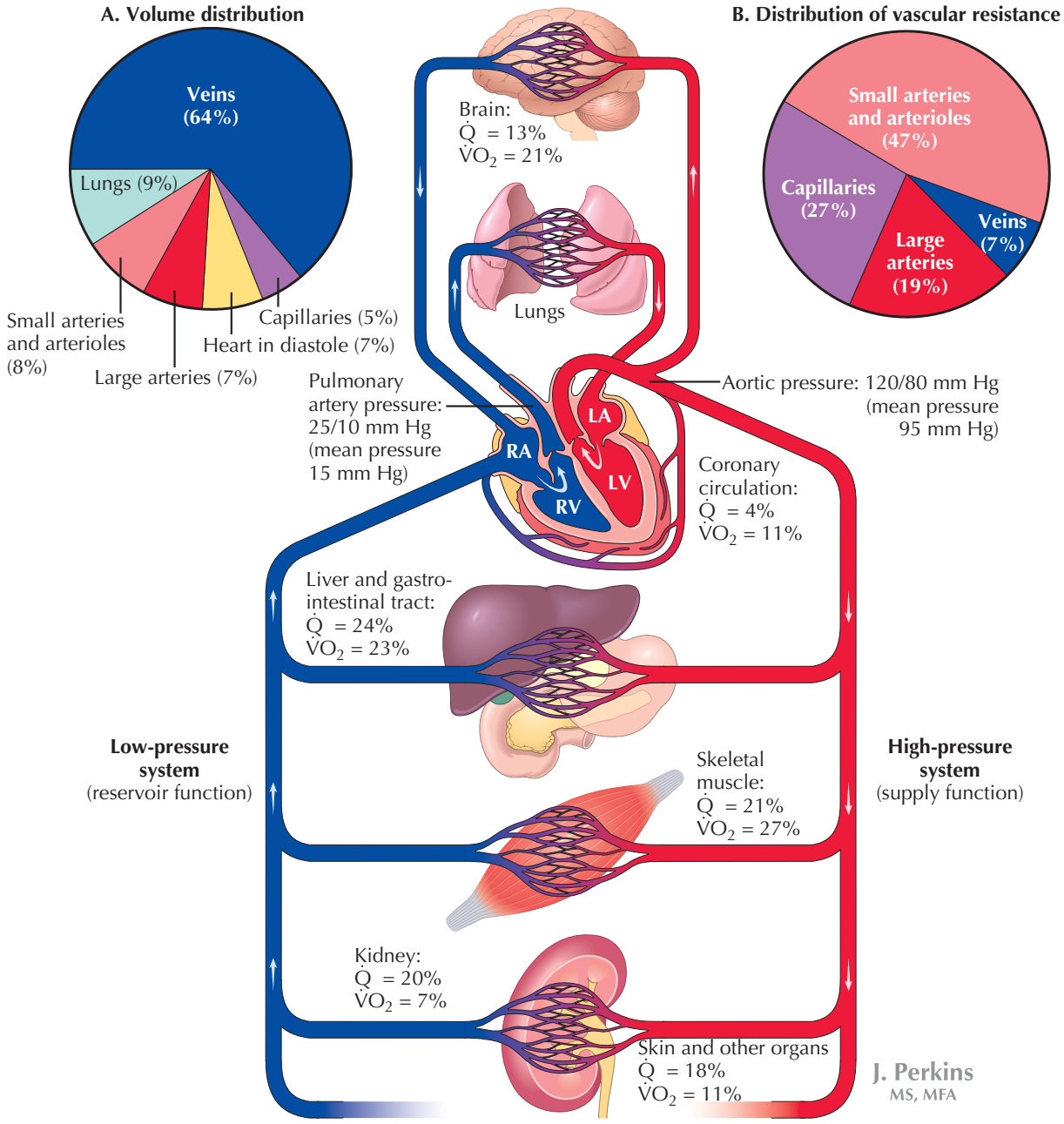


Figure 8.1 General Scheme of the Circulation The distribution of flow $\dot{Q}$ to various organs as percentage of cardiac output and the utilization of oxygen $\dot{V}O_2$ relative to total O_2 consumption are illustrated. The pie charts show distribution of blood volume throughout the system *(A)* and the distribution of vascular resistance as a percentage of total resistance *(B)*. The greatest volume of blood in the cardiovascular system is in the systemic veins. The greatest resistance to flow occurs in small arteries and arterioles. All values in the figure are those observed at rest; these are adjusted to meet changes in physiological requirements, for example during exercise.

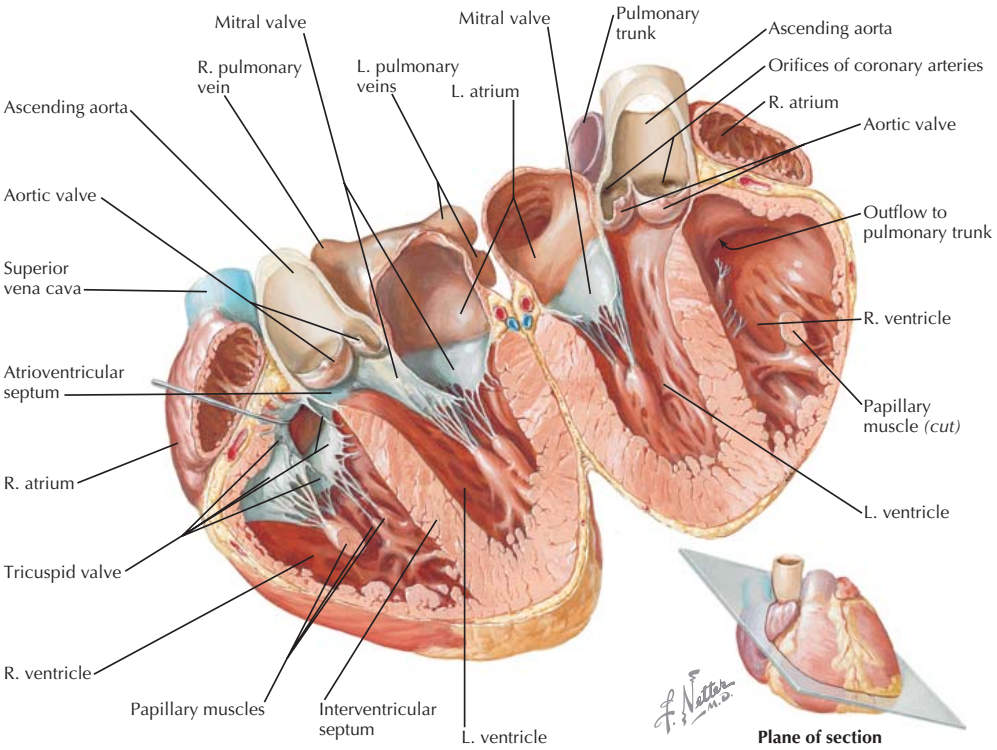


Figure 8.2 **Structure of the Heart** The muscular left ventricle pumps blood into the high-pressure systemic circulation, and the less muscular right ventricle pumps blood into the lower pressure pulmonary circulation. The mitral and tricuspid valves prevent backflow of blood into the atria, while the aortic and pulmonic valves prevent regurgitation of blood from the aorta and pulmonary artery to the ventricles.

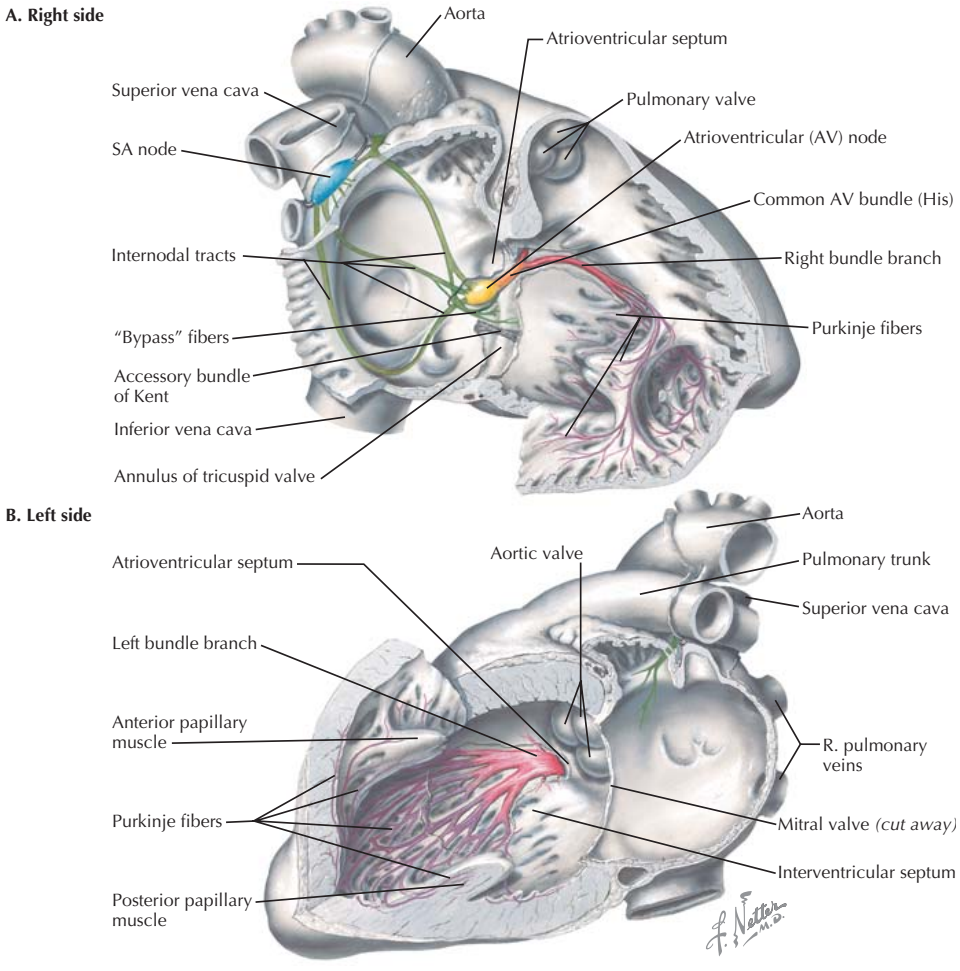


Figure 8.3 **Conduction System of the Heart** Contraction of cardiac muscle is initiated by electrical depolarization. The pacemaker for this electrical activity is in the sinoatrial (SA) node. Impulses travel from the SA node through internodal conducting pathways to the atrioventricular (AV) node, and then spread through the His-Purkinje system of the ventricle. The bypass fibers and Kent bundle are not normally part of the conducting system but may play a role in pathologic states.

CHAPTER 9 Cardiac Electrophysiology

Cells of the heart, like other excitable cells, have the ability to generate action potentials. These action potentials and their conduction throughout the heart are the basis of the rhythmic contraction and relaxation of the heart; the conduction of action potentials in the heart is recorded on the surface of the body as the electrocardiogram.

CARDIAC ACTION POTENTIALS

In a normal heart, the pacemaker activity of the **sinoatrial (SA) node** produces a resting heart rate of approximately 70 beats per minute. The SA node is a group of specialized, noncontractile cardiomyocytes in the wall of the right atrium, adjacent to the opening of the superior vena cava. The resting membrane potential of SA node cells is initially around –60 mV, but the cells undergo gradual, spontaneous depolarization, due to an inward current, i_f, mainly carried by Na^+; an inward Ca^{2+} current, i_{Ca}; and reduced activity of an outward K^+ current. The *diastolic depolarization* resulting from the inward currents is responsible for the pacemaker activity of the SA node cells. Once threshold is reached, the upstroke of the action potential occurs, due to opening of T-type and L-type Ca^{2+} channels (Fig. 9.1). Repolarization is caused by increased conductance of K^+ and closing of Ca^{2+} channels, completing the pacemaker cycle. Action potentials of **atrioventricular (AV) node cells,** found in the atrial septum at the junction of the atria and ventricles, are similar to those in the SA node, although the pacemaker activity of these cells is slower, overridden in normally functioning hearts by SA pacemaker activity.

In contrast to SA and AV nodal cells, depolarization of other cardiac cells is largely dependent on Na^+ influx rather than Ca^{2+} influx. Action potentials of ventricular and atrial myocytes and cells of the His-Purkinje system are characterized by five distinct phases (see Fig. 9.1):

- **Phase 4 (the resting membrane potential):** The resting membrane potential of these cells is mainly a function of K^+ efflux and is close to the Nernst potential for K^+. During phase 4, ion concentrations that were altered by the previous action potential are restored to resting levels by the Na^+/K^+-ATPase and a Na^+/Ca^{2+} exchanger, as well as an ATP-dependent Ca^{2+} pump.
- **Phase 0 (upstroke of the action potential):** Rapid depolarization occurs when the cells reach threshold and fast channels for Na^+ open. This is accompanied by reduced conductance of the inwardly rectified K^+ current (i_{K1}). The rapid upstroke results in rapid spread of depolarization through most of the conducting system of the heart.
- **Phase 1 (rapid repolarization to the plateau):** This phase is caused by inactivation of Na^+ channels and opening of voltage-sensitive K^+ channels, producing a transient outward K^+ current (i_{TO}).
- **Phase 2 (the plateau):** The membrane remains depolarized during the plateau due to opening of voltage-sensitive, slow L-type Ca^{2+} channels and inward current of Ca^{2+}. Simultaneously, an outward K^+ current occurs through a voltage-dependent K^+ channel (delayed rectifier K^+ channel).
- **Phase 3 (repolarization):** Gradual inactivation of the L-type Ca^{2+} channels leads eventually to activation of K^+ channels, causing rapid repolarization, substantially due to an inwardly rectified K^+ current (i_{K1}).

The plateau of the action potential is functionally important, because it normally prevents premature depolarization of cardiac cells and associated arrhythmias. There is an **effective refractory period,** beginning with phase 1 and extending through the plateau and much of phase 3, during which another action potential cannot be generated. This is followed by the **relative refractory period,** which lasts until the resting membrane potential is fully restored; during this period, it is more difficult to elicit another action potential than in a resting cell.

During the conduction of the wave of depolarization of the heart, forward propagation occurs as a result of the local



Chronotropic, dromotropic, and inotropic effects are those that alter heart rate, conduction velocity, and myocardial contractility, respectively. A positive chronotropic agent is a drug that increases heart rate. Stimulation of the sympathetic nervous system increases the chronotropic, dromotropic, and inotropic state of the heart, whereas the parasympathetic nervous system mainly reduces the chronotropic and dromotropic state.

currents created during action potentials, and unidirectional depolarization is maintained due to the refractory periods of cells once they have depolarized.

THE ELECTROCARDIOGRAM

An electrocardiogram (ECG or EKG) is a recording of changes in surface potential on the body, produced by the depolarization and repolarization of the heart. Electrocardiography may reveal the following:

- Abnormal cardiac rhythms and conduction.
- Presence, location, and extent of ischemia or infarction.
- Orientation of the heart in the thoracic cavity and size of chambers.
- Effects of abnormal electrolyte levels and some drugs.

These observations are facilitated by recording of the ECG with multiple lead configurations. A 12-lead ECG includes standard leads I, II, and III; six unipolar leads (V_1–V_6); and three augmented limb leads (AVL, AVR, and AVF). A normal ECG consists of a:

- P wave, caused by atrial depolarization.
- QRS complex, representing ventricular depolarization.
- T wave, representing ventricular repolarization.

In the normal ECG, each P wave leads to a QRS complex and T wave. The heart is considered to be in "sinus rhythm," because the rhythm is being regulated by the SA node. **Bradycardia** refers to a resting heart rate below 60 beats per minute; **tachycardia** is a resting heart rate above 100 beats per minute. Some causes of bradyarrhythmias in the presence of normal sinus rhythm include high vagal (parasympathetic) tone; drugs; and various metabolic, endocrine, and neurological disorders. Some causes of tachyarrhythmias with sinus rhythm include high sympathetic tone; drugs; low blood volume (dehydration); and metabolic, endocrine, and neurological disorders. The specific electrical events leading to the components of the ECG are detailed in Figures 9.2 to 9.4.

CLINICAL CORRELATE
Atrioventricular Block

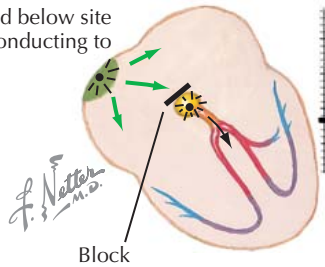
The normal conducting pathway in the heart is:

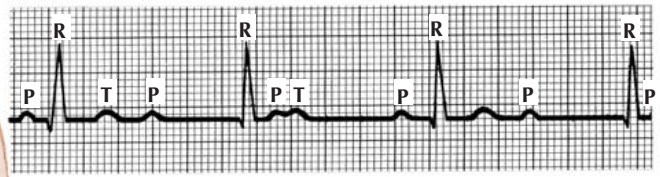
SA → AV → Bundle of His → Bundle branches → Purkinje fibers → Ventricular muscle

When conduction is disrupted in this pathway, arrhythmias result. Atrioventricular block (heart block) is a group of cardiac arrhythmias associated with altered conduction through the AV node:

- First-degree AV block is abnormally delayed conduction through the AV node (PR interval on the ECG exceeding 200 msec). Each P wave results in a QRS complex and thus ventricular contraction, as in normal sinus rhythm, but AV conduction is delayed. By itself, first-degree block does not produce bradycardia and is usually benign if not caused by underlying heart disease.
- Second-degree AV block is characterized by intermittent conduction through the AV node. As a result, some P waves on the ECG are followed by a QRS complex, whereas others are not. Thus, the ventricles contract less frequently than the atria. Myocardial ischemia or infarction may produce second-degree block.
- Third-degree AV block (complete block) occurs when the wave of depolarization is not conducted through the AV node (from atria to ventricles). On the ECG, both P-P intervals and R-R intervals are regular, but P waves are dissociated from the QRS complexes. When atrial pacemaker activity fails to be conducted to the ventricle, an escape pacemaker may arise in the AV node below the site of block or in the bundle of His, producing a ventricular rate of 40 to 55 beats per minute (as determined by the R-R interval) that is only partially responsive to sympathetic stimulation. When the conduction block occurs in the bundle of His, the ventricular escape rhythm will produce an inadequate heart rate of 20 to 40 beats per minute; cardiac output (flow rate from one ventricle) may be insufficient even at rest, and activity will be greatly restricted due to inability to adequately adjust output. The usual therapy is implantation of a cardiac pacemaker.

Impulses originate at SA node (P waves) and below site of block in AV node (junctional rhythm), conducting to ventricles.





Atria and ventricles depolarize independently. QRS complexes less frequent; regular at 40 to 55 beats/min but normal in shape.

Third-Degree Heart Block

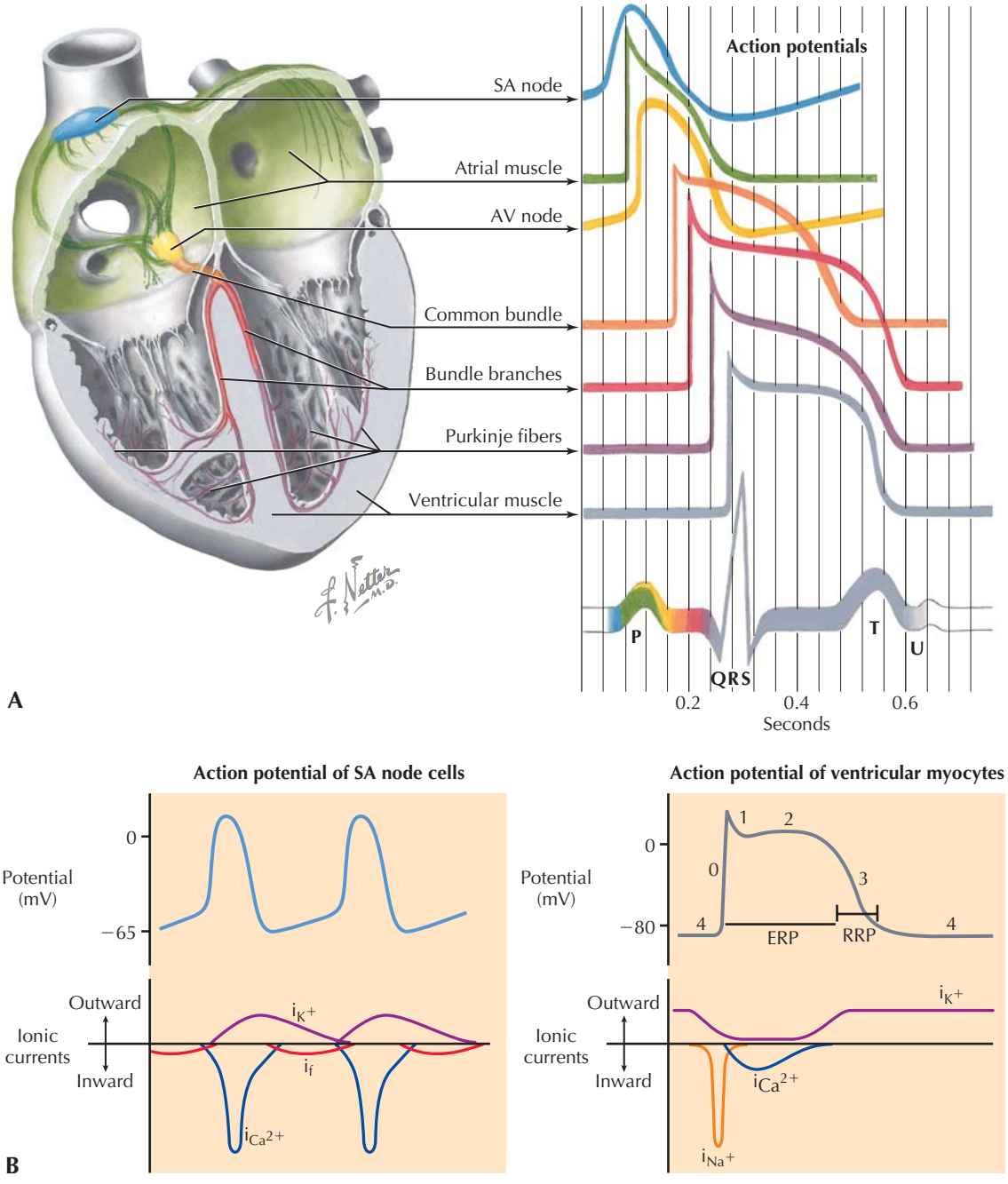


Figure 9.1 Electrical Activity of the Heart Action potentials vary as the wave of depolarization proceeds through the conducting pathway of the heart, beginning at the SA node and ending in the ventricular muscle. The ECG records changes in surface potential on the body associated with depolarization and repolarization of the heart. P waves, QRS complexes, and T waves constitute the normal ECG. In 50% to 70% of individuals, a U wave will also be recorded. Its origin is not well defined *(A)*. Differences in morphology of the action potentials are based on differences in specific ion currents *(B)*. In AV nodal cells, note the spontaneous depolarization from the resting membrane potential that results in the action potential. In ventricular myocytes (and also the His-Purkinje system), note the sharp phase 0 upstroke that produces rapid conduction of the wave of depolarization. The phase 2 plateau is important in preventing premature depolarization. The effective refractory period (ERP) is the period during which another action potential cannot be elicited; during the relative refractory period (RRP), it is more difficult to elicit an action potential than during phase 4.

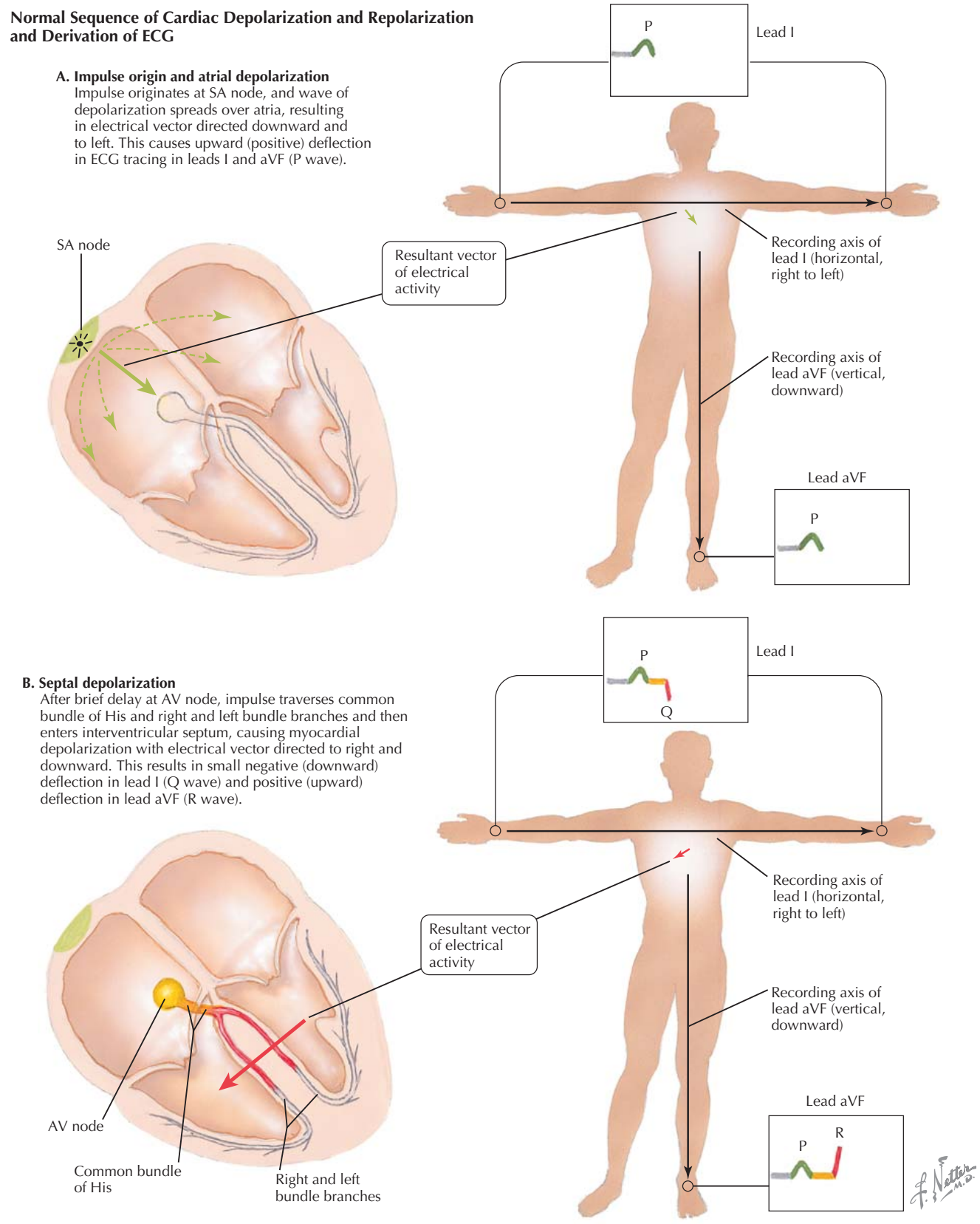


Figure 9.2 Cardiac Depolarization and Repolarization Part I This series of figures *(Figs. 9.2 to 9.4)* depicts the sequence of cardiac electrical events during the cardiac cycle and the surface recordings that result from these events and constitute the ECG. The initial events are depicted above, in which the firing of the SA node results in depolarization of the atria, recorded on the ECG as the P wave. This depolarization spreads to the AV node, the bundle of His, and bundle branches, with the resultant electrical activity vectors and surface ECG recordings. Note that the morphology of the ECG recording varies with lead placement.

Normal Sequence of Cardiac Depolarization and Repolarization and Derivation of ECG (continued)

C. Apical and early ventricular depolarization
Impulse continues along conduction system, causing depolarization of apical ventricular myocardium with electrical vector directed downward and to left. This results in large positive (upward) deflection (R wave) in lead I and extends R wave in lead aVF.

D. Late ventricular depolarization
As depolarization progresses over ventricles, vector shifts to become directed superiorly as well as to left, thus extending upward R wave in lead I and causing negative (downward) deflection (S wave) in lead aVF.

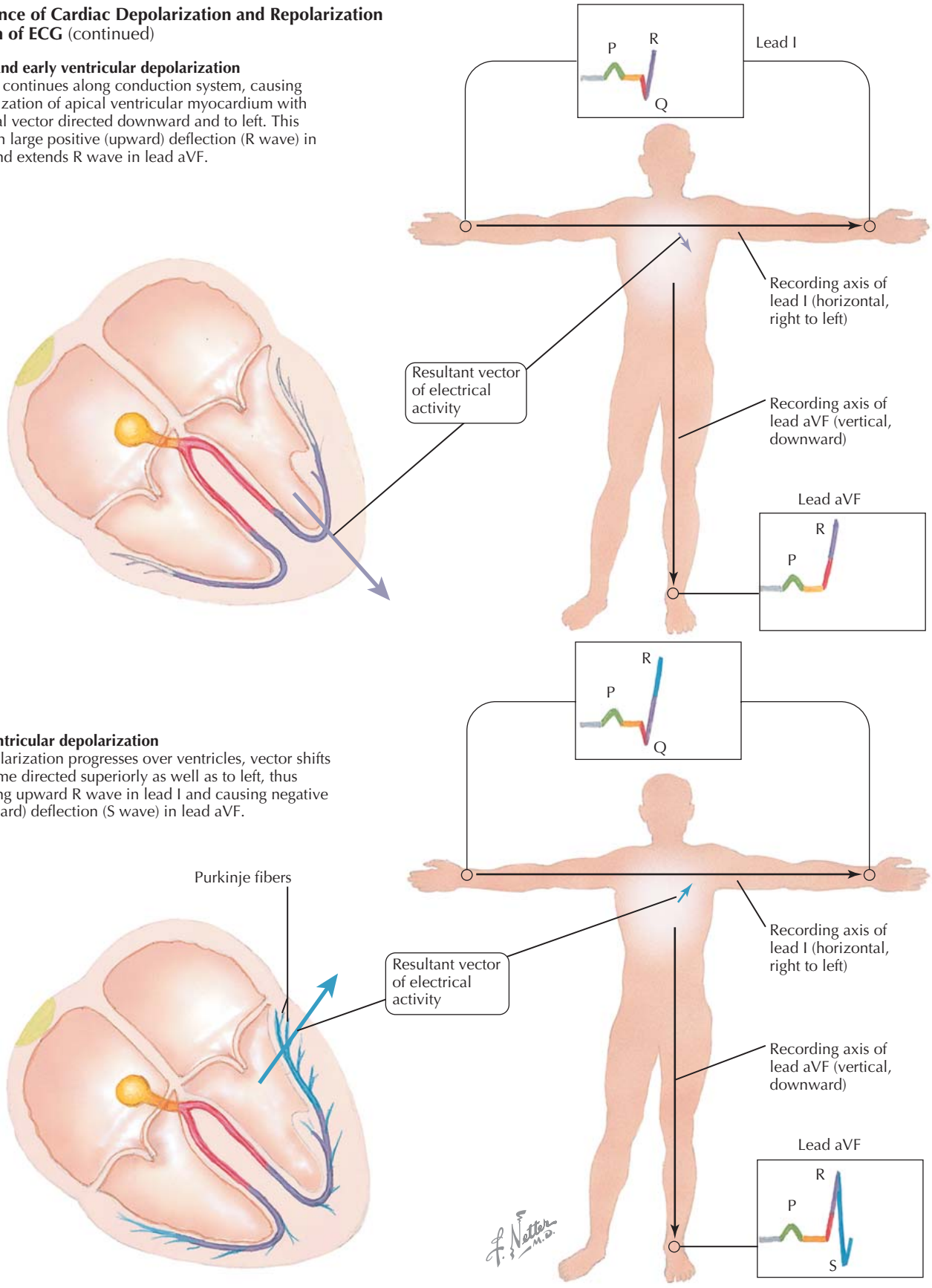
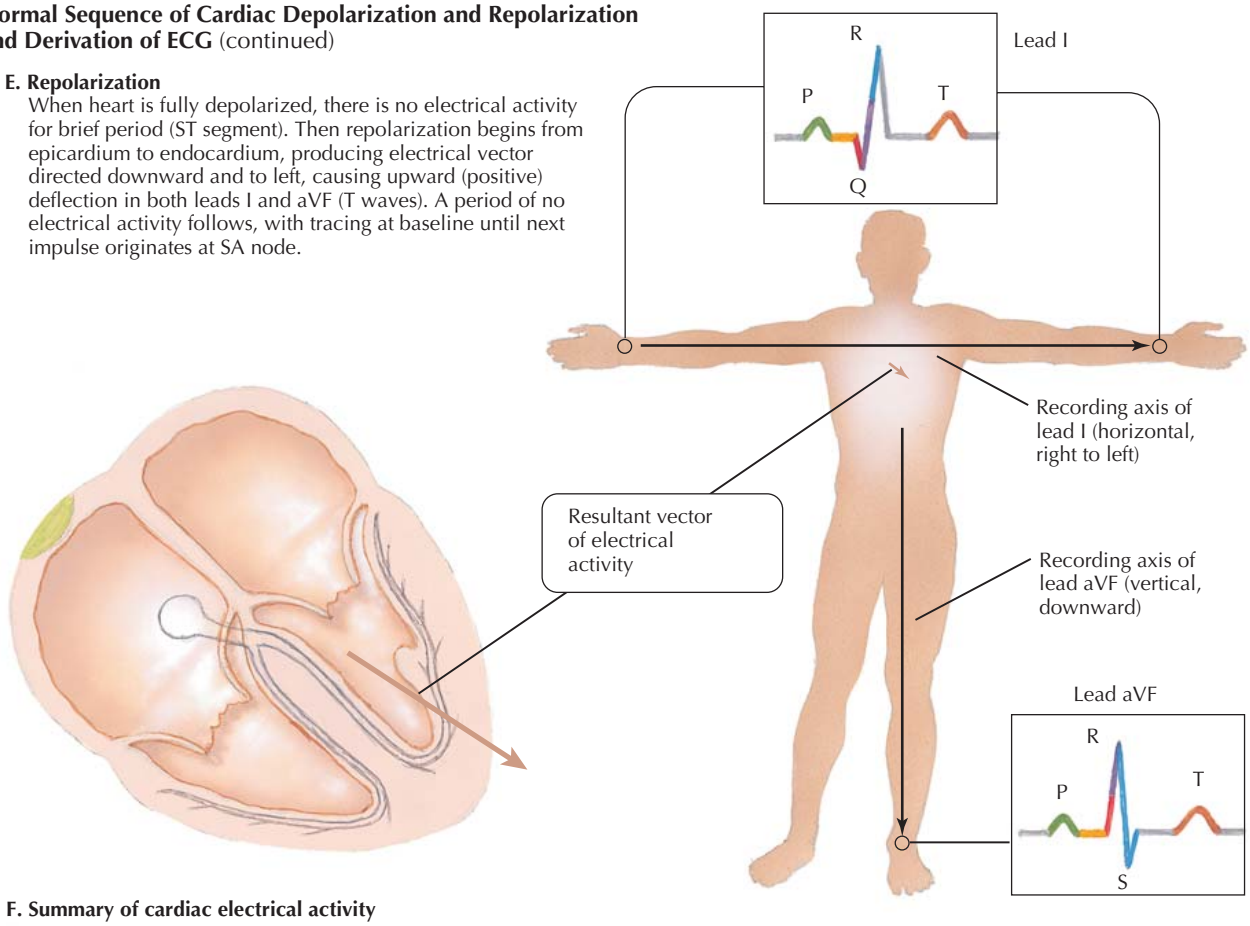


Figure 9.3 **Cardiac Depolarization and Repolarization Part II** Septal depolarization (see Fig. 9.2) is followed by apical and ventricular wall depolarization; resultant vectors of electrical activity produce the QRS complex of the ECG.

Normal Sequence of Cardiac Depolarization and Repolarization and Derivation of ECG (continued)

E. Repolarization

When heart is fully depolarized, there is no electrical activity for brief period (ST segment). Then repolarization begins from epicardium to endocardium, producing electrical vector directed downward and to left, causing upward (positive) deflection in both leads I and aVF (T waves). A period of no electrical activity follows, with tracing at baseline until next impulse originates at SA node.



F. Summary of cardiac electrical activity

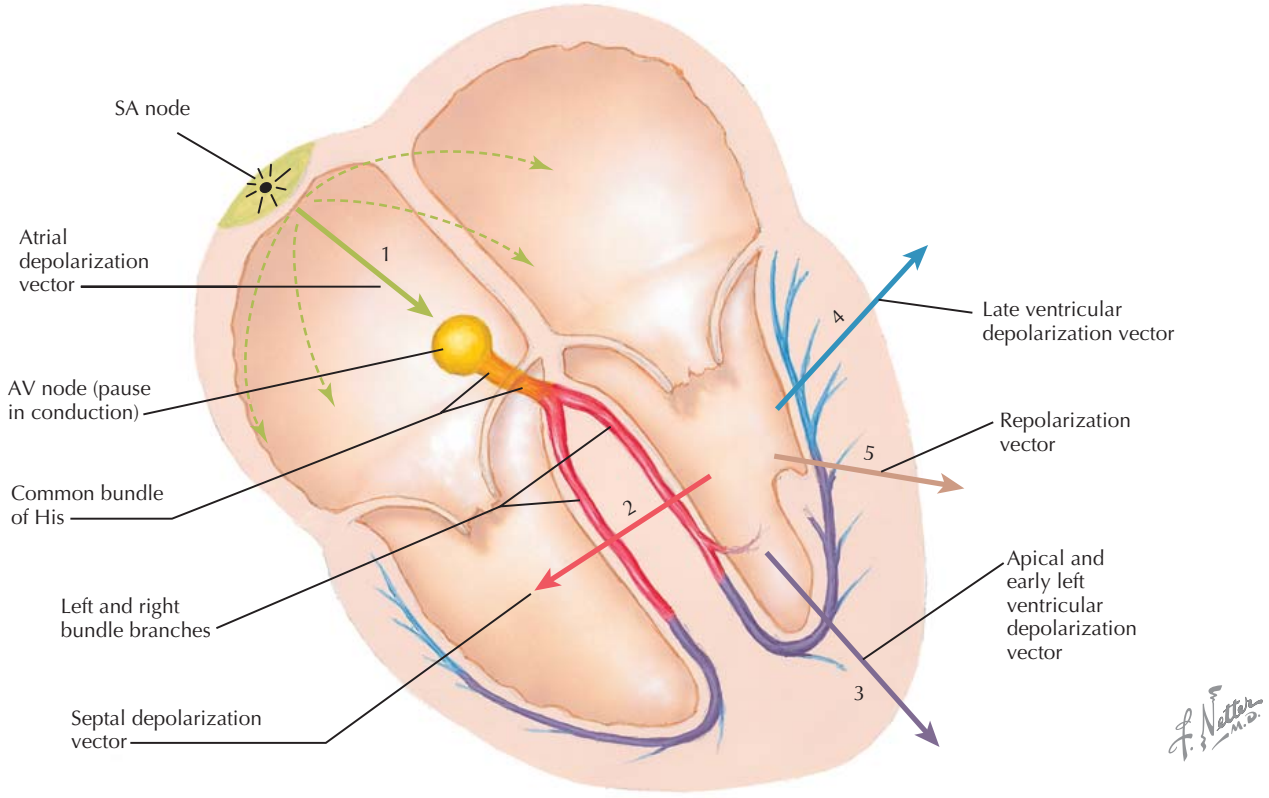


Figure 9.4 Cardiac Depolarization and Repolarization Part III Ventricular depolarization (see Fig. 9.3) is followed by ventricular repolarization; the resultant vector of electrical activity produces the T wave of the ECG. The cardiac electrical activity and resultant vectors *(1-5)* through the cycle are summarized in *F.*

CHAPTER 10 Flow, Pressure, and Resistance

Hemodynamics is the study of the forces involved in circulation of blood. Although arterial blood pressure is a convenient and readily measured parameter, understanding the broader hemodynamic state of an individual is essential when assessing cardiovascular disease.

BASIC HEMODYNAMICS

The rate of flow through the circulation (Q) is determined by the pressure gradient across the circulation (ΔP) and the resistance of the circulation (R):

$$Q = \Delta P/R$$

Pressure is defined as force per unit area. For example, in an auto tire, pressure is measured as pounds per square inch (PSI). The unit for measurement of blood pressure is most often mm Hg (1 mm Hg = 1 torr), and the pressure gradient (ΔP) for flow is arterial pressure minus venous pressure. Resistance is the impedance to flow and can be measured in units of mm Hg/mL/min. Resistance can be quantified as the pressure rise associated with an incremental rise in flow. The greatest resistance in the circulation occurs in the smallest arteries and arterioles (see Fig. 8.1). Factors that determine resistance are considered later in the chapter (see "Biophysics of Circulation").

BLOOD PRESSURE

The blood pressures in the venous systems of both pulmonary and systemic circulations are considerably lower than pressures in the respective arterial systems. In addition, blood pressures in the pulmonary circulation are lower than corresponding pressures in the systemic circulations. Systemic arterial pressure at rest is normally about 120/80 mm Hg (systolic/diastolic), compared with 25/10 mm Hg for pulmonary artery pressure. Some important definitions related to arterial pressure are as follows:

- **Systolic arterial pressure:** Peak arterial pressure reached during ejection of blood by the heart.
- **Diastolic arterial pressure:** Lowest arterial pressure reached during diastole, while the heart is relaxed and filling (not ejecting blood).



Flow, pressure, and resistance can be related in the formula

$$Q = \Delta P/R$$

where Q is flow, ΔP is the pressure gradient, and R is resistance to flow.

Rearranging this formula,

$$\Delta P = QR$$

This equation is analogous to Ohm's law, which states that V = IR, where V is electrical potential (electrical gradient), I is current (electrical flow), and R is impedance (electrical resistance).

- **Arterial pulse pressure:** The difference between systolic and diastolic pressures; dependent on stroke volume (volume ejected by one ventricle during one contraction) and arterial compliance.
- **Mean arterial pressure (MAP):** The average pressure over a complete cardiac cycle of systole and diastole; dependent on peripheral resistance and cardiac output (volume ejected by one ventricle per unit time).

Mean arterial pressure is not the simple arithmetic mean of systolic and diastolic pressures, because of the irregular shape of the arterial pressure curve (Fig. 10.1). MAP can be approximated by adding one third of the pulse pressure to the diastolic pressure.



Physiological pressures are usually given in units of mm Hg or cm H_2O. In other words, 1 mm Hg is the pressure that would support a column of mercury (Hg) at a height of 1 millimeter (mm), and 1 cm H_2O is the pressure that would support a column of water 1 centimeter (cm) high. Another way to conceptualize these units is that a column of water 1 cm high would exert 1 cm H_2O pressure at its base, and a column of mercury 1 mm high would exert 1 mm Hg pressure at its base. Although these may appear to be unconventional units for quantifying pressure, they are useful because water or mercury manometers are often used to measure pressure. In some texts, the unit *torr* is used; it is equal to 1 mm Hg.

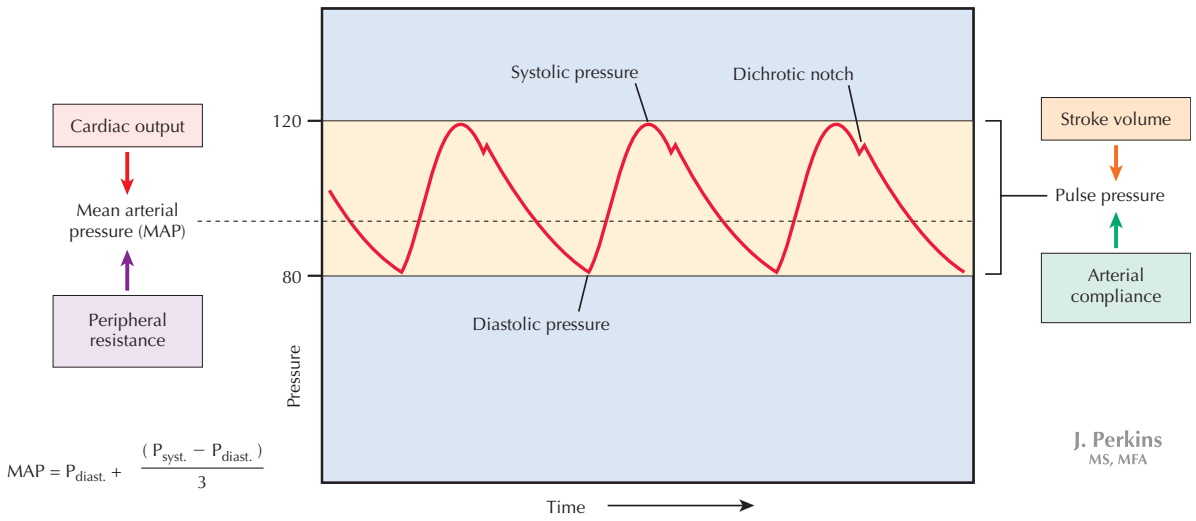


Figure 10.1 The Arterial Pressure Wave The arterial pressure wave represents the changes in pressure in the arterial system over periods of systole, during which the stroke volume is ejected from the left ventricle, and diastole, during which the heart is refilling and blood in the arterial system continues to flow downstream. Arterial pressure is affected by cardiac output, stroke volume, arterial compliance, and peripheral resistance. Mean arterial pressure can be approximated based on the formula shown. The first upward deflection in the curve marks the beginning of systole, the period of cardiac ejection. The transient irregularity in the downward slope of the wave is known as the dicrotic notch, which is produced by closure of the aortic valve, marking the beginning of diastole. During diastole, the heart refills, while blood in the arterial system runs downstream, reducing arterial pressure.

Pressure waves vary through the cardiovascular system (Fig. 10.2). Both high and low pressures are encountered in the ventricles (approximately 120/0 and 25/0 mm Hg at rest for left and right ventricles, respectively). High systolic pressure is necessary for pumping of blood through the circulation, whereas the low pressures are required for return of blood to the heart during diastole. Note that while mean pressures in the large arteries are somewhat lower than in the aorta, pressure pulsations are greater in larger arteries. This phenomenon is mainly attributable to two factors: changes in pressure travel more rapidly downstream than the actual blood flow, which accentuates the pulsatility downstream, and pressure changes are reflected back at branch points, again accentuating downstream pulsatility.

BIOPHYSICS OF CIRCULATION

Blood flow through vessels is a complex phenomenon, involving a nonhomogenous fluid flowing in a pulsatile manner through distensible, branching tubes of various dimensions. Under most conditions, this flow can be described by Poiseuille's law:

$$Q = \frac{\Delta P \pi r^4}{\eta 8L}$$

where Q is flow, ΔP is the pressure gradient from one end of a tube to the other, r^4 is the radius of the tube to the fourth power, η is the viscosity of the fluid, and L is the length of the tube. The effects of this relationship are illustrated in Figure 10.3.

Based on Poiseuille's law, flow (Q) through a tube will be:

- Directly proportional to the longitudinal pressure gradient (inflow pressure minus outflow pressure).
- Inversely proportional to the length of the tube.
- Inversely proportional to the viscosity of the fluid.
- Directly proportional to the fourth power of the radius of the tube.

For example, if the radius of a tube is doubled, flow will be increased by a factor of 16, assuming the pressure gradient is maintained. Physiological regulation of regional blood flow on a moment-to-moment basis mainly involves changes in radius (vasodilation and vasoconstriction) of the small arteries and arterioles, taking advantage of this powerful factor. Under normal circumstances, viscosity of blood is not an issue; however, changes in hematocrit are associated with large changes in blood viscosity, as occur in anemia and polycythemia.

Because Q = ΔP/R, resistance can be described as:

$$R = \frac{\eta 8L}{\pi r^4}$$



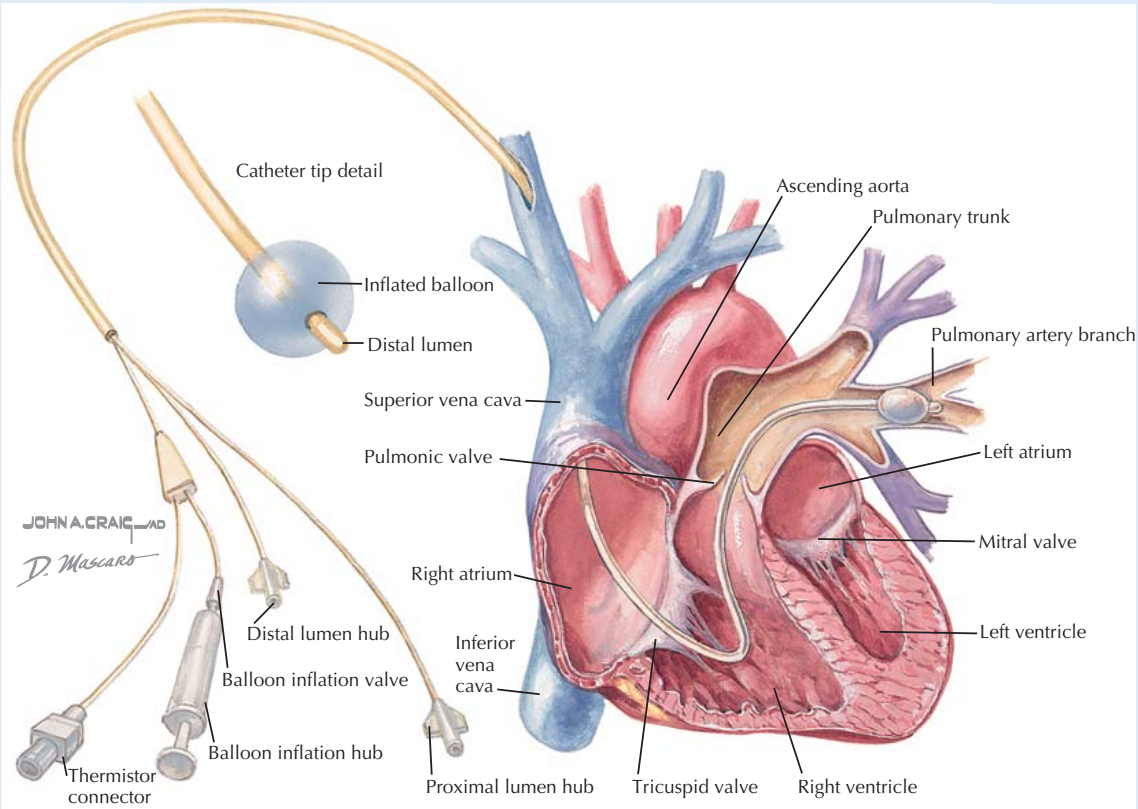
Of the factors affecting flow through a tube, the most important is the radius of the tube. While flow is inversely proportional to the length of the tube and the viscosity of the fluid, and directly proportional to the hydrostatic pressure gradient in the tube, it is directly proportional to the fourth power of the radius of the tube. Therefore, doubling the radius of the tube will cause a 16-fold increase in flow, if other factors are constant.

CLINICAL CORRELATE
Measurements of Blood Pressure

Arterial pressure is routinely measured by sphygmomanometry, in which a blood pressure cuff is inflated above the systolic pressure, compressing vessels and stopping blood flow. As pressure in the cuff is gradually released, the practitioner listens for the **sounds of Korotkoff** through a stethoscope. These sounds are produced by the pulsatile flow of blood in arteries under the cuff when the cuff pressure is between the systolic and arterial pressure. Thus, the sounds are first heard when cuff pressure falls below systolic pressure, and the sounds disappear when the cuff pressure falls below diastolic pressure. Arterial pressure can also be measured directly through an arterial catheter. Such a catheter can be passed in a retrograde direction (against the flow of blood) for measurement of pressures in the arteries, aorta, and left ventricle, as the catheter advances toward the heart.

Although arterial pressure monitoring is important for detection of hypertension, monitoring of additional pressures is often highly desirable in surgical and intensive care settings. Pulmonary capillary wedge pressure ("wedge pressure") is one such measurement. A venous catheter can be passed antegrade (in the direction of blood flow) for measurement of pressures in the veins, right atrium, and right ventricle. However, it is not possible to measure pulmonary venous and left atrial pressures by these direct methods. Instead, we must rely on measurement of pulmonary capillary wedge pressure.

With the aid of a partially inflated balloon, a catheter is passed from a systemic vein, through the right heart, into the pulmonary artery (PA), to a branch of the pulmonary artery. The lumen opens at the distal end of the catheter and is continuous; the balloon is on the outside of the catheter only. When the catheter can be advanced no further, the balloon is fully inflated (the catheter is actually a multilumen Swan–Ganz catheter—one lumen is continuous to the end of the catheter; another leads to the balloon, allowing inflation; other lumens may open along the length of the catheter). Inflating the balloon has no effect on patency of the catheter lumen through which pressure is measured. When the balloon is fully inflated, pressure falls downstream beyond that point. Vascular pressure beyond the point of occlusion equilibrates with downstream pressure, and wedge pressure (measured at the catheter tip) is thus an indicator of pulmonary venous and left atrial pressure. It also approximates left ventricular end-diastolic pressure (LVEDP), when LV pressure has equilibrated with the pressure in the left atrium and pulmonary veins with filling of the ventricle. Wedge pressure is useful in hemodynamic assessment (e.g., in acute heart failure).



Pulmonary Artery Catheterization Pulmonary artery catheters (Swan–Ganz catheters) are multilumen catheters that can be advanced into a branch of the pulmonary artery. With the tip thus wedged with the balloon inflated, flow is occluded and pressure can be measured beyond the balloon occlusion through one of the lumens. The measured *pulmonary capillary wedge pressure* is an approximation of left ventricular end diastolic pressure.

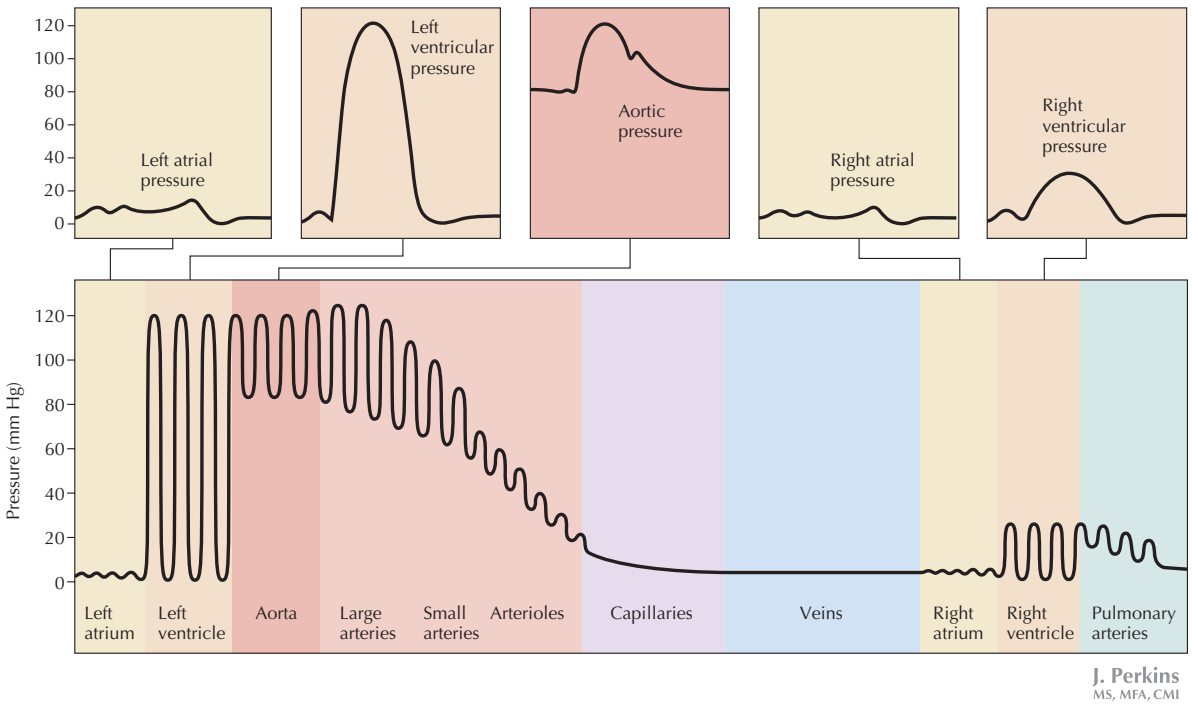


Figure 10.2 **Pulse Pressures through the Circulation** Changes in pressure pulses are illustrated as blood flows from the left ventricle (LV) to the aorta, through the systemic circulation, and back to the right ventricle (RV) and pulmonary artery (PA).

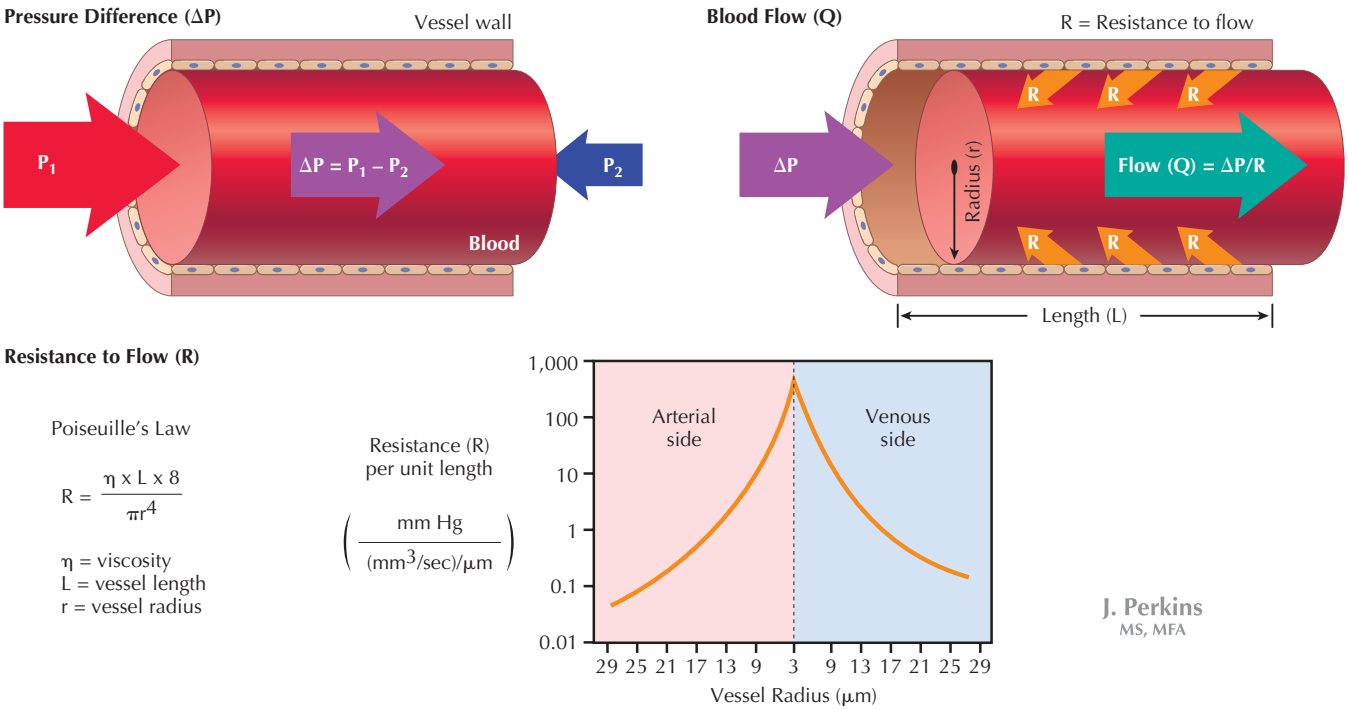


Figure 10.3 **Poiseuille's Law** Under normal physiological conditions, flow through vessels is governed by Poiseuille's law. By far, the greatest resistance to flow occurs in the smallest vessels constituting the microcirculation, particularly the arterioles. This is due to the small radius of these vessels, and the inverse relationship between resistance and the fourth power of the radius of a vessel.

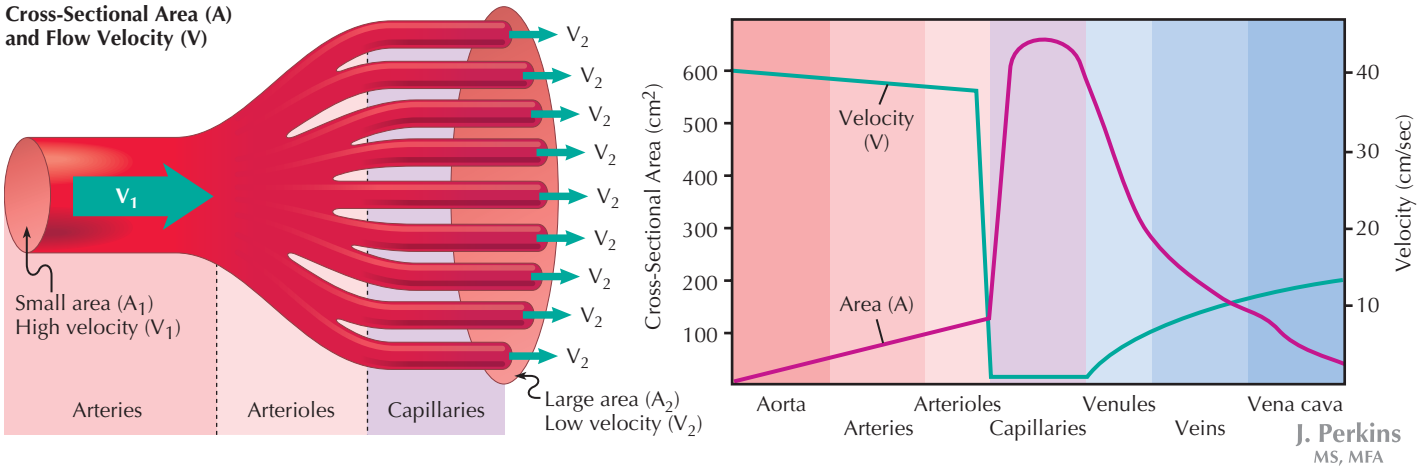


Figure 10.4 **Relationship between Velocity of Blood Flow and Cross-Sectional Area** Proceeding downstream from the aorta, branching of arterial vessels increases total cross-sectional area and thus results in diminished velocity of blood flow from the aorta to the capillaries. Velocity increases from the capillaries to the large veins with the confluence of vessels and the resulting decrease in total cross-sectional area.

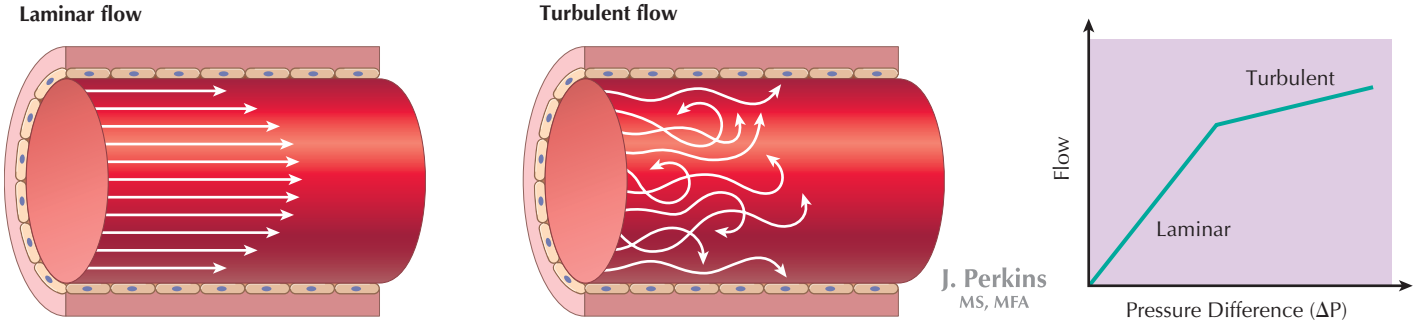


Figure 10.5 **Laminar and Turbulent Flow** Normally, laminar, or streamlined, flow occurs throughout most of the vascular system. Pathological conditions such as coarctation (narrowing of a vessel), valvular abnormalities, and low blood viscosity (as in anemia) produce turbulence, and are associated with murmurs in the heart or great vessels, or vascular bruits heard by auscultation. Turbulence produces an increase in the pressure gradient required to produce flow.

Key relationships to remember are as follows:

- Resistance is directly proportional to the length of the tube.
- Resistance is directly proportional to the viscosity of the fluid.
- Resistance is inversely proportional to the fourth power of the radius of the tube.

Flow (Q) can also be related to cross-sectional area (A) and linear velocity of the flow (V) in this formula:

$$Q = VA$$

In the cardiovascular system, the overall flow rate (cardiac output) is the same at every level of the circulation, because the circulation is in series. Thus, based on the Q = VA relationship, the velocity of blood flow is slowest in the capillaries, which have the greatest aggregate cross-sectional area ($600\ cm^2$) in the vascular system, and fastest in the aorta, where the cross-sectional area is only about $4\ cm^2$ (Fig. 10.4). The low velocity in capillaries is beneficial in terms of exchange of dissolved substances between blood and tissues.

Flow through vessels is generally laminar, with the greatest velocity of flow in the center of the vessel and lowest velocity near the vascular wall (Fig. 10.5). This streamlining of flow is caused by shear stress produced as blood flows past the stationary vessel wall. Turbulent flow, on the other hand, is characterized by irregularities in flow patterns, such as whorls, vortices, and eddies. Vascular disease often is associated with sites of turbulence.

Reynolds' Number (R_e) relates the factors associated with turbulence:

$$R_e = \frac{VD\partial}{\eta}$$

where V is velocity of flow, D is the diameter of the tube, ∂ is the density of the fluid, and η is the viscosity of the fluid. When R_e is below 2000, flow is usually laminar; values above 3000 result in turbulence. In the cardiovascular system, density of blood is always close to 1.0 and is not a factor; changes in the other variables are important, along with a number of other factors. Turbulence in blood vessels is associated with audible murmurs and is promoted by:

- high velocity of blood flow
- large vessel diameter
- low viscosity of blood (low hematocrit)
- abrupt changes in vessel diameter, for example in aneurysms (see "Clinical Correlate") or coarctation (narrowing)
- vascular branch points

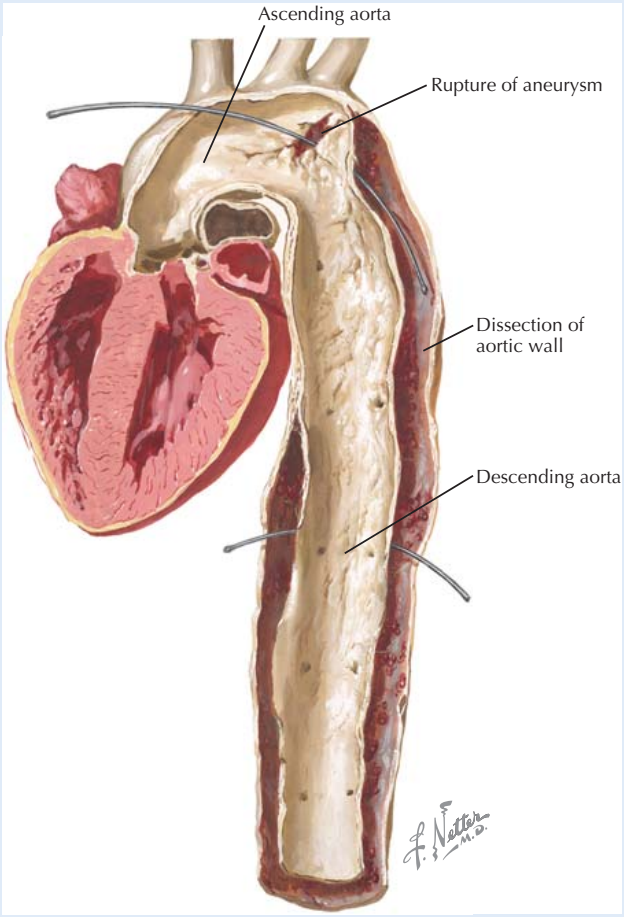
Wall tension (T) is another important biophysical parameter in this system and can be conceptualized as the force necessary to hold together a theoretical slit occurring in a vessel wall. This is defined by Laplace's law:

$$T = P_t r$$

where P_t is the transmural pressure (the difference between pressure inside and outside the vessel, in other words, the pressure gradient across the vascular wall), and r is the vessel radius. Because of the small radii of capillaries and venules, they are protected against rupture despite the transmural pressure gradient. Wall tension is an important consideration in large arteries, where transmural pressures are high and radii are large, especially when the vascular wall is diseased (see "Clinical Correlate").

CLINICAL CORRELATE
Aortic Aneurysm

An aneurysm is a saclike enlargement in the wall of an artery, caused by weakening of the vessel wall. With bulging, wall stress is further increased, through increased radius of the vessel and decreased wall thickness, according to Laplace's equation ($T = P_t r$). Risk factors for aortic aneurysm include hypertension, smoking, obesity, atherosclerosis, and hypercholesterolemia. Rupture of an aortic aneurysm is a medical emergency involving profuse internal hemorrhage and is often fatal. Dissection of an aneurysm is defined as bleeding into the vascular wall through a tear in the inner layer of the vessel (media intima), a common complication in thoracic aortic aneurysms. Aneurysms are treated by replacement of the affected aortic segment by a synthetic graft, or by endovascular implantation of a graft in the area of the aneurysm.



Ruptured and Dissecting Aortic Aneurysm

CHAPTER 11 The Cardiac Pump

Based on the biophysical principles described in Chapter 10, blood flows through the systemic and pulmonary circulations, with the energy for this flow being provided by the pumping action of the heart. Like early mechanical pumps, the heart functions in a cyclic manner, with periods of filling (diastole) and periods of contraction and ejection of blood (systole).

THE CARDIAC CYCLE

The cardiac cycle (or Wiggers diagram) consists of one cycle of ventricular systole and diastole. At rest the cycle is 0.86 seconds in duration if the heart rate is 70 beats per minute. The changes in ventricular pressure and volume, aortic pressure and flow, atrial pressure, venous pulse, electrocardiogram, and phonocardiogram are all interdependent, and understanding the interrelationships between these variables is a key step in comprehending the complexities of hemodynamics (Fig. 11.1).

Left ventricular volume and pressures in the left heart and aorta are illustrated in Figure 11.1. Tracings for the right ventricle and pulmonary artery are similar in shape but substantially lower than those for the left ventricle and aorta. Within this cardiac cycle diagram, there are two short intervals known as periods of **isovolumetric contraction** and **isovolumetric relaxation.** During these periods, all of the valves of the heart are closed. The isovolumetric contraction period for the left heart begins with mitral valve closure (the aortic valve is already closed) and ends with opening of the aortic valve; the isovolumetric relaxation period begins with aortic valve closure and ends when the mitral valve reopens.

There is some slight asynchrony between the left heart and the right heart in terms of valve opening and closure, although the sequences are the same. The sequence of valve opening and closure during the cardiac cycle is as follows:

- *Left heart:* Mitral closure, aortic opening, aortic closing, mitral opening.
- *Right heart:* Tricuspid closure, pulmonic opening, pulmonic closure, tricuspid opening.
- *Aggregate sequence:* Mitral closure, tricuspid closure, pulmonic opening, aortic opening, aortic closure, pulmonic closure, tricuspid opening, mitral opening.



Isovolumetric periods in the cardiac cycle refer to short intervals when all of the valves are closed. On the left side of the heart during isovolumetric contraction, ventricular pressure exceeds atrial pressure, and thus the mitral valve has closed. Ventricular pressure rises as the heart contracts, but it has not yet exceeded aortic pressure, and thus the aortic valve is still closed. During isovolumetric relaxation, ventricular pressure is less than aortic pressure, and thus the aortic valve is closed. However, ventricular pressure has not yet fallen below atrial pressure, and therefore the mitral valve is still closed. The overall sequence in the cardiac cycle in the ventricles consists of isovolumetric contraction, followed by ejection, isovolumetric relaxation, ventricular filling, isovolumetric contraction, and so forth.

The asynchrony between the left- and right-side valves is caused by differences in the pressure gradients between the sides of the circulation, and the degree of asynchrony varies during the respiratory cycle, because of the effects of thoracic pressure on filling and pressures within the heart and central circulation.

Ventricular Pressure

The cardiac cycle is initiated by the P wave of the electrocardiogram (ECG). Depolarization of the atria results in atrial contraction and final filling of the ventricles; this accounts for the slight increase in **left ventricular pressure** (**LVP**). When the wave of depolarization reaches the ventricle (QRS complex of the ECG) and ventricular contraction is initiated, LVP rises above **left atrial pressure** (**LAP**), producing mitral valve closure and marking the beginning of isovolumetric contraction. **Left ventricular end-diastolic pressure** (**LVEDP**) is normally about 5 mm Hg (RVEDP is normally about 2 mm Hg). From this point, LVP rises rapidly, as the ventricle attempts to contract against a fixed volume. When LVP rises above aortic pressure, the aortic valve opens, marking the end of isovolumetric contraction and the beginning of ventricular ejection. If aortic pressure is 120/80 mm Hg, this occurs at 80 mm Hg. LVP continues to rise for a period, but as the stroke volume is ejected, LVP reaches a peak (at approximately 120 mm Hg when aortic pressure is 120/80 mm Hg) and begins to fall. The T wave of the ECG occurs at this time,

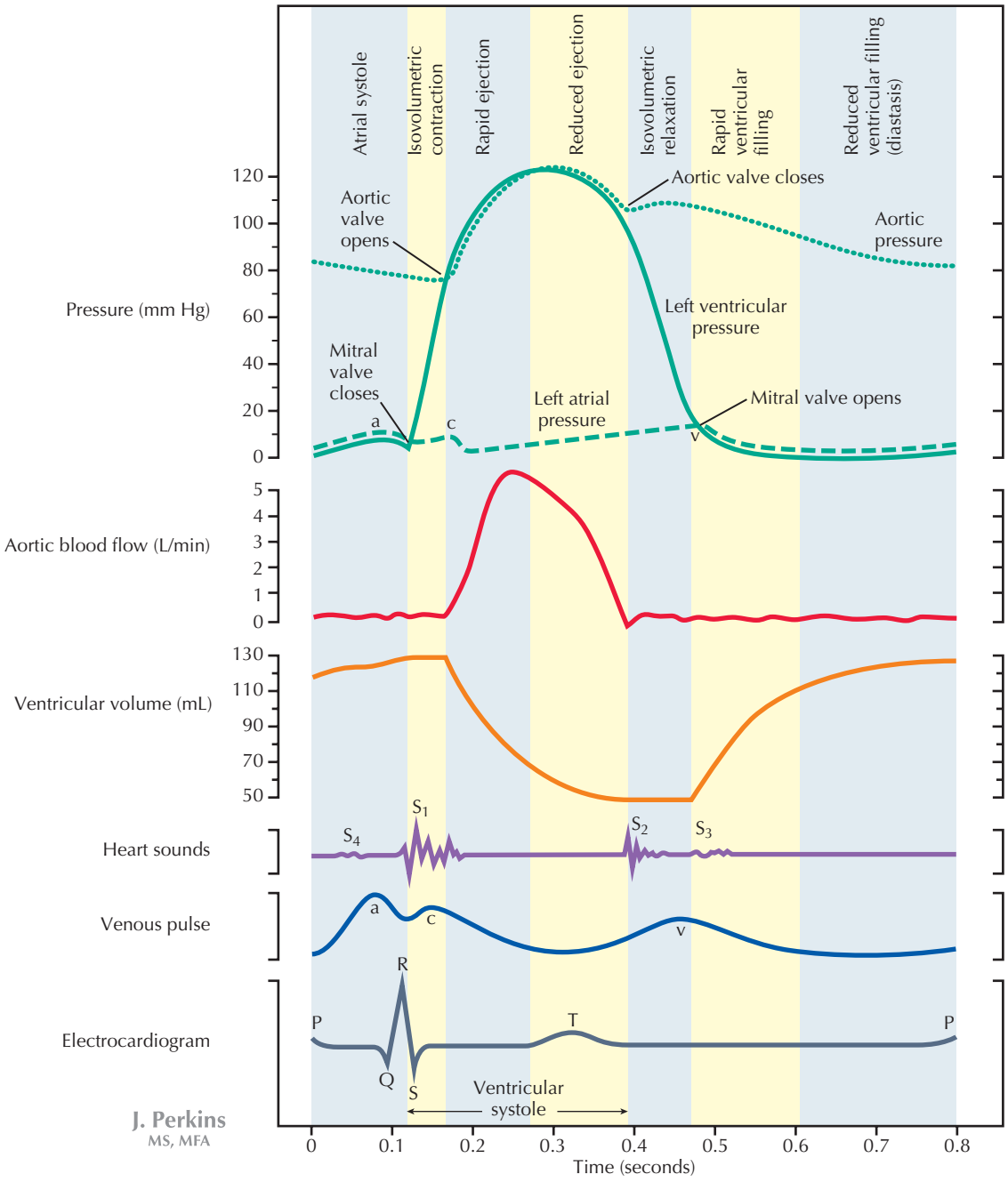


Figure 11.1 The Cardiac Cycle The cardiac cycle (or Wiggers diagram) is a simultaneous depiction of several parameters related to blood flow and volume, the electrocardiogram, and the echocardiogram through a cycle of cardiac systole and diastole. Ventricular systole begins with a short period of isovolumetric contraction, during which all of the heart valves are closed. This is followed by the ejection phase of systole, and then isovolumetric relaxation when the heart valves are again all closed. Cardiac filling occurs after isovolumetric relaxation. The temporal relationships between features of these various curves or tracings are predictable, based on functional relationships within the cycle. The a, c, and v waves are identified on both the venous pulse and atrial pressure curves.

as ventricular repolarization takes place. LVP falls below aortic pressure, but aortic valve closure is not immediate, due to the momentum associated with ventricular ejection. Closure of the aortic valve marks the end of ejection and the beginning of isovolumetric relaxation. During this period, the ventricle is beginning to relax, but the valves are closed, resulting in rapid fall of LVP. When LVP falls below LAP, the mitral valve opens, and ventricular filling begins. During the remainder of diastole, LVP remains slightly below LAP, consistent with the direction of blood flow during ventricular filling.

Aortic Pressure

The **aortic pressure** curve falls during diastole as blood flows to the peripheral circulation (see Fig. 11.1). The upstroke in this curve begins (at 80 mm Hg if aortic pressure is 120/80 mm Hg) with the opening of the aortic valve. As ejection proceeds, pressure rises to the systolic aortic pressure (120 mm Hg in this example), and then begins to fall. The dicrotic notch, a high frequency deflection in the aortic pressure curve, occurs when the aortic valve closes. **Aortic flow** reaches a peak during rapid ejection and is lowest during diastole when no ejection is occurring.

Ventricular Volume

The **left ventricular volume** curve illustrates the filling and emptying of the ventricle (see Fig. 11.1). At the time of the P wave, ventricular filling is nearly complete, but the final filling (approximately 15%) is produced by atrial contraction. This phase of ventricular filling is known as **active ventricular filling.** Ventricular filling ends when the mitral valve closes, at the left ventricular **end-diastolic volume (EDV).** Of course, ventricular volume remains constant during isovolumetric contraction. With opening of the aortic valve, rapid ejection of blood begins, and ventricular volume falls quickly. This is followed by a period of reduced ejection, which ends with aortic valve closure. At this point, left ventricular **end-systolic volume (ESV)** has been reached, and this volume remains constant during isovolumetric relaxation. The stroke volume is the difference between EDV and ESV. Normal EDV is approximately 140 mL and normal stroke volume is approximately 70 mL, although these values vary considerably. Opening of the mitral valve initiates a period of **rapid passive filling.** This is followed by a period of **slow passive filling** (also known as **diastasis**), as the ventricle fills more slowly with the diminished pressure gradient between the atrium and ventricle.

Atrial Pressure

The shape of the **left atrial pressure** curve reflects both cardiac events and venous return (flow of blood back to the atrium); it consists of the a, c, and v waves. Following the P wave on the ECG, atrial contraction produces the first rise in atrial pressure, the a wave (see Fig. 11.1). During isovolumetric contraction, there is another upward wave in the LAP curve, the c wave, caused by bulging of the mitral valve back into the left atrium, as the ventricle attempts to contract against a fixed volume. During the ejection phase of the left ventricle, LAP rises slowly while venous return from the pulmonary circulation fills the atrium (the mitral valve is closed during this period), producing the v wave. When LVP falls below LAP, the mitral valve opens and LAP falls as blood flows into the left atrium. For the remainder of diastole, LAP remains above LVP as the heart fills. Because there are no valves between the vena cavae and right atrium (or the pulmonary vein and left atrium), the **venous pulse** and the atrial pressure curve are similar in shape.



The events of the cardiac cycle are initiated when an action potential is generated in the sinoatrial (SA) node, producing depolarization and contraction of the atria, followed by contraction of the ventricles. When heart rate is increased, diastole is shortened, because the P wave (and thus, atrial and ventricular contraction) occurs earlier. As a result, the time for ventricular filling is diminished. However, at a resting heart rate of 70 beats per minute, there is a significant period of diastasis (slow ventricular filling), and, up to a point, increasing heart rate will not limit the time for rapid passive filling, the period during which most ventricular filling occurs. Very rapid heart rates allow insufficient time for ventricular filling and can even compromise cardiac output.

Phonocardiogram

The **phonocardiogram** is an acoustical recording reflecting the **heart sounds** generated during the cardiac cycle (see Fig. 11.1). S_1, the first heart sound, is generated by closure of the mitral and tricuspid valves (the mitral valve closes slightly before the tricuspid valve). S_2 is associated with closure of the aortic and pulmonic valves; again, the valve on the left side closes just before the right-side valve. During inspiration, closure of the pulmonic valve is delayed more distinctly, normally resulting in audible **physiological splitting** of S_2. This delay is caused by increased filling of the right ventricle, due to reduced intrathoracic pressure during inspiration. S_3, the third heart sound, is normal in children, and is associated with rapid ventricular filling. It is not heard in normal adults, and may be a sign of volume overload, as in congestive heart failure. S_4, caused by active ventricular filling, also is not audible in normal adults, but may be present in a variety of disease states.

REGULATION OF CARDIAC OUTPUT

Cardiac output is 5 liters (L) per minute (min) in the average, resting adult. The **cardiac output formula** is a key physiological concept, relating cardiac output (CO) to heart rate (HR) and stroke volume (SV):

$$CO = HR \times SV$$

At rest, HR is approximately 70 beats per minute and SV is approximately 70 mL, yielding CO of approximately 5000 mL/min (5 L/min). In order to maintain adequate arterial blood pressure and blood flow at rest, during increased activity, or during challenges to homeostasis such as exercise, CO must be adjusted through regulation of HR and SV. Many of the mechanisms that regulate HR or SV affect both parameters, and furthermore, are closely linked to mechanisms involved in blood pressure regulation.

The **autonomic nervous system** (ANS) plays an important role in regulation of cardiac output, through modulation of

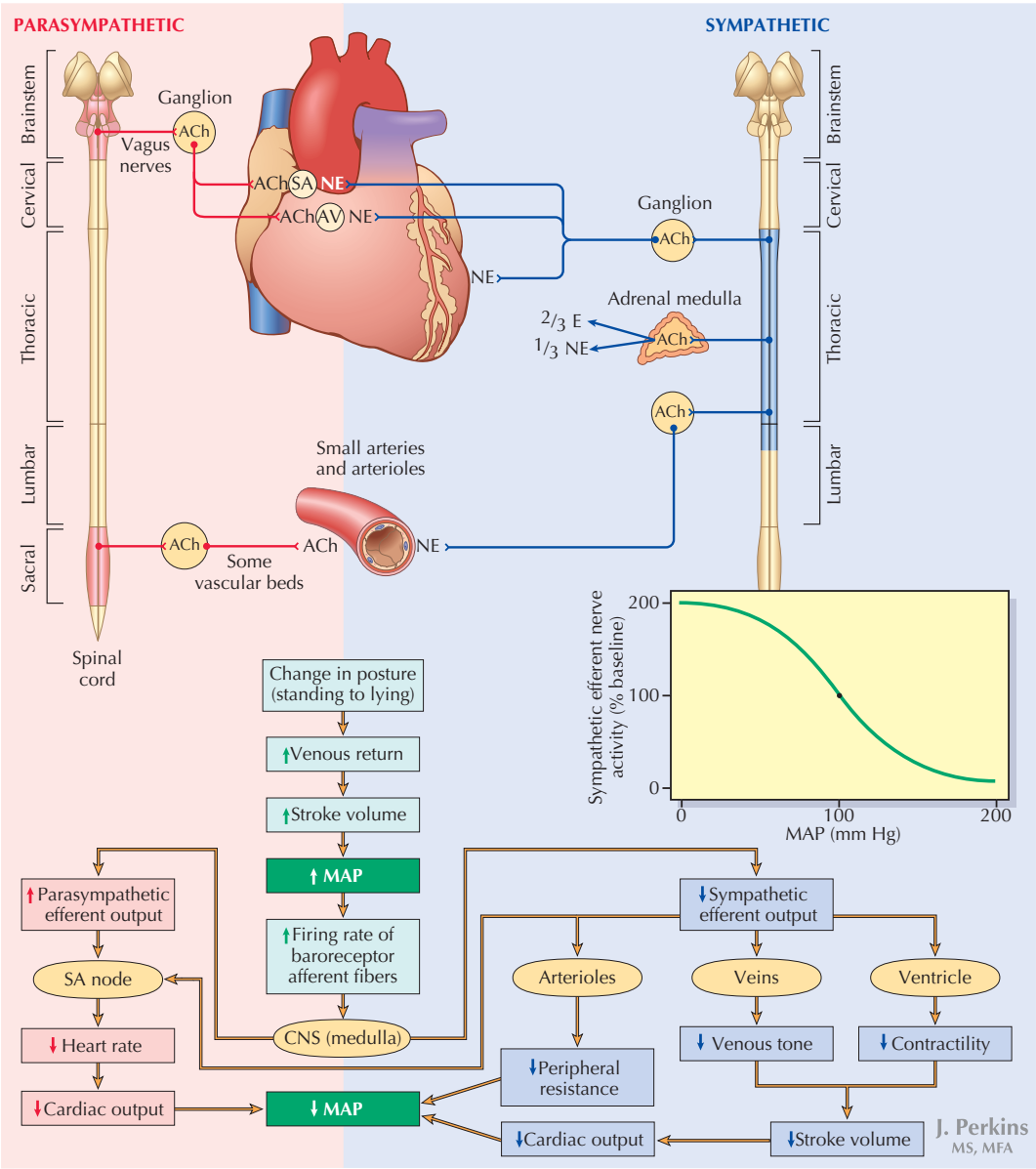


Figure 11.2 Autonomic Nervous System and Arterial Baroreceptor Reflexes Both sympathetic and parasympathetic nerves innervate the SA and AV nodes. The myocardium is innervated by sympathetic nerves. Arterial and venous vessels throughout most of the body are innervated by sympathetic nerves, whereas the parasympathetic nervous system innervates vessels in the genital organs and lower GI tract. Autonomic efferent activity is regulated by the baroreceptor reflex, in response to changes in arterial pressure detected at the carotid sinus and aortic arch baroreceptors. The response to a change in posture is illustrated. ACh, acetylcholine; E, epinephrine; MAP, mean arterial pressure; NE, norepinephrine.

the SA nodal pacemaker rate, myocardial contractility, and vascular smooth muscle tone (Fig. 11.2). Sympathetic nerve endings at the heart and vessels release norepinephrine, while parasympathetic nerves release acetylcholine at the heart (primarily the SA node) and in a few vascular beds (vessels in most regions do not have parasympathetic innervation). In addition to direct release of catecholamines by sympathetic nerves in the heart and vessels, circulating catecholamines (predominantly epinephrine) released by the adrenal gland contribute to cardiovascular regulation when the sympathetic nervous system is strongly activated.

Heart Rate Regulation

The arterial **baroreceptor reflex** is a key mechanism involved in autonomic regulation of cardiovascular function (see Fig. 11.2). The baroreceptors consist of specialized cells in the vascular wall of the carotid sinuses and aortic arch. Barorecep-

tors respond to the stretch associated with elevation of arterial pressure by increasing afferent impulses to the medullary cardiovascular center, where autonomic nervous system activity is regulated. In response to increased afferent input, sympathetic nerve activity is reduced, and parasympathetic outflow is increased. The effects of these autonomic responses on the heart and vessels result in a return of arterial blood pressure toward its original level; specific aspects of this regulation are discussed in the following text.

Mechanisms that contribute to **regulation of heart rate** include the following:

- The autonomic nervous system and baroreceptors.
- The Bainbridge reflex response to atrial stretch.
- Effects of thoracic pressure changes during respiration on venous return.

Under normal conditions, heart rate regulation is accomplished primarily by the autonomic nervous system and baroreceptor reflexes. Sympathetic nerves release norepinephrine at the SA node, which acts at β_1 receptors, increasing cAMP production and ultimately raising the activity of the pacemaker and elevating heart rate. Parasympathetic activation reduces heart rate through release of the neurotransmitter acetylcholine. Thus, when arterial pressure rises, the baroreceptor reflex results in a fall in the SA node pacemaker rate. The resulting reduction in heart rate contributes to a fall in CO, and a return to normal arterial pressure (see Fig. 11.2). Conversely, reduced arterial pressure will result in less stretch of baroreceptors, reduced afferent impulses to the cardiovascular center, greater sympathetic activity, and reduced parasympathetic activity, raising heart rate and returning arterial blood pressure to the normal level.

Another reflex potentially regulating heart rate is the **Bainbridge reflex.** When right atrial volume is increased, low-pressure stretch receptors (that is, receptors responding to stretch at the low pressures typical in the atria) initiate a neural reflex that increases heart rate through sympathetic nerves. Note that arterial baroreceptors respond to stretch by decreasing heart rate, whereas atrial baroreceptors respond to stretch by increasing heart rate. In the former case, the response is part of a mechanism to regulate arterial pressure, and in the latter case, the response is to increased blood volume. When atrial stretch results in increased HR, blood volume will be redistributed. In addition, a number of other mechanisms for regulating blood volume and pressure will be activated; these will be considered subsequently (see "Regulation of Arterial Blood Pressure" in Chapter 12).

Heart rate may also be affected by the respiratory cycle, particularly in infants and children. In so-called **respiratory sinus arrhythmia,** heart rate is increased during inspiration and decreased during expiration. The low-pressure baroreceptors within the atria are stretched by increased venous return during inspiration, producing the cyclic variation in HR.



The Bainbridge reflex and the arterial baroreceptor reflex produce opposite responses to an intravenous infusion. The Bainbridge reflex is usually observed when a rapid intravenous infusion is administered to a subject with a slow heart rate. Stretch of atrial receptors produces a reflexive increase in heart rate under these circumstances. On the other hand, when heart rate is high to begin with, for example, after hemorrhage, intravenous infusion usually decreases heart rate. In this circumstance, the increased ventricular filling associated with the infusion produces an increase in cardiac output and therefore an increase in arterial pressure. The rise in arterial pressure causes stretch of arterial baroreceptors, resulting in diminished sympathetic nervous system activity and enhanced parasympathetic activity, and a slowing of heart rate.

Stroke Volume Regulation

Stroke volume regulation is dependent on several parameters:

- **Preload:** The degree of stretch of myocardial fibers prior to contraction. Preload in the intact heart is closely related to end-diastolic volume of the ventricle. Increased preload is associated with increased force of contraction, and hence, increased stroke volume.
- **Afterload:** The force against which the heart contracts. In the intact heart, afterload is closely related to arterial pressure or left ventricular pressure during systole. Increased afterload opposes ejection by the heart and therefore will tend to reduce stroke volume.
- **Contractility (inotropism):** The intrinsic ability of cardiac muscle to generate force at a given fiber length. Specifically, contractility is *not* synonymous with force of contraction, because force of contraction is dependent on degree of initial stretch of the muscle fibers (preload).

The Frank-Starling Relationship

The **Frank-Starling relationship** is named for Otto Frank, who described the relationship between pressure generated in the frog heart and the diastolic volume, and for Earnest Starling, who demonstrated, in an intact, canine heart-lung preparation, the relationship between stroke volume and end-diastolic volume. The **cardiac function curve** illustrates this relationship (Fig. 11.3*A*). When preload is increased by raising atrial pressure, stroke volume (and therefore, cardiac output) rises, up to the optimum level of preload. This is an intrinsic mechanism for regulation of stroke volume and is not associated with a change in inotropism. The molecular basis for this relationship involves stretch of sarcomeres; at optimal preload, conditions for subsequent crossbridge formation and recycling are best.

Sympathetic Regulation of Stroke Volume

Stroke volume is also regulated by the **sympathetic nervous system** (Fig. 11.3*B*). Cardiac muscle is directly innervated by

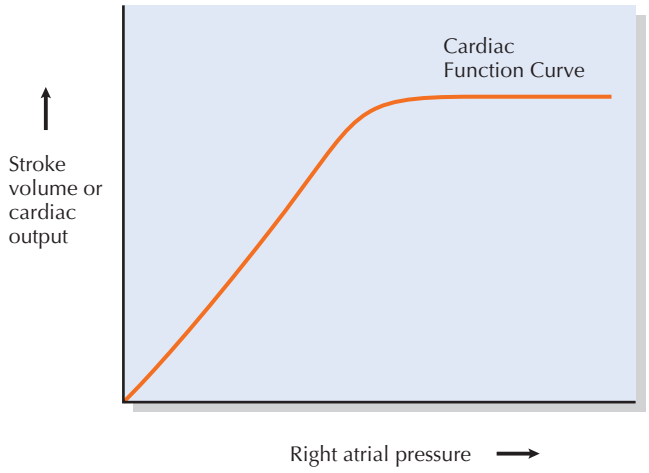


Figure 11.3 The Frank-Starling Relationship *A*, An increase in preload of the ventricle results in an increase in stroke volume and thus cardiac output. *B*, Sympathetic stimulation of the heart shifts this curve upward and to the left; heart failure results in a lower slope of the curve. The slope of the cardiac function curve is one measure of contractility of the heart. In this graph, it is assumed that afterload (arterial pressure) is held constant.

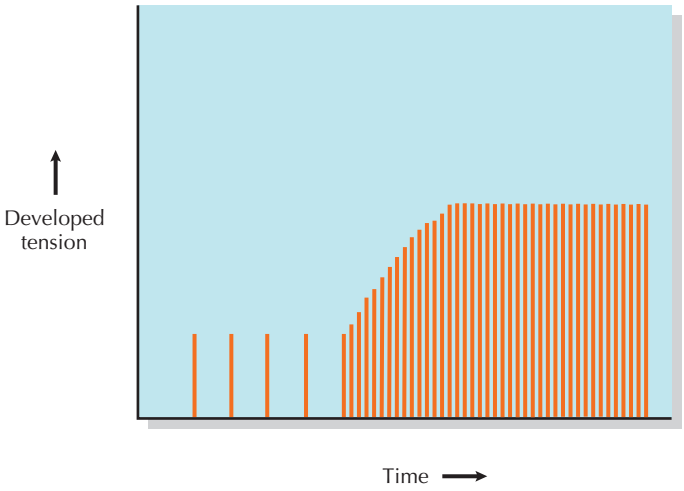


Figure 11.4 Effect of Heart Rate on Force of Contraction (Treppe or Staircase Effect) When the intervals between cardiac muscle contractions are long, the tension developed is low. Note the staircase-like increase in the force of contraction when frequency (heart rate) is increased. Because this effect is not dependent on changes in resting fiber length, contractility (inotropism) is increased.

sympathetic nerves, which release norepinephrine. Norepinephrine, through binding to β-adrenergic receptors (β_1), produces elevation of intracellular free Ca^{2+} levels, resulting in increased contractility of the heart. This is a true increase in inotropism or contractility, because it is independent of any change in preload. Release of epinephrine by the adrenal medulla may also produce greater contractility of the heart, although levels of circulating epinephrine rarely reach levels that significantly affect inotropic activity. The parasympathetic nervous system has only limited effects on contractility of human ventricles. Clinically, a number of drugs are used to promote inotropism in heart failure patients, including digitalis, dopamine, and dobutamine. Although the basic cardiac function curve simply describes the effects of preload on cardiac output or stroke volume, the slope of this curve is a measure of inotropism. With sympathetic stimulation, the slope is steeper, indicating enhanced contractility.

Treppe, also known as the **staircase effect,** is an intrinsic mechanism for regulation of stroke volume. When cardiac contractions are infrequent, force of contraction is reduced; as heart rate increases, force of contraction is elevated (Fig. 11.4). Because these changes occur independently of changes in preload, they reflect a change in contractility. The increased contractility at higher heart rates is associated with elevated free intracellular Ca^{2+} in myocardial fibers.

During a baroreceptor-mediated response to a fall in arterial pressure (see Fig. 11.2), many mechanisms contribute to the change in cardiac output. Sympathetic activation elevates heart rate, as discussed previously, but unless mechanisms are available for maintaining or elevating stroke volume simulta-

The Frank-Starling relationship is an important mechanism for matching cardiac output and venous return, and left- and right-side cardiac output. If output from the right ventricle is suddenly increased (for example, due to a change in posture), return to the left ventricle will be rapidly elevated. The resulting stretch of the left ventricle will cause an increase in its output, matching the rise in output that occurred on the right side. Thus, the Frank-Starling relationship maintains balance between right- and left-side output. It is also an important mechanism in the adjustment of stroke volume and cardiac output during the complex physiological changes associated with exercise or volume depletion (for example, in hemorrhage).

neously, elevation of heart rate is not an effective mechanism for raising cardiac output, because filling time for the heart is reduced. By raising contractility of the heart, sympathetic activation enhances stroke volume as well, and, simultaneously, sympathetic constriction of the systemic venous system elevates preload of the heart, allowing the Frank-Starling relationship to further augment stroke volume and cardiac output.

ASSESSMENT OF CARDIAC FUNCTION

Force–Velocity Curves

Assessment of cardiac function and, in particular, inotropism is important both clinically, in heart failure patients, and experimentally. In addition to analysis of the **cardiac function curve** and its slope, analysis of the **force–velocity relationship** in cardiac muscle illustrates the effects of preload and altered contractility on cardiac function (Fig. 11.5). Experimentally, force–velocity curves are usually constructed by measuring velocity of contraction of isolated segments of cardiac muscle against various afterloads. When velocity of contraction is plotted against afterload, an inverse relationship is revealed: when the force of contraction is higher (i.e., when the muscle contracts against higher afterload), velocity of shortening is reduced. Maximum force of contraction occurs at zero velocity, that is, during an isometric contraction. On the other hand, velocity is highest (V_m) at zero afterload. Changes in preload produce a family of curves, all with the same y-intercept (the same maximum velocity of contraction at zero afterload). These curves are another manifestation of the Frank-Starling relationship: greater preload generally results in greater force of contraction, and thus velocity of contraction, although V_m is unchanged. V_m is a measure of the contractile state of the tissue, representing the maximal rate at which actin and myosin filaments can interact to produce contraction. In contrast to the effects of changes in preload, positive inotropic influences such as sympathetic stimulation change V_m. The force–velocity curve is shifted upward and to the right, with an increase in the maximal force that can be developed by the muscle (during an isometric contraction, at the x-intercept) and an increase in V_m (at the y-intercept). An increase in V_m is indicative of a positive inotropic effect.

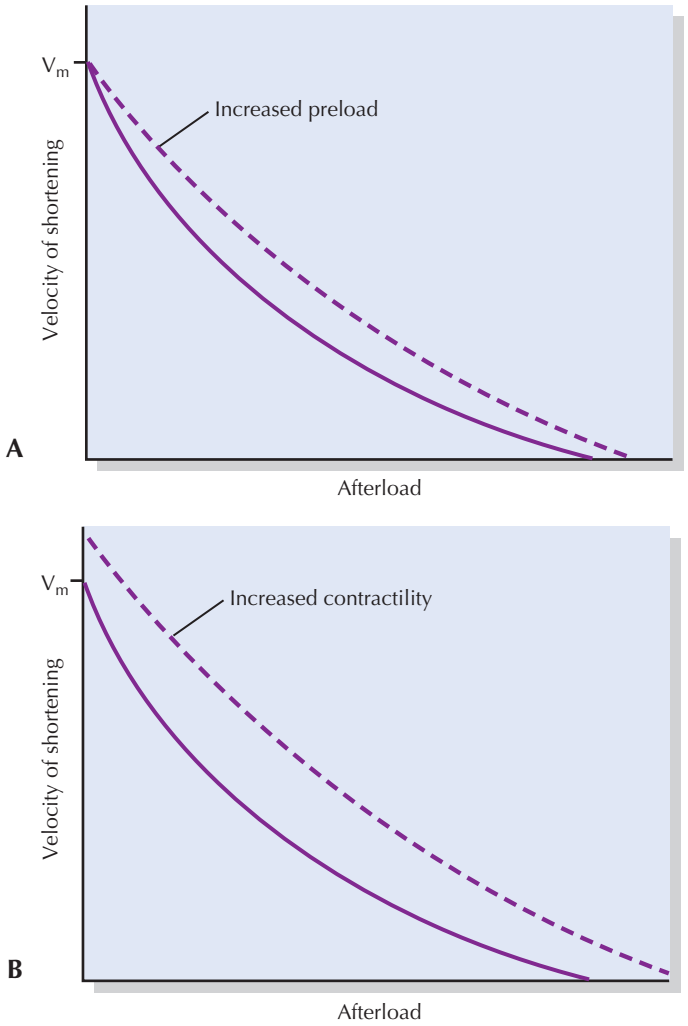


Figure 11.5 Force–Velocity Relationship in Cardiac Muscle Force–velocity curves depict the effect of afterload on velocity of contraction of cardiac muscle. *A*, When the force of contraction is higher (i.e., when the muscle contracts against higher afterload), velocity of shortening is reduced. Velocity is highest (V_m) at zero afterload. Increased preload shifts the curve upward, but V_m, a measure of contractility, is unchanged. *B*, Positive inotropic influences such as sympathetic stimulation change V_m. The force–velocity curve is shifted upward.

Pressure–Volume Relationship

The ventricular **pressure–volume loop** is a continuous measurement of ventricular volume against ventricular pressure during the cardiac cycle (Fig. 11.6). During the period of isovolumetric contraction, volume is constant, but pressure rises rapidly. During the ejection phase of the cycle, volume falls, while pressure remains high. Subsequently, during isovolumetric relaxation, volume is constant and pressure falls rapidly. This cycle is then repeated over and over, with each beat. The shape and the area within this loop are affected by changes in preload, afterload, and contractility.

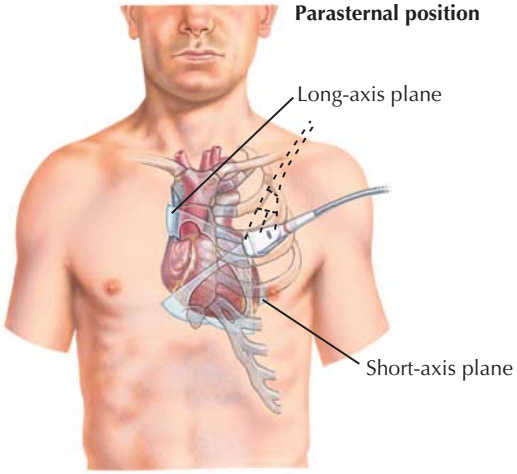
Ejection Fraction

A simple and useful measurement for assessment of myocardial function is the **ejection fraction.** Ejection fraction is the ratio of stroke volume to end-diastolic volume. In a healthy person at rest, this should be greater than 50%. If a positive inotropic drug is administered, ejection fraction will rise; in myocardial ischemia or heart failure, ejection fraction is diminished. Ejection fraction can be estimated noninvasively by echocardiography.

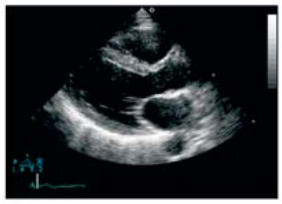
CLINICAL CORRELATE
Echocardiography

Echocardiography is a technique in which inaudible, high-frequency sound is transmitted through the thorax (transthoracic echocardiography) or esophageal wall (transesophageal echocardiography) into the heart. The echoes of the ultrasound, reflected at the interfaces of tissue and fluid, are recorded to produce a graphic image of the heart. In standard echocardiography, the resulting echocardiogram is a two-dimensional image of a slice of the heart. In Doppler echocardiography, the use of continuous wave Doppler ultrasound allows assessment of the velocity of blood flow within the heart. Using these techniques, it is possible to determine size and structure of valves and chambers; to determine ejection fraction and other parameters; and to detect abnormal wall motion, valvular regurgitation (leakage) or narrowing, bacterial growths (vegetation) within the heart, and other pathologies.

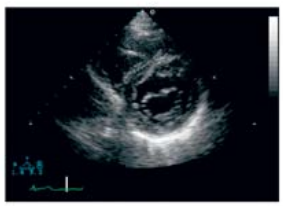
Transducer Positions in Echocardiographic Examination



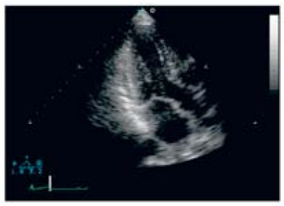
Left parasternal position allows views in long- and short-axis planes. Tilting transducer allows multiple sections.



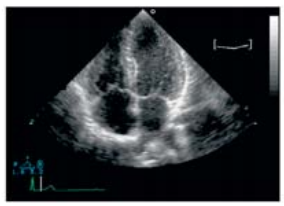
Normal long-axis view during systole



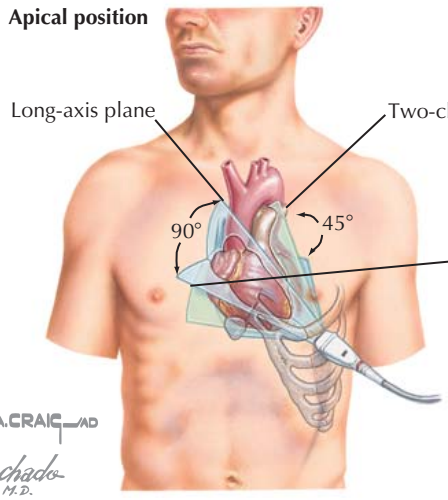
Normal short-axis view at mitral valve level



Normal apical long-axis view



Normal apical four-chamber view



Apical studies imaged from point of maximal impulse toward base. Four-chamber plane passes through atrioventricular valves; upward tilt gives five-chamber plane. Counterclockwise rotation of 45° gives two-chamber plane. 90° rotation gives long-axis plane.

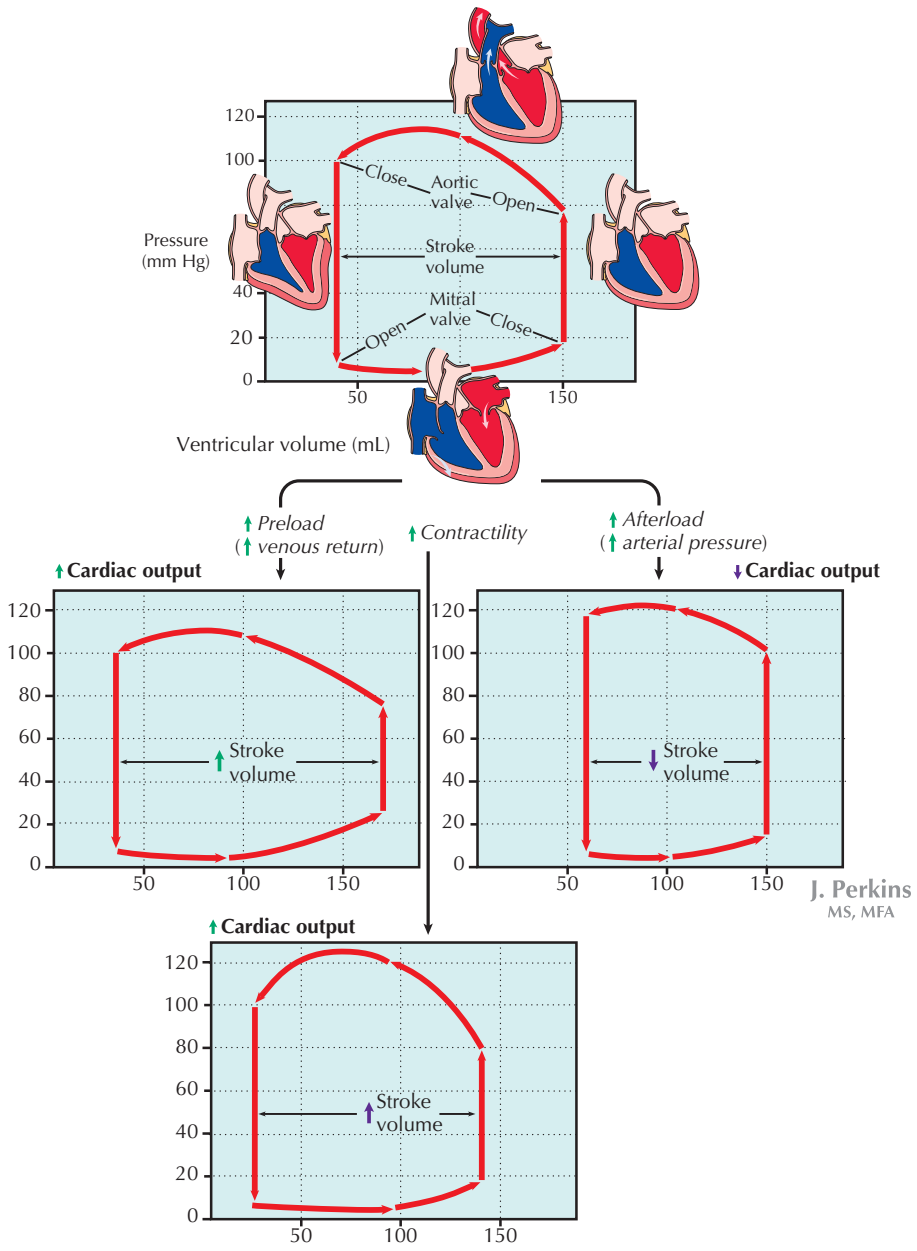


Figure 11.6 Ventricular Pressure–Volume Loop A continuous plot of ventricular volume and ventricular pressure during the cardiac cycle yields a closed loop. Following the *red arrows* from the bottom left of the top graph, during diastole, filling of the ventricle occurs with little change in pressure; during isovolumetric contraction, volume is constant, but pressure rises rapidly. During the ejection phase of the cycle, volume falls, while pressure remains high. During isovolumetric relaxation, volume is constant and pressure falls rapidly, to the starting point on the diagram. Changes in preload, afterload, and contractility affect stroke volume as illustrated.

VASCULAR FUNCTION AND CARDIAC OUTPUT

Regulation of cardiac output depends not only on adjustment of heart rate and stroke volume, but also on regulation of the function of veins and venous return. Venous return is defined as the flow returning to one side of the heart. Thus, since cardiac output is defined as flow from one ventricle, the normal value for venous return will be identical to cardiac output when averaged over time. If cardiac output is 5 L/min, venous return will also be 5 L/min. Matching of cardiac output and venous return is an important aspect of cardiovascular function.

Just as cardiac output is affected by various factors, so is venous return. Flow from the capillaries to the right atrium occurs despite a small pressure gradient. Because this

pressure gradient is small, venous return is affected by factors that are often different from those affecting the arterial system.



Cardiac output and venous return can be conceptualized as two sides of the same coin, cardiac output being the flow from one side of the heart and venous return being the flow back to one side of the heart. Measured over time, cardiac output and venous return must be equal, since cardiac output is completely dependent upon return of blood to the heart (venous return). A change in one of these parameters will produce an equivalent change in the other.

Venous Compliance and Gravitational Effects

An important factor affecting veins is **compliance** (the change in volume associated with a change in pressure). Compliance of veins is approximately 20-fold greater than that of arteries. Thus, when a person stands from a recumbent position, blood pools in the lower extremities as veins distend due to the hydrostatic pressure associated with the column of blood between the lower extremities and the right atrium. Cardiac output is transiently reduced upon standing as pooling occurs. To prevent **orthostatic hypotension** (decrease in blood pressure upon standing) and to restore venous return under these conditions, the most important compensatory mechanism is the **baroreceptor** reflex (see Fig. 11.2). Increased sympathetic outflow results not only in constriction of the arteries and augmentation of rate and contractile force of the heart, but also constricts veins, reducing the pooling effects of gravity. Veins, in fact, act as a reservoir of blood, which can be mobilized by sympathetic nervous system activation and venoconstriction, to increase venous return and, thus, cardiac output. This is an important mechanism in maintaining cardiac output during volume depletion as well. Movement of skeletal muscles is also important in preventing orthostatic hypotension. During walking, for example, movement of leg muscles compresses veins and augments venous return, because veins outside the central venous system contain one-way valves that prevent backflow of blood.

Effect of Respiration

Another factor affecting venous return is the **effect of respiration.** During inspiration, as the rib cage expands and the diaphragm moves down, negative pressure is created in the thorax. Simultaneously, pressure in the abdominal cavity rises, due to the downward movement of the diaphragm. Thus, veins in the abdomen are subjected to a positive pressure, which augments venous return toward the negative pressure in the thorax. During expiration, the gradient is reduced. With increased depth and frequency of respiration, for example during exercise, there is a pulsatile increase in venous return.

Cardiac Function and Vascular Function Curves

The interactions between vascular function and cardiac function can be illustrated by the simultaneous consideration of two relationships: the **cardiac function curve** (previously considered) and the **vascular function** curve (Fig. 11.7). The cardiac function curve illustrates the Starling relationship, in which right atrial pressure is the independent variable and cardiac output is the dependent variable. A rise in right atrial pressure (preload) produces a rise in cardiac output. The vascular function curve as illustrated is an unconventional graph, in which the independent variable (cardiac output) is plotted on the y-axis, and the dependent variable (right atrial pressure) is on the x-axis. This is an inverse relationship: a rise in cardiac output produces a fall in right atrial pressure (or preload). In other words, greater cardiac output will result in redistribution of blood volume, with reduction of preload. Note that the x intercept of the vascular function curve is the **mean circulatory pressure.** This is the pressure in the system when cardiac output is zero, and is dependent on blood volume and the compliance of the vascular system as a whole. Thus, if the heart is stopped, pressure equilibrates across the entire cardiovascular system. A positive mean circulatory pressure is necessary for the heart to effectively pump blood.



Mean circulatory pressure is the residual pressure that would exist throughout the cardiovascular system (after equilibration) if the heart were suddenly stopped and vascular tone throughout the system were to remain the same. The normal value for mean circulatory pressure is about 7 mm Hg and is a function of vascular tone (particularly venous tone) and blood volume. Without positive mean circulatory pressure, efficient circulation of blood would not be possible, because preload would be compromised at even a very low cardiac output.

Integration of the Cardiac and Vascular Function Curves

When the cardiac function and vascular function curves are plotted on the same graph, the two curves intersect at one point, the resting cardiac output and right atrial pressure (normally about 5 L/min and 2 mm Hg); in other words, this is the steady-state or equilibrium point for normal resting cardiovascular function. When one of the curves is altered, a new equilibrium point is reached. For example, an increase in blood volume (hypervolemia) will shift the vascular function curve upward and to the right (Fig. 11.7*B*). At the new equilibrium point for the two curves (point B), cardiac output is increased, due to higher preload. Venous constriction would have the same effect as increased volume. On the other hand, hypovolemia will shift the vascular function curve to the left and downward, and the new equilibrium point A represents lower cardiac output at rest. The cardiac mechanism resulting

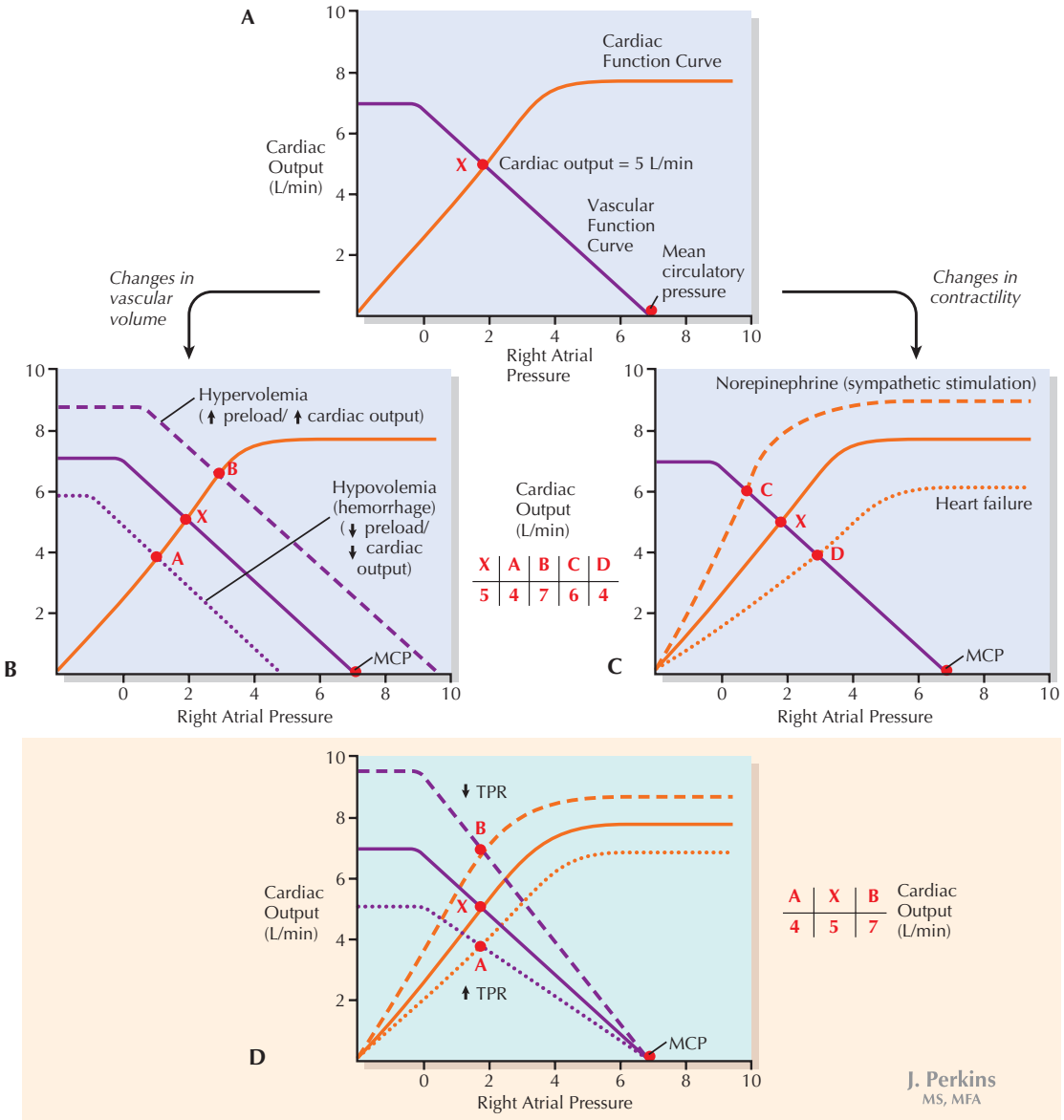


Figure 11.7 Cardiac Function and Vascular Function Curves *A*, In the cardiac function curve, right atrial pressure is the independent variable and cardiac output is the dependent variable. A rise in right atrial pressure produces a rise in cardiac output, as predicted by the Frank-Starling relationship. In the vascular function curve, the independent variable is cardiac output, plotted unconventionally on the y-axis, and the dependent variable is right atrial pressure. This is an inverse relationship; a rise in cardiac output produces a fall in right atrial pressure. The x-intercept of the vascular function curve is the mean circulatory pressure (MCP), the pressure throughout the system when cardiac output is zero. The two curves intersect at point X, the resting cardiac output and right atrial pressure. This is the normal resting steady state for cardiovascular function. When one of the curves is displaced, for example by a change in *(B)* blood volume, *(C)* contractility, or *(D)* total peripheral resistance (TPR), a new steady state is reached.

in these changes in cardiac output with changes in the vascular function curve is the Frank-Starling relationship.

Similarly, changes in the cardiac function curve also produce new equilibrium points between the two curves (Fig. 11.7*C*). An increase in contractility, for example due to sympathetic stimulation of the heart, will increase the slope of the cardiac function curve, with higher cardiac output at the new equilibrium. Heart failure is associated with a lower slope in the cardiac function curve, and cardiac output is reduced as a result.

Changes in total peripheral resistance (TPR) affect both the vascular function and cardiac function curves (Fig. 11.7*D*). In this analysis, it is assumed that arterial resistance (specifically, resistance in small arteries and arterioles) is altered, while

venous tone is unchanged. Thus, if TPR is diminished, the vascular function curve rotates up and to the right, because venous and right atrial pressure will be raised as a result of the lower arterial resistance. Note that mean circulatory pressure is unchanged, because total compliance of the vascular system is not significantly affected. The cardiac function curve shifts upward, as stroke volume is ejected against lower arterial pressure (reduced afterload) due to reduced TPR. Thus, the equilibrium point for the system moves from point X to point B, at which cardiac output is elevated from the original steady state. Opposite changes occur when TPR is elevated. The vascular function curve rotates downward and to the left, and the cardiac function curve shifts downward, due to the effects of increased afterload. The equilibrium shifts from point X to point A, at which cardiac output is reduced from the original steady state.

CLINICAL CORRELATE
Venous Pressure in Heart Failure

In right-heart failure, contractility of the right ventricle is reduced, often due to myocardial infarction. As a result, cardiac output will be reduced and venous pressure will be elevated. This knowledge can be useful diagnostically. If a normal individual is lying in bed with his upper body tilted up 30 to 60 degrees on a pillow, the external jugular vein is ordinarily collapsed just above the level of the clavicle. The height of the column of blood in the external jugular vein is a measure of central venous pressure or right atrial pressure. If a patient is in heart failure and the central venous pressure is elevated, the vein will be distended significantly above the clavicle.

CHAPTER 12 The Peripheral Circulation

The peripheral circulation consists of the systemic arteries, veins, and microcirculation. The structures of arteries and veins include three tissue layers (Fig. 12.1):

- **Tunica intima:** This innermost layer consists of a single endothelial cell layer forming the inner lining of the vessel; these cells rest on a basement membrane that separates the intima from the media.
- **Tunica media:** The media consists mainly of smooth muscle and is the contractile portion of the vascular wall.
- **Tunica adventitia:** The adventitia consists mainly of connective tissue.

There is variation in the absolute and relative thickness of media and adventitia between arteries and veins, as well as between small and large vessels; differences are also observed between vessel types in the connective tissue and cellular constituents of these layers. For example, the walls of large arterial vessels are rich in elastic tissue and have a relatively thick adventitia compared with smaller arteries. On the other hand, smaller arteries have a relatively more dominant, muscular medial layer. Capillaries, unlike other vessels, have no media or adventitia. Their vascular walls consist simply of endothelial cells and basement membrane.



The histological differences between various types of vessels reflect their functional roles. The thin wall of the capillaries, consisting of only an intimal layer, allows the efficient exchange of nutrients, waste, and dissolved gases between blood and tissues. On a relative basis, the muscular tunica media is more prominent in small arteries and arterioles than in large arteries or veins, reflecting their role in regulation of blood flow. Larger arteries have thick adventitia with significant elastic tissue, consistent with their role as "distributing vessels," whereas veins have more compliant adventitia. The tunica media of veins contains smooth muscle arranged both circularly and longitudinally, reflecting the function of veins as "capacitance vessels." Similarly, elastic tissue in the adventitia of veins is less prominent than in arteries.

THE MICROCIRCULATION AND LYMPHATICS

The microcirculation consists of vessels less than 100 micrometers (μm) in diameter and includes arterioles, metarterioles, capillaries, and venules (Fig. 12.2). Muscular arterioles may directly feed into capillaries or into metarterioles that structurally are between capillaries and arterioles. Precapillary sphincters are bands of smooth muscle found at the point at which blood enters capillaries. Constriction and relaxation of the smallest arteries, arterioles, and precapillary sphincters regulates flow into capillary beds (see "Regulation of Blood Flow").

The thin wall of capillaries consists of a single layer of endothelial cells and the associated basement membrane. This simple structure is well adapted for the diffusion of gases, nutrients, and wastes between blood and the interstitial fluid of tissues, which occurs only in capillaries. The exchange of fluid between the vascular space and interstitial space also occurs across the capillary wall by simple diffusion (see Fig. 2.1). The net filtration pressure for diffusion of fluid out of capillaries is governed by the Starling equation. Entering the capillary at the arteriolar end, hydrostatic pressure is approximately 30 mm Hg; it falls to approximately 10 mm Hg at the venular end of the capillary. Interstitial hydrostatic pressure is uniform within a local region; plasma oncotic pressure is high in plasma and substantially lower in the interstitial space. Thus, there is usually net filtration of fluid out of the capillary at the arteriolar end. Toward the venular end of the capillary, where capillary hydrostatic pressure is lower, net reabsorption of fluid into the capillary usually occurs.

Excess interstitial fluid is returned to the circulation through the lymphatic system (Fig. 12.3). Movement of fluid from the



Edema is the swelling associated with an increase in interstitial fluid in a tissue or body cavity. The amount of fluid in the interstitial space depends on the rate at which interstitial fluid is produced and the rate at which it is removed. When high capillary hydrostatic pressure, low capillary oncotic pressure, or leakage of proteins from the vascular space (producing high interstitial oncotic pressure) results in excessive fluid in the interstitial space, it is ordinarily removed by the lymphatic system. Edema may occur with blockage of the lymphatic system or excessive flux of fluid from the vascular space.

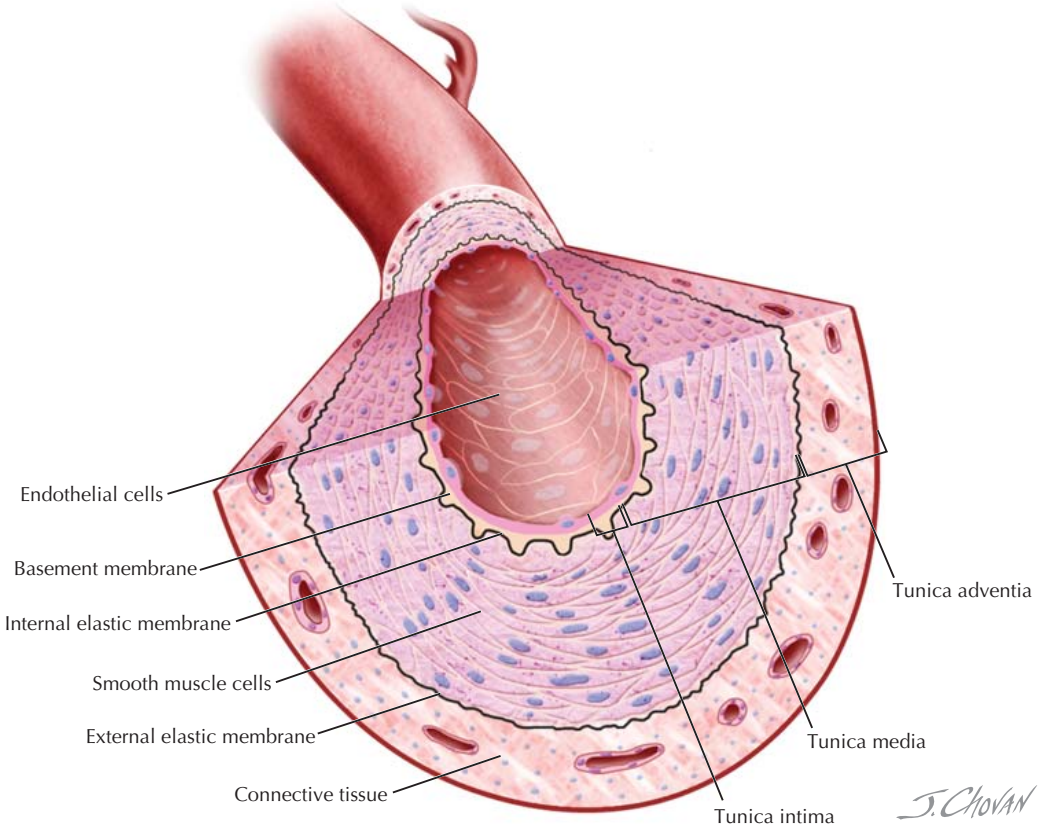


Figure 12.1 The Vascular Wall The vascular walls of arteries and veins have three tissue layers, with the relative thickness of medial and adventitial layers varying among various vessel types. The capillary wall consists of only the intimal layer of endothelial cells and basement membrane. The vessel illustrated above is a large artery, with prominent medial smooth muscle. The walls of large arteries and veins have their own vascular supply (vasa vasora). The tunica media of arteries is bounded by an internal elastic membrane (IEL) and an external elastic membrane (EEL).

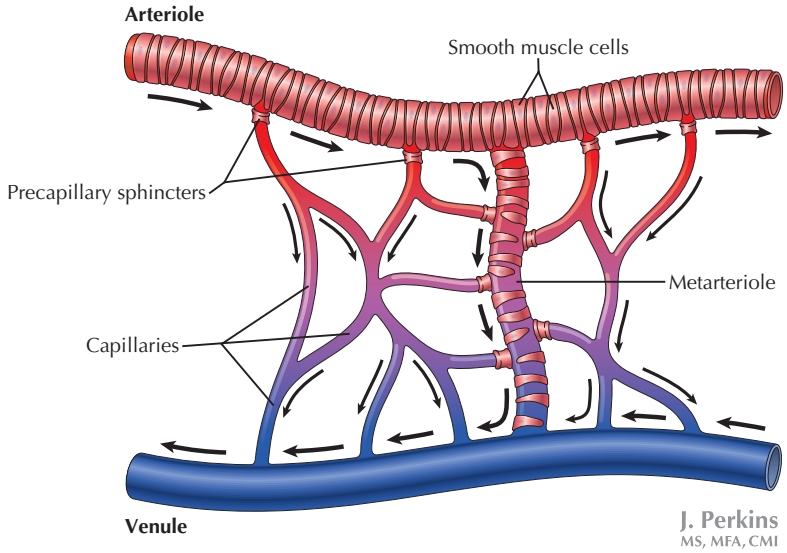


Figure 12.2 Components of the Microcirculation Arterioles, metarterioles, capillaries, and venules constitute the microcirculation. Direction of blood flow is indicated by arrows. Blood flow is regulated by constriction and dilation of smooth muscle of the arterioles, metarterioles, and precapillary sphincters. Sympathetic nerves extend to arterioles, metarterioles, and venules in the microcirculation.

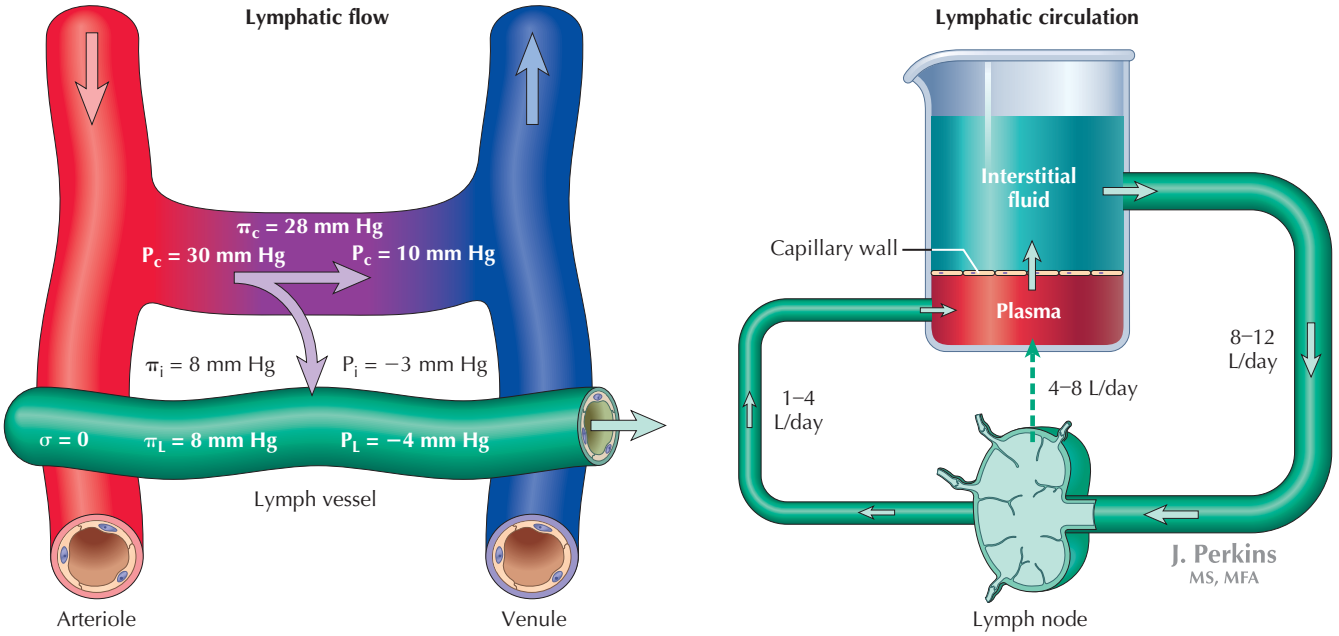


Figure 12.3 The Lymphatic Circulation Diffusion of fluid from the vascular space to the interstitial space is governed by the Starling equation (see Chapter 1). Excess fluid in the interstitial space is transported by the lymphatic system back to the central venous circulation. Movement of fluid from interstitium to the lymphatic system is driven solely by the hydrostatic pressure gradient, because there is no oncotic pressure gradient (protein flows freely through the lymphatic vessel wall). (P_c = HP_c, hydrostatic capillary pressure.)

interstitium into the capillaries is driven by the hydrostatic pressure gradient between the interstitial space and the lymph, because there is no significant oncotic pressure gradient (the protein reflection coefficient of lymphatic capillaries is zero), and there are one-way valves through which fluid and protein flow into lymphatic vessels. Lymph flows into larger lymphatic vessels and is returned into the central venous circulation through the thoracic duct.

REGULATION OF BLOOD FLOW

Flow through a specific tissue can be altered either by changes in perfusion pressure or changes in resistance of the arterial vessels perfusing the tissue. Obviously, when blood flow requirements of a specific tissue are altered, the most efficient mechanisms for adjusting blood flow will involve a change in regional resistance. On the other hand, when systemic metabolic needs vary, for example during exercise, regulation of flow is accomplished through changes in both systemic hemodynamics (blood pressure and cardiac output) and regional resistances, resulting in changes in both overall flow (cardiac output) and flow distribution between various tissues.

At the tissue level, both intrinsic and extrinsic factors may influence smooth muscle tone in the resistance vessels (arterioles, precapillary sphincters, and small arteries) in response to local and systemic events. Both smooth muscle and endothelial cells participate in this regulation. Basic aspects of smooth muscle structure and function are discussed in Section 2.

Regulation of Vascular Tone by Endothelial Cells

The role of the endothelium in regulation of smooth muscle contraction and relaxation is a relatively recent discovery. The endothelium participates in this regulation through these processes (Fig. 12.4):

- release of vasodilators such as nitric oxide and prostacyclin
- release of the vasoconstrictors endothelin
- conversion of angiotensin I to angiotensin II

Of particular importance is the endothelium's role in vascular regulation through production of **nitric oxide** (NO). When endothelial cells are exposed to **endothelium dependent vasodilators** such as acetylcholine, histamine, and bradykinin, the enzyme nitric oxide synthetase (NOS) is activated, resulting in the production of the short-lived but powerful vasodilator NO from the amino acid arginine:

$$\text{L-arginine} \xrightarrow{\text{NOS}} \text{NO} + \text{L-citrulline}$$

Nitric oxide diffuses to adjacent smooth muscle cells and acts on smooth muscle guanylyl cyclase, elevating cGMP. cGMP causes reduction in free intracellular Ca^{2+}, producing

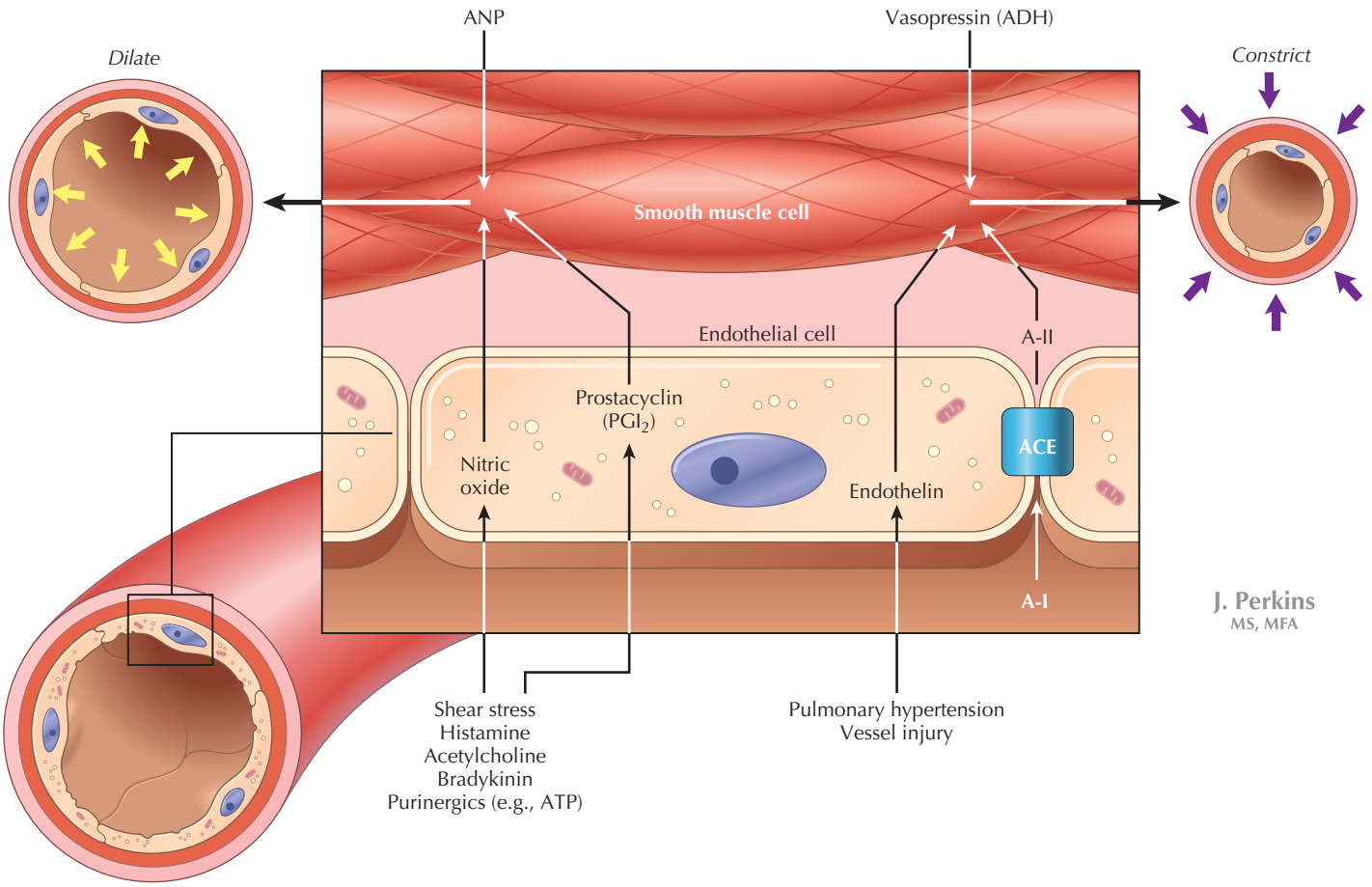


Figure 12.4 Control of Arteriolar Tone The greatest resistance to flow occurs in the small arteries and arterioles. The state of constriction or relaxation of these vessels is regulated in part by the sympathetic nervous system and the release of norepinephrine. Circulating hormones, including vasopressin (ADH) and angiotensin II (A-II), may contribute to constriction through their actions on vascular smooth muscle; atrial natriuretic peptide (ANP) is a smooth muscle dilator. The endothelium plays an important role in regulating vascular tone by its release of nitric oxide (NO) and prostacyclin (PGI_2) in response to many factors, including shear stress, acetylcholine, and bradykinin. Endothelin is a potent, endothelium-derived vasoconstrictor important in some pathophysiologic states. The endothelial cell surface also has angiotensin-converting enzyme, which forms angiotensin II by cleavage of circulating angiotensin I (A-I, an inactive precursor).

relaxation of smooth muscle and thus vasodilation. This mechanism is particularly important in vascular responses to inflammatory stimuli, as well as in parasympathetic-mediated vasodilation in the genital system and lower gastrointestinal tract (vessels in other regions are not innervated by the parasympathetic nervous system). In addition, many substances that directly act on smooth muscle cells to produce constriction (for example, norepinephrine) also release endothelial NO. This simultaneous release and action of NO results in a dampened response to vasoconstrictors in healthy vessels, as opposed to vessels in which the endothelium has been damaged. Many of the same stimuli that release NO also release **prostacyclin** (PGI_2) from endothelial cells, a vasodilator metabolite of arachidonic acid. Although prostacyclin is less important than NO in regulation of vascular tone, both mediators are important in preventing activation of platelets and their adherence to the vascular wall. The actions of prostacyclin are opposed by **thromboxane A_2**, which is a major product of arachidonate in activated platelets. Thus, thromboxane A_2 is a potent prothrombotic substance and vasoconstrictor, important in inflammatory states and hemostasis.

The release of NO by **shear stress** is believed to participate in vascular control as follows: When blood flow to a region is increased (for example, by vasodilation in the arterial microcirculation), the higher flow causes elevated shear stress in the endothelial cells of vessels supplying the region, which respond by increasing NO production. Adjacent smooth muscle cells relax when exposed to NO, resulting in vasodilation and further augmentation of flow.

Endothelin is a powerful vasoconstrictor protein released by endothelial cells when vessels are damaged. Its role in vascular regulation in normal tissues is controversial, although it is an

The nitric oxide produced by endothelial cells is sometimes referred to as "EDRF," or endothelium-dependent relaxing factor. This name is based on the original discovery by Robert Furchgott that vessel segments experimentally denuded of endothelium did not display smooth muscle relaxation when stimulated by acetylcholine and other "endothelium-dependent" vasodilators. Subsequent studies during the 1980s by several investigators led to the identification of EDRF as nitric oxide. The journal *Science* named nitric oxide "Molecule of the Year" in 1993, and the Nobel Prize in Medicine or Physiology went to Furchgott, Louis Ignarro, and Ferid Murad for their work in this area.

important pathophysiologic mediator, for example in pulmonary hypertension and preeclampsia. **Angiotensin-converting enzyme** (ACE) is an enzyme found on the surface of endothelial cells. This enzyme cleaves angiotensin I to **angiotensin II,** a potent vasoconstrictor. Like the posterior pituitary hormone **vasopressin,** angiotensin II is important in long-term regulation of blood pressure through its effects on renal sodium and water retention (see Section 5), and plays a role in acute responses to hypotensive crises such as hemorrhage. However, neither angiotensin II nor vasopressin is believed to be important in short-term regulation of vascular function.

Until the second half of the 20th century, the endothelium was generally believed to function mainly as a lining or barrier between blood and tissues. In the past few decades, appreciation of its role in many physiological processes has blossomed. The endothelium is important in regulating vascular tone, angiogenesis (formation of blood vessels), and the hemostatic process (healthy endothelium is "antithrombogenic" due to its formation of nitric oxide and prostacyclin). In addition, the endothelium has a role in metabolism. An example is conversion of angiotensin I to angiotensin II by its angiotensin-converting enzyme. The endothelium has an important role in disease processes, for example in atherosclerosis, in which diminished endothelial nitric oxide production and alterations in other endothelial functions are among the earliest changes observed.

Local Control of Blood Flow

Local regulation of blood flow occurs through mechanisms that involve responses to local metabolic products and transmural pressure (pressure gradient across the vascular wall) (Fig. 12.5*A*). If blood flow to a region is occluded temporarily, when flow is reestablished, **reactive hyperemia** occurs. In other words, blood flow is elevated above the original level. Reactive hyperemia occurs as a result of **local metabolites** that accumulate during the occlusion. These metabolites, which include CO_2, H^+, K^+, lactic acid, and adenosine, act directly on smooth muscle of arterioles and precapillary sphincters in the region to produce vasodilation. Thus, flow is elevated until the tissue levels of O_2 are restored and accumulated metabolites are removed. In contrast to reactive hyperemia, **active hyperemia** refers to the increase in flow that occurs in tissues when metabolism is elevated (Fig. 12.5*B*). An example of this is the greatly increased flow to skeletal muscles during exercise. Ongoing production of local metabolites in the working skeletal muscles causes vasodilation, thus enhancing flow to the muscles.

Autoregulation of local blood flow can occur without changes in local metabolism (Fig. 12.5*C*). In many tissues and organs, if blood flow is artificially increased by raising the perfusion pressure to the vascular bed, flow will be immediately elevated as expected; however, it soon returns toward the basal rate. According to the **myogenic hypothesis,** smooth muscle cells constrict in response to elevated transmural pressure, in other words, in response to stretch. This is a mechanism whereby flow to a tissue is kept fairly constant, despite changes in pressure, when metabolic needs of the tissue are not changing. Myogenic regulation does not involve the vascular endothelium, but is a direct response of smooth muscle cells.

Extrinsic Regulation of Peripheral Blood Flow

Extrinsic regulation of peripheral blood flow involves vasoconstriction or vasodilation in response to neural mechanisms and circulating vasoactive substances. Smooth muscle cells have several types of adrenergic receptors:

- α-Receptors, which mediate the constrictor responses to catecholamines. Receptors of the subtype α_1 are the predominant subtype in vascular tissue; α_2-receptors also produce vasoconstriction by inhibiting reuptake of norepinephrine. α_1-Adrenergic vasoconstriction is mediated by the second messenger inositol trisphosphate, and α_2 vasoconstriction is mediated by reduced cAMP levels.
- β_2-Receptors, which mediate dilator responses to catecholamines. β_2-Adrenergic vasodilation is mediated by the second messenger cAMP.

When the sympathetic nerves are stimulated, the responses of vessels will be dependent on the type of adrenergic receptors activated (a function of receptor density and agonist concentration), with the predominant systemic response being vasoconstriction. The major arterial response to sympathetic nervous system activation is α-receptor–mediated vasoconstriction, for example in baroreceptor-mediated responses (see Fig. 11.2). Note that generalized arterial constriction produces elevation of arterial blood pressure, because arterioles and small arteries are the major site of action, and constriction of these vessels produces increased peripheral resistance. Sympathetic activation results in widespread constriction of veins, elevating venous pressure and enhancing preload on the heart. β_2-receptors are present in some arterial

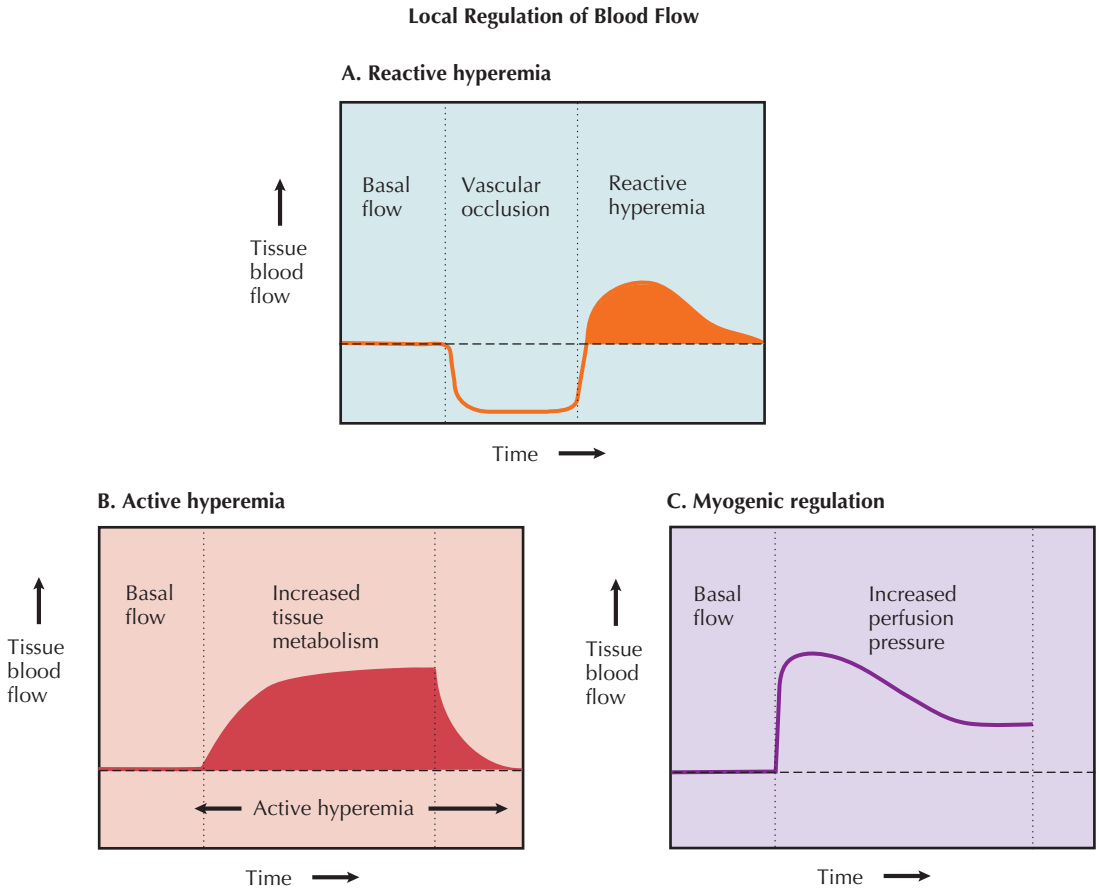


Figure 12.5 Local Regulation of Blood Flow Regional blood flow is controlled by local as well as neural and humoral factors. *A*, Reactive hyperemia occurs when blood flow is reestablished after occlusion. Buildup of vasodilatory metabolites such as CO_2, H^+, K^+, lactic acid, and adenosine results in relaxation of arterioles and precapillary sphincters directly exposed to these substances. Hence, a period of increased blood flow (hyperemia) occurs upon reperfusion. *B*, Active hyperemia refers to the increase in blood flow to a tissue when metabolism in the tissue is elevated; this hyperemia is a result of increased production of vasodilatory metabolites. *C,* Myogenic regulation refers to the autoregulation of blood flow that occurs when perfusion pressure is increased (with no change in metabolic activity in the tissue). Initially, when perfusion pressure is raised, flow to the tissue rises as expected, but returns toward the baseline. Smooth muscle of the arterial microcirculation constricts in response to a rise in transmural pressure, thus autoregulating blood flow.

vessels, for example, in skeletal muscle, where sympathetic outflow in anticipation of exercise produces increased blood flow to muscle.



While the sympathetic nervous system innervates vessels in most parts of the circulation, parasympathetic innervation of blood vessels is absent in most tissues. Exceptions are the genital organs, salivary glands, and lower gastrointestinal tract. In circulations innervated by the parasympathetic nervous system, release of acetylcholine stimulates endothelial cells to release nitric oxide, producing nitric oxide–dependent vasodilation of underlying smooth muscle. Because acetylcholine is short-lived in the circulation, it affects only the vessels that are directly innervated by parasympathetic nerves.

In addition to release of catecholamines at sympathetic nerve endings in the vasculature, epinephrine may be released into the bloodstream by the adrenal medulla during sympathetic nervous system activation. In this case, epinephrine acts as a circulating hormone; other circulating hormones that affect vascular tone include angiotensin II and vasopressin.

Chemoreceptors also participate in the extrinsic regulation of vascular tone. The aortic and carotid bodies are densely vascularized groups of specialized cells found in the proximity of the arterial baroreceptors. Although they are more important in regulation of respiration (see Section 4), they respond to reduced arterial P_{O_2}, and to a lesser extent to elevated P_{CO_2} and H^+ concentration, by initiating a neural reflex that produces arterial and venous constriction.

REGULATION OF ARTERIAL BLOOD PRESSURE

From the foregoing, it should be clear that local, intrinsic mechanisms for vascular regulation are mainly aimed at regulation of regional blood flow, whereas neural and humoral mechanisms are often aimed at regulation of arterial blood pressure. The maintenance of mean arterial pressure (MAP) near its normal level is necessary for adequate perfusion of tissues throughout the systemic circulation. Rearranging the flow equation ($Q = \Delta P/R$), the relationship $\Delta P = R \times Q$ results, where ΔP is the pressure gradient, R is resistance, and Q is flow. The pressure gradient is the difference between arterial and central venous pressure. For the overall systemic circulation, Q is equal to cardiac output and R is total peripheral resistance (TPR), yielding

$$\Delta P = CO \times TPR$$

Because venous pressure is very low, this equation can be essentially reduced to:

$$MAP = CO \times TPR$$

Thus, regulation of arterial blood pressure involves regulation of cardiac output and systemic resistance, through the various mechanisms already described. Blood pressure is monitored at several points in the system (Fig. 12.6):

- aortic arch and carotid sinus baroreceptors
- renal juxtaglomerular apparatus
- low-pressure (cardiopulmonary) baroreceptors

Short-Term Regulation of Blood Pressure by Arterial Baroreceptors

The **high-pressure arterial baroreceptors** of the aortic arch and carotid sinus and the associated baroreceptor reflexes are most important for moment-to-moment regulation of arterial pressure. During normal, quiet daily activities, an inverse relationship is usually observed between changes in blood pressure and heart rate, reflecting this role of the baroreceptor reflex in maintaining pressure: when pressure falls, heart rate rises; when pressures rises, heart rate falls. These fluctuations in heart rate reflect changes in sympathetic and parasympathetic outflow from the medullary cardiovascular centers, in response to the degree of baroreceptor stretch.

Efferent sympathetic nerve activity is inversely related to MAP between the range of 60 to 160 mm Hg in a normal individual (see Fig. 11.2). At pressures below 60 mm Hg, sympathetic nerve activity is maximal. In addition to MAP, baroreceptors are also sensitive to pulse pressure. If pulse pressure is dampened while MAP is held constant, afferent nerve impulses from the baroreceptors to the cardiovascular center will be less frequent, and sympathetic efferent activity and thus arterial blood pressure will be elevated.

The arterioles of the **juxtaglomerular apparatus** of the kidneys also contain high-pressure baroreceptors; in this case, stretch results in release of the enzyme renin by the kidney. Renin enzymatically cleaves the plasma protein angiotensinogen (a liver product) to form angiotensin I, which is converted to angiotensin II by endothelial angiotensin-converting enzyme. This mechanism is important in short-term regulation of blood pressure only during pathophysiologic states such as hemorrhage.



"Resetting" of arterial baroreceptor sensitivity occurs when blood pressure is chronically elevated. In a healthy person with normal blood pressure, baroreceptors function to return arterial pressure to the normal level when pressure falls or rises. With chronic hypertension, a new set-point is established, whereby baroreceptor activity is aimed at maintaining the higher resting blood pressure. Although this change appears, on the surface, to be maladaptive, it allows adequate short-term regulation of blood pressure despite higher basal blood pressure.

Role of Low-Pressure Baroreceptors and Atrial Stretch

Low-pressure baroreceptors are found in low-pressure sites of the circulation, specifically the atria and large vessels of the pulmonary circulation, and respond to changes in blood volume. The Bainbridge reflex was discussed earlier; increased atrial stretch initiates a reflexive increase in heart rate. Reduction of blood volume, for example during hemorrhage, is detected by low-pressure baroreceptors in the left atrium, as well as arterial baroreceptors. Neural afferent signals through the vagus nerve to the hypothalamus result in vasopressin release by the posterior pituitary. Like angiotensin II, vasopressin participates in short-term responses to hemorrhage, but not in acute regulation of blood pressure under normal circumstances.

Increased blood volume and stretch of atria stimulates atrial myocytes to secrete stored **atrial natriuretic peptide (ANP).** ANP dilates some vessels (although it has little role in acute blood pressure regulation) and has important effects on sodium and water balance (see Section 5) and long-term regulation of blood pressure (see following section).

Long-Term Regulation of Blood Pressure

In contrast to moment-to-moment regulation of blood pressure, which relies heavily on baroreceptor reflexes and adjustments to cardiac and vascular function, **long-term regulation of blood pressure** is accomplished mainly by mechanisms that control blood volume through neural and humoral pathways (Fig. 12.7). These mechanisms are covered in further detail in Sections 5 and 7. Briefly, when blood volume is depleted and blood pressure is consequently reduced, direct effects of reduced renal perfusion, as well as increased sympathetic nerve activity, stimulate renin production by the kidneys

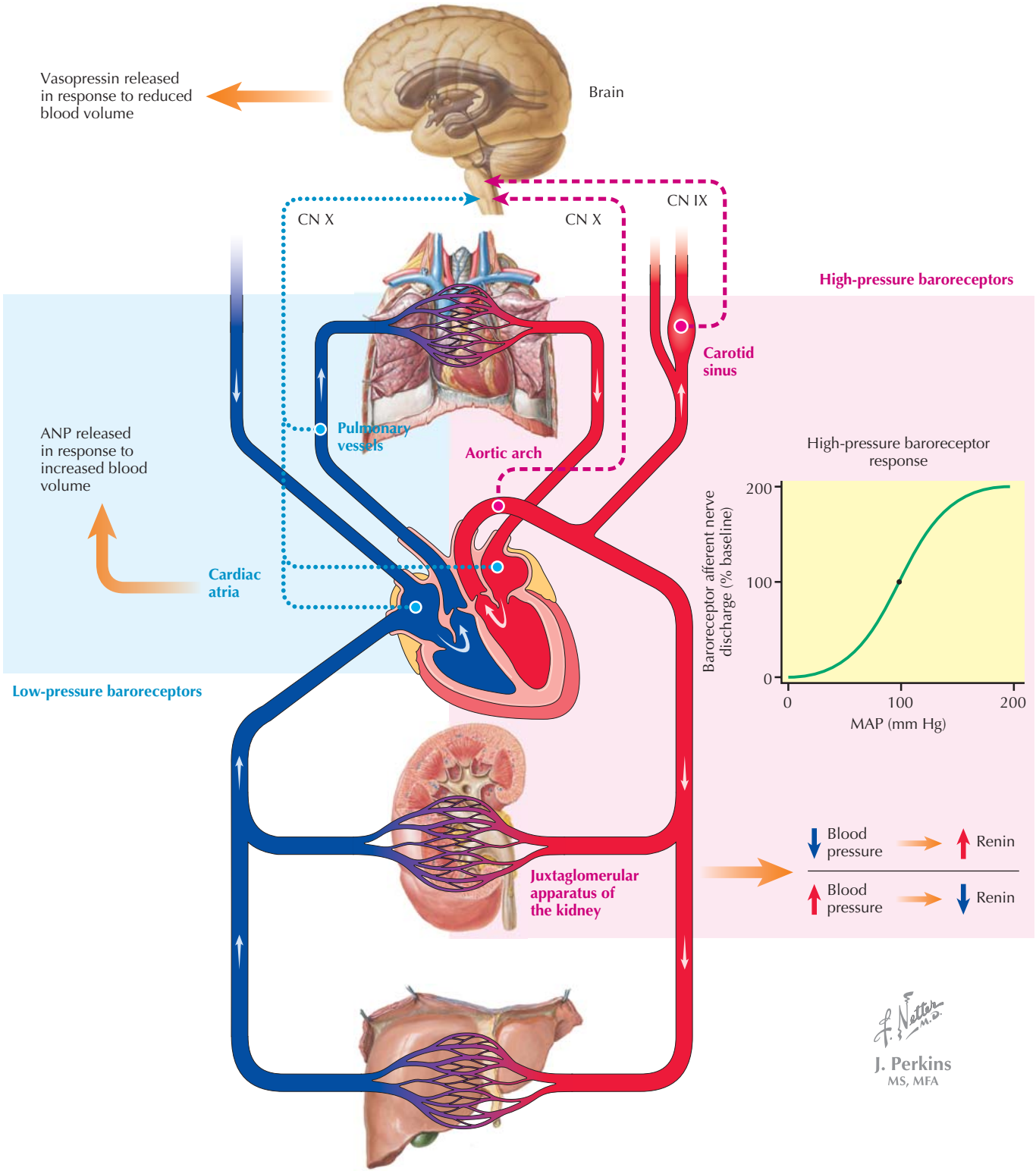


Figure 12.6 **Monitoring of Blood Pressure** To maintain adequate blood flow to tissues, the body has a complicated system for monitoring and regulating blood pressure. High-pressure baroreceptors in the aortic arch and carotid sinus are extremely important in acute regulation of blood pressure, through their effects on the autonomic nervous system. Afferent arterioles in the renal juxtaglomerular apparatus also contain high-pressure baroreceptors; these are involved in regulation of renin release, and consequently, regulation of sodium and water balance, important in long-term regulation of blood pressure. Low-pressure baroreceptors in the heart and pulmonary circulation respond to changes in blood volume and modulate sympathetic activity and vasopressin release. The cardiac atria also release atrial natriuretic peptide (ANP) in response to elevated blood volume.

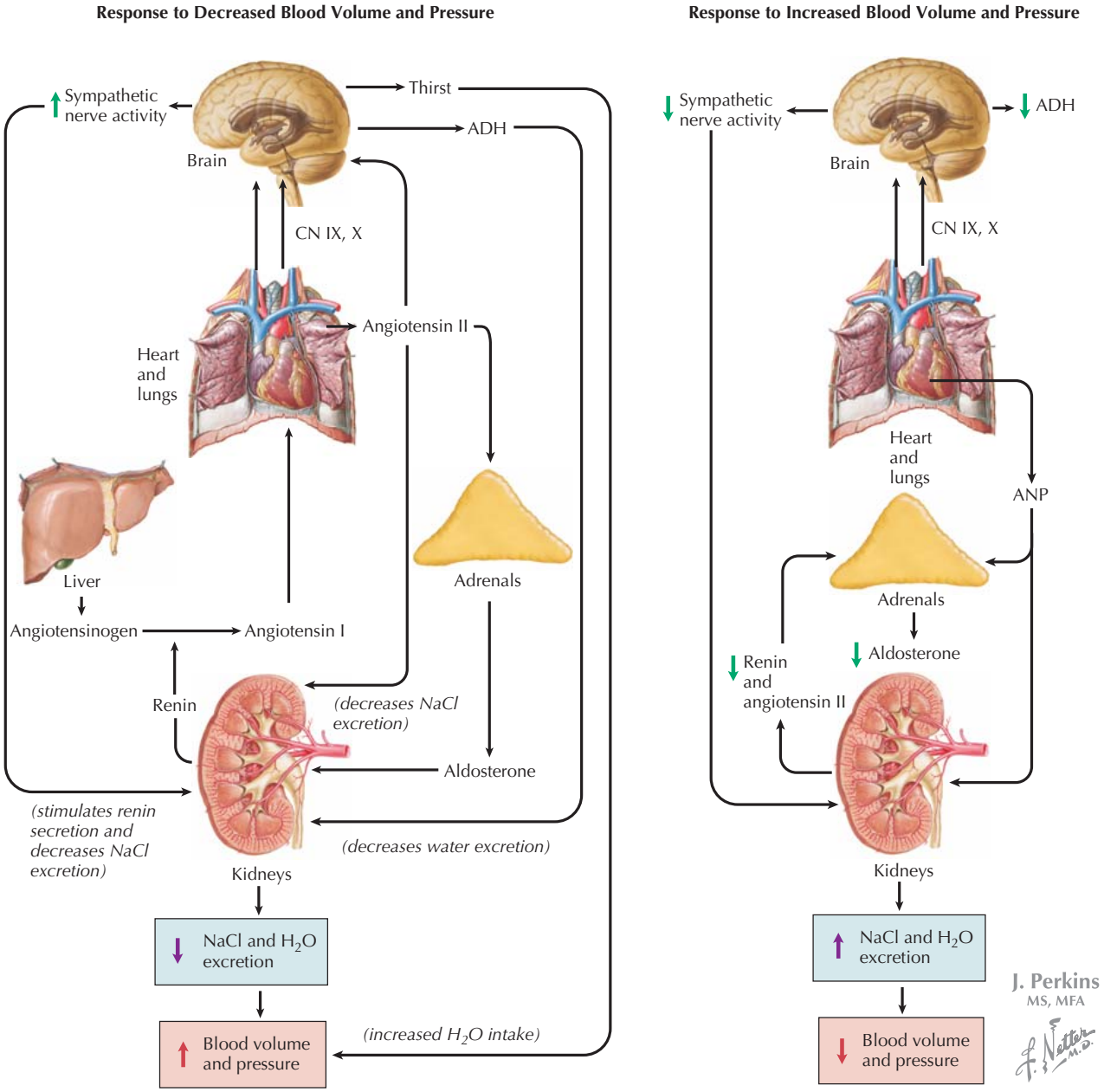


Figure 12.7 Long-Term Response to Changes in Blood Volume and Pressure In addition to evoking mechanisms for acute adjustment of blood pressure, changes in blood volume and pressure will also activate renal mechanisms for adjusting blood volume. Reduced blood volume (and therefore arterial pressure) will stimulate the renin-angiotensin-aldosterone system, with the end result of sodium and water retention. Reduced blood pressure will also activate the sympathetic nervous system, which will stimulate renin secretion as well as have direct effects on the kidneys. On the other hand, increased volume will stimulate atrial natriuretic peptide (ANP) release by the heart. ANP has direct renal effects (natriuresis and diuresis) and also inhibits aldosterone release by the adrenal medulla.

(sympathetic activation occurs in part due to baroreceptor responses). Renin action produces elevation of angiotensin I, which is subsequently cleaved to angiotensin II by endothelial cell angiotensin-converting enzyme (much of this enzymatic cleavage occurs in the pulmonary circulation). **Angiotensin II** has direct effects on sodium retention by the kidney and has the important effect of stimulating aldosterone release by the zona glomerulosa of the adrenal cortex. **Aldosterone** also promotes renal sodium (and hence fluid) retention. Low blood volume, through reflexes discussed earlier, stimulates posterior pituitary antidiuretic hormone (ADH; also known as vasopressin). ADH release, as well as thirst, is also stimulated by elevated plasma osmolality associated with volume depletion. ADH promotes water retention by the kidney.

Thus, the effects of multiple hormones (ADH, angiotensin II, aldosterone) on sodium and fluid retention and water intake result in an increase in blood volume, which helps to maintain blood pressure. These mechanisms are important in the physiological responses to hemorrhage or dehydration; various aspects are also implicated in elevation of blood pressure in some forms of hypertension.

The **diving reflex** is a specialized mechanism for regulation of blood pressure and heart rate. This reflex is an adaptation for conservation of oxygen in diving mammals, allowing protracted stays underwater without breathing. During diving, the heart rate is slowed by increased vagal activity, while pressure is maintained by arterial vasoconstriction. Thus, blood flow to vital organs is maintained, while blood flow to much of the body besides the coronary and cerebral circulations is reduced; the work of the heart is also reduced. Although the diving reflex is weaker in humans, its effects can still be observed when the face is submerged in cold water and breath is held. Receptors in the face and nasal cavities are stimulated, and reflexive bradycardia and peripheral vasoconstriction occur. The diving reflex is thought to be responsible for the survival of some children after long periods of accidental submersion in cold water.

SPECIAL CIRCULATIONS

Blood flow to various tissues is regulated by local and extrinsic mechanisms, and the importance of these varies among tissues (Fig. 12.8). In addition, there are unique aspects of some circulations. A number of these "special circulations" merit individual consideration.

Cerebral Circulation

The **cerebral circulation** is supplied by the arterial **circle of Willis,** which is derived from the internal carotid and the vertebral arteries. Because the brain is a vital tissue, housed in a rigid case (the cranium), it is necessary to closely regulate its blood flow. Flow below 35 milliliters per minute (mL/min) causes neuronal dysfunction; high flow may result in cerebral edema and high intracranial pressure, which also produce dysfunction. In a normal individual, cerebral blood flow is maintained at a constant level of 50 mL/min for mean arterial pressures between 50 mm Hg and 150 mm Hg. This level is maintained by autoregulation (myogenic regulation).

Cerebral blood flow is also under the control of arterial P_{CO_2}, although this blood gas does not vary significantly in a healthy person except during extreme exercise or hyperventilation or hypoventilation. Decreased arterial P_{CO_2} will produce vasoconstriction and reduced cerebral blood flow; high arterial P_{CO_2} levels will cause vasodilation and increased flow. Note that this response is to *arterial* P_{CO_2}. Global cerebral blood flow is not significantly regulated by local metabolic factors (CO_2, O_2, K^+, H^+, etc.), but metabolic regulation participates in distribution of cerebral blood flow to various parts of the brain, depending on neuronal activity in those regions.

The circle of Willis provides a high degree of collateralization between the large arteries that supply oxygenated blood to the brain. The redundant pathways for blood flow help to ensure adequate blood flow to the brain in case of injury or disease, for example due to stenosis of vessels or blockage due to thrombosis. There is considerable variation in the exact anatomic structure of the circle of Willis between individuals, such that fewer than half of the population has the most common structure illustrated in many textbooks.

In addition, there are two reflexes that may affect cerebral blood flow:

- **CNS ischemic reflex:** If the vasomotor center in the medulla becomes ischemic, strong sympathetic outflow acts on the heart and peripheral circulation to increase arterial blood pressure above the autoregulatory range for cerebral blood flow, thus increasing blood flow to the brain in a "last-ditch" effort to reverse the ischemia. The cerebral circulation is itself not innervated by sympathetic nerves.
- **Cushing reflex:** An increase in intracranial pressure, usually associated with traumatic head injury, may impede cerebral blood flow. A strong sympathetic outflow will result, raising arterial pressure in an attempt to overcome the high intracranial pressure that is impeding flow. This is also a last-ditch mechanism to preserve cerebral perfusion. High arterial pressure is accompanied by bradycardia, due to activation of arterial baroreceptors.

Coronary Circulation

Like any metabolically active tissue, the myocardium receives its own arterial supply. The **coronary circulation** is fed by the right and left coronary arteries that originate at the base of the aorta (Fig. 12.9). These are also called epicardial arteries because they lie on the surface of the heart (epicardium) and supply branches into the myocardium. These branches form a very extensive microcirculation, supplying oxygen and nutrients and removing metabolites from the highly metabolically active myocardium. The heart has a very large arteriovenous O_2 gradient, even at rest.

The left coronary artery gives rise to the left anterior descending (LAD) artery and the circumflex artery; likewise, the right coronary artery gives rise to several branches. The venous drainage of the heart returns blood to the coronary sinus, which empties into the right atrium. The layers of the heart, from inside to outside, are as follows:

- **Endocardium:** The innermost layer is connective tissue, lined by endothelial cells.

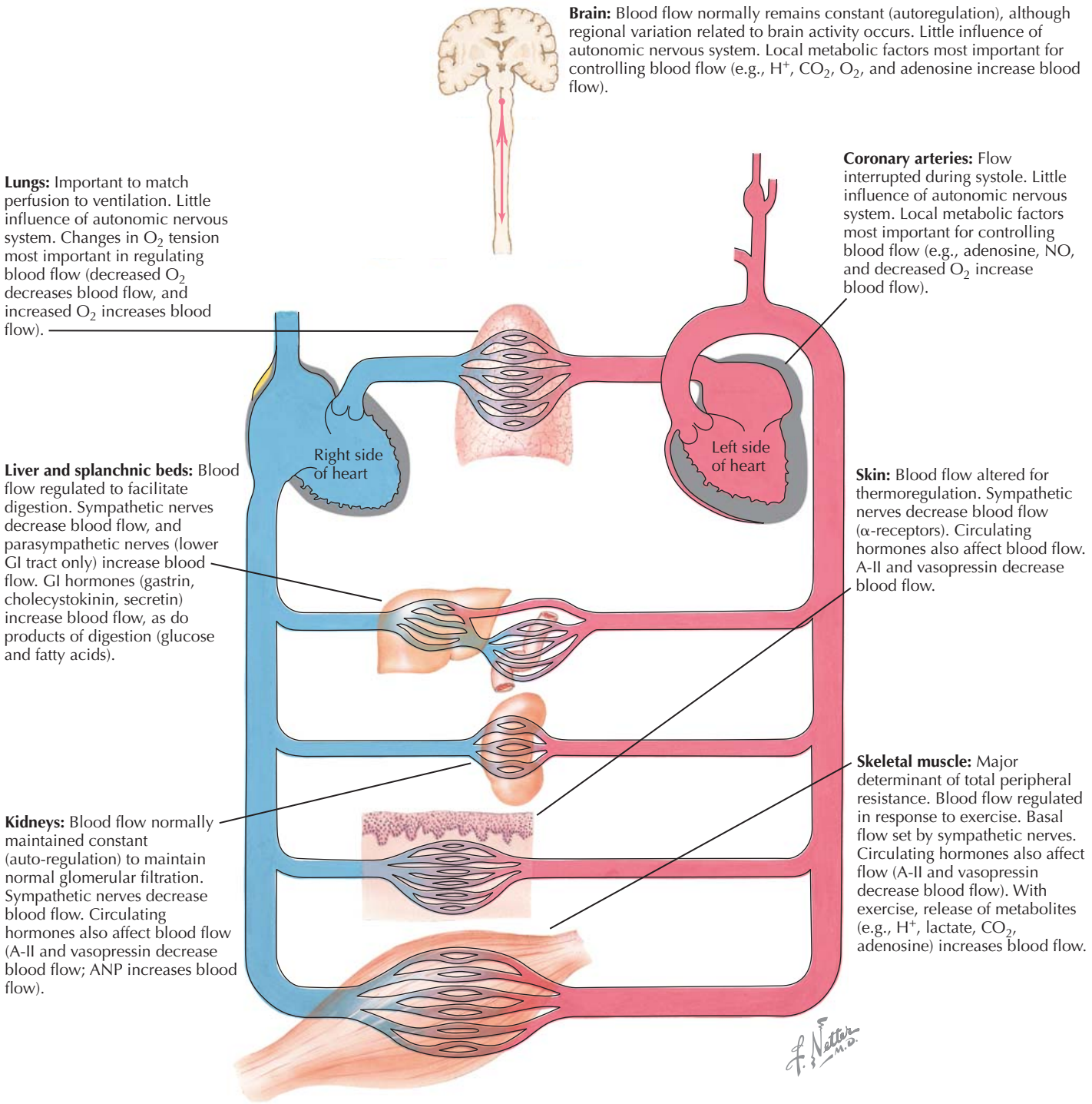


Figure 12.8 Circulation to Special Regions Mechanisms regulating blood flow vary among regions in the systemic circulation, reflecting the physiological functions and needs of the tissues.

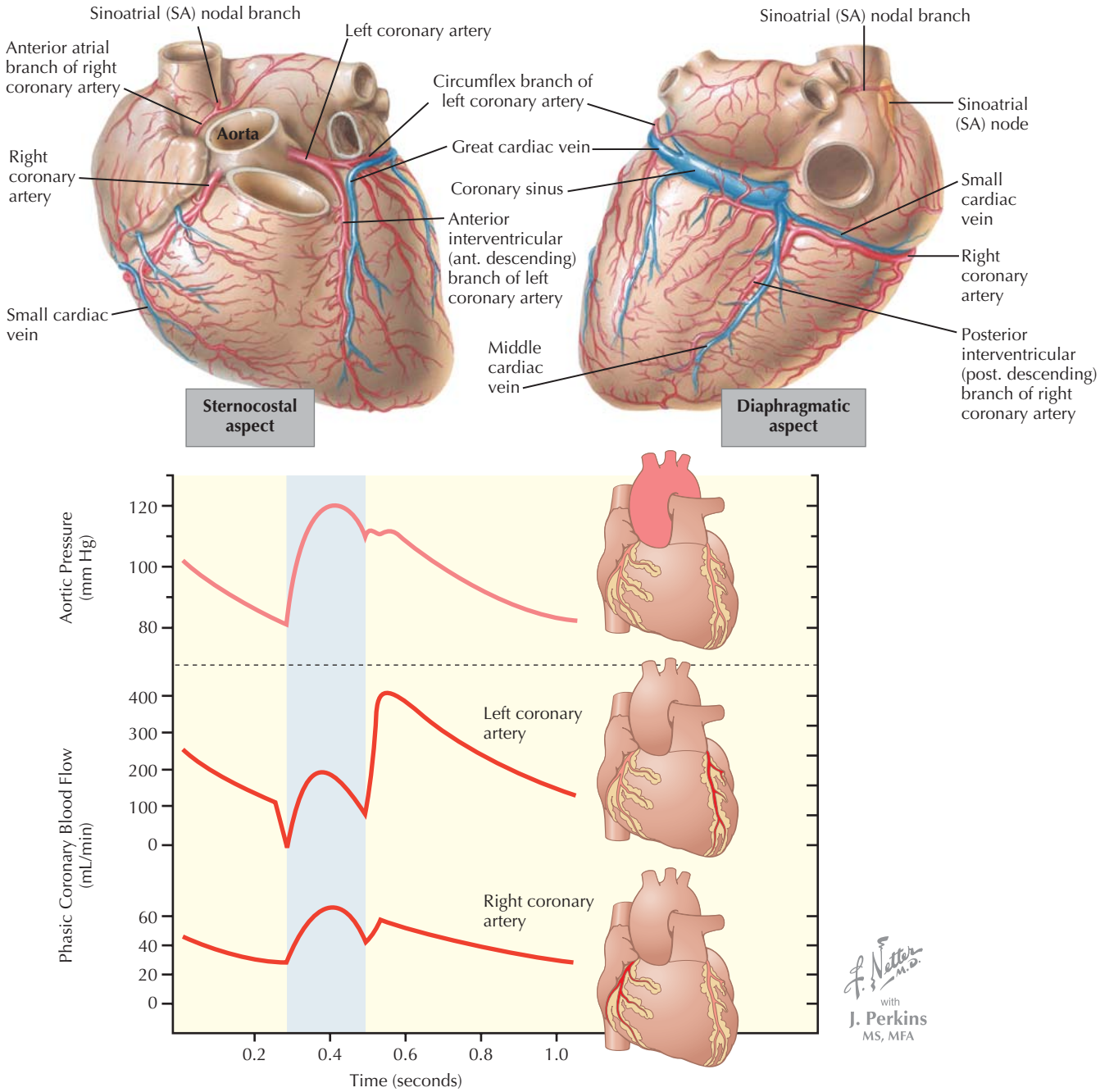


Figure 12.9 **Coronary Circulation** The coronary arteries supply arterial blood to the muscular wall of the heart. The pressure gradient for flow through the arteries is affected by tissue pressure in the wall of the heart during systole, particularly in the left coronary circulation. Thus, while flow through both right and left coronary arteries is related to aortic pressure, these compressive forces reduce left coronary flow during systole. During diastole, flow is greatly enhanced in the left coronary circulation by the actions of vasodilator metabolites that build up during systole. The metabolite adenosine is believed to be particularly important in this enhancement of coronary flow.

- **Myocardium:** The muscular layer that forms the bulk of the heart wall. The subendocardium is the inner ⅓ of the myocardium, and the subepicardium is the outer ⅓ of the myocardium.
- **Epicardium:** The outer, connective tissue layer of the heart. It forms the visceral pericardium. The parietal pericardium is a sac enclosing the heart; the pericardial cavity is the space between the visceral and parietal pericardium.

Flow to the myocardium is affected by factors that are in some ways different from those regulating flow in other circulations. In particular, coronary blood flow is affected greatly by the following:

- Compression of the coronary circulation caused by contraction of myocardium.
- Powerful metabolic vasodilation during diastole.

The pumping action of the left ventricle generates the normal resting arterial pressure of 120/80 mm Hg to supply blood to the systemic circulation. In doing so, the myocardium of the left ventricle, and in particular, the subendocardium, must generate an extravascular tissue pressure that is higher than left ventricular and arterial pressures. This intramyocardial pressure impedes left coronary flow during systole, when the net coronary perfusion pressure is arterial pressure minus the intramyocardial pressure. Thus, left coronary artery flow is low during systole (see Fig. 12.9). During isovolumetric contraction, there is a rapid decrease in flow because tissue pressure has exceeded arterial pressure. During the remainder of systole, the shape of the left coronary flow curve is similar to the aortic pressure curve, but remains low due to high intramyocardial pressure.

With the onset of isovolumetric relaxation, left coronary artery flow increases markedly due to two factors. During systole, when flow is low, metabolites (H^+, CO_2, K^+, prostaglandins, lactic acid, adenosine, and others) accumulate, and O_2 tension falls. These changes produce coronary vasodilation; adenosine is believed to be the major factor involved. The vasodilation, combined with the fall in intramyocardial pressure, results in the large increase in left coronary flow during diastole.

Flow through the right coronary artery is less affected by intramyocardial pressure, because tissue pressure in the right ventricle does not nearly reach that of the left ventricle, and does not exceed arterial pressure. Thus, the shape of the right coronary artery blood flow curve (see Fig. 12.9) resembles the aortic pressure curve, with the highest flow occurring during systole.

Sympathetic nerves innervate coronary arteries and can affect blood flow, but to a lesser extent than in most other circulations. Activation of the sympathetic nervous system increases the work of the heart, and thus metabolic vasodilation largely overrides sympathetic coronary vasoconstriction. However, it is believed that sympathetic vasoconstriction may limit the extent of metabolic vasodilation, and thus, in a compromised heart (for example, in coronary heart disease), sympathetic stimulation may contribute to ischemia.

Autoregulation of coronary blood flow can be demonstrated experimentally but is a less important factor in normal regulation of coronary flow than metabolic factors or the effects of intramyocardial pressure.

Blood Flow in Exercise and Effects on Specific Circulations

The importance of regional differences in regulatory mechanisms governing blood flow can be gleaned by considering the changes in flow that occur during exercise. Regulation of arterial blood pressure and flow during **dynamic exercise** is a complex process, involving large changes in cardiac output and regional resistances (Fig. 12.10). Dynamic exercise, also called aerobic exercise, involves rhythmic contraction/relaxation of large skeletal muscle groups, for example during jogging, swimming, or aerobics. Young, fit individuals are able to exercise at levels associated with cardiac outputs of 20 to 30 L/min, by increasing both heart rate and stroke volume. Sympathetic nervous system activation results in vasoconstriction and reduced flow (as a proportion of cardiac output) in many, but not all, regional circulations (see Fig. 12.10):

- Coronary blood flow increases, mainly as a result of metabolic vasodilation.
- Skin blood flow is reduced at first, but will eventually rise as a result of thermoregulatory mechanisms.
- Skeletal muscle flow increases dramatically, as constrictor effects of catecholamines are overridden by metabolic vasodilation (and to some extent, activation of β-adrenergic receptors).

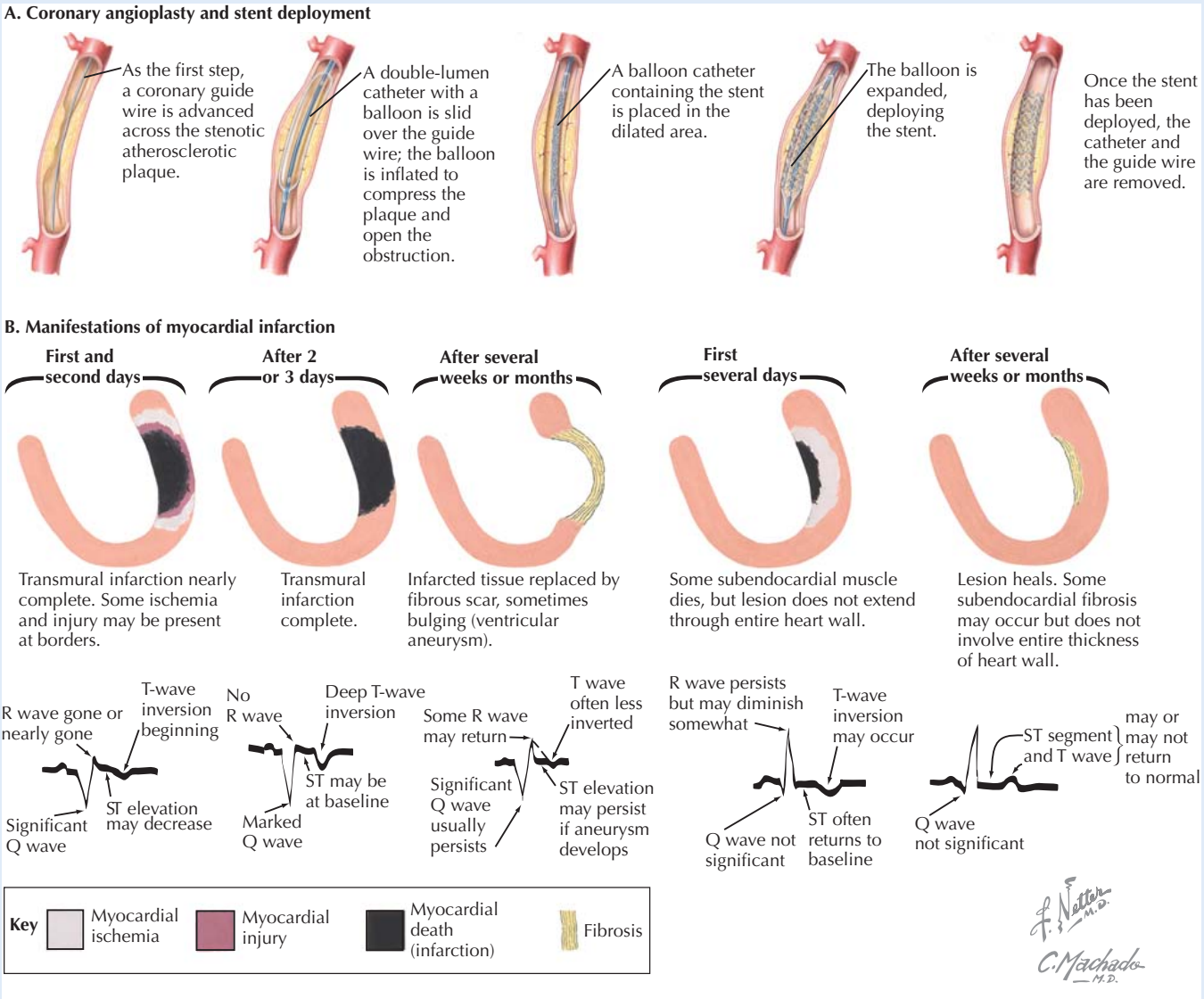
Total peripheral resistance is reduced as a result of these changes. Thus, aerobic exercise is associated with high cardiac output and low resistance. Constriction of veins results in increased central venous pressure, augmenting cardiac filling pressure and stroke volume. Arterial blood pressure is elevated during dynamic exercise, but it is mainly systolic pressure (and thus pulse pressure) that rises, due to the large stroke volume. Diastolic pressure may be slightly elevated or slightly reduced, because low peripheral resistance results in a rapid fall in arterial pressure during diastole.

Fetal Circulation

Although the **fetal circulation** is not a special circulation in the same sense as the cerebral and coronary circulations, there

CLINICAL CORRELATE
Myocardial Ischemia

Myocardial ischemia is reduced blood flow to heart muscle, resulting in poor oxygenation. Angina, arrhythmias, myocardial infarction, and sudden death may result. In patients with coronary heart disease, buildup of atherosclerotic plaque in epicardial coronary arteries results in reduced perfusion of the affected vessels. Functionally, ischemia and infarction may result in reduced contractility of the heart, arrhythmias, electrocardiogram (EKG) changes, wall motion abnormalities, and even ventricular aneurysm. Myocardial infarction is one of the major causes of congestive heart failure. Severe cases of coronary occlusion are treated by angioplasty or coronary artery bypass graft surgery. In bypass surgery, a section of vessel, typically a piece of saphenous vein, is grafted to bypass the blockage. In angioplasty, a balloon catheter is employed to open the occluded artery. To reduce the occurrence of restenosis (reocclusion), a stent is often deployed.



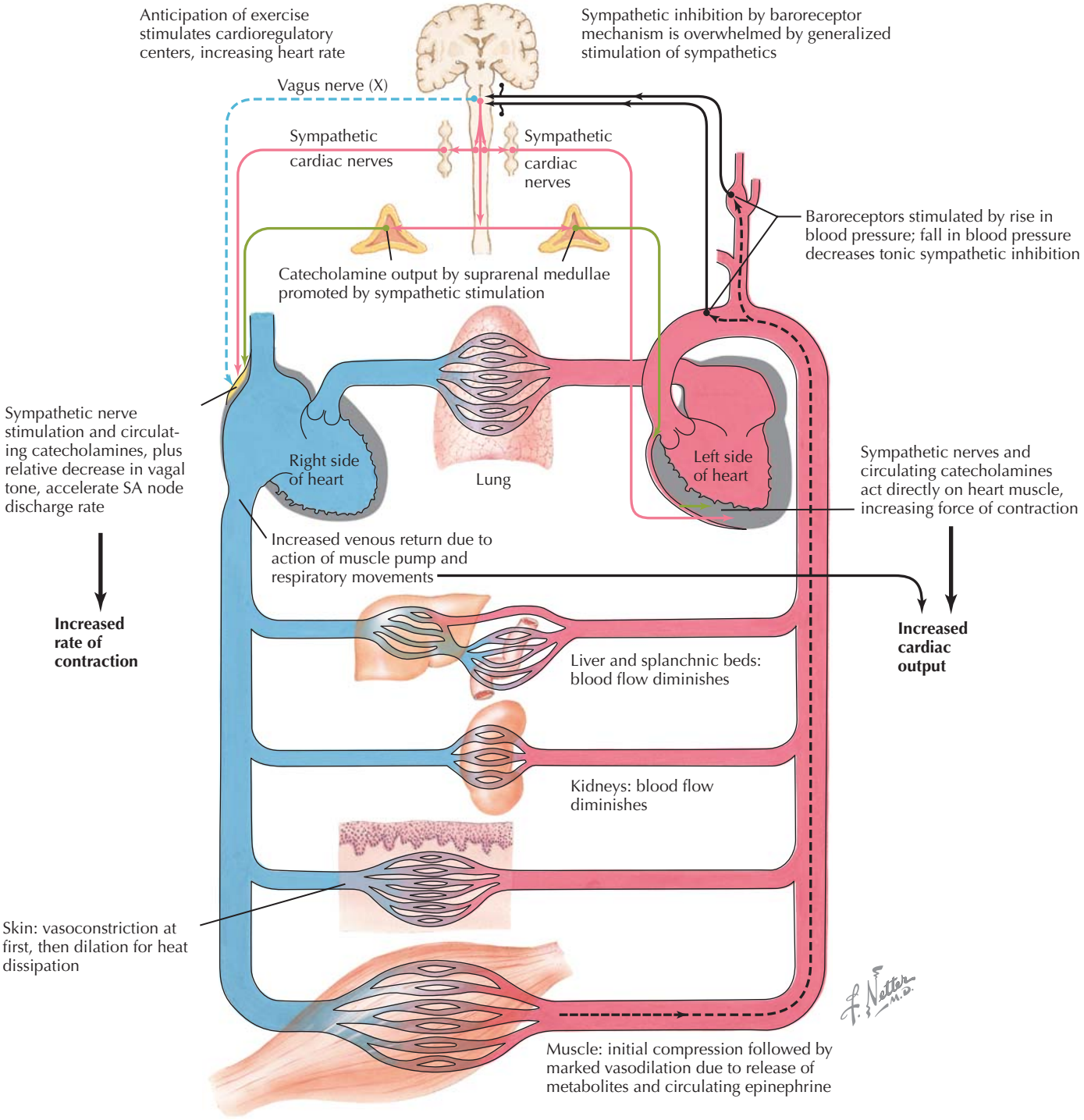
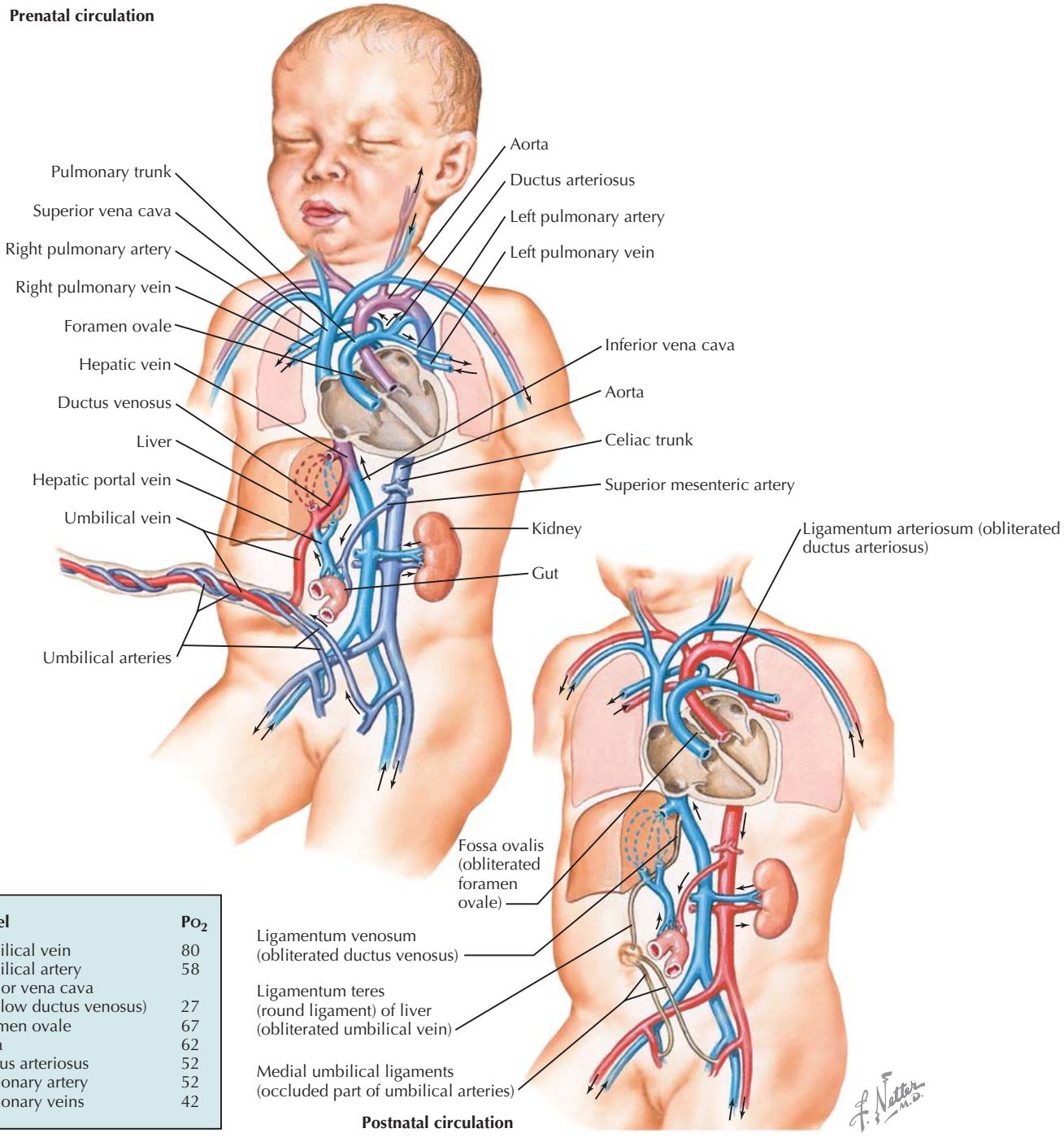


Figure 12.10 Circulatory Response to Exercise Dynamic (aerobic) exercise elicits an integrated circulatory response. The autonomic nervous system is important in the neural regulation of this response, affecting heart rate, contractility, and vascular tone. During exercise, skeletal muscle blood flow is greatly elevated due mainly to the production of vasodilatory metabolites.



Vessel	Po_2
Umbilical vein	80
Umbilical artery	58
Inferior vena cava (below ductus venosus)	27
Foramen ovale	67
Aorta	62
Ductus arteriosus	52
Pulmonary artery	52
Pulmonary veins	42

Figure 12.11 Fetal and Neonatal Circulation The fetal circulation is specifically adapted to efficiently exchange gases, nutrients, and wastes through placental circulation. Upon birth, the shunts (foramen ovale, ductus arteriosus, and ductus venosus) close and the placental circulation is disrupted, producing the series circulation of blood through the lungs, left atrium, left ventricle, systemic circulation, right heart, and back to the lungs.

are several significant differences between the prenatal and postnatal circulations that merit discussion. The fetus, enveloped in the amniotic sac and floating in the amniotic fluid, is dependent on the placental circulation for exchange of gases and nutrients. To adapt the circulation to prenatal life, there are six structures in the fetus not normally seen in adults (Fig. 12.11):

- Two large umbilical arteries, which branch from the systemic arterial circulation and supply the placental

circulation, where gas exchange and nutrient and waste exchange occur.

- The umbilical vein, which returns placental blood to the systemic venous circulation, supplying O_2 and nutrients to the fetus.
- The ductus venosus, a shunt between the umbilical vein and the inferior vena cava. Although most of the placental blood passes through the liver, a fraction of the placental circulation passes directly into the vena cava through the ductus venosus.
- Foramen ovale, a "right-to-left" shunt through which most of the blood from the inferior vena cava flows into the left atrium, bypassing the right heart and the pulmonary circulation.
- Ductus arteriosus, another right-to-left shunt between the pulmonary artery and the aorta. Pulmonary vascular resistance is high in the fetus, due to the collapsed state of the lungs and low oxygen tension in the lungs; 90% of pulmonary arterial blood flows through the ductus arteriosus to the aorta.

These structures all normally close shortly after birth, although anatomical closure, as opposed to functional closure, requires more time. Inflation of the lungs and inhalation of oxygen-rich air reduces pulmonary vascular resistance, reversing flow through the ductus arteriosus. High oxygen tension initiates closure of the ductus. With increased venous return from the lungs to the left atrium and reduced flow to the right atrium due to occlusion of the placental circulation, left atrial pressure rises above right atrial pressure, closing a valve over the foramen ovale. With closure of the ductus arteriosus and foramen ovale, the "adult" pattern of circulation of blood through the right heart, lungs, left heart, and systemic circulation is established.



Unlike the adult, the fetal circulation can be considered a parallel circulation. Much of the right ventricular output is shunted past the lungs to the aorta through the ductus arteriosus, mixing with blood ejected by the left ventricle. Flow through the pulmonary circulation is not critical, since oxygenation of blood does not take place in the lungs in utero. With closure of the foramen ovale and ductus arteriosus shortly after birth, the fetal circulation is transformed to a series circulation.

Review Questions

CHAPTER 8: OVERVIEW OF THE HEART AND CIRCULATION

1. The greatest volume of blood is found in the:

A. systemic arteries.
B. systemic veins.
C. pulmonary arteries.
D. pulmonary veins.
E. chambers of the heart.

2. Contraction of which chamber of the heart is best described as a constriction of the chamber resulting in shortening from base to apex?

A. Left atrium
B. Right atrium
C. Left ventricle
D. Right ventricle
E. All of the above

3. Of the following parts of the circulation, which receives the smallest blood flow (as a percentage of cardiac output) at rest?

A. Coronary circulation
B. Liver and gastrointestinal tract
C. Skeletal muscle
D. Kidneys
E. Cerebral circulation

CHAPTER 9: CARDIAC ELECTROPHYSIOLOGY

4. Rapid phase 3 repolarization of cardiac myocytes during the action potential is mainly associated with:

A. opening of Na^+ channels.
B. reduced conductance of the inwardly rectified K^+ current (i_{K1}).
C. opening of voltage-sensitive slow L-type Ca^{2+} channels.
D. inactivation of Na^+ channels.
E. activation of K^+ channels.

5. The electrocardiogram may reveal:

A. abnormalities in cardiac rhythm and conduction.
B. location and extent of myocardial ischemia.
C. orientation of the heart and size of chambers.
D. effects of abnormal electrolyte levels.
E. All of the above.

6. Conduction velocity is slowest in the:

A. atrial myocytes.
B. AV node.
C. bundle of His.
D. Purkinje fibers.
E. ventricular myocytes.

CHAPTER 10: FLOW, PRESSURE, AND RESISTANCE

7. Given a resting heart rate of 75 and arterial blood pressure of 130/80 mm Hg, what is the approximate mean arterial pressure (MAP)?

A. 90 mm Hg
B. 97 mm Hg
C. 105 mm Hg
D. 110 mm Hg
E. 115 mm Hg

8. The highest pulse pressure in the circulation is observed in the:

A. left ventricle.
B. right ventricle.
C. aorta.
D. pulmonary artery.
E. systemic arterioles.

9. Which of the following changes would result in the greatest increase in flow through a tube, assuming that other factors are held constant?

A. Doubling of the pressure gradient between ends of the tube
B. Reducing the viscosity of the fluid by half
C. Doubling the viscosity of the fluid
D. Reducing the length of the tube by half
E. Doubling the radius of the tube

10. Which of the following conditions favors laminar flow in a tube?

A. Wide tube diameter
B. Rapid velocity of fluid flow
C. High viscosity of fluid
D. High density of fluid
E. Pulsatility of flow

11. Wall tension in a blood vessel would be increased by:

A. reduction of vessel radius.
B. reduction of hydrostatic pressure within the vessel lumen.
C. reduction of hydrostatic pressure in the interstitial space.
D. reduction of transmural pressure.
E. None of the above.

CHAPTER 11: THE CARDIAC PUMP

12. The beginning of the isovolumetric contraction period for the right ventricle is marked by:

A. closure of the aortic valve.
B. closure of the pulmonic valve.
C. closure of the mitral valve.
D. closure of the tricuspid valve.
E. opening of the mitral valve.

13. The correct order of valve opening and closure during a cardiac cycle is:

A. mitral closure, tricuspid closure, pulmonic opening, aortic opening, aortic closure, pulmonic closure, tricuspid opening, mitral opening.
B. tricuspid closure, mitral closure, pulmonic opening, aortic opening, aortic closure, pulmonic closure, tricuspid opening, mitral opening.
C. mitral closure, tricuspid closure, aortic opening, pulmonic opening, aortic closure, pulmonic closure, tricuspid opening, mitral opening.
D. mitral closure, tricuspid closure, pulmonic opening, aortic opening, pulmonic closure, aortic closure, tricuspid opening, mitral opening.
E. mitral closure, tricuspid closure, pulmonic opening, aortic opening, aortic closure, pulmonic closure, mitral opening, tricuspid opening.

14. In respiratory sinus arrhythmia, the increase in heart rate during inspiration is initiated by:

A. reduced stretch of arterial baroreceptors.
B. increased stretch of arterial baroreceptors.
C. release of atrial natriuretic peptide.
D. reduced stretch of atrial stretch receptors.
E. increased stretch of atrial stretch receptors.

15. Activation of the sympathetic nervous system will produce:

A. increased heart rate.
B. arterial vasoconstriction.
C. constriction of veins.
D. increased myocardial contractility.
E. All of the above.

16. An increase in myocardial contractility will result in which of the following changes in the force–velocity relationship?

A. An increase in the maximum force of contraction without change in V_m
B. An increase in the maximum force of contraction and an increase in V_m
C. A decrease in the maximum force of contraction without change in V_m
D. A decrease in the maximum force of contraction and an increase in V_m
E. A decrease in the maximum force of contraction and a decrease in V_m

17. When the vascular function curve and cardiac function curves are plotted on the same graph, the point of intersection represents the:

A. point at which baroreceptor activation occurs.
B. resting cardiac output and central venous pressure.
C. normal mean circulatory pressure.
D. normal mean arterial pressure.
E. point of maximum contractility.

CHAPTER 12: THE PERIPHERAL CIRCULATION

18. Release of nitric oxide by the endothelial cells in a small artery would be expected to produce all of the following effects **except:**

A. elevation of cGMP in smooth muscle underlying the endothelium.
B. inhibition of platelet adhesion to the vascular wall.
C. elevation of free intracellular Ca^{2+} in the underlying smooth muscle.
D. vasodilation of the vessel.
E. increased hydrostatic pressure in downstream capillaries.

19. In an experimental model, the perfusion pressure for an artery is increased. A rise in blood flow through the artery is observed, but despite continued high perfusion pressure, flow falls over a 2-minute period toward the baseline level. This reduction in flow is most likely the result of:

A. autoregulation of blood flow.
B. reactive hyperemia.
C. active hyperemia.
D. shear stress–induced nitric oxide release.
E. increased sympathetic nerve activity.

20. Vasodilation is evoked by binding of adrenergic transmitter by which type of vascular adrenergic receptor?

A. α_1
B. α_2
C. β_1
D. β_2
E. All of the above

21. Afferent nerve activity from the arterial baroreceptors will be greatest when:

A. MAP and pulse pressure are both high.
B. MAP is high and pulse pressure is low.
C. MAP and pulse pressure are both low.
D. MAP is low and pulse pressure is high.
E. MAP and pulse pressure are in the normal resting range.

22. Left coronary artery blood flow is highest during:

A. early systole.
B. late systole.
C. early diastole.
D. mid diastole.
E. late diastole.

Section 4

RESPIRATORY PHYSIOLOGY

The components of the respiratory system are the lungs, airways, and the muscles of breathing. The primary function of this system is to facilitate the exchange of oxygen and carbon dioxide between the body and the environment. The respiratory system participates in additional, important physiological processes, including acid–base regulation, temperature regulation, immune function, and metabolic functions, among others. In the following chapters, the basic physiology of ventilation, pulmonary perfusion, and gas transport are covered, as well as the critical role of the respiratory system in acid–base balance.

Chapter 13 **Pulmonary Ventilation and Perfusion and Diffusion of Gases**

Chapter 14 **The Mechanics of Breathing**

Chapter 15 **Oxygen and Carbon Dioxide Transport and Control of Respiration**

Review Questions

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CHAPTER 13 Pulmonary Ventilation and Perfusion and Diffusion of Gases

Respiration is a complex process that begins with ventilation of the lungs and diffusion of gases between the lungs and blood. Meanwhile, the lungs are perfused with blood, which transports gases between lungs and tissues, where the biochemical processes involved in cellular respiration occur.

BLOOD FLOW IN THE LUNGS

The general principles of blood flow are discussed in Section 3, but the systemic and pulmonary circulations are different in some important aspects. Although right ventricular output is the same as left ventricular output (normally about 5 liters per minute [L/min] at rest), pressures in the pulmonary circulation are lower than pressures at equivalent points in the systemic circulation (Fig. 13.1). To accommodate high flow rate at lower pressure, resistance is also low in the pulmonary circulation. This low resistance is a result of the dense microcirculation and shorter vessels in the lungs compared with the systemic circulation.

Passive Control of Pulmonary Resistance

Pulmonary resistance is subject to **passive control** by pulmonary artery pressure and lung volume. Ordinarily, some pulmonary capillaries are collapsed. When **pulmonary artery pressure** increases, **recruitment** and **distension** of pulmonary capillaries occurs. In other words, collapsed capillaries are recruited to the circulation by the higher perfusion pressure, and individual capillaries distend, further reducing resistance. Such recruitment and distension are important in reducing pulmonary vascular resistance during high cardiac output, for example, in exercise. **Lung volume** has different effects on extra-alveolar vessels and alveolar capillaries. As lung volume increases, the associated traction causes distension of extra-alveolar vessels, reducing resistance within them. In contrast, with increased lung volume, alveolar vessels are compressed by the inflation of alveoli. Thus, as lungs are inflated from a very low volume, resistance first falls due to the effects on extra-alveolar vessels, but as inflation continues, resistance begins to rise as alveolar vessels are compressed.

Active Control of Pulmonary Resistance

Pulmonary vascular resistance is also subject to **active control** by **chemical and humoral substances** (Fig. 13.2). Hypoxia affects pulmonary vessels differently than it affects systemic vessels. In the systemic circulation, tissue hypoxia results in metabolic vasodilation of the arterial microcirculation. In contrast, in the pulmonary system, when **alveolar oxygen concentration** ($P_{A_{O_2}}$) falls, vasoconstriction of arterioles in the hypoxic region occurs. This is the most important mechanism

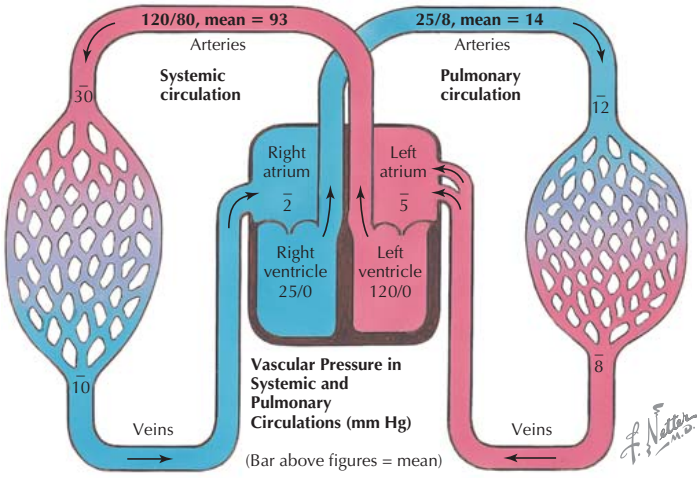


Figure 13.1 Pulmonary and Systemic Circulations The pulmonary circulation exists in series with the systemic circulation, and for this reason, equal cardiac output and stroke volumes are ejected from the right and left ventricles. Pressures and resistances are lower in the pulmonary circulation than in the systemic circulation.

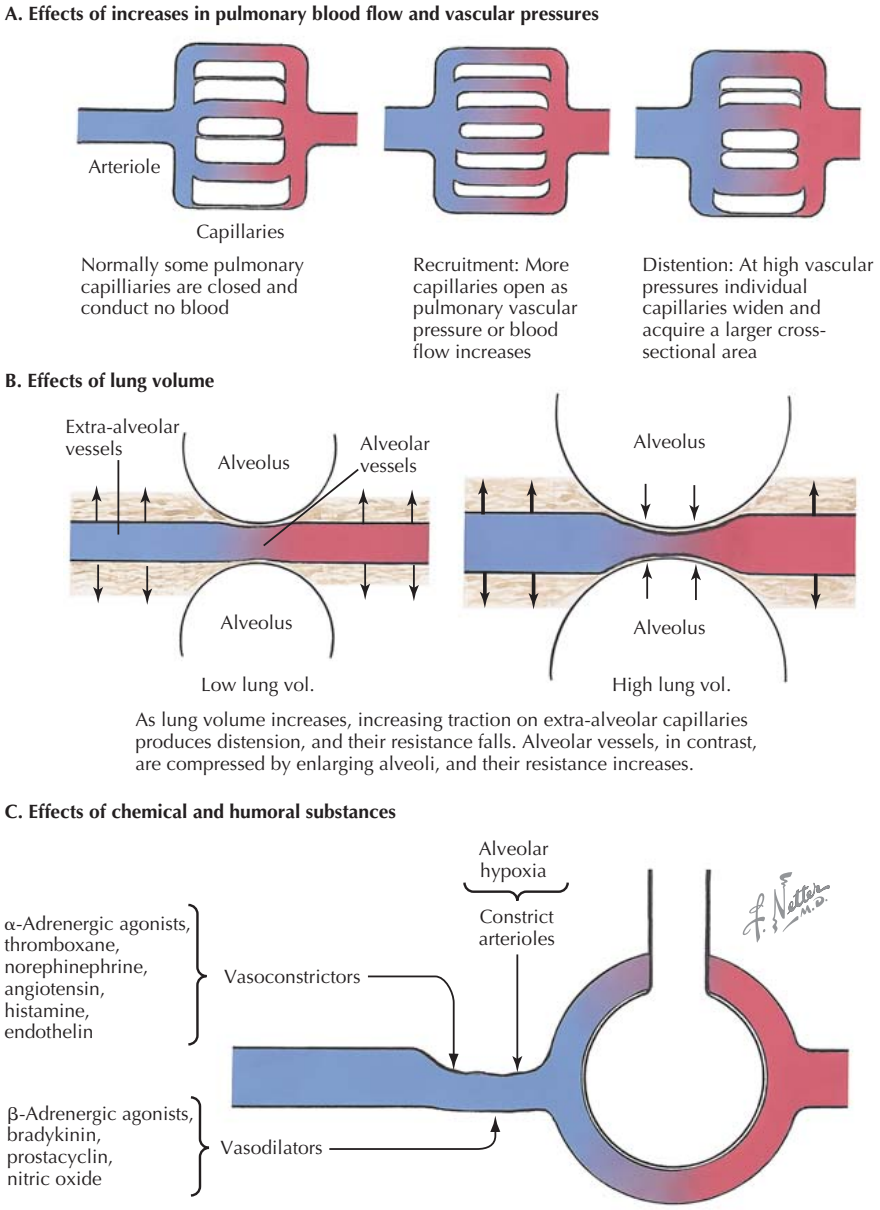


Figure 13.2 **Pulmonary Vascular Resistance** Resistance in the pulmonary circulation is affected by pulmonary artery pressure and blood flow, lung volume, and chemical and humoral substances. Elevation of pulmonary artery pressure causes distension of vessels and recruitment of capillaries that are otherwise collapsed *(A),* resulting in reduced resistance. An increase in lung volume causes traction and thus distension of extra-alveolar vessels, but results in compression of alveolar capillaries *(B);* the combination of these two effects results in lowest pulmonary vascular resistance at intermediate lung volumes. Pulmonary vessels also constrict and dilate in response to a number of chemical and humoral mediators *(C).*

for short-term regulation of regional pulmonary blood flow, and results in better perfusion of well-oxygenated portions of the lungs.

FUNCTIONAL ANATOMY OF THE LUNGS AND AIRWAYS

The human lungs consist of the three lobes of the right lung and two lobes of the left lung (Fig. 13.3). The bronchi, blood vessels, lymphatic vessels, and nerves leave and enter at the hilum of each lung. The airways consist of the trachea (windpipe), right and left main bronchi, smaller bronchi, and bronchioles (Figs. 13.4 and 13.5). The trachea branches into the right and left main bronchi, which enter the lungs, further divide, and become smaller in diameter. Up to 23 generations of branching airways are present in the system beginning at the trachea and leading to the alveoli.

Conducting Zone of the Lung

Airways from the trachea to the terminal bronchioles constitute the **conducting zone** of the lungs and are not capable of gas exchange, which takes place only in the respiratory bronchioles and alveoli. The conducting zone is also known as **anatomical dead space,** due to the lack of gas exchange in this area. In an adult, the anatomical dead space contains approximately 150 milliliters (mL) of air. The trachea has

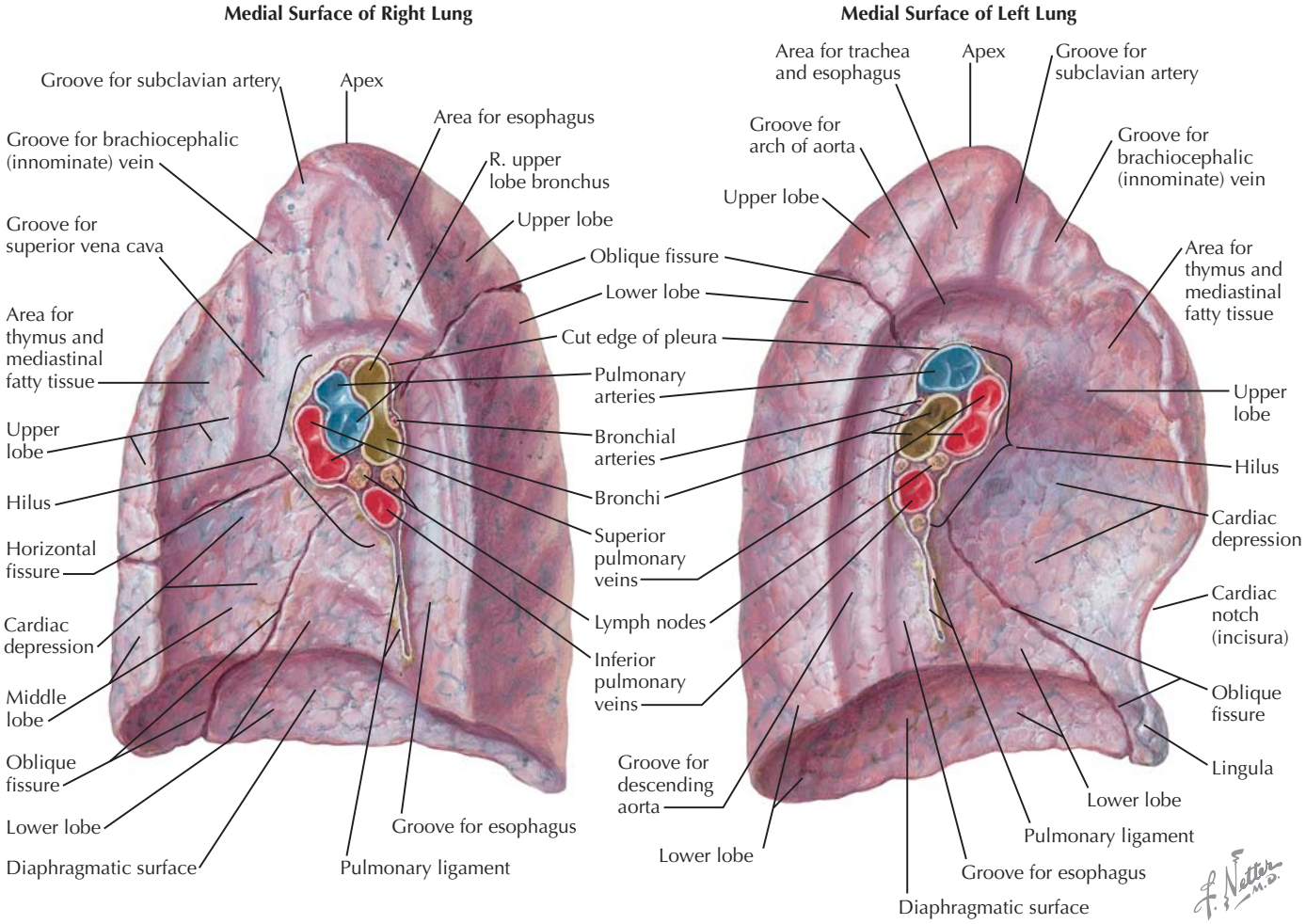


Figure 13.3 **Gross Anatomy of the Lung** The three lobes of the right lung and the two lobes of the left lung are depicted in this medial view of the lungs. Blood vessels, nerves, right and left main bronchi, and lymphatics enter and exit the lungs at the hilum.

cartilaginous rings that extend around three quarters of its circumference, providing the structural support necessary to hold airways open, but also allowing coughing. Cartilaginous plates are present in the walls of bronchi but are lost at the level of the bronchioles.

Most of the conducting system is lined by ciliated, **pseudostratified columnar epithelial cells,** mucous-secreting **goblet cells,** and several other cell types, with ciliated cells and goblet cells constituting the majority of cells lining the larger airways (Fig. 13.6). Mucus prevents desiccation of the epithelium and traps particulate matter in inspired air. Particles are carried upward (out of the lung) by ciliary action. This process is referred to as **mucociliary transport.** The epithelium becomes **cuboidal epithelium** in bronchioles, where ciliated cells are predominant. Goblet cells diminish and are absent in terminal bronchioles. **Clara cells** in bronchioles secrete substances that line the bronchioles and play a role in the defense system of the airways; they also act as stem cells for regeneration of bronchiolar epithelium.

The walls of the conducting airways also contain smooth muscle, which is regulated by the autonomic nervous system. Sympathetic stimulation dilates airways through the effects of norepinephrine (or circulating epinephrine) on β_2 receptors on smooth muscle cells. Parasympathetic stimulation constricts airways through muscarinic receptor activation by acetylcholine. Airway dilation is characteristic of the "fight-or-flight" response (see Chapter 7, page 87).

Respiratory Zone of the Lung

Inspired air passes through the trachea, bronchi, and bronchioles, eventually entering the terminal bronchioles, respiratory bronchioles, and alveoli. The respiratory bronchioles and alveoli are the **respiratory zone of the lungs,** where gas exchange occurs. There are an estimated 300 million alveoli in the human lungs, with an exchange area of 50 to 100 m^2. This enormous surface area, along with the thinness of the air–blood interface, allows for efficient gas exchange. This interface, known as the **alveolar-capillary membrane,** consists

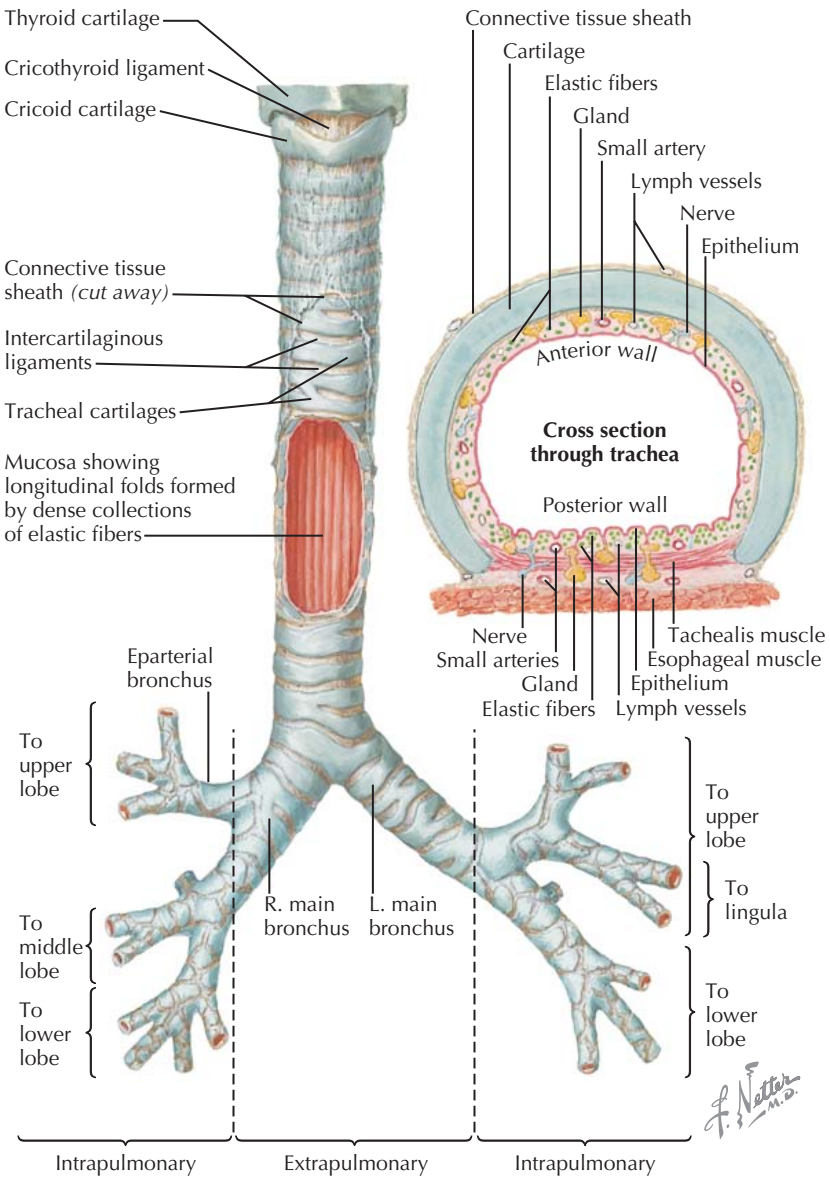


Figure 13.4 **Structure of the Trachea and Major Bronchi** The trachea divides into the right and left main bronchi before entering the lungs. The airways branch up to 23 times, leading to the alveoli. The airways from trachea to the terminal bronchioles are the conducting zone of the lung. With branching, diameter of airways diminishes. Collagen is less prevalent in the walls of smaller airways and is lost in the bronchioles.

of the capillary endothelium, the alveolar epithelium, and the basement membrane, upon which these two single-cell layers are formed. It is approximately 500 nanometers (nm) thick. Most of the alveolar surface is surrounded in this manner by pulmonary capillaries, allowing for "sheet flow" of blood around alveolar sacs, with a broad surface area for gas exchange (Figs. 13.7 and 13.8).

Alveoli are lined by type I and type II epithelial cells:

- **Type I epithelial cells** compose more than 90% of the surface area. Their squamous structure is adapted for gas diffusion across the alveolar-capillary membrane.
- **Type II epithelial cells** are cuboidal cells that secrete surfactant, a complex lipoprotein that lines the surface of alveoli and reduces their surface tension, increasing compliance of the lung (see "Surfactant and Surface Tension" in Chapter 14).

PULMONARY VOLUMES AND CAPACITIES

To describe pulmonary function in health and disease, it is necessary to understand the volumes and capacities associated with the lungs and breathing. There are four basic pulmonary volumes:

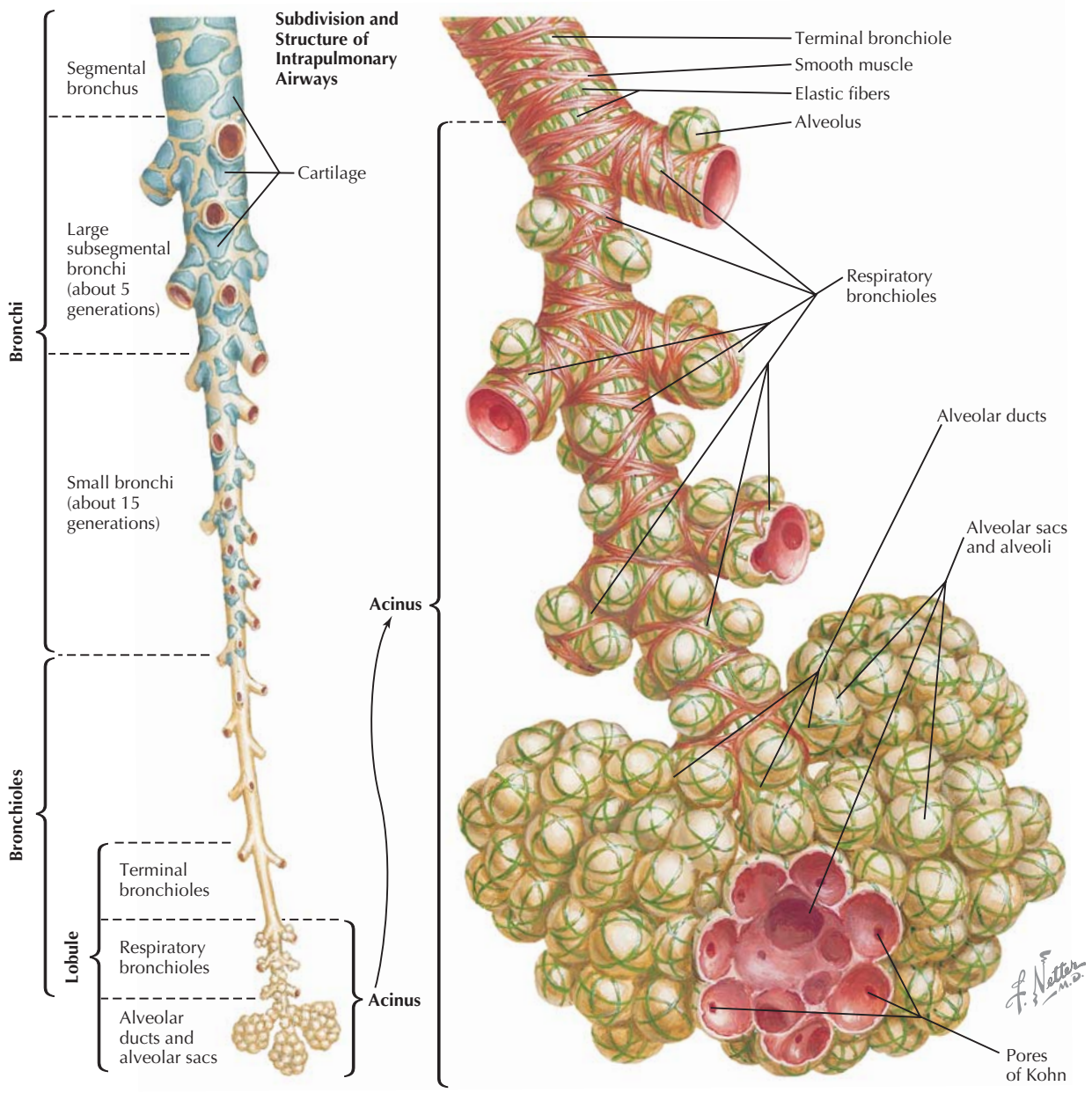
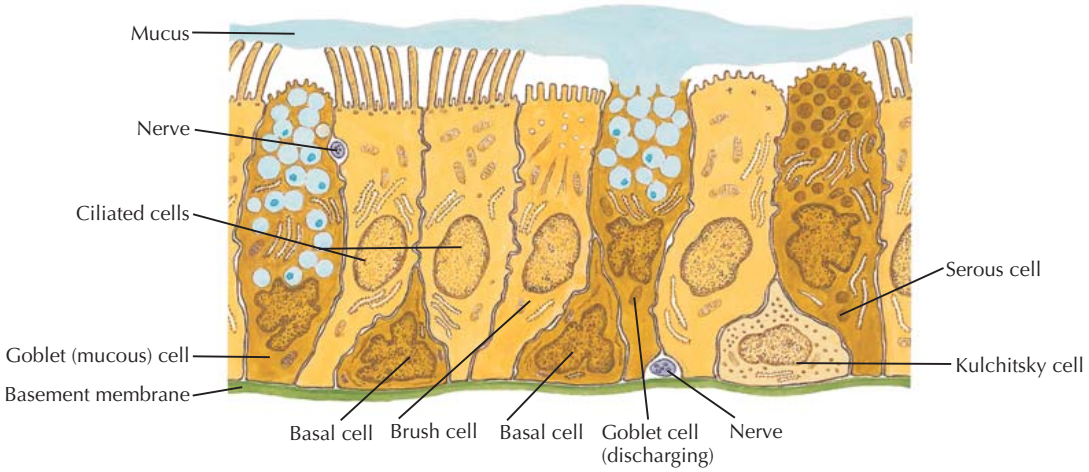


Figure 13.5 Intrapulmonary Airways After branching up to 23 times, the conducting system leads to the terminal bronchioles in the pulmonary lobules. Respiratory bronchioles and alveolar ducts give rise to alveolar sacs, the major site of gas exchange. The respiratory zone (gas exchange region) consists of structures distal to the terminal bronchioles (alveolar sacs, ducts, and respiratory bronchioles).

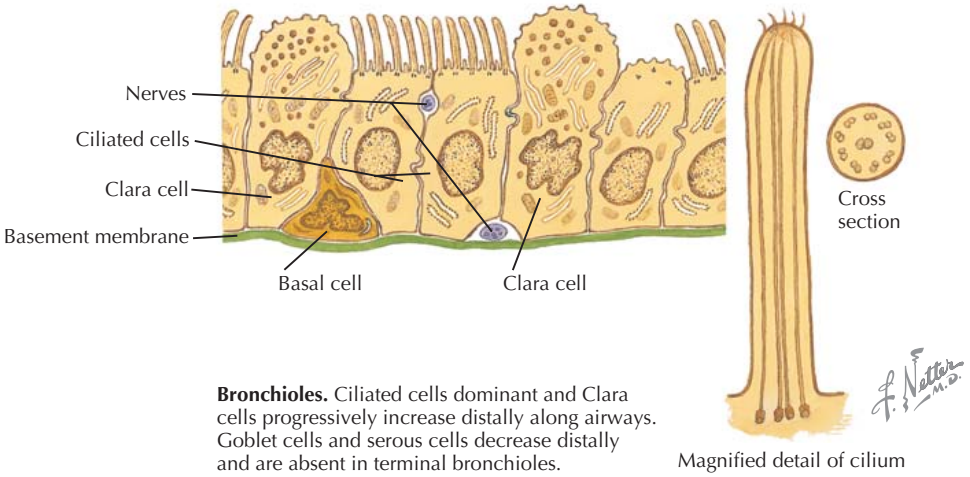
- **Tidal volume (V_T):** The volume of air inhaled and exhaled during breathing. Resting V_T is approximately 500 mL.
- **Residual volume (RV):** The volume remaining in the lungs after a maximal exhalation.
- **Expiratory reserve volume (ERV):** The additional volume a subject is *capable* of exhaling after a normal, quiet expiration.
- **Inspiratory reserve volume (IRV):** The additional volume a subject is *capable* of inhaling after a normal, quiet inspiration.

Four capacities associated with pulmonary function are:

- **Total lung capacity (TLC):** The volume of gas in the lungs after maximal inspiration. TLC is approximately 7 L in healthy adults.
- **Vital capacity (VC):** The maximum volume of air that a subject can exhale after maximal inspiration. The normal value is approximately 5 L. **Forced vital capacity (FVC)** is vital capacity measured during expiration at maximum force.



Trachea and large bronchi. Ciliated and goblet cells predominant, with some serous cells and occasional brush cells and Clara cells. Numerous basal cells and occasional Kulchitsky cells are present.



Bronchioles. Ciliated cells dominant and Clara cells progressively increase distally along airways. Goblet cells and serous cells decrease distally and are absent in terminal bronchioles.

Figure 13.6 Ultrastructure of Tracheal, Bronchial, and Bronchiolar Epithelium The trachea and bronchi are lined mainly by pseudostratified columnar epithelium and goblet cells, with several other, less common cell types. The goblet cells have the important function of mucus secretion. Kulchitsky cells are neuroendocrine-like cells that secrete paracrine factors and are part of the "diffuse neuroendocrine system" (DNES). The functions of brush and serous cells are not well defined; basal cells are pulmonary epithelial stem cells. The epithelial lining of bronchioles contains columnar epithelial cells; goblet cells are lost in terminal bronchioles. Clara cells are secretory cells of the bronchioles.

- **Functional residual capacity (FRC):** The volume remaining in the lungs after expiration during normal, quiet breathing.
- **Inspiratory capacity (IC):** The maximum volume that can be inspired after expiration during normal, quiet breathing.

Spirometry

These capacities and volumes are measured by **spirometry** and related techniques. In spirometry, the subject breathes in and out of a device known as a spirometer. Essentially, a spirometer is composed of two vessels: one contains water and



Full appreciation of pulmonary volumes and capacities requires understanding the relationships between these parameters. For example, total lung capacity is the sum of four of the described volumes:

$$TLC = RV + ERV + V_T + IRV$$

Similarly, vital capacity, functional residual capacity, and inspiratory capacity can be equated to the sums of particular lung volumes:

$$VC = IRV + V_T + ERV$$
$$FRC = ERV + RV$$
$$IC = V_T + IRV$$

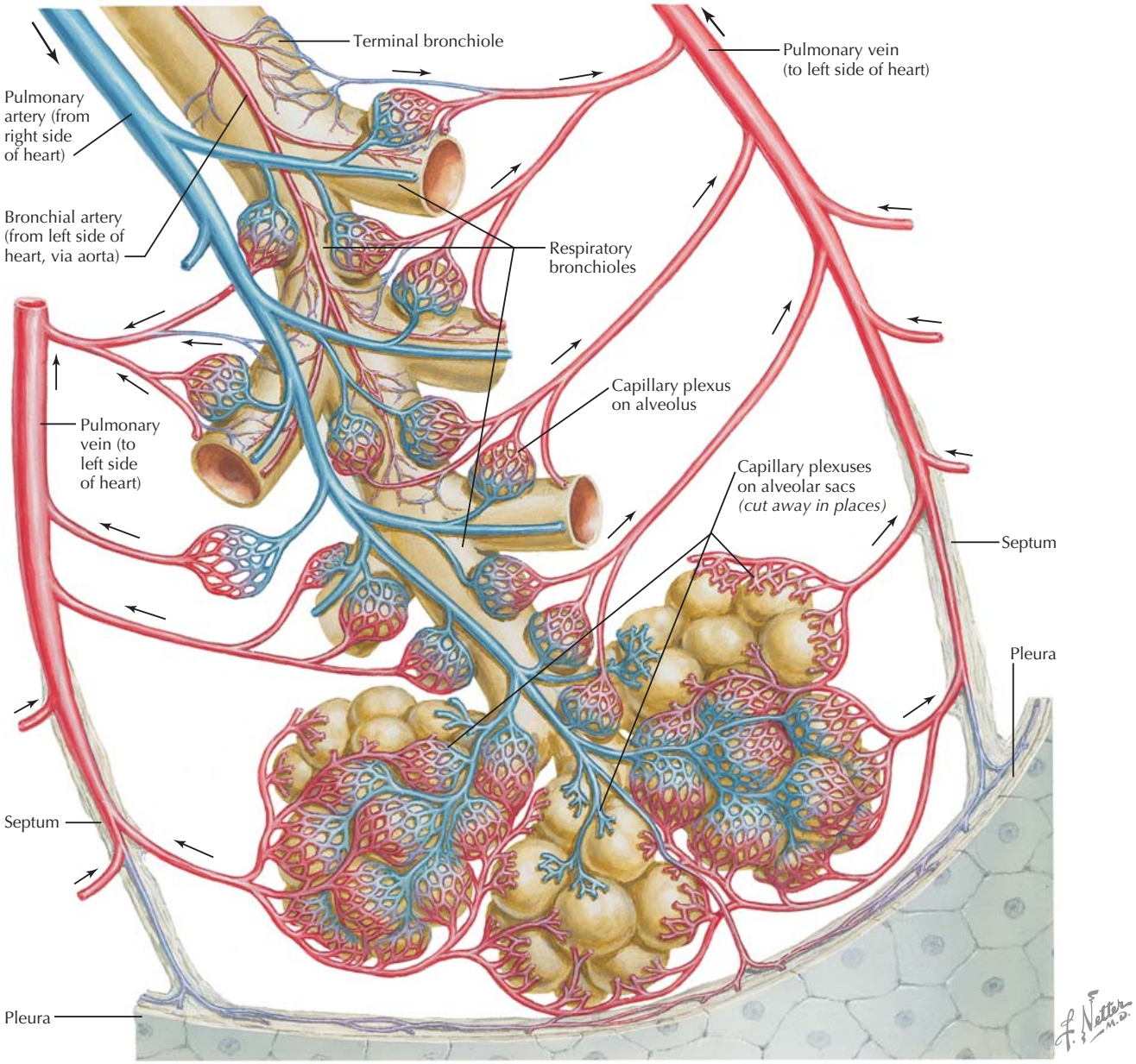


Figure 13.7 Intrapulmonary Blood Circulation The pulmonary circulation is a low-pressure, low-resistance circulation. Blood from the right ventricle and pulmonary artery is distributed to the pulmonary capillaries, where gas exchange takes place. The interface between the alveolar lumen and pulmonary capillary blood consists of a single layer of alveolar epithelium, basement membrane, and the one-cell-layer-thick capillary endothelium. Capillaries cover alveoli in this manner, providing for efficient gas exchange.

the other floats upside down in the first (Fig. 13.9). As the subject breathes through the attached tube, air flows in and out of the inner vessel, which consequently moves up and down. This up-and-down motion is recorded as a spirogram (Fig. 13.10), which is calibrated to reflect changes in volume of the inner vessel.

Tidal volume is measured by spirometry during normal, quiet breathing and is the difference between end inspiratory and end expiratory levels (see Fig. 13.10). Note that the actual end inspiratory and end expiratory volumes are unknown, because the spirometer records *changes* in volume rather than actual volume inside the lung. By having the subject expire maximally, expiratory reserve volume can be determined, because ERV is the difference between the resting end expiratory level and maximal expiratory level. Likewise, inspiratory reserve volume can be measured by having the subject inspire maximally and comparing the maximal inspiratory level to the end inspiratory level during normal, quiet breathing. Vital capacity (VC) and inspiratory capacity (IC) can be

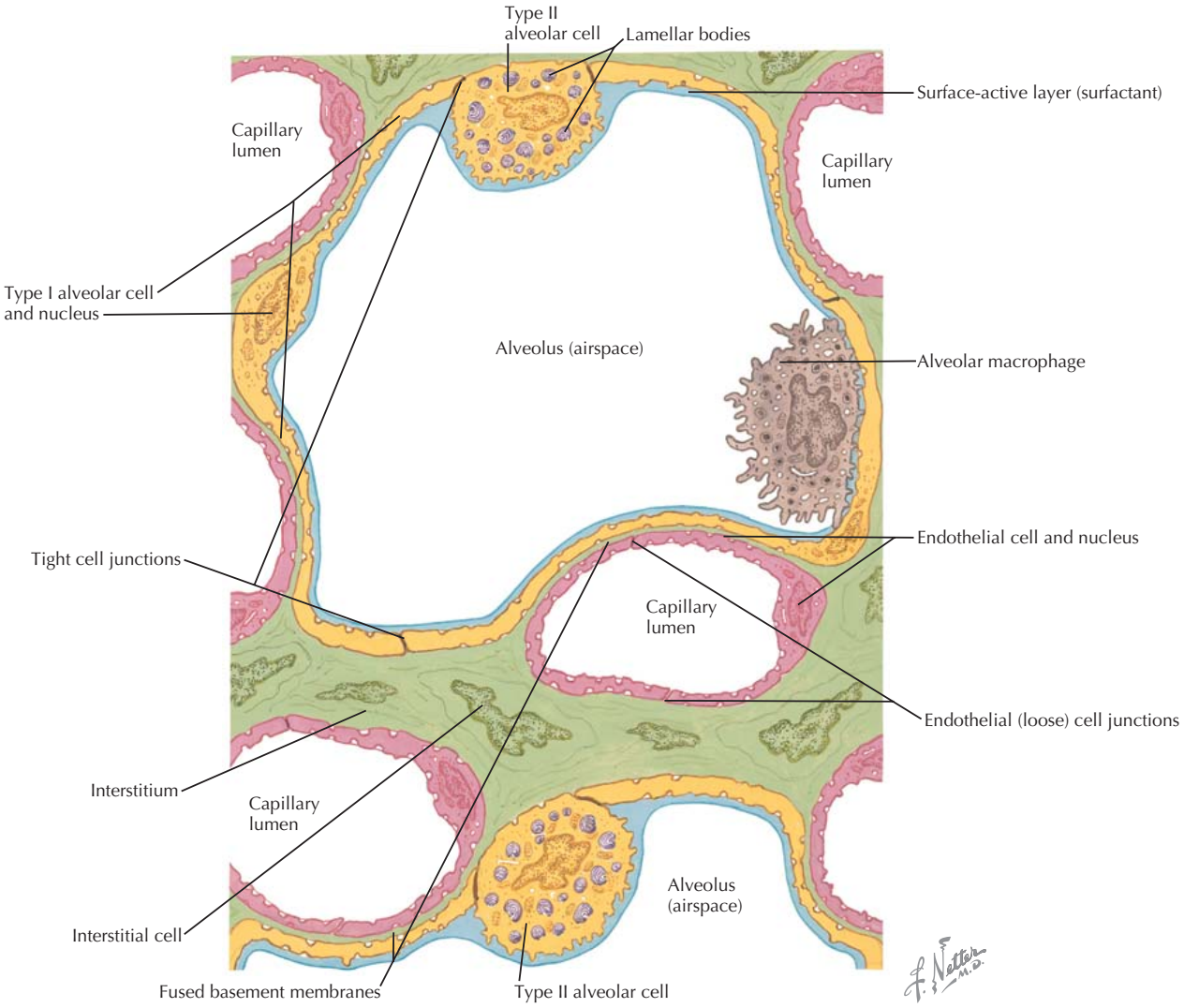


Figure 13.8 Ultrastructure of Pulmonary Alveoli and Capillaries The alveolar epithelium consists of type I and type II alveolar epithelial cells. Type I cells constitute the largest surface area; type II epithelial cells secrete surfactant. Gas diffusion takes place across the thin alveolar-capillary membrane composed of alveolar epithelium, basement membrane, and capillary endothelium. Interstitial tissue is minimal in most of the interface between the alveolar epithelium and capillary endothelium in healthy lungs.

determined by similar comparisons: VC is the difference between the maximal inspiratory and expiratory levels; IC is the difference between maximal inspiratory level and resting end-expiratory level.

Measurement of Capacities (FRC, RV, and TLC)

In order to measure total lung capacity, residual volume, and functional residual capacity, one of these parameters must be measured indirectly, for example by nitrogen washout, helium dilution, or body plethysmography. In the **helium dilution technique,** a small volume of helium is added to the spirometer before the subject begins the test, resulting in a known initial helium concentration within the volume of the system. When the subject begins breathing (beginning at FRC), this initial helium concentration becomes diluted, as the gas equilibrates between the lungs of the subject and the spirometer. Because helium does not diffuse through the alveolar-capillary membrane and is inert, a stable equilibrium is reached quickly. This final concentration is dependent only on the initial concentration of helium within the spirometer and the volume of the spirometry system plus FRC. After measuring the final concentration of helium, FRC can be determined from the formula:

$$C_1V_S = C_2 \times (V_S + FRC)$$

where C_1 is the initial, measured concentration of helium in the spirometer, V_S is the known volume of the spirometry system, and C_2 is the measured concentration of helium during breathing (after equilibrium is reached).

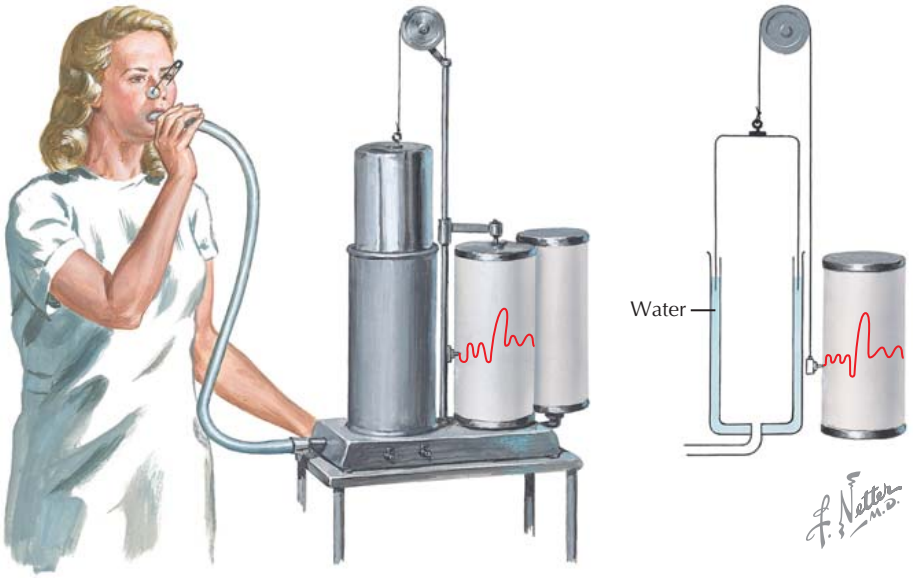


Figure 13.9 The Spirometer Pulmonary function testing involves multiple instruments and techniques. One basic instrument is the spirometer. The subject breathes in and out of a tube, resulting in vertical displacement of the inner canister, which floats upside down in water. The recorded tracing is analyzed to obtain several basic lung volumes and capacities (see Fig. 13.10).

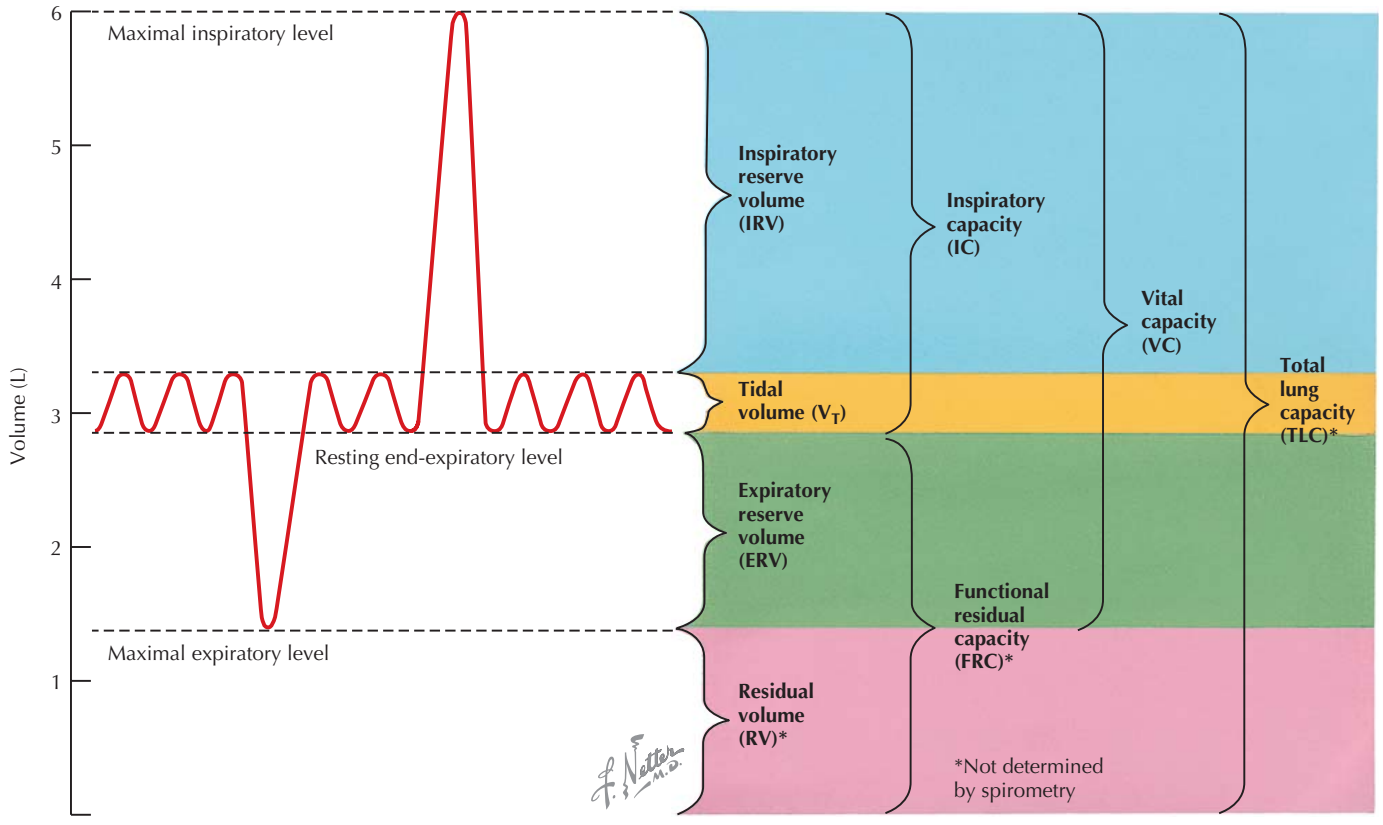


Figure 13.10 Measurement of Lung Volumes and Capacities by Spirometry In this spirogram, beginning on the left, the subject breathed quietly for a few breaths, exhaled maximally, breathed quietly for a few breaths, inhaled maximally, and then breathed normally again. Note that residual volume, functional residual capacity, and total lung capacity cannot be measured by spirometry alone. FRC is measured by another technique (often helium dilution); when FRC is known, TLC and RV can be calculated from the spirometry tracing. The volumes represented in the tracing are those of a typical healthy adult.

Once FRC is known, TLC and RV can be readily calculated from spirometry measurements (see Fig. 13.10):

$$TLC = FRC + IC$$
$$RV = TLC - VC$$

Whole-body plethysmography is based on **Boyle's law,** which states that the product of pressure and volume for a gas is constant:

$$P_1V_1 = P_2V_2$$

To employ whole-body plethysmography to measure FRC, the subject is put into an airtight box equipped with a mouthpiece through which he breathes outside air. During normal, quiet breathing, the subject is asked to stop and relax after a normal, quiet exhalation. At that point, the mouthpiece is closed, and the subject attempts to inhale through the closed mouthpiece. This attempt causes the air in the lungs (FRC) to expand due to the negative pressures created by the expansion of the chest wall, and results in an equal reduction of the volume of the air in the box outside the patient's body. The pressure of the air in the box increases due to this reduction in volume. Changes in pressure in the box are used to calculate the change in volume in the box using Boyle's law. This change in volume is the same as the change in volume of the lungs from the resting value (FRC). Based on the change in pressure in the respiratory system (measured at the mouthpiece during the attempt to inhale) and the change in volume of the lungs, the initial volume (FRC) can be calculated using Boyle's law.

VENTILATION AND ALVEOLAR GAS COMPOSITION

Ventilation is the movement of air in and out of the respiratory system. During normal, quiet breathing, the volume of air inhaled and exhaled with each breath is approximately 500 mL. This is known as the resting **tidal volume.** The normal, resting **respiratory rate** is 12 to 20 breaths per minute (min). Taking an average rate of 15 breaths per minute, the **minute ventilation** ($\dot{V}_E$, the volume exhaled per minute) is calculated by the formula:

$$\dot{V}_E = R \times V_T$$

where R is the respiratory rate and V_T is the tidal volume. Thus, 15 breaths/min × 500 mL yields a $\dot{V}_E$ of 7500 mL/min (7.5 L/min).

Minute ventilation ($\dot{V}_E$) is greater than **alveolar ventilation** ($\dot{V}_A$, ventilation of the respiratory zone of the lungs), because a portion of the tidal volume remains in the anatomical dead space (the conducting zone) and is not involved in gas exchange. Because anatomical dead space is approximately 150 mL, this **dead space ventilation** ($\dot{V}_D$) is roughly 150 mL × 15/min, or 2250 mL/min. Alveolar ventilation is calculated by the formula:



The symbols used in respiratory physiology can be confusing. The uppercase V is used to designate volume, whereas airflow rates are designated by the symbol $\dot{V}$. Uppercase A used as a subscript, as in $\dot{V}_A$, specifies that the parameter refers to the alveolar space. Thus, $\dot{V}_A$ is alveolar ventilation. Lowercase a and v are used to specify arterial and venous measurements, respectively, as in Pa_{CO_2} or Pv_{CO_2} (partial pressure of carbon dioxide in arterial and venous blood, respectively). $P_{A_{CO_2}}$ refers to partial pressure of carbon dioxide in alveolar gas.

$$\dot{V}_A = R(V_T - V_D)$$

where R is respiratory rate, V_T is tidal volume, and V_D is dead space volume. Stated another way,

$$\dot{V}_A = \dot{V}_E - \dot{V}_D$$

Of the 500 mL tidal volume, only 350 mL is entering the alveoli with each breath, and of the 7500 mL/min minute ventilation, only the alveolar ventilation of 5250 mL/min (7500 mL/min − 2250 ml/min) is available for gas exchange.

Composition of Alveolar Air

The composition of alveolar air is dependent on several factors, including the composition of inspired air, alveolar ventilation, and the concentration of dissolved gases in mixed venous blood. Our atmosphere is composed of 21% oxygen, 79% nitrogen, and less than 1% other gases, including carbon dioxide, with a total atmospheric pressure of 760 mm Hg at sea level. Gas concentrations may also be expressed as fractional concentrations in an inspired gas mixture; in our atmosphere, $F_{iO_2} = 0.21$ and $F_{iN_2} = 0.79$. According to **Dalton's law,** the sum of the partial pressures of gases in a mixture is equal to the total pressure. Thus, for dry air at sea level:

$$P_{O_2} = 0.21 \times 760 \text{ mm Hg} = 160 \text{ mm Hg}$$
$$P_{N_2} = 0.79 \times 760 \text{ mm Hg} = 600 \text{ mm Hg}$$
$$P_{tot} = 760 \text{ mm Hg}$$

As air is inspired, it warms rapidly to body temperature and becomes saturated with water vapor. At 37°C, the vapor pres-



At the same minute ventilation ($\dot{V}_E$), deep, slow breathing yields greater alveolar ventilation ($\dot{V}_A$) than rapid, shallow breathing. Comparing alveolar ventilation when respiratory rate is 15/min and tidal volume is 500 mL to alveolar ventilation at a respiratory rate of 30/min and tidal volume of 250 mL:

$$\dot{V}_A = 15/\text{min}\ (500\,\text{mL} - 150\,\text{mL}) = 5250\,\text{mL/min}$$
$$\dot{V}_A = 30/\text{min}\ (250\,\text{mL} - 150\,\text{mL}) = 3000\,\text{mL/min}$$

Thus, slower, deeper ventilation produces greater alveolar ventilation than more rapid ventilation at proportionally less tidal volume.

sure of water is 47 mm Hg and must be accounted for when determining the gas composition of inspired air. In **inspired air:**

$$P_{H_2O} = 47 \text{ mm Hg}$$
$$P_{O_2} = 0.21 \times (760 - 47) \text{ mm Hg} = 150 \text{ mm Hg}$$
$$P_{N_2} = 0.79 \times (760 - 47) \text{ mm Hg} = 563 \text{ mm Hg}$$
$$P_{tot} = (150 + 563 + 47) \text{ mm Hg} = 760 \text{ mm Hg}$$

This composition of inspired air is constant throughout the conducting zone of the lung, where no gas exchange occurs. Within the respiratory zone, oxygen diffuses from alveolar air to blood, while carbon dioxide diffuses from blood to alveolar air, resulting in alveolar air composition that is different from composition of inspired air. The relationship between partial pressure of oxygen and carbon dioxide in alveolar air is described by the important **alveolar gas equation:**

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}}/R$$

where $P_{A_{O_2}}$ and $P_{I_{O_2}}$ are the partial pressures of oxygen in alveolar air and inspired air, respectively; $P_{A_{CO_2}}$ is partial pressure of carbon dioxide in alveolar air; and R is the **respiratory quotient,** which usually has a value of 0.8. This equation can be used to predict the partial pressure of oxygen in alveolar air based on measurement of carbon dioxide in systemic arterial blood in a healthy person, because P_{CO_2} is normally fully equilibrated between blood and alveolar air in the alveolar capillaries. For example, at 760 mm Hg atmospheric pressure (sea level), when $P_{a_{O_2}}$ in an arterial blood gas determination (ABG) is 40 mm Hg:

$$P_{A_{O_2}} = 150 \text{ mm Hg} - 40 \text{ mm Hg}/0.8 = 100 \text{ mm Hg}$$

Because P_{O_2} is also fully equilibrated between alveolar air and blood as it passes through alveolar capillaries, and nearly all of pulmonary blood flow is exposed to alveolar air, the normal value for $P_{a_{O_2}}$ is nearly 100 mm Hg. Partial pressures of oxygen and carbon dioxide in inspired and alveolar air and mixed venous and arterial blood are illustrated in Figure 13.11.

DIFFUSION OF GASES

Diffusion of gas ($\dot{V}_{gas}$) between alveolar gas and capillary blood follows Fick's law,

$$\dot{V}_{gas} = \frac{A \times D(P_1 - P_2)}{T}$$

where A is the area of a membrane separating two compartments, T is the thickness of the membrane, D is the diffusion constant, and P_1 and P_2 are the gas concentrations in the two compartments. Thus, diffusion of a gas is:

- **Directly** related to the surface area for diffusion.
- **Directly** related to the difference in partial pressure of the gas on each side of the membrane.
- **Directly** related to the diffusion constant of the gas.
- **Inversely** related to the thickness of the membrane.

The diffusion constant of a gas is directly related to solubility and inversely related to the square root of its molecular weight.

Perfusion-Limited Gas Transport

The concentrations of dissolved gases in blood equilibrate with the gas concentrations of alveolar air as blood flows through pulmonary capillaries (Fig. 13.12). Under resting conditions, the transit time for blood through the alveolar capillary is only approximately 0.75 seconds (sec). In normal, healthy lungs at rest, oxygen and carbon dioxide are equilibrated between blood and alveolar gas by the time blood has passed one third of the way through an alveolar capillary. Transport of these gases is **perfusion-limited** under these conditions, because the only way to increase gas transfer is to increase perfusion (blood flow, rather than diffusion, is the limiting factor for exchange). As a consequence, cardiac output can be increased substantially without compromising oxygenation of blood despite reduced transit time through the alveolar capillaries, for example during exercise. Nitrous oxide (laughing gas; N_2O) is a textbook example of perfusion-limitation. N_2O, unlike many other gases including O_2 and CO_2, is not bound by blood components but exists only as dissolved gas in blood. As a result, in a subject breathing a gas mixture containing N_2O, blood and alveolar P_{N_2O} equilibrate rapidly in blood flowing through the alveolar capillary, reaching this equilibrium one fifth of the way through the capillary.

The respiratory quotient (R) is the ratio of carbon dioxide production to oxygen consumption and is dependent on metabolism. For pure carbohydrate metabolism, R has a value of 1.0, because oxidative metabolism of one mole of glucose requires six moles of oxygen and produces six moles of carbon dioxide. During pure lipid metabolism, the approximate value of R would be 0.7, whereas the respiratory quotient for amino acids varies. Under metabolic conditions involving oxidation of a typical mixture of substrates, the respiratory quotient is approximately 0.8 (0.8 moles of carbon dioxide are produced for each mole of oxygen consumed).

Transit time is the time required for blood or a formed element to pass through a portion of the circulation. Because blood volume in the entire pulmonary circulation is approximately 500 mL and cardiac output at rest is about 5000 L/min (83 ml/sec), transit time through the entire pulmonary circulation is approximately 6 seconds. Of this, about 0.75 second is transit time through the alveolar capillaries, during which all exchange of gases takes place. In healthy lungs, oxygen is equilibrated between blood and alveolar gas by the time blood has passed one third of the way through an alveolar capillary.

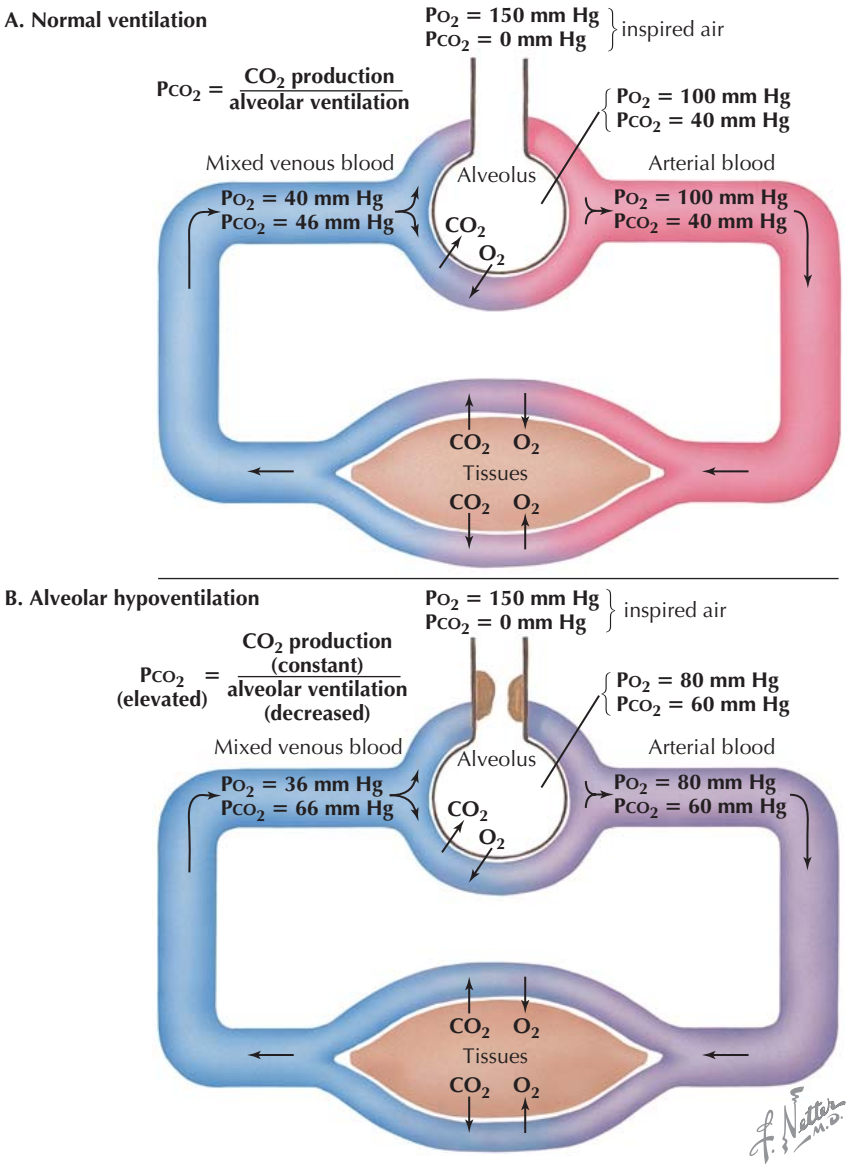


Figure 13.11 Partial Pressures of Oxygen and Carbon Dioxide in Blood and Alveolar Air
The normal partial pressures of gases in mixed venous blood entering the alveolar capillaries are indicated on the left side of part *A*. As blood flows through the alveolar capillaries in healthy lungs, oxygen and carbon dioxide levels equilibrate between alveolar air and blood. Thus, partial pressures of oxygen and carbon dioxide determined by arterial blood gas (ABG) measurement are approximately equal to the partial pressures in alveolar air in healthy subjects. During hypoventilation (*B,* indicated by partial blockage of the airway), P_{O_2} is reduced and P_{CO_2} is elevated in arterial blood (the subject is hypoxic and hypercapnic) as well as in the alveolar gas.

Diffusion-Limited Gas Transport

During very strenuous aerobic exercise in which cardiac output is greatly increased, or in some disease states such as interstitial fibrosis, oxygen transport may be **diffusion-limited.** In other words, P_{O_2} is not completely equilibrated between alveolar air and blood leaving the alveolar capillary. The classic example of a diffusion-limited gas is carbon monoxide (CO). When a subject breathes a gas mixture containing CO, CO diffuses from the alveolar air to blood. However, CO is bound to hemoglobin with very high affinity, and as a result, large amounts of CO can be transferred to blood with little change in blood P_{CO}. Thus, the partial pressures of CO in alveolar air and blood do not fully equilibrate during the transit of blood through the alveolar capillary, and its transport is limited only by the diffusion capacity of the alveolar membrane.

Diffusion in the lung can be assessed using a measurement known as **diffusion capacity of the lung for CO** (D_{LCO}). CO is useful for this purpose because its transport is diffusion-limited. According to Fick's law,

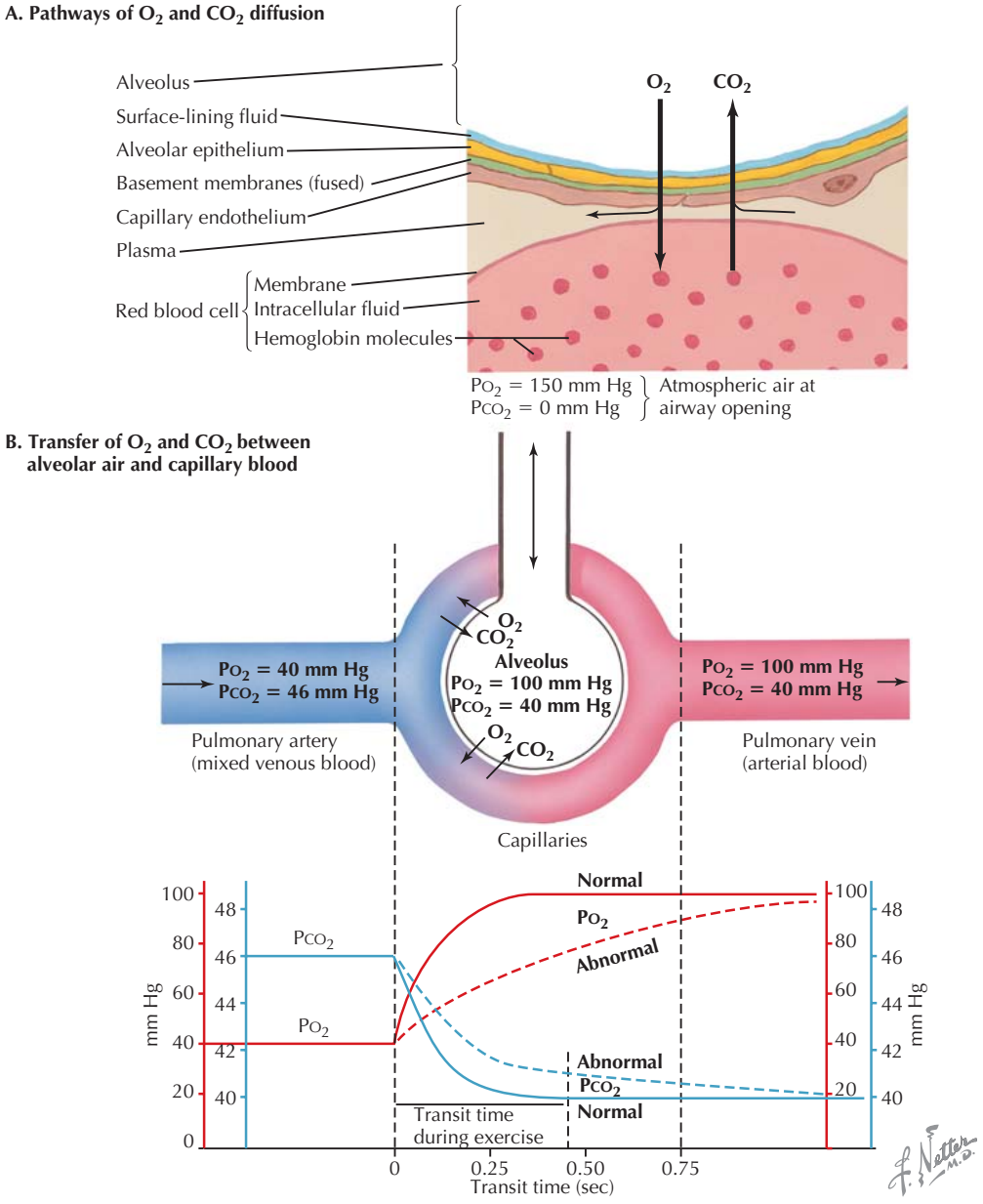


Figure 13.12 **O_2 and CO_2 Exchange** Diffusion of carbon dioxide and oxygen between blood and alveolar air occurs by diffusion through the thin alveolar-capillary membrane *(A)*. Partial pressures of gases in inspired air, alveolar air, and blood are illustrated in the center panel. At resting cardiac output, blood normally traverses the length of the alveolar capillary in 0.75 sec, and O_2 and CO_2 are equilibrated between blood and alveolar air as blood passes through the first third of the capillary *(B)*. When the alveolar-capillary membrane is thickened by interstitial fibrosis, the resulting diffusion barrier impedes gas exchange *(dashed lines)*.

$$\dot{V}_{CO} = \frac{A \times D_{CO} \times (P_{CO_1} - P_{CO_2})}{T}$$

$$D_{LCO} = \frac{\dot{V}_{CO}}{P_{A_{CO}}}$$

D_{LCO} is defined as a transfer factor equal to $(A/T) \times D_{CO}$ and is substituted in the above equation, yielding

$$\dot{V}_{CO} = D_{LCO} \times (P_{CO_1} - P_{CO_2})$$

Rearranging and substituting $P_{A_{CO}}$ for $P_{CO_1} - P_{CO_2}$ (because the concentration of CO in blood is initially zero),

VENTILATION AND PERFUSION GRADIENTS

Optimal function of the lung requires proper balance between ventilation and perfusion. In other words, ventilation should be matched to blood flow for efficient exchange of gases

CLINICAL CORRELATE
DLCO and Interstitial Pulmonary Fibrosis

Interstitial fibrosis is a type of restrictive lung disease, in which functional lung volume is reduced. It is an inflammatory disease in which deposition of connective tissue and subsequent scar formation in the interstitial space of the alveolar-capillary membrane results in thickening of the membrane. As a consequence, diffusion across the alveolar-capillary membrane is impeded, and mechanical properties of the lung are altered (resulting in "restriction"; discussed in context in Chapter 14). Changes in the diffusing capacity of the lung in interstitial fibrosis are typically assessed by measurement of D_{LCO}. Beginning at residual volume, the subject takes in a single, large breath of air containing 0.3% CO and 10% helium, inhaling to total lung capacity, holds this breath for 10 seconds, and then exhales. A sample of exhaled air is collected after exhalation of dead space volume for measurement of the final concentration of gases in alveolar air. D_{LCO} is then determined by the formula $D_{LCO} = \dot{V}_{CO}/P_{A_{CO}}$. $P_{A_{CO}}$ in this formula is the initial value upon inspiration of the gas mixture and is calculated based on CO concentration in inspired air and helium dilution; $\dot{V}_{CO}$ is calculated based on alveolar volume, breath-hold time, and the change in CO concentration in alveolar air.

between the environment and the blood. However, neither ventilation nor perfusion of the lung is uniform from apex to base.

In the standing position, the weight of the lungs stretches the top portion of the organ, such that the alveoli near the apex have larger volume than those near the base. Thus, the smaller alveoli toward the base of the lung have greater compliance than those that are already stretched by gravitational forces, and as a result, ventilation is greater toward the bottom of the lung. In other words, there is an increasing ventilation gradient from top to bottom of the lung.

Zones of the Lung

An even larger gradient (than the one for ventilation) exists for pulmonary blood flow (perfusion) in the standing position (Fig. 13.13), whereby greater flow occurs toward the bottom of the lungs. This is the result of gravitational effects on vascular pressures and the relationship between vascular pressure and alveolar pressure as blood flows through alveolar capillaries. Perfusion pressure in most regional circulations is the difference between arterial and venous pressure. However,

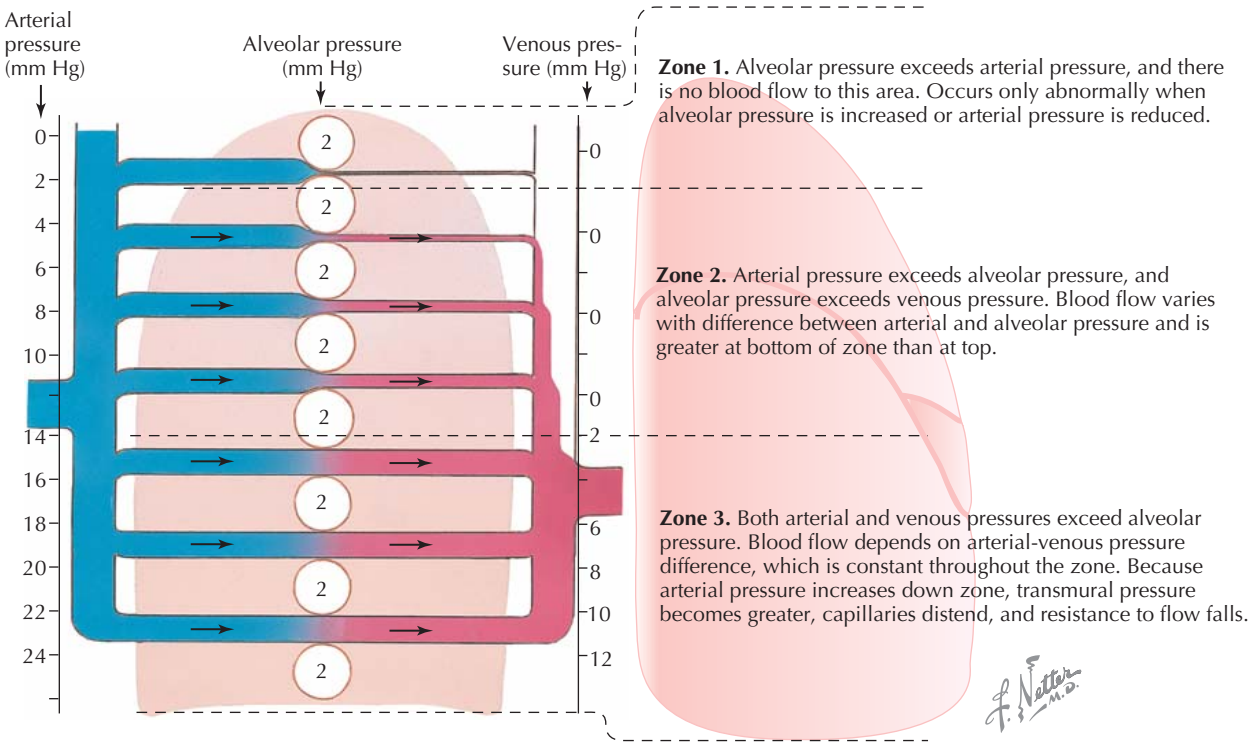


Figure 13.13 Distribution of Pulmonary Blood Flow As a result of gravity, blood flow through the lungs is not uniformly distributed in the standing position. At the apex of the lungs, hydrostatic pressure is reduced, potentially resulting in collapse of capillaries by alveolar pressure; as a result, flow is reduced toward the apex, and may cease if alveolar pressure is increased or blood pressure is reduced (zone 1). In the middle of the lungs (zone 2), arterial pressure exceeds alveolar pressure, but alveolar pressure is higher than venous pressure. Flow in zone 2 is more than that in zone 1, but less than flow in zone 3, where higher hydrostatic pressure causes distension of vessels and therefore reduced vascular resistance.

in the pulmonary system, as blood flows through a capillary, the rate of flow is potentially affected by air pressure in the alveoli on either side of the capillary. Blood enters the lung at the hilum, approximately midway between apex and base; above this point of entry, hydrostatic pressure in the pulmonary vessels is reduced by the effect of gravity. At the very top of the lung, alveolar pressure may even exceed arterial pressure under some conditions, producing a region of no blood flow, **zone 1.** In regions of the lung in which alveolar pressure is higher than venous pressure but less than arterial pressure, perfusion pressure is equal to arterial pressure minus alveolar pressure. This occurs in **zone 2** of the lung (see Fig. 13.13). Thus, as blood passes through alveolar capillaries in zone 2, the pressure gradient for blood flow is the difference between pulmonary arterial pressure and the pressure within the alveoli, which exceeds venous pressure. In contrast, in **zone 3** (lower portions of the lung) pulmonary vascular pressures are elevated by the effect of gravity, and both arterial and venous pressures exceed alveolar pressure. The higher hydrostatic pressure causes distension of vessels and therefore reduced resistance; as a result, blood flow is greatest in zone 3 of the lung.

The Ventilation-to-Perfusion Ratio

As a result of these gradients in ventilation and perfusion, the ratio $\dot{V}_A/\dot{Q}_C$ (where $\dot{Q}_C$ is pulmonary capillary blood flow) is greatest at the top of the lung and lowest at the bottom (Fig. 13.14), and ventilation and perfusion are best matched in the middle portion. Because resting pulmonary blood flow is approximately 5 L/min (equal to cardiac output of the systemic circulation) and alveolar ventilation is also approximately 5 L/min, $\dot{V}_A/\dot{Q}_C$ is approximately 1 in this middle region, less than 1 at the base of the lung, and more than 1 toward the apex.

Dead Space and Shunt: Extremes of $\dot{V}_A/\dot{Q}_C$ Imbalance

Dead space and **shunt flow** are extremes of imbalance. Alveoli that are ventilated but not perfused constitute **physiological dead space** (as opposed to anatomical dead space). In dead space, $\dot{V}_A/\dot{Q}_C = \infty$. In contrast to dead space (ventilation without perfusion), **shunt flow** represents perfusion without ventilation. In other words, shunted blood returning to the left heart has not been exposed to ventilated alveoli. If alveolar capillaries are perfused in an area of the lung that is not ventilated (for example, when an airway is blocked) **physiological shunt** is present ($\dot{V}_A/\dot{Q}_C = 0$). Shunt can also be **anatomical** (bypassing the alveoli). In addition to blood flow originating in the pulmonary arteries, the pulmonary veins receive some flow from the bronchopulmonary (bronchial) circulation, which originates from the systemic circulation and perfuses tissues in the conducting zone of the lungs. Thus, blood from the bronchopulmonary circulation returning to the left heart is not oxygenated. The venous admixture of oxygenated and deoxygenated blood resulting from anatomical shunt accounts for most of the small **alveolar-to-systemic arterial P_{O_2} gradient** (**A-a P_{O_2} gradient**) in healthy subjects (6 to 9 mm Hg). While $\dot{V}_A/\dot{Q}_C$ varies even within normal lungs, ventilation–perfusion imbalances are a central issue in pulmonary pathophysiology (discussed in various contexts in following pages).

HYPOXEMIA

Hypoxemia (low Pa_{O_2}) may result from one of five causes, all of which reflect problems related to ventilation, perfusion, or diffusion. In the simplest case, ventilation (breathing) in an atmosphere with low P_{O_2} (for example, at high altitude) will cause hypoxemia that can be corrected by breathing air with higher P_{O_2}. A second cause of hypoxemia is **hypoventilation**. With insufficient ventilation (for example, with shallow breathing), $P_{A_{CO_2}}$ rises and $P_{A_{O_2}}$ falls, due to inefficient exchange of alveolar air with the atmosphere. Consequently, hypoxemia and **hypercapnea** (high Pa_{CO_2}) result. Hypoxemia of this type can be corrected by adjusting respiratory rate and tidal volume, or breathing air containing a high concentration of oxygen.

Diffusion abnormalities are a third cause of hypoxemia. Poor diffusion (for example, due to thickening of the alveolar-capillary membrane) will produce hypoxemia with an elevated **alveolar-to-systemic arterial P_{O_2} gradient** (**A-a P_{O_2} gradient**); this abnormal gradient occurs because P_{O_2} is not fully equilibrated between alveolar air and the blood leaving alveolar capillaries. Although hypoxemia will be corrected by administration of 100% oxygen, the A-a P_{O_2} gradient will remain elevated.

Shunt flow also produces hypoxemia. In the presence of shunt flow, venous admixture of oxygenated and deoxygenated blood produces an elevated A-a P_{O_2} gradient. In congenital abnormalities of the heart in which right-to-left shunting of blood occurs through atrial or ventricular septal defects, large A-a P_{O_2} gradients may be seen. Airway obstruction also results in shunt flow and increased A-a P_{O_2} gradient. Hypoxemia (low arterial P_{O_2}) caused by shunt flow can be differentiated from hypoxemia caused by other defects by measurement of Pa_{O_2} before and after several minutes of breathing of 100% oxygen. Neither the hypoxemia nor the A-a P_{O_2} gradient associated with shunt flow can be fully corrected by breathing 100% oxygen, due to venous admixture of shunt flow to oxygenated blood.

Ventilation–perfusion imbalance is a fifth cause of low Pa_{O_2}. As discussed earlier, gradients in ventilation and perfusion produce some degree of ventilation–perfusion imbalance even in a healthy subject in the standing position, and regional ventilation–perfusion imbalances contribute to the normal, small A-a gradient P_{O_2}. If the imbalance is abnormally pronounced, mixing of blood from areas of the lung that are well perfused but underventilated with blood from other areas (where ventilation and perfusion are better balanced) causes an exaggerated A-a P_{O_2} gradient and hypoxemia. This type of hypoxemia can be corrected by administration of 100% oxygen.

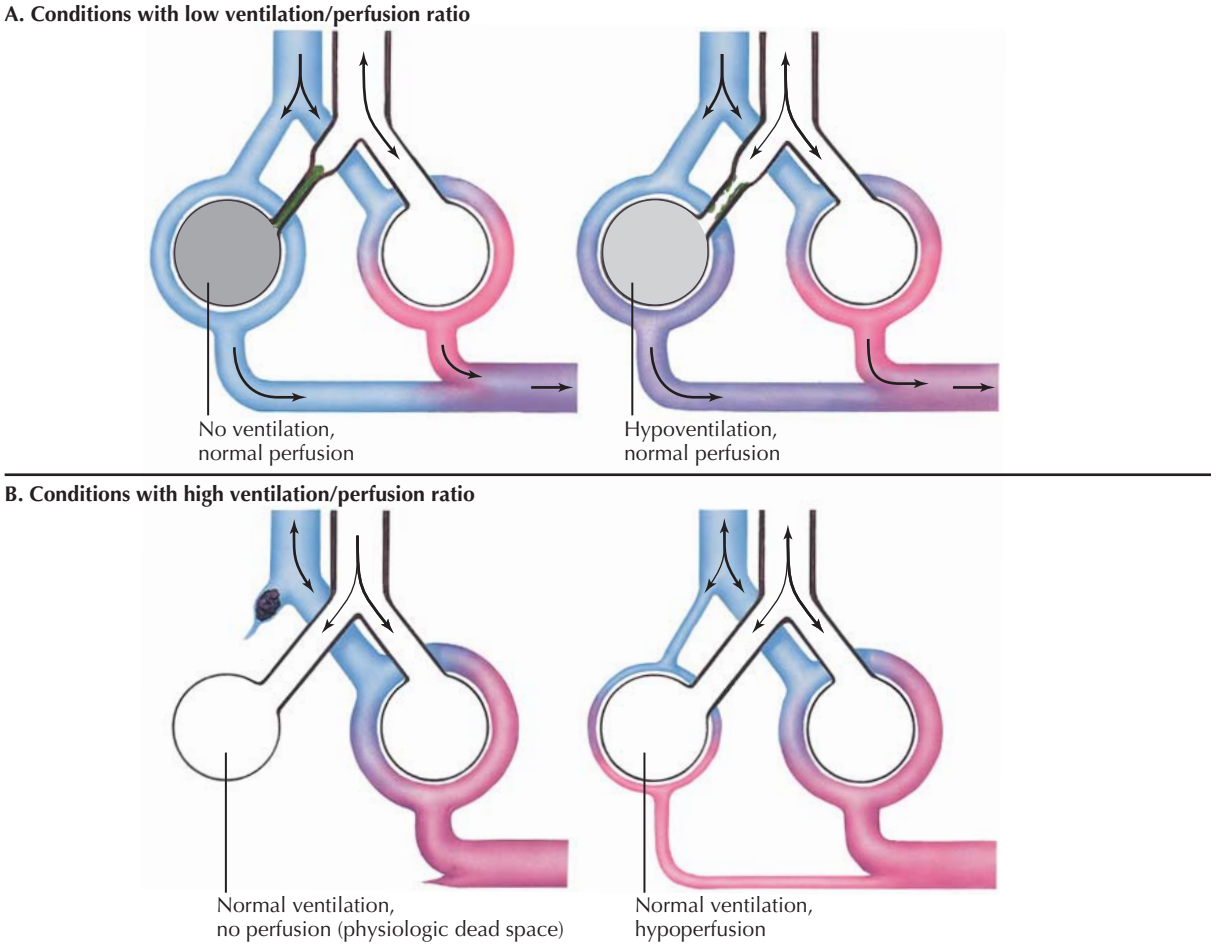


Figure 13.14 Ventilation–Perfusion ($\dot{V}_A/\dot{Q}_C$) Relationships In the standing position, the effects of gravity result in gradients in both perfusion and ventilation of the lung from base to apex. Because the perfusion gradient is steeper than the ventilation gradient, the ratio of ventilation to perfusion, $\dot{V}_A/\dot{Q}_C$, is lowest at the bottom of the lung and greatest at the top of the lung *(B)*. $\dot{V}_A/\dot{Q}_C$ is also affected by various other conditions affecting ventilation and perfusion (*A* and *B*).

CHAPTER 14 The Mechanics of Breathing

The physical forces resulting in ventilation of the lungs are analogous to those creating blood flow in the cardiovascular system. A pressure gradient is required, and in the case of the lung, the gradient is created by movement of the chest wall and diaphragm. Flow of air occurs against the resistance of the airways, analogous to the resistance of blood vessels. However, factors affecting pressure, flow, and resistance are complex, and often different, in the two systems. This chapter details the physical forces involved in ventilation of the lungs and some of the changes that take place in disease.



Mechanically, the lungs and chest wall can be conceptualized as a respiratory pump, acting in unison to produce pressures required to generate airflow. Flow is driven by the pressure gradient between the alveolar space and the mouth opening, produced by the elastic properties of the system and activity of respiratory muscles. An additional characteristic of this pump is airway resistance (R_{aw}), defined by the formula:

$$R_{aw} = \frac{(P_A - P_{ATM})}{\text{rate of airflow}}$$

where P_A is alveolar pressure and P_{ATM} is atmospheric pressure. This formula can be rearranged to:

$$\text{rate of airflow} = \frac{(P_A - P_{ATM})}{R_{aw}}$$

This formula is analogous to the formula for blood flow ($Q = \Delta P/R$, where ΔP is the pressure gradient along which flow occurs, and R is the resistance to flow).

BASIC MECHANICS OF THE VENTILATORY APPARATUS

Ventilation occurs as a result of mechanical forces associated with the chest wall and lungs. Both the lungs and the chest wall are **elastic;** that is, they passively recoil after being distended. **Elastic recoil pressure** is the pressure caused by distension. Functionally, the chest wall includes the diaphragm and abdominal muscles in addition to the rib cage. The **visceral pleura** (outer lining) of the lungs apposes the **parietal pleura** of the chest wall, and the small, fluid-filled space between the pleurae, the **pleural cavity,** contains only a few milliliters (mL) of fluid. The muscles of breathing are illustrated in Figure 14.1. The **diaphragm** is the major muscle for inspiration during normal, quiet breathing. As it contracts and its domes descend, the thoracic space is enlarged, decreasing alveolar pressure and resulting in inward flow of air through the airways. During more active ventilation, for example during exercise, the **intercostal muscles** have greater involvement in inspiration, elevating the ribs and expanding the chest as they contract. Expiration is a passive process during normal, quiet breathing and results from passive recoil of the lungs. During active breathing, various muscles of the abdominal wall, along with some of the intercostal muscles, contribute to the force, resulting in expiration.

Elastic Recoil of the Chest Wall and Lungs

The interactions between the forces of the chest wall and lungs during normal, quiet breathing are illustrated in Figure 14.2. In the context of elastic properties of the system at all lung volumes, from **functional residual capacity** (**FRC**; the volume of air in the lungs after normal, quiet expiration) to total lung capacity (TLC), chest wall and lung forces are illustrated in Figure 14.3. At FRC, the mechanical system is at rest, and the pressure within the airways and alveolar space is equal to atmospheric pressure (see Fig. 14.2*A*). In this state, muscles of the chest wall are relaxed, and the outward elastic recoil pressure of the chest wall is equal and opposite to the inward elastic recoil pressure of the lungs. In other words, at FRC, although the tendency of the chest wall is to expand and the tendency of the lungs is to collapse, these two forces are in balance, keeping the volume of the lungs at FRC. The algebraic sum of the negative recoil pressure created by the chest wall and the positive recoil pressure of the lungs is zero; pleural pressure (pressure in the pleural cavity) is negative (subatmospheric). Note the balance between chest wall recoil and lung recoil pressures at FRC in Figure 14.3.

Forces during Inspiration and Expiration

Inspiration occurs when the rib cage expands and the diaphragm moves downward, creating negative pressure within the lungs (see Fig. 14.2*B*). Pleural pressure is more negative than in the resting state, as the chest wall exerts greater outward pressure. Air flows into the lung until alveolar pressure reaches atmospheric pressure. At the end of inspiration, during normal, quiet breathing (tidal volume of 500 mL), chest wall

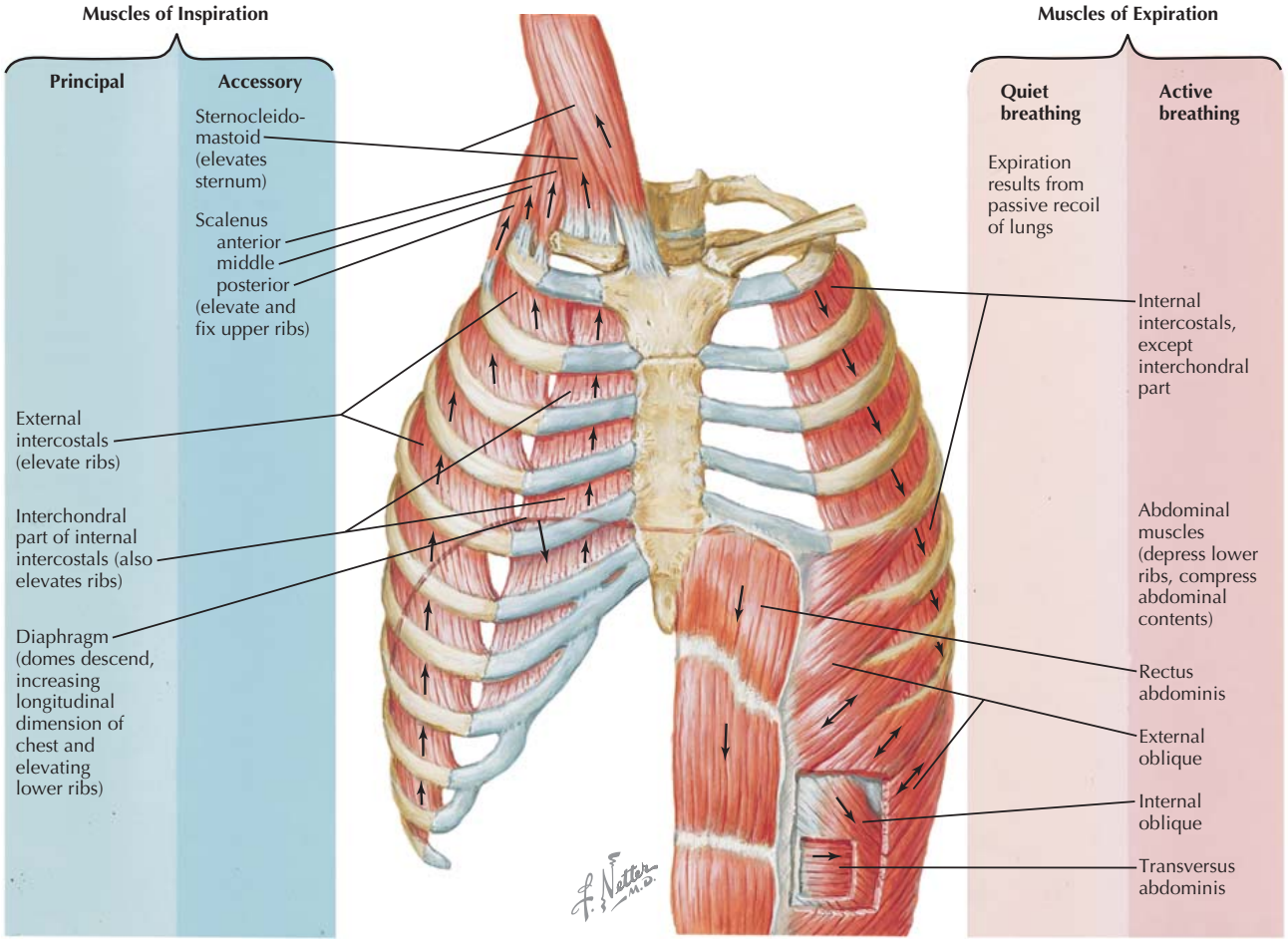


Figure 14.1 Respiratory Muscles Contraction of the diaphragm is the main factor producing inspiration during normal, quiet breathing; expiration is a passive process in this type of breathing, caused by passive recoil of the lungs. Active breathing requires the activity of additional muscles and involves energy expenditure for both inspiration and expiration.

recoil pressure is still negative, but recoil pressure of the total respiratory system is positive due to increased recoil pressure of the lungs (see Fig. 14.3). At total lung capacity, both chest wall and lung recoil pressures are positive.

During **expiration,** with the relaxation of inspiratory muscles, the elastic recoil pressure of the respiratory system (increased due to its expansion) results in elevation of alveolar pressure above atmospheric pressure, causing outward airflow until atmospheric pressure is reached in the lungs (see Fig. 14.2*C*). The system returns to FRC, unless air is actively expired beyond that level; expiration is eventually limited by the large negative elastic recoil pressure of the chest wall as residual volume (RV) is approached.



During normal, quiet breathing, inspiration is mainly driven by the contraction of the muscular diaphragm, whereas expiration is a passive process, driven by the positive elastic recoil pressure of the respiratory system achieved during inspiration. In this type of breathing, pleural pressure is always negative. During active expiration, contraction of abdominal muscles compresses the viscera, forcing the diaphragm upward, producing positive pleural pressure. Thus, in contrast to quiet breathing, in which work is performed only for inspiration, energy is expended for both inspiration and expiration in active breathing.

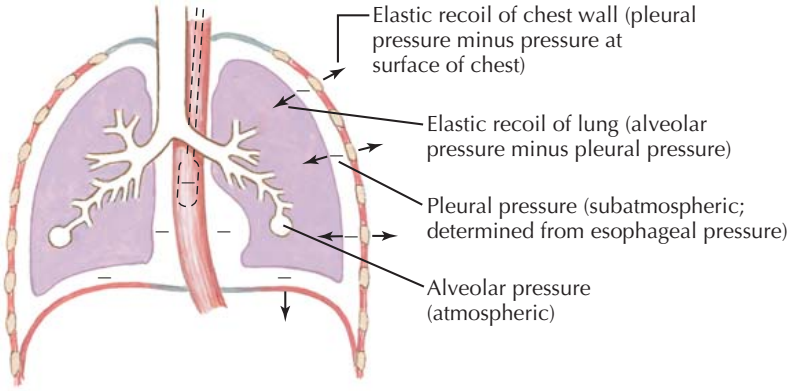
COMPLIANCE, ELASTANCE, AND PRESSURE–VOLUME RELATIONSHIPS

Elastance is defined as the tendency of a hollow organ to return to its original size when distended; it can be quantified as elastic recoil pressure. The **elastic recoil** of the lungs and chest wall can be related to pleural pressure:

- Elastic recoil of the lungs is equal to alveolar pressure minus pleural pressure.
- Elastic recoil of the chest wall is equal to pleural pressure minus atmospheric pressure.

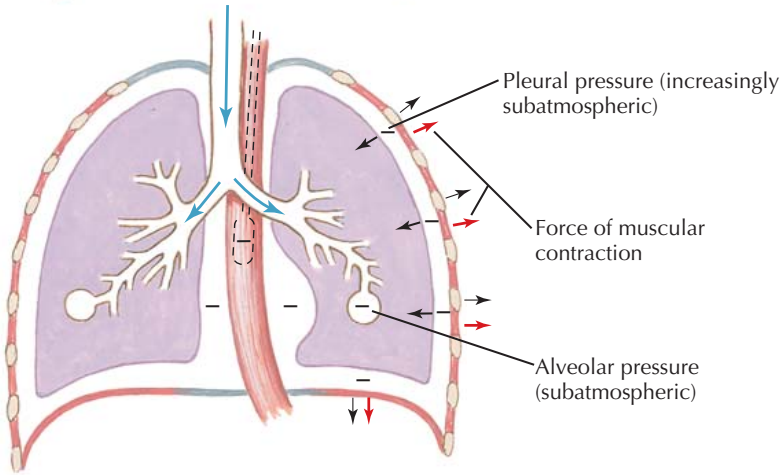
A. At rest

1. Respiratory muscles are at rest.
2. Recoil of lung and chest wall are equal but opposite.
3. Pressure along tracheobronchial tree is atmospheric.
4. There is no airflow.



B. During inspiration

Inspiratory muscles contract and chest expands; alveolar pressure becomes subatmospheric with respect to pressure at airway opening. Air flows into lungs.



C. During expiration

Inspiratory muscles relax; recoil of lung causes alveolar pressure to exceed pressure at airway opening. Air flows out of lung.

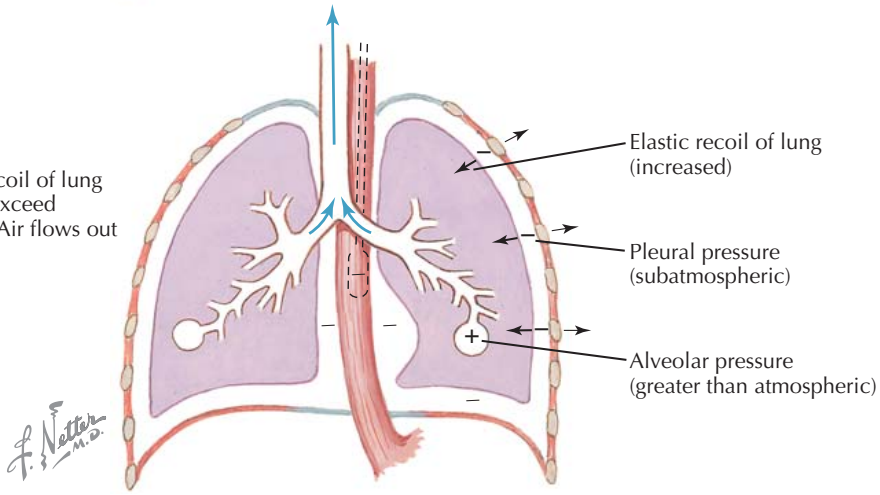
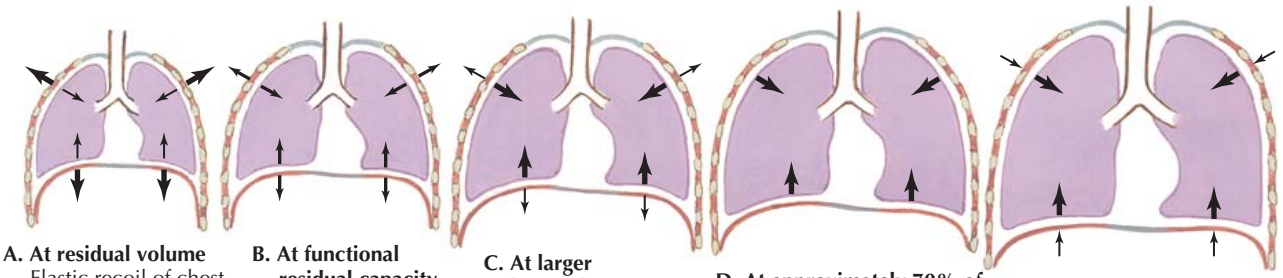


Figure 14.2 Forces during Quiet Breathing Normal, quiet breathing is produced mainly by contraction of the diaphragm, resulting in inspiration as alveolar pressure falls below atmospheric pressure; expiration occurs when the diaphragm relaxes and recoil pressure of the lungs elevates alveolar pressure above atmospheric pressure. The dynamic interactions of elastic recoil pressure of the lungs and chest wall and contraction and relaxation of the diaphragm producing airflow are illustrated *(A–C)*. Pleural pressure is always negative during quiet breathing.



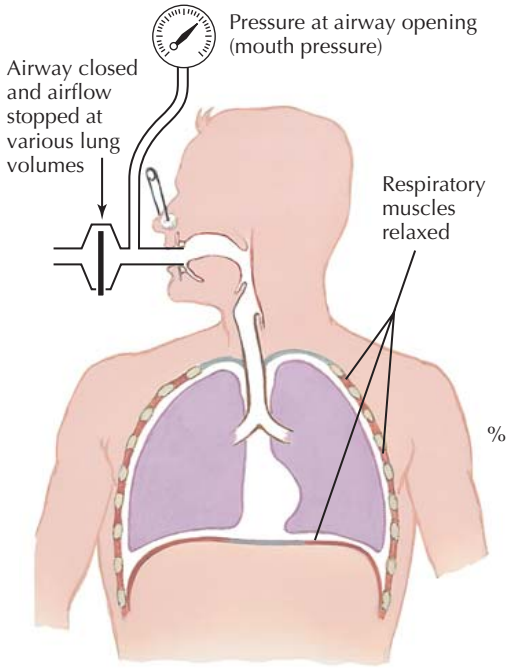
A. At residual volume Elastic recoil of chest wall directed outward is large. Recoil of lung directed inward is very small

B. At functional residual capacity Elastic recoils of lung and chest wall are equal but opposite

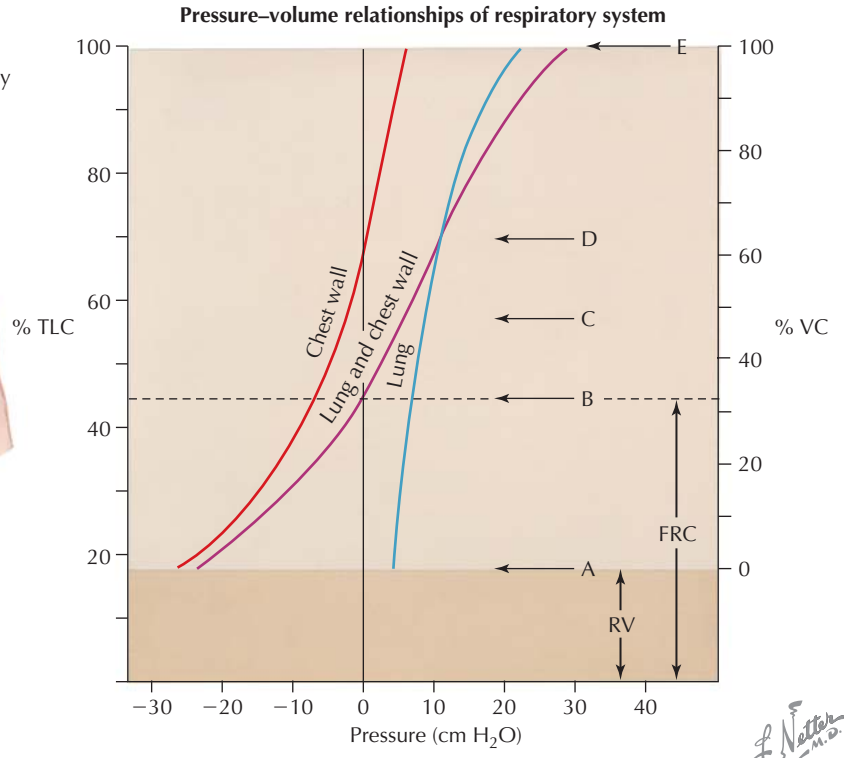
C. At larger lung volume Elastic recoil of chest wall becomes smaller, and recoil of lung increases

D. At approximately 70% of total lung capacity Equilibrium position of chest wall (its recoil equals zero)

E. At total lung capacity Elastic recoil of both lung and chest wall directed inward, favoring decrease in lung volume



F. Pressure recorded at airway opening is same as alveolar pressure when airflow is stopped; provides a measure of elastic recoil of respiratory system when respiratory muscles are relaxed



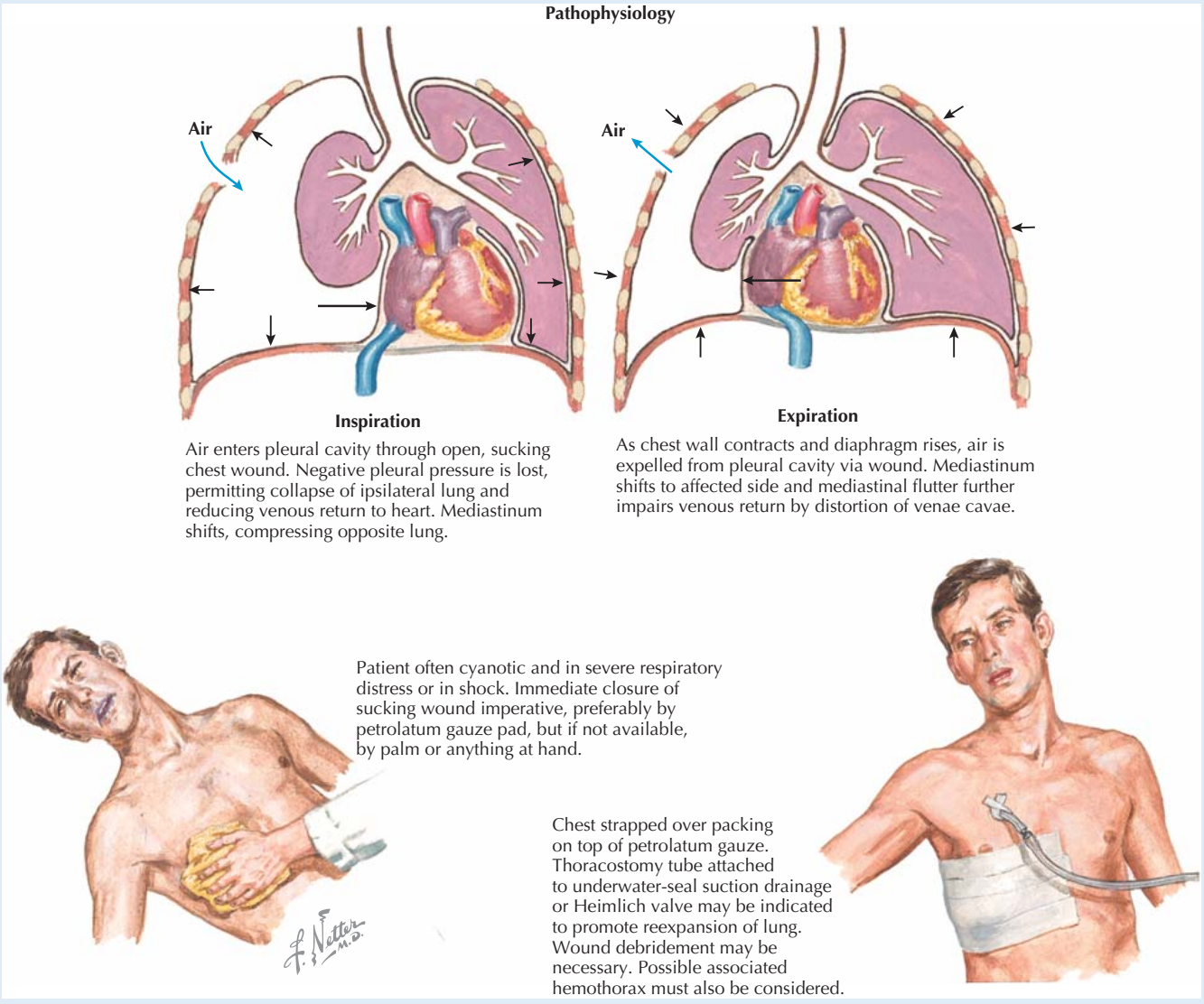
G. Elastic recoil pressure of respiratory system is algebraic sum of recoil pressures of lung and chest wall

Figure 14.3 Elastic Properties of Respiratory System: Lung and Chest Wall Elastic recoil pressure of the respiratory system is the algebraic sum of recoil pressures of the lungs and chest wall *(G)*. These pressures can be measured at various lung volumes from residual volume to total lung capacity *(A–E)*, and represent the forces resulting in inspiration and expiration. Above functional residual volume (FRC), the net recoil pressure of the respiratory system is positive, and relaxation of inspiratory muscles will result in expiration; above FRC, net recoil pressure is negative and relaxation of expiratory muscles will cause inspiration. At FRC, the system is in equilibrium. Elastic recoil when respiratory muscles are relaxed can be determined by stopping airflow *(F)*. RV, residual volume.

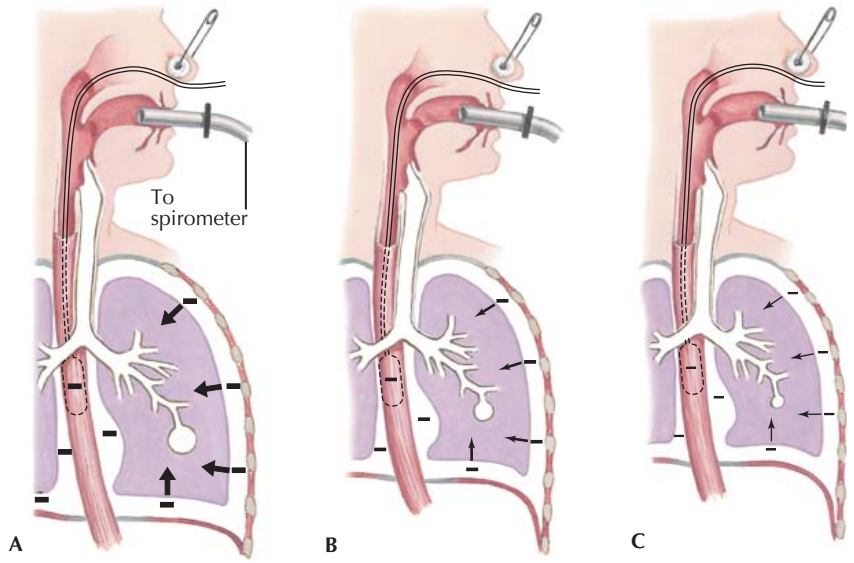
Lung compliance (CL) is a measure of the distensibility of the lung and is the inverse of lung elastance. Thus, CL is measured as the change in lung volume resulting from a change in transpulmonary pressure, where transpulmonary pressure is the pressure across the lung, or the difference between alveolar and pleural pressure (Fig. 14.4). Experimentally, compliance can be measured in an isolated lung (Fig. 14.5). Referring to the experimental preparation in Figure 14.5 in which the lung is filled with air, as pressure applied to the lung is changed, the volume of the lung changes. The slope of this curve is the compliance of the lung. Note that the slope differs between inflation and deflation, with the volume at a given pressure being lower during inflation than during deflation, a phenomenon known as **hysteresis.** The difference in the inflation and

CLINICAL CORRELATE
Pneumothorax

Pneumothorax is a condition in which air accumulates in the pleural cavity, due to injury to the chest wall or lungs or as a result of pulmonary disease. Ordinarily, the pleural cavity contains only a few milliliters of fluid. Introduction of air into the pleural space through an open (sucking) pneumothorax will uncouple the mechanical forces associated with the chest walls and lung, causing collapse of the lung on the damaged side, thereby affecting ventilation in that lung. In a tension pneumothorax, air is able to enter the pleural space but cannot leave (a piece of tissue acts as a one-way valve). Air accumulates with each breath, raising intrathoracic pressure and thereby causing severe dyspnea (shortness of breath) and circulatory collapse. Tension pneumothorax is an unstable condition requiring immediate medical intervention.



Open Pneumothorax



During a slow expiration from TLC, flow is periodically interrupted and measurements are made of lung volume and of transpulmonary pressure. Transpulmonary pressure is the difference between alveolar and pleural pressures. Pleural pressure is determined from pressure in the esophagus. Because there is no airflow, alveolar pressure is the same as pressure at the airway opening.

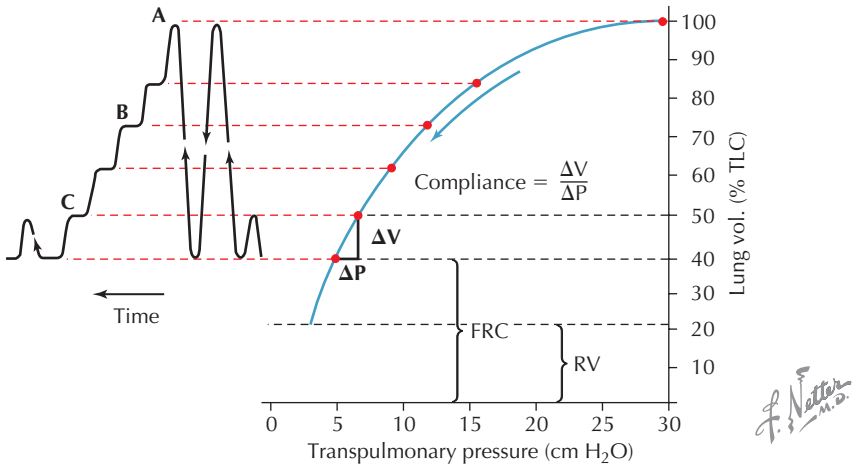


Figure 14.4 Measurement of Elastic Properties of the Lung Lung compliance (ΔV/ΔP) is a measure of lung distensibility and can be measured by determining transpulmonary pressure at various lung volumes *(A, B,* and *C).* Transpulmonary pressure is the difference between alveolar and pleural pressure. Alveolar pressure is the same as pressure measured at the airway opening when flow is stopped; pleural pressure is measured by esophageal balloon catheter. Note that lung compliance is highest at residual volume, and is reduced at greater lung volumes. TLC, total lung capacity.

deflation curves is mainly associated with the effects of surface tension during inflation, when surface tension at the liquid-air interface of the lung must be overcome as volume rises. When a fluid-filled lung (in which surface tension is not an issue) is exposed to the same manipulations, compliance is greater and hysteresis is less pronounced.

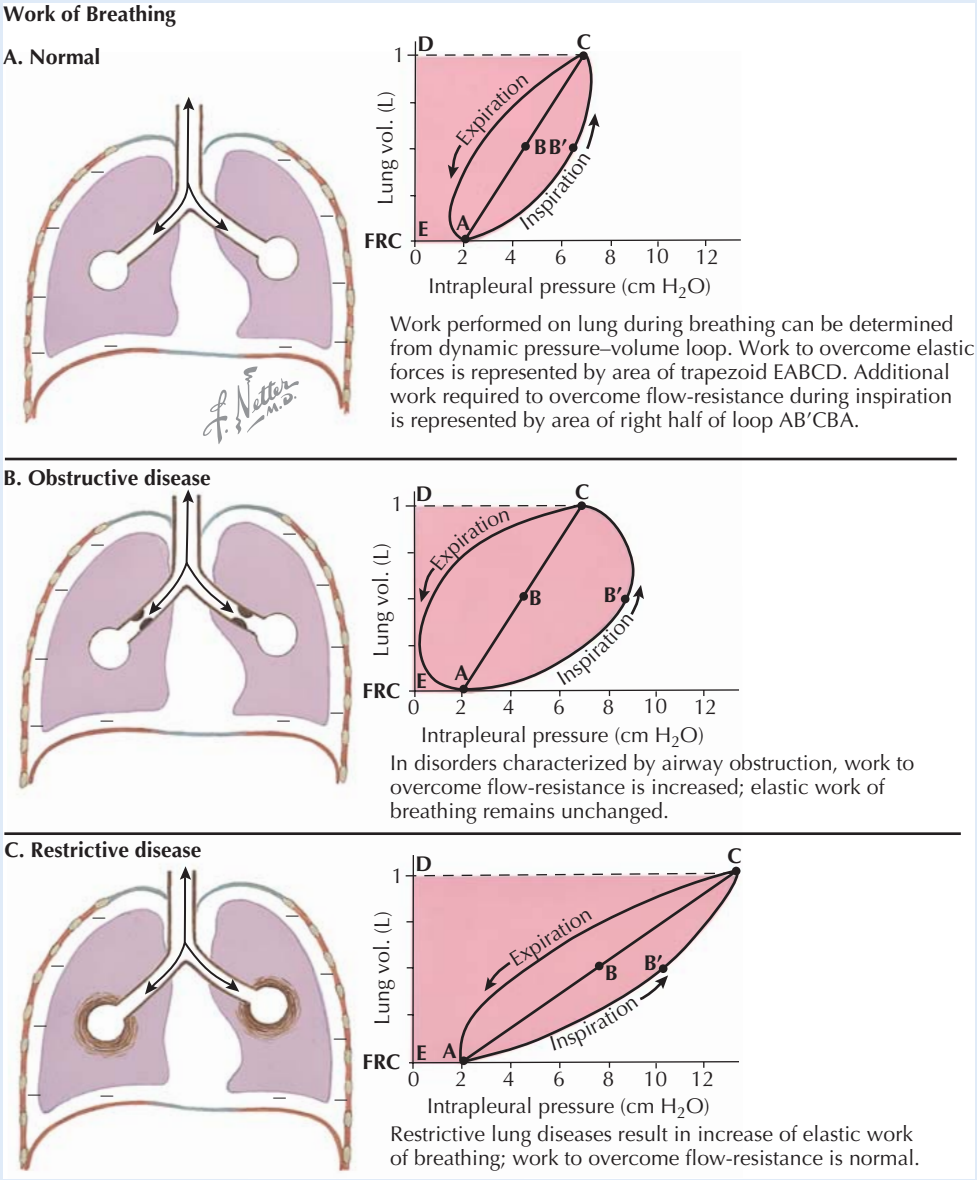
Like the lungs, the chest wall also is characterized by compliance and elastance. These properties become apparent when the chest wall is punctured, creating a **pneumothorax** (see "Pneumothorax" Clinical Correlate).

SURFACTANT AND SURFACE TENSION

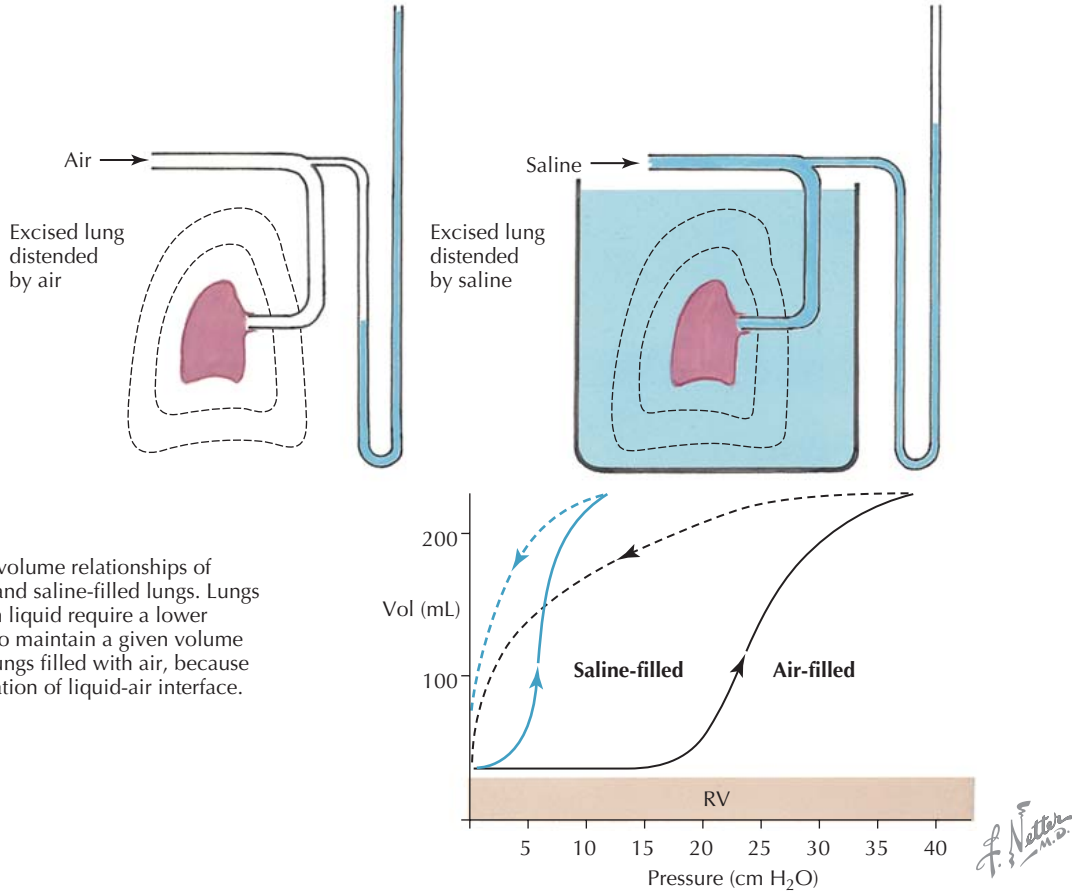
Surface tension is the elastic-like force at the surface of a liquid (at the gas-liquid interface) caused by intermolecular attraction of the liquid molecules at that surface. In the lung, surface tension reduces lung compliance and has the potential for causing collapse of small airways. The potential problems of surface tension and low pulmonary compliance are overcome by the production of **surfactant** by type II alveolar epithelial cells. Surfactant is a complex lipoprotein containing the phospholipid **dipalmitoyl phosphatidyl choline.** It is

CLINICAL CORRELATE
Compliance in Pulmonary Diseases

Lung diseases are often classified as restrictive and obstructive diseases. Restrictive diseases are characterized by reduced functional volume of the lung, whereas obstructive diseases are characterized by reduced flow rate. Restrictive diseases include interstitial lung diseases (for example, idiopathic pulmonary fibrosis, sarcoidosis, and asbestosis); examples of obstructive lung diseases include chronic obstructive pulmonary disease (COPD) and asthma. In restrictive diseases, compliance of the respiratory system is reduced, resulting in lower FRC and total lung capacity, and reduced slope of the pressure–volume relationship. Obstructive lung disease does not directly affect lung compliance but may ultimately change compliances. For example, in emphysema, often associated with tobacco smoking and COPD, elastic fibers in the lungs are destroyed, alveolar architecture is compromised, and lung compliance is increased (elasticity is reduced). FRC and total lung capacity are increased, and the slope of the pressure–volume relationship is greater. Despite increased compliance and greater tidal volume, emphysema sufferers have reduced ability to exchange gas, based on the destruction of alveoli.



Work of Breathing in Obstructive and Restrictive Lung Disease Compared to work performed in normal breathing *(A)*, in obstructive disease, while compliance may be unchanged, the work of breathing is increased by the elevated airway resistance *(B)*. In restrictive disease, lung compliance is low, and the elastic work of breathing is increased *(C)*.



Pressure–volume relationships of air-filled and saline-filled lungs. Lungs filled with liquid require a lower pressure to maintain a given volume than do lungs filled with air, because of elimination of liquid-air interface.

Figure 14.5 Compliance and Surface Forces of the Lung Measurement of the pressure–volume relationship in an isolated lung results in the illustrated pressure–volume loops. Greater pressure is required to inflate an air-filled lung compared with a saline-filled lung, due to the surface tension at the air-alveolar interface in the former. Surfactant is produced by type II alveolar epithelial cells and reduces surface tension of the air-filled lung; without it, even greater force would be required to inflate the lungs with air. RV, residual volume.

amphipathic and lines the surface of the alveolar epithelium and small airways (with hydrophilic regions of the phospholipid oriented toward the epithelial surface and hydrophobic regions facing the lumen). Surfactant reduces surface tension of airways and alveoli and increases lung compliance, reducing the work of breathing.

AIRWAY RESISTANCE

Flow of air in and out of the lungs is dependent on the pressure gradient from the opening of the mouth to the alveoli. At the end of inspiration or expiration, the gradient is zero. **Poiseuille's law,** presented in the context of blood flow in Section 3, also applies to flow of air (Q) through tubes (see Fig. 14.5):

$$Q = \frac{\Delta P \pi r^4}{\eta 8 L}$$

where ΔP is the pressure gradient from one end of a tube to the other, r^4 is the radius of the tube to the fourth power, η is the viscosity of air, and L is the length of the tube. Thus, based on this relationship, airflow (Q) through a tube should be:

- Directly proportional to the longitudinal pressure gradient (inflow pressure minus outflow pressure).
- Inversely proportional to the length of the tube.
- Inversely proportional to the viscosity of air.
- Directly proportional to the fourth power of the radius of the tube.

In the respiratory system as a whole, the *greatest resistance to flow actually occurs in medium-sized airways* (fourth to eighth generation). Recall from Section 3 that in parallel tubes, total resistance is less than the resistance of the individual tubes. Considering both the diameter and number of tubes at this level, resistance is higher in the medium-sized bronchi (in aggregate) than in the larger or smaller airways.

The effects of surface tension in the lung have often been incorrectly presented in textbooks in the context of **Laplace's law,** which states that in a sphere, surface tension creates pressure (P):

$$P = \frac{2T}{r}$$

where T is surface tension and r is radius of the sphere. According to this construct, in an isolated alveolus, this pressure is the pressure tending to cause its collapse (or the equivalent pressure required to keep the alveolus open). Laplace's law would lead to the prediction that when multiple spherical units are subjected to the same inflation pressure through a branching tube, larger units would expand and smaller units would collapse, as the higher surface tension in smaller units causes air to flow toward larger units in which surface tension is lower. Textbooks have typically illustrated this situation as a Y-tube with two alveoli attached, or as alveoli in the configuration of a "bunch of grapes." According to this line of argument, a major role of surfactant is to overcome the effects of surface tension in alveoli of different sizes and promote more uniform inflation of the lungs.

This argument is incorrect for several reasons: alveoli are actually prismatic in shape (appearing polygonal in histological sections) and exist in a honeycomb-like geometry with common walls, sometimes even with pores between them. Thus, alveoli do not act as independent units, and inflation of an alveolus affects inflation of adjacent alveoli. Rather than viewing surfactant's role in terms of alveolar surface tension, its effects on the overall compliance of the lung and on small airway patency should be emphasized.

(From Prange H: Laplace's Law and the alveolus: A misconception of anatomy and a misapplication of physics. Advan Physio Edu 27:34–40, 2003.)

CLINICAL CORRELATE
Treatment of Asthma with Sympathetic Adrenergic Drugs

Asthma is a chronic respiratory disease, characterized by episodic bronchoconstriction and mucus secretion, resulting in increased airway resistance and dyspnea (labored breathing). Asthma can be life-threatening in severe cases. Asthma attacks may be initiated by a variety of factors, including inhaled allergens and irritants, cold air, stress, and exercise, which exacerbate the ongoing airway inflammation in asthmatics. Drugs used to prevent asthma attacks are mainly aimed at reducing inflammation, whereas drugs used to relieve acute attacks are generally bronchodilators (e.g., inhaled β_2-adrenergic agonists such as salbutamol or terbutaline). These drugs reduce airway resistance by relaxing bronchial smooth muscle.

Poiseuille's law applies to laminar flow of air but becomes less precise with turbulent flow. Laminar flow occurs in small airways, whereas flow in the largest airways is turbulent; flow in the remainder of the system tends to be transitional, with some turbulence (Fig. 14.6). Factors producing **turbulent and laminar flow** are discussed in Section 3, in the context of blood flow. In the largest airways, high velocity and airway diameter contribute to producing turbulent flow. In small, peripheral airways, smaller diameter and lower velocity result in laminar flow of air.

Effects of Autonomic Nerves on Airway Resistance

Airway resistance is also affected by the autonomic nervous system:

- **Activation of parasympathetic nerves** innervating smooth muscle of conducting airways causes bronchoconstriction and promotes glandular secretions in the lungs.
- **Activation of sympathetic nerves** innervating smooth muscle of conducting airways results in bronchodilation and reduced airway resistance (through activation of β_2-adrenergic receptor-linked pathways) in mammalian species, although human lungs have little sympathetic innervation. Release of epinephrine by the adrenal medulla during sympathetic activation will also reduce airway resistance through activation of the pulmonary β_2-receptor mechanism.

Lung Volume and Airway Resistance

In addition, there is a relationship between **lung volume and airway resistance.** At high lung volume, the diameter of airways tends to be increased by the radial traction the expanded lungs place on the airways. At low lung volumes, in the absence of traction, small airways have a greater tendency to collapse.

DYNAMIC COMPRESSION OF AIRWAYS DURING EXPIRATION

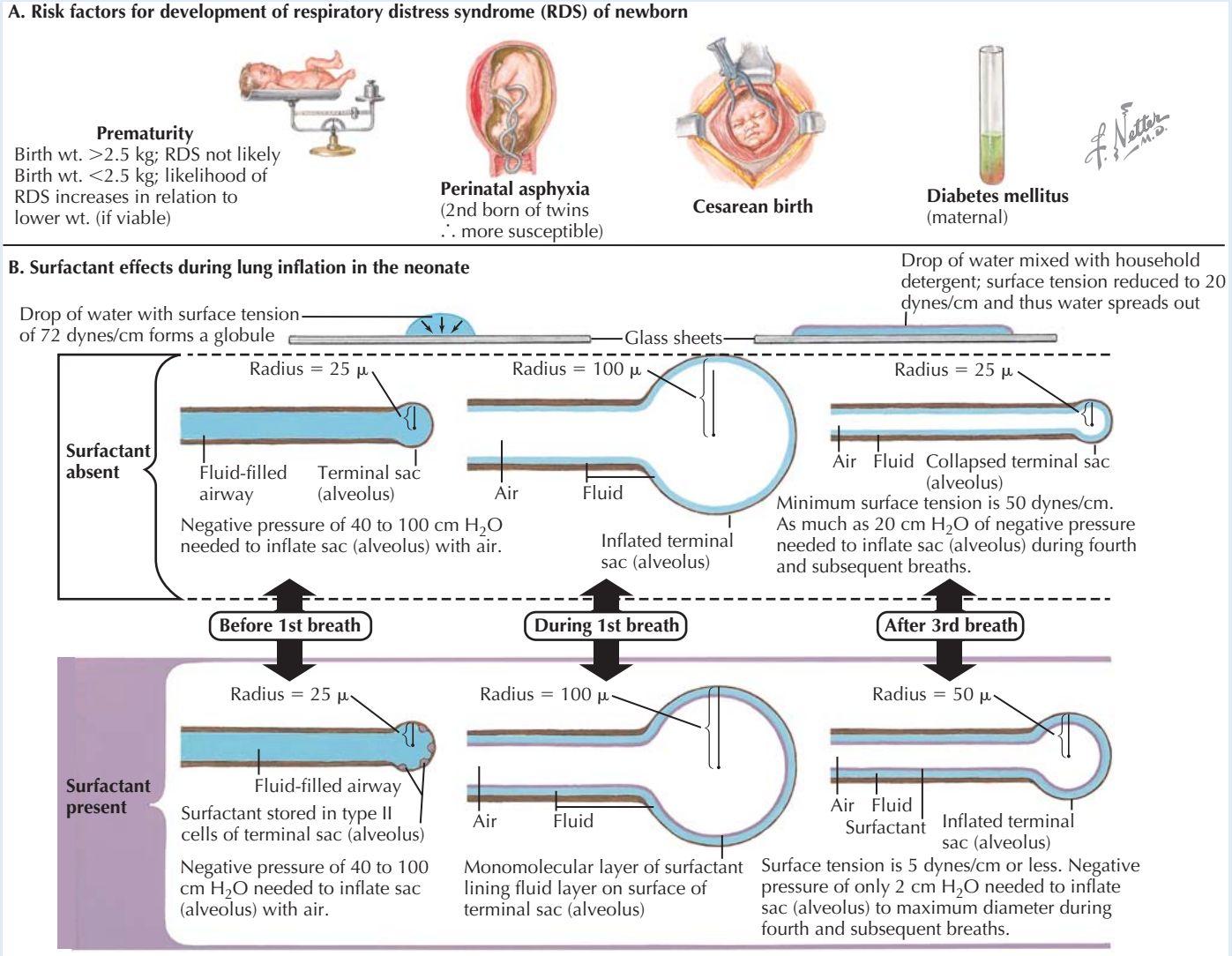
Airway resistance is also affected by **dynamic compression,** which is the compression of airways during *forced expiration*. An **expiratory flow–volume curve** is illustrated in Figure 14.7 (*A,* solid line), in which a subject performs a **forced vital capacity maneuver,** inspiring to total lung capacity and then exhaling as forcibly as possible to residual volume. Note that in the expiratory flow–volume curve generated:

- The peak of this curve represents the **peak expiratory flow rate (PEFR).**
- The downward slope (expiratory phase) of the flow-volume curve is **effort-independent;** during this phase of the curve, flow is limited by **dynamic compression** of the airways.

When less effort is exerted, lower peak flow is reached, but the associated flow–volume curve converges with the maximum effort curve and the downslope is the same, consistent with the effort-independence of expiratory flow during active expiration (see Fig. 14.7*A, dotted line*).

CLINICAL CORRELATE
Respiratory Distress Syndrome of the Newborn

Immediately after delivery, a newborn takes its first breath. Negative pressure of 40 to 100 cm H_2O is required to draw air into the collapsed airways and inflate the alveoli. During this first breath, in a healthy, normal, term infant, surfactant stored in type II alveolar epithelial cells is released and forms a mononuclear layer at the air-fluid interface of the small airways and alveoli. By the third breath, only a small negative pressure is required to inflate the lung. Respiratory distress syndrome (previously known as hyaline membrane disease) is the most common cause of death in premature infants, and is caused by a lack of surfactant production. Without surfactant, the negative pressure required to inflate the lungs remains high (C_L is low) and portions of the lung collapse, leading to respiratory distress and potentially respiratory failure and death. Treatment consists of ventilatory support and surfactant therapy through the breathing tube.



The initial inflation of the collapsed lungs of a neonate requires large negative pressure (40 to 100 cm H_20), but surface tension is reduced in subsequent breaths as surfactant lines the alveoli and small airways, reducing the work required to inflate the lungs. Premature birth is often associated with surfactant deficiency and respiratory distress.

During normal, quiet breathing, pleural pressure is always negative. However, during active expiration, contraction of expiratory muscles results in elevation of pleural pressure above atmospheric pressure (see Fig. 14.7). Under these circumstances, during expiration, alveolar pressure is the sum of the positive pleural pressure and the elastic recoil pressure of the lungs. Pressure in the airways falls between the alveoli and the opening of the mouth, reaching atmospheric pressure at the mouth. Thus, at some point downstream from the alveoli, an **equal pressure point** is reached, at which airway

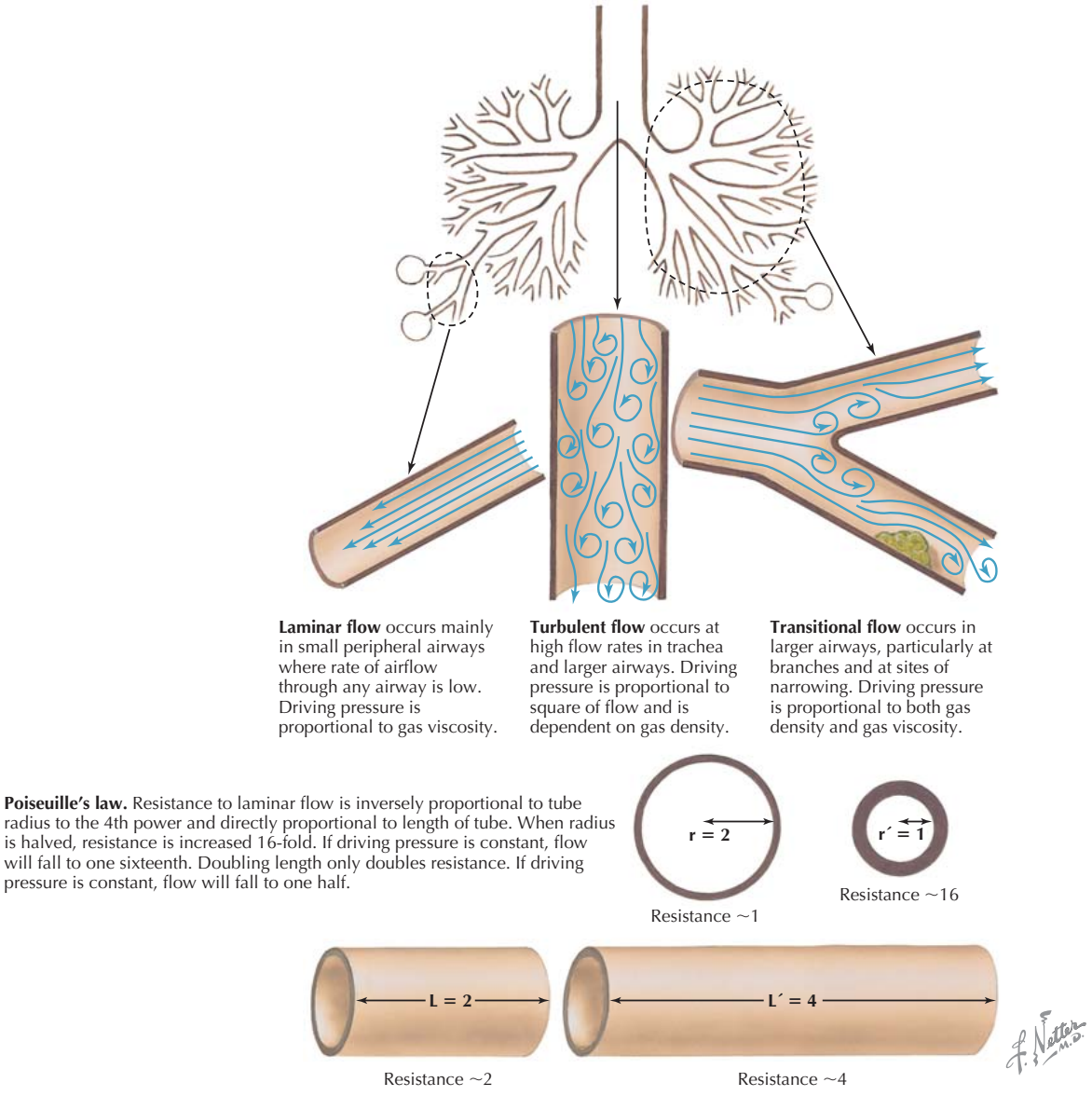
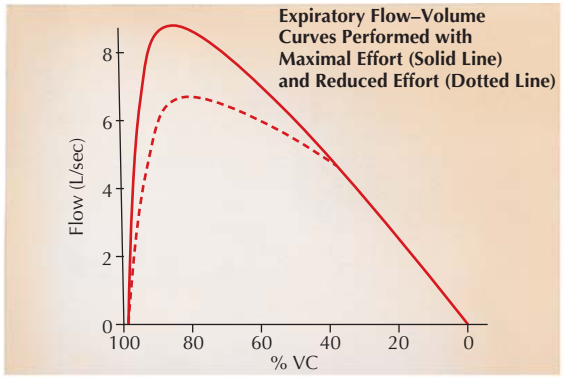


Figure 14.6 **Flow** Airflow through large airways tends to be turbulent, whereas flow in smaller airways tends to be laminar. Laminar flow is described by Poiseuille's law. Airway diameter, according to this law, is the greatest factor in determining resistance and flow (flow is proportional to the fourth power of the radius of a tube).

pressure is equal to pleural pressure. Beyond this point, airways will be compressed. This **dynamic compression** of airways limits expiratory flow rate and accounts for the effort-independent nature of airflow in active expiration. When greater effort is exerted, greater compression occurs, so that airflow remains the same.

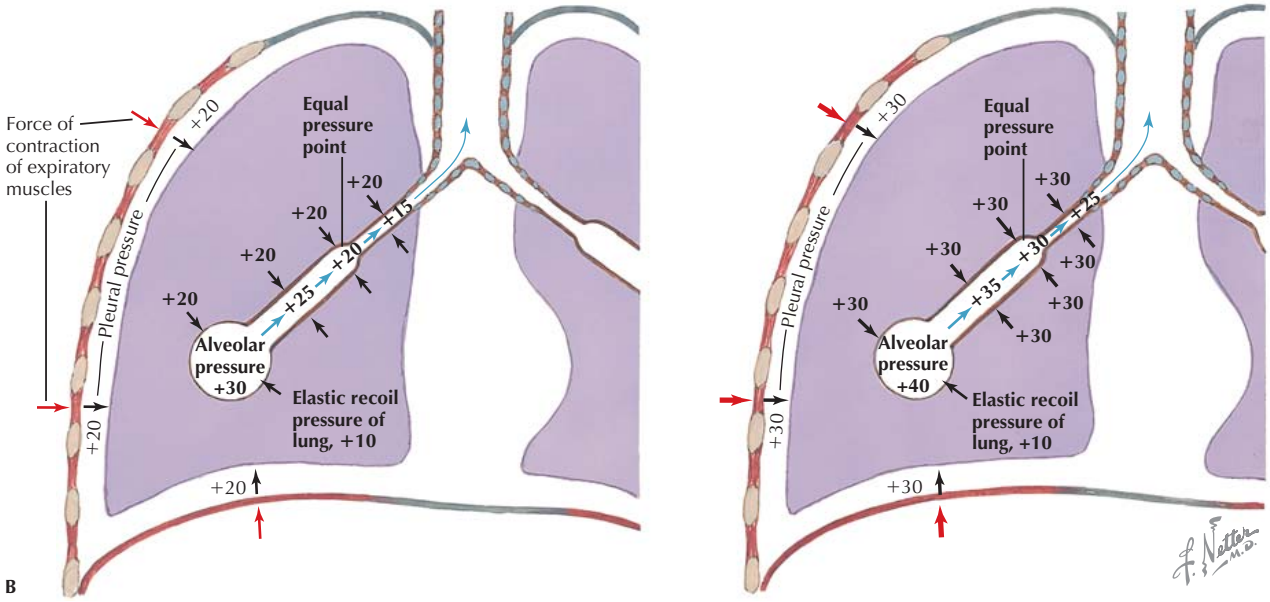
OBSTRUCTIVE AND RESTRICTIVE PULMONARY DISEASES AND PULMONARY FUNCTION TESTS

Measurements of flow–volume relationships are important in assessing **obstructive and restrictive pulmonary diseases** (see "Compliance in Pulmonary Diseases" Clinical Correlate). Severe chronic obstructive pulmonary disease (COPD) is characterized by emphysema, in which inflammation leads to destruction of alveolar walls and capillaries, resulting in high lung compliance. Reduced elastic recoil of the alveoli and airways also results in early formation of the equal pressure point (at a point closer to the alveolus) during expiration, and, as a result of this dynamic compression, "trapping" of air takes place in the lung. These changes ultimately produce an increase in total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV). The changes in flow are clinically assessed by spirometry and related tests (Fig. 14.8). Notably, expiratory flow rate and FEV_1 (the forced



A

Determinants of Maximal Expiratory Flow



B

At onset of maximal airflow, contraction of expiratory muscles at a given lung volume raises pleural pressure above atmospheric level (+20 cm H_2O). Alveolar pressure (sum of pleural pressure and lung recoil pressure) is yet higher (+30 cm H_2O). Airway pressure falls progressively from alveolus to airway opening in overcoming resistance. At equal pressure point of airway, pressure within airway equals pressure surrounding it (pleural pressure). Beyond this point, as intraluminal pressure drops further, below pleural pressure, airway will be compressed.

With further increases in expiratory effort, at same lung volume, pleural pressure is greater and alveolar pressure is correspondingly higher. Fall in airway pressure and location of equal pressure point are unchanged, but beyond equal pressure point, intrathoracic airways will be compressed to a greater degree by higher pleural pressure. Once maximal airflow is achieved, further increases in pleural pressure produce proportional increases in resistance of segment downstream from equal pressure point, so rate of airflow does not change.

Figure 14.7 Expiratory Flow–Volume Relationship The expiratory flow–volume curve generated during a forced vital capacity maneuver *(solid line in graph)* is characterized by a peak expiratory flow rate (PEFR) at the top of the curve and a downward slope during the remainder of expiration *(A)*. The maximal expiratory flow rate at various lung volumes along this downward slope is effort-independent, due to dynamic compression of airways *(B)*. When effort is reduced *(dotted line in graph)*, PEFR is lower, but note the overlap in the downward slope of the two lines, consistent with the effort-independence of maximal expiratory flow rate.

expiratory volume in the first second of a vital capacity maneuver) and the **FEV_1-to-FVC ratio** is less than the normal value of 75% (although FEV_1 is reduced, FVC is only slightly lower than normal). In contrast, in restrictive diseases such as interstitial fibrosis, thickening of alveolar walls results in decreased lung compliance. Lung volumes are reduced as a result (Fig. 14.9). Although FEV_1 is reduced, the FEV_1-to-FVC ratio is usually normal or elevated, because FVC is also diminished in restrictive disease. Various **pulmonary function tests** and typical findings in obstructive and restrictive disease are summarized in Figure 14.10.



Because of **dynamic compression** of airways, maximum expiratory flow is effort-independent. For any given lung volume, the associated maximum expiratory flow cannot be exceeded by increasing expiratory effort. The explanation for this phenomenon is that increased expiratory effort physically compresses airways as well as alveoli, increasing resistance and limiting airflow.

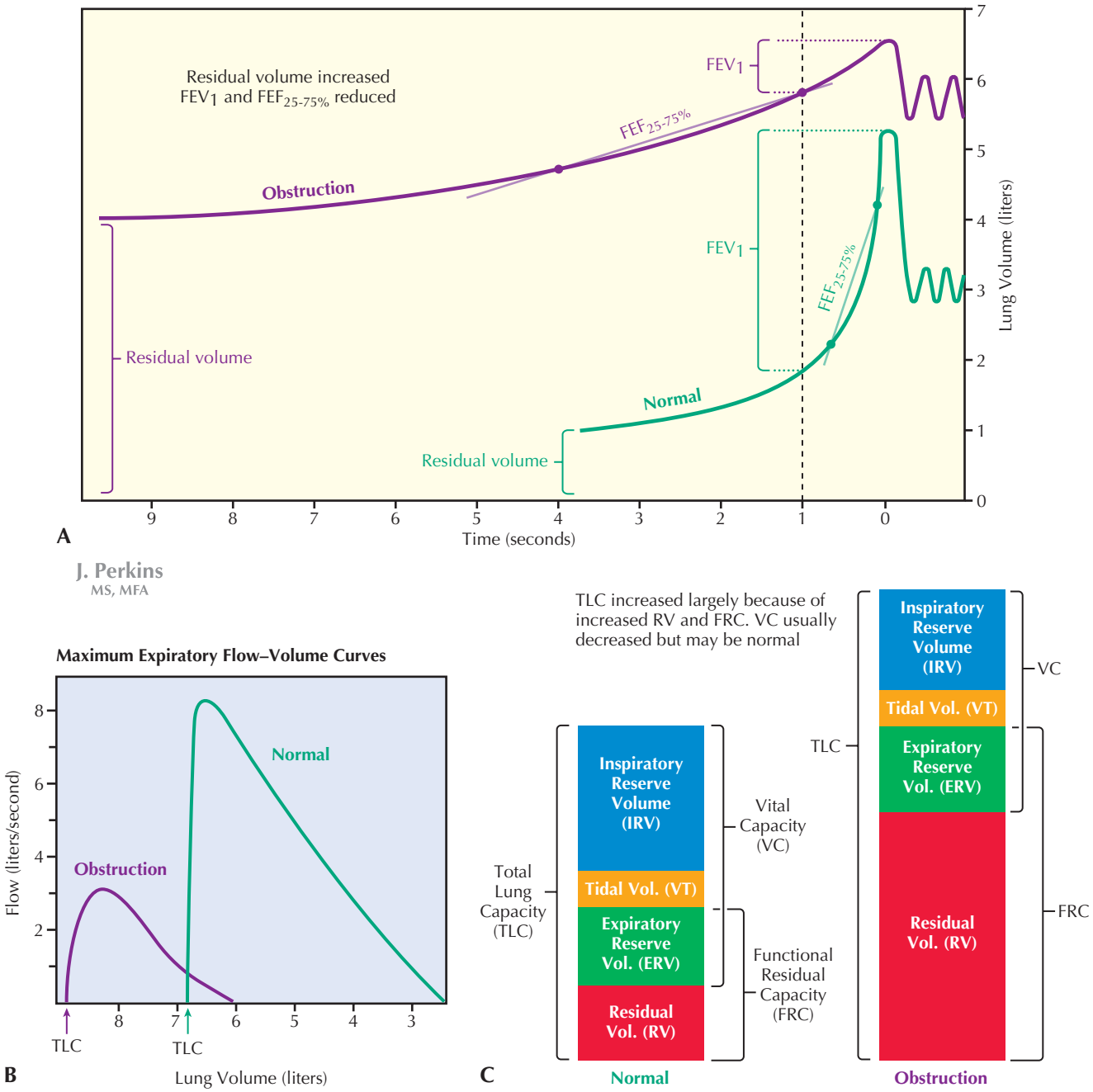


Figure 14.8 Pulmonary Function in Obstructive Lung Disease In emphysema, a chronic obstructive lung disease often associated with smoking, there is inflammatory destruction of elastic tissues in the lung, resulting in reduced elastic recoil of the lung. Changes in lung volumes *(A),* flow–volume curves *(B),* and spirometric measurements *(C)* associated with emphysema are illustrated. Notably, FEV_1 is reduced in obstructive lung disease, as is the ratio of FEV_1 to FVC *(A).* $FEF_{25–75\%}$, the expiratory flow rate during the middle portion of a forced expiration, is also reduced. FEF, forced expiratory flow rate; FEV, forced expiratory volume.

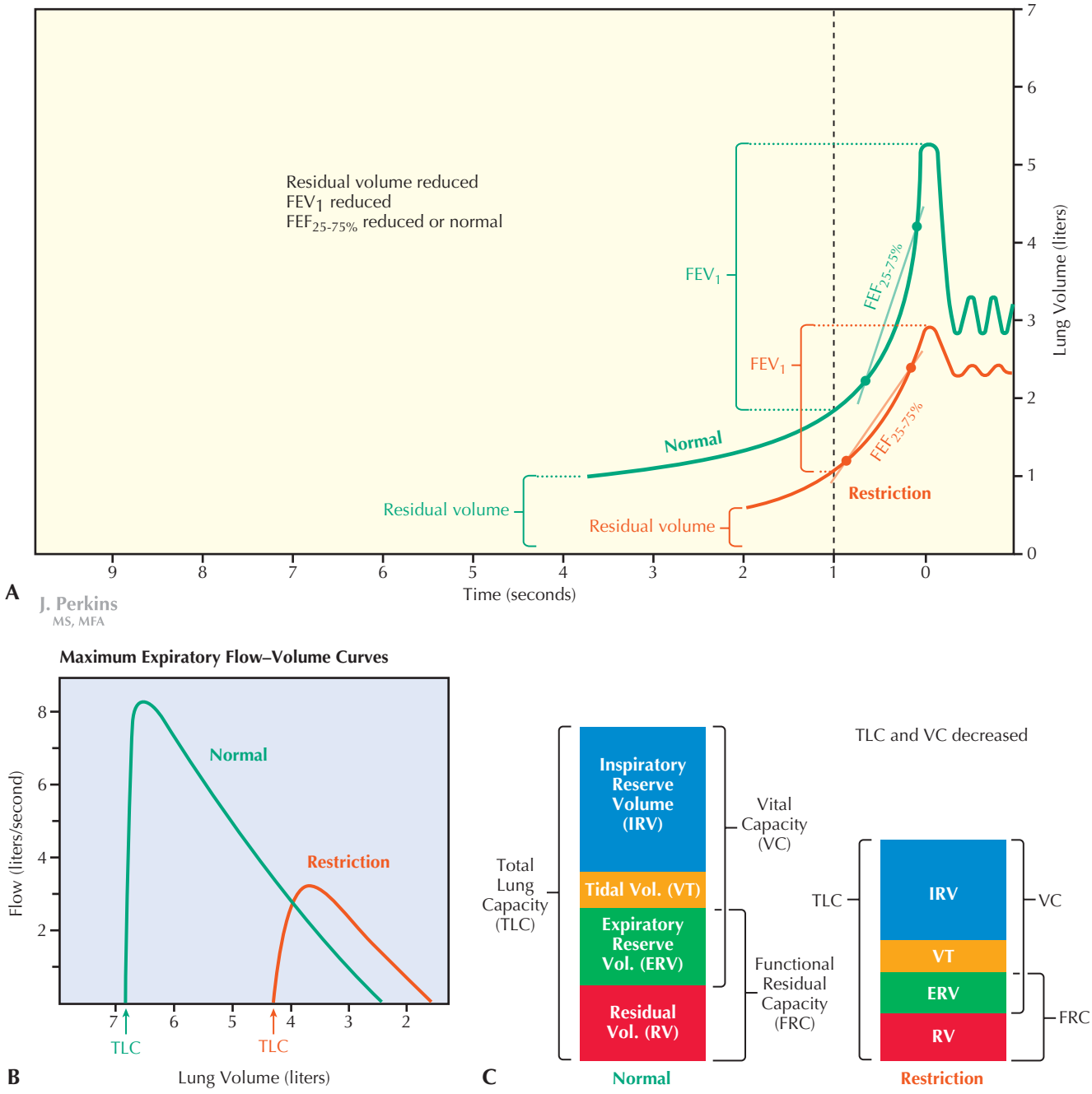


Figure 14.9 **Pulmonary Function in Restrictive Lung Disease** Lung compliance is reduced in restrictive lung diseases such as interstitial fibrosis, resulting in diminished lung volumes. Changes in spirometric measurements *(A),* flow–volume curves *(B),* and lung volumes *(C)* associated with restrictive lung disease are illustrated. Because both FEV_1 and FVC are reduced in restrictive lung disease *(A),* the ratio of FEV_1 to FVC is usually normal but may even be increased when FVC is greatly reduced. $FEF_{25-75\%}$, the expiratory flow rate during the middle portion of a forced expiration, is normal or reduced in restrictive disease. FEF, forced expiratory flow rate; FEV, forced expiratory volume.

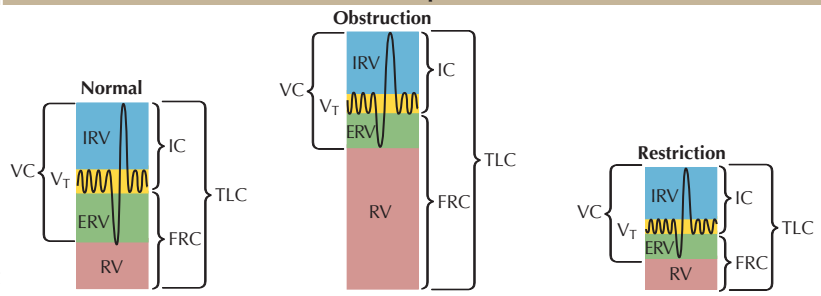
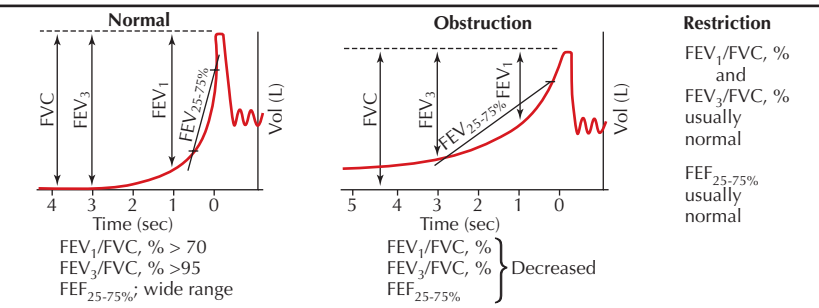
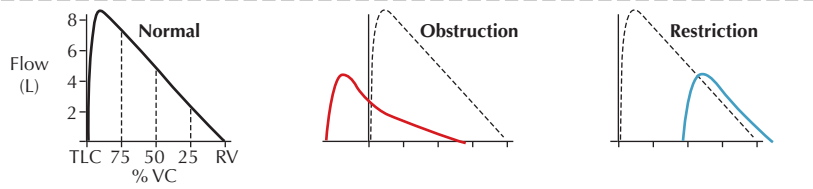
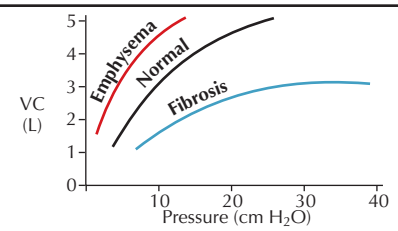
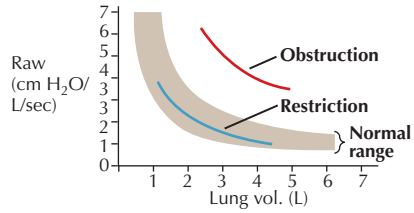
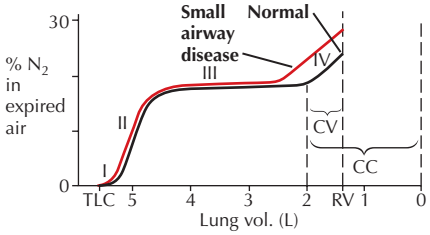
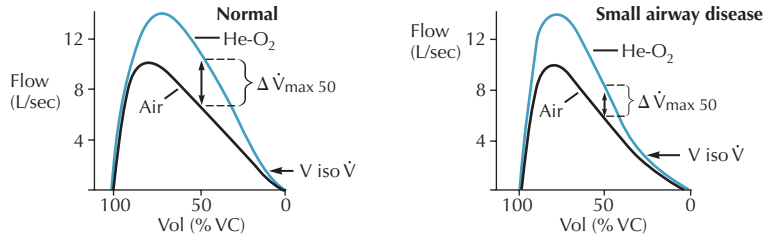
Test	Symbol	Method	Interpretation
Lung volumes and capacities Vital capacity Inspiratory capacity Expiratory reserve volume Tidal volume Functional residual capacity Residual volume Total lung capacity	**VC** **IC** **ERV** **V_T** **FRC** **RV** **TLC**	Spirometer Spirometer Spirometer He dilution or body plethysmograph FRC − ERV VC + RV or FRC + IC	
Expiratory flow rates Forced expiratory volume in 1 second in 3 seconds Forced mid-expiratory flow	**FEV_1** **FEV_3** **$FEF_{25-75\%}$ (FMF)**	Spirometer	 **Restriction** FEV_1/FVC, % and FEV_3/FVC, % usually normal $FEF_{25-75\%}$ usually normal
Maximal expiratory flow–volume curve Maximal expiratory flow at 75 50 25	**MEFV** **$\dot{V}_{max\ 75}$** **$\dot{V}_{max\ 50}$** **$\dot{V}_{max\ 25}$** % of VC	Spirometer with simultaneous recording of flow and volume and volume of integrated pneumotachograph	
Lung elasticity Static recoil pressure Static compliance	**P_{stat}** **C_{stat}**	Pleural pressure is recorded with esophageal balloon while airflow is arrested at different lung volumes; changes in lung volume recorded with spirometer or pneumotachograph	 Static elastic recoil of lung is increased and static compliance reduced in diseases such as pulmonary fibrosis. Conversely, in emphysema, static lung compliance is increased and elastic recoil is reduced.
Airway resistance	**R_{aw}**	Body plethysmograph to determine alveolar pressure and pneumotachograph to measure airflow	 In obstructive lung disease, airway resistance is increased. If obstruction involves only small airways (<2 mm diameter), only minimal changes in overall resistance may result. In restrictive disorders, resistance is often reduced because of increased traction on intrathoracic airway walls.
Diffusing capacity	**Dco**	Low concentration of CO inhaled; expired gas analyzed for CO	Diffusing capacity is reduced when alveolar walls are destroyed and pulmonary capillaries are obliterated by emphysema and when alveolar-capillary membrane is thickened by edema, consolidation, or fibrosis.

Figure 14.10A Pulmonary Function Tests Tests of pulmonary function are defined and illustrated, with comparisons between values observed in normal lungs and in restrictive and obstructive disease.

Test	Symbol	Method	Interpretation
Tests for small airway disease Closing volume Closing capacity	**CV** **CC**	Following a full inspiration of O_2 the expired lung volume from TLC to RV is plotted against the N_2 concentration	 Airways in the lower lung zones close at low lung volumes and only those alveoli at top of lungs continue to empty. Because concentration of N_2 in alveoli of upper zones is higher, the slope of the curve abruptly increases (phase IV). Phase IV begins at larger lung volumes in individuals with even minor degrees of airway obstruction, increasing both CV and CC.
Maximal expiratory flow–volume curve breathing 80% He and 20% O_2	$\Delta\dot{V}_{max\ 50}$ **V iso $\dot{V}$**	Spirometer or pneumotachograph to record flow and volume	 During a maximal expiratory maneuver, resistance to airflow is normally due to turbulence and convective acceleration. Breathing He, which is less dense than air, lowers resistance and increases flow at all but the lowest volumes. In small airway disease, resistance to laminar flow makes up a larger portion of total resistanc and airflow is relatively independent of gas density. Increase in expiratory flow at 50% of VC while breathing He-O_2 ($\Delta\dot{V}_{max\ 50}$) will be less, and volume at which flows while breathing He-O_2 and while breathing air are identical (V iso $\dot{V}$) will be higher in patients with small airway disease than in normal individuals.

Gas exchange	Symbol	Method	Normal values	Abnormalities
Partial pressure of O_2 in arterial blood	P_{O_2}	Arterial blood is collected anaerobically in heparinized syringe	60 to 100 mm Hg breathing room air at sea level; falls slightly with air	Hypoxemia indicative of ventilation/perfusion abnormalities, shunts, diffusion defect, alveolar hypoventilation
Partial pressure of CO_2 in arterial blood	P_{CO_2}		36 to 44 mm Hg	P_{CO_2} proportional to metabolic rate (CO_2 production) and inversely related to volume of alveolar ventilation
Arterial blood pH	pH		7.35 to 7.45 pH	Acidosis (pH <7.35) Respiratory (inadequate alveolar ventilation) Metabolic (gain of acid and/or loss of base) Alkalosis (pH >7.45) Respiratory (excessive alveolar ventilation) Metabolic (gain of base or loss of acid)
Alveolar-arterial O_2 difference	$A\text{-}aD_{O_2}$ $A\text{-}aP_{O_2}$		<10 mm Hg breathing room air	Primarily reflects mismatching of ventilation and perfusion and/or shunts; may also be affected by diffusion defects
Dead space/tidal volume ratio	$\dot{V}_D/\dot{V}_T$	Determined from arterial and mixed expired P_{CO_2}	<0.3	Elevated ratio indicates wasted ventilation; i.e., that volume of gas which does not take part in gas exchange
Shunt fraction	$\dot{Q}_S/\dot{Q}_T$	Determined from P_{O_2} after a period of breathing 100% O_2	<5%	Elevation indicates increased amount of mixed venous blood entering systemic circulation without coming into contact with alveolar air, either because of shunting of blood past lungs to left side of heart or perfusion of regions of lung which are not ventilated



Figure 14.10B **Pulmonary Function Tests *(cont'd)***

CHAPTER 15 Oxygen and Carbon Dioxide Transport and Control of Respiration

While Fick's law describes the diffusion of gases across the alveolar-capillary membrane, many other factors are important in determining the actual content of gases in blood and in the process of gas transport. The contribution of other factors can be gleaned by considering that average oxygen consumption in humans at rest is 250 milliliters of oxygen per minute (mL O_2/min), a rate that cannot be supported simply by diffusion and delivery of dissolved gas to tissues. In fact, transport of gases is a complex process that affects other processes beyond respiration, including acid–base balance, which will also be discussed in this chapter.

TRANSPORT OF OXYGEN

The concentration of dissolved gas in a liquid is directly proportional to the partial pressure of the gas in the atmosphere to which the liquid is exposed (Henry's law) and the solubility of the gas in the solvent. For each mm Hg P_{O_2}, only 0.003 mL O_2 will dissolve in 100 mL of blood at body temperature. Because Pa_{O_2} (P_{O_2} in arterial blood) is normally approximately 100 mm Hg (equilibrated with PA_{O_2}, P_{O_2} in alveolar air), the amount of **dissolved oxygen** in arterial blood is normally only 0.3 mL O_2/100 mL blood (Fig. 15.1). The actual measured concentration of oxygen in normal arterial blood is approximately 20.4 mL O_2/100 mL blood. What accounts for this large difference? The answer is binding of O_2 to the **hemoglobin** in red blood cells. The average concentration of hemoglobin (Hb) is 15 g/100 mL blood, and each gram (g) of hemoglobin binds 1.34 mL O_2 when fully saturated. Therefore, by far, the bulk of oxygen transport is accomplished by hemoglobin.

Oxygen Binding Capacity and Oxygen Content of Blood

The oxygen binding capacity of blood is given by the following formula:

$$O_2 \text{ binding capacity} = (1.34 \text{ mL } O_2/\text{g Hb}) \times (\text{g Hb}/100 \text{ mL blood})$$

Thus, for the normal hemoglobin concentration of 15 g/100 mL blood,

$$O_2 \text{ binding capacity} = (1.34 \text{ mL } O_2/\text{g Hb}) \times (15 \text{ g Hb}/100 \text{ mL blood}) = 20.1 \text{ mL } O_2/100 \text{ mL blood}$$

Oxygen content of blood can be calculated by the following formula:

$$O_2 \text{ content} = \% \text{ saturation} \times O_2 \text{ binding capacity} + \text{dissolved oxygen}$$

Given normal values of 15 g hemoglobin/100 mL blood and approximately 100% oxygen saturation of arterial blood at P_{O_2} of 100 mm Hg, oxygen content in arterial blood can be calculated as shown below:

$$\text{Arterial } O_2 \text{ content} = 100\% \times (1.34 \text{ mL } O_2/\text{g Hb}) \times (15 \text{ g Hb}/100 \text{ mL blood}) + (0.003 \text{ mL } O_2/100 \text{ mL blood/mm Hg}) \times (100 \text{ mm Hg}) = 20.4 \text{ mL } O_2/100 \text{ mL blood}$$

Arteriovenous Oxygen Gradient and Oxygen Consumption

Compared with this arterial O_2 content (20.4 mL O_2/100 mL blood), in normal venous blood, in which P_{O_2} is approximately 40 mm Hg and hemoglobin is 75% saturated,

$$\text{Venous } O_2 \text{ content} = 75\% \times (1.34 \text{ mL } O_2/\text{g Hb}) \times (15 \text{ g Hb}/100 \text{ mL blood}) + (0.003 \text{ mL } O_2/100 \text{ mL blood/mm Hg}) \times (40 \text{ mm Hg}) = 15.2 \text{ mL } O_2/100 \text{ mL blood}$$

Each deciliter of blood delivers approximately 5 mL of O_2 to the tissues as it passes through the systemic circulation, because the arteriovenous difference in oxygen content of blood is 5 mL. Based on this arteriovenous difference in



Oxygen binding capacity is the maximum amount of oxygen that can be bound to hemoglobin in blood (at 100% saturation). The actual oxygen content of blood depends on the degree of saturation of hemoglobin. Dissolved oxygen is a minor portion of the oxygen content of blood; in a person breathing normal air, it is only 0.3 mL/100 mL blood, compared to the total content of oxygen of 20.4 mL/100 mL blood at 100% saturation.

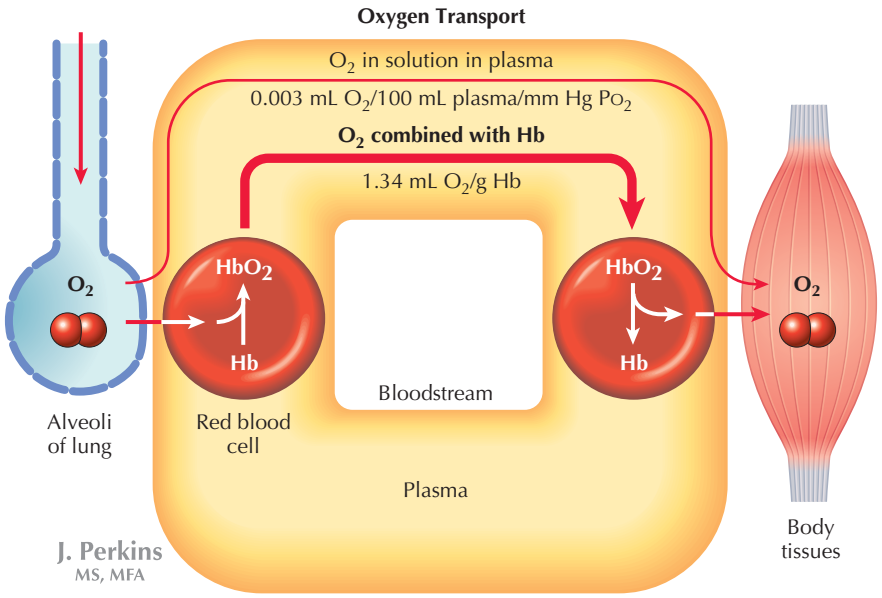


Figure 15.1 Oxygen Transport Oxygen diffuses into the blood flowing through alveolar capillaries and is transported to tissues, where it diffuses out of the blood along its concentration gradient. Transport of oxygen in the blood is mainly in the form of oxygen combined with hemoglobin, with only a minor portion carried in the form of dissolved oxygen.

oxygen content of blood and cardiac output, oxygen consumption can be estimated. Thus, at rest,

$$O_2 \text{ consumption} = [a - v]_{O_2} \times \text{cardiac output} =$$
$$(5 \text{ mL } O_2/100 \text{ mL}) \times 5000 \text{ mL/min} = 250 \text{ mL } O_2/\text{min}$$

At the usual respiratory quotient (CO_2 production/O_2 consumption) of 0.8, CO_2 production is 200 mL/min.

THE OXYHEMOGLOBIN DISSOCIATION CURVE

As discussed, at P_{O_2} of 100 mm Hg, hemoglobin is nearly 100% saturated with oxygen (actually, 97.5%), and at 40 mm Hg, hemoglobin is 75% saturated. The **oxyhemoglobin dissociation curve** (Fig. 15.2) describes the relationship between oxygen saturation of blood (S_{O_2}) and P_{O_2}. The sigmoidal shape of the curve is due to cooperative binding of hemoglobin. Each molecule of hemoglobin is capable of binding four oxygen molecules; when one molecule binds to an oxygen binding site, the other three sites bind oxygen more readily, causing the middle portion of the curve to be steep. Thus, exposure of blood to the high P_{O_2} in the respiratory zone of the lung results in binding of a substantial amount of oxygen. Note also that due to the sigmoidal shape, $P_{A_{O_2}}$ can fall substantially without greatly affecting the degree of saturation of hemoglobin (at P_{O_2} of 80 mm Hg, S_{O_2} is still above 95%). On the other hand, as P_{O_2} falls in blood coursing through systemic capillaries, typically to 40 mm Hg, blood P_{O_2} is on the steep portion of the curve, which facilitates delivery of oxygen to the tissues. Dissociation of one molecule of oxygen from a molecule of hemoglobin makes dissociation of the other bound oxygen molecules from that molecule more likely.

To summarize:

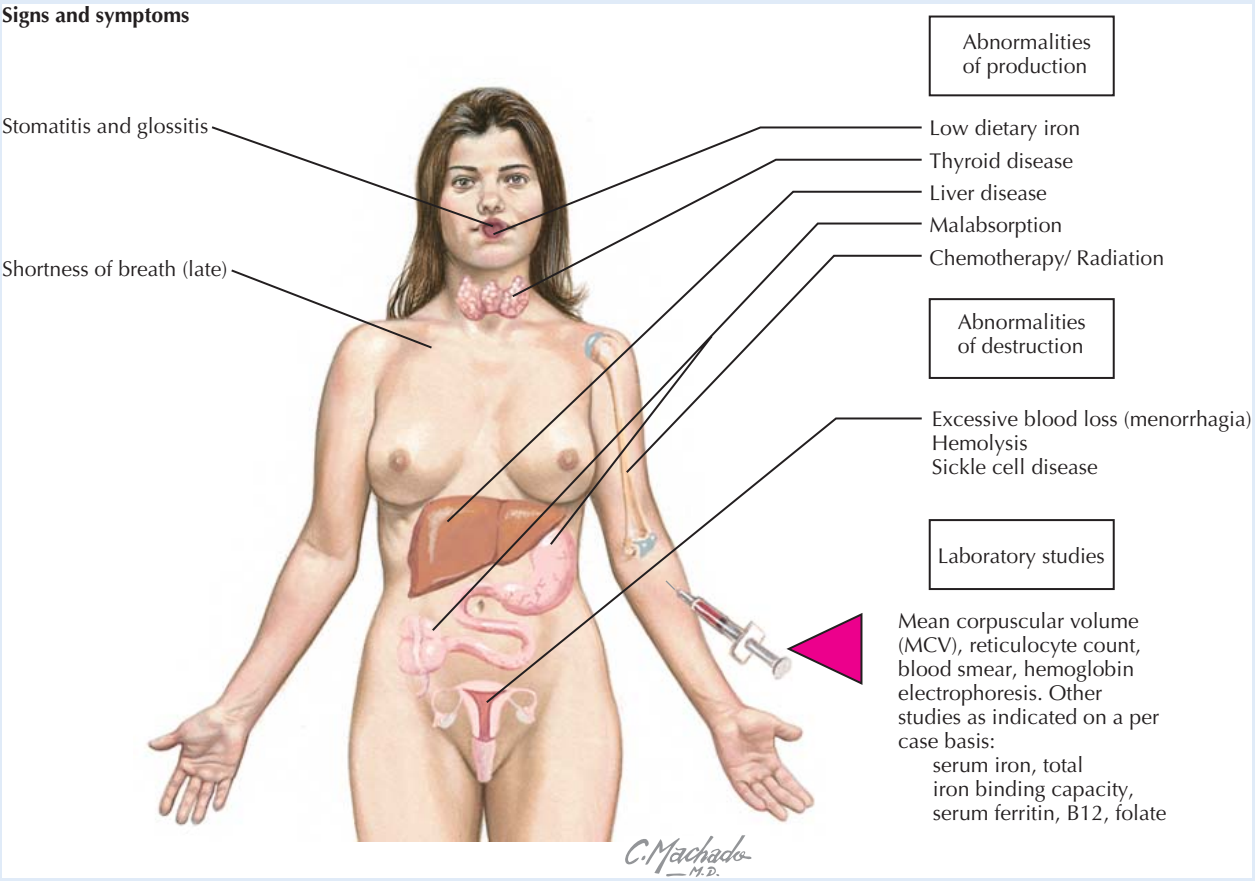
- Cooperative binding of oxygen to four binding sites per hemoglobin molecule is responsible for the sigmoidal shape of the oxyhemoglobin dissociation curve.
- In the lungs, blood will become fully saturated with oxygen over a wide range of P_{O_2}, due to the flat, upper portion of the oxyhemoglobin dissociation curve.
- At the lower P_{O_2} levels in tissue capillaries, small changes in P_{O_2} result in dissociation of relatively large amounts of oxygen, due to the steep middle portion of the curve, facilitating oxygen delivery to the tissues.

Factors Affecting the Oxyhemoglobin Dissociation Curve

In addition to these qualities, another important characteristic of the oxyhemoglobin dissociation curve is that it is shifted to the right under conditions of increased P_{CO_2}, low pH, and high temperature (see Fig. 15.2). These conditions occur locally during tissue hypoxia and increased metabolism (for example, during exercise), and the rightward shift of the curve results in decreased hemoglobin affinity for oxygen, and thus enhances delivery of oxygen to tissues. The metabolite of red blood cell glycolysis, **2,3-diphosphoglycerate** (**2,3-DPG;** also known as 2,3-bisphophoglycerate), also shifts the curve to the right and is elevated during hypoxia.

CLINICAL CORRELATE
Anemia

Anemia is the state of low hemoglobin or red blood cell count in blood, resulting in reduced oxygen binding capacity. It may be the result of blood loss, insufficient erythropoiesis (reduced red blood cell production), or hemolysis (red blood cell destruction). Iron deficiency may also cause anemia in menstruating women. Hypoxia associated with anemia cannot be corrected by administration of oxygen, because only the minor proportion of oxygen that is dissolved in arterial blood will be raised by elevating alveolar oxygen concentration, and oxyhemoglobin (oxygen bound to hemoglobin) will remain low due to the hemoglobin deficiency. Although mild anemia can be treated by a variety of interventions that address the primary cause of the anemia, severe anemia requiring immediate medical attention must be treated by blood transfusion.



Anemia Destruction of red blood cells, bleeding, or abnormalities of red blood cell production are causes of anemia. Laboratory studies are useful in differential diagnosis of the cause.

Oxygen delivery to the fetus involves transfer of oxygen from maternal blood to fetal blood across the placenta. Fetal blood contains a form of hemoglobin known as fetal hemoglobin (hemoglobin F) that has higher affinity for oxygen than adult hemoglobin (hemoglobin A), facilitating transfer of oxygen from maternal to fetal blood. Thus, the oxyhemoglobin dissociation curve for hemoglobin F is shifted to the left, compared with the dissociation curve for hemoglobin A. At a given P_{O_2}, oxygen saturation of hemoglobin F will be higher than that of hemoglobin A. Hemoglobin F is replaced by hemoglobin A within the first 3 months of life.

TRANSPORT OF CARBON DIOXIDE

The concentration of carbon dioxide is highest in the mitochondria, where it is produced during cellular respiration. From there, it diffuses to the interstitium and eventually into the blood, which transports it to the alveoli. Within the blood, CO_2 is transported in three forms (Fig. 15.3):

- Approximately 7% of CO_2 in blood is **dissolved CO_2.** Because solubility of CO_2 in plasma is relatively high (20 times the solubility of O_2), the dissolved form of CO_2 has a significant role in its transport.

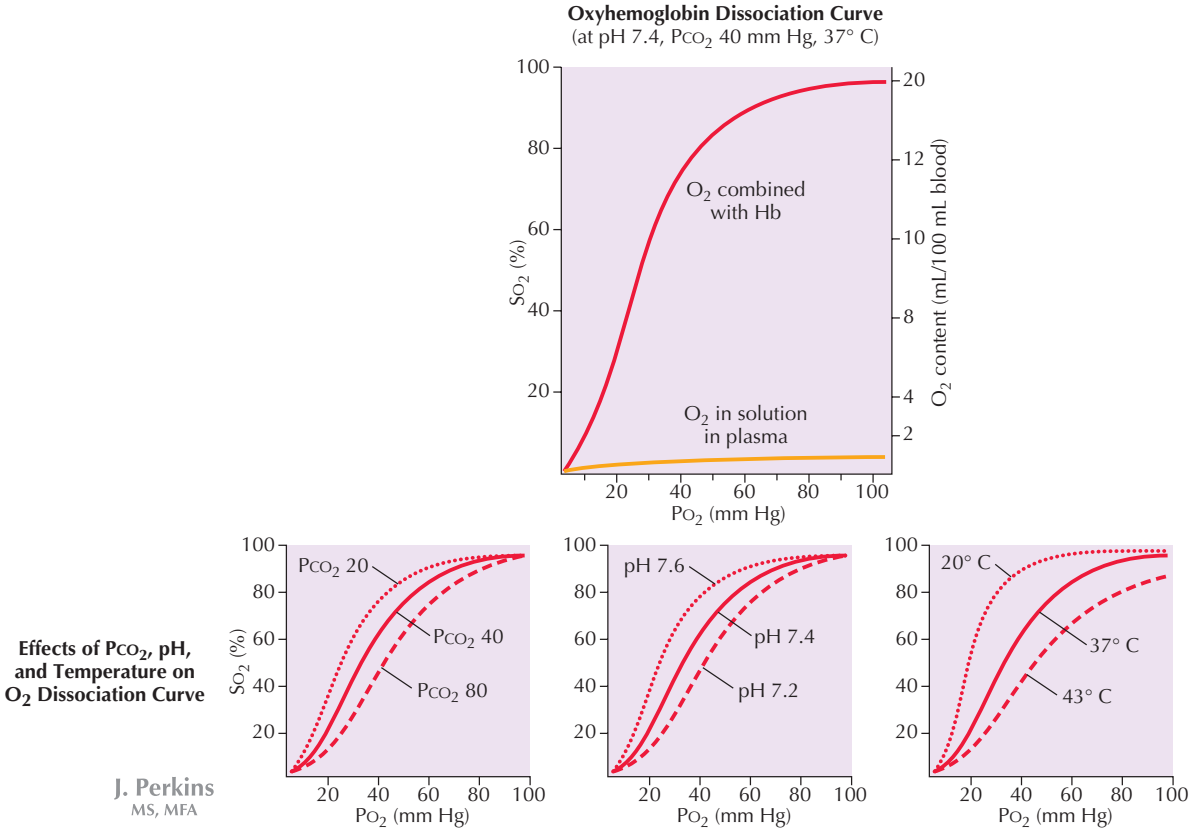


Figure 15.2 **Oxyhemoglobin Dissociation Curves** The oxyhemoglobin binding curve describes the association between partial pressure of oxygen and the degree of oxygen saturation of hemoglobin. Saturation of hemoglobin is nearly 100% (97.5%) when P_{O_2} is 100 mm Hg. The sigmoidal shape of this curve results in a high degree of oxygen saturation of blood after passing through alveolar capillaries and significant dissociation of oxygen from hemoglobin at the P_{O_2} levels to which blood is exposed as it perfuses systemic capillaries. The values given for oxygen content on the graph are those expected at the normal blood hemoglobin concentration of 15 g/100 mL blood. Note that the amount of dissolved hemoglobin in blood is very low over a wide range of P_{O_2}. High P_{CO_2}, low pH, and high temperature shift the oxyhemoglobin dissociation curve to the right, which promotes oxygen dissociation from hemoglobin in capillaries supplying actively metabolizing tissues.

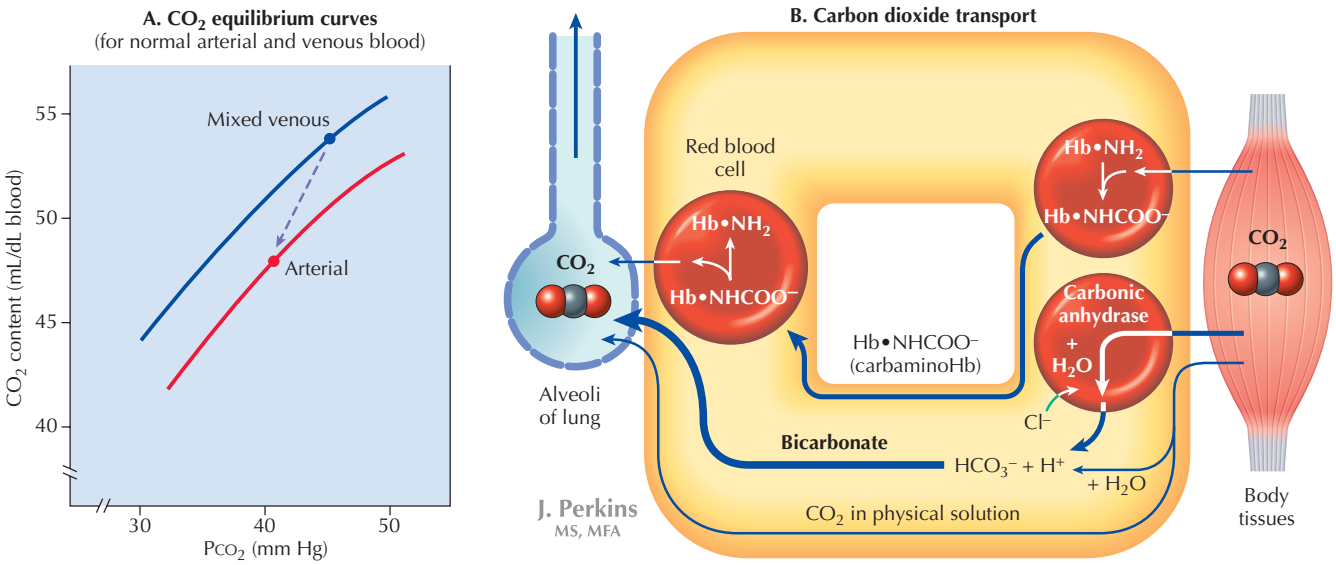
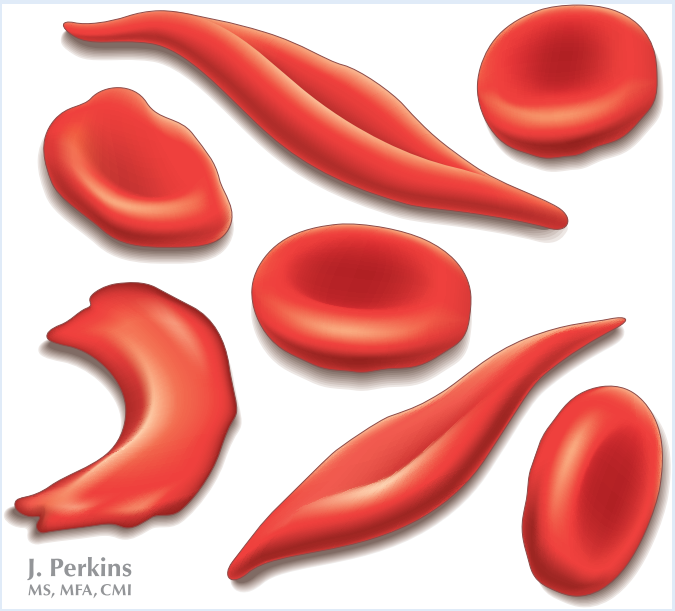


Figure 15.3 **Carbon Dioxide Transport** Carbon dioxide is transported in blood as bicarbonate anion (approximately 70%), carbaminohemoglobin (approximately 23%), and dissolved CO_2 (approximately 7%). The CO_2 equilibrium (dissociation) curve *(A)* is steep and linear, unlike the oxyhemoglobin dissociation curve, accounting for the relatively small difference in P_{CO_2} between arterial and venous blood (40 mm Hg vs. 45 mm Hg). Note also that the dissociation curve is shifted to the left when hemoglobin is in the form of deoxyhemoglobin, as in venous blood (the Haldane effect).

CLINICAL CORRELATE
Sickle Cell Disease

Patients suffering from sickle cell disease have a variant form of hemoglobin known as hemoglobin S. The allele causing this disease is recessive and is most common in people of sub-Saharan African origin. Hemoglobin S has the tendency to polymerize when it is deoxygenated, causing red blood cells to assume a sickle-like shape. In a "sickle cell crisis," red blood cells lodge in the microcirculation, causing painful ischemia and infarction of tissue. Sickle cell disease confers resistance to malaria, a parasite attacking red blood cells, and is believed to have evolved and persisted in sub-Saharan Africa due to evolutionary advantage associated with malaria resistance.



Sickled Red Blood Cells

In normal venous blood, the partial pressures of carbon dioxide and oxygen are similar (approximately 45 mm Hg and 40 mm Hg, respectively). According to Henry's law, the concentration of dissolved gas in a solution is directly proportional to its partial pressure. Although this law applies to both oxygen and carbon dioxide, because the solubility of carbon dioxide is 20 times that of oxygen, at similar partial pressures, much more carbon dioxide is present in blood in the form of dissolved gas than is the case for oxygen.

Although the approximate values given earlier for CO_2 transport as dissolved gas, carbaminohemoglobin, and bicarbonate anion are prevalent in the literature and textbooks, the value for carbaminohemoglobin may be significantly overstated, because the original studies of CO_2 carriage in blood were performed in the absence of 2,3-DPG, which binds with higher affinity to hemoglobin than CO_2.

- Up to 23% of CO_2 may be combined with protein, including hemoglobin (as **carbaminohemoglobin,** which gives venous blood its bluish tinge). CO_2 binds to terminal amino groups of blood proteins.
- About 70% of CO_2 in blood is carried in the form of **bicarbonate anion** (HCO_3^-).

Carbon Dioxide Transport in the Form of Bicarbonate Ion

The bulk of CO_2 is transported in the form of HCO_3^- within red blood cells (see Fig. 15.3). CO_2 dissolved in blood reacts with H_2O to form carbonic acid (H_2CO_3), which dissociates to form H^+ and HCO_3^-:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

This reaction, which is normally slow, is catalyzed by the enzyme **carbonic anhydrase** in red blood cells. As HCO_3^- is formed, it diffuses out of the red blood cell while Cl^- diffuses into the cell to maintain electrochemical equilibrium. This process is known as the **chloride shift.** Most of the H^+ formed is buffered within the red blood cell by binding to hemoglobin. The reaction forming H_2CO_3 is driven forward in capillary blood, as CO_2 diffuses from tissues into the blood. At the lungs, the reverse reaction occurs, as CO_2 is breathed off.

The Haldane Effect

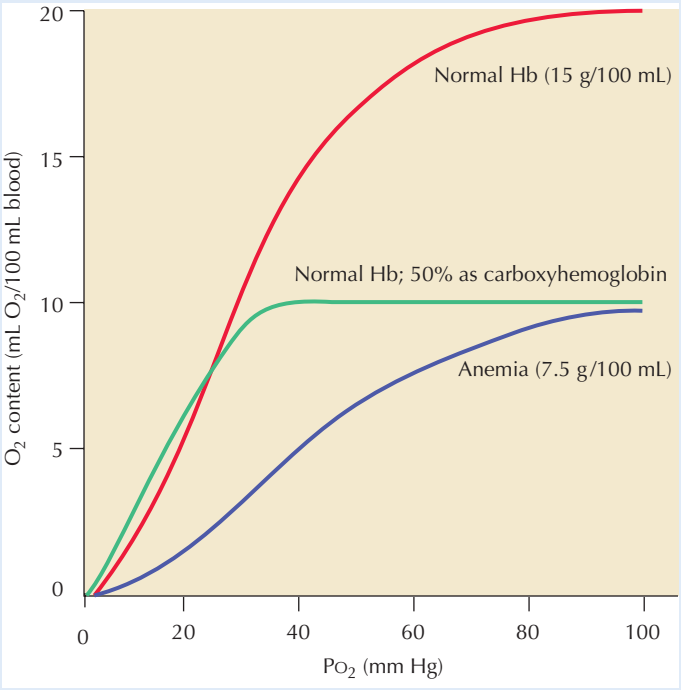
Unlike the sigmoidal oxyhemoglobin dissociation curve, the dissociation curve for CO_2 in blood is linear (see Fig. 15.3). However, it is shifted to the left when hemoglobin is in the form of deoxyhemoglobin, as in venous blood. This is known as the **Haldane effect.** As a result of the Haldane effect, as hemoglobin is deoxygenated in systemic capillaries, its affinity for CO_2 is increased, facilitating CO_2 transport. Binding affinity for H^+ (generated in red blood cells along with HCO_3^-) is also increased. In the pulmonary circulation, as hemoglobin is oxygenated, its affinity for CO_2 is reduced, and as a result, transfer of CO_2 from blood to alveolar air is facilitated.

CARBON DIOXIDE TRANSPORT AND ACID–BASE BALANCE

Normal blood pH is approximately 7.4 and is regulated within a tight range (7.35 to 7.45) by renal and respiratory mechanisms and by various other buffering systems (Fig. 15.4 and see Chapter 20). Significant deviation of pH from the normal range is incompatible with life, as protein structure is affected and enzymatic function is disturbed. CO_2 transport plays an important role in maintaining **acid–base equilibrium.** The **"acid load"** of the body consists of volatile acid, which is CO_2 in its various forms, and nonvolatile acids such as lactic acid and amino acids. Nonvolatile acids are buffered by intracellular and extracellular mechanisms; the bicarbonate buffering system of extracellular fluids including blood are

CLINICAL CORRELATE
Carbon Monoxide Poisoning

Carbon monoxide (CO) is a toxic compound produced during combustion of gasoline, propane, charcoal, natural gas, and other fuels. Prolonged exposure to air containing CO concentrations as low as 0.04% can be lethal. CO binds to hemoglobin, myoglobin, and cytochrome oxidase, producing its toxic effects. Its affinity for hemoglobin is 240 times higher than that of oxygen, and as a result, CO displaces oxygen bound to hemoglobin, forming carboxyhemoglobin and reducing oxygen-carrying capacity of hemoglobin (note the effects of a small concentration of CO on the oxyhemoglobin dissociation curve, compared with the effects of severe anemia). In addition, because binding at oxygen-binding sites of hemoglobin is cooperative, the presence of bound CO on hemoglobin increases hemoglobin affinity for oxygen (the oxyhemoglobin dissociation curve is shifted to the left), compromising dissociation of oxygen from hemoglobin and thus its delivery at normal tissue pH. Carbon monoxide poisoning is treated by respiration with 100% oxygen. Hyperbaric oxygen is also used as a treatment (patients are placed in high-pressure chambers and breathe pure oxygen), although the degree of benefit derived from this therapy is somewhat controversial. The pulse oximeter typically used in clinical settings to monitor arterial S_{O_2} relies on colorimetric measurements, but because carboxyhemoglobin, like oxyhemoglobin, is red in color, false, high S_{O_2} readings are obtained when this instrument is used in patients suffering from CO poisoning. Stated another way, the finger-probe and earlobe-probe pulse oximeters cannot differentiate between carboxyhemoglobin and oxyhemoglobin. CO poisoning results in symptoms of hypoxia, but without the typical blue appearance.



Oxygen Content of Blood: Effects of Carbon Monoxide and Anemia The arterial oxygen content of normal blood containing 15 g Hb/100 mL blood is approximately 20 mL/100 mL. In severe anemia, if hemoglobin is reduced by half, oxygen content at 100% saturation is also reduced by half. In carbon monoxide poisoning, CO binds tightly to hemoglobin, reducing the number of sites available for oxygen binding, and also shifting the oxyhemoglobin curve to the left. In the example shown above, half of the oxygen binding sites have been occupied by CO, forming carboxyhemoglobin. Thus, despite normal hemoglobin concentration, oxygen content is reduced by half in arterial blood at Pa_{O_2} of 100 mm Hg. Due to the left-shift of the dissociation curve, delivery of O_2 to tissues at normal tissue pH and P_{O_2} is greatly compromised, and thus venous P_{O_2} is profoundly reduced.

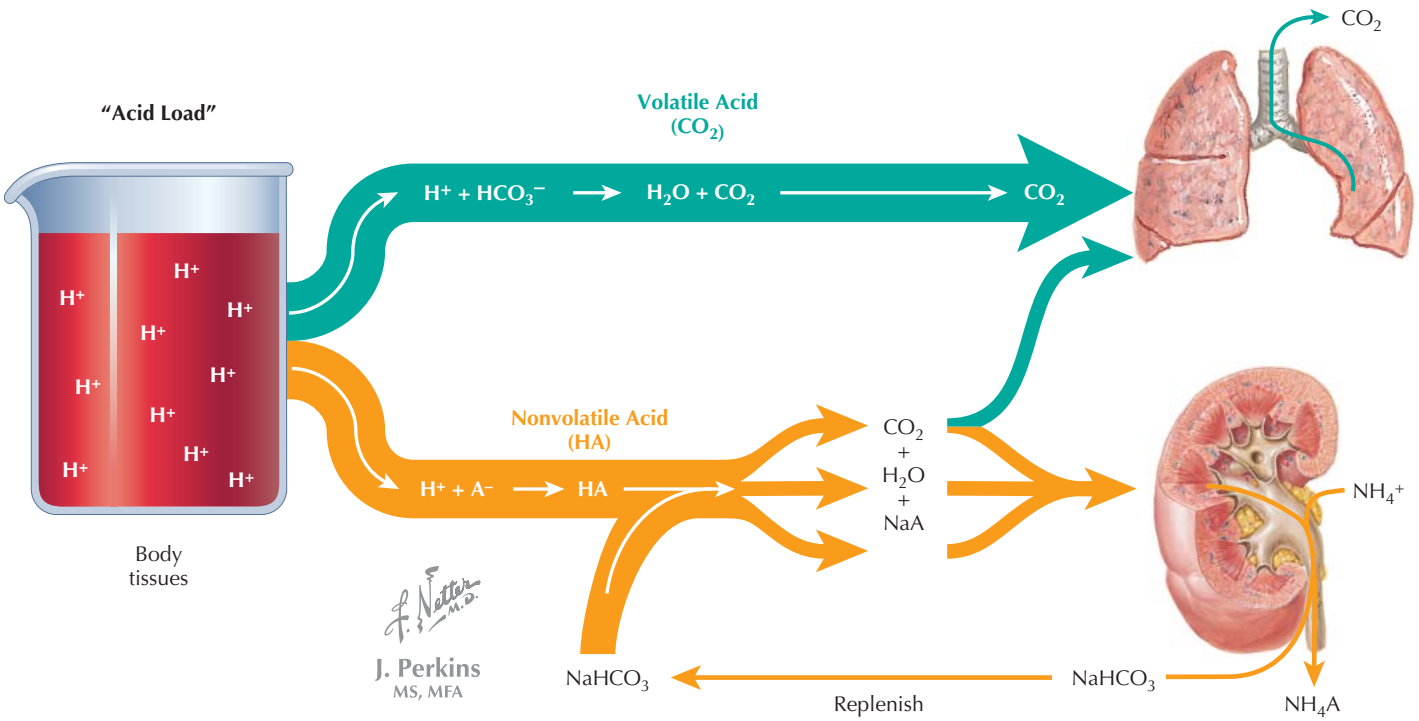


Figure 15.4 Role of Lungs and Kidneys in Acid–Base Balance The lungs and kidneys have a critical role in maintaining proper acid–base balance in the face of the acid load created by cellular metabolism of nutrients. Carbon dioxide ("volatile acid") produced by oxidative metabolism of carbohydrates and fats is efficiently eliminated by respiration in the lungs to maintain pH balance, whereas nonvolatile acids are primarily buffered by bicarbonate anion in extracellular fluid and intracellular proteins, with the kidneys replenishing the bicarbonate anion and excreting acid. H^+ is also eliminated in the urine as bicarbonate is regenerated. When a metabolic acid–base disturbance occurs, intracellular and extracellular buffering systems (involving primarily proteins and bicarbonate, respectively) are the first line of defense, along with rapid compensation by the lungs, which adjust the rate of CO_2 (volatile acid) elimination. Over a longer period (hours to days), renal mechanisms compensate by adjusting acid secretion and bicarbonate regeneration. When a respiratory acid–base disturbance occurs, the compensation is primarily renal.

important in this regard. Acid balance is also maintained by renal excretion of acid (renal mechanisms are covered in Chapter 20). Normally, CO_2 formed during metabolism of lipids and carbohydrates is readily eliminated by the respiratory system, but disturbances in respiration can result in acid–base imbalance, because changes in CO_2 elimination will directly affect carbonic acid levels. In addition, by adjusting respiration, the respiratory system can compensate for pH imbalances produced by metabolic disturbances.

The Henderson-Hasselbalch Equation

The pH of buffer systems can be calculated by the **Henderson-Hasselbalch equation:**

$$pH = pK + \log \frac{[A^-]}{[HA]}$$

where K is the acid dissociation constant. For the bicarbonate buffer system,

$$pH = pK + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

The pK for this system is 6.1. H_2CO_3 exists in low concentrations in extracellular fluids but is in equilibrium with dissolved CO_2, and thus, $0.03 \times P_{CO_2}$ (0.03 mmol/L/mm Hg is the solubility coefficient for P_{CO_2}) can be substituted for $[H_2CO_3]$ and the equation becomes:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 \times P_{CO_2}}$$

Substituting normal values for arterial $[HCO_3^-]$ and P_{CO_2} yields the normal pH of 7.4:

$$pH = 6.1 + \log \frac{[24]}{0.03 \times 40} = 7.4$$

Based on these equations, it should be apparent that changes in P_{CO_2} will result in alteration of pH. If hypoventilation results in a rise in alveolar $P_{A_{CO_2}}$, for example, the accompanying rise in Pa_{CO_2} will cause a fall in blood pH.

ACID–BASE DISTURBANCES

Acid–base disturbances are covered briefly in the following discussion, and in detail in Chapter 20. **Acidemia** is defined as increased acidity of blood (pH below 7.35), whereas **alkalemia** is increased alkalinity of blood (pH above 7.45). Technically, **acidosis** and **alkalosis** are more general terms referring

Table 15.1 Acid–Base Disorders

Disorder	pH	1° Alteration	Defense Mechanisms
Metabolic acidosis	↓	↓ [HCO_3^-]	Buffers, ↓P_{CO_2}, ↑NAE
Metabolic alkalosis	↑	↑ [HCO_3^-]	Buffers, ↑P_{CO_2}, ↓NAE
Respiratory acidosis	↓	↑ P_{CO_2}	Buffers & ↑NAE
Respiratory alkalosis	↑	↓ P_{CO_2}	Buffers & ↓NAE

NAE, net acid excretion.
(Reprinted with permission from Hansen J: Netter's Atlas of Human Physiology, Philadelphia, Elsevier, 2002.)

to low pH and high pH, respectively, in body fluids and tissues but are usually used synonymously with acidemia and alkalemia. Alterations in pH caused by respiratory abnormality are referred to as **respiratory acidosis** or **respiratory alkalosis.** Respiratory alkalosis is caused by hyperventilation, whereas respiratory acidosis is caused by hypoventilation (due to either an acute cause, such as airway obstruction or central nervous system [CNS] depression, or a chronic lung disease). In contrast, when the primary cause of the acid–base imbalance is metabolic, for example due to a metabolic disease or abnormal renal function, it is described as **metabolic acidosis** or **metabolic alkalosis.** Compensation for respiratory acidosis or alkalosis occurs by renal mechanisms, whereas respiratory adjustments compensate for metabolic acidosis or alkalosis (Table 15.1). The general role of the kidney and lungs in acid–base balance is illustrated in Figure 15.4.



Differentiating between metabolic and respiratory causes of acidosis and alkalosis is usually a relatively simple process. To identify the condition:

- First examine the pH. Values below 7.35 are defined as acidosis; pH above 7.45 is by definition alkalosis.
- Second, examine the Pa_{CO_2}. If the pH disturbance is respiratory in origin, the Pa_{CO_2} level will be abnormal and predictive of the pH change. In other words, in respiratory acidosis, Pa_{CO_2} will be elevated above 40 mm Hg, whereas in respiratory alkalosis (caused by hyperventilation), Pa_{CO_2} will be lower than 40 mm Hg. If the condition is acute, HCO_3^- level will be normal; if the respiratory condition is chronic, HCO_3^- will be elevated in acidosis and depressed in alkalosis, reflecting renal compensation. Because of the compensation, pH will be closer to normal in chronic acidosis or alkalosis than would be expected based on a change in Pa_{CO_2} alone.
- If Pa_{CO_2} level is abnormal in the opposite direction predicted for it to be the primary alteration, the disturbance is metabolic. Examination of HCO_3^- should reveal that its level is consistent with a primary metabolic disturbance: HCO_3^- will be high in metabolic alkalosis and low in metabolic acidosis. Pa_{CO_2} levels will be depressed in metabolic acidosis and elevated in metabolic alkalosis, reflecting respiratory compensation. Because of this compensation, the pH will be closer to normal than would be predicted based on a change in HCO_3^- alone.

CONTROL OF RESPIRATION

Although breathing can be controlled voluntarily (for example, during breath holding or hyperventilation), it is ultimately an involuntary process that closely controls Pa_{O_2} and Pa_{CO_2}. Changes in both depth and rate of respiration are involved in this process. Three essential components of the involuntary control system are as follows:

- brainstem respiratory centers
- peripheral and central chemoreceptors
- mechanoreceptors in lungs and joints

Ultimately, signals involved in control of breathing are integrated in the **medullary respiratory center,** resulting in regulation of the activity of respiratory muscles (see Fig. 14.1) and affecting tidal volume and respiratory rate and pattern. Within the medulla, respiratory control is accomplished by the:

- **Ventral respiratory group,** which includes the nucleus retroambiguous, nucleus ambiguous, and nucleus retrofacialis and innervates both inspiratory and expiratory muscles. It is involved in regulation of inspiratory force and in voluntary expiration.
- **Dorsal respiratory group** within the nucleus tractus solitarius, which innervates inspiratory muscles.

The medullary respiratory center receives input from two important pontine areas:

- The **pneumotactic center,** which regulates rate and depth of respiration by cyclical inhibition of inspiration. This center has input from the cerebral cortex.
- The **apneustic center,** which stimulates inspiration. It is antagonized by the pneumotactic center.

Damage to the pons or upper medulla may result in **apneusis** (breathing characterized by prolonged inspiratory efforts and

brief, intermittent exhalations). Experimentally, apneusis can be produced by ablation of the pneumotactic center and transection of the vagus nerve.

Role of Central and Peripheral Chemoreceptors

Sensory information from central and peripheral chemoreceptors is important in this regulation of respiration by the brainstem. **Central chemoreceptors** located at the ventrolateral surface of the medulla respond indirectly to changes in arterial Pco_2 and play a critical role in acute regulation of Pa_{CO_2}. The blood-brain barrier is largely impermeable to HCO_3^- and H^+, but CO_2 readily diffuses across the barrier and into the cerebrospinal fluid (CSF), where it affects CSF pH (by mechanisms discussed earlier). Thus, when Pa_{CO_2} is altered, respiration is affected:

- A rise in Pa_{CO_2} will cause a fall in CSF pH, which is detected by central chemoreceptors, resulting in an increase in respiratory rate.
- A fall in Pa_{CO_2} will cause a rise in CSF pH, which is detected by central chemoreceptors, resulting in decreased ventilation.

Peripheral chemoreceptors, located in the carotid bodies and aortic bodies (see Section 3), also convey information concerning the quality of arterial blood to the respiratory center in the brainstem, thereby affecting ventilation. Unlike the central chemoreceptors, these receptors respond directly to changes in Pa_{O_2} and Pa_{CO_2}, as well as pH. Through the peripheral chemoreceptor mechanism, ventilation is stimulated by the following:

- A fall in Pa_{O_2}: The ventilatory effects of changes in Pa_{O_2} are relatively small when Pa_{O_2} is above 60 mm Hg, but peripheral chemoreceptors are very responsive when Pa_{O_2} falls below this level.
- A rise in Pa_{CO_2}: Changes in Pa_{CO_2} affect respiration through both central and peripheral chemoreceptors, although the central chemoreceptor mechanism is more responsive to the changes.
- A fall in pH: Changes in H^+ concentration in arterial blood affect peripheral chemoreceptors directly, independently of the effects of Pa_{CO_2}.

Chemical control of respiration by Pa_{O_2} and Pa_{CO_2} is illustrated in Figure 15.5.

Additional Mechanisms Controlling Respiration

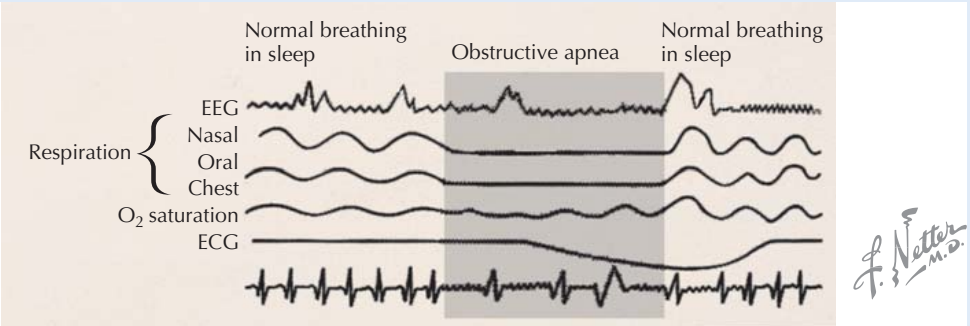
Respiration is also controlled by a number of additional peripheral mechanisms:

- **Pulmonary mechanoreceptors** respond to inflation of the lung and result in termination of inspiration. The afferent signals from these receptors in the smooth muscle of airway walls are transmitted through the vagus nerve to the medulla, where they inhibit the apneustic center, thereby terminating inspiration. This response to lung inflation is known as the **Hering-Breuer reflex** (specifically, the Hering-Breuer inspiratory-inhibitory reflex).
- **Irritant receptors** in the large airways respond to noxious gases and particulate matter, for example, in cigarette smoke. Activation of these receptors results in afferent

CLINICAL CORRELATE
Sleep Apnea

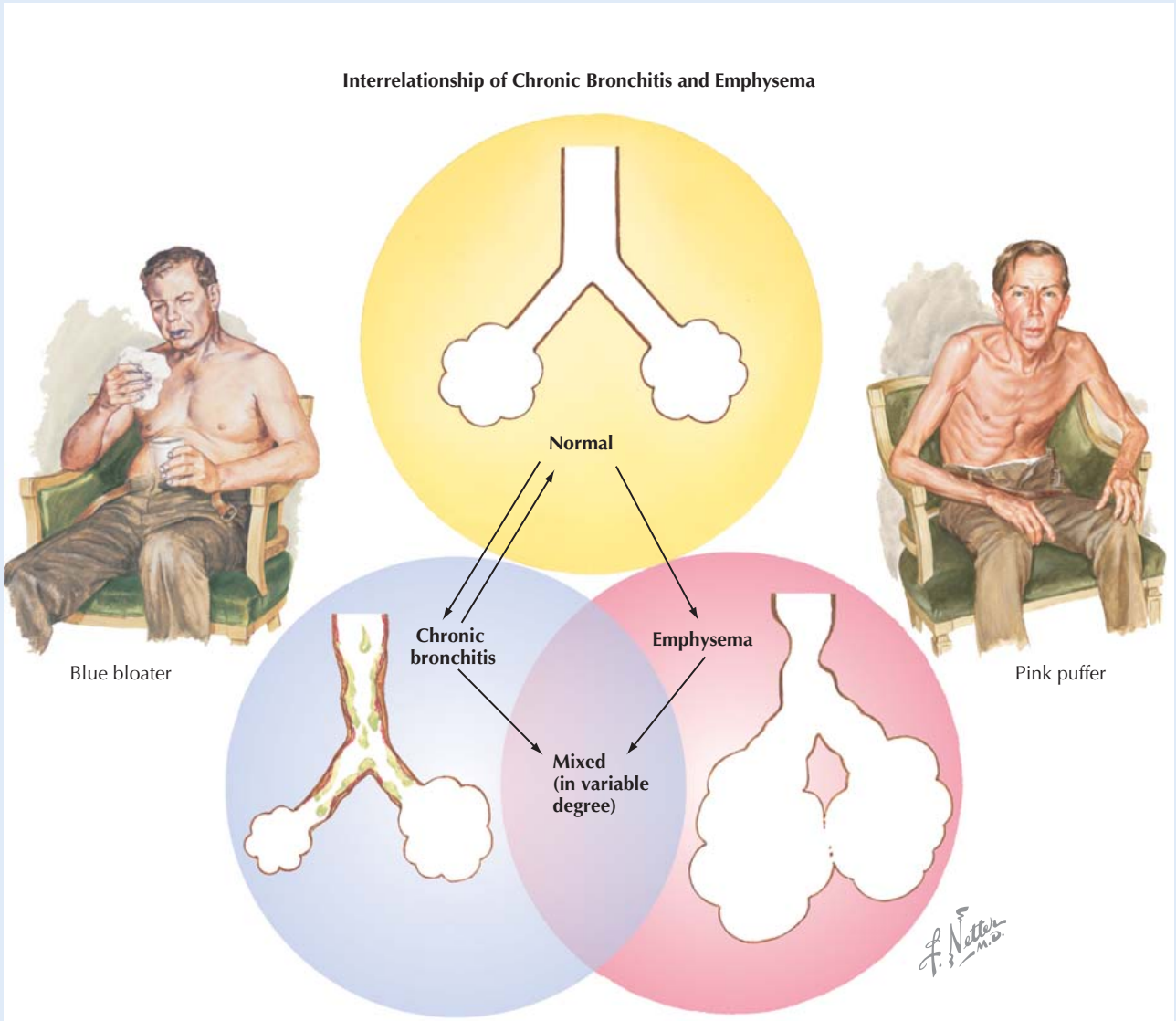
Sleep apnea is a disorder whereby normal breathing is periodically interrupted during sleep; the pauses in breathing can be the length of two to three breaths, and thus there can be a significant reduction in gas transport during these episodes. Sleep apnea can be central, obstructive, or complex (both central and obstructive). In central sleep apnea, brain centers are dysregulated, resulting in a lack of effort to breathe; in obstructive sleep apnea, although respiratory effort is normal, obstruction prevents airflow. Disrupted sleep and fatigue are common symptoms. Chronic sleep apnea is associated with increased incidence of heart disease and stroke.

Recordings from patient with obstructive sleep apnea



CLINICAL CORRELATE
Respiratory Control in Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is most often associated with tobacco smoking and may be exacerbated by occupational exposure to certain pollutants. It is characterized by chronic bronchitis (coughing with sputum production) and emphysema (destruction of alveolar walls resulting in fewer, enlarged "alveoli" with reduction in total surface area for gas diffusion). As a result, patients with this disease become hypoxic and hypercapnic (Pa_{O_2} is below normal and Pa_{CO_2} is elevated); pH is somewhat lower than normal, although significant compensation occurs by elevation of HCO_3^- through renal mechanisms. In other words, the patients suffer from chronic respiratory acidosis, with metabolic compensation. In this state of chronic hypercapnea, normal CSF pH is maintained by elevation of HCO_3^- in the CSF. The CNS is chronically exposed to high P_{CO_2}, and the central chemoreceptors become unresponsive to CO_2. Thus, patients with COPD develop "hypoxic respiratory drive," in which respiratory drive is mainly mediated by peripheral chemoreceptor responses to low Pa_{O_2}. When an acute exacerbation arises in such a patient, if supplemental O_2 is administered carelessly, results can be catastrophic and even fatal: Pa_{O_2} will rise, but respiratory drive may fail as a result, causing a fall in minute ventilation and a further rise in Pa_{CO_2}. Ventilatory support with some supplemental oxygen may be beneficial, but suppression of ventilatory drive must be avoided.



COPD is characterized by chronic bronchitis and emphysema. COPD patients usually suffer to some extent from both and are classified based on the dominant symptomatology. "Pink puffers" suffer mainly from emphysema and have ruddy complexions and elevated respiratory rate; "blue bloaters" suffer mainly from chronic bronchitis, resulting in hypoxema, cyanosis (bluish lips and skin), and often, symptoms of right heart failure, including swelling of feet and ankles ("bloating").

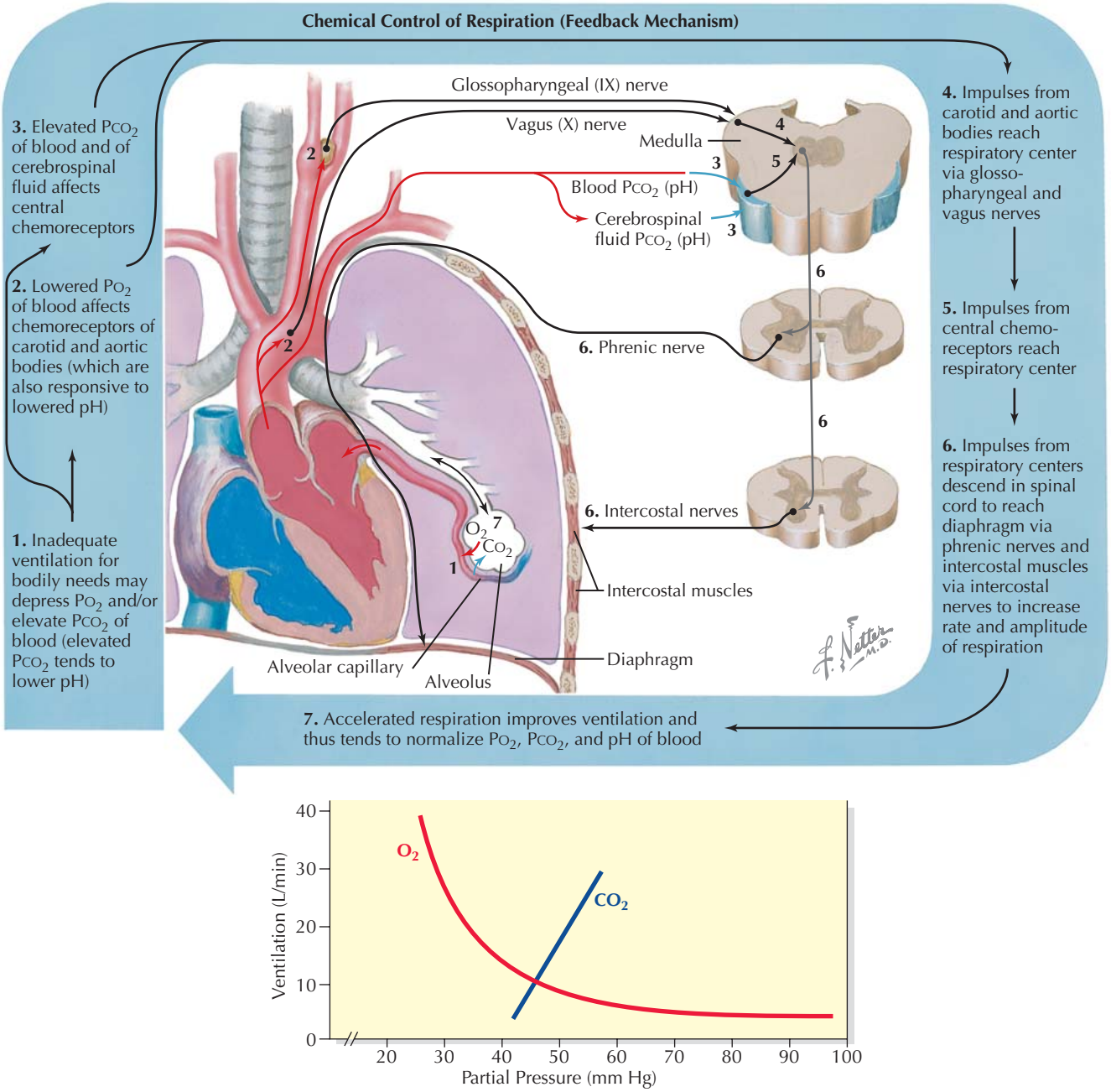


Figure 15.5 **Control of Respiration** Central and peripheral chemoreceptors regulate respiration by responding to arterial blood gas levels. Central chemoreceptors respond primarily to changes in arterial P_{CO_2}, which diffuses into the CSF and alters pH of the CSF (the blood-brain barrier is largely impermeable to HCO_3^- and H^+), while peripheral chemoreceptors in the carotid bodies and aortic bodies respond to changes in Pa_{O_2}, and also Pa_{CO_2} and pH. Brainstem respiratory centers adjust the rate and depth of respiration, producing changes in Pa_{O_2} and Pa_{CO_2} (and thus pH). In the bottom graph, the effects of Pa_{CO_2} and Pa_{O_2} on minute ventilation are illustrated.

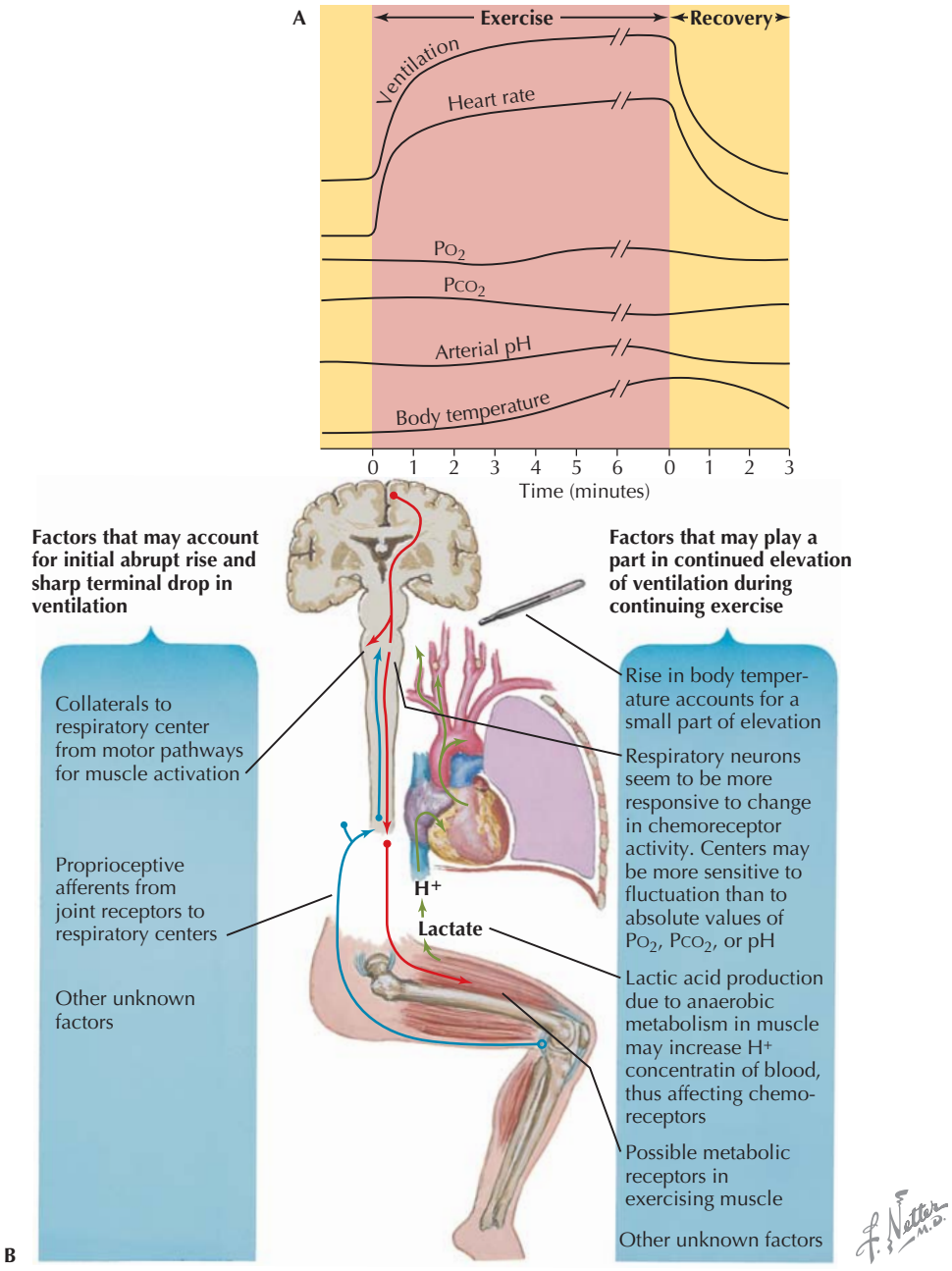


Figure 15.6 Respiratory Response to Exercise Increased oxygen consumption and carbon dioxide production during exercise requires adjustments of cardiac output and respiration *(A)*. Factors accounting for the rapid adjustments in respiration at the onset and termination of exercise, as well as feedback mechanisms during continued exercise, are illustrated *(B)*.

signals to the CNS mainly through the vagus nerve and causes reflexive bronchoconstriction and coughing.

- **Juxtacapillary receptors** (J receptors) in the alveoli are stimulated by hyperinflation of the lungs and various chemical stimuli; reflexive rapid, shallow breathing occurs as a result.
- **Joint and muscle mechanoreceptors** are stimulated during movement of joints and muscles, producing an increase in respiratory rate.

Respiratory Control in Exercise

Control of respiration is a critical component of the **integrated response to exercise** (Fig. 15.6). During dynamic (aerobic) exercise, oxygen consumption rises from the average resting rate of 250 mL O_2/min to as high as 4 L O_2/min, without substantial change in either Pa_{O_2} or Pa_{CO_2}. At the onset of dynamic exercise, there is a rapid increase in respiration through neural and reflexive mechanisms, although the control

mechanisms are not fully understood. Activation of motor pathways results in collateral activation of the respiratory center, and respiration is further stimulated by afferent signals from muscle and joint mechanoreceptors and other, unknown factors. With continuing exercise, feedback mechanisms become important. The rise in core body temperature and elevation of lactic acid production (and plasma H^+ concentration) contribute to the further, more gradual rise in ventilation. Although Pa_{O_2} and Pa_{CO_2} change only modestly (except at high levels of exercise), respiratory control systems may be more sensitive to such changes during exercise. When exercise is terminated, ventilation diminishes rapidly at first but requires some time to fall to the resting level, due to the continued activation of feedback mechanisms until the metabolic alterations associated with exercise (including the elevation of lactic acid) are reversed.

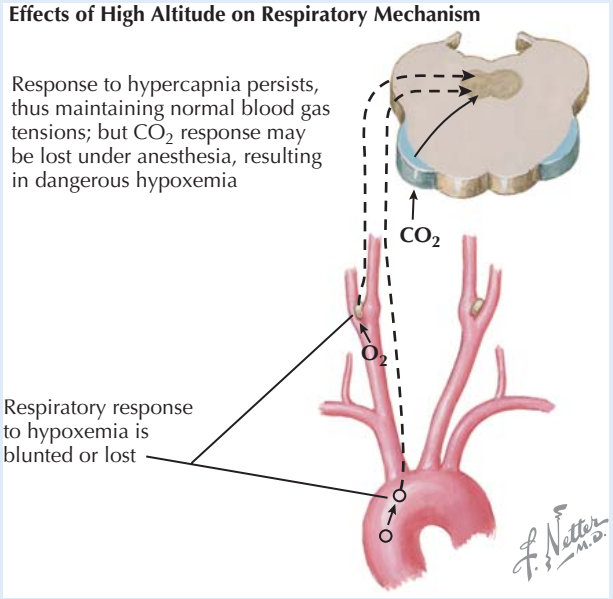
Adaptation to High Altitude

The control of respiration is also important in **adaptation to high altitude.** At the lower atmospheric pressures associated with high altitudes, the P_{O_2} of inspired air is reduced, resulting in hypoxemia. The fall in Pa_{O_2} stimulates ventilation through peripheral chemoreceptors, but this effect is tempered by the resulting fall in Pa_{CO_2} and the accompanying alkalosis, which inhibit ventilation through central and peripheral chemoreceptor mechanisms. Over a period of time, renal compensatory mechanisms result in elevation of plasma HCO_3^-, and as pH returns to normal, ventilation again increases. In addition to increased ventilation, other factors that contribute to the adaptation to high altitude include the following:

- Hypoxemia stimulates red blood cell production; the resulting **polycythemia** (and higher plasma hemoglobin) increases the oxygen-carrying capacity of blood.
- Elevation of **2,3-DPG** causes a rightward shift of the oxyhemoglobin dissociation curve, and thus, oxygen more readily dissociates from hemoglobin at the tissue level.

CLINICAL CORRELATE
Acute Altitude Sickness

Acute altitude sickness is a relatively common response to high altitude (greater than 8000 feet above sea level) in people who are accustomed to living at low altitudes, especially when the ascent is rapid. Symptoms include headache, tachycardia, shortness of breath, nausea and vomiting, loss of appetite, lightheadedness, and fatigue. In most cases, symptoms are mild and resolve in a matter of days as acclimation takes place. In rare, extreme cases, life-threatening pulmonary edema or cerebral edema may develop. Pulmonary edema occurs as a result of pulmonary vasoconstriction and an increase in pulmonary vascular permeability. As discussed earlier, pulmonary vasoconstriction is a normal response to alveolar hypoxia, but it is exaggerated in high-altitude pulmonary edema. The cause of high-altitude cerebral edema has not been established but likely involves cerebral vasodilation in response to hypoxemia, resulting in high capillary hydrostatic pressure. Descent to lower altitude is a critical component of treatment in these severe cases.



Review Questions

CHAPTER 13: PULMONARY VENTILATION AND PERFUSION AND DIFFUSION OF GASES

1. The reduction in pulmonary vascular resistance that occurs when pulmonary artery pressure is increased is mainly a result of:

A. recruitment and distension of pulmonary capillaries.
B. autoregulation by myogenic mechanisms.
C. redistribution of pulmonary blood flow.
D. metabolic vasodilation.
E. active vasodilation of pulmonary arterioles.

2. Which of the following lung volumes or capacities can **NOT** be measured by spirometry alone?

A. Tidal volume
B. Expiratory reserve volume
C. Inspiratory reserve volume
D. Total lung capacity
E. Vital capacity

3. With regard to the ventilation, the perfusion, or the ventilation-to-perfusion ratio in regions of the lung in a person in the standing position,

A. perfusion is highest at the top of the lung.
B. ventilation is lowest at the bottom of the lung.
C. the ventilation-to-perfusion ratio is greatest at the top of the lung.
D. the ventilation-to-perfusion ratio approaches infinity in areas of shunt.
E. the ventilation-to-perfusion ratio is zero in areas of dead space.

4. Diffusion of gas through a membrane:

A. is inversely related to the surface area for diffusion.
B. is directly related to the difference in partial pressure of the gas on each side of the membrane.
C. requires active transport.
D. is inversely related to the diffusion constant of the gas.
E. is directly related to the thickness of the membrane.

5. In zone 2 of the lung (in a standing person),

A. both pulmonary arterial and venous pressures exceed alveolar pressure.
B. both pulmonary arterial and venous pressures are below alveolar pressure.
C. alveolar pressure is higher than pulmonary venous pressure but less than arterial pressure.
D. the ventilation-to-perfusion ratio approaches zero.
E. the ventilation-to-perfusion ratio approaches infinity.

CHAPTER 14: THE MECHANICS OF BREATHING

6. The mechanical system that produces breathing is at rest (outward elastic recoil pressure of the chest wall is equal to and opposing inward elastic recoil pressure of the lungs) at:

A. residual volume.
B. functional residual capacity.
C. 60% of total lung capacity.
D. 70% of total lung capacity.
E. total lung capacity.

7. In the respiratory system as a whole, the greatest resistance to flow occurs in the:

A. respiratory bronchioles.
B. terminal bronchioles.
C. medium-sized airways.
D. bronchi.
E. trachea.

8. Dynamic compression of airways is responsible for:

A. effort independence of expiratory flow.
B. the vital capacity of the lung.
C. normal resting tidal volume.
D. the total lung capacity that can be achieved during inspiration.
E. peak flow during expiration.

9. In severe chronic obstructive pulmonary disease (COPD),

A. lung compliance is reduced.
B. elastic recoil of the lung is decreased.
C. total lung capacity is reduced.
D. functional residual capacity is reduced.
E. residual volume is reduced.

10. Which of the following is **NOT** a characteristic or function of surfactant?

A. Decreases pulmonary compliance
B. Reduces the work of breathing
C. Reduces surface tension of alveoli and small airways
D. Deficient in respiratory distress syndrome
E. Contains dipalmitoyl phosphatidyl choline

CHAPTER 15: OXYGEN AND CARBON DIOXIDE TRANSPORT AND CONTROL OF RESPIRATION

11. Which of the following changes will result in the greatest increase in oxygen content of arterial blood, assuming normal alveolar oxygen concentration?

A. An increase in hematocrit from 40 to 45
B. An increase in alveolar oxygen concentration from 100 to 150 mm Hg
C. A 10% increase in blood level of 2,3-DPG
D. A fall in blood pH from 7.4 to 7.35
E. A 10% increase in alveolar ventilation

12. Lab tests reveal that a patient has blood pH of 7.3, elevated arterial P_{CO_2}, and slightly elevated arterial plasma bicarbonate level. The acid–base status is:

A. metabolic acidosis.
B. metabolic alkalosis.
C. respiratory acidosis.
D. respiratory alkalosis.
E. impossible to determine from these values.

13. The major mechanism of long-term adaptation to high altitude is:

A. increased heart rate.
B. increased respiratory rate.
C. reduced 2,3-DPG in blood.
D. polycythemia.
E. reduced plasma bicarbonate.

14. In the control of respiration, central chemoreceptors respond mainly to changes in:

A. arterial pH.
B. arterial P_{CO_2}.
C. 2,3-DPG in blood.
D. arterial HCO_3^-.
E. arterial O_2.

15. The rapid adjustment of respiratory rate at the onset of exercise is mediated in part by:

A. a fall in arterial pH.
B. a rise in arterial P_{CO_2}.
C. 2,3-DPG in blood.
D. mechanoreceptors in joints.
E. a rise in body temperature.

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Section 5
RENAL PHYSIOLOGY

The kidneys are the primary avenue for regulating extracellular fluid (ECF) and electrolyte homeostasis. Their "job" is to regulate proper ECF volume and solute composition on a minute-to-minute basis. This is accomplished by intrarenal physical forces and feedback systems, as well as input from the nervous and endocrine systems. At the same time, the kidneys excrete waste (excess fluid and electrolytes, as well as urea, bilirubin, drugs, and potential toxins) and provide key endocrine functions.

Chapter 16 **Overview, Glomerular Filtration, and Renal Clearance**

Chapter 17 **Renal Transport Processes**

Chapter 18 **Urine Concentration and Dilution Mechanisms**

Chapter 19 **Regulation of Extracellular Fluid Volume and Osmolarity**

Chapter 20 **Regulation of Acid–Base Balance by the Kidneys**

Review Questions

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CHAPTER 16 Overview, Glomerular Filtration, and Renal Clearance

STRUCTURE AND OVERALL FUNCTION OF THE KIDNEYS

The kidneys perform a host of functions, including the following:

- Regulation of fluid and electrolyte balance: The kidneys regulate the volume of extracellular fluid through reabsorption and excretion of NaCl and water. They also regulate the plasma levels of other key substances (Na^+, K^+, Cl^-, HCO_3^-, H^+, glucose, amino acids, Ca^{2+}, phosphates). Key renal processes that allow regulation of circulating substances are as follows:
  - *Filtration* of fluid and solutes from the plasma into the nephrons
  - *Reabsorption* of fluid and solutes out of the renal tubules into the peritubular capillaries
  - *Secretion* of select substances from the peritubular capillaries into the tubular fluid, which facilitates excretion of the substances; both endogenous (e.g., K^+, H^+, creatinine, ACh, NE) and exogenous (e.g., para-aminohippurate, salicylic acid, penicillin) can be secreted in the urine
  - *Excretion* of excess fluid, electrolytes, and other substances (e.g., urea, bilirubin, acid [H^+])
- Regulation of plasma osmolarity: "Opening" and "closing" specific water channels in the renal collecting ducts produces concentrated and dilute urine (respectively), allowing regulation of plasma osmolarity and extracellular fluid (ECF) volume.
- Excretion of metabolic waste products: Urea (from protein metabolism), creatinine (from muscle metabolism), bilirubin (from breakdown of hemoglobin), uric acid (from breakdown of nucleic acids), metabolic acids, and foreign substances such as drugs are eliminated in urine.
- Producing/converting hormones: The kidney produces **erythropoietin** and **renin.** Erythropoietin stimulates red blood cell production in bone marrow. **Renin,** a proteolytic enzyme, is secreted into the blood and converts angiotensinogen to angiotensin I (which is then converted to angiotensin II by angiotensin-converting enzyme [ACE] in lungs and other tissues). The renin-angiotensin system is critical for fluid–electrolyte homeostasis and long-term blood pressure regulation. The renal tubules also convert 25-hydroxyvitamin D to the active **1,25-dihydroxyvitamin D,** which can act on kidney, intestine, and bone to regulate calcium homeostasis.
- Metabolism: Renal **ammoniagenesis** has an important role in acid–base homeostasis (discussed further in Chapter 20). During starvation, the kidney also has the ability to produce glucose through **gluconeogenesis.**

The kidneys are bilateral, retroperitoneal organs that receive their blood supply from the renal arteries (Fig. 16.1*A*). Each kidney is approximately the size of an adult fist, surrounded by a fibrous capsule. The parenchyma is divided into the cortex and outer and inner medulla. The cortex contains renal corpuscles, which are **glomerular capillaries** surrounded by **Bowman's capsules.** The corpuscles are connected to **nephrons,** which are the tubules that are considered the functional units of the kidneys. The outer stripe of the outer medulla contains the thick ascending loops of Henle and collecting ducts, whereas the inner stripe contains the pars recta, thick and thin ascending loops of Henle and collecting ducts (Fig. 16.2). These empty urine into the calyces, and ultimately, the ureter, which leads to the bladder. Thus, a portion of the plasma fraction of blood entering the kidney is filtered through the **glomerular capillary membrane into Bowman's space,** flows into the nephrons, and becomes tubular fluid. After the tubular fluid is processed in the nephron, the remaining fluid (urine) flowing through the collecting ducts exits the renal pyramids into the minor calyces. The minor calyces combine to form the major calyces, which empty into the ureter (see Fig. 16.1*B*). The ureters lead to the bladder, where the urine is stored until excretion (micturition).

The Nephron

Each kidney contains more than 1 million nephrons. There are two populations of nephrons, **cortical** (or superficial) and **juxtamedullary** (deep) nephrons. Most of the nephrons are cortical (~80%), while ~20% are juxtamedullary. The populations are similar in that they are composed of the same structures, but differ in their location within the kidney and in the length of segments. The cortical nephrons originate from glomeruli in the upper and middle regions of the cortex, and their loops of Henle are short, extending only to the inner stripe of the outer medulla (see Fig. 16.2). The glomeruli of juxtamedullary nephrons are located deeper in the cortex (by

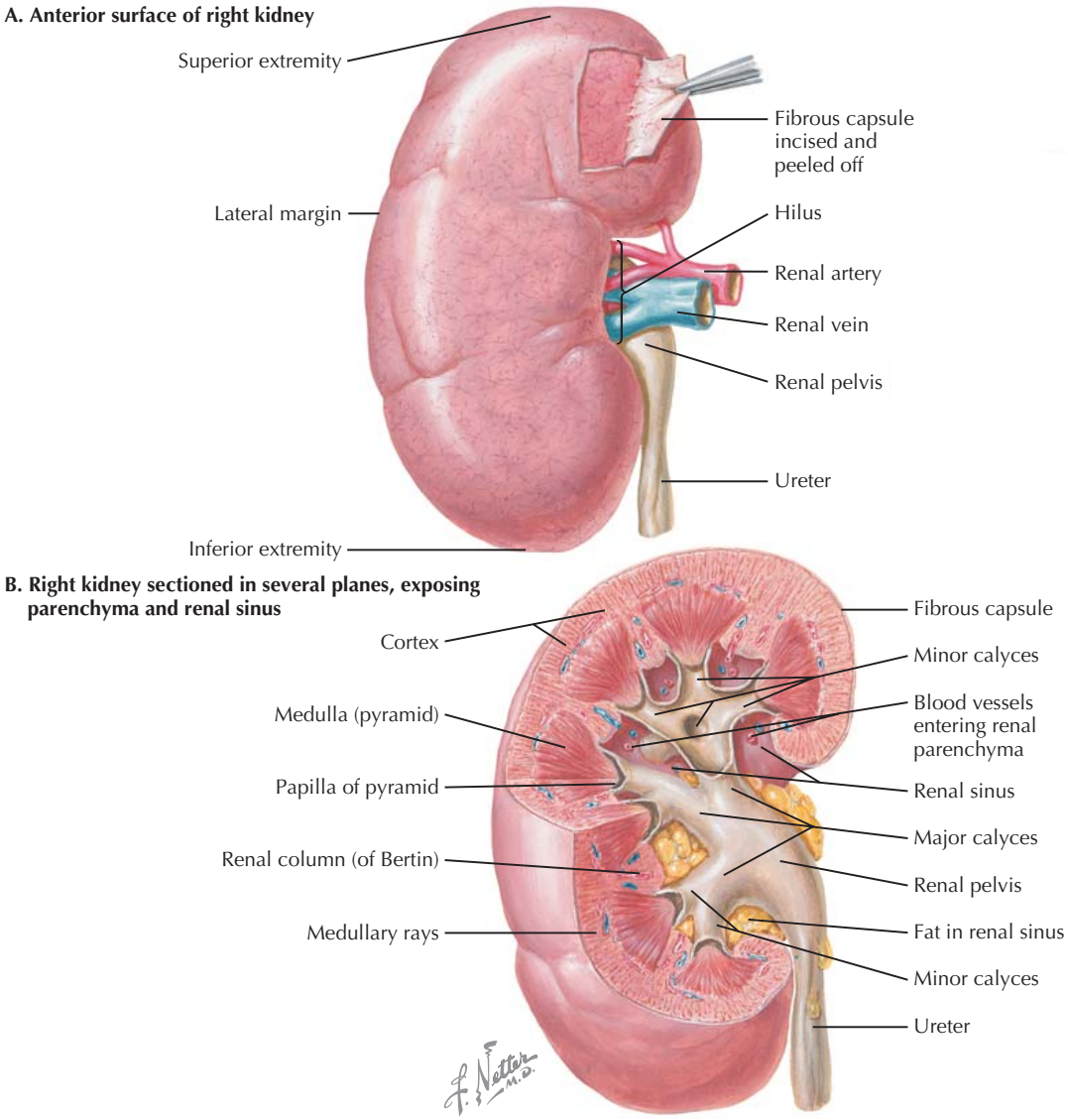


Figure 16.1 Anatomy of the Kidney The kidneys are bilateral organs with arterial blood supply from the abdominal aorta through the renal arteries *(A)*. The plasma is filtered at the glomeruli, which are located in the cortex. About 20% of the cardiac output enters the kidney (~1 L/min), and excess fluid and solutes are excreted as urine. The urine collects in the renal sinuses and exits the kidney via the ureter *(B),* which leads to the bladder for storage until elimination.

the medullary junction) and have long loops of Henle, extending deep into the inner medulla, forming the papillae.

As stated, all nephrons have the same basic structures, but the location of the nephrons and the length of specific segments vary, with important consequences. The primary nephron segments are listed in sequential order in Table 16.1 with functions and distinctive characteristics.

Blood Flow

Blood flow to the kidneys (**renal blood flow, RBF**) is about 1 liter per minute (L/min), or ~20% of the cardiac output. The blood enters the kidneys via the renal arteries and follows the path shown:

→ interlobar arteries
→ arcuate arteries (at corticomedullary junction)
→ interlobar/cortical radial arteries
→ afferent arteriole (site of regulation)
→ **glomerular capillaries**
→ efferent arteriole
→ cortical peritubular capillaries (or vasa recta in deep nephrons)
→ venule
→ veins

The plasma fraction of the blood is filtered at the **glomerulus.** Blood enters the capillary from the *afferent arteriole* and exits the capillary by the *efferent arteriole.* Efferent arterioles associated with cortical nephrons, lead to the **peritubular capillar-**

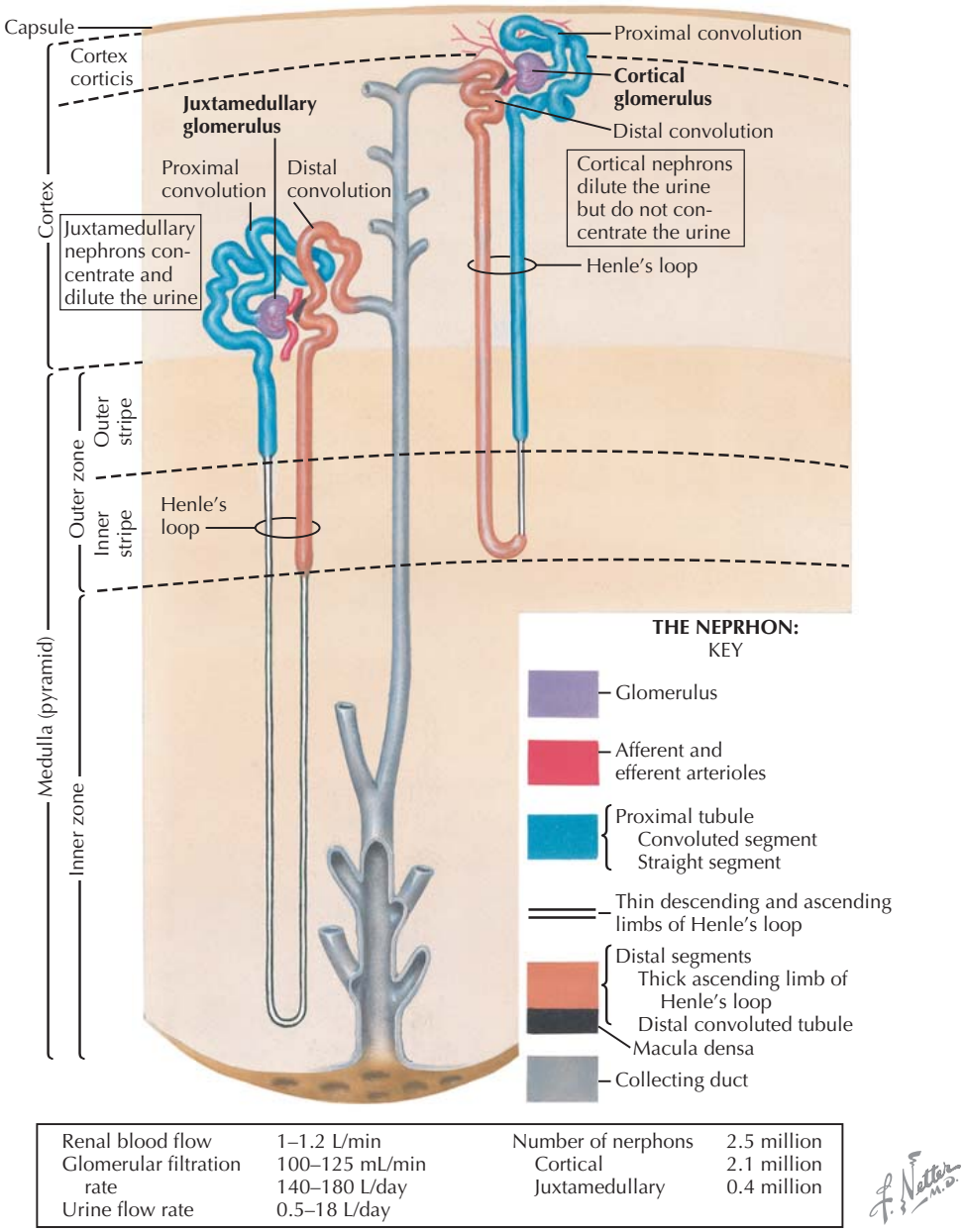


Figure 16.2 **Nephron Structure** The nephron is the functional unit of the kidney, and the structure differs depending on the location of the glomerulus. The glomeruli of cortical (superficial) nephrons are located in the upper cortical zone of the kidney and have loops of Henle that extend only to the outer zone of the medulla. The glomeruli of the juxtamedullary (deep) nephrons are located at the cortico-medullary junction and have loops of Henle that extend deep into the inner medulla. There are ~5 times more cortical than juxtamedullary nephrons in the human kidney.

ies, which collect material reabsorbed from the nephrons; efferent arterioles of the juxtaglomerular nephrons lead to the **vasa recta** (straight vessels), which collect material reabsorbed from medullary tubules.

The Glomerulus

The glomerulus is a capillary system, from which an ultrafiltrate of plasma enters into Bowman's space (Fig. 16.3). The glomerular capillary has a fenestrated endothelium and **basement membrane,** which prevent filtration of blood cells, proteins, and most macromolecules into the glomerular ultrafiltrate. The glomerulus is surrounded by epithelial cells (**podocytes**) a single layer thick, which contribute to the filtration barrier. Filtration by the glomerulus occurs according to size and charge—because the basement membrane and podocytes are negatively charged, most proteins (also negatively charged) cannot be filtered. There are also **mesangial cells** that

Table 16.1 Nephron Segments: General Functions and Differences between Segments in Cortical vs. Juxtamedullary Nephrons

Segments	Description and General Functions of Segment	Characteristics in Cortical Nephrons	Characteristics in Juxtamedullary Nephrons
Glomerulus	The capillary net that filters plasma, making ultrafiltrate. Upon entering the proximal tubule, ultrafiltrate is called tubular fluid.	Located superficially, in the outer and mid-cortex; their efferent arterioles give rise to the peritubular capillaries.	Located deep in the cortex, by the medullary junction; efferent arterioles give rise to the vasa recta, which are adjacent to deep nephrons and aid in concentration of urine.
Proximal Convoluted Tubule	Has brush border villus membrane and is main site of reabsorption of solutes and water.	Shorter than proximal convoluted tubules in juxtamedullary nephrons.	Longer than in cortical nephrons, allowing relatively more reabsorption of solutes.
Proximal Straight Tubule	Additional reabsorption.	Much longer than in deep nephrons.	Shorter than in cortical nephrons.
Thin descending loop of Henle (tDLH)	Impermeable to solutes but permeable to water; thus, it *concentrates* tubular fluid as water diffuses out.	Much shorter than in deep nephrons.	Very long, forming pyramids, crucial for concentrating tubular fluid.
Thick ascending loop of Henle (TALH)	Impermeable to water, but has Na^+-K^+-$2Cl^-$ transporters that reabsorb more solutes and *dilute* the tubular fluid. Sets up and maintains interstitial concentration gradient.	Longer than deep nephrons, dilutes tubular fluid.	Dilutes tubular fluid and is critical in producing the large concentration gradient in the inner medulla.
Distal convoluted tubule	Electrolyte modifications; aldosterone acts on late distal segments.	Similar in cortical and deep nephrons.	Similar in cortical and deep nephrons.
Collecting ducts (CD)	Site of free water reabsorption through water channels (aquaporins) controlled by ADH. CDs are also important for acid–base balance: the **α-intercalated cells** allow H^+ secretion; **β-intercalated cells** have HCO_3^-/Cl^- exchangers, which allow HCO_3^- secretion, when necessary.	The cortical collecting ducts (CCD) reabsorb some Na^+ and Cl^- and secrete K^+ (from aldosterone-sensitive principal cells). Less effect on urine concentration compared with deep nephrons because the ducts do not extend far into medulla. CCDs also have **α**- and **β**-intercalated cells for acid–base regulation.	Because they extend deep into the medulla, the final concentration of urine occurs here. The inner medullary collecting ducts (IMCD) have principal cells (with aldosterone-sensitive Na^+ and K^+ channels), as well as intercalated cells (as seen in CCDs). Medullary CDs are a key site of ADH-dependent urea reabsorption, which contributes to the high medullary interstitial fluid osmolarity.

ADH, antidiuretic hormone.

support the glomerulus but can also contract, decreasing surface area for filtration.

The Juxtaglomerular Apparatus

Another important structural and functional aspect is the juxtaglomerular apparatus—this is the area where the distal convoluted tubule returns to its "parent" glomerulus. At this site, specialized **macula densa** cells are in contact with the distal convoluted tubule and afferent arteriole, forming the **juxtaglomerular apparatus** (see Fig. 16.3). The macula densa cells of the juxtaglomerular apparatus are important in sensing tubular fluid flow and sodium delivery to the distal nephron, and because of their proximity to the afferent arteriole, macula densa cells can regulate renal plasma flow and **glomerular filtration rate (GFR)** (autoregulation). Macula densa cells also participate in the regulation of the release of the enzyme **renin** from juxtaglomerular cells adjacent to the afferent arterioles. The renin secretion aids in fluid and electrolyte homeostasis (see Chapter 19). Macula densa cells also receive input from adrenergic nerves through β_1-receptors.

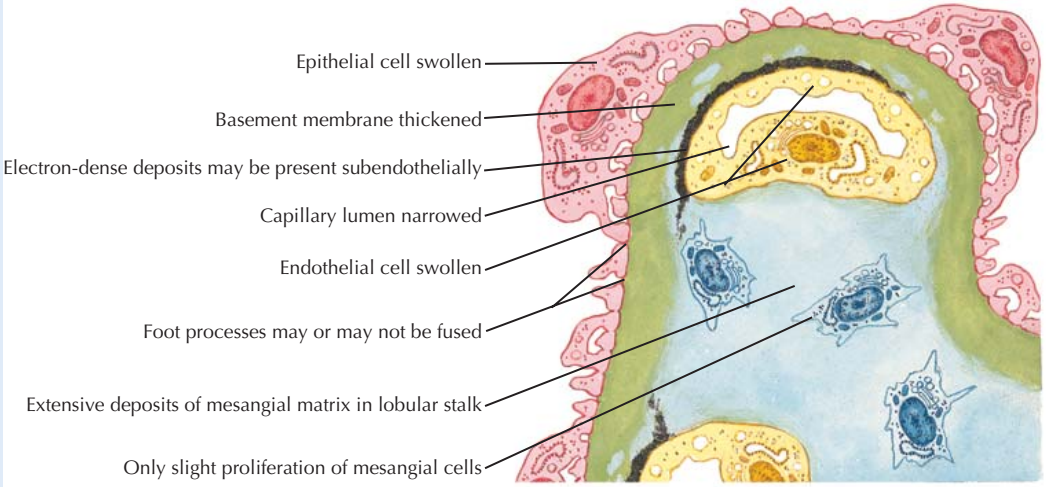
CLINICAL CORRELATE
Glomerulonephritis

The glomerulus is a key site for renal damage. Diseases and drugs that damage the glomerular basement membrane reduce the negative charge and allow large proteins (especially albumin) to be filtered. Because there is no mechanism for reabsorbing large proteins in the nephron, the protein is excreted in the urine (proteinuria). In addition, diseases (such as diabetes) that increase mesangial matrix deposition increase rigidity and decrease area of filtration of the glomerulus, reducing renal function.

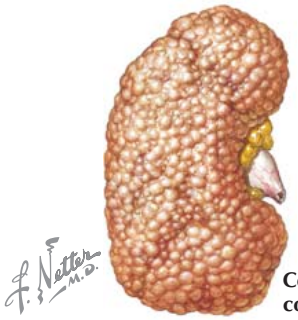
Acute glomerulonephritis is usually caused by different factors in children and adults. In children, a common cause is streptococcal infection. In adults, acute glomerulonephritis can arise as a complication from drug reactions, pneumonia, immune disorders, and mumps. Acute glomerulonephritis can be asymptomatic (about 50% of cases) or can be associated with edema, low urine volume, headaches, nausea, and joint pain. Treatment is aimed at reducing the inflammation, usually with steroids or immunosuppressive drugs, while determining and addressing the cause, when possible. In most cases patients recover completely.

In contrast, **chronic glomerulonephritis** is associated with long-term inflammation of glomerular capillaries, resulting in thickened basement membranes, swollen epithelial cells, and narrowing of the capillary lumen. Major causes of chronic glomerulonephritis are diabetes, lupus nephritis, focal segmental glomerulosclerosis, and IgA nephropathy. The rate of progression of kidney damage to chronic renal failure (GFR less than 10 to 15 mL/min) is widely variable and can take as few as 5 years or more than 30 years, depending on the overall cause of the inflammatory process. Chronic glomerulonephritis can lead to other major systemic complications including hypertension, heart failure, uremia, and anemia. Treatment is dependent on the cause of the damage, and in the case of diabetes-induced disease, angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors are beneficial in slowing the renal damage. As the damage progresses toward end-stage renal failure, the GFR is insufficient to rid the body of waste, and uremia is one of the results. Patients usually start hemodialysis when their GFR is less than 20 mL/min. Dialysis can be used for years, although many patients opt for renal transplantation, which is a common procedure.

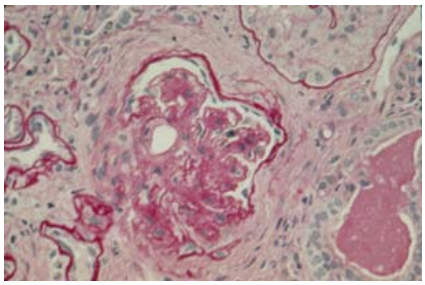
Chronic glomerulonephritis: Electron microscopic findings



Late stage of chronic glomerulonephritis



Contracted, pale, coarsely granular kidney



Glomeruli in various stages of obsolescence. Deposition of PAS-stained material, hyalinization, fibrous crescent formation, tubular atrophy, interstitial fibrosis

Chronic Glomerulonephritis The upper panel illustrates key features of chronic glomerular damage, including swollen epithelial cells, a grossly thickened basement membrane, fused foot processes, and increased matrix proteins. These abnormalities destroy the normal filtration barriers. The lower left panel depicts the effects of severe glomerulonephritis on the whole kidney, and the lower right panel gives a representative micrograph of damaged glomeruli.

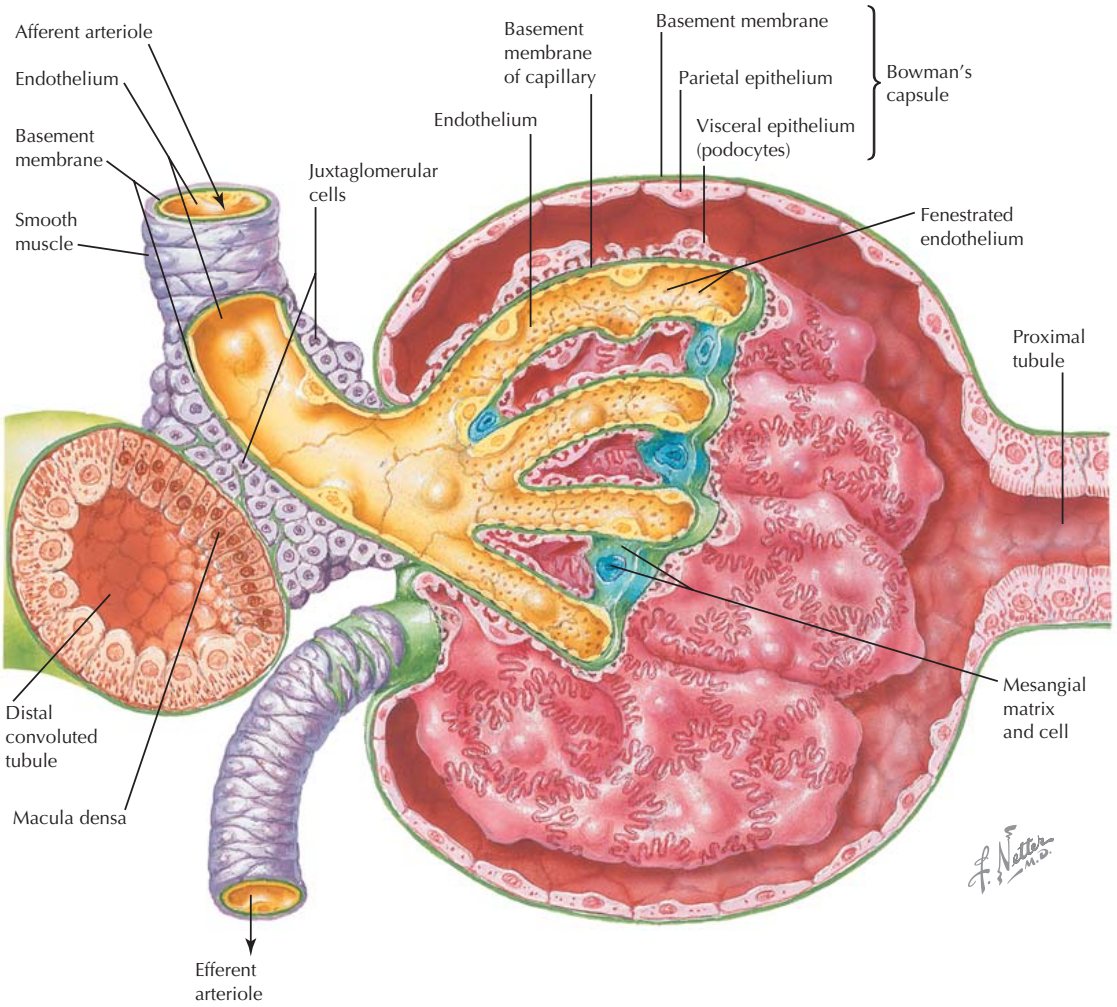


Figure 16.3 Anatomy of the Glomerulus Plasma is filtered at the glomerular capillaries into Bowman's space, and the ultrafiltrate then flows into the proximal tubule. The glomerular endothelial barrier prevents filtration of the cellular elements of the blood, so the ultrafiltrate does not contain blood cells or plasma proteins. The cells of the macula densa are in contact with the afferent arteriole through the juxtaglomerular cells, forming the juxtaglomerular apparatus. The macula densa monitors NaCl delivery to the distal tubule and regulates renal plasma flow (autoregulation).

Renal Plasma Flow

While whole blood enters the renal arteries, only *plasma* is filtered at the glomerular capillaries, and thus, when discussing glomerular filtration, **renal plasma flow (RPF)** is an important factor. RPF can be determined by the following equation:

$$RPF = RBF \times (1 - HCT)$$

In the normal adult male, RBF = ~1 L/min, and hematocrit (HCT) is ~40% (0.4). Thus,

$$RPF = 1 \text{ L/min} \times 0.6 = 600 \text{ mL/min}$$

To determine the **effective renal plasma flow (EPRF)**, which is the plasma flow entering the glomeruli and available for filtration, the plasma clearance of the inorganic acid **para-aminohippurate (PAH)** is used. PAH is filtered at the glomeruli, and under normal circumstances the remaining PAH in the peritubular capillaries is *secreted* into the proximal tubule, so that essentially no PAH enters the renal vein (Fig. 16.4 and see "Analysis of Renal Function" Clinical Correlate).

GLOMERULAR FILTRATION: PHYSICAL FACTORS AND STARLING FORCES

Glomerular filtration is determined by the Starling forces and the permeability of the glomerular capillaries to the solutes in the plasma. In general, with the exception of formed elements (red blood cells, white blood cells, platelets) and most proteins, plasma is available for filtration at the glomerular capillaries. Because the molecules must travel through several barriers to move from the capillary lumen to Bowman's space

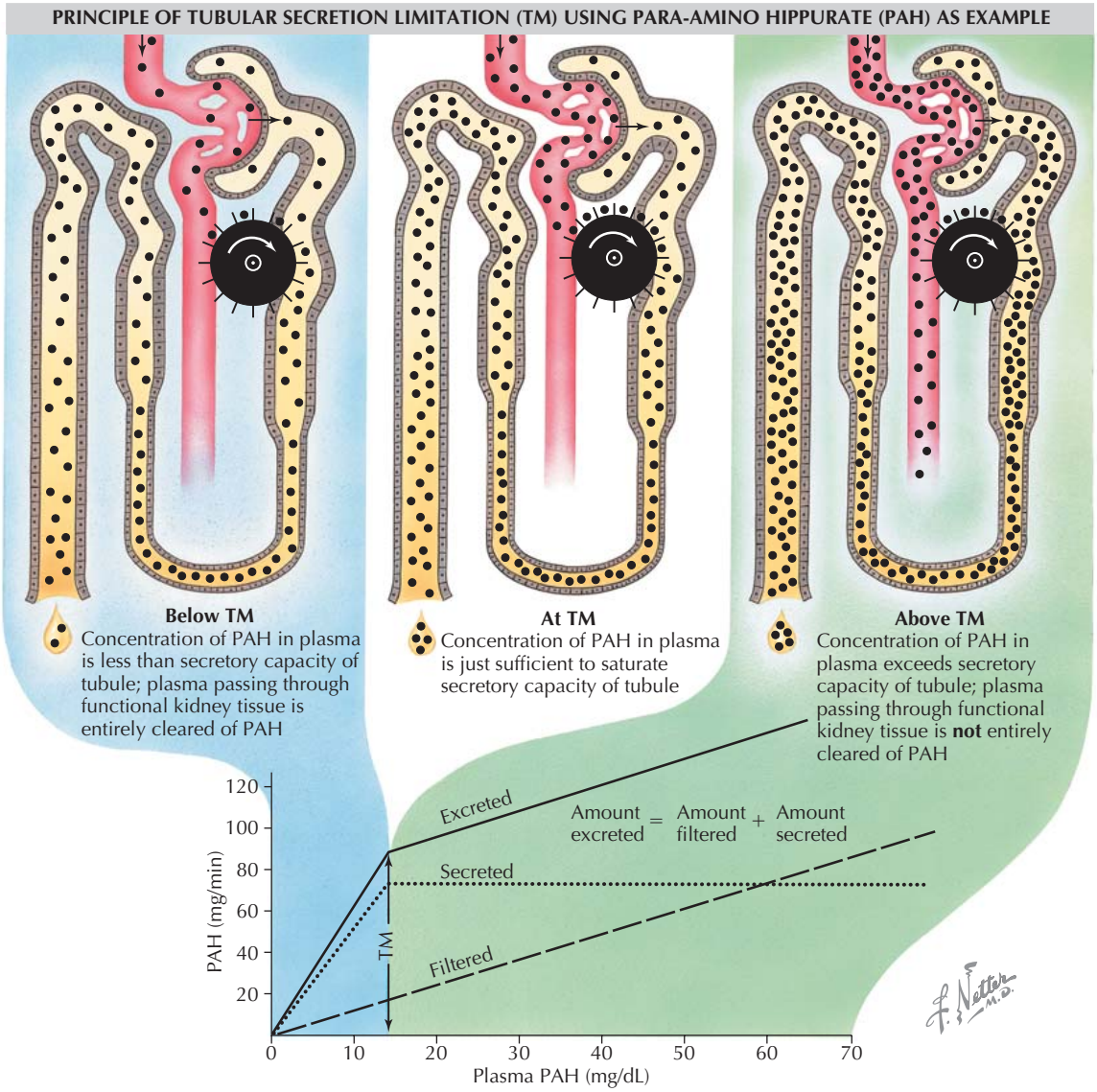


Figure 16.4 Renal Handling of Para-amino Hippurate (PAH) PAH is filtered at the glomerulus and also secreted into the proximal tubule. When the plasma concentration of PAH is below the tubular transport maximum (TM), PAH is effectively cleared from the blood entering the kidney. However, if the plasma concentration exceeds the TM, PAH is not entirely removed and is found in the renal vein.

(fenestrated epithelium → basement membrane → between podocytes → filtration slit → Bowman's space), there are size limitations, and ultimately the effective pore size is ~30 Å. Small molecules such as water, glucose, sucrose, creatinine, and urea are freely filtered. As molecular size increases, or net negative charge of molecules increases (for example, among proteins), filtration becomes increasingly restricted.

Myoglobin, a small protein that is released from muscle following damage, is only 20 Å, but its shape restricts free passage, and only about 75% is filtered. Most proteins are negatively charged or of high molecular weight and will not be filtered unless there is damage to the glomerular barriers, or the negative charge of the protein is affected by viral or bacterial processes. In those cases, protein will enter the renal tubule and be excreted in urine (proteinuria).

Starling forces govern fluid movement into or out of the capillaries (see Chapter 1). The pressures that determine glomerular filtration dynamics are glomerular capillary hydrostatic pressure (HP_{GC}) forcing fluid out of the capillary, glomerular capillary oncotic pressure (π_{GC}) attracting fluid into the glomerular capillary, Bowman's space hydrostatic pressure (HP_{BS}) opposing capillary hydrostatic pressure, and Bowman's space oncotic pressure (π_{BS}) attracting fluid into Bowman's space (typically there is negligible protein in the

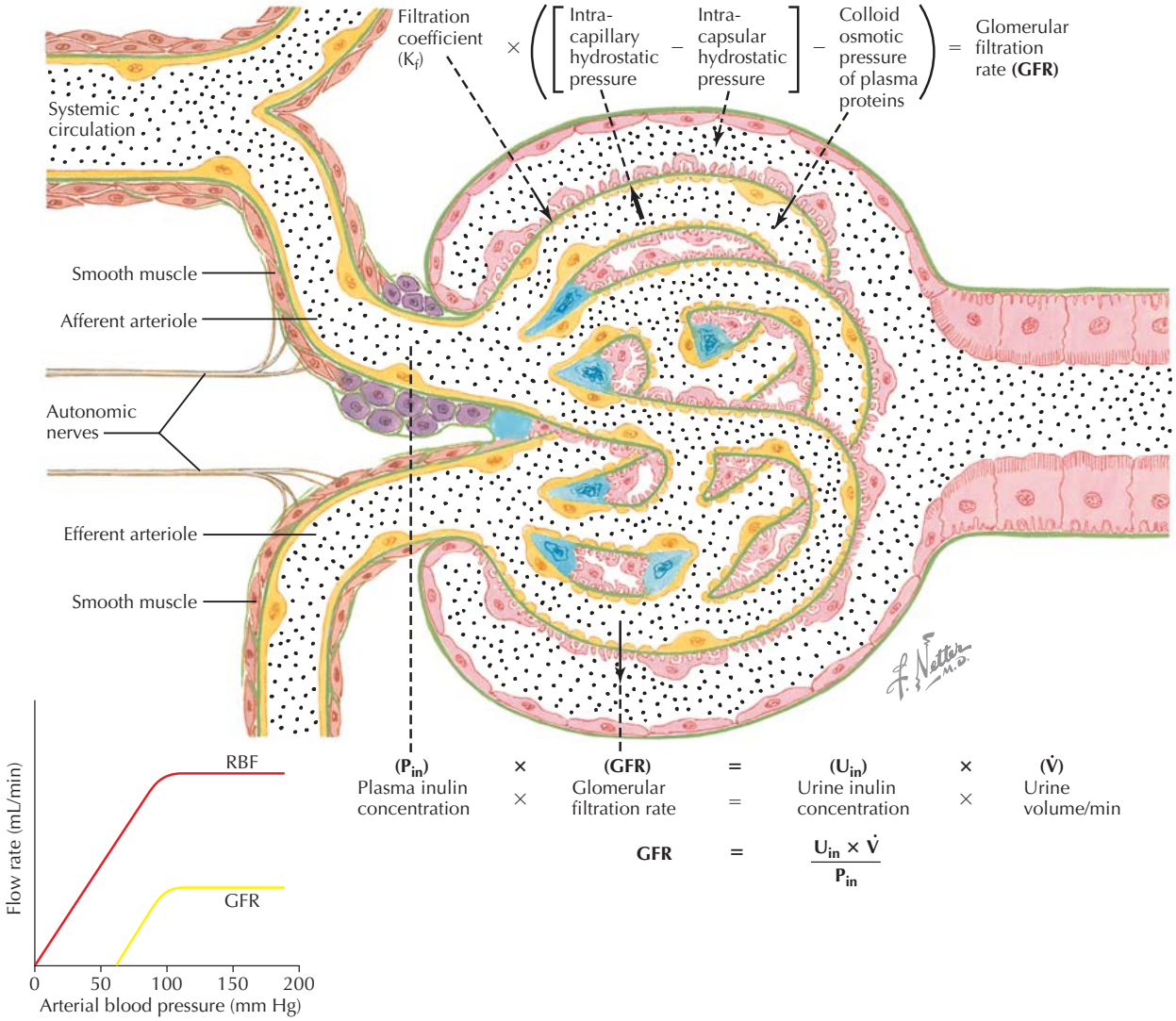


Figure 16.5 Glomerular Filtration Blood enters the glomerular capillaries from the afferent arterioles, and ~20% of the fluid is filtered into the nephrons (filtration fraction). The glomerular filtration rate (GFR) can be described on the basis of the forces governing filtration *(upper equation),* or from the clearance of inulin *(lower equation).* The graph illustrates that renal blood flow (RBF) and GFR remain fairly constant over a wide range of mean arterial blood pressures (MAP)—this occurs in part through autoregulation and tubuloglomerular feedback.

Bowman's space, so π_{BS} is not significant). Thus, assuming π_{BS} is zero,

$$\text{Net filtration pressure} = (HP_{GC} - HP_{BS}) - \pi_{GC}$$

The glomerular capillaries are different from other capillaries (which have significantly reduced pressures at the distal end of the capillary), because the efferent arteriole (at the other end of the glomerulus) can constrict and maintain pressure in the glomerular capillary. Thus, there is very little reduction in HP_{GC} through the capillary, and filtration can be maintained along its entire length. Afferent and efferent arteriolar resistance can be controlled by neural influences, circulating hormones (angiotensin II), myogenic regulation, and tubuloglomerular feedback signals, allowing control of glomerular filtration by both intrarenal and extrarenal mechanisms.

Glomerular Filtration Rate

Glomerular filtration rate (GFR) is considered the benchmark of renal function. GFR is the amount of plasma (without protein and cells) that is filtered across all of the glomeruli in the kidneys, per unit time. In a normal adult, GFR is ~100 to 125 mL/min, with men having higher GFR than women. Many factors contribute to the regulation of GFR, which can be maintained at a fairly constant rate, despite fluctuations in mean arterial blood pressure (MAP) from 80 to 180 mm Hg (Fig. 16.5).

GFR is determined by the net filtration pressure, as well as physical factors associated with the glomeruli, or *Kf* (hydraulic permeability and total surface area, which reflects nephron number and size). The equation is:

$$GFR = Kf\,[(HP_{GC} - HP_{BS}) - \pi_{GC}]$$

Maintaining normal GFR is critical for eliminating excess fluid and electrolytes from the blood and maintaining overall homeostasis. Significant alteration of any of the parameters in the equation above can affect GFR. For example, a hemorrhage that reduces MAP below 80 mm Hg may decrease HP_{GC} enough to dramatically decrease or stop filtration. Filtration can also be reduced if the HP_{BS} is increased (for example, during distal blockage by kidney stones), or if *Kf* is reduced (for example, in glomerulosclerosis).

In general, the nephrons are associated with filtration, reabsorption, secretion, and excretion:

- The **filtered load** (FLx) of a substance (the amount of a specific substance filtered per unit time) is equal to the plasma concentration of the substance (Px) times GFR:

$$FLx = Px \times GFR$$

- The **urinary excretion** (Ex) of a substance is the urine concentration of the substance (Ux) times the volume of urine produced per unit time ($\dot{V}$):

$$Ex = Ux \times \dot{V}$$

- Most substances are reabsorbed (to some extent); reabsorption rate of a substance (Rx) is equal to the filtered load (FLx) of the substance minus the urinary excretion of a substance (Ex):

$$Rx = FLx - Ex$$

- Select substances are actively secreted (e.g., creatinine, PAH, H^+, K^+). The secretion rate of a substance (Sx) is equivalent to the excretion rate minus the filtered load of the substance:

$$Sx = Ex - FLx$$

Renal handling of key substances will be discussed in Chapter 17.

RENAL CLEARANCE

Because GFR is a primary measure of the health of kidney function, GFR is routinely analyzed. This can be done in several ways. The physical factors and pressures can all be measured experimentally, but this is not practical in humans. Instead, the principle of **renal clearance** is utilized. Renal clearance is the *volume of plasma cleared of a substance per unit time*. The clearance equation incorporates the urine and plasma concentrations of the substance, and the urine flow rate and is usually reported in mL/min or L/day:

$$Cx = (Ux \times \dot{V})/Px$$

This equation can be used to easily determine the GFR: the clearance of a substance is equated to the GFR if the substance is freely filtered, but not reabsorbed or secreted. In this case, *the amount filtered will equal the amount excreted* [FLx = Ex], and thus:

$$\text{since } FLx = Px \times GFR \text{ and } Ex = Ux \times \dot{V}$$

$$\text{when } \mathbf{Flx = Ex}$$

then,

$$Px \times GFR = Ux \times \dot{V}$$

and, rearranging the equation,

$$GFR = (Ux \times \dot{V})/Px$$

Thus, for such a substance, GFR = Cx.

Although there is no endogenous substance that exactly meets these requirements (i.e., the substance is freely filtered, but not reabsorbed or secreted, and, therefore, FLx = Ex), the polyfructose molecule **inulin** does meet these criteria. It is not broken down in the blood, is freely filtered, and is not reabsorbed or secreted by the kidney. To measure inulin clearance (and thereby determine GFR), inulin is infused intravenously, and when a stable plasma level is achieved, timed urine



The RPF feeds the glomerular capillaries, but not all of the plasma presented to the capillaries is filtered. The filtration fraction (FF) is the proportion of the RPF that becomes glomerular filtrate:

$$FF = GFR/RPF$$

In the normal adult, FF = (125 mL/min ÷ 600 mL/min) × 100 = ~20%, so ~20% of the plasma entering the kidneys is filtered. At the individual nephrons, the unfiltered plasma exits the efferent arteriole to the peritubular capillaries.



If the clearance of inulin (C_{in}) is 100 mL/min, it means that 100 mL of plasma is completely cleared of inulin each minute. Contrast that to the clearance of glucose, which is 0 mL/min in a normal person, indicating that no plasma is cleared of glucose (and therefore there is no glucose in the urine). The renal clearance of any filtered substance can be calculated, and when the clearance is compared with the GFR, it gives a general idea of whether there was net reabsorption or net secretion of the substance—this is because the GFR is the total rate of filtration that is occurring at any given time.

- If the clearance of X is less than the GFR, there is net reabsorption.
- If the clearance of X is greater than the GFR, there is net secretion, because more was cleared from the plasma than can be accounted for by GFR alone.

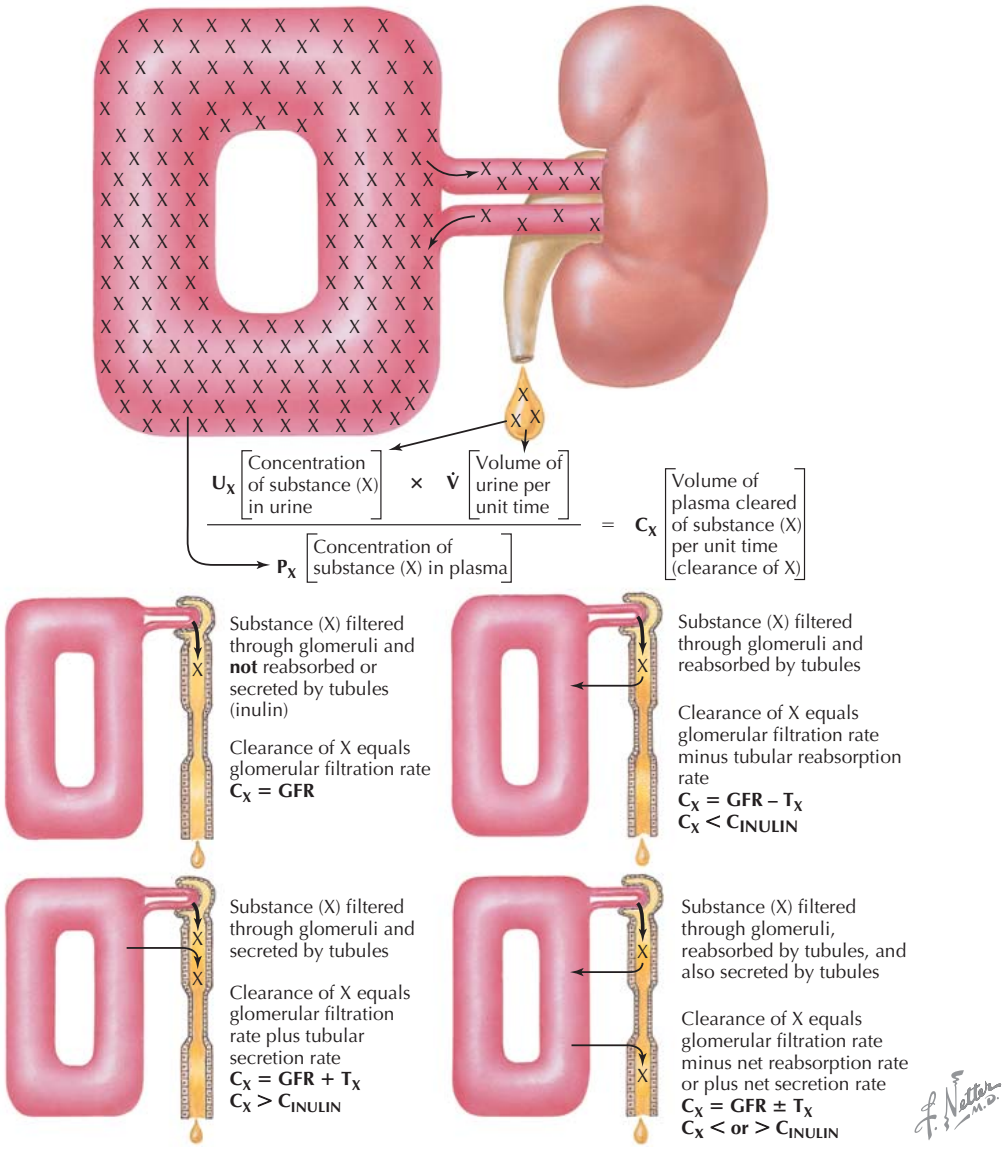


Figure 16.6 Renal Clearance Principle "Clearance" describes the volume of plasma that is cleared of a substance per unit time. The renal clearance of a substance provides information on how the kidney handles that substance. Since inulin is freely filtered, and not reabsorbed or secreted, all of the filtered inulin is excreted in the urine. Thus, C_{in} is equated with the glomerular filtration rate (GFR), and the net handling of other substances can be determined, depending on whether their clearance is greater than (net secretion), less than (net reabsorption), or equal to C_{in}.

Plasma creatinine is used clinically to estimate GFR. In most cases, the body produces creatinine at a constant rate, so the excretion rate is also constant. Since GFR is equated with the clearance of creatinine [$GFR = (U_{Cr} \times \dot{V}) \div P_{Cr}$], if creatinine excretion ($U_{Cr} \times \dot{V}$) is constant, the GFR is proportional to $1/P_{Cr}$. So, when the GFR decreases, less creatinine is filtered and excreted, and plasma creatinine builds up. As a clinical application, this allows a rapid approximation of the GFR by simply analyzing the P_{Cr}. P_{Cr} is normally ~1 mg%, so GFR is proportional to 1/1, or 100%. If P_{Cr} rises to 2, GFR is ½, or 50%, and so on.

collections are made. The calculated clearance of inulin can be equated to the GFR (see Fig. 16.5):

$$C_{inulin} = GFR$$

Infusing inulin to determine clearance is not routinely used because of the invasive nature of the procedure. Instead, the renal clearance of the *endogenous* substance **creatinine** is used to approximate GFR. Creatinine is a by-product of muscle metabolism and is freely filtered by the kidneys. It is not reabsorbed, but there is ~10% secretion into the renal tubules from the peritubular capillaries, and thus, creatinine clearance overestimates GFR by ~10% (Fig. 16.6).

REGULATION OF RENAL HEMODYNAMICS

Regulation of the GFR occurs by changes in blood flow to the glomeruli via intrinsic feedback systems, hormones, vasoactive substances, and renal sympathetic nerves.

Intrinsic systems include the myogenic mechanism and tubuloglomerular feedback (TGF). Utilizing the **myogenic mechanism,** the renal arteries and arterioles respond directly to increases in systemic blood pressure by constricting, thereby maintaining constant filtration pressure in the glomerular capillaries. **Tubuloglomerular feedback (TGF)** is a regulatory mechanism that involves the macula densa of the juxtaglomerular apparatus. The kidney is unique in that the glomerular capillaries have arterioles (resistance vessels) on *either end* of the capillary network. Constriction of the afferent or efferent arterioles can elicit immediate effects on the HP_{GC}, controlling GFR. Because the juxtaglomerular apparatus functionally associates the distal tubule to the afferent arteriole, the tubular flow past the macula densa can control afferent arteriolar resistance (see Fig. 16.3). Decreases in flow and tubular fluid sodium concentration in the distal tubule will decrease afferent arteriolar resistance and increase GFR in that nephron; conversely, if distal tubular flow or osmolarity is high, TGF will increase afferent arteriolar resistance, decreasing GFR. These systems allow minute-to-minute regulation of GFR over a wide range of systemic blood pressures (MAP 80 to 180 mm Hg).

Many substances (including nitric oxide and endothelin) regulate renal hemodynamics, but this section will focus on the renin-angiotensin-aldosterone system (RAAS), atrial natriuretic peptide (ANP), sympathetic nerves/catecholamines, and intrarenal prostaglandins. Although angiotensin II and the sympathetic nervous system are activated to preserve systemic blood pressure, the kidneys will respond to excessive constriction by intrarenal autoregulation, preserving blood flow to the glomeruli. This balance between extrarenal and intrarenal control is necessary to maintain proper GFR.

Control of renal hemodynamics occurs through the following neurohumoral and paracrine mechanisms:

- The **renin-angiotensin-aldosterone system (RAAS)** is activated in response to low renal vascular flow. Renal vascular baroreceptors stimulate **renin** secretion by the juxtaglomerular cells at the ends of the afferent arterioles. This, in addition to the modulation of renin secretion by the macula densa, will activate the RAAS (see detailed description in Chapter 19). The renin will act locally and through the systemic circulation to produce angiotensin II, and thus control GFR.
- **Angiotensin II** exerts both direct and indirect effects on the GFR. It is a vasoconstrictor, and in the kidneys, it acts directly on the renal arteries, and to a greater extent at the afferent and efferent *arterioles,* increasing resistance, reducing HP_{GC}, and decreasing GFR; angiotensin II actually has greater effect on the efferent arteriole than afferent arteriole. At the same time, it can constrict *glomerular* mesangial cells, reducing Kf, and thus, GFR.
- **Atrial natriuretic peptide (ANP)** is released from the right cardiac atrial myocytes in response to stretch (at high blood volume). To regulate GFR, ANP dilates the afferent arteriole, and constricts the efferent arteriole, increasing HP_{gc}, and thus, GFR. The enhanced flow increases sodium and water excretion, reducing blood volume.
- **Sympathetic nerves** and **catecholamine secretion** (NE and Epi) are stimulated in response to reductions in systemic blood pressure and cause vasoconstriction of the renal arteries and arterioles. At tonic levels of sympathetic nerve activity, the intrarenal systems will counteract this effect, to ensure the kidney vasculature remains dilated, preserving GFR. During high sympathetic nerve activity (hemorrhage, strenuous exercise), sympathetic nerve activity overrides the intrarenal regulatory mechanisms and reduces renal blood flow and GFR.
- **Intrarenal prostaglandins** (PGE_2 and prostacyclin [PGI_2]) are vasodilators and serve to counteract primarily angiotensin II–mediated vasoconstriction, acting at the level of the arterioles and glomerular mesangial cells. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin will block prostaglandin synthesis and restrict the compensatory renal vasodilation.



With blood loss from hemorrhage, the sympathetic nervous system (SNS) and hormone systems (RAAS, antidiuretic hormone [ADH], aldosterone) are activated to preserve systemic blood pressure, and prevent fluid loss. If MAP falls below 80 mm Hg, the high level of vasoconstriction will overwhelm the intrarenal regulation of GFR, and GFR will drop. This can result in acute renal failure (GFR < 25 mL/min) if blood volume is not restored quickly.

CLINICAL CORRELATE
Analysis of Renal Function

This correlate will focus on the variety of calculations associated with renal function and give examples of their solution.

A constant amount of inulin (in isotonic saline) was infused intravenously to a healthy 25-year-old male. After 3 hours, the man emptied his bladder completely, and then urine was collected after another 2 hours. A blood sample was obtained at the time of urine collection. Blood and urine were analyzed, with results shown below. Analyses of several parameters of renal function were performed.

	Urine	Plasma
Inulin concentration	1000 mg%	20 mg%
Creatinine concentration	1375 mg%	25 mg%
PAH concentration	300 mg%	1 mg%
Sodium concentration	2.5 mEq/L	140 mEq/L

Urine volume (UV) = 240 mL
Urine collection time = 2 hours
Hematocrit (HCT) = 0.42

The following parameters can be calculated:

Urinary flow rate ($\dot{V}$), the rate at which urine is produced. Urine flow is dependent on general fluid homeostasis and fluid intake. Under normal circumstances, if fluid intake is increased, urine flow will increase. If a person ingests ~3 L of fluid in food and drink, the urinary losses will be slightly less, with the balance made up by insensible losses (breathing, sweating).

$\dot{V}$ = urine volume/time
= 240 mL/120 min
= 2 mL/min

Glomerular filtration rate (GFR), the volume of plasma filtered by the glomeruli per unit time. Normal GFR in an adult is ~100 mL/min, or ~144 L/day. The GFR in men is typically higher than in women.

GFR is determined by inulin clearance:

$C_{in} = (U_{in} \times \dot{V})/P_{in}$
= (1000 mg% × 2 mL/min)/20 mg%
= 100 mL/min

GFR can also be determined by creatinine clearance, which overestimates GFR by ~10% because of creatinine secretion:

$C_{cr} = (U_{cr} \times \dot{V})/P_{cr}$
= (1375 mg% × 2 mL/min)/25 mg%
= 110 mL/min

Effective renal plasma flow (eRPF), the fraction of the renal plasma flow entering the glomeruli and available for filtration. *eRPF is equated with the clearance of PAH:*

eRPF = C_{PAH}
= (300 mg% × 2 mL/min)/1 mg%
= 600 mL/min

Effective renal blood flow (eRBF), the fraction of renal blood flow entering the glomeruli. It is usually ~20% of cardiac output.

eRBF = (eRPF)/(1 − HCT)
= 600 mL/min/(1 − 0.42)
= 1034 mL/min, or 1.034 L/min

Filtration fraction (FF), the fraction of the renal plasma flow that is filtered per unit time.

FF = GFR/RPF
= (100 mL/min)/(600 mL/min)
= 0.17, or 17% of the RPF entering the kidney was filtered per minute

Filtered load of sodium (FL_{Na}), the amount of plasma sodium that is filtered per unit time.

FL_{Na} = Plasma Na × GFR
= 140 mEq/L × 100 mL/min
= 14 mEq/min

Urinary excretion of sodium (UV_{Na} or E_{Na})

$U\dot{V}_{Na}$ = Urine concentration of Na × $\dot{V}$
= 2.5 mEq/L × 2 mL/min
= 0.005 mEq/min

Reabsorbed sodium (R_{Na})

$R_{Na} = FL_{Na} - U\dot{V}_{Na}$
= 14 mEq/min − 0.005 mEq/min
= 13.095 mEq/min

Fractional excretion of sodium (FE_{Na}), the fraction of filtered sodium that is excreted. Usually 99+% of filtered sodium is reabsorbed, so less than 1% of the amount filtered is excreted.

$FE_{Na} = [(U/P)_{Na}/(U/P)_{in}] \times 100$
= [(2.5/140)/(1000/20)] × 100
= 0.035%

Fractional reabsorption of sodium (FR_{Na}), the fraction of filtered sodium that is reabsorbed back into the capillaries.

$FR_{Na} = [1 - (E_{Na}/FL_{Na})] \times 100$
= [1 − (0.005/14)] × 100
= 99.97%

CHAPTER 17 Renal Transport Processes

GENERAL OVERVIEW OF RENAL TRANSPORT

When the plasma filtered into Bowman's space enters the proximal tubule, the process of reabsorption begins. In general, nephrons reabsorb the majority of the fluid and solutes that pass though them, with the proximal tubule having the greatest reabsorptive function, and the distal sites fine-tuning the process. In addition, there is secretion of select substances from the peritubular capillaries into different segments of the renal tubule.

The proximal tubule (PT) is the site of bulk reabsorption of fluid and nutrients. The proximal tubule is composed of three segments, S1, S2, and S3, which differ in the depth of the brush border and amount of mitochondria in the PT cells. This allows for a high capacity for reabsorption. From S1 to S3 segments, the brush border becomes progressively deeper and the high concentration of cellular mitochondria observed in the S1 segment decreases. The high number of mitochondria in the S1 is consistent with a high rate of active transport in that segment. As the filtrate is reabsorbed, and less is present in the tubule in subsequent segments, the deeper brush border increases surface area, which enhances continued reabsorption.

SODIUM-DRIVEN SOLUTE TRANSPORT

Sodium, Chloride, and Water

Sodium is the major extracellular cation, and regulation of its levels is necessary for maintenance of general fluid and electrolyte homeostasis (Chapter 1). As seen with the intestinal absorption of essential nutrients (see Section 6), sodium is also a major driving force for the renal reabsorption of fluid, electrolytes, and a variety of nutrients. As sodium transporters carry sodium and other solutes, they generate the driving force for water reabsorption. When the water leaves the tubule, the concentration of additional electrolytes and solutes in the tubular fluid increases, providing gradients for their diffusion into the cell.



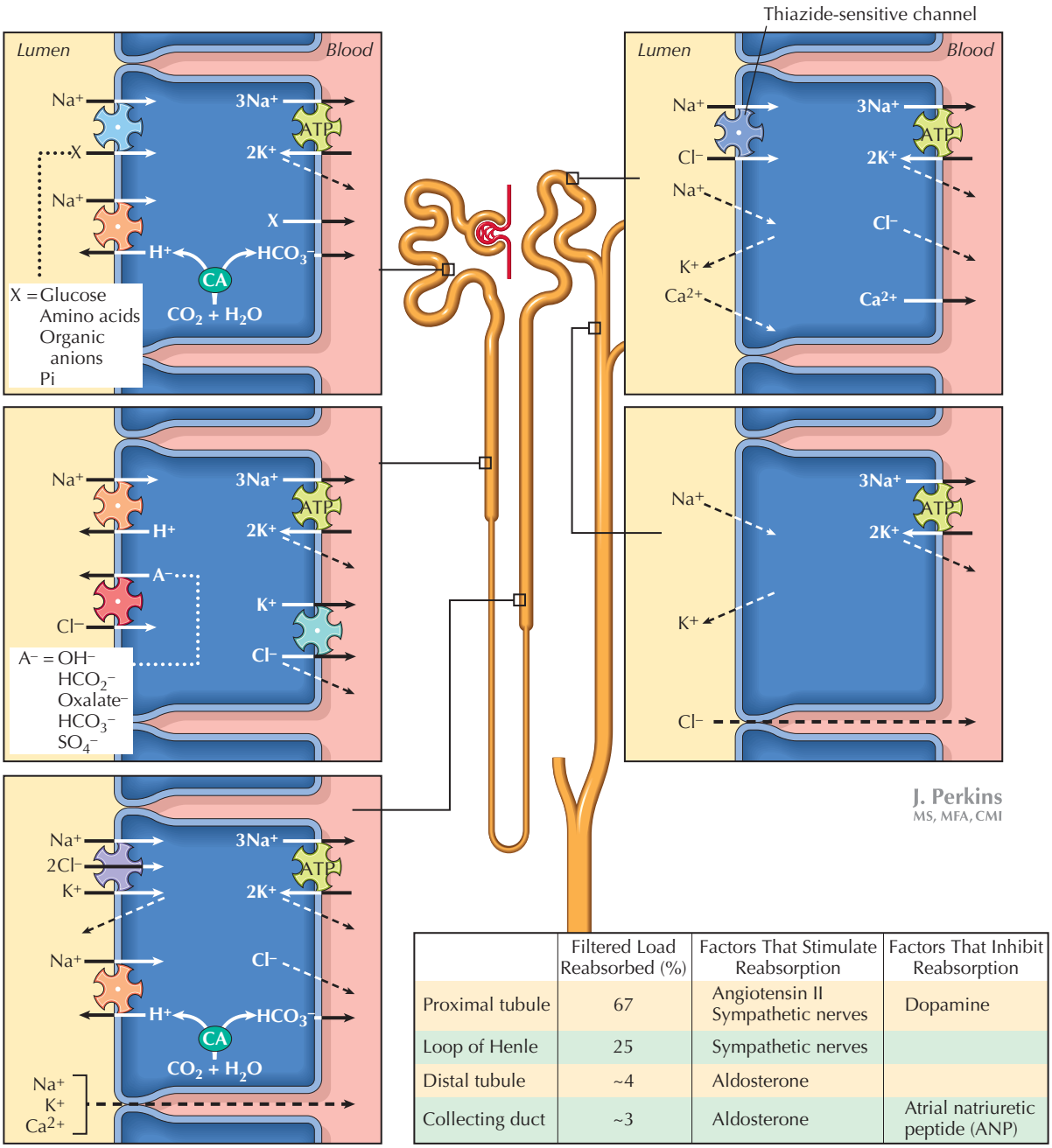
In general, of the total filtrate coming into the nephrons, the proximal tubule reabsorbs:

- 65% to 70% of the Na^+ and H_2O
- 80% to 85% of the K^+
- 65% of the Cl^-
- 75% to 80% of the phosphate
- 100% of the glucose
- 100% of the amino acids

Following this bulk reabsorption, "fine-tuning" of reabsorption occurs in subsequent segments of the nephron.

Approximately 65% to 70% of the water in tubular fluid is reabsorbed from the proximal tubule back into the peritubular capillaries, primarily following sodium reabsorption. The filtered load (FL) of sodium through the glomeruli is high (~25,000 mEq/day), and to maintain body fluid homeostasis, greater than 99% of the FL_{Na} must be reabsorbed back into the blood. This is accomplished by apical secondary active transport of sodium down a concentration gradient established by the basolateral **Na^+/K^+ ATPase** pumps. Figure 17.1 illustrates the primary sites and transporters for sodium reabsorption along different segments of the nephron.

- *Proximal convoluted tubule (S1 and S2 segments):* Bulk flow occurs by secondary active sodium cotransport with several substances including **glucose, amino acids, phosphate, and organic acids.** The proximal tubule also has **Na^+/H^+ antiporters,** which allow H^+ secretion into the proximal renal tubular fluid.
- *Proximal straight tubule (S3 segment):* **Na^+/H^+ antiporters** continue to reabsorb sodium and secrete H^+ into the tubular fluid. The reabsorption of sodium and fluid also provides the electrochemical gradient that facilitates **chloride** reabsorption. Cl^- concentration increases along the proximal tubule segments as water is reabsorbed. Chloride enters the cells in the S3 segment down its electrochemical gradient through antiporters, resulting in apical secretion of anions such as OH^-, HCO_3^-, SO_4^-, and oxalate. Cl^- reabsorption also occurs paracellularly, or between the cells. (The whole PT reabsorbs ~65% to 70% of FL_{Na}.)
- *Thin descending limb of Henle (tDLH):* This segment is impermeable to sodium and most other solutes but is permeable to water in the presence of antidiuretic hormone (ADH), and thus *concentrates* the tubular fluid (more on this in Chapter 18).



	Filtered Load Reabsorbed (%)	Factors That Stimulate Reabsorption	Factors That Inhibit Reabsorption
Proximal tubule	67	Angiotensin II Sympathetic nerves	Dopamine
Loop of Henle	25	Sympathetic nerves	
Distal tubule	~4	Aldosterone	
Collecting duct	~3	Aldosterone	Atrial natriuretic peptide (ANP)

Figure 17.1 Nephron Sites of Sodium Reabsorption Sodium reabsorption is critical for proper fluid and electrolyte homeostasis. More than 99% of the filtered load is reabsorbed through a variety of transport mechanisms. The gradient for sodium transport into the cells is maintained by basolateral Na^+/K^+ ATPase pumps.

- *Thick ascending limb of Henle (TALH):* This segment is impermeable to water, but specialized apical **Na^+-K^+-$2Cl^-$ cotransporters** facilitate reabsorption of electrolytes and *dilution* of the tubular fluid entering the distal tubule. These transporters are the targets for **loop diuretics** such as **furosemide** and **bumetanide.** In addition, there is a backleak of K^+ out of the cells into the lumen, creating a lumen-positive transepithelial potential difference (compared with interstitial fluid). This allows paracellular movement of cations (Ca^{2+}, Mg^{2+}, Na^+, K^+) out of the tubular lumen. In addition to the Na^+-K^+-$2Cl^-$ cotransporter, there are also **Na^+/H^+ antiporters,** which reabsorb Na^+ and secrete H^+ into the tubule. (TALH reabsorbs ~20% to 25% of FL_{Na}.)
- *Distal tubule (DT):* The early DT has **Na^+-Cl^- cotransporters** that can be inhibited by **thiazide diuretics.** The late DT has Na^+ (and K^+) channels that are increased by the hormone **aldosterone,** resulting in greater Na^+ and

water reabsorption. This aldosterone-sensitive epithelial sodium channel (ENaC) is blocked by amiloride, which is a potassium-sparing diuretic (discussed later). Aldosterone also responds to elevated plasma K^+, and increases distal and collecting tubule secretion of K^+. (DT reabsorbs ~4% of FL_{Na}.)

- *Collecting tubule:* Like the late DT, the collecting tubule has Na^+ (and K^+) channels that are increased by aldosterone. (CT reabsorbs ~3% of FL_{Na}.)

Glucose Transport

Because of the large FL_{Na}, the reabsorption of sodium is not a rate-limiting step in the reabsorption of other solutes. For many solutes, the rate-limiting step is the number of specific transporters available for the solute. Glucose is a good example of this concept. The sodium-glucose carriers have a high **transport maximum (TM),** and under normal conditions, the filtered load of glucose is low enough that the transporters can carry all of the solute back into the blood, leaving none in the tubular fluid and urine (Fig. 17.2). Thus, the renal clearance of glucose is normally zero.

However, if the FL of glucose is high, there may be too much glucose present in the tubular fluid and the carriers can become saturated. The renal threshold describes the point where the first nephrons exceed their TM, resulting in glucose in the urine (**glucosuria**). When the plasma glucose concentration (and hence the filtered load of glucose) is under the renal threshold for reabsorption, all of the glucose in tubular fluid will be reabsorbed (see Fig. 17.2). However, when it exceeds the threshold, the transporters are saturated (TM exceeded) and glucose appears in the urine.



The plasma concentration at which the renal threshold for glucose reabsorption is exceeded (and glucosuria is observed) is ~250 mg%. However, the calculated plasma threshold is 300 mg%. This difference between real and calculated values is explained by nephron heterogeneity (also called splay), whereby different nephron populations have higher and lower TMs for glucose. The average TM (for both kidneys) is the basis for the calculation of the threshold for plasma glucose levels (at which glucosuria occurs), despite the fact that some nephrons have a lower TM that will be exceeded when plasma glucose is over ~250 mg%.

This concept is important in diabetes mellitus, in which the inability to efficiently transport glucose into tissues leads to high plasma glucose concentrations. The fasting plasma glucose is much higher than normal in diabetes (greater than 130 mg% compared to 80 to 90 mg%), resulting in increased FL of glucose. With feeding, the plasma levels can easily exceed the TM of some nephrons, causing glucosuria. In addition, because glucose is an osmotic agent, the glucosuria will be associated with diuresis (loss of water through increased urine volume).

BICARBONATE HANDLING

Plasma **bicarbonate** is necessary for acid–base homeostasis. At normal whole body pH balance, 100% of the filtered bicarbonate (HCO_3^-) is effectively reabsorbed. However, this occurs *indirectly* through a process involving H^+ secretion (through cation exchange and active H^+ pumps). In the tubular lumen, filtered HCO_3^- and secreted H^+ form CO_2 and H_2O (a reaction catalyzed by brush border carbonic anhydrase, CA), which diffuse into the cell (Fig. 17.3). Once in the cell, the CO_2 and H_2O are converted back to carbonic acid (by intracellular CA); HCO_3^- is transported out of the cell via basolateral HCO_3^-/Cl^- exchangers or Na^+-HCO_3^- cotransporters, depending on the nephron segment. The H^+ generated from this process is secreted back into the tubular lumen and can be used to reabsorb more HCO_3^-, or can be buffered and excreted (see Chapter 20). This mechanism is present in three segments of the nephron, facilitating reabsorption of filtered bicarbonate in the PT (80% of filtered load), TALH (15%), and CD (5%).

Under normal conditions, the renal clearance of HCO_3^- is 0, meaning there is none in the urine. The regulation of bicarbonate handling is an integral part of acid–base homeostasis and will be discussed in Chapter 20.

POTASSIUM HANDLING

As with all of the major electrolytes, potassium balance is important to overall homeostasis, and dietary intake must be matched by urinary and fecal excretion. Plasma K^+ concentration must be maintained at relatively low levels (3 to 5 mEq/L) and is regulated by the kidneys. Potassium is pumped into cells (via Na^+/K^+ ATPase, which is stimulated by insulin and epinephrine), and the excess in the extracellular fluid (ECF) is excreted in urine. Figure 17.4 illustrates potassium handling through the nephron and the effects of dietary K^+ intake.

Potassium handling varies along the nephron:

- *Proximal tubule:* Potassium reabsorption occurs by **paracellular movement,** not by entry into the cells. Reabsorption initially occurs via **solvent drag,** initiated by water reabsorption. In the S2 and S3 segments, the positive potential of the tubular lumen allows (paracellular) potassium reabsorption by **diffusion** down the electrochemical gradient (this accounts for ~70% reabsorption of filtered potassium).
- *Thick ascending limb of Henle:* The Na^+-K^+-$2Cl^-$ cotransporters in the TALH use the sodium and chloride gradients to facilitate transport of K^+ (~20% of filtered potassium).
- *Late distal tubules:* Potassium can be secreted into the DTs via aldosterone-sensitive K^+ channels.
- *Collecting ducts:* Potassium is *secreted* into the collecting ducts through aldosterone-sensitive apical K^+ channels

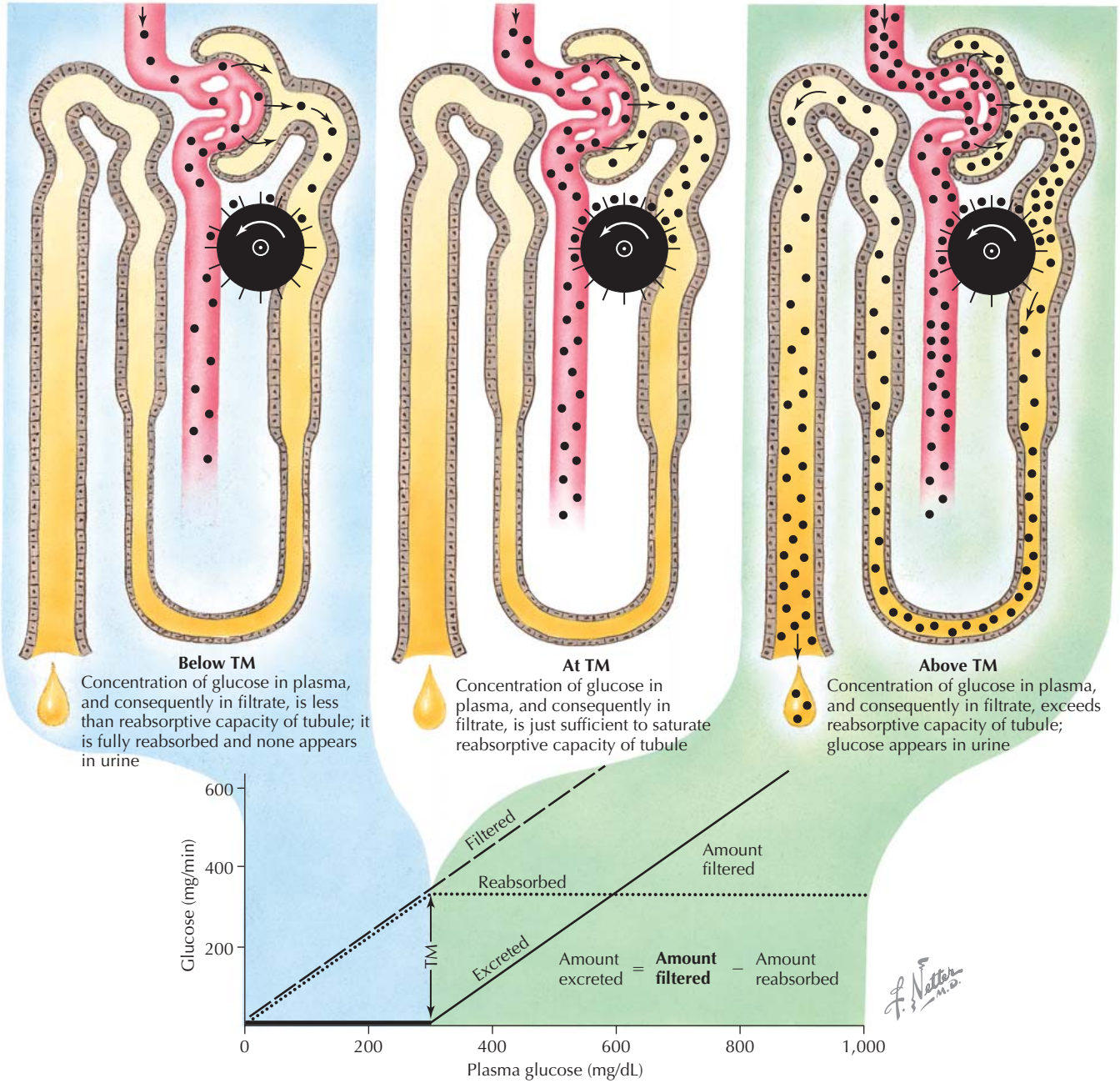


Figure 17.2 Renal Handling of Glucose Glucose is freely filtered at the glomerulus and is 100% reabsorbed in the proximal tubules by sodium-glucose cotransporters. However, if blood glucose levels become elevated, as in diabetes, the maximal tubular reabsorption rate (TM) is exceeded, and glucose appears in the urine *(far right panel)*.

in principal cells. K^+ is also secreted into the collecting ducts by α-intercalated cells, in exchange for H^+. Under normal conditions there is a net secretion of K^+. Net reabsorption can occur during dietary K^+ depletion.

Renal potassium handling is influenced by the following:

- *Dietary potassium intake:* Increased intestinal K^+ absorption elevates plasma K^+ concentration. The

Loop diuretics, such as furosemide (Lasix) and bumetanide, inhibit the Na^+-K^+-$2Cl^-$ cotransporters, causing natriuresis/diuresis, which is beneficial in controlling hypertension. Extended use can cause urinary K^+ loss, and plasma K^+ must be monitored. Potassium-sparing diuretics, such as thiazides, target the distal tubule Na^+-Cl^- cotransporters and control potassium losses.

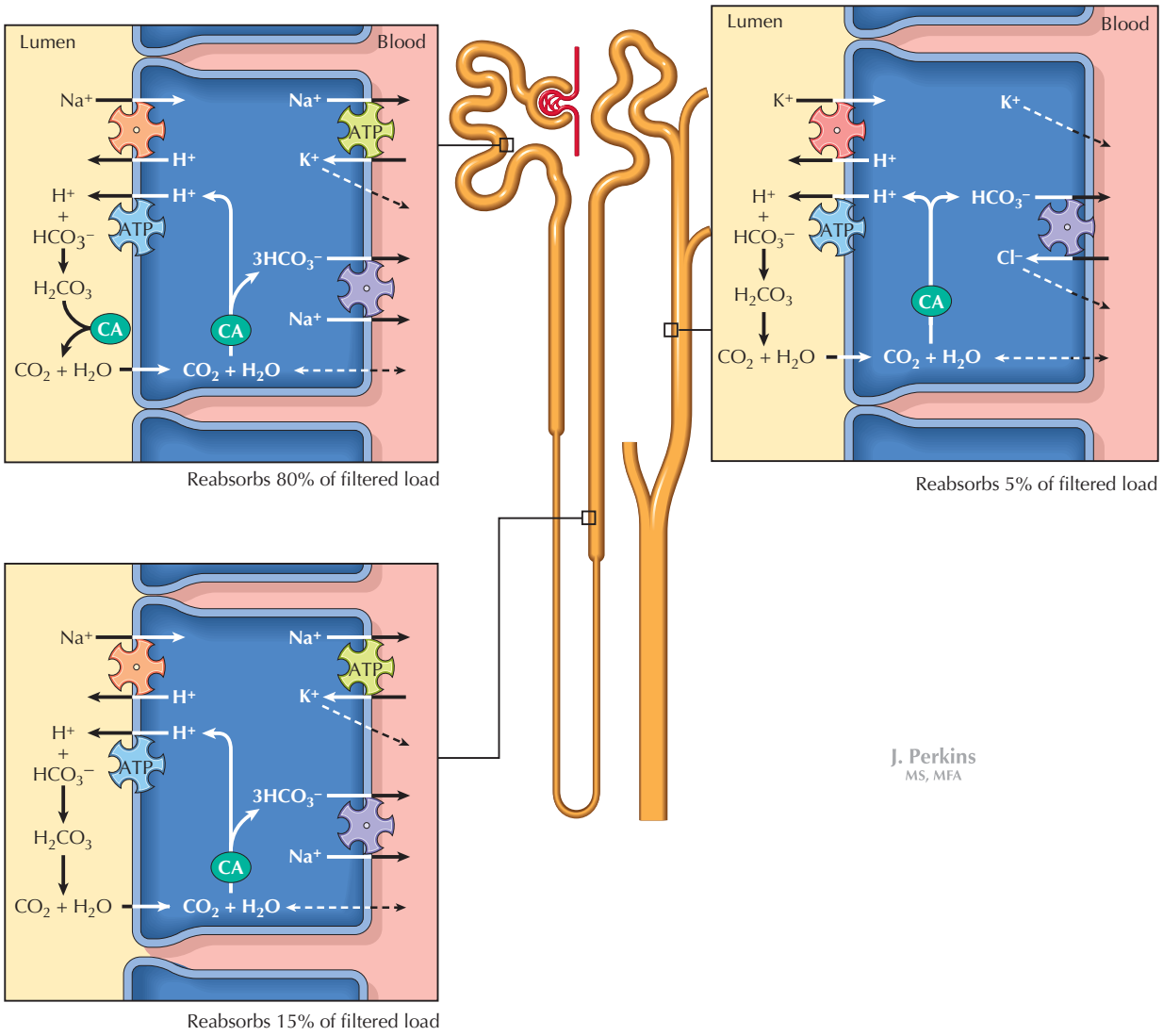


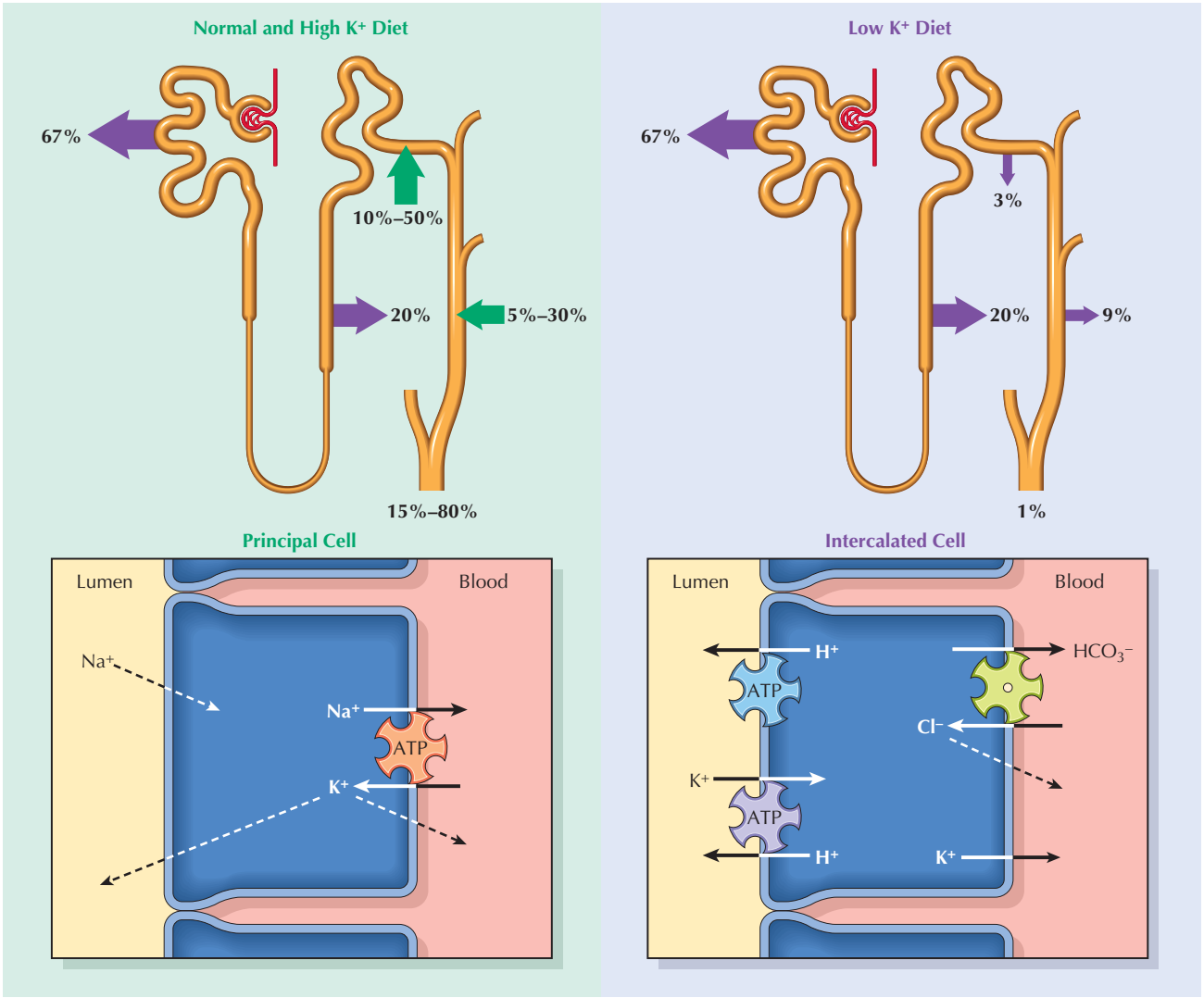
Figure 17.3 Renal HCO_3^- Reabsorption Bicarbonate is freely filtered at the glomerulus and is reabsorbed along the nephron through a process involving secretion of H^+. Under normal conditions, 100% of the filtered bicarbonate is reabsorbed.

mineralocorticoid aldosterone increases basolateral Na^+/K^+ ATPase activity, pumping more K^+ into the cells (see Chapter 19). K^+ is then secreted into the collecting ducts through apical channels in the principal cells. When dietary K^+ intake is low, K^+ secretion from the principal cells is inhibited, and K^+ reabsorption from the collecting duct α-intercalated cells predominates.

- *Plasma volume:* In addition to responding to increased plasma K^+ concentrations, aldosterone is also released in response to decreased plasma volume, as part of the renin-angiotensin-aldosterone system (RAAS). Aldosterone increases the Na^+/K^+ ATPase, Na^+/H^+ antiporters, and Na^+-Cl^- cotransporters in the late distal tubules and CDs, independent of plasma potassium levels. This increases K^+ secretion into the renal tubules, as stated earlier.
- *Acid–base status:* To compensate for acidosis, H^+ can be secreted into the collecting ducts from the principal cells while K^+ is reabsorbed. Conversely, during alkalosis, H^+ will be retained, and K^+ will be secreted from CD α-intercalated cells (see Chapter 20).
- *Tubular fluid flow rate:* When tubular fluid flow is high, the concentration gradient for K^+ (from collecting duct cell to the lumen) is high, and K^+ secretion will increase.

CALCIUM AND PHOSPHATE TRANSPORT

Calcium and phosphate are important during fetal and childhood development for bone and tissue growth, and continue to be important in the adult for bone health. The kidneys control plasma levels of calcium and phosphate by altering



Physiologic Factors That Stimulate K^+ Secretion	Physiologic Factors That Stimulate K^+ Reabsorption	Factors That Alter K^+ Secretion (Stimulate)	Factors That Alter K^+ Secretion (Inhibit)
Aldosterone Hyperkalemia	Low K^+ diet	Increased urine flow rate Acute and chronic alkalosis Chronic acidosis	Acute acidosis

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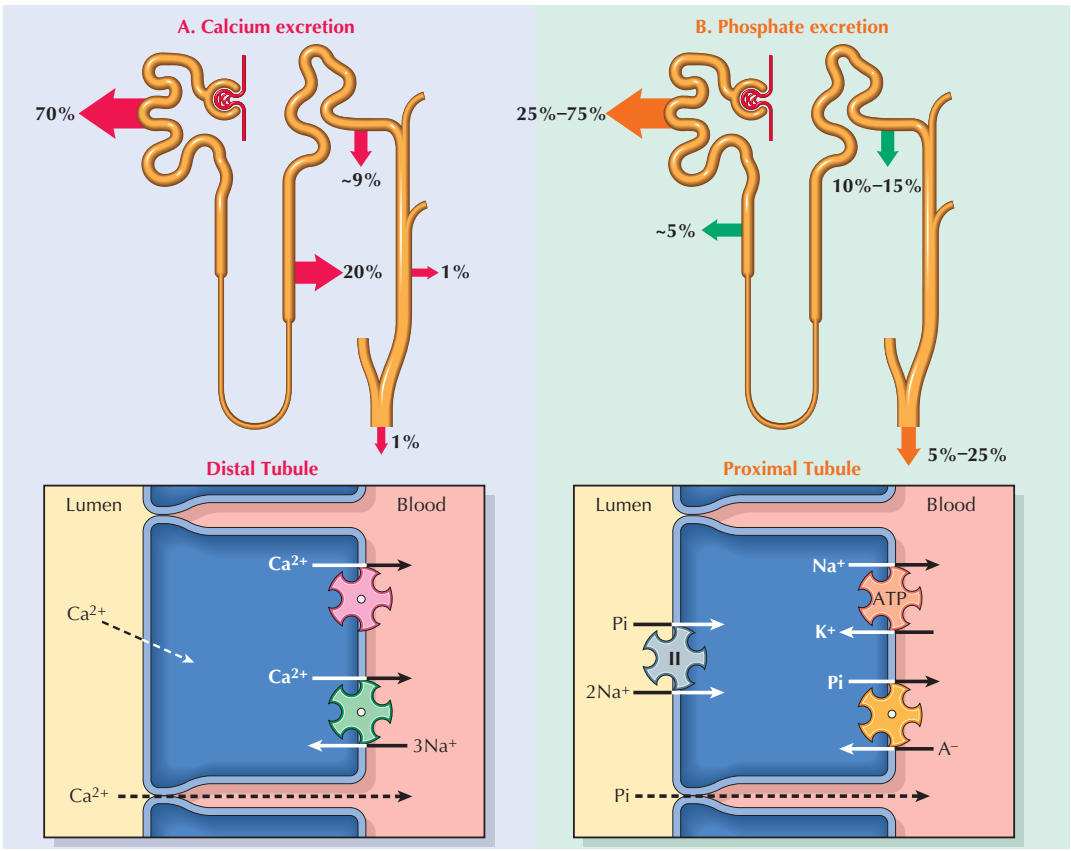
Figure 17.4 Renal Potassium Handling To maintain normal plasma K^+ concentration (3.5 to 5 mEq/L), the kidney must control K^+ excretion, and the amount of K^+ excreted changes with dietary intake. Diets low in K^+ stimulate avid K^+ reabsorption throughout the nephron, whereas diets high in K^+ stimulate distal K^+ secretion (in *green*).

their rate of reabsorption. Most of the calcium and phosphate in the body (99% and 85%, respectively) is found in bone matrix. Renal phosphate and calcium reabsorption are both regulated by PTH (see Chapter 30).

Calcium Handling

About 40% of plasma Ca^{2+} is bound to proteins, leaving 60% free for filtration at the glomeruli. The kidneys reabsorb ~99% of the filtered Ca^{2+} at sites throughout the nephron (Fig. 17.5*A*):

- *Proximal tubule:* Ca^{2+} reabsorption is paracellular, via solvent drag initiated by bulk reabsorption of Na^+ and water. This accounts for ~70% of Ca^{2+} reabsorption.
- *Thick ascending limb of Henle (TALH):* Reabsorption is paracellular, again in parallel with Na^+ reabsorption. In addition, the lumen-positive transepithelial potential



Modulation of Ca^{2+} Transport (Decreased Excretion)

Factor	Nephron Site	Mechanism
↑ PTH	DCT	Activate Ca^{2+} channels
↓ ECF	Proximal tubule	Solvent drag
↑ Pi intake	DCT	↑ PTH secretion

Modulation of Pi Transport (Increased Excretion)

Factor	Nephron Site	Mechanism
↑ PTH	Proximal tubule	↓ Apical symporter
↓ ECF	Proximal tubule	↑ Solvent drag/symporter
↑ Pi intake	Proximal tubule	↓ Apical symporter

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Figure 17.5 Renal Calcium and Phosphate Handling Calcium is reabsorbed along much of the nephron, and very little is excreted. Regulation of distal calcium reabsorption is by parathyroid hormone (PTH), which opens apical calcium channels. Under normal conditions, ~75% of the filtered load of phosphate is reabsorbed, with all of the reabsorption occurring in the proximal tubule via Na^+-Pi cotransporters. This is highly dependent on the dietary intake of phosphate as well as PTH levels. In response to PTH, proximal tubular reabsorption of phosphate is inhibited, and phosphate excretion increases. This also occurs with diets high in phosphate. Low-phosphate diets significantly increase Pi reabsorption, recruiting transporters in sites distal to the proximal convoluted tubule (in *green*), which can reduce phosphate excretion to 5% to 10%.

favors paracellular reabsorption of divalent cations in this segment (~20% of reabsorption). Because Ca^{2+} follows sodium reabsorption, changes in sodium reabsorption (such as with loop diuretics) will also reduce Ca^{2+} reabsorption.

- *Distal tubule:* Although this segment accounts for only ~8% to 9% of Ca^{2+} reabsorption, this is the site of hormonal control. Transport is transcellular and is facilitated by the high electrochemical gradient from the tubule into the cell. Once in the cell, transport into the interstitium is through active Ca^{2+} ATPase and Na^+/Ca^{2+} exchangers on the basolateral membrane (see Fig. 17.5*A*). The transporters in the distal tubule are under hormonal control by parathyroid hormone (PTH).

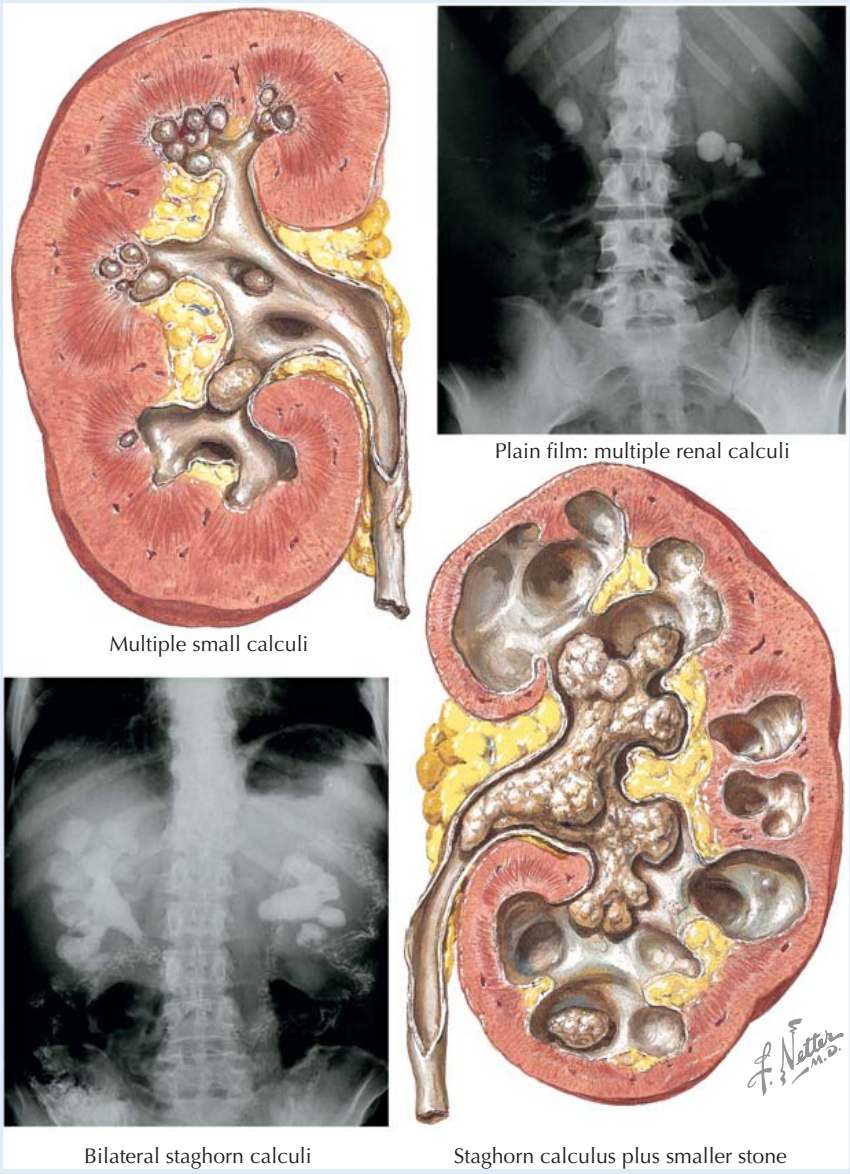
Renal handling of Ca^{2+} is regulated by the effects of PTH on calcium transporters. Low plasma Ca^{2+} directly stimulates PTH release from the parathyroid glands (see Chapter 30). PTH activates apical calcium channels and stimulates basolateral Ca^{2+} transporters in the distal tubule.

Phosphate Handling

Phosphates are required for bone matrix formation as well as for intracellular high-energy mechanisms (e.g., ATP

CLINICAL CORRELATE
Kidney Stones (Renal Calculi)

Kidney stones are solid aggregates of minerals that form in the kidney (nephrolithiasis) or ureters (urolithiasis). The size of stones is variable, and many small stones will pass through the ureters and urethra without problem. However, if stones grow large enough (2 to 3 mm), they can block the ureter and cause intense pain and vomiting. The most common stones are calcium oxalate, and it is the presence of oxalate (not the calcium) that drives mineral precipitation. Treatment depends on size of the stone and duration of the blockage. Typically, unless there are severe symptoms, small stones will be left to pass; however, long-term (more than 30 days) blockage can result in renal failure, and intervention with stent placement and laser or ultrasound may be performed.



Renal Calculi

formation and utilization). The majority of plasma phosphate (Pi) (more than 90%) is available for filtration, and Pi reabsorption and excretion are highly dependent on diet and age. As with glucose, Pi has a TM that can be saturated. Under normal dietary conditions, transporters are present only in the proximal tubules, and ~75% of the filtered phosphate is reabsorbed by apical Na^+-Pi cotransporters (see Fig. 17.5*B*). The remaining 25% of the Pi load is excreted; part of the Pi can be used to buffer H^+, forming titratable acids (see Chapter 20).

In growing children and with diets low in Pi, Na^+-Pi cotransporters are also present in the proximal straight tubules and distal tubules, facilitating reabsorption of up to 90% of the filtered Pi load.

Renal Pi reabsorption is primarily controlled by diet and parathyroid hormone (PTH), both of which affect the number of Na^+-Pi cotransporters in the apical membranes:

- *Diet:* High dietary Pi causes reduction in the number of Na^+-Pi cotransporters in the apical membrane, increasing Pi excretion. Conversely, low dietary Pi will increase transporters on the proximal tubule brush border, as well as in sites distal to the proximal tubule. This will allow avid Pi uptake and reduced urinary Pi excretion.
- *PTH:* PTH is secreted from the parathyroid glands in response to high plasma Pi concentrations or low plasma calcium concentrations. It decreases apical Na^+-Pi cotransporters, reducing reabsorption and increasing urinary excretion of Pi.

Plasma Ca^{2+} and phosphate regulation are intertwined because of the constant bone resorption and deposition. In response to low plasma Ca^{2+}, vitamin D increases intestinal calcium and phosphate absorption, and PTH induces bone resorption—both actions increase Ca^{2+} *and* phosphate in ECF. At the kidneys, PTH increases calcium reabsorption but compensates for the additional ECF phosphate by decreasing phosphate transporters and increasing urinary phosphate excretion. Thus, by this mechanism the kidneys regulate extracellular Ca^{2+} and phosphate concentrations.

CLINICAL CORRELATE
Hyponatremia

Hyponatremia is defined as the state of low plasma sodium (less than 135 mEq/L). This can be caused by several mechanisms that result in low sodium concentrations and reduced plasma osmolarity. During hyponatremia, fluid shifts *into* cells, reestablishing normal ECF osmolarity but causing cellular swelling. This can have important effects, especially on brain tissues which are confined to a bony space and are unable to tolerate swelling:

- Rapid fluid shifts into cells can be a critical problem, because acute cerebral swelling can lead to disoriented mental status, seizures, coma, and death. In these cases, reducing the ECF is necessary to draw the fluid out of cells. Water restriction and/or ADH (V1) antagonists are used to increase urinary free water excretion.
- If the hyponatremia is established over time (for example, in Addison's disease), brain tissues compensate for fluid shifts by decreasing intracellular content of osmolytes (organic solutes such as inositol and glutamine). This reduces the osmotic force that would draw fluid into the cells and allows the cells to maintain normal volume. Because of this, treatment of hyponatremia should involve slow restoration of salt and fluid balance to normal levels. Otherwise, the brain cells will shrink, inducing an acute, potentially critical, intracellular imbalance. Gradual correction of this type of hyponatremia will allow the osmolytes to increase in brain cells.

Exercise-associated hyponatremia (EAH) can occur as a result of fluid and electrolyte losses through sweat during long-term exercise (marathons, triathlons). Although most people do not experience a serious drop in ECF Na^+ concentration, the critical cases of EAH are most likely to occur from a combination of the following:

- An initial imbalance of fluid and electrolyte losses, due to overhydration during the exercise.
- Acute syndrome of inappropriate ADH secretion (SIADH) that can occur because of *large* fluid losses. Recall that both increased osmolarity and fluid losses can stimulate ADH, but that the system is more sensitive to changes in ECF osmolarity than to changes in fluid volume. However, if the volume loss continues and becomes severe, when a dehydrated athlete drinks too much hypotonic fluid, the increase in ADH will cause excessive free water reabsorption by the collecting ducts, rapidly decreasing the ECF sodium concentration. In this scenario, the need to compensate for the volume will override the sodium levels, ADH secretion will continue, and plasma Na^+ can fall to critically low levels (below 125 mEq/L).

Early symptoms include bloating, nausea, vomiting, and headaches, which can progress to disorientation, seizures, and death if not immediately treated. Hyponatremia can be prevented by restricting water intake (drinking only when thirsty). Although overhydration during the exercise is a direct cause of hyponatremia, risk factors for developing EAH include low body weight, female sex, and inexperience with marathons. ADH V2 receptor antagonists are used to treat severe hyponatremia.

Postsurgical acute hyponatremia frequently occurs in elderly patients. The stress of surgery can cause an acute SIADH, rapidly increasing free water reabsorption and reducing ECF Na^+ concentration. As stated earlier, treatment should begin immediately, with water restriction (to limit further fluid retention) and a V2 antagonist. Correcting the hyponatremia restores normal function.

Pseudohyponatremia occurs when there is an incorrect, low measurement of plasma sodium due to conditions that produce high lipid or proteins (e.g., hyperlipidemia, hyperproteinemia) in the blood. In this case, the substances reduce the total plasma fluid and although the amount of sodium is normal, the clinical measurement may be falsely low. Thus, the person is not hyponatremic and treatment will focus on reducing the lipids and/or proteins.

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CHAPTER 18 Urine Concentration and Dilution Mechanisms

THE LOOP OF HENLE AND COLLECTING DUCT CELLS

Ultimately, the regulation of plasma osmolarity and volume are the responsibility of the loop of Henle and collecting ducts (CDs) and the vasa recta. Changes in the permeability of the loop of Henle to solutes and water allow for the concentration and dilution of the tubular fluid, as well as the ability of the kidneys to regulate overall water and solute reabsorption. Reabsorption is facilitated by the vasa recta that surround the medullary tubules and collecting ducts.

The descending and ascending limbs of the loops of Henle have specific permeability characteristics:

- *Descending limbs of Henle's loop are concentrating segments:* permeable to water, impermeable to reabsorption of solutes (urea can be secreted into the tubule, further concentrating the tubular fluid).
- *Thick ascending limbs of Henle's loop are diluting segments:* impermeable to water, but Na^+-K^+-$2Cl^-$ transporters reabsorb electrolytes, thus diluting the tubular fluid.

With this mechanism in place, the tubular fluid entering the distal tubule has an osmolarity of ~100 mosm/L; the fine-tuning to concentrate urine will occur in the collecting ducts. There are **antidiuretic hormone (ADH)**–sensitive water channels in the collecting duct cells that allow solute-free water reabsorption and concentration of the hypo-osmotic tubular fluid. However, this concentration can only be achieved if an osmotic gradient exists from tubular lumen to the interstitial space.

URINE CONCENTRATING MECHANISM

The Medullary Interstitium

The ability to reabsorb solute-free water in both the descending limb of Henle and the collecting ducts is possible because of the osmolar concentration gradient within the medullary interstitial fluid and the presence of specific water channels in the collecting duct cells. Water can only move when there is an osmotic gradient; the factors contributing to the water movement are illustrated by the numbers in red in Figure 18.1. In this interstitial gradient, the osmolarity is ~300 mosm/L at the corticomedullary border and rises to ~1200 mosm/L in the deepest part of the medulla. With this gradient in place, if water channels are present, water from the tubules readily diffuses into the interstitium (with its higher osmolar concentration), and then into the vasa recta network.

Medullary Countercurrent Multiplier

The interstitial osmolar gradient from cortex to inner medulla is formed and maintained by the coordinated efforts of the ascending and descending limbs of Henle and their selective permeability to solutes. Important factors contributing to establishing and maintaining the gradient are the Na^+-K^+-$2Cl^-$ transporters in the *thick ascending limb of Henle* (TALH), water absorption in the descending limb of Henle, the constant flow of tubular fluid through the loops, and urea recycling (urea reabsorption from the collecting ducts and urea diffusion from the medullary interstitium into the thin limb of Henle). Creation of the gradient begins with the following:

- The *Na^+-K^+-$2Cl^-$ transporters in the TALH,* which transport solutes into the interstitium, increasing interstitial fluid osmolarity and decreasing tubular fluid osmolarity.
- This *increased interstitial osmolarity promotes free water reabsorption from the descending limb of Henle,* which increases tubular fluid osmolarity in the descending limb (concentrating limb).
- As *tubular fluid flows from the descending limb, the more concentrated tubular fluid flows into the TALH* and the solutes are transported into the interstitium through Na^+-K^+-$2Cl^-$ transporters, further increasing interstitial fluid osmolarity. The higher interstitial osmolarity facilitates more free water reabsorption from the descending limb, concentrating the tubular fluid. This cycle (movement of concentrated tubular fluid into the TALH, transport of solutes by the Na^+-K^+-$2Cl^-$ transporters into the interstitium, and water movement out of the descending limb of Henle) is repeated until the full interstitial gradient is established ("countercurrent multiplier" concept). The osmolar concentration in the

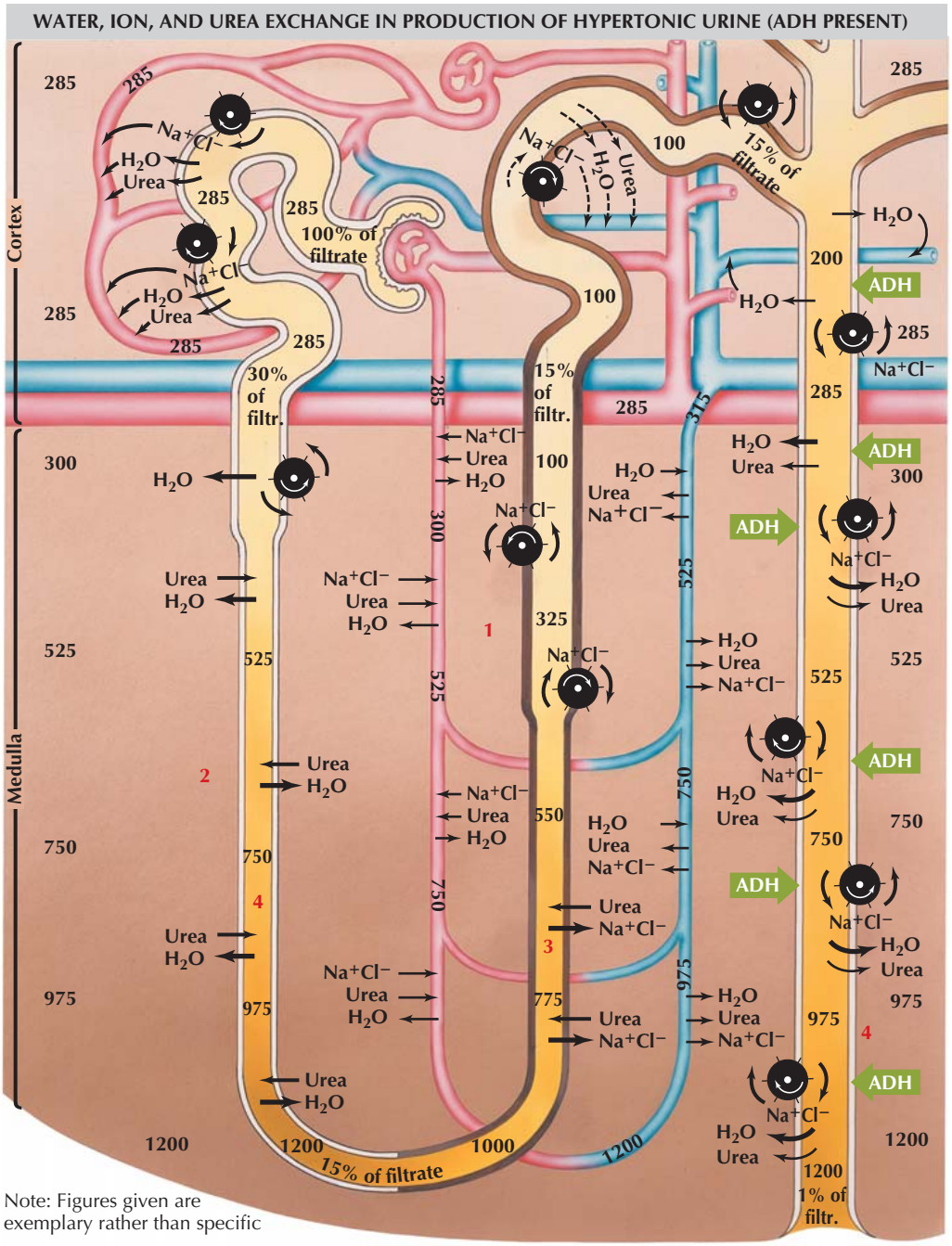


Figure 18.1 **Medullary Interstitial and Tubular Concentration Gradients** The concentration gradient is established by *(1)* transport of solutes, but not water, out of the thick ascending limb of Henle (TALH) via the Na^+-K^+-$2Cl^-$ transporters (diluting limb); *(2)* free water reabsorption from the descending limb of Henle, which increases the tubular fluid osmolarity in the descending limb (concentrating limb); *(3)* as more tubular fluid flows from the descending limb to the TALH, the more concentrated tubular fluid allows further transport of solutes into the interstitium; and *(4)* urea recycling contributes to the gradient, because it remains in the tubular fluid in the loop of Henle contributing to the tubular fluid osmolarity while water is reabsorbed from the descending limb, and when ADH is present, both water *and* urea reabsorption increases in the medullary collecting ducts (CDs), and the urea is recycled to the inner medulla.

interstitium deep in the medulla is dependent on the length of the loops of Henle (the longer the loops, the higher the concentrating ability). In humans, the highest interstitial concentration (deep in the inner medulla) is ~1200 mosm/L. This allows the concentration of tubular fluid to reach ~1200 mosm/L at the bottom of the loops of Henle (see Fig. 18.1).

- Finally, *urea recycling* contributes to developing and maintaining the interstitial osmolar gradient, because
  - it remains in the tubular fluid while water is reabsorbed from the descending limb, contributing to the tubular fluid osmolarity, and
  - ADH increases both water *and* urea reabsorption in the medullary (but not cortical) collecting ducts (CD); the urea is recycled into the inner medulla, contributing to the interstitial concentration gradient.



The ability to concentrate urine differs between species. Animals that live in desert environments (desert rodents, camels) have exceptionally long loops of Henle and have the ability to concentrate their urine to more than 2000 mosm/L, allowing tremendous fluid retention. The medullary interstitium of these animals appears to have additional osmotic agents (~20% extra "osmolytes" such as sorbitol and myo-inositol) to help accomplish this action.

Concentration of the Urine

As discussed in Chapter 1, to maintain plasma (and thus cellular) osmolarity, fluid volume must be controlled. Either a small increase in plasma osmolarity (~1%) or a significant decrease (a greater than 10% loss) in plasma volume (from, for example, hemorrhage or severe dehydration) will elicit release of antidiuretic hormone (ADH, also called vasopressin) from the posterior pituitary gland. This hormone binds to V2 receptors on principal cells of the renal collecting ducts (Fig. 18.2). The ADH increases apical water channels, or **aquaporins** (in the principal cells, AQP-2), which allow only water to be reabsorbed, effectively concentrating solutes in the tubular fluid, which at this point is considered urine.

The urine-concentrating mechanism depends on the plasma level of ADH and the osmolar concentration of the interstitial fluid surrounding the collecting ducts. Plasma ADH is tightly regulated, and water channels are continually being inserted and removed from the apical membranes of the CD cells, to maintain extracellular fluid balance through the regulated retention and excretion of water in the urine. The ability of the ADH to effectively promote water reabsorption is dependent on the medullary concentration gradient. ADH-dependent urea recycling plays an important role in the ability to concentrate urine, because the additional urea added to the interstitium when ADH is elevated helps maintain the interstitial gradient for water reabsorption. Therefore, dehydration → higher plasma osmolarity → higher ADH levels → increased AQP and water reabsorption → more concentrated urine. Under extreme conditions, the urine can be concentrated maximally to 1200 mosm/L, with minimal urinary water loss.

DILUTION OF URINE

When there is excess extracellular fluid, plasma osmolarity is reduced and pituitary ADH release is inhibited. This affects water reabsorption in both the descending limb of Henle and the CDs. If less water is absorbed out of the tubular fluid in the descending limb, the tubular fluid cannot be concentrated to as high a level, and there is increased tubular fluid flow to the TALH, which reduces the amount of solutes that can be transported into the interstitium. This effectively disrupts the interstitial gradient, as illustrated in Figure 18.3. This decrease in ADH results in fewer water channels in the CDs, and less medullary water and urea reabsorption, producing diuresis (increased production of hypotonic urine). When the excess fluid is excreted, the plasma osmolarity will increase, stimulating ADH, and the interstitial concentration gradient will be reestablished over several hours.

FREE WATER CLEARANCE

Increased urine output in response to expansion of plasma volume entails both sodium excretion (natriuresis) and water excretion (diuresis). The ability to excrete hypotonic urine is as important to fluid homeostasis as the ability to excrete concentrated urine, and impairment of this mechanism can be life-threatening (see exercise-induced hyponatremia). The concept of free water clearance is useful in quantifying water excretion during diuresis; it is defined as water excretion in excess of the water required for iso-osmotic excretion of the solutes present in the urine. Free water clearance is



Micturition is the process of emptying the bladder (urination). Micturition is under voluntary control, because the external sphincter of the bladder is skeletal muscle. However, the micturition reflex system is under both sympathetic and parasympathetic control. While the bladder is filling, the sympathetic nerves relax the smooth muscle of the bladder wall, accommodating the urine, and contract the internal urethral sphincter smooth muscle. When the bladder becomes "full," mechanoreceptors signal a spinal reflex arc that stimulates parasympathetic contraction of the bladder (detrusor muscle) and relaxation of internal sphincters. The external urethral sphincter is skeletal muscle, and is voluntarily relaxed, allowing urination.

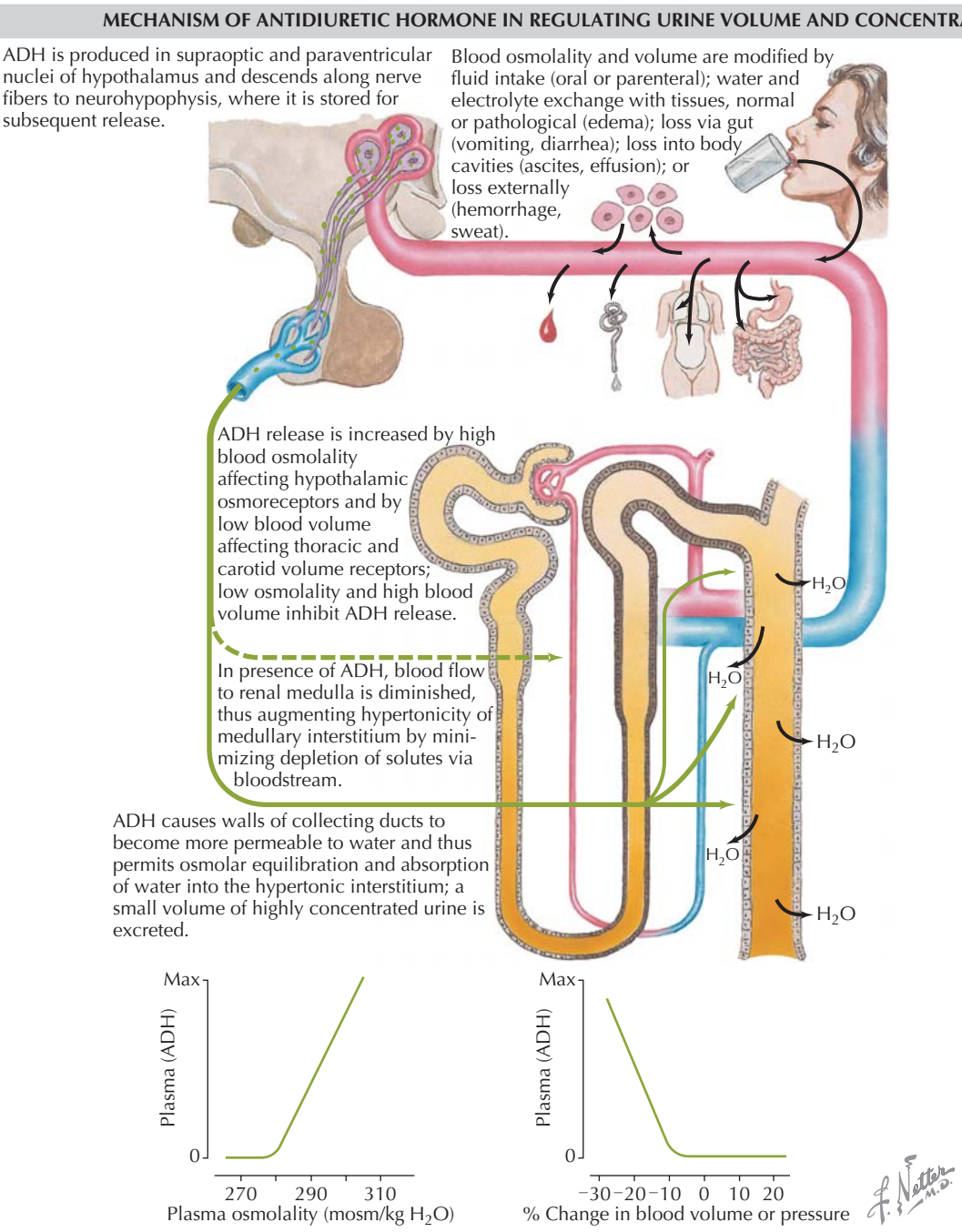


Figure 18.2 **The Renal Response to ADH Secretion** The scheme above illustrates the release and action of antidiuretic hormone (ADH). In response to dehydration, ADH is secreted from the posterior pituitary gland into the circulation. It acts on the kidneys to increase water channels in the collecting ducts, allowing solute-free water absorption, and also increases urea reabsorption in the medullary collecting ducts. The additional urea is added to the inner medullary interstitium and contributes to the high interstitial osmolar concentration.

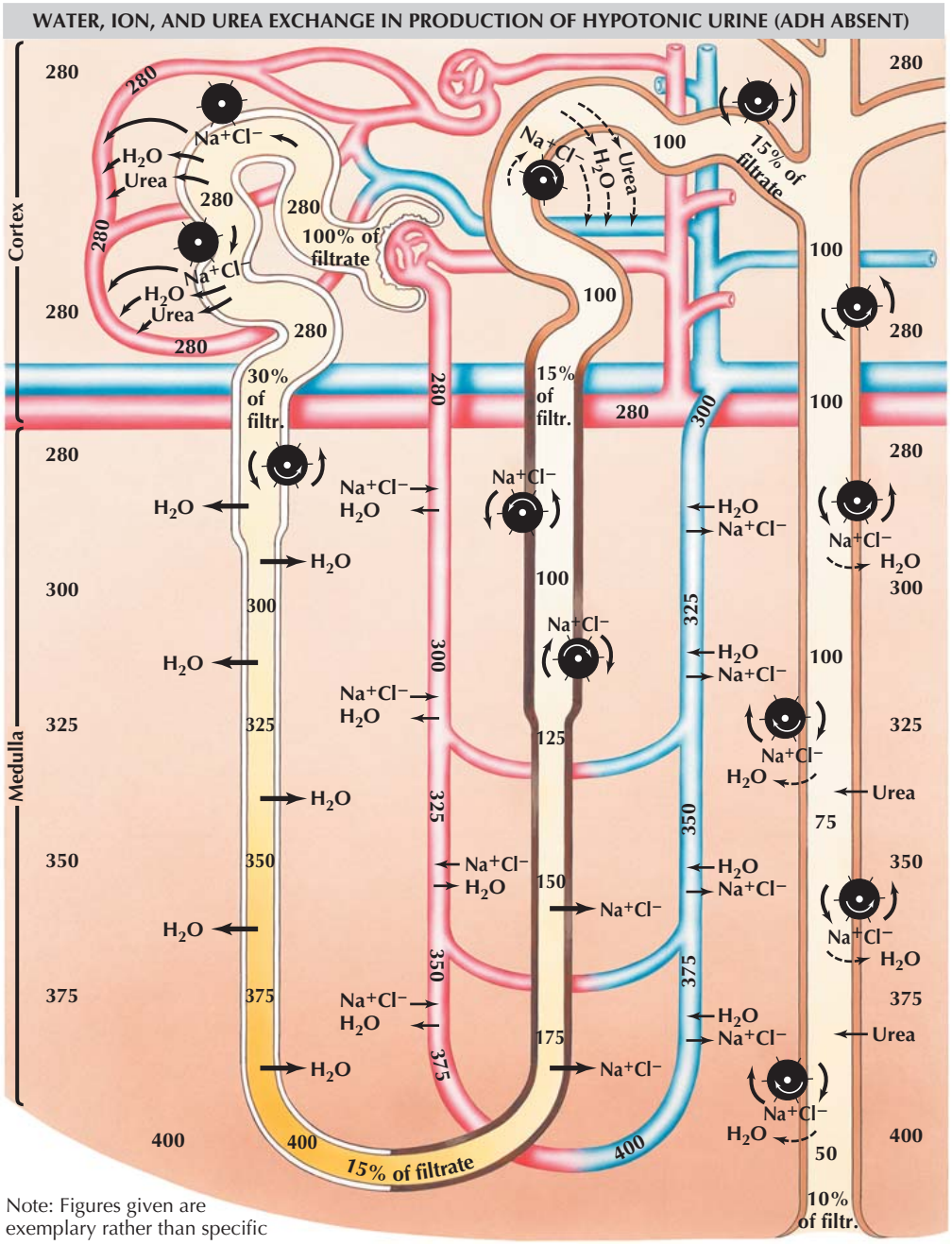


Figure 18.3 **Dilution of Urine** Excess extracellular fluid (ECF) will decrease antidiuretic hormone (ADH) secretion and reduce water channels in the collecting ducts. The disruption of the interstitial concentration gradient and lack of water channels produce diuresis.

determined by subtracting the osmolar clearance from the urine flow rate,

$$C_{H_2O} = \dot{V} - (Uosm/Posm) \times \dot{V}$$

Thus, in dilute urine (e.g., U/P is less than 1) the C_{H_2O} is a positive number, implying that water was excreted. In contrast, if the urine is concentrated (e.g., U/P is greater than 1), the C_{H_2O} is negative, implying that water was retained. If urine osmolarity equals plasma osmolarity, the C_{H_2O} equals zero.

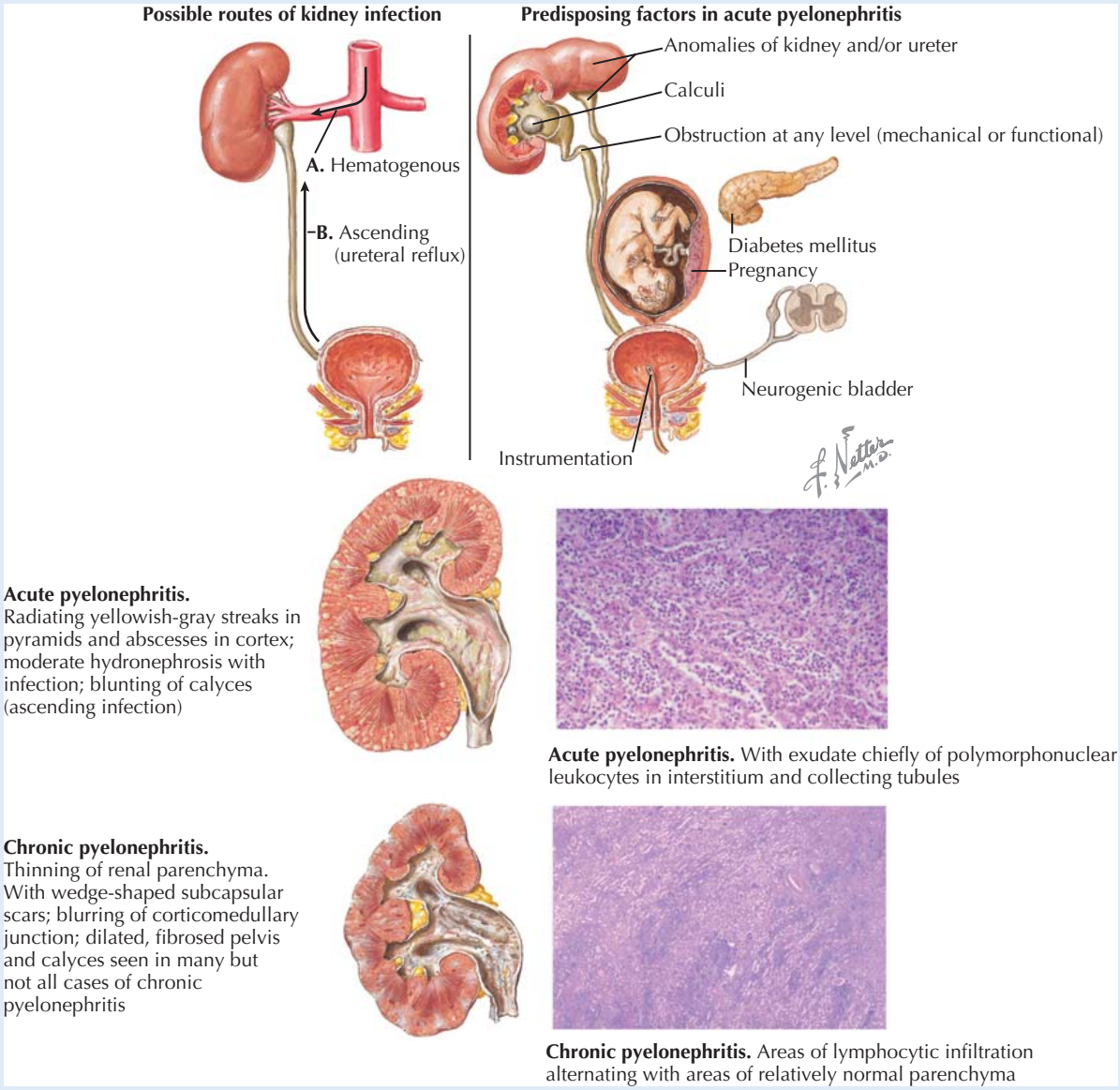
CLINICAL CORRELATE
Chronic Pyelonephritis

Pyelonephritis is inflammation of the renal pelvis, caused by bacterial infection. While acute kidney infections are usually caused by urinary tract infections (UTI), they can recur, and with each occurrence they can further damage the kidney. UTIs typically arise from contamination from bowel microorganisms, although with recurring infections that reach the kidney, potential underlying causes such as kidney stones or other anatomical abnormalities should be considered. Increased risk of pyelonephritis is associated with diabetes, pregnancy, prostate enlargement, compromised immunity, and sexual behavior and spermicide use.

The complications arising from **chronic pyelonephritis** relate to the area that is infected. The smooth muscle lining of the renal pelvis exhibits peristaltic activity that helps direct the newly collected urine toward the ureters for transit to the urinary bladder. The infection causes abscesses and necrosis of the pelvic tissue, which can lead to fibrosis and scarring.

As more of the medulla (tubules and parenchyma) becomes damaged with repeated infections, the ability to maintain the interstitial concentration gradient is compromised. Because high interstitial osmolarity provides the gradient that allows ADH-dependent free water reabsorption and urine concentration, loss of the deep gradient restricts the ability to excrete concentrated urine and thus can cause polyuria, despite dietary water restriction. The loss of tubules also reduces glomerular filtration rate (GFR), and thus renal function as a whole is diminished.

Pyelonephritis is treated with antibiotics over a period of several weeks. Increased fluid intake is recommended to flush any lower urinary tract bacteria out though increased urine production.



Chronic and Acute Pyelonephritis

CHAPTER 19 Regulation of Extracellular Fluid Volume and Osmolarity

INTRARENAL REGULATION OF SODIUM AND FLUID REABSORPTION

Renal sodium handling is closely regulated as part of the important process of extracellular fluid (ECF) homeostasis. A number of intrarenal factors can alter sodium (and thus, fluid) reabsorption in response to changes in systemic volume status:

- **Glomerular filtration rate (GFR):** Increases in GFR will increase the filtered load of sodium, and because the percentage of sodium reabsorbed in the proximal tubule does not change, the absolute amount of sodium entering the loop of Henle increases. Assuming that fractional reabsorption of sodium in the distal segments is unchanged, more sodium will be excreted. Conversely, if GFR decreases, the absolute amount of sodium entering the loop of Henle will decrease, as will sodium excretion (if fractional reabsorption in later segments is unchanged).
- **Tubular fluid flow rate:** While the tubular fluid flow rate may change, compensatory mechanisms within the kidney serve to regulate it within a normal range. This is necessary, because low flow rates will result in decreased delivery of sodium to the loop of Henle, low osmolar gradient in the interstitium, and poor ability to reabsorb water in the collecting duct. On the other hand, rapid tubular flow rates will wash out the osmolar gradient in the medullary interstitium. For this reason, tubuloglomerular feedback mechanisms are important in controlling the flow rate. When tubular flow is rapid, the macula densa cells of the juxtaglomerular apparatus secrete a vasoactive substance (adenosine or ATP) into the interstitial fluid adjacent to the afferent arteriole. The afferent arteriole constricts, which reduces HP_{GC}, and thus decreases the pressure for filtration, reducing GFR and tubular flow.
- **Baroreceptors** located in the afferent arteriolar vessel walls respond to changes in blood pressure. When stretched, they stimulate juxtaglomerular cells, causing the release of renin (this is an intrarenal mechanism, and does not involve the CNS vasomotor center).
- **Medullary blood flow:** If blood flow in the vasa recta increases, the medullary interstitial concentration gradient will be reduced, resulting in decreased solute reabsorption (Na^+-K^+-$2Cl^-$) in the thick ascending limb of Henle (TALH) and decreased water reabsorption in the thin descending limb of Henle (tDLH). The reduction in sodium reabsorption in the loop of Henle will increase the delivery of sodium and fluid to the distal tubules and collecting ducts (CDs). Because the concentration gradient is reduced, urine will not be effectively concentrated, and natriuresis/diuresis will occur.

NEUROHUMORAL CONTROL OF RENAL SODIUM REABSORPTION

The kidneys constantly respond to changes in blood pressure and ECF volume status, and this regulation is accomplished by intrarenal controls noted earlier, as well as several important neural and humoral mechanisms:

- **Sympathetic nerves** increase sodium reabsorption through several mechanisms. Sympathetic nerves innervate afferent and efferent arterioles (via α-adrenergic receptors). During sympathetic stimulation, arterioles constrict, decreasing GFR, and thus decreasing sodium excretion. There is also direct sympathetic innervation of the proximal tubule and loop of Henle, which, when activated, stimulates sodium reabsorption.
- The **renin-angiotensin-aldosterone system (RAAS)** has an important role in regulation of the renal retention of sodium and water, and thus, in the regulation of ECF volume and solute composition. In response to low tubular sodium concentration and low tubular fluid flow, juxtaglomerular cells produce the proteolytic enzyme **renin** and secrete it into the afferent arterioles (Fig. 19.1). Renin cleaves angiotensinogen (a plasma protein secreted by the liver) to angiotensin (Ang) I, which is converted to **Ang II** by angiotensin-converting enzyme (ACE) in the lung (and other tissues); Ang II stimulates adrenal medullary release of the mineralocorticoid aldosterone. In the kidney, Ang II has dual effects: it directly stimulates sodium (and thus, water) reabsorption in the proximal tubule and has vasoconstrictor effects on afferent and efferent arterioles, which result in a lower GFR, and sodium retention.
- **Aldosterone** binds to the cytoplasmic mineralocorticoid receptors in the late distal tubules and collecting tubules and stimulates Na^+ and water retention (and K^+

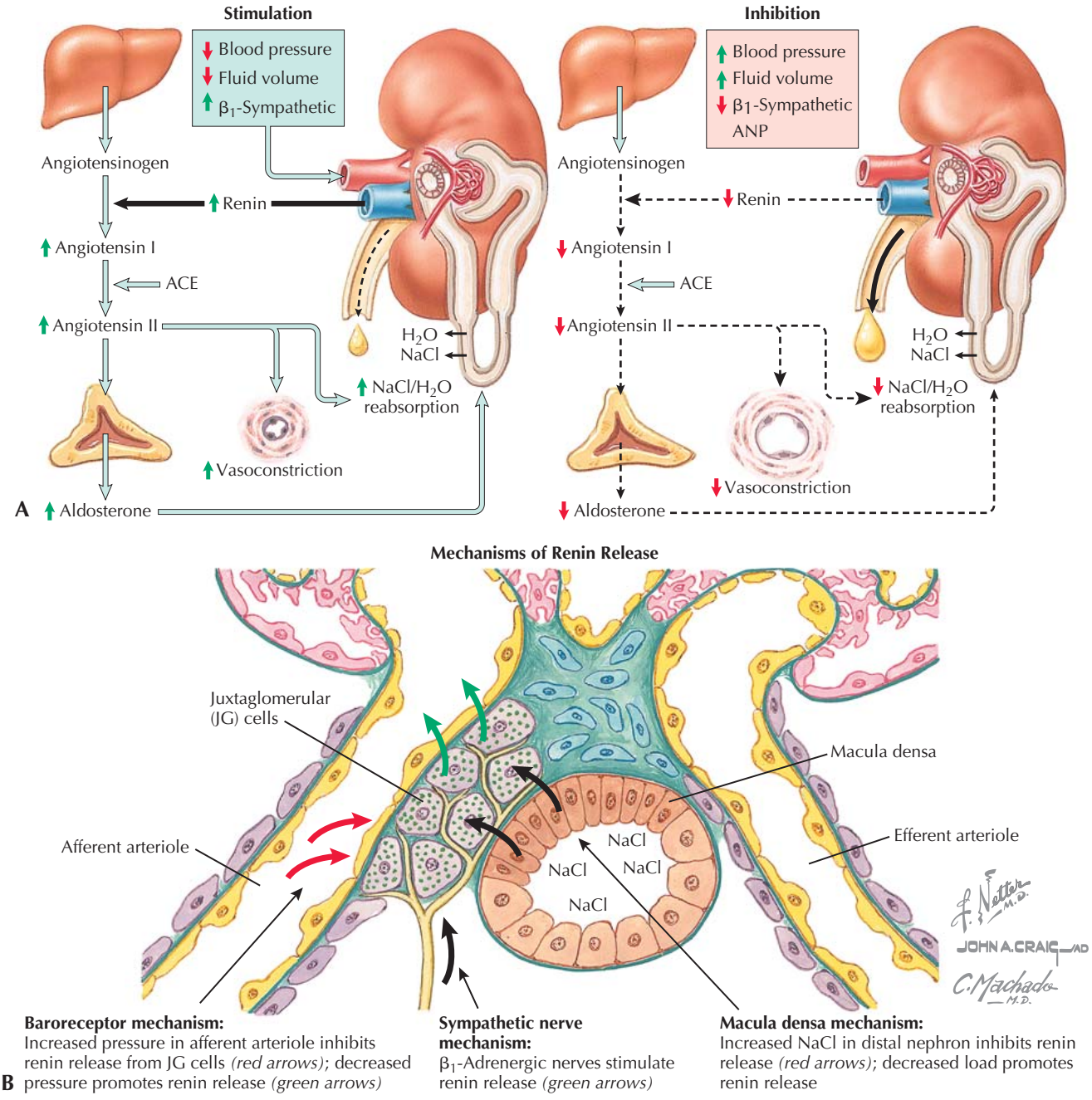


Figure 19.1 Mechanism of Renin Secretion and Factors Regulating the Renin-Angiotensin-Aldosterone System Renin is secreted from the juxtaglomerular cells in response to reduced sodium concentration and flow in the distal tubule *(B)*. The cascade of events initiated to promote sodium and water reabsorption is illustrated in *A*.

secretion). Aldosterone increases apical Na^+ channels and Na^+/H^+ antiporters and increases basolateral Na^+/K^+ ATPase activity. This further increases sodium and water retention and limits urinary losses.

- **Atrial natriuretic peptide** (**ANP**) is primarily produced by myocytes in the right atrium of the heart and is released into the blood in response to atrial stretch (as with increased blood volume). ANP opposes the actions of Ang II by increasing GFR and inhibiting collecting tubule Na^+ reabsorption. ANP causes natriuresis and diuresis, reducing ECF volume.
- **Urodilatin** is a natriuretic peptide related to ANP that is produced in the renal tubular cells and secreted *into the tubules* (not found in blood). The peptide acts at the collecting tubules to decrease Na^+ reabsorption, resulting in natriuresis/diuresis.

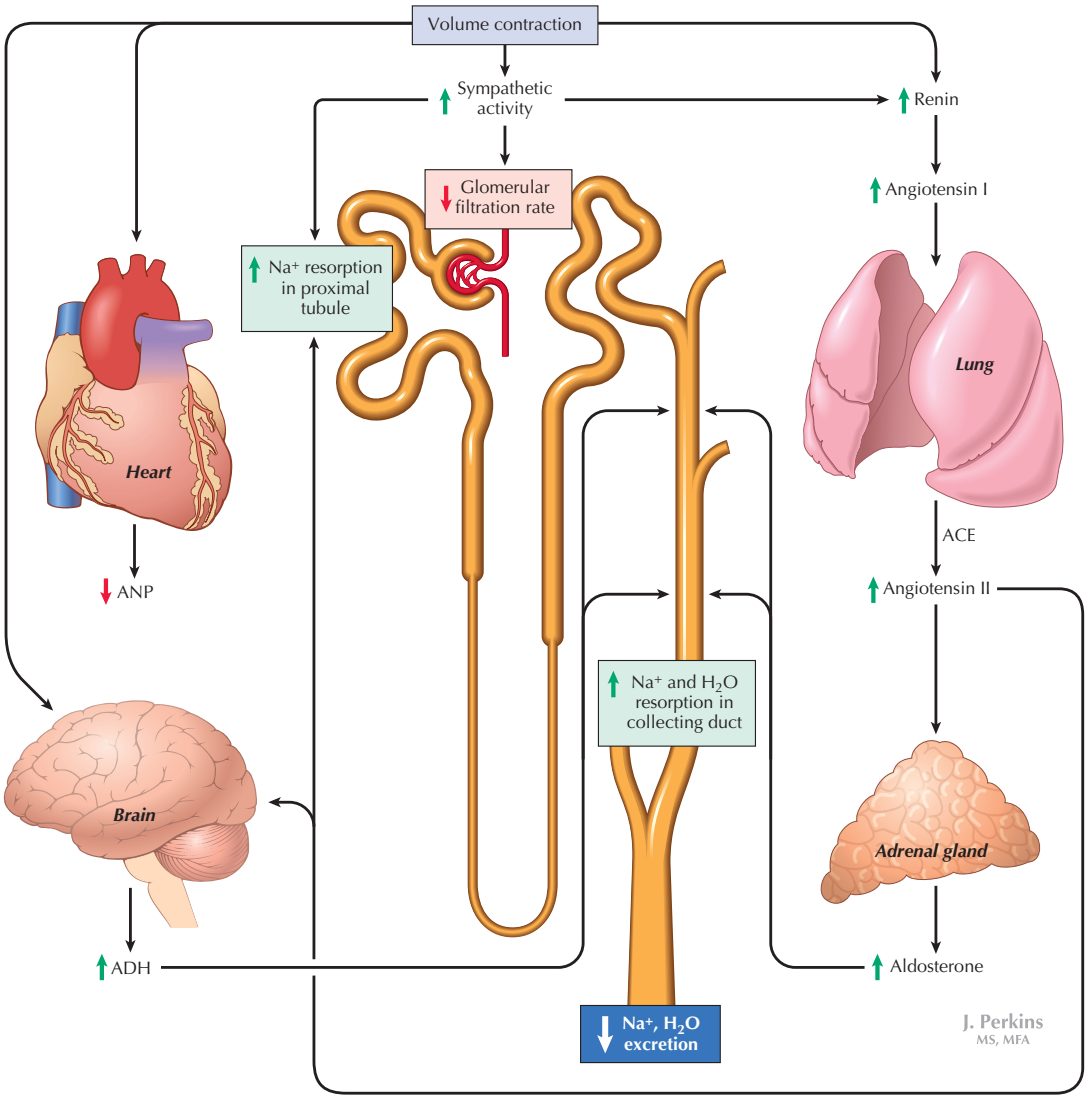


Figure 19.2 Renal Response to Volume Contraction In response to volume contraction (dehydration), the renin-angiotensin-aldosterone system is activated, stimulating renal sodium and fluid retention; antidiuretic hormone secretion from the anterior pituitary is stimulated to increase water reabsorption in the renal collecting ducts, and the sympathetic nerves are stimulated to increase renal sodium reabsorption and decrease glomerular filtration rate.

RENAL RESPONSE TO CHANGES IN PLASMA VOLUME AND OSMOLARITY

As discussed earlier, control of ECF is a continual process, with changes in plasma osmolarity and volume signaling multiple neural and hormonal systems to regulate the renal concentration and dilution of the urine. The integration of these systems is illustrated in the overall response to ECF volume contraction and expansion (Figs. 19.2 and 19.3). When plasma volume is contracted, fluid and sodium conservation systems are activated. During volume contraction, the kidneys respond to:

- Increased sympathetic nervous system (SNS) activity, which increases renal vascular resistance and decreases GFR; proximal tubular sodium (and water) reabsorption increases.
- Activation of the RAAS, which increases Ang II and aldosterone, enhancing sodium (and water) reabsorption in the proximal tubules and CDs, respectively.
- The increase in antidiuretic hormone (ADH), which increases water channels in the CDs, enhancing solute-free water absorption.

These systems limit further volume contraction by decreasing the loss of fluid in urine. When plasma volume is expanded, these systems are reversed, allowing elimination of fluid and reduction of plasma volume and ECF (Fig. 19.3). Furthermore, the increase in **ANP** from the right

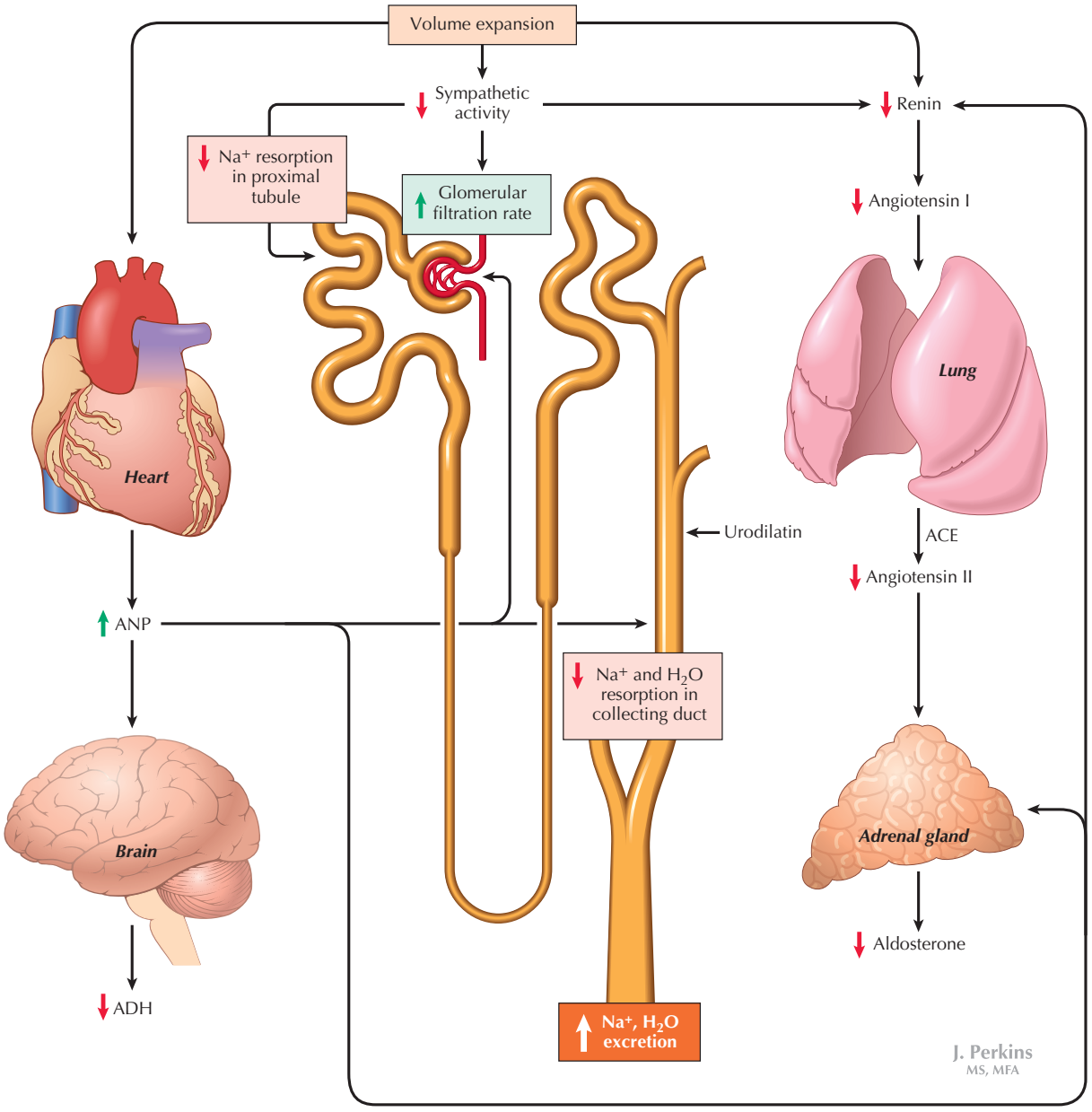


Figure 19.3 Renal Response to Volume Expansion In response to volume expansion, sodium- and fluid-retaining mechanisms are decreased (RAAS, ADH), and the increased stretch on the cardiac right atrium releases atrial natriuretic peptide, which acts at the kidneys to decrease sodium and water retention, creating a diuresis and natriuresis, eliminating the excess fluid.

Because of the potent vasoconstrictor and sodium-retaining effects of angiotensin II on the kidney, inhibition of Ang II is a major therapeutic intervention for treatment of hypertension. **Angiotensin-converting enzyme (ACE) inhibitors** (e.g., captopril, enalapril) prevent conversion of Ang I to Ang II, whereas **angiotensin receptor blockers (ARB)** (e.g., losartan, candesartan) block Ang II AT_1 receptors. Both interventions decrease systemic vascular resistance and increase urinary sodium and water excretion.

To maintain homeostasis, almost all of the filtered sodium must be reabsorbed—loss of even a few percent of the filtered sodium can result in severe sodium deficiency. Although the fine-tuning by aldosterone increases sodium reabsorption only about 2% to 3%, in aldosterone insufficiency (Addison's disease), these losses can lead to severe ECF sodium depletion, ECF volume contraction, and circulatory collapse.

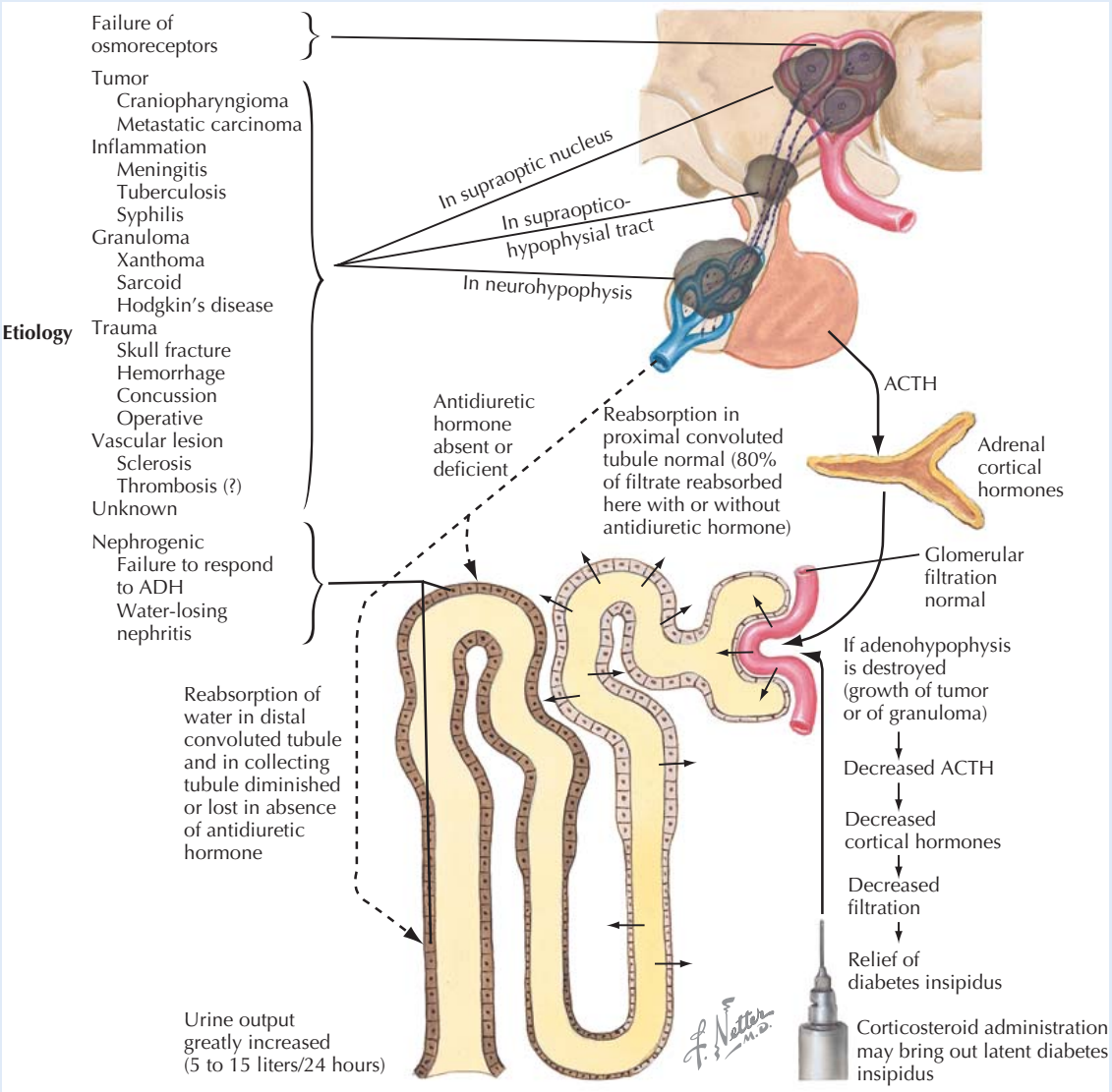
cardiac atrium has a key role in producing natriuresis and diuresis by:

- Inhibiting aldosterone secretion.
- Decreasing ADH.
- Increasing GFR by relaxing mesangial cells (and also through renovascular effects).
- Decreasing sodium (and water) reabsorption in the CDs by reducing Na^+ channels (ENaC).

CLINICAL CORRELATE
Diabetes Insipidus

ADH allows the kidneys to concentrate urine. Insufficiency of ADH secretion results in **diabetes insipidus (DI)**, a disease in which large volumes of hypotonic urine are excreted. **Central diabetes insipidus** is usually caused by trauma, disease, or surgery affecting the posterior pituitary gland or hypothalamus. **Nephrogenic DI** is rare and involves a reduction in ADH V2 receptors or reduction in the AQP2 water channels in the collecting ducts of the kidney, reducing sensitivity of the cells to ADH.

Fluid intake must increase to compensate for the urinary losses, which can range from 3 to 18 liters per day. Mortality is rare, although children and elderly people are at greater risk, from severe dehydration, cardiovascular collapse, and hypernatremia. ADH analogs such as DDAVP (e.g., desmopressin) are used to treat central DI. The analogs act like endogenous ADH and increase water channels in the collecting ducts. Nephrogenic DI can respond to indomethacin as well as dihydrochlorothiazide, which is a diuretic that has a paradoxical effect to increase water reabsorption in DI.



Central Diabetes Insipidus The causes of central diabetes insipidus, with the effects on the kidneys, are depicted in this scheme.

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CHAPTER 20 Regulation of Acid–Base Balance by the Kidneys

CONTROL OF EXTRACELLULAR FLUID pH

Why is systemic acid–base status important, and what is the role of the kidneys? As noted in Chapter 15, the blood (and extracellular fluid [ECF]) pH must be maintained within a narrow range (7.35 to 7.45) to allow normal cellular functions. This physiologic pH range corresponds to a narrow range in H^+ concentration (45 to 35 nanomoles per liter [nM/L]). The narrow physiologic window for H^+ concentration demonstrates the necessity for tight control of pH at all times.

Because acid balance is critical for controlling ECF pH, the daily entry of H^+ into the ECF must equal the losses. Net gain of H^+ can occur from ingestion of acid contained in foods (acidic drinks, proteins), cell and protein metabolism, hypoventilation, and diarrhea (loss of HCO_3^- results in gain in H^+, described later). Net losses of acid can result from hyperventilation, vomiting, and of course urinary acid excretion. Under normal conditions, the daily gain of acid from normal metabolism (sulfuric acid, phosphoric acid, keto acids, etc.) and diet (proteins) will be equaled by acid excreted in the urine. CO_2 is a volatile acid and can be excreted by the lungs, but when it is in the blood it is dissolved, and contributes to the overall acid pool. A general scheme is illustrated in Figure 20.1.

In general, we ingest and produce ~40 to 80 *millimoles* (mM) of acid each day. This is a huge amount compared with the ~40 *nanomolar* level (at pH 7.4) that is maintained in the ECF. This excess acid must be:

- **Buffered,** to prevent a fall in pH to below physiologic levels (e.g., below 7.35).
- **Excreted** in the urine, which is the job of the kidneys.

Buffering of Acid

The body handles excess acid using intracellular and extracellular buffers, in a continuous regulatory "dance," escorting acid in and out of cells and through the blood to the kidneys for excretion.

Extracellular Buffering

Bicarbonate (HCO_3^-) is the major ECF buffer, available for consuming free H^+ through the following reaction:

$$HCO_3^- + H^+ \overset{\leftarrow}{\rightarrow} H_2CO_3 \overset{CA}{\Leftrightarrow} CO_2 + H_2O$$

The carbonic acid can be converted to CO_2 and H_2O, in the presence of carbonic anhydrase (CA). This occurs in ECF and tissues, allowing diffusion of CO_2 and H_2O into and out of tissues. CO_2 does not normally contribute to the *net gain* in acid (because the H^+ gained in the above reaction is utilized, as water is formed in the lungs when the CO_2 is blown off during respiration). However, CO_2 does contribute to the net acid gain during **hypoventilation.**

As described in Chapter 15, the **Henderson-Hasselbalch** equation describes the relation between acid–base status and pH as:

$$pH = 6.1 + \log[\text{base/acid}]$$

where the base is plasma bicarbonate (normally ~24 mM/L of ECF), and acid is the $P_{CO_2} \times 0.03$ (solubility constant) (normally 40 mm Hg × 0.03 = 1.2 mM/L of ECF). And thus, under normal conditions,

$$pH = 6.1 + \log[24/1.2]$$
$$pH = 7.4$$

The kidneys control the amount of base (free bicarbonate) in the ECF. This is accomplished by generating new bicarbonate, or excreting excess bicarbonate (in alkalosis). Although the amount of acid is also controlled by urinary acid excretion, in acidosis and alkalosis respiration can also regulate ECF acid. ECF phosphates and proteins also contribute to the buffering, but to a very small extent.



What makes a good buffer? Good buffers have a pK that is close to the physiologic pH of 7.4. In the ECF, the best buffer would be phosphate (HPO_4^{2-}), which has a pK of 6.8 (which at a pH of 7.4 results in a base to acid ratio of 4:1 [HPO_4^{2-}: $H_2PO_4^-$]). However, there is relatively little phosphate in the ECF (~1 mM/L), so it is not an effective ECF buffer. Instead, bicarbonate (pK = 6.1 and base to acid ratio is 20:1 [HCO_3^-: H_2CO_3] at pH of 7.4) is the main ECF buffer, because of its high ECF concentration (~24 mEq/L). The large amount of free bicarbonate allows ready buffering of additional acid load.

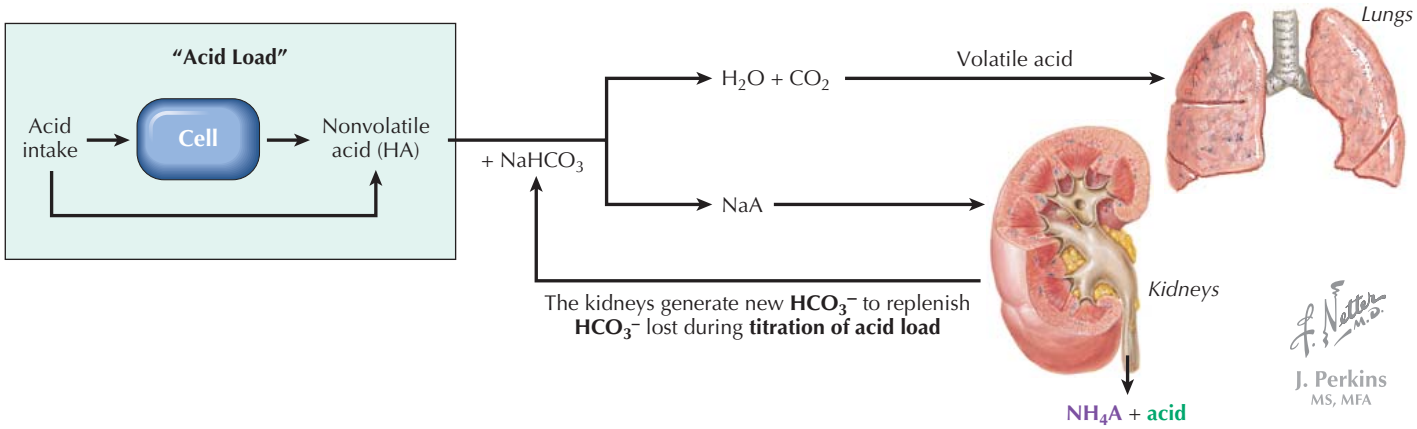


Figure 20.1 General Scheme for Eliminating Excess Acid New acid is added daily from diet and metabolism and must be buffered (primarily by ECF bicarbonate), and then excreted in the urine.

Intracellular Buffering

Although phosphates offer minor buffering in the ECF, when needed they provide major buffering capacity *within* the cells, because of their high concentration. In addition, cellular proteins contribute to the buffering process. Movement of H^+ into and out of cells occurs through cation exchange (H^+/K^+ and Na^+/H^+ antiporters). The buffering process minimizes the effects of generated and ingested acid on pH of the ECF and allows shuttling of acid to the kidneys, where it can be excreted.

HCO_3^- AND H^+ HANDLING THROUGH THE RENAL TUBULE

HCO_3^-

As previously described, the process of bicarbonate reabsorption occurs in the proximal tubule, thick ascending limb of Henle (TALH), and collecting duct and is dependent on the secretion of H^+ into the tubular lumen (see Fig. 17.3). This cycle effectively reclaims 100% of the filtered bicarbonate back into the ECF, and under normal conditions there is no urinary excretion of bicarbonate.

The exception to this occurs in alkalosis, when acid–base balance depends on the removal of HCO_3^-. This is accomplished in the collecting ducts (CD), where the **β-intercalated cells** have the ability to secrete HCO_3^- into the tubule for excretion, via HCO_3^-/Cl^- antiporters. Again, this transporter is only active during alkalosis, when its activation results in HCO_3^- loss and H^+ accumulation.

H^+

H^+ is secreted into distal segments of the nephron in excess of filtered bicarbonate, with significant secretion occurring from the **α-intercalated cells** of the collecting ducts (see Fig. 17.3, *upper right panel*). These cells have lumenal H^+ ATPase pumps and actively secrete H^+ into the tubular fluid. One of the pumps is the H^+/K^+ pump, discussed in Chapter 17, which contributes to net potassium reabsorption during potassium depletion. The H^+/K^+ ATPase is aldosterone-sensitive. The basolateral membranes have HCO_3^-/Cl^- exchangers that transport HCO_3^- into the interstitium, from which it is enters the blood. Excess acid secreted along the nephron must be buffered (to allow continued secretion of H^+) and excreted. Factors that can regulate H^+ secretion in the nephron are given in Table 20.1.

RENAL MECHANISMS CONTRIBUTING TO NET ACID EXCRETION

The ingested/generated acid load is always buffered in the plasma and is then dissociated from the buffers in the kidneys in the process of bicarbonate metabolism. The free H^+ is secreted into the tubular lumen (in PT, TALH, CD), where it is incorporated into either phosphates (to become a **titratable acid**), or **ammonia** (to become **ammonium**). This buffers the acid controlling urine pH.

A key concept is that a new bicarbonate ion is generated for every H^+ ion that is excreted, and this is always in a 1:1 ratio (1 HCO_3^- reabsorbed to 1 H^+ excreted). This occurs because both the secretion of H^+ into the renal tubule and excretion of ammonium (NH_4^+) result in HCO_3^- reabsorption (Fig. 20.2). If the secreted H^+ ends up being excreted as a titratable acid or ammonium, the amount excreted is directly equated with generation of new bicarbonate.

Production of Titratable Acids

The primary form of titratable acid is phosphoric acid ($H_2PO_4^-$). Remember, phosphate is a strong buffer (pK 6.8) but is not readily available in the ECF, because of its low

Table 20.1 Factors Influencing H^+ Secretion by the Nephron

Factor	Principal Site of Action
INCREASED H^+ SECRETION—PRIMARY	
↓HCO_3^- concentration (↓pH)	Entire nephron
↑Arterial P_{CO_2}	Entire nephron
INCREASED H^+ SECRETION—SECONDARY	
↑Filtered load of HCO_3^-	Proximal tubule
↓ECF volume	Proximal tubule
↑Angiotensin II	Proximal tubule
↑Aldosterone	Collecting duct
Hypokalemia	Proximal tubule
DECREASED H^+ SECRETION—PRIMARY	
↑HCO_3^- concentration (↑pH)	Entire nephron
↓Arterial P_{CO_2}	Entire nephron
DECREASED H^+ SECRETION—SECONDARY	
↓Filtered load of HCO_3^-	Proximal tubule
↑ECF volume	Proximal tubule
↓Aldosterone	Collecting duct
Hyperkalemia	Proximal tubule

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concentration (~1 mM/L). However, in the tubular fluid, the amount of filtered phosphate (FLPi) is significant (FLPi = 1 mM/L × ~140 L/day (GFR) = ~140 mM Pi/day), and part of this can be used for buffering and excreting H^+ (bicarbonate cannot be used, because it is completely reabsorbed). The amount of phosphate available to form titratable acid depends on (1) the amount of basic phosphate (HPO_4^{2-}) available to bind with H^+, and (2) the renal handling of phosphate.

- **Phosphate buffering:** According to the Henderson-Hasselbalch equation, at a blood pH of 7.4, there will be 4 times the amount of base (HPO_4^{2-}) to acid ($H_2PO_4^-$), and this base is available for buffering excess H^+. Thus, the ~140 mM/day of filtered phosphate includes about 116 mM/day of HPO_4^{2-} that could be used as buffer—however, not all of this is available because of the tubular handling of phosphate.
- **Renal handling of phosphate:** In the normal adult, ~75% of the filtered phosphate is reabsorbed and therefore unavailable for generating titratable acid. Thus only 25% of the filtered HPO_4^{2-} can be used, or ~29 mM/day (116 mM/day × 0.25 = 29 mM/day).

Formation of titratable acids occurs in the CDs at the α-intercalated cells. At this point of the nephron, phosphate reabsorption is complete and the final reabsorption of HCO_3^- is occurring. Thus, the excess H^+ that is actively secreted can bind to the HPO_4^{2-}, creating the titratable acid $H_2PO_4^-$, which is then excreted. Under normal conditions, titratable acids will be the main source of acid excretion, but their maximal rate of excretion is fixed because titratable acid formation depends on the amount of phosphate reabsorption occurring, and this is not enough to eliminate the daily acid load. The remaining acid is buffered by NH_3, and when the acid load increases, ammoniagenesis will be further stimulated to handle the load.

Ammoniagenesis

The proximal tubule cells are capable of producing ammonia from glutamine, extracted from the tubular fluid as well as peritubular capillary blood. The ammonia can buffer H^+ by forming ammonium (NH_4^+) that can ultimately be excreted in the urine. A key aspect of this reaction is that the excretion of NH_4^+ produces new HCO_3^- that is reabsorbed into the plasma.

In the proximal tubular cells, the glutamine is hydrolyzed to produce glutamate and one NH_3. The glutamate is further metabolized to α-ketoglutarate, producing another NH_3. The two NH_3 are immediately combined with two H^+, forming two NH_4^+. Additional α-ketoglutarate metabolism yields two HCO_3^-. Thus, a single glutamine generates two HCO_3^-, which are reabsorbed as *new* HCO_3^-, and two NH_4^+, which are secreted into the tubular fluid (see Fig. 20.2, *upper right*).

The NH_4^+ produced in the proximal tubule is not directly excreted. Instead it is reabsorbed in place of K^+ by the Na^+-K^+-$2Cl^-$ transporters. The NH_3 stays in the interstitial fluid, increasing the medullary interstitial concentration of NH_3. The dissociated H^+ is secreted into Henle's loop in exchange for Na^+. The NH_3 gradient promotes secretion of NH_3 into the tubular lumen of the collecting ducts; NH_3 immediately binds free H^+ in the collecting ducts, re-forming NH_4^+ that is excreted in the urine (see Fig. 20.2, *lower right*).

Net Acid Excretion

Acid balance is determined by the difference between acid intake and urinary excretion of acid. Under normal conditions, intake will equal excretion. **Net acid excretion** (NAE) describes the total amount of acid that is excreted in the urine:

$$NAE = TA + NH_4^+ - HCO_3^-$$

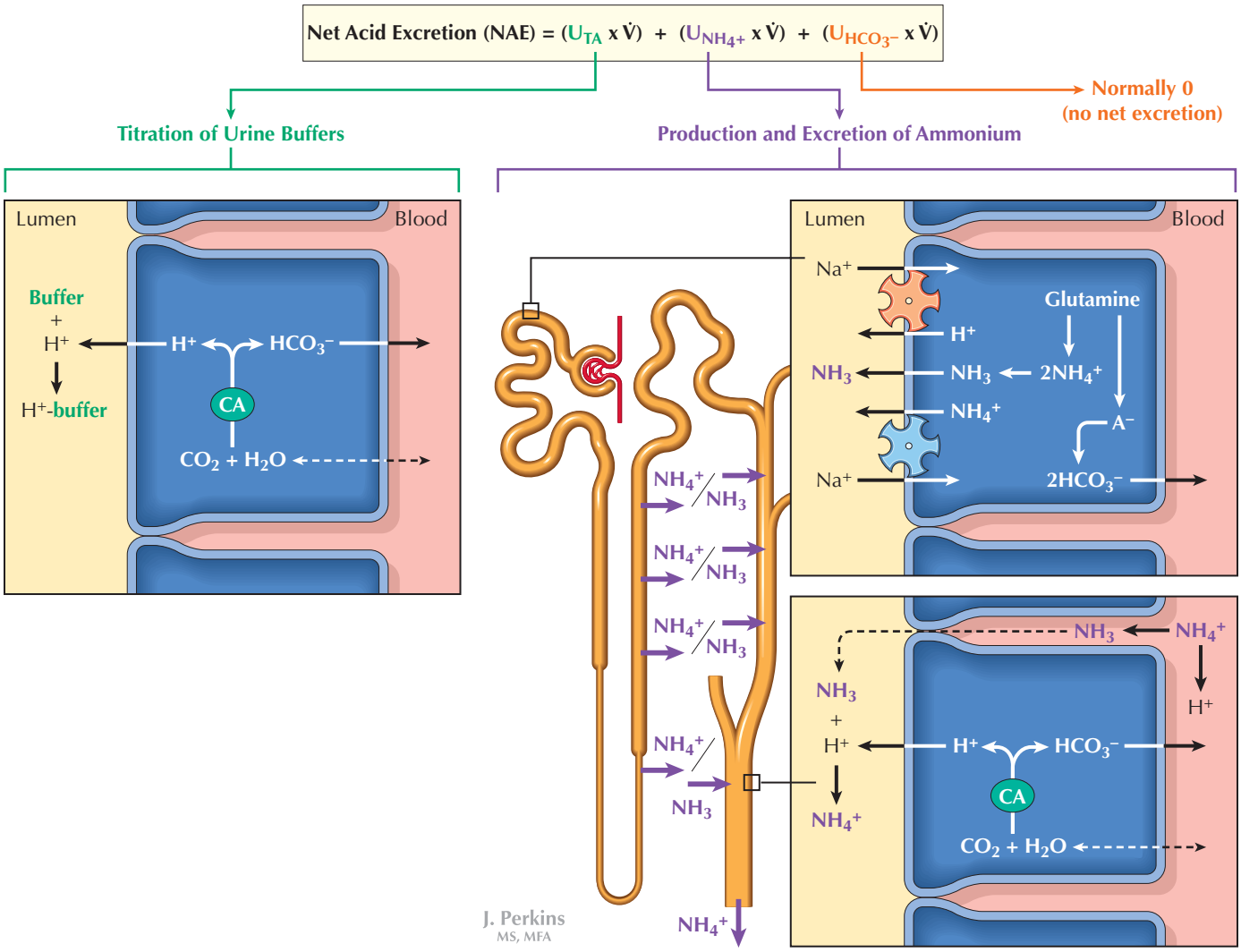


Figure 20.2 Renal Handling of Acid Excretion H^+ is excreted as titratable acids (mainly phosphoric acids) and ammonium (NH_4^+). With either mechanism, excretion of an H^+ results in generation of a new HCO_3^- that enters into the blood.

where TA is titratable acids. Under most conditions, urinary HCO_3^- is zero (all HCO_3^- is normally reabsorbed). However, when HCO_3^- appears in the urine, it implies that H^+ was added to the ECF (recall the 1:1 relationship between bicarbonate reabsorbed or excreted and H^+ transported in the opposite direction). In the equation above, the HCO_3^- is subtracted from the TA and NH_4^+ to account for the newly accumulated acid. HCO_3^- excretion is indicative of alkalosis or renal tubular acidosis, and in both conditions, there is an equimolar gain of acid for the HCO_3^- excreted.

Urine pH

Normal urine pH varies between 4.4 and 8 according to the acid–base status, with average values around 5.5 to 6.5. The minimal attainable urine pH is 4.4, which represents 1000-fold greater concentration of H^+ than the blood pH of 7.4. This is the greatest concentration difference against which the H^+ pumps can effectively secrete H^+. This maximal level of urine acidity is only attained with severe metabolic acidosis.

ACIDOSIS AND ALKALOSIS

When pH falls outside of the normal physiologic range, acidosis (pH less than 7.35) or alkalosis (pH greater than 7.45) results. A disturbance is designated as:

- **Respiratory** (acidosis or alkalosis) if it is caused by abnormal CO_2, or
- **Metabolic** (acidosis or alkalosis), if the pH change is consistent with the alteration in HCO_3^-.

Table 20.2 Sample Values for Uncompensated Acid–Base Imbalances

	pH	P_{CO_2} (mm Hg)	HCO_3^- (mM or mEq/L)
Primary respiratory acidosis	7.32	50	24
Primary metabolic acidosis	7.32	40	18
Primary respiratory alkalosis	7.54	28	24
Primary metabolic alkalosis	7.54	40	34

The acid–base status is assessed by examining the plasma values of pH, P_{CO_2}, and HCO_3^- (the *arterial blood gases*), which are the key components of the Henderson-Hasselbalch equation. Under normal conditions in arterial blood, these values will be:

	pH	P_{CO_2} (mm Hg)	HCO_3^- (mM)
Normal	7.4	40	24

When pH is altered, the primary disturbance can be identified by determining which component (P_{CO_2} or HCO_3^-) is altered in the direction consistent with the change in pH. Increased P_{CO_2} or decreased HCO_3^- will produce respiratory and metabolic acidosis, respectively; decreased P_{CO_2} or increased HCO_3^- will produce respiratory and metabolic alkalosis, respectively (Table 20.2 and Fig. 20.3).

In general, compensation for metabolic disturbances will include altered respiratory rate: hyperventilation to blow off excess CO_2 in acidosis, or hypoventilation to retain CO_2 in alkalosis (discussed in Chapter 15). Compensation for respiratory disturbances will include altered renal bicarbonate and acid handling. **Metabolic compensation** occurs over several hours through the renal excretion of acid (in acidosis), or bicarbonate (in alkalosis), to return the pH toward normal. The examples in Table 20.2 represent *uncompensated* disturbances. The following paragraphs will focus mainly on metabolic disturbances.

Acidosis

Acidosis can result from either gain of acid or loss of bicarbonate. Net acid gain can arise from either decreased respiration (increasing CO_2), or from the accumulation of acids from metabolic sources (**metabolic acidosis**) outlined in the following text:

- Keto acids, from β-oxidation of fatty acids, which occurs during starvation and poorly controlled diabetes.
- Phosphoric acid, in renal failure, as a result of the inability to excrete the acids due to low GFR.
- Lactic acid, which is released from damaged tissues during hypoxia or heart failure.
- Ingestion of substances such as antifreeze (ethylene glycol) and Sterno® (containing methanol).

Bicarbonate losses are always caused by metabolic disturbances and mainly occur as a result of:

- Increased fecal elimination with prolonged diarrhea, because HCO_3^- is secreted as a buffer and is lost with other constituents of the chyme (including the HCO_3^- that is also secreted into the ileum and colon).
- Increased urinary excretion because of insufficient HCO_3^- reabsorption in the proximal tubule.
- Elevated H^+ secretion into the collecting ducts—this causes HCO_3^- secretion from the β-intercalated cells of the collecting ducts to buffer the urine (distal renal tubular acidosis).

Whether due to addition of acid or loss of bicarbonate, the resulting acid load must be buffered systemically and then excreted by the kidneys. To compensate for acid gain, the plasma level of free bicarbonate falls as it forms H_2CO_3 to buffer the free acid. When pH is under 7.35, respiration will increase to "blow off" CO_2 and reduce acid load. Chronically, the main compensation will occur in the kidneys—increased acid secreted into the renal tubules will combine with phosphates and ammonia to form titratable acids and ammonium for excretion (see Fig. 20.2).

Although there can be an immediate increase in titratable acids because some excess HPO_4^{2-} is present, the ability to excrete titratable acids is limited by the amount of phosphate reabsorbed. The main urinary buffering of H^+ is by ammonia (forming NH_4^+). Ammoniagenesis increases during acidosis over a period of hours to days, allowing a great increase in ammonium excretion. The increase in NAE will increase pH toward normal values, although in severe cases of diabetic ketoacidosis, the kidneys may not be able to attain normal pH values until blood glucose is restored.

ANION GAP

The anion gap is used to differentiate between acidosis resulting from acid gain and acidosis caused by bicarbonate loss. This diagnostic tool utilizes the fact that the only way to lose bicarbonate is through HCO_3^-/Cl^- exchangers located in the β-intercalated cells of the collecting ducts and in the lower GI tract. Thus, if HCO_3^- is lost, Cl^- is gained, and this is reflected in the plasma concentrations of these anions. The anion gap (AG) is the difference in concentration between the

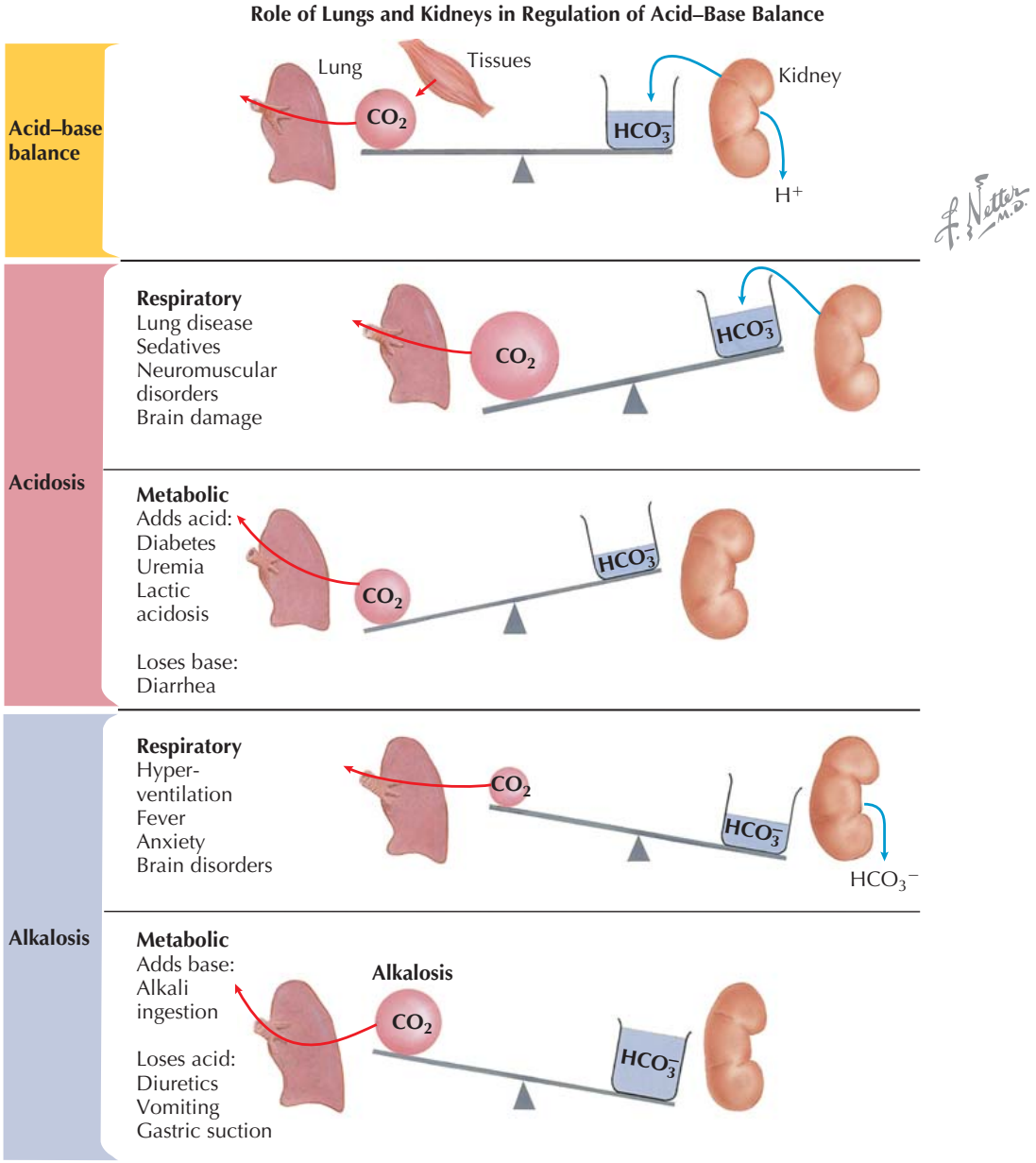


Figure 20.3 Role of the Lungs and Kidneys in the Regulation of Acid–Base Balance This scheme illustrates the changes in acid and base status in primary respiratory and metabolic disturbances. Under normal conditions *(upper panel),* the acid–base status is in balance, with kidneys absorbing all filtered HCO_3^-, and the daily gain of acid excreted by the kidneys. In both respiratory and metabolic imbalances, acid gain (acidosis) or loss (alkalosis) is compensated for by the renal excretion of acid or HCO_3^-, respectively. When blood pH is outside of the physiologic window (less than 7.35 or above 7.45), there is also respiratory compensation by hyperventilation or hypoventilation.

major cation, Na^+, and the major plasma anions, Cl^- and HCO_3^-. When Cl^- and HCO_3^- concentrations are subtracted from the Na^+ concentration, the "anion gap" is normally ~8 to 12 mEq/L. The anion gap represents the sum of the concentrations of about 10 anions present in the plasma and includes proteins, lactate, citrate, phosphates, sulfates, etc.:

$$AG = Na^+ - (Cl^- + HCO_3^-)$$

As illustrated in Figure 20.4, *middle panel,* when acidosis results from acid loading, the anion gap increases, as a result of the lower plasma bicarbonate (used to buffer the acid). In contrast, when HCO_3^- is lost, it is replaced by Cl^-, and the anion gap is normal (see Fig. 20.4, *right panel*). Thus, the anion gap can help determine the cause of the metabolic acidosis, with the specific cause of the acid load or base loss remaining to be determined.

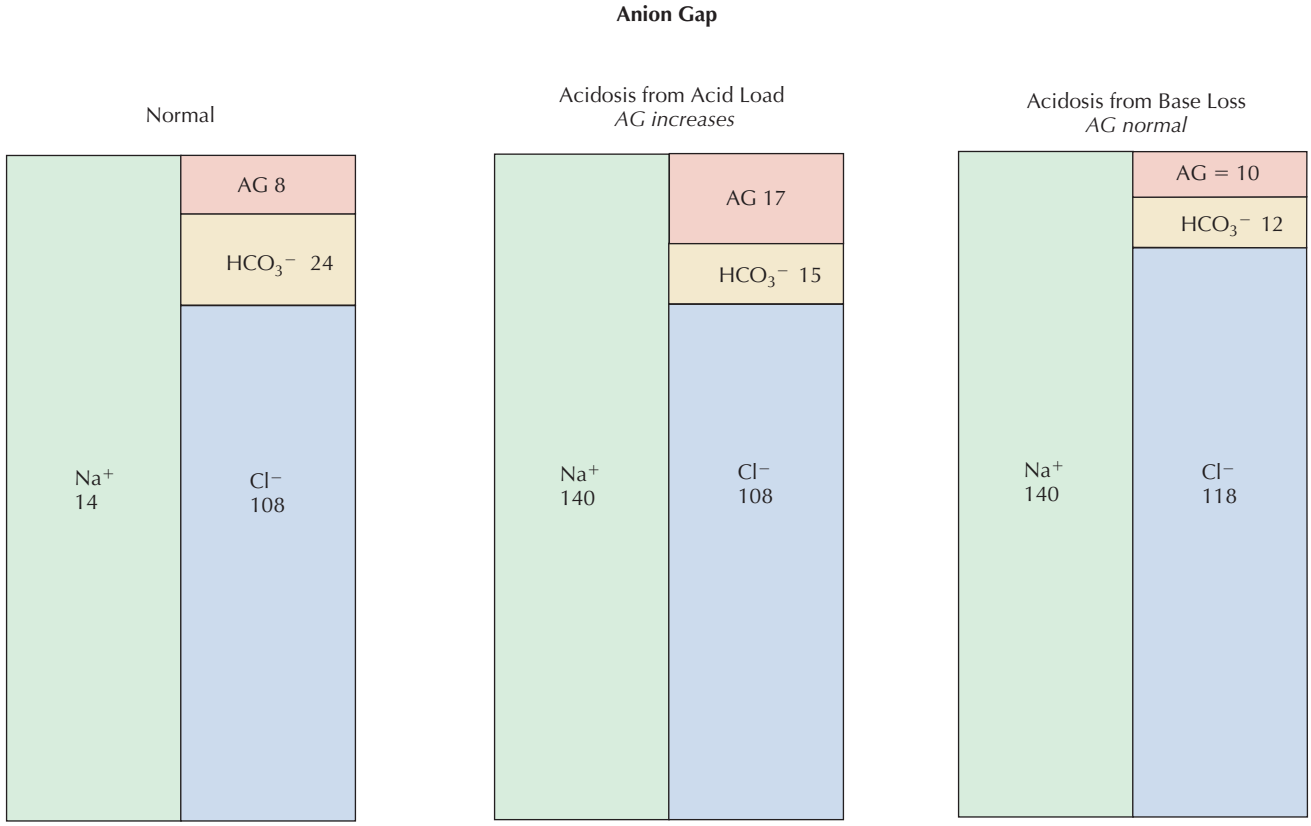


Figure 20.4 Plasma Anion Gap In cases of metabolic acidosis, measurement of the anion gap will reveal whether the disruption in pH was from acid loading or base loss.

Why don't the renal HCO_3^-/Cl^- exchangers always work during alkalosis? It is important to recall that under normal conditions the HCO_3^-/Cl^- exchangers in the β-intercalated cells are not active, because HCO_3^- is being retained, not excreted. However, these exchangers are expressed during alkalosis and depend on the lumenal concentration of Cl^- to effectively transport the HCO_3^- into the tubule. The importance of distal lumenal Cl^- is illustrated in contraction alkalosis, as seen with chronic vomiting and volume depletion.

In response to the alkalosis caused by loss of H^+ during vomiting, the renal HCO_3^-/Cl^- exchangers are expressed but are unable to function because of the low level of Cl^- in the collecting duct fluid. The low Cl^- is a result of fluid- and sodium-retaining mechanisms (e.g., sympathetic nervous system [SNS], renin-angiotensin system, aldosterone, antidiuretic hormone [ADH]) stimulated in response to volume depletion. Chloride is avidly reabsorbed with the sodium and water, leaving little in the distal areas of the nephron. The problem can be corrected by isotonic fluid replacement, which will decrease SNS and renin-angiotensin system activation and aldosterone and ADH release, and increase Na^+ and Cl^- delivery to the collecting ducts. The HCO_3^-/Cl^- exchanger will then be able to function, and excess HCO_3^- will be excreted, correcting the alkalosis.

Alkalosis

Alkalosis results from the loss of fixed acid or gain of HCO_3^-. Chronic hyperventilation (for example, at high altitude) will cause the loss of CO_2 and result in respiratory alkalosis. **Metabolic alkalosis** can result from:

- Vomiting, which results in the loss of significant amounts of H^+ in the form of HCl and volume contraction.
- Sodium bicarbonate overdose.
- Chronic diuretic usage, which can cause hypokalemia, volume contraction, aldosterone excess, and chloride depletion, all of which are associated with alkalosis.

During alkalosis, HCO_3^-/Cl^- exchange by transporters in β-intercalated cells of the renal collecting ducts is activated, allowing secretion and excretion of bicarbonate until normal pH is attained.

CLINICAL CORRELATE
Metabolic Ketoacidosis

A common cause of ketoacidosis is poorly controlled diabetes. When glucose is not able to efficiently enter cells there are two immediate consequences: elevated blood glucose, and increased cellular β-oxidation of fatty acids to provide an alternate energy source in the absence of intracellular glucose. If the rate of oxidation is high, metabolites including ketoacids (or ketone bodies) enter the blood, decreasing the pH. Several problems ensue:

- **Acidosis:** The ketoacids are filtered at the glomeruli and eliminated in the urine, but the production overwhelms excretion. Plasma bicarbonate may not be sufficient to buffer the acid load, and in severe cases the free bicarbonate will be heavily consumed, and blood pH will be dangerously reduced (i.e., below 7.2). Contributing to this problem, ketone bodies interfere with the production of ammonia from glutamine in the nephron, and thus decrease new bicarbonate generation (further decreasing plasma bicarbonate levels).
- **Glucosuria:** Glucose is excreted in the urine, because the elevation in filtered glucose load overwhelms the renal sodium-glucose transporters. The glucose pulls water with it, creating polyuria (high urine volume).
- **Volume expansion and cellular contraction:** When glucose increases in the blood, it exerts additional osmotic force, keeping water in the vascular space. This expands the ECF, while the ICF decreases. Blood pressure may increase, and the concentration of other plasma constituents, including electrolytes and proteins, will be diluted. Ultimately, diabetic ketoacidosis may actually result in dehydration due to osmotic diuresis and vomiting.
- **Toxicity:** The keto acids in the blood are toxic and ultimately may cause coma and death if blood glucose level is not corrected. The most severe consequences are seen primarily in type 1 (insulin-dependent) diabetes, and death from ketoacidotic coma is rarely seen in people with type 2 (insulin-resistant) diabetes. With insulin treatment, β-oxidation of fatty acids and therefore ketoacid production are reduced, and urinary excretion is able to eliminate the excess acid.

Review Questions

CHAPTER 16: OVERVIEW, GLOMERULAR FILTRATION, AND RENAL CLEARANCE

1. If the clearance of a freely filtered substance is **less than** the clearance of inulin, then the substance:

A. is filtered and completely reabsorbed.
B. is filtered and completely secreted.
C. underwent net reabsorption.
D. underwent net secretion.
E. was neither secreted nor reabsorbed.

2. Diabetic nephropathy is associated with thickened glomerular capillary basement membranes. The decrease in glomerular filtration rate results from:

A. a reduction in renal blood flow.
B. a reduction in glomerular capillary hydrostatic pressure.
C. a reduction in the permeability of the glomerular filtration barrier.
D. an increase in the glomerular capillary hydrostatic pressure.
E. an increase in the permeability of the glomerular filtration barrier.

3. The kidneys perform all the following functions EXCEPT:

A. production of aldosterone.
B. excretion of excess body acid.
C. regulation of fluid and electrolyte homeostasis.
D. activation of vitamin D.
E. ammoniagenesis.

4. Renal blood flow (RBF) in a young man was determined to be 1 L/min. If his inulin clearance is 125 mL/min, and hematocrit is 0.4, what is his renal filtration fraction?

A. 15%
B. 20%
C. 25%
D. 30%
E. 35%

CHAPTER 17: RENAL TRANSPORT PROCESSES

5. Reabsorption of glucose occurs in the:

A. proximal tubule.
B. thin descending limb of Henle.
C. thick ascending limb of Henle.
D. distal tubule.
E. collecting duct.

6. Potassium handling by the kidneys is affected by all of the following **EXCEPT:**

A. dietary potassium.
B. plasma potassium concentration.
C. plasma aldosterone.
D. plasma antidiuretic hormone.
E. acidosis.

7. "Loop" diuretics such as furosemide or bumetanide produce a diuresis by targeting which of the following transporters?

A. Na^+-glucose cotransporters
B. Na^+/H^+ antiporters
C. Na^+/K^+ ATPase
D. Na^+-K^+-$2Cl^-$ cotransporters
E. Na^+-HCO_3^- cotransporters

CHAPTER 18: URINE CONCENTRATION AND DILUTION MECHANISMS

8. Antidiuretic hormone (ADH)–sensitive water channels (aquaporins) are located in the:

A. proximal tubule.
B. thin descending limb of Henle.
C. thick ascending limb of Henle.
D. distal tubule.
E. collecting duct.

9. All of the following factors contribute to establishing or maintaining the medullary interstitial concentration gradient EXCEPT:

A. distal tubule sodium reabsorption.
B. Na^+-K^+-$2Cl^-$ cotransporters on the thick ascending limb of Henle.
C. solute-free water reabsorption in the descending limb of Henle.
D. the counter-current multiplier effect.
E. urea recycling.

10. A patient with chronic pyelonephritis has the following laboratory values:

Urine flow = 3 mL/min P_{osm} = 300 mosm/L
U_{osm} = 200 mosm/L

The free water clearance in this person is:

A. −3.
B. −1.
C. 0.
D. +1.
E. +3.

CHAPTER 19: REGULATION OF EXTRACELLULAR FLUID VOLUME AND OSMOLARITY

11. Select the **TRUE** statement regarding the renin-angiotensin-aldosterone system.

A. Renin secretion is stimulated by high tubular fluid sodium concentration.
B. Angiotensin I is converted to angiotensin II exclusively in the pulmonary circulation.
C. Angiotensin II directly stimulates proximal tubular sodium reabsorption.
D. High tubular fluid flow rate in the distal tubule will stimulate renin secretion.
E. Aldosterone stimulates proximal tubule sodium reabsorption.

12. A severely dehydrated patient is admitted to the Emergency Department. Which of the following would **NOT** be elevated in this patient?

A. Plasma atrial natriuretic peptide (ANP)
B. Plasma renin
C. Plasma antidiuretic hormone (ADH)
D. Sympathetic nervous system activity
E. Plasma aldosterone

13. Diabetes insipidus:

A. usually involves reduction of renal V2 receptors for antidiuretic hormone (ADH).
B. is associated with increased water channels (aquaporins) in the collecting ducts.
C. results in excretion of large quantities of hypertonic urine.
D. occurs mainly in children.
E. results in excretion of large quantities of hypotonic urine.

CHAPTER 20: REGULATION OF ACID–BASE BALANCE BY THE KIDNEYS

14. Renal tubular hydrogen secretion *increases:*

A. when ECF volume is increased.
B. when arterial P_{CO_2} is decreased.
C. when plasma bicarbonate concentration is low due to metabolic acidosis.
D. when plasma aldosterone is low.
E. when plasma antidiuretic hormone is low.

15. Net acid excretion (NAE) is dependent on all of the following factors **EXCEPT:**

A. excretion of ammonium.
B. excretion of bicarbonate.
C. excretion of sodium.
D. excretion of titratable acids.
E. distal H^+ secretion.

16. Using the following blood values, determine the acid–base disorder:

pH	P_{CO_2}	HCO_3^-	Na^+	K^+	Cl^-
7.28	26 mm Hg	14 mEq/L	136 mEq/L	5.0 mEq/L	100 mEq/L

A. Metabolic alkalosis
B. Metabolic acidosis from acid gain
C. Metabolic acidosis from diarrhea
D. Respiratory acidosis
E. Respiratory alkalosis

17. When compared to normal values, in *acute uncompensated respiratory alkalosis,* plasma:

A. pH and P_{CO_2} are high, and HCO_3^- is normal.
B. pH and P_{CO_2} are low, and HCO_3^- is high.
C. pH is high, and P_{CO_2} and HCO_3^- are low.
D. pH is high, P_{CO_2} is low, and HCO_3^- is normal.
E. pH is high, P_{CO_2} is low, and HCO_3^- is high.

18. The major titratable acids (TA) excreted in the urine are in the form of:

A. $H_2PO_4^-$.
B. lactic acid.
C. K_2PO_4.
D. H_2CO_3.
E. keto acid.

Section 6

GASTROINTESTINAL PHYSIOLOGY

What makes the gastrointestinal (GI) tract interesting? It is an area of our bodies that we are acutely aware of multiple times a day. We have hunger pangs and feel "full"; we become thirsty, hear intestinal sounds, expel gasses, and feel the urge to defecate. Also, GI-related distress and pathology is high on the list of personal and medical complaints. Homeostasis in the whole organism relies on the input of nutrients (gas exchange, food, and water), so the GI tract is a critical component of the supply side.

Chapter 21 **Overview of the Gastrointestinal Tract**

Chapter 22 **Motility through the Gastrointestinal Tract**

Chapter 23 **Gastrointestinal Secretions**

Chapter 24 **Hepatobiliary Function**

Chapter 25 **Digestion and Absorption**

Review Questions

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CHAPTER 21 Overview of the Gastrointestinal Tract

STRUCTURE AND OVERALL FUNCTION OF THE GASTROINTESTINAL TRACT

The GI tract can be thought of as one long tube with an input (mouth) and output (anus), with specialized areas, and direct input from associated organs (liver, pancreas, and gallbladder) (Fig. 21.1). Along the tract there are sphincters that separate major sections of the tract, allowing the regulation of flow of food into the stomach and **chyme** (food and digestive juices) out of the stomach and through the intestines.

A brief tour down the tract:

- **Mouth:** Mechanical digestion occurs through **mastication** (chewing), and chemical digestion begins on the predominant dietary carbohydrate, **starch,** and to a small degree on **lipids.** The salivary glands secrete saliva, which helps buffer, digest, and lubricate the food so it can be swallowed.
- **Esophagus:** As soon as swallowing occurs, the bolus of food enters the esophagus through the relaxation of the upper esophageal sphincter. The esophagus is a tube that allows passage of the bolus of food through the chest and into the stomach. At the end of the esophagus the **lower esophageal sphincter** (**LES**) relaxes to allow the bolus into the stomach.
- **Stomach:** This is a pouch in the tract that is specialized for the storage of food, secretion of digestive enzymes and hydrochloric acid (HCl), and mixing of the food and digestive juices to make **chyme.** The **pyloric sphincter,** at the distal end of the stomach, regulates the entry of chyme into the small intestine.
- **Small intestine:** The small intestine is made of three sections, the **duodenum** (~1 foot long), the **jejunum** (~8 feet long), and the **ileum** (~10 feet long). Secretions from the liver, gallbladder, and pancreas enter the small intestine via the common bile duct and through the sphincter of Oddi, into the duodenum. A key aspect of the small intestine is the presence of finger-like projections in the intestinal mucosa (the **villus brush border**), which increases the surface area for absorption. Through the tract, there is only one layer of intestinal epithelial cells, or **enterocytes,** between the lumen of the tract and the systemic blood supply. While this effectively keeps the lumenal contents in the small intestine, when absorption occurs, there is rapid and efficient movement of nutrients into the blood. However, the enterocytes are vulnerable to the harsh environment of the gut lumen and need to be protected. This protection is conferred by intestinal buffers and mucus. Despite the protection, intestinal cells will slough off and be replaced by new cells every 3 to 4 days.

  The majority of digestion occurs in the jejunum by pancreatic enzymatic action. When nutrients are digested to the constitutive elements (e.g., monosaccharides, monoglycerides, amino acids, etc.), absorption can occur all along the small intestine, although most nutrients are absorbed by the mid- jejunum. The **terminal part of the ileum** is also the site of vitamin B12 absorption and recycling of bile. Chyme that remains in the tract leaves the small intestine through the **ileocecal sphincter,** into the large intestine (colon).
- **Large intestine:** The large intestine does not have a brush border, and the primary functions are dehydration of chyme to produce feces, and then storage of the feces until defecation. The large intestine consists of the cecum, appendix, colon, rectum, and anal canal. At the end of the rectum, the **internal** and **external anal sphincters** regulate expulsion of feces.

Another important aspect of the tract is that its musculature is smooth muscle, except for the mouth, upper esophagus, and external anal sphincter, which have skeletal muscle. Skeletal muscle allows voluntary control of both input (chewing, swallowing) and output (defecating). The rest of the tract has **longitudinal** and **circular** bands of smooth muscle that allow for propulsion and mixing of the chyme. Figure 21.2 illustrates these muscle layers, as well as the **oblique** layer that is unique to the stomach. The oblique layer aids in the mixing component that is important in stomach motility.

Other distinct aspects of the GI tract include a large blood and lymphatic system, secretion of substances from a variety of glands, and a nervous system that is unique to the GI tract (Fig. 21.3).

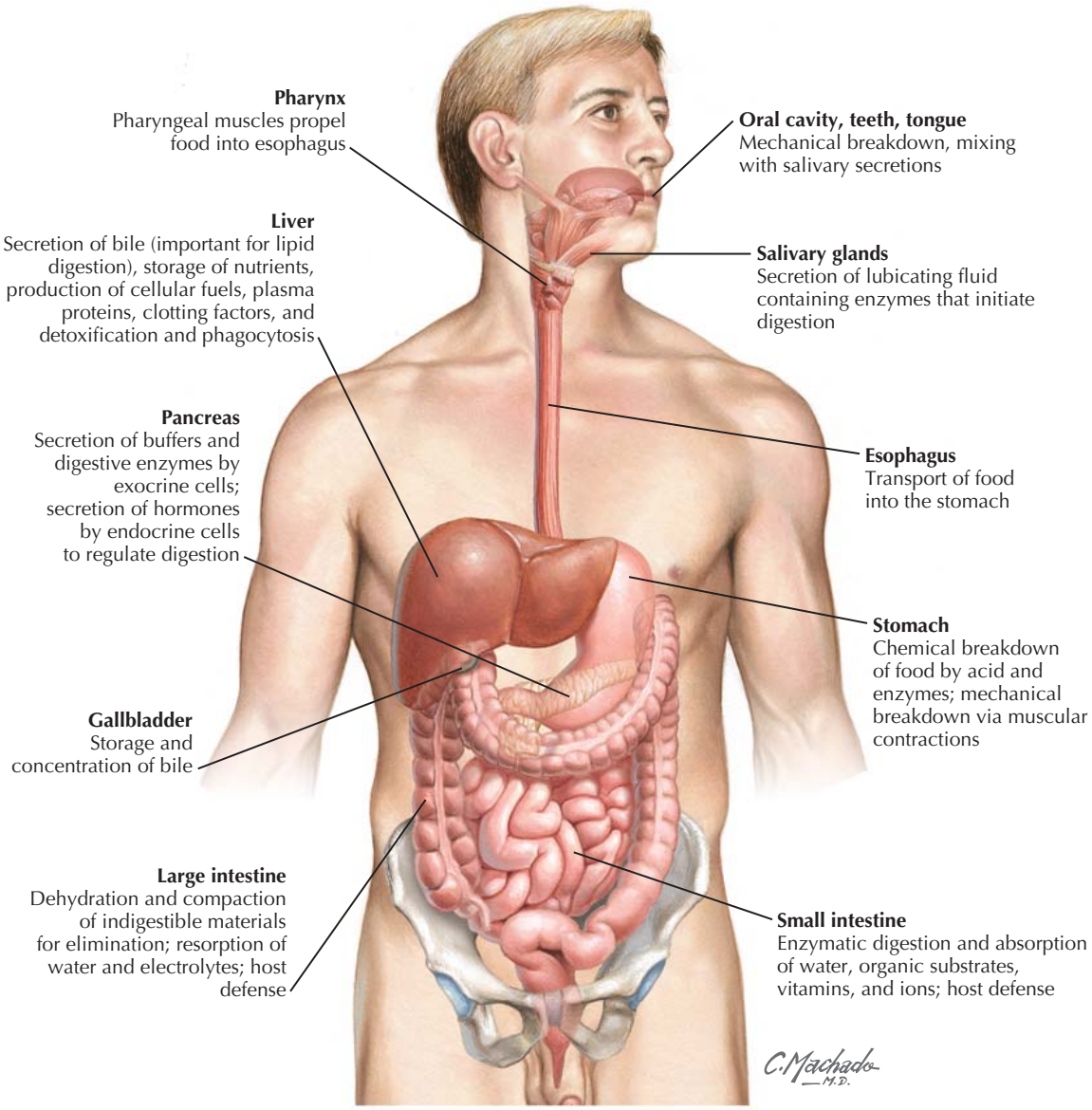


Figure 21.1 Overview of Gastrointestinal Tract The GI tract begins at the mouth and is made up of discrete areas that aid the digestion and absorption of nutrients. Each area of the tract contributes to the efficient processing of the nutrients. This includes the GI-associated organs (liver, pancreas), which provide important secretions including bile, enzymes, and buffers.

Blood Supply

The GI tract has a large blood supply to perform the myriad of functions necessary for digestion, absorption, and propulsion. Oxygen, nutrients, and hormones are brought by the blood to aid in the many secretory, absorptive, and propulsive functions. In addition, efficient absorption of nutrients through the intestinal cells requires a high blood flow, which ensures that there is always a gradient for nutrient entry into the bloodstream.

Blood supply to the GI tract is from the splanchnic bed (superior and inferior mesenteric arteries), with the capillary system



During active digestion, blood flow to the GI tract increases to ~3 times normal to facilitate the metabolic and digestive needs. This rerouting of blood from other tissues (especially skeletal muscle) to the gut can significantly alter the distribution of cardiac output. The proportions of cardiac output perfusing various tissues are described in Section 3 (Chapter 8) for the normal resting state. These proportions are altered postprandially, favoring blood flow to the GI tract.

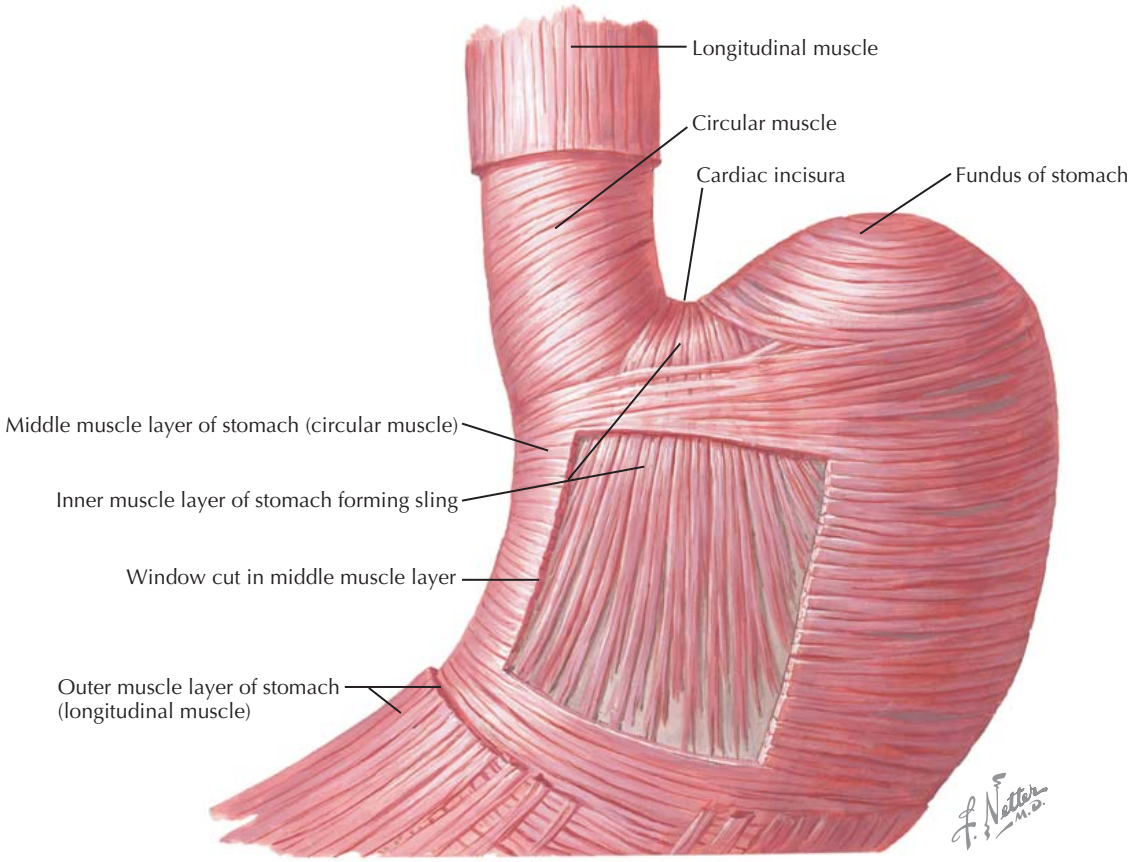


Figure 21.2 Musculature of the Stomach The stomach has longitudinal, circular, and oblique muscle layers. The oblique layer helps mix and grind the chyme.

extending into all of the villi. Blood flows out of the tract through the **portal veins,** directly to the liver (Fig. 21.4). This is the **"first pass"** effect, whereby absorbed substances are routed directly to the liver (without entering into the general circulation), where much processing occurs.

Glandular Secretions

To efficiently move and digest the chyme, a tremendous amount of substances are secreted into the lumen of the tract. Glands produce liters of saliva, mucus, buffers, and enzymes to facilitate the process.

Lymphatics

Lymph lacteals (lymphatic capillaries) are found throughout the intestines and extend into the villi of the small intestine, allowing absorption of lipids. The lymphatic system is also extensive in the liver, where it absorbs fluids and proteins and transports them to the systemic venous blood. Lymphatic transport of proteins contributes substantially to plasma oncotic pressure and provides binding proteins for circulating substances including hormones, calcium, and iron.

General Functions of the GI Tract

- Digestion: Both mechanical and chemical digestion occur in the tract. **Mechanical** digestion refers to the physical breakdown of the food by initial chewing and grinding in the stomach. **Chemical** digestion is through specific enzymatic action and gastric acid (HCl).
- Endocrine: A great number of hormones are produced by GI-associated cells (from stomach, intestines, pancreas, and liver). Some are hormones, entering the general circulation and affecting other parts of the GI tract as well as other organs. There are also hormones produced that act on adjacent GI tissues in a paracrine manner. In fact, the first substance identified as a "circulating hormone" was the GI hormone **secretin.**
- Expulsion: After absorption of nutrients through the tract, the fecal waste matter (fiber, undigested material, bacteria, fat from sloughed cells) is expelled through defecation.
- Protection: We constantly ingest bacteria and antigens, and the GI tract keeps this under control through degradation by gastric HCl, as well as immune activity (IgA and Peyer's patches).

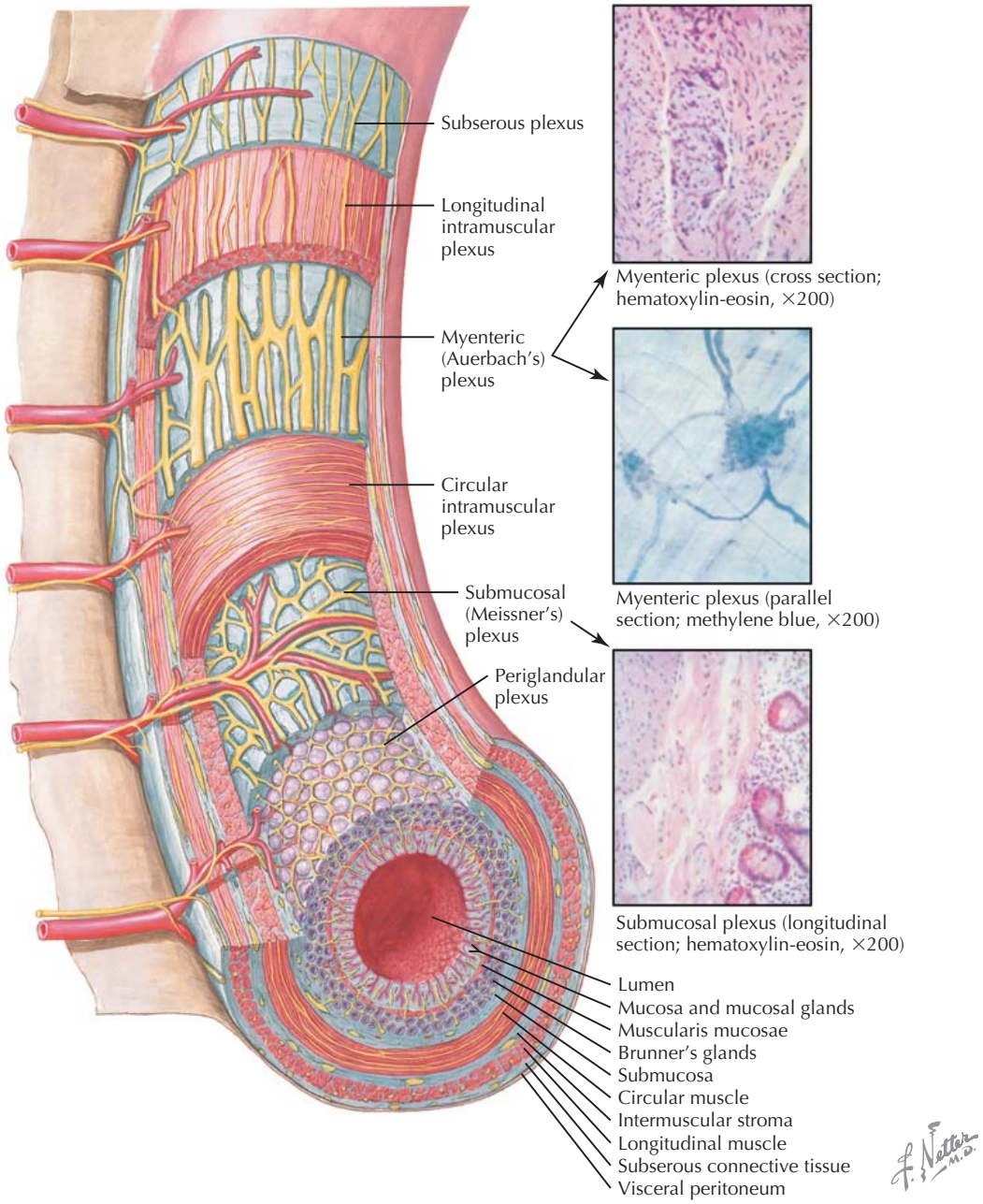


Figure 21.3 The Enteric Nervous System The myenteric plexus (nerve net) is between the longitudinal and circular muscle layers of the GI tract, and stimulation of these nerves affects muscle contraction. The submucosal plexus is between the circular muscle and submucosa, and stimulation can affect GI secretions. The enteric nerves can function without extrinsic nerves, through local mechanisms.

- Motility: The chyme needs to be propelled through the tract to allow the digestion, absorption, and expulsion to occur. There are several different forms of propulsion through the tract, and if an area loses the ability to move chyme, serious pathology can occur.
- Absorption: The ultimate goal for the elaborate GI system is getting bulk nutrients into the body. The intestines absorb most of the nutrients that are digested, and the majority of absorption occurs in the first half of the small intestine (through the jejunum). This is accomplished because of the large surface area provided by the villi on the enterocytes of the small intestine.
- Secretion: The secretion of mucus, buffers, hormones, and enzymes facilitates lubrication, digestion, motility, and absorption through the tract.
- Storage: Both the stomach and large intestine act as storage sites. The stomach accommodates food as it is mixed with the gastric acid and enzymes promoting

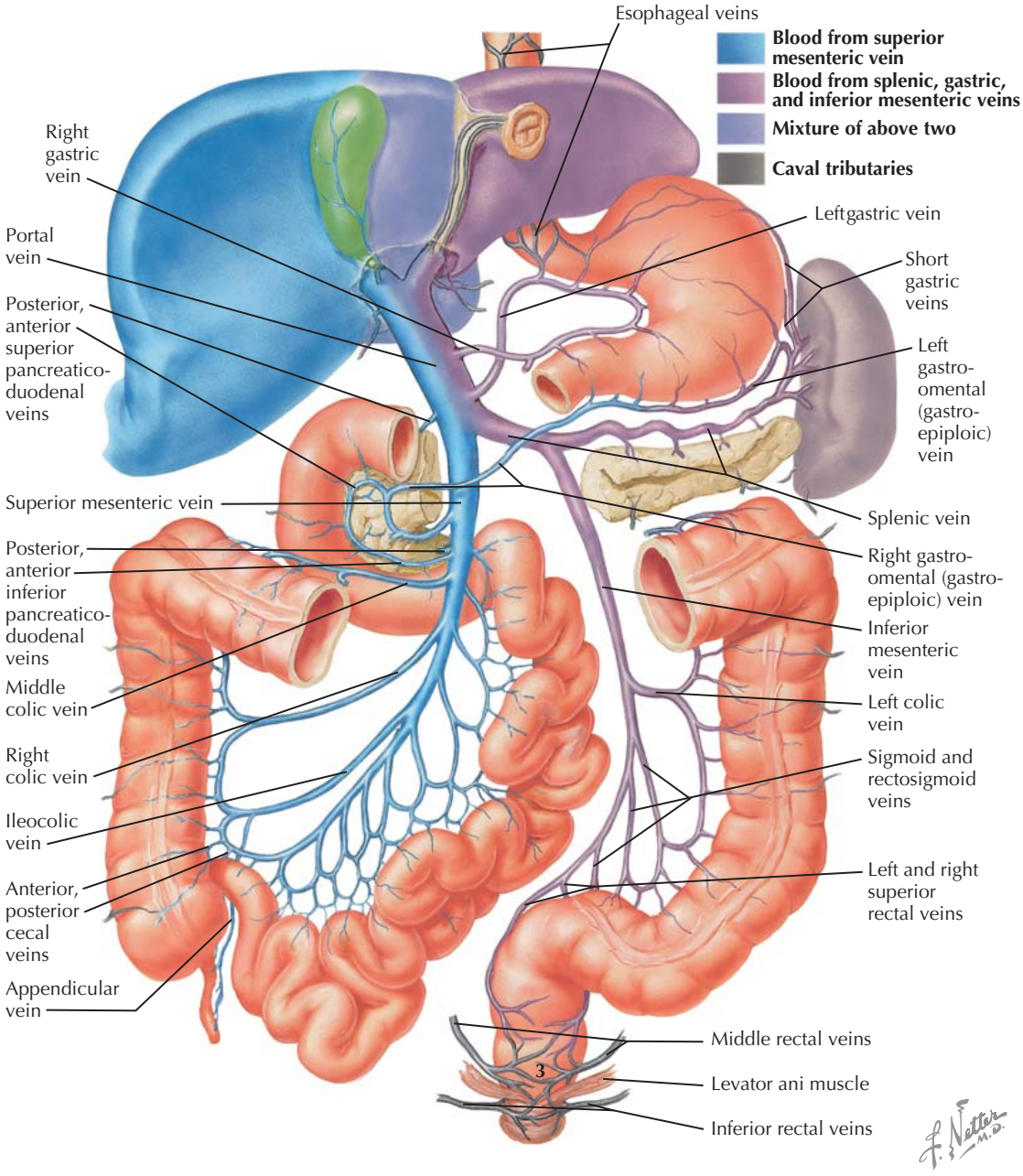


Figure 21.4 The Portal System The portal vessels carry venous blood directly from the intestines to the liver through the portal vein.

breakdown of food into chyme that is small enough to pass through the pyloric sphincter into the duodenum. This storage is facilitated by **receptive relaxation,** mediated by the vagus nerve (see Chapter 22). If the relaxation did not occur, it would dramatically limit the quantity of food that could be ingested during a meal and enter the stomach. On the opposite end, the large intestine dehydrates the chyme to produce feces, and the type of motility there allows retention of the feces until expulsion.

THIRST AND HUNGER: BEHAVIORAL RESPONSES TO MAINTAIN THE MILIEU INTERIEUR

Thirst

To maintain a homeostatic internal environment, we have behavioral responses to ensure adequate ingestion of fluid and nutrients: thirst and hunger. **Thirst** is a response to cell and vascular dehydration causing elevated plasma osmolarity. The

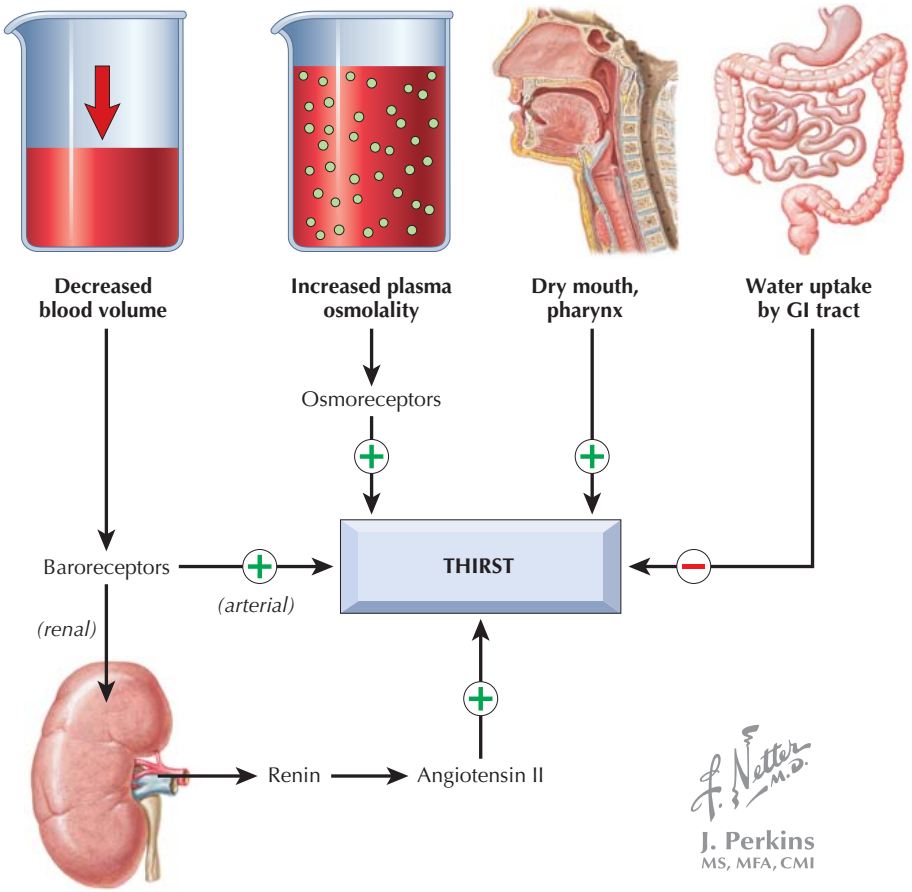


Figure 21.5 Thirst The thirst response is initiated by either a small increase in plasma osmolarity (1% to 2%) or a significant decrease in blood volume (~10%). The mechanism is depicted in this illustration. *(Modified from Widmaier E, Raff H, Strang K: Vander, Sherman, and Luciano's Human Physiology, 9th ed., New York, Mc-Graw Hill, 2003.)*

loss of fluid can be a result of urine and fecal fluid loss, as well as **insensible loss** of water from sweating and breathing (Fig. 21.5). The feeling of thirst can be stimulated when hypothalamic osmoreceptors sense elevated plasma osmolarity, or arterial baroreceptors sense low blood pressure (often associated with reduced extracellular fluid volume). Both the baroreceptors and osmoreceptors regulate the thirst response (mediated through the hypothalamus) and the release of **antidiuretic hormone** (**ADH**, also known as **vasopressin**). ADH has effects on renal retention of water (discussed in Section 5) and vascular smooth muscle contraction (discussed in Section 3). Thirst is controlled at both central and local levels. Dry mouth can be relieved temporarily by rinsing the mouth with fluid; however, if the overall cause is dehydration, the thirst response will return rapidly.

Appetite and Hunger

Although the mechanisms are not as clearly understood as those involved in thirst, hunger is a powerful behavioral response to ensure nutrient intake (Fig. 21.6). The main site of control, as with thirst, resides in the hypothalamus, which has both the hunger and satiety centers. The basic control of the centers is through essential nutrients such as glucose and fatty acids. Stimulation of appetite can occur through low blood glucose, as well as through sensory input (e.g., smelling, seeing food). The GI tract also plays a role, releasing hormones that stimulate (ghrelin, galanin, orexin) and decrease (cholecystokinin, peptide YY) hunger at the level of the hypothalamus. A key factor in satiety is the hormone leptin, which can be released from adipose tissues in response to insulin. Leptin receptors are present on the hypothalamus (as well as other tissues) and leptin stimulates the satiety center. In addition to such specific factors, the hunger



The control of plasma osmolarity is so important that a small (2%) change (e.g., from 300 to 306 mosm/L) can induce thirst and ADH secretion. In contrast, a 12% to 15% reduction in extracellular fluid (ECF) volume is needed to stimulate the same ADH response if osmolarity is unchanged. Thus, when thirst is stimulated by dehydration, sufficient fluid has been lost to raise plasma osmolarity and stimulate ADH.

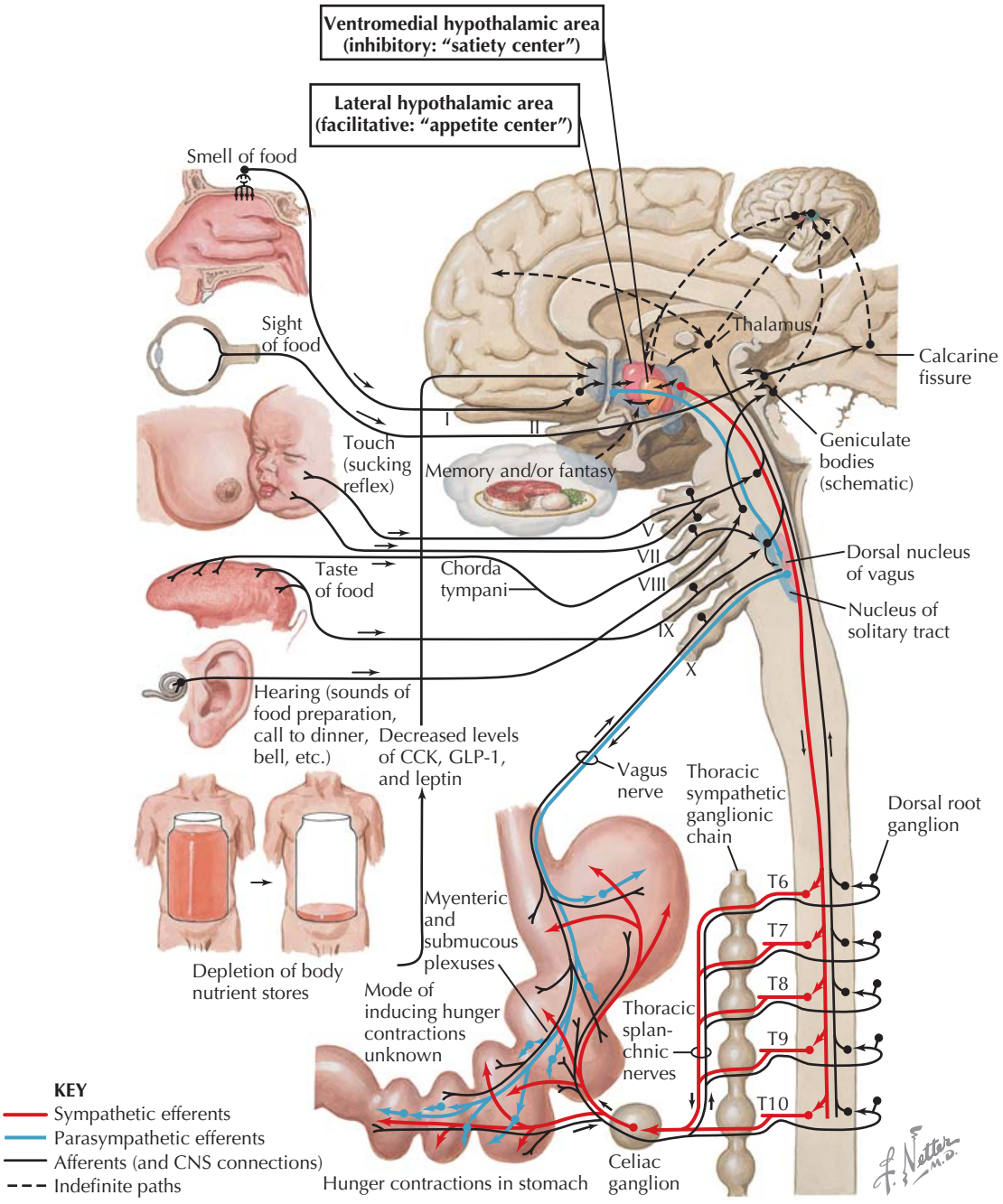


Figure 21.6 Appetite and Hunger The feelings of hunger and satiety are not completely understood; however, general pathways are outlined above. The hypothalamus (see Chapter 26) plays important roles in both hunger (lateral hypothalamic area) and satiety (ventromedial hypothalamic area) and responds to endocrine and nerve input. Multiple hormonal systems facilitate the feeling of satiety: cholecystokin, peptide YY and GLP-1 (glucagon-like peptide-1) are released in response to ingested food, decreasing hunger. In addition, the hormone leptin is released in response to insulin and acts at the satiety center of the hypothalamus. In contrast, hunger "pains" are elicited through vagal stimulation of the enteric nerves, and the release of other GI hormones, including ghrelin and orexin, stimulate the appetite center of the hypothalamus. CCK, cholecystokinin.

Sweat is hypo-osomotic. Its concentration of salts (mainly sodium and chloride) is less than found in plasma. Thus, sweating depletes the extracellular fluid (ECF) of more fluid than salt, which increases the plasma osmolarity. That stimulates the thirst response and reduces fluid losses by the kidney and colon, helping to maintain blood pressure (see Fig. 21.5).

response is affected by body mass and will provide nutrients for energy expenditure.

FLUID SHIFTS AND pH THROUGH THE TRACT

Although only ~2 liters of fluid is ingested daily, the fluid flux in and out of the GI tract is actually about 9 liters. This is necessary for digestion of the chyme; however, the secretions need to be reabsorbed back into the bloodstream with the added nutrients (Fig. 21.7). With the addition of secretions, the pH of the chyme changes. In the stomach, gastric acid secretion brings the pH to ~2, allowing for indiscriminant digestion of food. To protect the small intestine from the corrosive effects of the acid, buffers (pH ~8) are secreted into the duodenum from the liver, pancreas, and gallbladder, as well as from intestinal crypt cells. This raises the pH of the chyme in the first few centimeters of the duodenum to ~5. The addition of the buffers through the tract brings the pH of the chyme up to ~7.4 by the early jejunum. This is optimal for the pancreatic enzyme action.

While you are conscious of the salivary secretions that occur in anticipation of, and during, feeding, the other fluid fluxes tend to go unnoticed, although at times intestinal sounds called **borborygmi** may be heard—these are the result of fluid and gas fluxes in the lumen.

THE ENTERIC NERVOUS SYSTEM

The GI tract is unique in having an intrinsic nervous system, made up of the **myenteric** and **submucosal plexuses** (see Fig. 21.3). This **enteric nervous system** (**ENS**) is able to function independently, using input from mechanoreceptors, chemoreceptors, and osmoreceptors located in the luminal epithelium of the tract. The ENS receives input from the central and autonomic nervous system (CNS and ANS) and hormones, which help fine-tune and regulate the ENS. Without autonomic innervation, the ENS would still function, but in a less coordinated manner.

Located between the circular and longitudinal muscle layers, the **myenteric (Auerbach's) plexus** regulates contraction and relaxation of the musculature, causing motility and mixing of the luminal contents. The submucosal plexus (Meissner's

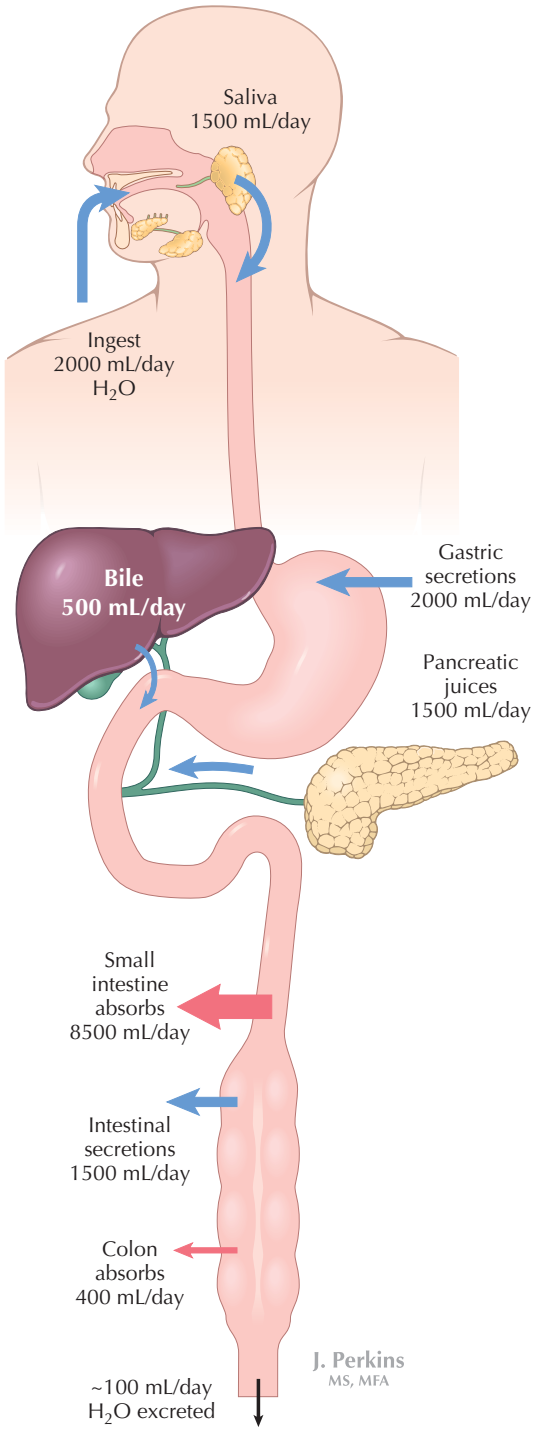


Figure 21.7 Fluid Shifts through the GI Tract While we ingest ~2 liters (L) of fluid in food and drink each day, the GI tract adds ~8 L of secretions to facilitate digestion and absorption of the nutrients. These secretions, including buffers, acid, and enzymes, are absorbed back into the blood (primarily by absorption in the small intestine) so that only ~200 milliliters (mL) of fluid is excreted in feces each day.

plexus) is located between the circular muscle and submucosa and regulates local fluid secretions.

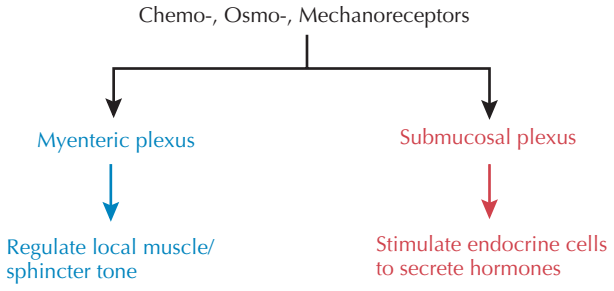
THE GI TRACT AS AN ENDOCRINE ORGAN

Endocrine cells in the gastric and intestinal epithelia synthesize and release a variety of hormones into the bloodstream. The hormones act on other areas of the gastrointestinal system, such as the liver and pancreas, in addition to the stomach and intestines. These hormones regulate GI function, as well as hunger and satiety and insulin secretion. In addition, some hormones act on adjacent cells in a paracrine manner. An example of this is the action of somatostatin (produced in gastric pit cells) on adjacent parietal cells. GI hormones will be covered in Chapter 23.

INTEGRATED REGULATION OF GI FUNCTION

Proper GI function results from the integrated responses from central and local factors including:

- **Central nervous system (CNS):** Sensory input to the CNS provides initial stimulus for salivary and gastric acid secretion and is integral to many reflexes. Simply smelling or seeing food will initiate a central response. The CNS acts thorough the sympathetic and parasympathetic nervous systems.
- **Enteric nervous system (ENS):** The myenteric and submucosal nerve plexuses are unique to the GI tract. These nerve nets receive input from the PNS and SNS, as well as hormones, peptides, and lumenal receptors that sense the chemical composition of the chyme.
- **Parasympathetic nervous system (PNS):** In general, the PNS promotes secretion and motility in the GI tract, and many of the actions are through the vagus nerve.
- **Sympathetic nervous system (SNS):** The SNS slows secretion and motility in the GI tract. Think of what happens in "fight or flight" reactions, in which you need more blood flow to skeletal muscle, and require less perfusion of the intestines.
- **Lumenal receptors:** The GI tract has many different receptors that react to the chyme in the lumen of the tract and act locally on the ENS to regulate motility and secretions through the general scheme:



  - **Mechanoreceptors** sense stretch of the smooth muscle, and the generated signal is transduced through the myenteric plexus, stimulating contractions.
  - **Chemoreceptors** sense the chemical composition of the chyme and regulate motility and secretion of buffers to control luminal pH during the influx of acidic chyme into the duodenum.
  - **Osmoreceptors** sense the osmolarity of the chyme in the small intestine. This is important, because there is only a one-cell barrier between the chyme in the lumen of the small intestine and the capillaries, and hypertonic chyme can exert an osmotic force, pulling fluid out of the cells (and ultimately the plasma). Thus, the osmoreceptors control the amount of chyme entering the small intestine, as well as the amount of secretions necessary to buffer the chyme.
- **Hormones:** As stated above, the GI tract produces a variety of endocrine, paracrine, and autocrine factors, which increase the efficiency of the tract (both for motility and secretions).

Lastly, while all of these areas are important in the coordinated function of the GI tract, it bears noting that the **parasympathetic nerves,** primarily via the **vagus,** are responsible for multiple effects early in the digestive process. Some of the actions they stimulate or participate in include the following:

- Initiating salivation upon seeing, smelling, tasting food during the cephalic phase of salivation (through facial and glossopharyngeal nerves).
- Initiating acid production when food is in the mouth during the cephalic and gastric phases of gastric acid secretion (vagus).
- Stimulating pancreatic enzyme secretion during the cephalic and gastric phases of pancreatic secretion (vagus).
- Stimulating pancreatic enzyme and buffer secretion during the intestinal phase of pancreatic secretion (vagus).
- Stimulating primary (swallowing center of medulla and vagus) and secondary esophageal peristalsis (vagus, with enteric nerves).
- Initially relaxing the sphincter of Oddi during cephalic and gastric phases (vagus).
- Causing receptive relaxation of stomach and duodenum (vagus), to accommodate entry of food/chyme.
- Stimulating the synthesis of bile by the liver (vagus).
- Stimulating intestinal motility (ileal motility and colonic mass movements) (vagus to upper colon, pelvic nerves on lower colon; with gastrin and cholecystokinin [CCK]).

Thus, if vagal innervation of these areas is impaired, the digestive and propulsive processes will be dysregulated.

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CHAPTER 22
Motility through the Gastrointestinal Tract

ELECTRICAL POTENTIALS

Motility in the gastrointestinal (GI) tract involves both mixing and propulsive movements, and is determined by the mechanical activity of the intestinal smooth muscle. The movements serve to mix, transport, and eliminate matter. To accomplish the muscle contraction, electrical potentials must be generated.

The electrical activity in the GI tract is unique. Unlike other tissues, there are undulations in the **resting membrane potential** known as **slow waves,** which are generated by the **interstitial cells of Cajal (ICC)**. The ICC are located throughout the GI tract between the longitudinal and circular muscle layers, and the undulations in their resting potential are probably caused by the small changes in membrane charge resulting from Na^+/K^+ ATPase activity. The ICC act as pacemakers, determining the number of waves that occur per minute along different segments of the GI tract. Because of gap junctions between cells, the slow waves (also called the **basic electrical rhythm** [**BER**]) can be propagated over relatively long segments of the tract.

Under resting conditions, the slow waves undulate between −70 and −80 millivolts (mV) and do not cause contractions. However, if the slow waves are depolarized (made less negative) by nerve activity or circulating hormones, the amplitude of the waves may increase, and when peaks of the slow wave cross the threshold of −40 mV, the cells will generate one or more **action (or spike) potentials.**

Neurotransmitters such as acetylcholine (ACh) and substance P (tachykinin) released from parasympathetic nerves terminating on the myenteric plexus depolarize the slow waves, generating action potentials and causing contractions (Figs. 22.1 and 22.2). With greater neurotransmitter release, the amplitude of the waves is higher, producing greater depolarization. This results in more action potentials, increasing the strength of the contraction. Some GI hormones (cholecystokinin [CCK], gastrin) can also depolarize the slow waves, causing contractions. In addition, local mechanoreceptors sensing stretch or chemoreceptors sensing composition of chyme signal the myenteric plexus to fire excitatory motor neurons, depolarizing the slow waves and causing contraction



The **action potentials (AP)** generated by depolarization of the slow waves are caused by the entry of **calcium** into the smooth muscle via voltage-gated channels. The calcium binds to calmodulin, initiating events that result in smooth muscle contraction.

Table 22.1 Slow Waves

Area	Frequency of Slow Waves	General Actions when Depolarized above Threshold
Stomach	3/minute	Mixing
Duodenum	12/minute	Propulsion
Ileum	10/minute	Propulsion
Proximal Colon	3/hour 11/minute	Haustra formation and storage Mass movements and propulsion
Distal Colon	10/hour 17/minute	Haustra formation and storage Mass movements and propulsion

(Fig. 22.3). The characteristic frequency of the slow waves for any section of the tract determines the maximum rate at which contractions could occur, and thus the BER sets the maximal rate of propulsion possible (Table 22.1).

There are also inhibitory motor neurons that are stimulated by the sympathetic nerves and release **vasoactive intestinal peptide (VIP)** and nitric oxide (NO), which hyperpolarize the slow waves (make them more negative), relaxing the smooth muscle (see Fig. 22.3). The interplay between excitatory and inhibitory motor neurons results in a variety of propulsive and mixing movements through the tract (see "Site-Specific Propulsion").

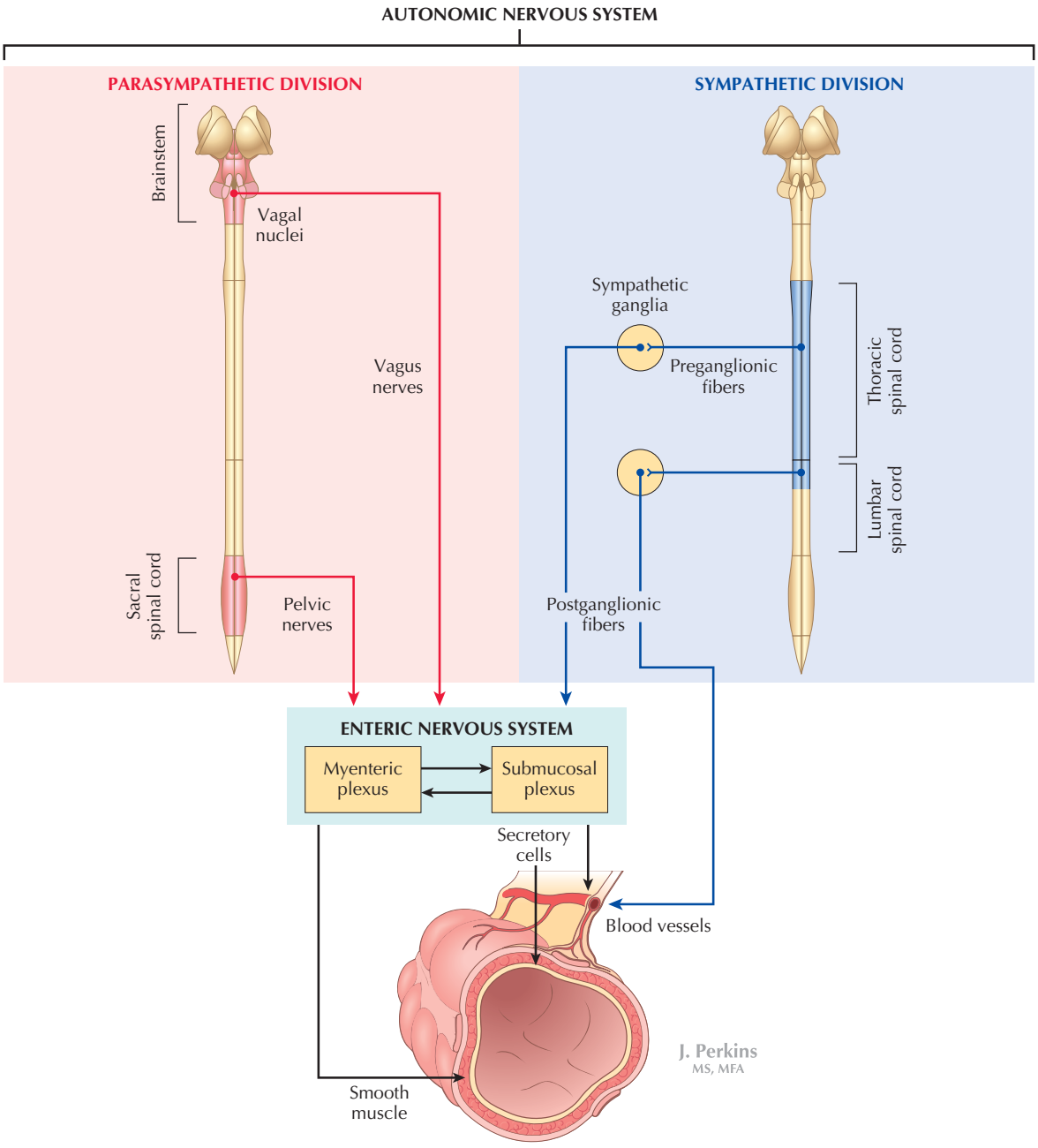


Figure 22.1 Regulation of Enteric Nervous System by Autonomic Nervous System This diagram illustrates basic connections between the enteric nervous system (myenteric and submucosal plexuses) and the autonomic nervous system. In general, stimulation from the parasympathetic nerves enhances motility and secretions through the ENS, whereas sympathetic stimulation reduces motility and secretions.

INTERDIGESTIVE HOUSEKEEPING: THE MIGRATING MYOELECTRIC COMPLEX

Fasting, or the interdigestive state, is characterized by long periods of quiescence, with short periods of waves of contractions. The contractions, called the **migrating myoelectric complex** (MMC), originate in the mid-stomach and continue to the terminal ileum during each cycle and serve to sweep the undigested material and bacteria out of the stomach and small intestine, into the colon. This protects the delicate upper GI tract (small intestine) from damage and sequesters most of the bacteria in the colon, a drier environment less hospitable to bacteria.

There are four phases of the MMC that occur in 75- to 120-minute cycles during fasting, based on contractile activity. Phases I, II, and IV have little activity. Phase III is most

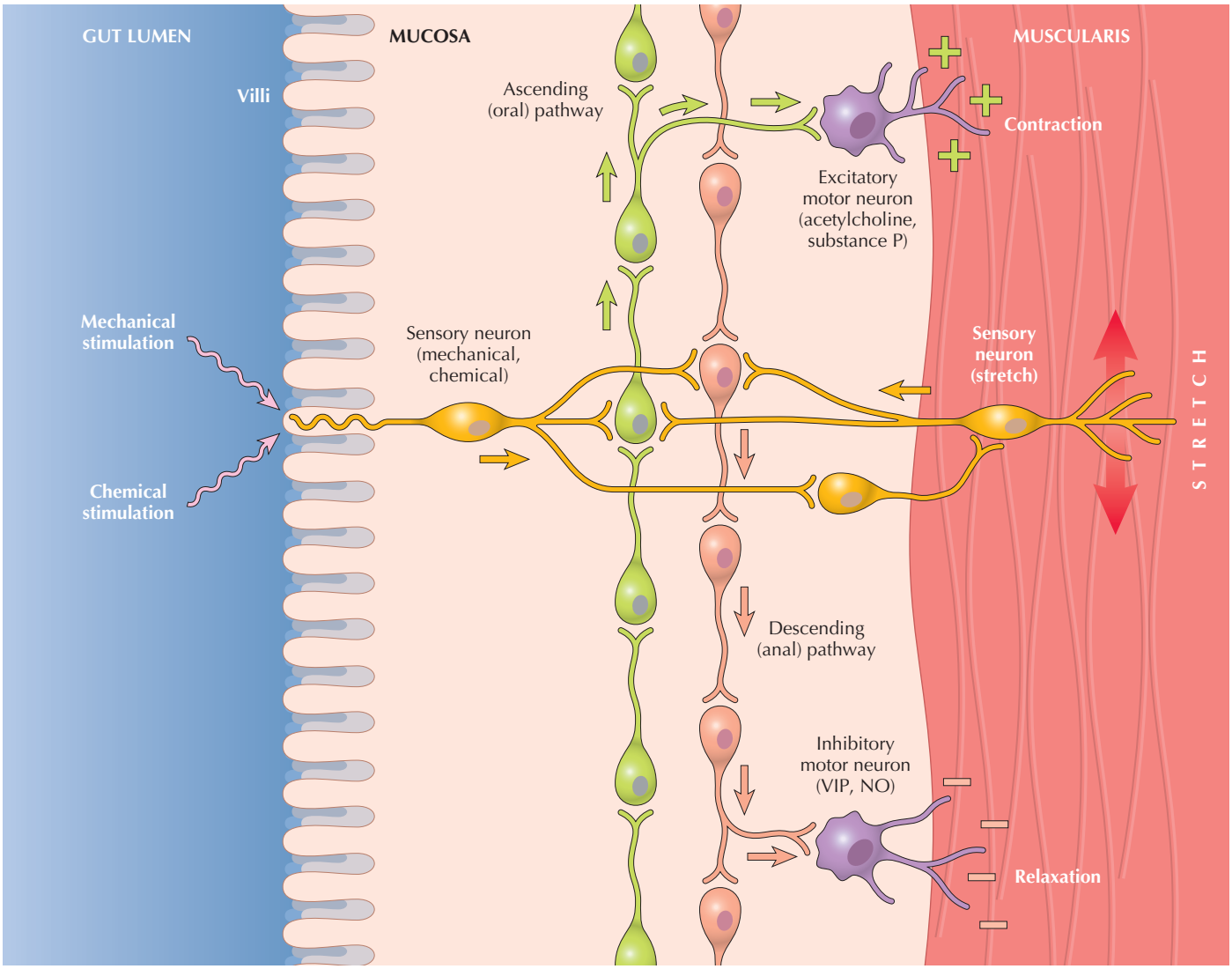


Figure 22.2 Local Control of Motility In response to the presence of chyme in the lumen of the small intestine, mechanoreceptors and chemoreceptors transduce signals to ascending and descending neurons. The ascending *(green)* pathway leads to excitatory motor neurons behind the bolus of chyme, stimulating depolarization of the slow waves, generation of an action potential, and contraction. At the same time, the descending *(orange)* pathway ends in inhibitory motor neurons, which hyperpolarize the slow waves in the muscle, causing relaxation in front of the bolus. The overall result is a peristaltic contraction, moving the bolus toward the anus.

important of the four, when the hormone **motilin** is released from Mo cells of the small intestine into the circulation. Motilin stimulates strong sequential contractions, sweeping bacteria and undigested matter down the tract from mid-stomach into the colon. Phase III lasts only 6 to 10 minutes in each cycle. Motilin acts through the enteric and autonomic nerves to stimulate contractions, which proceed for a few feet aborally, and then start up again slightly further down the intestine. This pattern is repeated until the complex reaches the terminal ileum, and then a new complex is initiated in the stomach.

These cycles begin about 3 hours after the last meal and repeat until ingestion of food. With ingestion, the normal propulsive patterns resume.

SITE-SPECIFIC PROPULSION

Mouth and Esophagus

Food is first moved by chewing and then **swallowing.** There are three stages of swallowing.

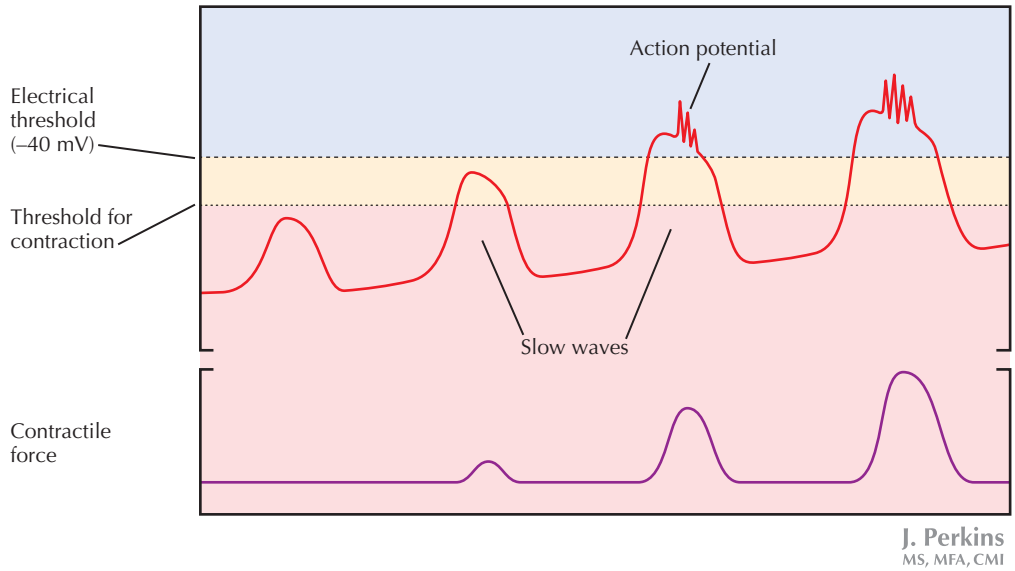


Figure 22.3 Slow Waves Slow waves are present from mid-stomach through the rectum and are the resting membrane potential of the GI smooth muscle. Depolarization of the slow waves above –40 mV stimulates action potentials, which causes contraction of the smooth muscle.

In the voluntary **oral** stage, the bolus of food is moved to the back of the mouth into the pharyngeal region, stimulating touch receptors and initiating the swallowing reflex (Table 22.2). In the **pharyngeal** stage, the bolus of food moves to the back of the pharynx, the larynx moves toward the epiglottis to prevent food entering the trachea, and the upper esophageal sphincter relaxes. The pharyngeal muscles contract, propelling the bolus through the upper esophageal sphincter into the esophagus. During the pharyngeal phase, the swallowing reflex prevents respiration. The last is the **esophageal** stage. When the bolus enters the esophagus, voluntary control of the movement is lost. A wave of **primary esophageal peristalsis** is generated by the swallowing center in the medulla (efferent vagal nerves terminate on the myenteric plexus → excitatory signal → depolarized slow waves → contraction). The alternating contraction and relaxation helps carry the bolus of food through the esophagus to the stomach.

During swallowing, if the bolus is dry and does not move quickly through the esophagus, **secondary esophageal peristalsis** is initiated by local mechanoreceptors sensing stretch. The **lower esophageal sphincter** has a high resting muscle tone, to prevent reflux of gastric acid. The basal tone is maintained by enteric nerves, hormones, and vagal cholinergic fibers: The tone can be increased by sympathetic stimulation. As the bolus nears the lower esophageal sphincter, noncholinergic vagal fibers acting on inhibitory interneurons release VIP and NO, causing relaxation of the sphincter (Fig. 22.4). The bolus then passes into the stomach. If the lower esophageal sphincter is unable to relax, pathology can occur (see "Smooth Muscle Disorders: Achalasia and Hirschsprung's Disease" Clinical Correlate). In addition, the esophagus, like the rest of the tract, is highly vascularized, and damage to the esophageal capillaries (acid reflux, portal hypertension) can result in esophageal bleeding, which can be life-threatening (see "Portal Hypertension and Esophageal Varices in Obstructive Liver Disease" Clinical Correlate in Chapter 24).

Stomach

As the bolus enters the stomach, **receptive relaxation** increases the stomach size, allowing accommodation of the meal. This is vagally-mediated through the release of VIP. As the stomach fills, the stretch and chemical contents stimulate contractions, which help mix the food with the gastric secretions, forming chyme. As the chyme mixes, the contents separate, with carbohydrates and readily digested substances in the lower part (antrum), large chunks in the body of the stomach, and most fats floating at the top. The **transit time** through the stomach depends on the amount and type of food ingested. Small, easily digested meals (high in carbohydrates such as pasta and sugar) move through the stomach quickly (30 to 60 minutes). Meals with more solid foods (meats) and high fat content (fried foods) take much longer (3 to 4 hours) to clear the stomach.

Figure 22.5 illustrates the waves of contractions that begin mid-stomach and move the chyme toward the antrum and pylorus (which acts as a sphincter). Regulation of the tone of the pyloric sphincter occurs through both neural and hormonal pathways (Table 22.3).

For the most part, pyloric tone is high, so as the stomach is filling and contractions are starting, most of the acidic chyme moving into the antrum undergoes retropulsion away from the sphincter (see Fig. 22.5*B, 1* and *2*). As the waves of

CLINICAL CORRELATE
Bariatric Surgery

Receptive relaxation is crucial for the storage function of the stomach, which allows the contents to be well mixed with gastric acid and enzymes and some digestion to occur. If vagal innervation to the fundus is lost, the accommodation will not occur, and stomach pressures will quickly rise, imparting a feeling of "fullness," and the inability to physically get more into the stomach. Reducing the storage ability of the stomach is the rationale behind gastric bypass and stomach stapling in severely obese persons.

- **Adjustable gastric banding** restricts the size of the pylorus, so that only small amounts of food can comfortably enter the stomach. This restricts food intake because of discomfort, but does allow food to enter the intact stomach.
- **Vertical banded gastroplasty** was a common procedure involving both stomach stapling and banding, to create a small pouch while leaving the rest of the tract intact. It is considered dangerous and is performed less frequently today.
- **Gastric bypass,** a common surgery, involves keeping only a small part of the fundus and attaching it to the early jejunum. This leaves little space for food (about a tablespoon-full). In this procedure, the main body of the stomach is "stapled" off and the duodenum is reattached to the jejunum, allowing the digestive juices (primarily from the pancreas and liver) to mix with the food. The overall effect is a reduction in food intake, and weight loss.

Bariatric surgery is not without risk and can be associated with vomiting, diarrhea, reflux, leaking from the surgical sites, and infection. It is usually only recommended in morbidly obese patients.

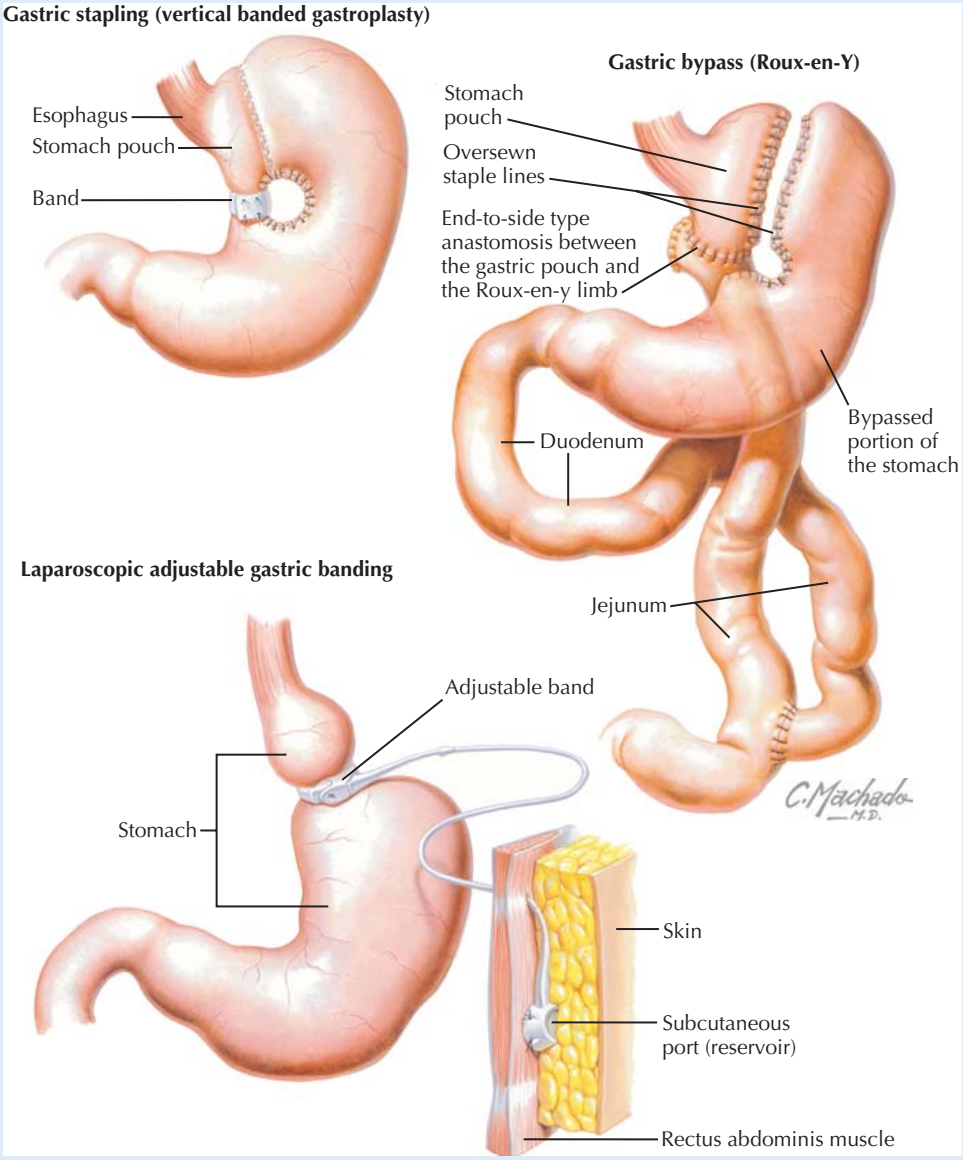


Table 22.2 Main Reflexes through the GI Tract

Reflex	Action	Mediated By
Swallowing	Contraction of pharynx and upper esophagus, inhibition of respiration	Touch receptors in pharynx to swallowing center of the medulla; back to pharynx and upper esophagus through cranial nerves, and to the rest of the esophagus through vagal nerves
Reflexive relaxation of stomach and duodenum	Relaxes the fundus and body of stomach when food, water, or gas is present. Also occurs in duodenum when bolus enters.	Vagal fiber release of VIP
Vomiting	Expulsion of upper intestinal and gastric contents by reverse peristalsis	Irritation of pharynx, esophagus, stomach, or intestines, via vagal and sympathetic afferents to vomiting center; or stimulation of chemoreceptor trigger zone (in medulla near area postrema) to vomiting center
Peristalsis	Contraction behind bolus, relaxation ahead of bolus	Mechanoreceptor and hormone action on enteric nerves
Gastrocolic	Mass movements in colon after meal	PNS and hormones (CCK, gastrin)
Gastroileal	Increased segmentation in ileum in response to gastric emptying	PNS and hormones (CCK, gastrin)
Ileogastric	Chyme in the ileum decreases gastric emptying	Enteric and autonomic nerves
Enteroenteric (aka Intestinointestinal)	If one area of SI is overdistended (e.g., by bacterial infection) the rest of the SI will relax, causing cessation of motility	Enteric and autonomic nerves
Colonocolonic	Distension of one area of colon will relax other areas	Enteric and sympathetic nerves
Rectosphincteric (aka Defecation Reflex)	Feces entering the rectum will cause peristalsis and relax the internal anal sphincter	Both local (enteric nerves) and PNS
These reflexes do not act in an all-or-nothing manner; many act at the same time to create efficient movement of the chyme.		

VIP, vasoactive intestinal peptide; PNS, parasympathetic nervous system; CCK, cholecystokinin; SI, small intestine.

Table 22.3 Effects of Nerves and Hormones on Gastric Emptying

Effector	Action on Pyloric Sphincter
Sympathetic nerves	Constriction
Parasympathetic vagal nerves Excitatory via ACh motor neuron Inhibitory via VIP motor neuron	 Constriction Relaxation
Hormones—gastrin, GIP, CCK, secretin	Constriction

ACh, acetylcholine; VIP, vasoactive intestinal peptide; GIP, glucose insulinotropic peptide; CCK, cholecystokinin.

contraction progress into the antrum, the **antral cycle** occurs, with relaxation of the sphincter and ejection of some chyme into the duodenal bulb (see Fig. 22.5*B, 3*). This cycle (ejection into duodenum) is under tight control, and as chyme enters the antrum and duodenum, the release of hormones decreases gastric emptying by constricting the sphincter (see Table 22.3). Thus, relaxation via vagal inhibitory signals allows the antral cycle to occur, while the other factors prevent too much acidic chyme from entering the duodenum at once.

Small Intestine

When chyme enters the duodenal bulb, receptive relaxation also occurs via the vagus nerve. In the small intestine, there are

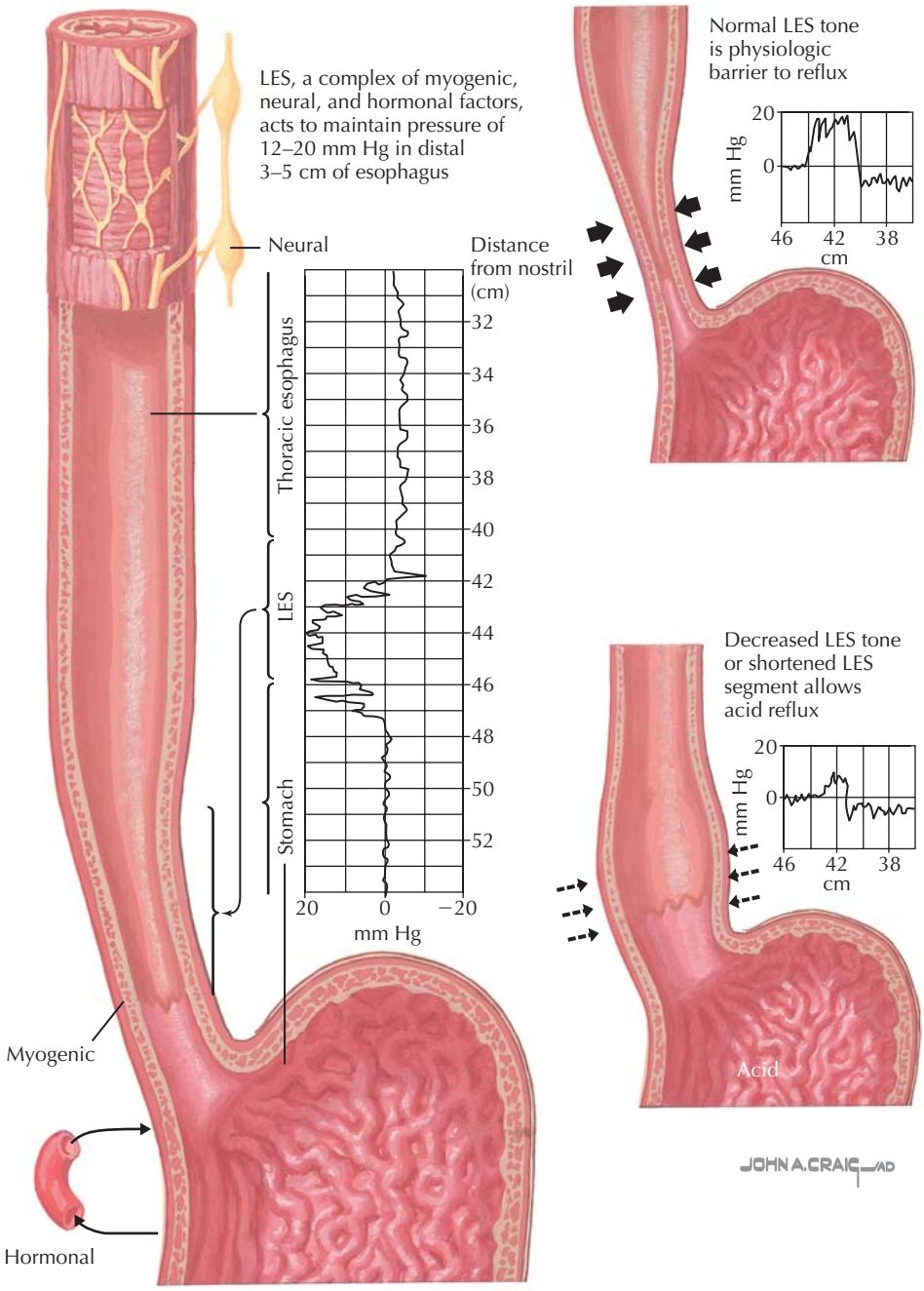
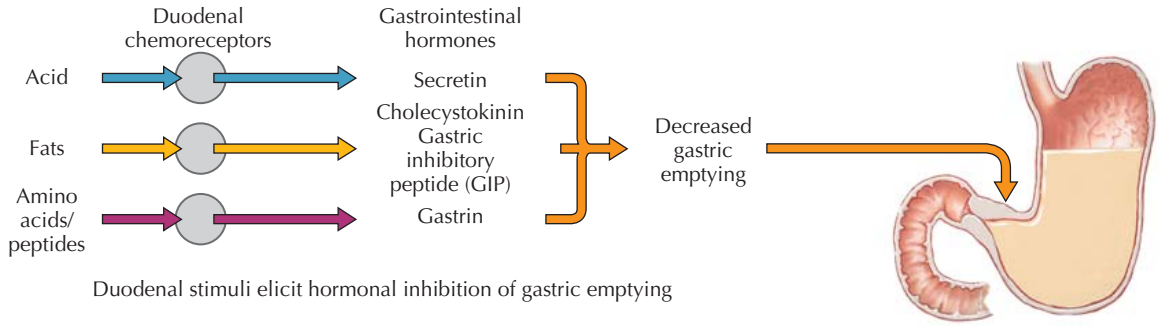
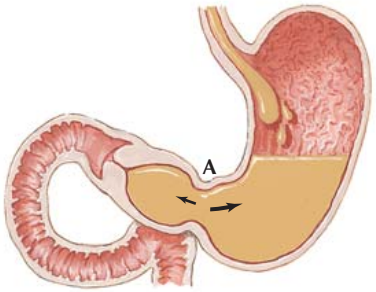


Figure 22.4 **Lower Esophageal Sphincter** The resting tone of the lower esophageal sphincter (LES) is usually very high, preventing reflux of stomach contents. When food is swallowed, esophageal peristalsis is initiated by the vagus nerve and is propagated by the enteric nerves. As the bolus of food reaches the LES, local nitric oxide (NO) and vasoactive intestinal peptide (VIP) are released, and the sphincter tone relaxes, allowing the bolus to enter the stomach. If LES tone is decreased when at rest, acid reflux can occur.

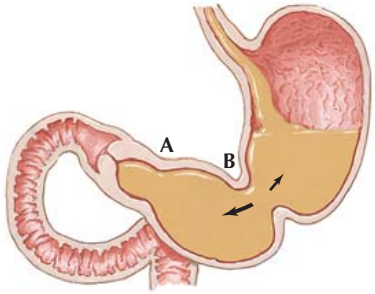
A. Factors affecting gastric emptying



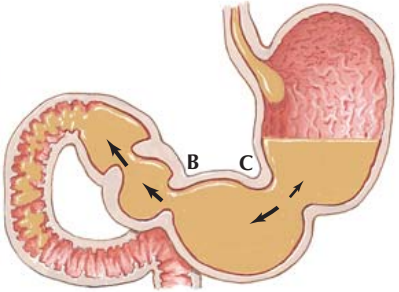
B. Sequence of gastric motility



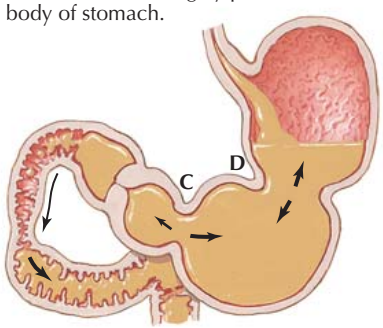
1. Stomach is filling. A mild peristaltic wave (A) has started in antrum and is passing toward pylorus. Gastric contents are churned and largely pushed back into body of stomach.



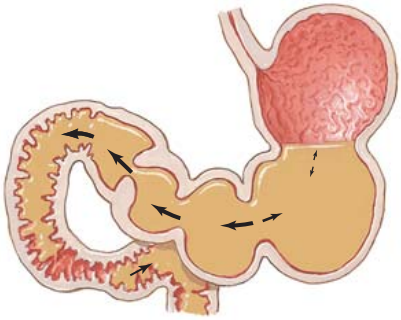
2. Wave (A) fading out as pylorus fails to open. A stronger wave (B) is originating at incisure and is again squeezing gastric contents in both directions.



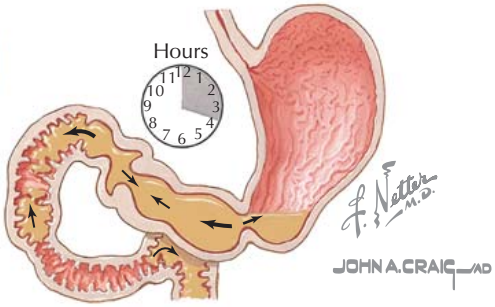
3. Pylorus opens as wave (B) approaches it. Duodenal bulb is filled, and some contents pass into second portion of duodenum. Wave (C) starting just above incisure.



4. Pylorus again closed. Wave (C) fails to evacuate contents. Wave (D) starts higher on body of stomach. Duodenal bulb may contract or may remain filled as peristaltic wave originating just beyond it empties second portion.



5. Peristaltic waves are now originating higher on body of stomach. Gastric contents are evacuated intermittently. Contents of duodenal bulb area pushed passively into second portion as more gastric contents emerge.



6. 3 to 4 hours later, stomach is almost empty. Small peristaltic wave empties duodenal bulb with some reflux into stomach. Reverse and antegrade peristalsis present in duodenum.

Figure 22.5 Gastric Motility The presence of food in the stomach stimulates gastric motility through release of vasoactive intestinal peptide (VIP) stimulated by vagal nerves. The stomach contractions force the gastric contents toward the pylorus, where most of the contents are pushed back into the body of the stomach *(1).* As spurts of chyme enter the duodenum *(3),* duodenal hormones are released into the blood, circulate back to the stomach, and decrease gastric emptying *(A).* Thus, there is a coordinated effect of local and autonomic nerves, and hormones, controlling gastric motility: The entire sequence is depicted in *B,* images *1–6.*

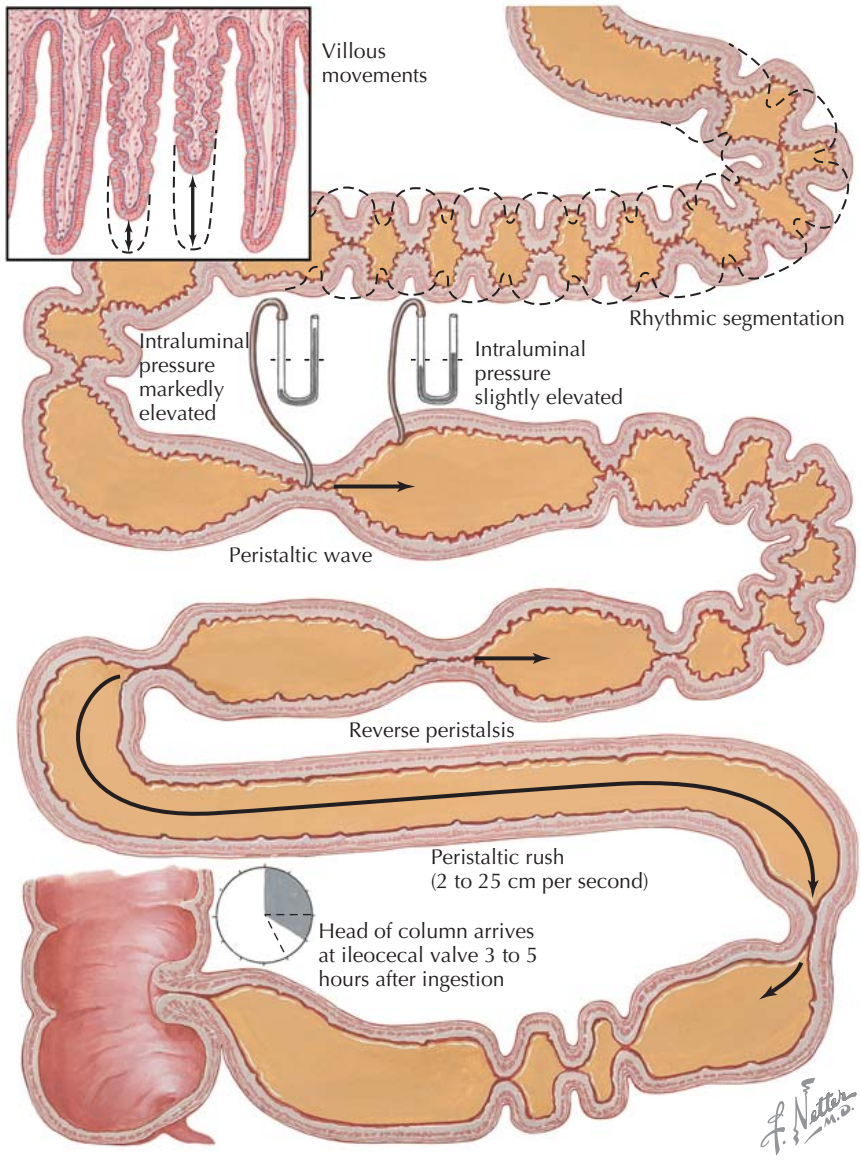


Figure 22.6 Peristalsis and Segmentation Motility in the small intestine is primarily under local control of the myenteric plexus and consists of both peristalsis and segmentation. Segmentation forms pockets of chyme and serves to mix and propel the chyme, although normally peristalsis creates aboral movement (away from mouth). Peristaltic rushes can occur when the intestines are irritated, moving chyme rapidly through the intestines.

two types of propulsion, peristalsis and segmentation. **Peristalsis** follows the "law of the intestines," according to which contraction takes place behind the bolus of chyme and relaxation ahead of the chyme (Fig. 22.6). This process is accomplished by the simultaneous stimulation of excitatory and inhibitory motor neurons (see Fig. 22.2). In this manner, the chyme is propelled aborally (away from the mouth). In the small intestines, there can also be **peristaltic rushes,** which quickly propel the chyme over long segments. These occur when there is irritation or bacteria in the segments, and the movement facilitates removal of the irritant. Because this quickly sweeps the chyme through the intestines, much less absorption occurs, and this can result in **diarrhea** (see Fig. 22.6). **Reverse peristalsis** can also occur (seen in vomiting), rapidly moving intestinal and stomach contents toward the mouth.

Segmentation is the formation of moving pockets of chyme, by close constriction of circular muscle (see Fig. 22.6). Unlike peristalsis, which contracts behind the bolus, segmentation contracts in the middle of the bolus, spreading the chyme proximally and distally. These constrictions occur rhythmically and are the most frequent type of contractions in the small intestine. Because the simultaneous constriction moves in waves, the "pockets" slowly move aborally, mixing contents backward and forward. Although much mixing occurs, there is also net aboral movement. Segmentation and peristalsis

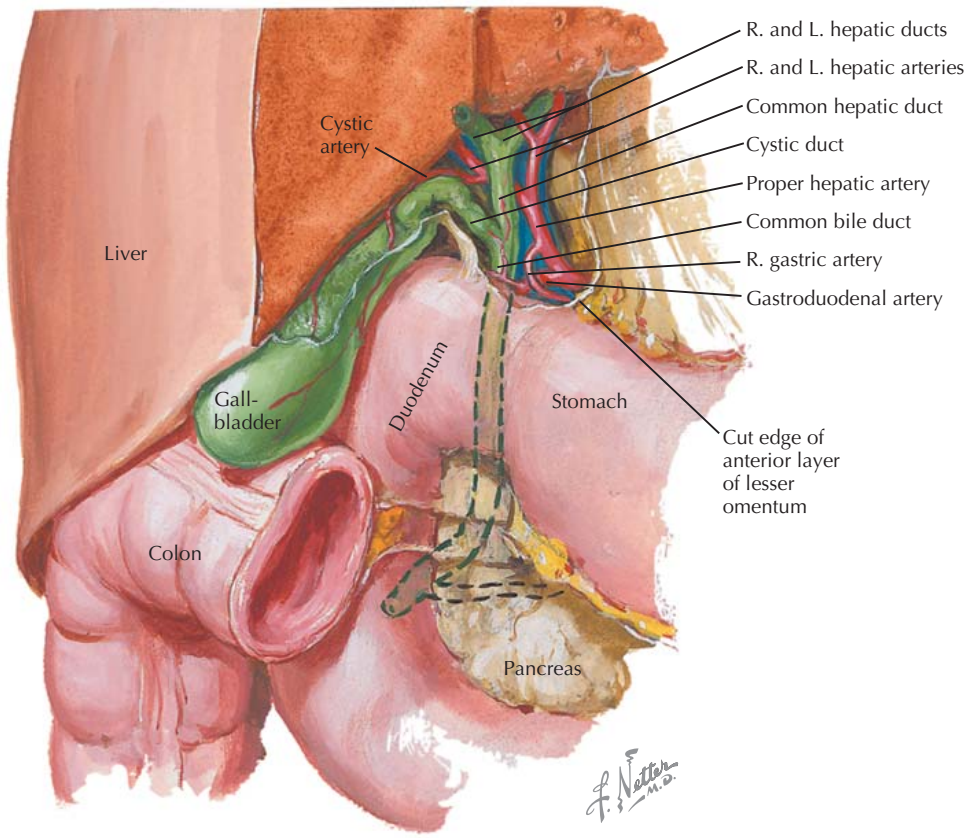


Figure 22.7 Structure of the Gallbladder The gallbladder is the storage site for bile and is located adjacent to the liver. It can store between 25 and 50 milliliters (mL) of bile, which is released by vagal stimulation and cholecystokinin. When food and chyme are in the stomach, the vagus stimulates initial contraction. Subsequently, when chyme enters the duodenum, cholecystokinin is released, causing strong contractions and emptying of the gallbladder. Bile is concentrated (salts and water removed) in the gallbladder, allowing more storage.

occur in adjacent segments of the small intestine throughout the digestion and absorption of the chyme. This pattern is orchestrated by the myenteric nerves (with fine-tuning by autonomic nerves and hormones).

Gallbladder

The gallbladder is a specialized structure for concentration and storage of bile during the interdigestive state (Fig. 22.7). When chyme first enters the duodenum, cholecystokinin (CCK) is secreted into the blood (in response to the presence of fats and glucose in the chyme). CCK, in combination with vagal stimulation, causes contraction of the gallbladder, forcing bile out into the cystic duct and the common bile duct. CCK (and vagal stimulation) also relaxes the **sphincter of Oddi,** allowing the contents of the common bile duct to enter the duodenum.

Large Intestine (Colon)

The colon also has specialized forms of propulsion: segmental propulsion and mass movements. The muscle structure of the large intestine is different from the small intestine, in that there are three bands of longitudinal muscle, called the **taenia coli,** which run the length of the organ. When they contract, they form sacs called **haustra;** this is **segmental propulsion** (Fig. 22.8). The haustra stay in formation for long periods, which helps "store" the chyme as it is dehydrated and made into feces. The ileocecal sphincter regulates the amount of chyme entering the colon. The sphincter is usually tonically closed, but movement of chyme in the terminal ileum relaxes the sphincter, allowing small amounts of chyme to enter the colon. The **ileocecal sphincter** is controlled by the enteric nerves, as well as hormones (CCK and gastrin) and autonomic nerves.

Although segmental propulsion is very slow, **mass movements** periodically occur (usually 1 to 3 times daily). Mass movements are peristaltic in nature, but contractions extend over a longer period of time (seen in Fig. 22.8, descending colon). These strong contractions occur when the distal colon is relaxed and force the feces to travel quickly through the descending colon, into the rectum. The mass movements are stimulated by the parasympathetic nerves (vagal in the proxi-

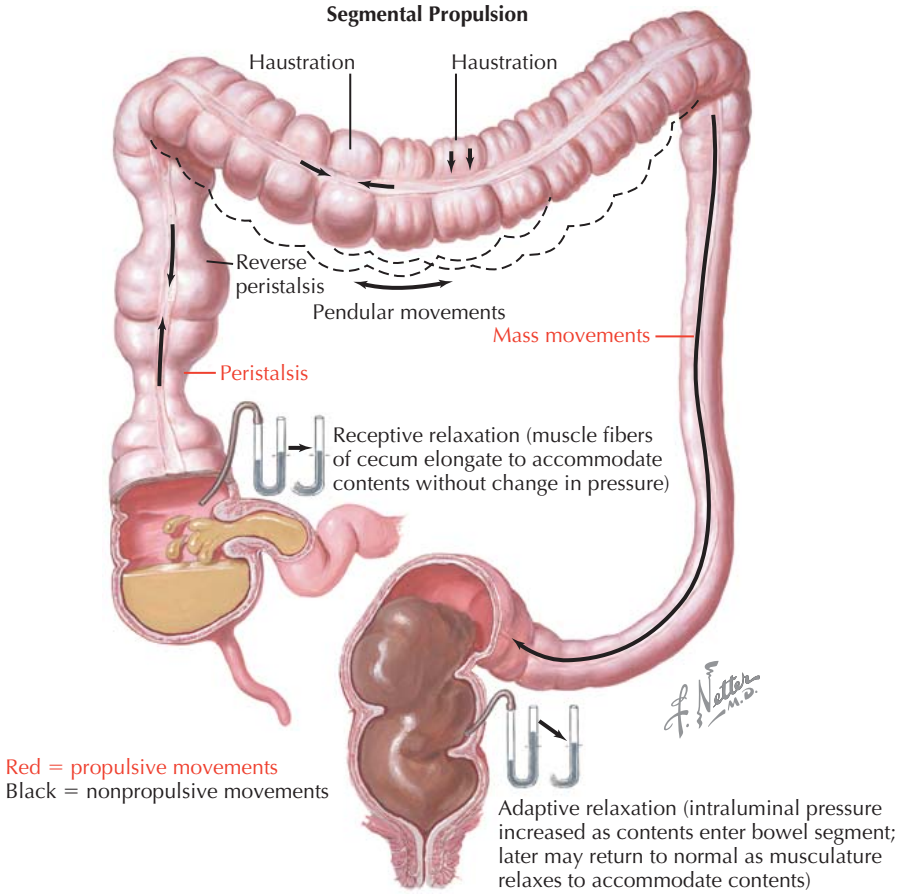


Figure 22.8 Motility in the Colon The colon is specialized for storage, and when bands of longitudinal muscle (taenia coli) contract, they form haustra. This is called segmental propulsion, which is very slow, and allows time for additional sodium and fluid absorption (colonic salvage). The slow movement dries out the chyme, producing feces. Several times a day mass movements will occur, creating peristaltic movements that force the chyme/feces toward the rectum. Factors that increase intestinal motility can cause diarrhea, by minimizing formation of haustrae and increasing mass movements.

mal colon, and pelvic nerves in the distal colon and rectum) as well as the hormones CCK and gastrin. These factors are all active when there is chyme in the upper GI tract (during active digestion), and their stimulation of mass movements serves to clear the lower GI tract of chyme and feces, in preparation for new waste coming down the tract. Conversely, stimulation of the sympathetic nerves (from the superior mesenteric in the proximal colon, and inferior mesenteric and superior hypogastric nerves in the distal colon) inhibits colonic movements, consistent with the overall actions of the sympathetic nervous system (SNS) on the GI system (Fig. 22.9).

DEFECATION AND THE RECTOSPHINCTERIC (DEFECATION) REFLEX

When feces are moved into the rectum, the rectal distension is sensed by local mechanoreceptors that signal the myenteric nerves to relax the **internal anal sphincter** and initiate peristalsis, further pushing feces into the rectum. This local effect is reinforced by the parasympathetic nervous system (PNS), which initiates stronger contractions via pelvic nerves. At the same time, an afferent signal is sent centrally, stimulating the **urge to defecate.** This is the **rectosphincteric,** or **defecation, reflex** (Fig. 22.10). This is a rapid reflex, and in response to the urge to defecate, we voluntarily constrict the **external anal sphincter,** to prevent defecation. If defecation cannot occur, there is some relaxation of the rectum, the internal anal sphincter constricts again, and the external anal sphincter can be relaxed, until another movement pushes feces into the rectum and the reflex recurs. At the appropriate time for defecation, the external anal sphincter voluntarily relaxes, intra-abdominal pressure increases (**Valsalva maneuver**), and defecation occurs. This reflex takes time to fully develop in children, and is usually intact by 2 to 4 years of age.

REGULATION OF MOTILITY

Motility is regulated by the enteric nerves, autonomic nerves, and hormones. The enteric nerves respond to luminal receptors that sense the presence and composition of the chyme, as

well as signals from autonomic nerves and hormones. As previously stated, the PNS primarily promotes motility, whereas the SNS slows or stops motility. A general rule is that most of the GI hormones inhibit gastric motility and/or emptying, thus allowing the duodenum to process the chyme that is released (Fig. 22.11). However, gastrin is an exception: it tends to stimulate gastric motility and activity of the antral cycle, thus increasing gastric emptying. These hormones work together to regulate the exit of chyme from the stomach. The relaxation of the pylorus by gastrin and the PNS is moderated by the effects of gastric inhibitory peptide (GIP), CCK, and secretin, which increase pyloric tone.

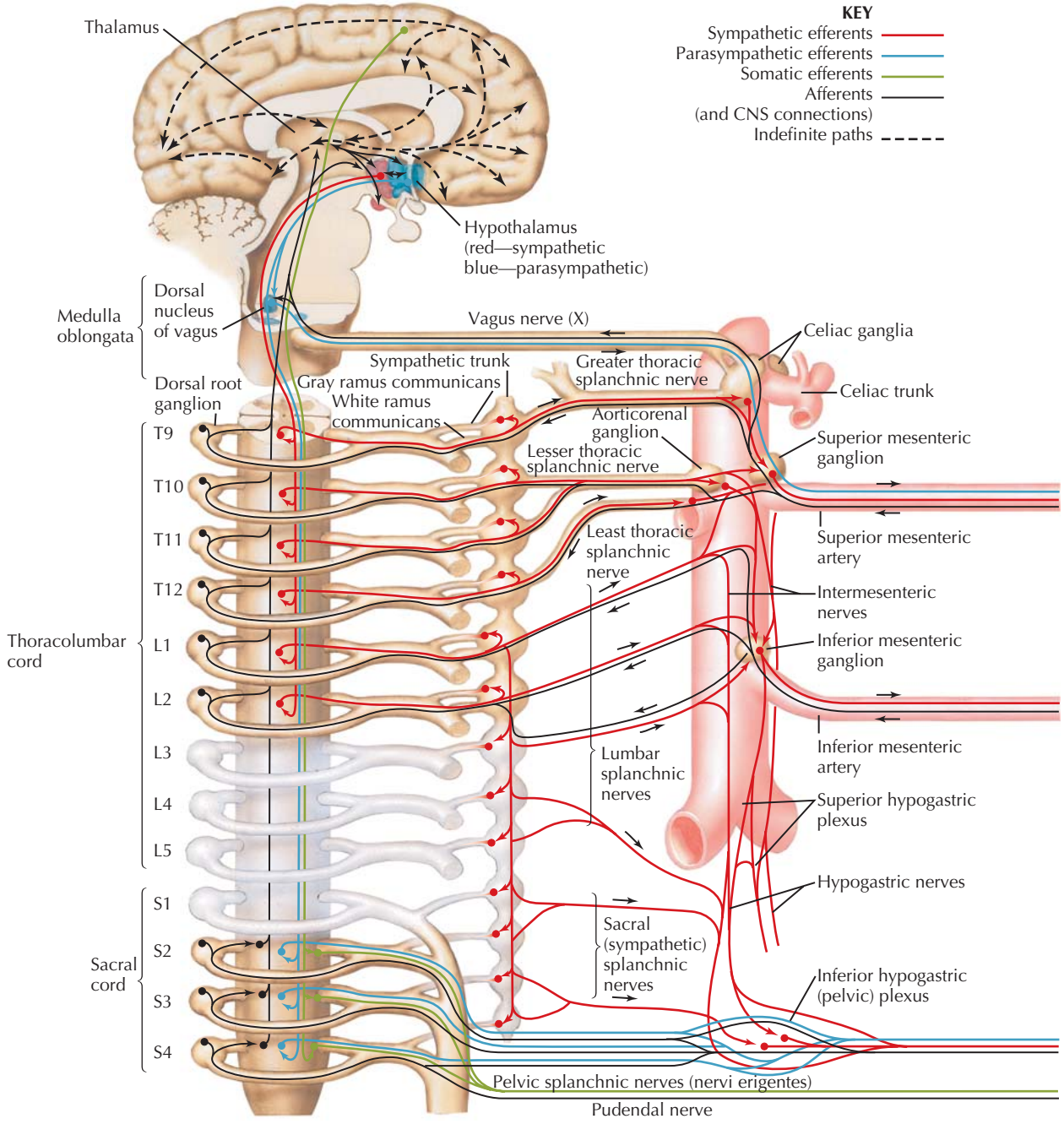


Figure 22.9 Autonomic Innervation of the Colon The small intestines and colon are innervated by both sympathetic and parasympathetic nerves. Sympathetic fibers from the spinal cord lead to the celiac, superior mesenteric ganglia, and inferior mesenteric ganglia. Parasympathetic fibers arise from the vagus (innervate through transverse colon) and pelvic (innervate descending colon, sigmoid, and rectum) nerves. Sympathetic stimulation reduces motility and secretions, whereas parasympathetic stimulation increases motility, secretions, and relaxation of the internal anal sphincter.

In addition, CCK and gastrin have stimulatory effects on motility in the lower small intestine and colon. They initiate mass movements in the colon, facilitating removal of the undigested waste matter. Motilin has the specific function of stimulating contractions during fasting (the MMC) (see Fig. 22.11).

VOMITING AND DIARRHEA

Vomiting is a reflex action that is under central regulation by the vomiting center in the medulla oblongata. Stimuli for vomiting also initiate salivation, and usually **retching** precedes vomiting. During retching, intestinal and gastric contents rise into the esophagus, but not into the mouth, due to a closed upper esophageal sphincter. The reflex can be stimulated by factors within the GI tract, as well as centrally through the chemoreceptor trigger zone (Box 22.1).

The events induced by all stimuli are consistent. **Reverse peristalsis** occurs (with aboral constriction, and relaxation behind the bolus) from the middle of the small intestine to the pylorus, which relaxes to allow chyme to enter the stomach. The stomach fills, and strong abdominal muscle contractions force gastric contents into the esophagus, causing retching. With further stimulus, the upper esophageal sphincter relaxes, allowing contents to rise into the mouth. Because the vomitus includes intestinal and stomach contents, acid, bile, and electrolytes are excreted. Chronic vomiting can result in esophageal damage and metabolic disorders.

Box 22.1 Examples of Stimuli Initiating Vomiting Reflex

- Irritant in stomach or small intestine, enteric virus, or bacteria (local effect through enteric chemoreceptors)
- Systemic irritant sensed by chemoreceptor trigger zone in fourth ventricle of brain (near area postrema)
- Head injury (concussion) (central effect)
- Abnormal stimulation of vestibular organs (central effect via autonomic nervous system [ANS] to chemoreceptor trigger zone, then to vomiting center)

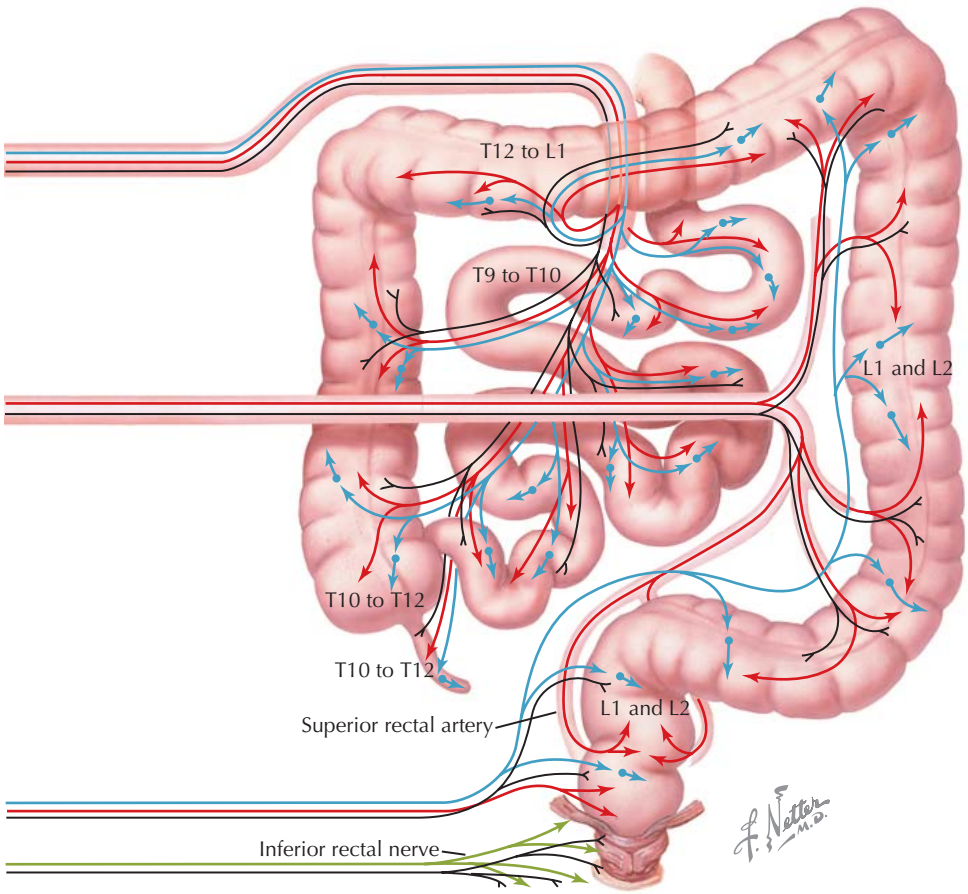


Figure 22.9 cont'd.

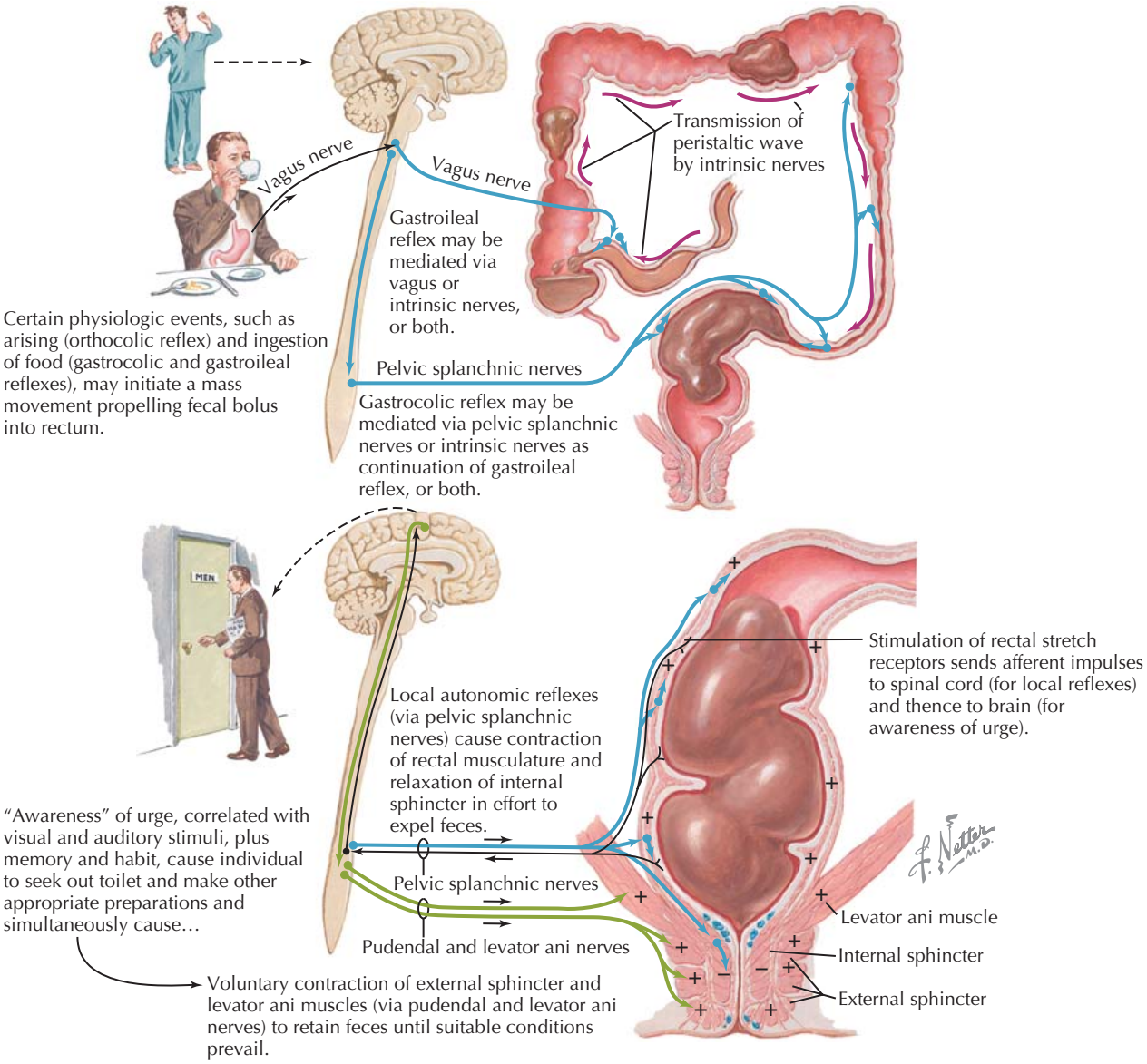


Figure 22.10 Defecation The sequence of events leading to defecation are detailed in this illustration. The defecation (or rectosphincteric) reflex is triggered by distension of the rectum by feces. This is sensed by the mechanoreceptors which activate the myenteric nerves, and impulses are transduced to the spinal cord (and back) to relax the internal anal sphincter (IAS). The spinal cord conveys signals to the brain to stimulate the urge to defecate. These reflex actions cause the voluntary contraction of the external anal sphincter (EAS) until defecation occurs. During defecation, the EAS relaxes, the person increases intra-abdominal pressure, and feces are eliminated from the rectum.

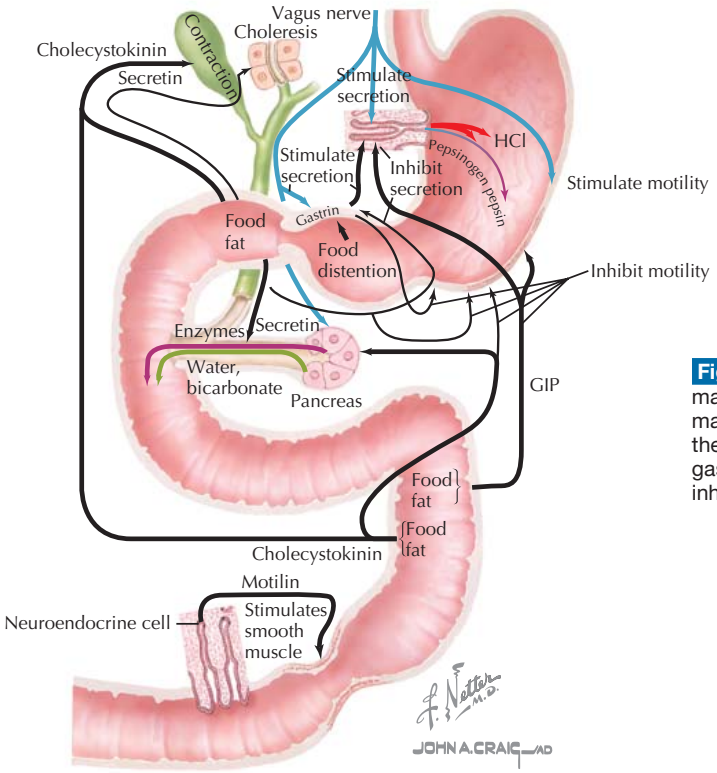
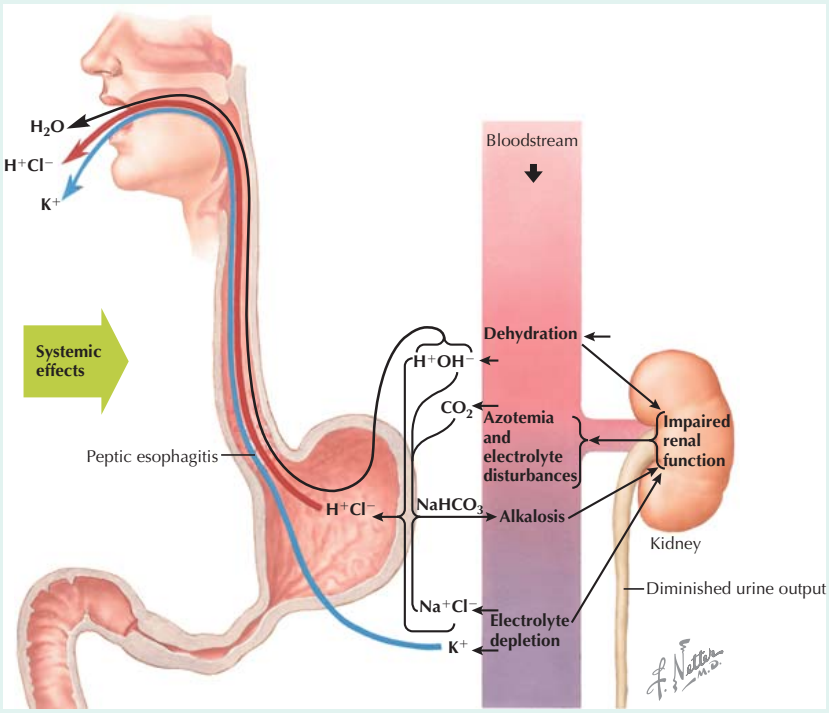


Figure 22.11 **Effect of Major GI Hormones on GI Motility** The main effects of GI hormones on GI motility are depicted in this scheme. While many hormones have effects on gastric motility, a few stimulate motility in the small and large intestines, including motilin (small intestine only) and gastrin (both small and large intestines, not shown on figure). GIP, gastric inhibitory peptide.

Think about homeostasis . . . With chronic vomiting or diarrhea, there is significant loss of fluids and electrolytes. Vomiting causes a disproportionate loss of H^+ and K^+ (from stomach acid). If vomiting continues over an extended time, in addition to dehydration, the loss of H^+ and K^+ can lead to **metabolic alkalosis** and **hypokalemia** (low plasma K^+).

In contrast, chronic diarrhea results in dehydration and a disproportionate loss of HCO_3^-, which can result in **metabolic acidosis** (see Chapter 20).



Vomiting Vomiting leads to a disproportionate loss of H^+, Cl^-, and K^+, as well as loss of fluid from the extracellular space. Prolonged vomiting results in dehydration, alkalosis, and hypokalemia (low plasma K^+).

Diarrhea occurs when chyme and fecal matter move too quickly through the colon. This can result from irritation of the lower GI tract (from bacteria or virus), diseases (irritable bowel syndrome, ulcerative colitis, Crohn's disease), or nervous stress. Movement in the colon is usually very slow (segmental propulsion), allowing absorption of almost all of the water and salt from the chyme, producing feces. If abnormal motility occurs, the fecal matter will move through the colon with minimal absorption, producing diarrhea. When this is in response to bacterial irritation, rapid motility serves to wash the irritant out of the tract, and the diarrhea abates with the loss of the bacteria or virus.

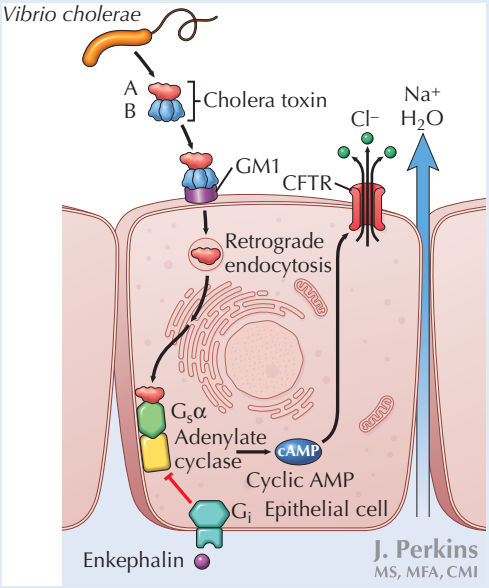
In general, **osmotic diarrhea** is the most common type of diarrhea. It is caused by hypermotility, which forces the chyme/feces through the lower GI tract too rapidly for proper absorption of fluid and electrolytes. In contrast, **secretory diarrhea** is specifically caused by increased secretion of solutes into the lumen of the gut. The hallmark example of this occurs with **cholera toxin** (see "Cholera" Clinical Correlate).

REFLEXES

All of the reflexes ultimately serve to promote the efficient digestion and elimination of ingested material. One of the most important reflexes, the rectosphincteric reflex, was discussed earlier in relation to defecation. A variety of GI-related reflexes are described in Table 22.2.

CLINICAL CORRELATE
Cholera

Cholera is disease caused by the bacterium *Vibrio cholerae,* which is contracted in a fecal-oral manner, usually through ingestion of contaminated water. In the small intestine, the bacteria produce cholera toxin, which has devastating effects on the intestinal epithelium. The toxin modifies the G protein G_s, and as a result, GTPase activity is inhibited, causing prolonged activation of adenyl cyclase. The resulting high level of cAMP activates the CFTR (see "Cystic Fibrosis" Clinical Correlate in Chapter 2), which causes active Cl^- secretion into the lumen of the small intestine. The Cl^- efflux is accompanied by Na^+ efflux (preserving electroneutrality), and water follows the electrolytes. This *isotonic* secretion of electrolytes and water depletes the vascular space while maintaining plasma osmolarity. In this manner, the vascular space is rapidly contracted, causing severe dehydration and shock. Antibiotic therapy and intravenous hydration is the most desirable therapy; otherwise, oral rehydration therapy (ORT, containing water, electrolytes, and glucose) from an uncontaminated source can be given. The glucose in the ORT promotes sodium and electrolyte absorption and actually draws more of the secreted Na^+ and Cl^- back into the vascular space, along with water. This is effective in reducing the diarrhea and maintaining hydration. Without antibiotics, and with availability of uncontaminated water, the bacteria will be cleared from the GI tract in 7 to 10 days, as the enterocytes slough off and are replaced by new cells.



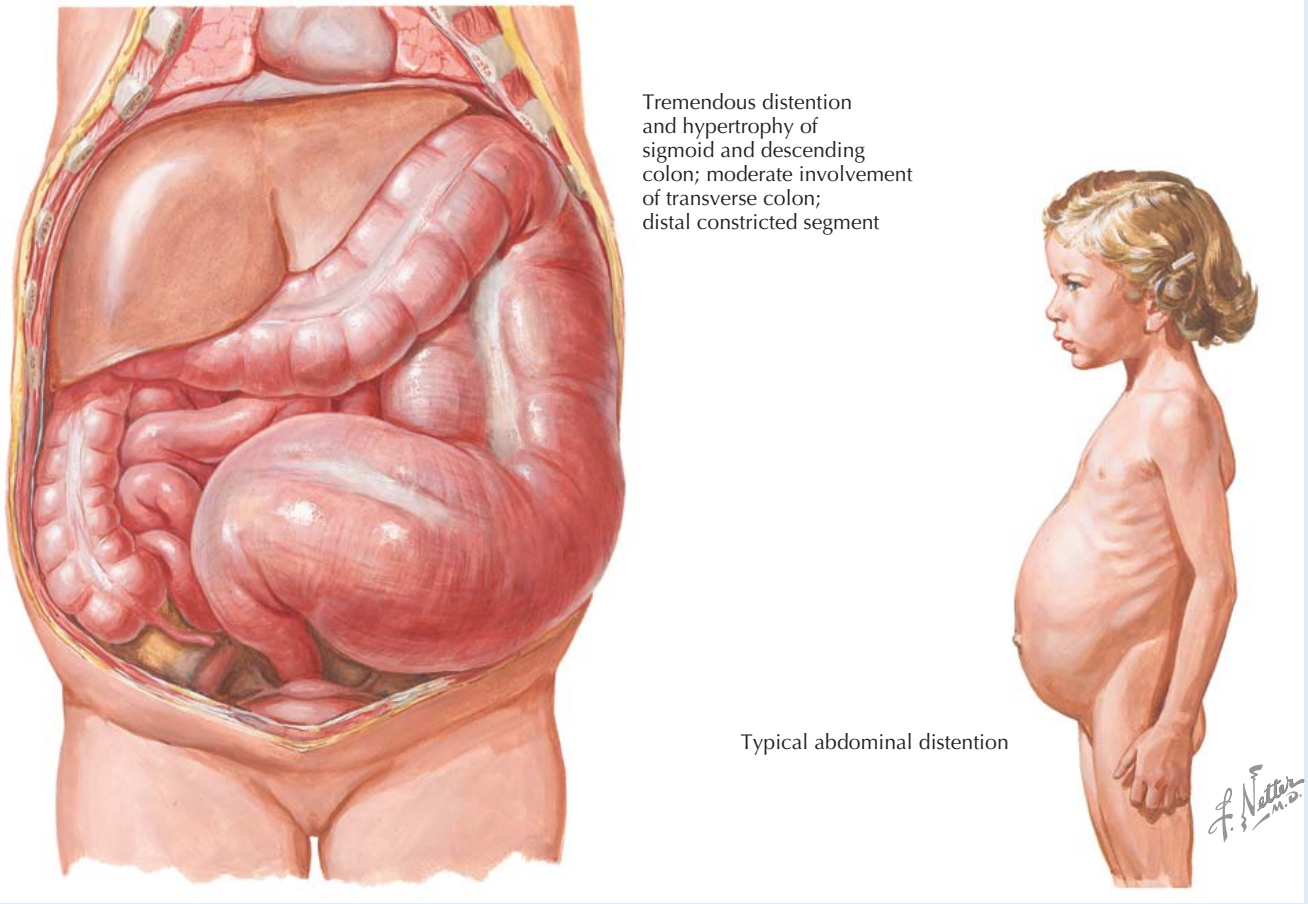
Actions of Cholera Toxin in Intestinal Cells

CLINICAL CORRELATE
Smooth Muscle Disorders: Achalasia and Hirschsprung's Disease

The enteric nervous system (ENS) can be thought of as the central processing center responding to a variety of signals and making the appropriate connections. Because of this, if the ENS is absent from an area in the tract, pathology ensues. Smooth muscle diseases such as achalasia and Hirschsprung's disease involve aganglionic areas of the digestive tract (loss of nerves in some areas).

Achalasia is a loss of the ENS in the lower part of the esophagus and always involves the **lower esophageal sphincter.** The aganglionic region is not able to stimulate contractions and cannot transduce the signal to relax the lower esophageal sphincter. As a result, the sphincter tone is very high. Because the lower esophageal sphincter is not able to relax, the food and fluid can take hours, rather than seconds, to leave the esophagus. Over time (months to years) this causes dilation of the esophagus. This condition is very painful and can eventually lead to anorectic behavior. Also, because the ingested food sits in the esophagus for long periods of time, partial digestion occurs, and the contents can further damage the esophageal mucosa. The etiology of achalasia is unknown, and treatment usually only partially alleviates the problem. Pharmacologic intervention with nitrites (isosorbide dinitrite) or calcium channel blockers (nifedipine or verapamil) is used but has limited efficacy, and the primary treatment is by balloon dilation or surgically cutting the sphincter (**esophagomyotomy**). This allows food and fluids to pass through the lower esophageal sphincter into the stomach but usually produces gastric reflux, and the patients must be treated with oral medication for **GERD** (gastroesophageal reflux disease).

Hirschsprung's disease (or **megacolon**) is a congenital disease that involves the loss of the ENS in the distal part of the colon and always involves the internal anal sphincter (IAS). The normal defecation reflex mediated by the myenteric plexus (feces in rectum → stretch → relaxation of IAS) does not occur, so very little defecation occurs and feces build up in the rectum and colon. This dilates the colon, and symptoms include little or no bowel movements and vomiting. Drugs are not effective; surgical removal of the aganglionic region typically restores the ability to defecate.



Hirschsprung's Disease (Megacolon)

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CHAPTER 23 Gastrointestinal Secretions

SALIVARY SECRETION AND REGULATION

Salivary Gland Secretion

Salivary secretions make foods easier to ingest (and digest) by lubricating, cooling, and adding digestive enzymes to the food. There are three sets of salivary glands producing the secretions: the parotid, the submandibular, and the sublingual. Secretion from these glands is under the control of cranial nerves VII and IX (Figs. 23.1 and 23.2 and Table 23.1). There are a few unique aspects of salivary gland secretion that bear noting:

- A large volume of fluid is produced by relatively small glands.
- Saliva is always hypotonic to plasma.
- Compared with plasma, saliva is relatively rich in K^+.
- Salivary secretion is primarily regulated by cranial parasympathetic nerves, which control blood flow to the glands.

Approximately 1.5 liters (L) of saliva is secreted daily, most of which occurs with eating. When food enters the mouth, salivation is stimulated. The saliva serves to:

- Lubricate the food (water and mucins).
- Start digestion.
- Protect the mouth and gastrointestinal (GI) tract by cooling hot foods.
- Protect the tract through the antimicrobial actions of white blood cells (WBCs), IgA, and opsonins.
- Aid coagulation by secreting platelet-activating factor.
- Provide oral hygiene by buffering and cleansing the oral cavity—swallowing and spitting allow us to get rid of bacteria, whereas low flow while we sleep allows bacteria to accumulate, causing halitosis (bad breath).

Digestion of starch and lipids begins in the mouth. The serous glands secrete **salivary α-amylase** (or, **ptyalin**), which begins starch digestion by breaking α1-4 linkages of glucose polymers (oligosaccharides). This is the same enzyme as pancreatic α-amylase. In addition, **Von Ebner's glands** of the tongue produce a serous secretion that includes the enzyme **lingual lipase,** which is active at low pH and can hydrolyze dietary triglycerides (TGs) in the stomach, yielding free fatty acids (FA) and diglycerides. This is the same as gastric lipase but is different from pancreatic lipase (which hydrolyzes TGs to two FAs and one monoglyceride).

Production of Saliva

Salivary glands are exocrine glands, with secretions draining through ducts. The primary secretion is produced at the blind ends of the ducts, in the acini (Fig. 23.3). The glands are highly vascularized, and the parasympathetic nerves stimulate active secretion by increasing blood flow to the acini. Isotonic **ultrafiltrate** from the plasma diffuses through the acinar cells into the lumen, where this **"primary secretion"** is mixed with the additional products of the serous and mucous cells (α-amylase and mucins, respectively). The secretion drains down the striated ducts, and the electrolyte content is modified depending on the rate of flow through the ducts. Thus, as the rate of flow increases, there is less time for Na^+ and Cl^- reabsorption, and concentration of these electrolytes in saliva is higher (see Fig. 23.3*B*). Under conditions of reduced vascular volume (dehydration, hemorrhage), Na^+ and water reabsorption by the ductal cells is increased by **antidiuretic hormone** (**ADH**) and the mineralocorticoid **aldosterone** (see Chapter 19). The ADH increases water reabsorption (Na^+ follows), while aldosterone increases Na^+ reabsorption (water follows). Thus, when plasma volume is low, saliva production is decreased to conserve fluid. As indicated, regardless of flow rate, the saliva is always *hypotonic* to plasma.

When the saliva enters the mouth, it mixes with secretions from Von Ebner's glands (and other minor glands), adding lipase to the fluid. In addition, **R proteins** found in the saliva bind to the essential vitamin B12 in the stomach, protecting it from degradation. In the duodenum, pancreatic proteases cleave the R proteins and B12 binds to **intrinsic factor** (secreted by the gastric parietal cells), which protects it until it is absorbed in the terminal ileum. If any part of the pathway (especially intrinsic factor) is lost, B12 cannot be absorbed, and because B12 is critical for maturation of red blood cells, **pernicious anemia** develops.

Neural Control of Saliva

Salivary flow is dependent on parasympathetic nerves (glossopharyngeal and facial). They innervate the blood vessels of

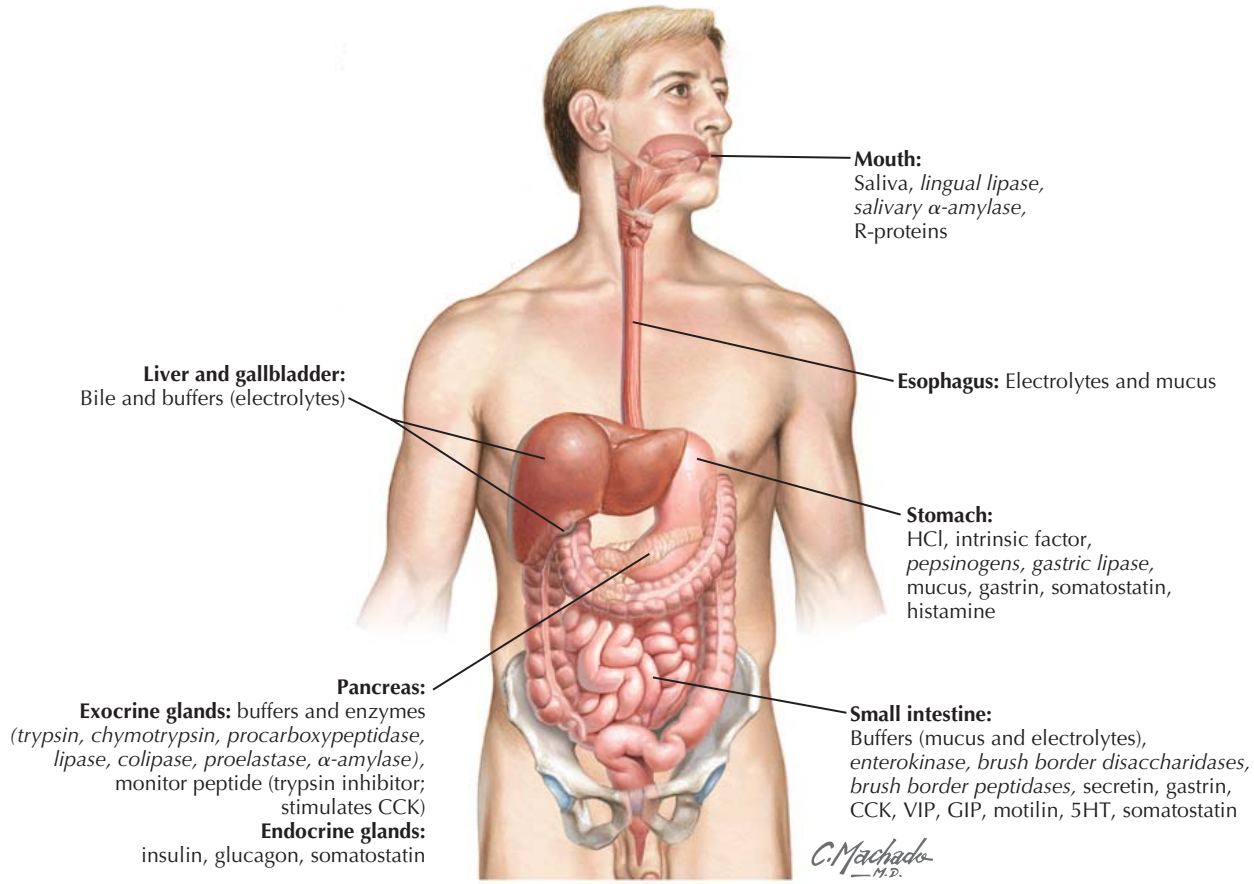


Figure 23.1 Major Secretions into the GI Tract In order to digest and absorb ingested nutrients, liters of secretions are added daily to the GI tract from associated glands, organs, and tissues. The general sources of digestive enzymes, acid, buffers, and bile are shown in the figure above. CCK, cholecystokinin; 5HT, serotonin; GIP, gastric inhibitory peptide; VIP, vasoactive intestinal peptide.

Table 23.1 Salivary Gland Secretions

Gland	Secretion	Cranial Nerve
Parotid	Watery fluid, without mucins (serous), ~25% of total	Glossopharyngeal (IX)
Submaxillary	Mixed serous/mucous fluid, ~70% of total	Facial (VII)
Sublingual	Mucous fluid, 5% of total	Facial (VII)

Table 23.2 Regulation of Salivary Flow

Increase Salivary Flow	Reduce Salivary Flow
• Parasympathetics (CN VII & IX), ACh, VIP • CNS (in cephalic, "sensory" phase) • Nausea • Esophageal distension • Chewy, flavorful foods • Dry, acidic foods • Meats, sweets, and bitter foods	• Sympathetics, NE • Hormones (ADH, aldosterone) conserve water and salt when volume depleted • Sleep • Dehydration (activates hormones) • Drugs, chemotherapy • Aging (decreases ANS tone; glands can atrophy)

ACh, acetylcholine; ADH, antidiuretic hormone; ANS, autonomic nervous system; CN, cranial nerve; CNS, central nervous system; NE, norepinephrine; VIP, vasoactive intestinal peptide.

salivary glands, and when stimulated, increase blood flow, increasing ultrafiltrate secretion into the acini. If the parasympathetic nerves are severed, salivation will significantly decrease, and the glands will atrophy. The sympathetic nerves also innervate blood vessels around the glands as well as the myoepithelial cells in the acini. Sympathetic stimulation (for example, during stress) reduces blood flow but contracts the myoepithelial cells, releasing preformed mucous saliva. After that, flow will decrease (resulting in dry mouth). The salivatory nucleus in the brainstem transduces a sensory, central nervous system (CNS) effect, for example, when visual or olfactory input stimulates salivation (Table 23.2).

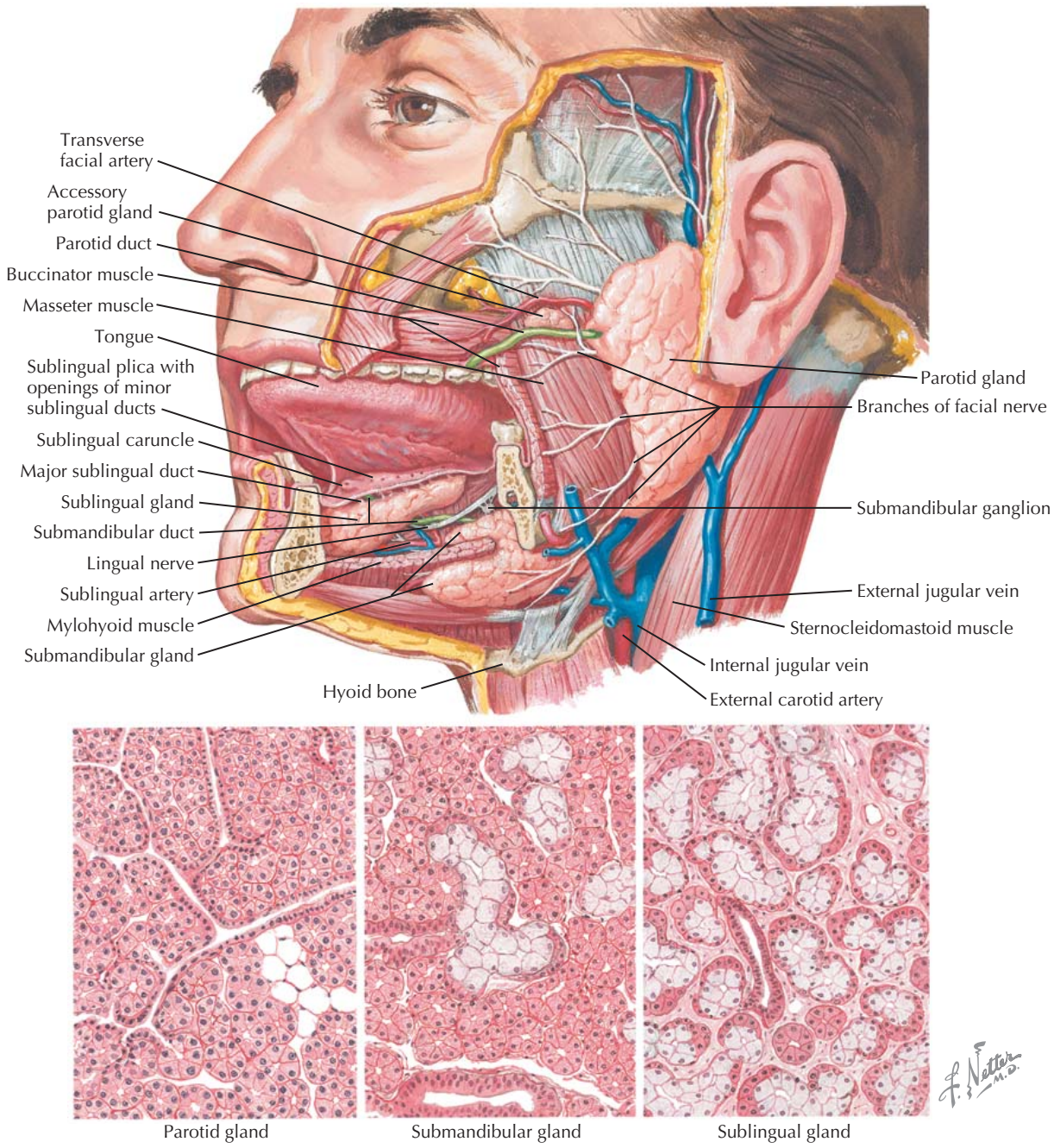


Figure 23.2 Salivary Gland Structure There are three paired salivary glands: the parotid, the submandibular, and the sublingual. The glands are specialized to secrete mainly serous (parotid), mucous (sublingual), or mixed (submandibular) saliva (see representative histology). About 1.5 liters of saliva is secreted daily, with the greatest secretion while eating.

Esophagus

Glands in the esophageal mucosa produce serous and mucous secretions, which lubricate the bolus of food and help propel it to the stomach. This is especially important if food gets stuck and secondary peristalsis occurs. The increased salivation and esophageal secretion aid movement of the food into the stomach.

GASTRIC PIT SECRETIONS AND REGULATION OF HCL SECRETION

The Gastric Pit

Gastric secretions facilitate and regulate digestion, lubricate the bolus of food, and protect the gastric mucosa. The mixing

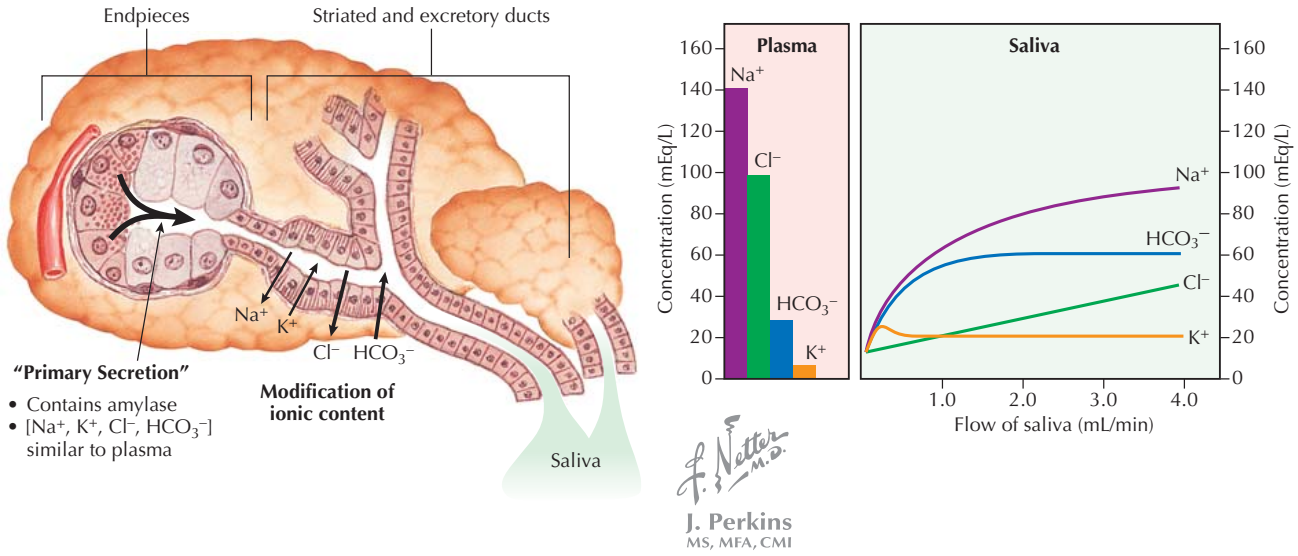


Figure 23.3 Salivary Acinar Cells During salivary secretion, blood flow to the acini is increased by parasympathetic stimulation, and ultrafiltrate from plasma (mostly serous fluid) enters the acini. Filtrate from the cells enters the lumen of the acinar cells, mixing with secreted mucus and α-amylase, creating the primary secretion. This secretion is modified as it passes through the ducts into the mouth. Lingual lipase (secreted from the Von Ebner's glands of the tongue) is added to the saliva in the mouth. The graph illustrates the effect of increasing salivary secretion on composition of saliva. The changes are due to the reduced modification of saliva through the ducts as flow increases.

of gastric juices with food produces **chyme.** The gastric pit is made of a variety of cells (Fig. 23.4):

- Superficial epithelial cells or surface mucous cells are formed from undifferentiated cells in the pit, then migrate to the surface. They secrete mucus and bicarbonate (HCO_3^-), which protect the gastric epithelium from the corrosive acid in the lumen, and are replaced every few days.
- Mucous neck cells protect the gastric mucosa by secreting mucus.
- Stem/regenerative cells differentiate to replace other cells in the pit.
- Parietal cells secrete HCl and intrinsic factor.
- Chief cells secrete pepsinogens and gastric lipase.
- Endocrine cells secrete somatostatin, and mast cells secrete histamine.

Because of the harsh physical environment, cells lining the stomach (and intestines) are continually replaced. This requires substantial energy expenditure, as well as a constant supply of proteins and lipids to make new cells.

Secretions from the Pit Cells

The gastric secretions primarily serve to digest the food; however, they also contribute to the regulation of acid secretion, motility, and protecting Vitamin B12. The gastric secretions consist of:

- HCl: Digests food, kills ingested bacteria, converts inactive pepsinogens to pepsins.
- Intrinsic factor: Essential gastric secretion required for B12 absorption in the terminal ileum.
- Pepsinogens: The inactive form of pepsins, which are proteases that are activated in the acid environment. Thus, protein digestion begins in the stomach.
- Gastrin: A gut hormone secreted from G-cells located in the antrum of the stomach and the duodenum. Gastrin stimulates HCl secretion and gastric motility (mixing), as well as lower GI motility (mass movements).
- Lipase (gastric lipase): Continues process of lipid digestion.
- Mucus: Thick mucus is secreted with HCO_3^-. The HCO_3^- remains trapped in the mucus layer at the epithelial cell surface, effectively buffering the cells from the acid environment in the lumen (Fig. 23.5).
- Other factors: Somatostatin (SS) inhibits HCl secretion; histamine stimulates HCl secretion.

In general, factors that stimulate gastric activity (e.g., vagus, gastrin) elicit secretion from chief, parietal, and mucus cells.

Production and Regulation of Gastric HCl

Acid secretion is important for the indiscriminate digestion of ingested matter. However, because of its corrosive nature, there are multiple factors that regulate its secretion from **parietal cells.** One factor that keeps HCl secretion under control is parietal cell morphology. Stimulated parietal cells are well organized, with tubulovesicles fusing with the plasma membrane to form intricate canaliculi that increase surface area for secretion of H^+. In contrast, unstimulated

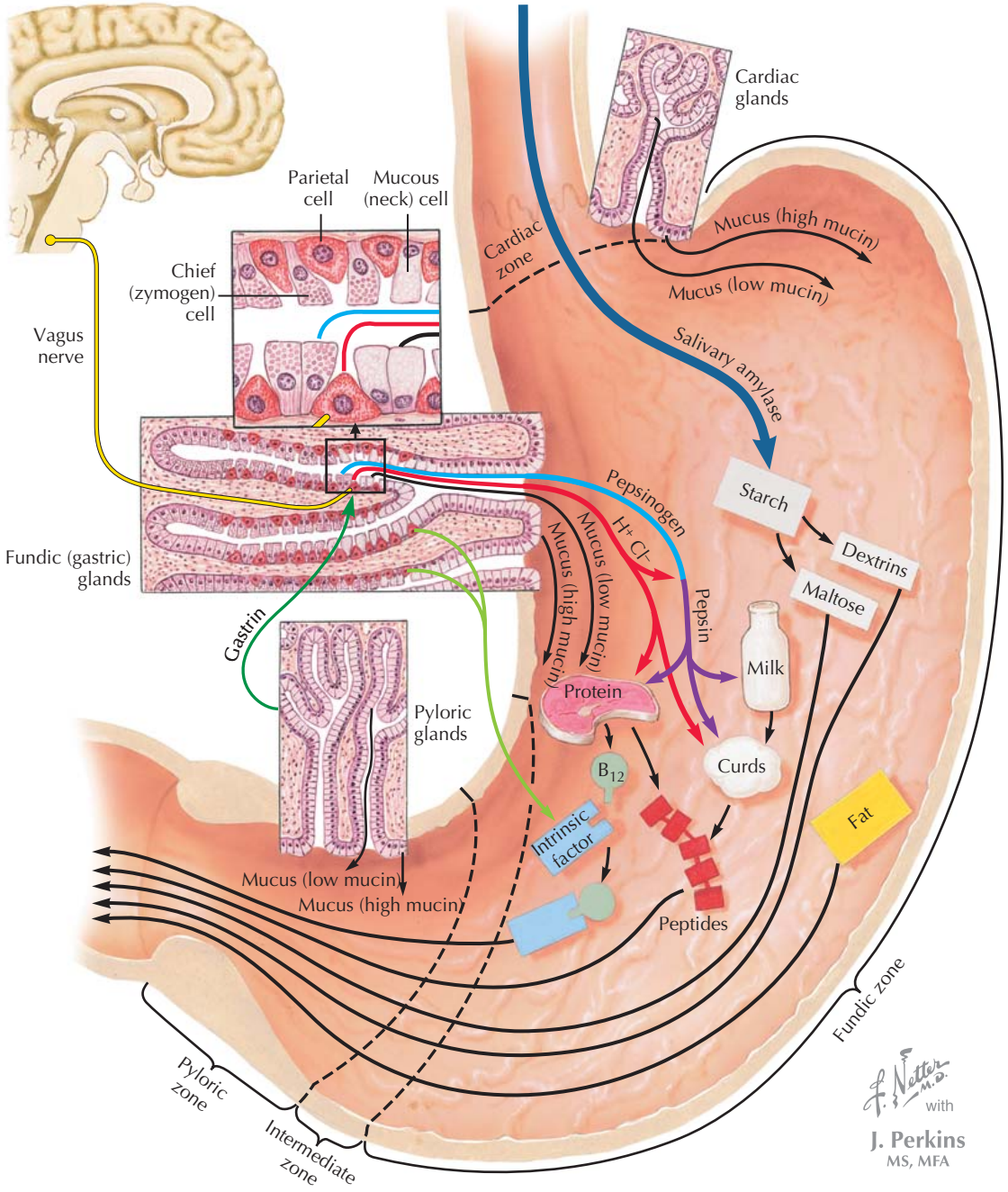
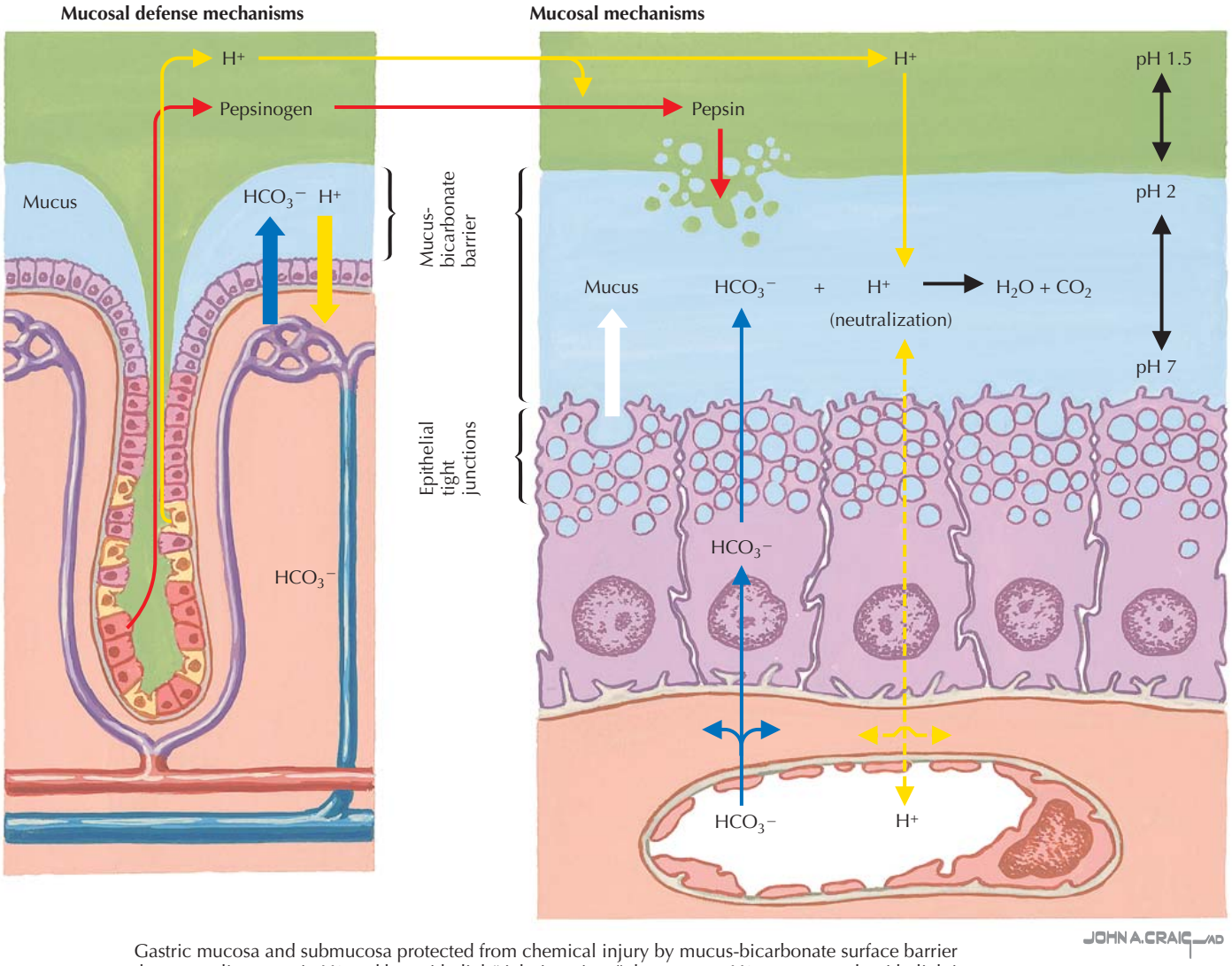


Figure 23.4 Digestion in the Stomach The stomach secretes concentrated HCl, which breaks ingested food into smaller fragment and activates the enzymes pepsin and lipase, to digest proteins and fats, respectively. The parietal cells, which secrete HCl, also secrete the protein intrinsic factor, which binds to vitamin B12 to prevent the vitamin's digestion by pancreatic proteases in the small intestine. In general, about 25% of nutrient digestion occurs before the chyme reaches the duodenum.

cells have less surface area exposed to the luminal surface of the gastric pits, keeping potential H^+ secretion minimal (Fig. 23.6).

Parietal cells secrete H^+ against a million-fold concentration gradient in the lumen. The gradient is maintained by **tight junctions,** which prevent H^+ leak back into the blood. The transport of H^+ against the gradient is accomplished by the apical **H^+/K^+ ATPase,** or **proton, pump**. This active antiport pump is the rate-limiting step in H^+ transport and is the site of regulation of acid secretion. Key aspects of acid production and secretion include the following:

- The production of H^+ from intracellular conversion of CO_2 to carbonic acid in the reaction ($CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$) (carbonic anhydrase is required



Gastric mucosa and submucosa protected from chemical injury by mucus-bicarbonate surface barrier that neutralizes gastric H^+ and by epithelial "tight junctions" that prevent H^+ access to subepithelial tissue

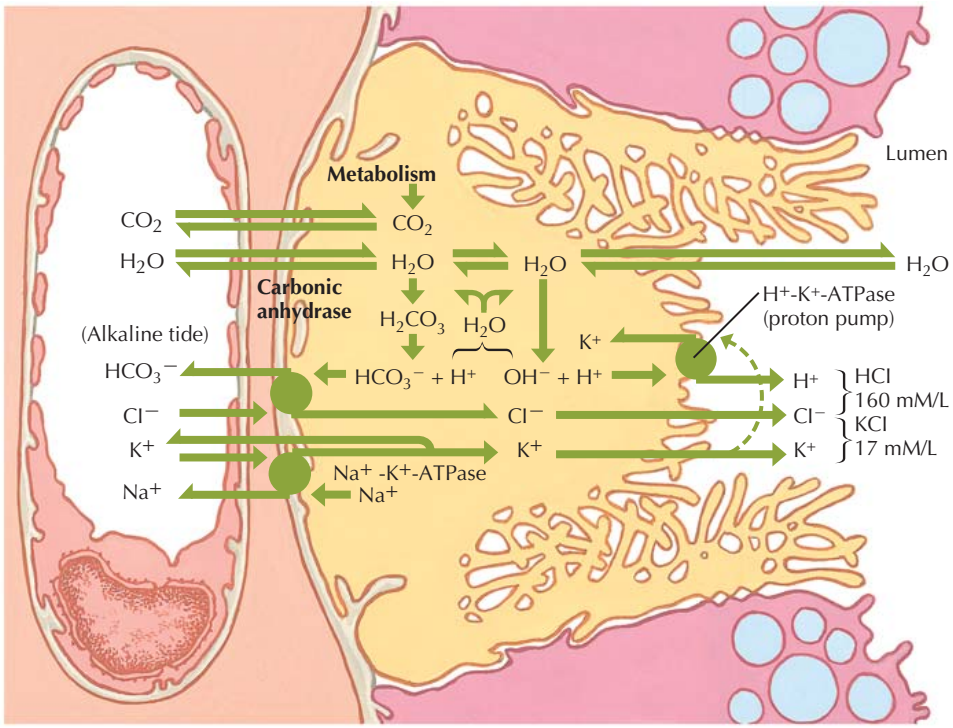
Figure 23.5 Protection of Gastric Mucosa Thick mucus from the surface epithelial cells traps the secreted bicarbonate on the surface of the gastric mucosa. The bicarbonate-containing mucus layer protects the cells from the caustic acid (pH ~1.5), keeping the pH at the cell surface ~7.0.

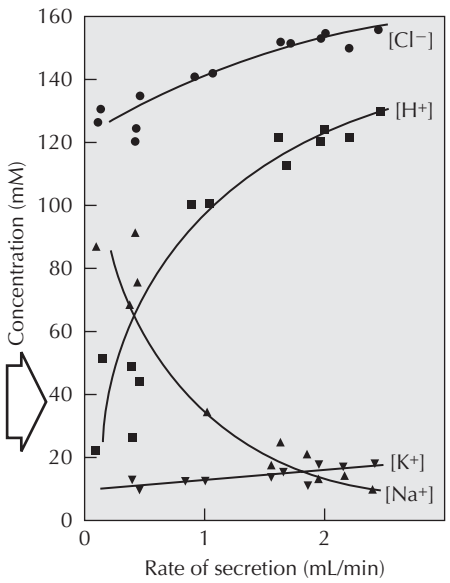
for this conversion). H^+ is then available for secretion by the proton pump.

- The entry of chloride into the cells via the HCO_3^-/Cl^- exchanger at the basolateral membrane, and diffusion of chloride into the lumen of the pit through the apical membrane (down its concentration gradient).
- The exit of HCO_3^- from the cell into the blood via basolateral HCO_3^-/Cl^- exchangers. In the actively secreting parietal cell, the large amount of HCO_3^- entering the blood is described as an **alkaline tide.**
- The movement of potassium back into the lumen with Cl^-.

This process primarily produces HCl in the lumen but also produces some KCl. Regulation of acid production takes place through stimulation and inhibition of the **proton pump,** which is the target for most therapeutic interventions to reduce acid secretion (for gastroesophageal reflux disease [GERD], ulcers, etc). Proton pump inhibitors (PPI) such as omeprazole and histamine H2 blockers (ranitidine, cimetidine) are used for this purpose.

Constituents of the gastric juices vary with the rate of secretion (see Fig. 23.6). Quiescent, nonstimulated cells produce fluid at a low rate; the fluid contains higher levels of Na^+ and Cl^- (more bufferlike) and low concentrations of H^+.





Gastric fluid ion concentration as a function of gastric secretion rate

Parietal cell mechanisms of acid (H^+) secretion involve series of chemical exchanges across basal membrane, with final active exchange of H^+ for K^+ mediated across apical (secretory) membrane by H^+-K^+ ATPase (proton pump).

JOHN A. CRAIG, MD

Figure 23.6 Parietal Cell HCl Production The apical H^+/K^+ ATPase (proton pump) causes the active secretion of H^+ into the lumen of the gastric pits. This combines with secreted Cl^- to form concentrated HCl. HCl production is stimulated by vagal efferent fibers, gastrin, and histamine, which are active when there is food in the stomach. The H^+/K^+ ATPase is the target for proton pump inhibitors (PPI) to decrease gastric acid release in patients with GERD or ulcers.

However, when cells are stimulated, Na^+ concentrations drop and H^+ concentrations increase in the juice, producing more HCl.

Regulation of Gastric Acid Secretion

There are three phases of gastric acid secretion:

- **Cephalic phase:** Food in the mouth initiates vagal release of acetylcholine (ACh) at the parietal cell, stimulating acid secretion. Vagal fibers also terminate on enterochromaffin-like (ECL) cells and G-cells, stimulating histamine and gastrin secretion, respectively; histamine and gastrin promote acid secretion.
- **Gastric phase:** Stretch, initiated by food in the stomach, releases gastrin from antral G-cells. The gastrin in the bloodstream circulates back to the stomach, stimulating the proton pump of the parietal cells. At the same time, the vagus also stimulates the proton pump directly, as well as by increasing gastrin-releasing peptide (GRP) and histamine, which also act on the pump.
- **Intestinal phase:** When chyme enters the duodenum and jejunum, hormones are released that feed back to regulate acid secretion (see following).

Several factors **stimulate** acid secretion:

- The *vagus* acts directly at parietal cells and indirectly through stimulation of gastrin and histamine release and inhibition of local somatostatin release (Fig. 23.7).
- *Histamine,* from ECL cells, diffuses through the mucosa to act on adjacent parietal cells.
- *Gastrin,* carried through the blood, acts directly on parietal cells.
- *Insulin,* carried through the blood, acts directly on parietal cells and promotes HCl secretion.
- *Caffeine* (a phosphodiesterase inhibitor) increases cAMP in the parietal cells, increasing proton pump activity.
- *Stress,* although not well understood, appears to increase acid secretion in certain people and may be a cofactor in ulcer formation (with *Helicobacter pylori*).

Several factors **inhibit** acid secretion:

- *Somatostatin (SS),* released from endocrine cells in the gastric pit, acts in a paracrine manner on the parietal cells, as well as on G-cells to inhibit gastrin.

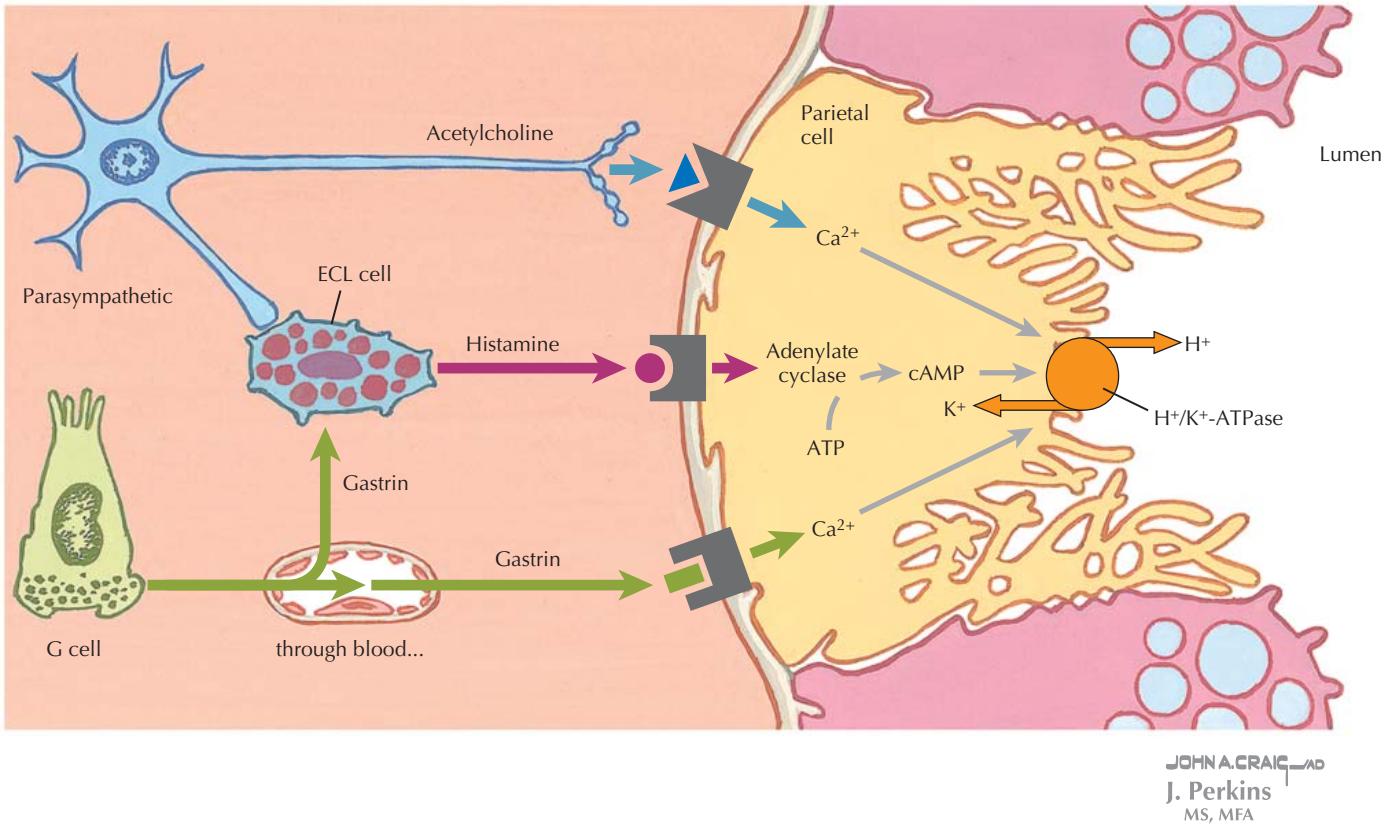


Figure 23.7 Signal Transduction Mechanisms Regulating HCl Secretion Stimulation of the proton pump can be achieved by both calcium and cAMP-mediated messenger systems.

- *Glucose insulinotropic peptide* or *gastric inhibitory peptide (GIP),* released from the duodenum and jejunum, acts directly on the parietal cells.
- *Secretin,* released from the duodenum and jejunum, acts at the G-cells to suppress gastrin.
- *Peptide YY,* released from various areas of the GI tract in response to fats, helps shut off acid and pancreatic secretions when chyme is leaving the upper GI tract. The effects on gastric acid may be through suppression of ACh release from cholinergic fibers, and/or stimulation of paracrine somatostatin.

While these factors regulate acid secretion, it is important to understand that they are not all-or-nothing events—for the most part they work in concert to modulate the amount of acid being secreted during the digestive period. Thus, for example, while the vagus, gastrin, and histamine are stimulating acid secretion, secretin works to moderate gastrin release, and somatostatin and GIP act on the parietal cells, keeping acid secretion at a reasonable rate. The dynamic nature of the system is critical to proper function. One reason that potentiation of acid secretion can occur is that various factors use different second messenger systems (see Fig. 23.7).

SECRETIONS FROM THE SMALL INTESTINE: BUFFERS, ENZYMES, AND HORMONES

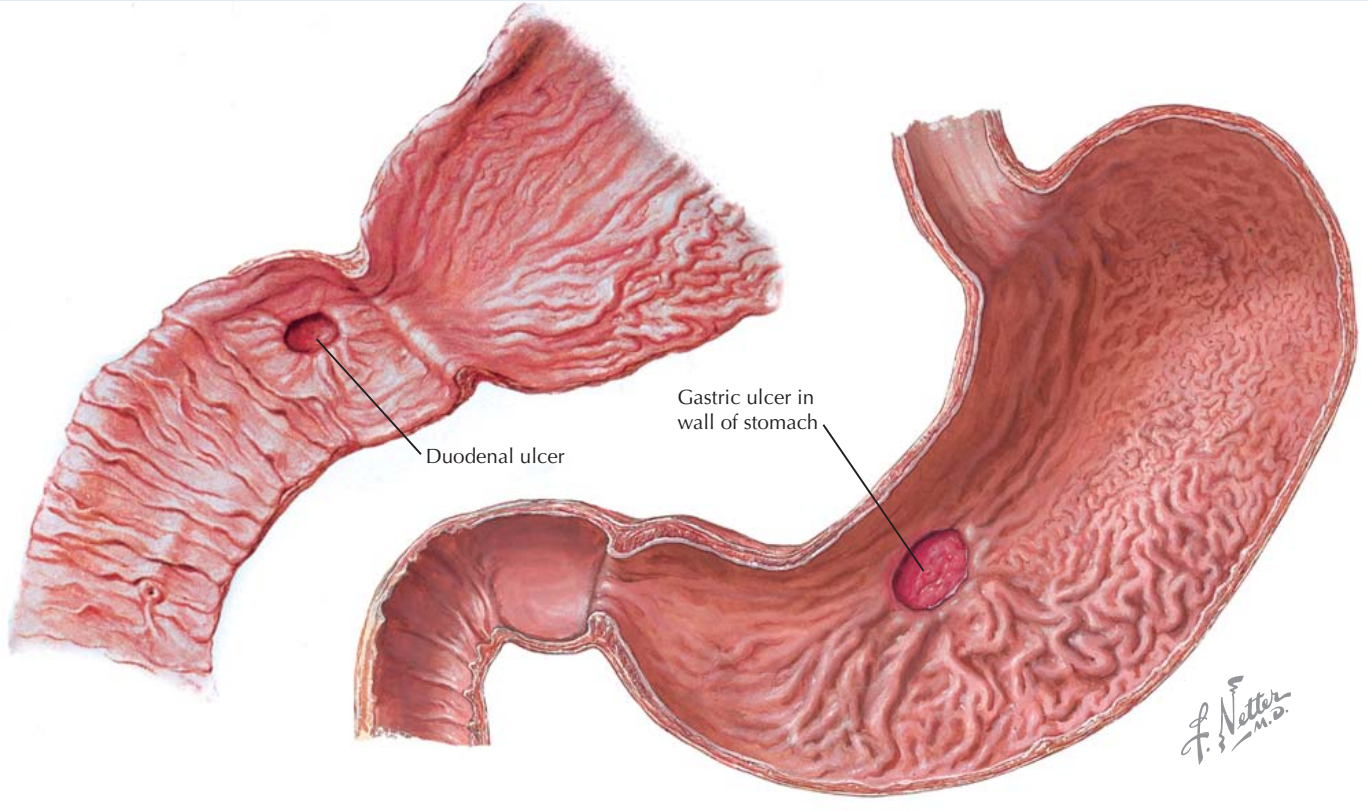
The **crypts of Lieberkühn,** located at the bottom of the villi in the small intestine, have a variety of cell types that produce and secrete buffers, enzymes, and hormones that facilitate digestion and absorption of the nutrients in the chyme (Fig. 23.8). **Brunner's glands** are located in the duodenum and secrete thick mucus, which helps to protect the early part of the small intestine from the acidic chyme leaving the stomach. These glands are stimulated by secretin and activity of the vagus. The **Paneth cells** are deep in the crypts and are stimulated by secretin to secrete ions and water, which buffer the chyme. They also secrete **lysozyme,** which has antimicrobial actions. **Goblet cells** are located throughout the small intestine and secrete mucus. Cells also release the enzyme **enterokinase,** which cleaves the inactive zymogen trypsinogen, forming the active enzyme trypsin. This occurs in the duodenum, activating the powerful protease in the presence of chyme.

The small intestine produces and secretes a variety of endocrine hormones that regulate digestion and motility (Table 23.3; the major actions of the hormones are in bold). The effects on digestion are detailed in Chapter 26.

CLINICAL CORRELATE
Ulcers

Ulcerations were thought to result mainly from ingestion of **NSAIDs** (**nonsteroidal anti-inflammatory drugs** such as aspirin) and stress until about 25 years ago, when Australian investigators discovered ***Helicobacter pylori*** residing in the gastric and duodenal mucosa of patients with gastric and duodenal ulcers. It is now known that *H. pylori* accounts for almost all non-NSAID–related gastric ulcers and nearly all duodenal ulcers. How can the bacteria live in the acidic (pH 2) environment of the stomach? *H. pylori* is resistant to HCl and can burrow into the mucosal layer because it secretes **urease,** which breaks urea into CO_2 + ammonia (NH_3). This disrupts the bicarbonate–mucus layer protecting the gastric mucosa and allows acid and pepsins to infiltrate the mucosa, initiating ulcerations. Interestingly, while most people have the bacteria (fecal-oral contamination from food or water), a critical number of bacteria must be present to initiate enough **urease** production to disrupt the mucosa and expose the epithelium to ulceration. Treatment is with antibiotics (long term) and proton pump inhibitors (PPIs).

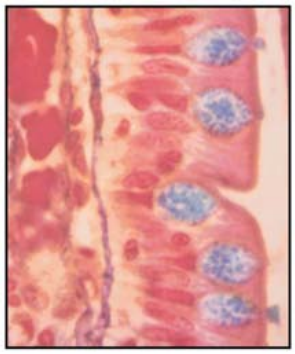
NSAIDS, including aspirin, ibuprofen, and similar drugs, can also cause gastric ulcers. Because prostaglandins are cytoprotective (by decreasing parietal cell acid production and increasing mucus production), the suppression of prostaglandins (especially PGE_2) by NSAIDs can lead to ulcerations. The ulcerative effect is enhanced when the drugs are taken on an empty stomach or in the presence of caffeine, which stimulates acid secretion. Stress, coffee, and NSAIDs (particularly when taken on an empty stomach) may have additive effects in aggravating existing ulcers. Treatment is with PPIs (and behavior modification).



Ulcerations of Stomach and Duodenum

PANCREATIC BUFFER AND ENZYME SECRETIONS

The pancreas synthesizes and releases both endocrine secretions (into blood) and exocrine secretions (through ducts). The exocrine secretions serve to help buffer the acidic chyme and are crucial for the proper digestion of chyme, because approximately 70% to 75% of digestion occurs in the proximal small intestine by the pancreatic enzymes. The exocrine secretions exit the pancreatic ducts into the common bile duct, mixing with liver and gallbladder secretions. The bile duct enters the duodenum through the **sphincter of Oddi,** at the **papilla of Vater** (Fig. 23.9*A*).

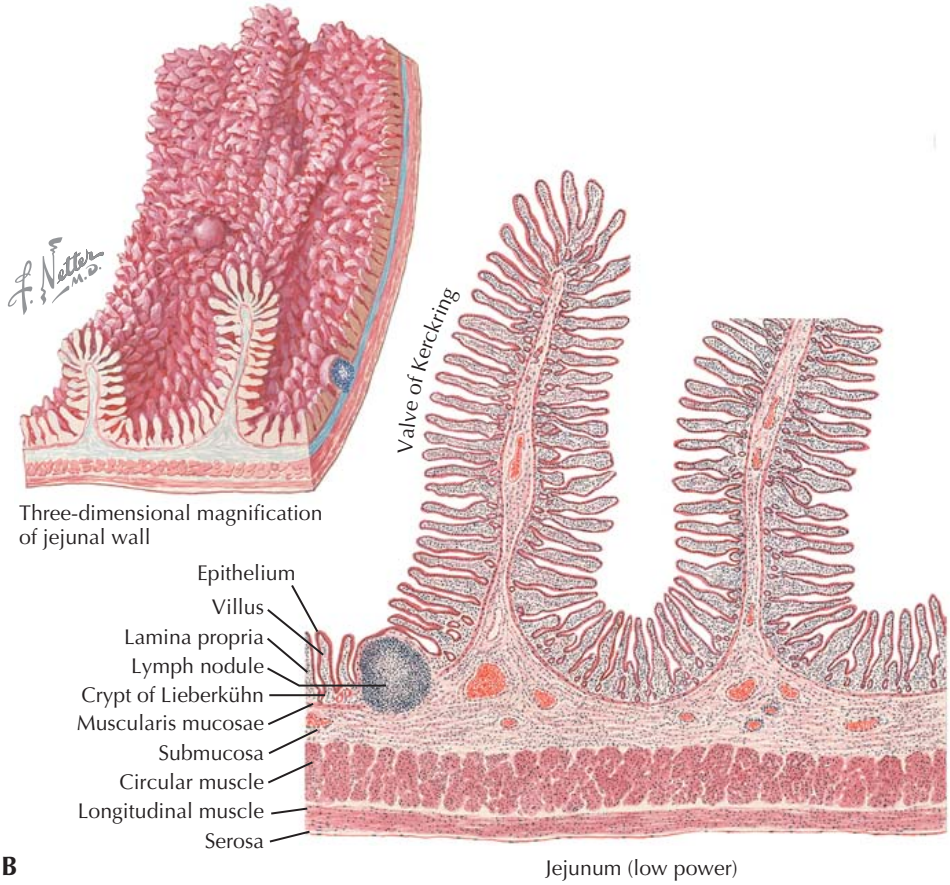


Goblet cells and striated border of human jejunal villus (azan stain, ×650)



Floor of crypt of Lieberkühn with granulated, oxyphilic cells of Paneth (hematoxylin-eosin, ×325)

A



Three-dimensional magnification of jejunal wall

Jejunum (low power)

B

Figure 23.8 Crypts of Lieberkühn and Cell Types *A,* Micrographs of goblet and Paneth cells in small intestinal mucosa. *B*, Brush border lining of the small intestine, illustrating crypts of Lieberkühn within villus projections.

Table 23.3 Major GI Hormones

GI Hormones	Site of Secretion	Primary Stimuli	General Actions
Gastrin	G-cells in antrum of stomach and duodenum	Stretch, peptides and amino acids, vagus (through GRP)	**↑gastric H^+** ↑gastric mixing ↑lower GI tract motility
Secretin	S-cells of the duodenum	Acidic chyme	**↑pancreatic buffer (HCO_3^-) secretion** **↑biliary and small intestine buffer secretion** ↓gastric H^+ (by ↓gastrin) ↓gastric emptying
Cholecystokinin (CCK)	I-cells of the duodenum and jejunum	Small peptides and amino acids, fats	**↑pancreatic enzyme secretion** contracts gallbladder and relaxes sphincter of Oddi ↑pancreatic and biliary buffer secretion ↓gastric emptying ↑lower GI tract motility
Gastric inhibitory peptide, *aka* glucose insulinotropic peptide (GIP)	Duodenum and jejunum	Fatty acids, glucose, amino acids	**↓gastric H^+ secretion** **↑pancreatic insulin secretion** ↓gastric emptying
Motilin	Mo cells of the duodenum	Fasting	**↑phase III contractions of the MMC**

GRP, gastrin-releasing peptide; MMC, migrating myoelectric complex.
(Reprinted with permission from Hansen J: Netter's Atlas of Human Physiology, Philadelphia, Elsevier, 2002.)

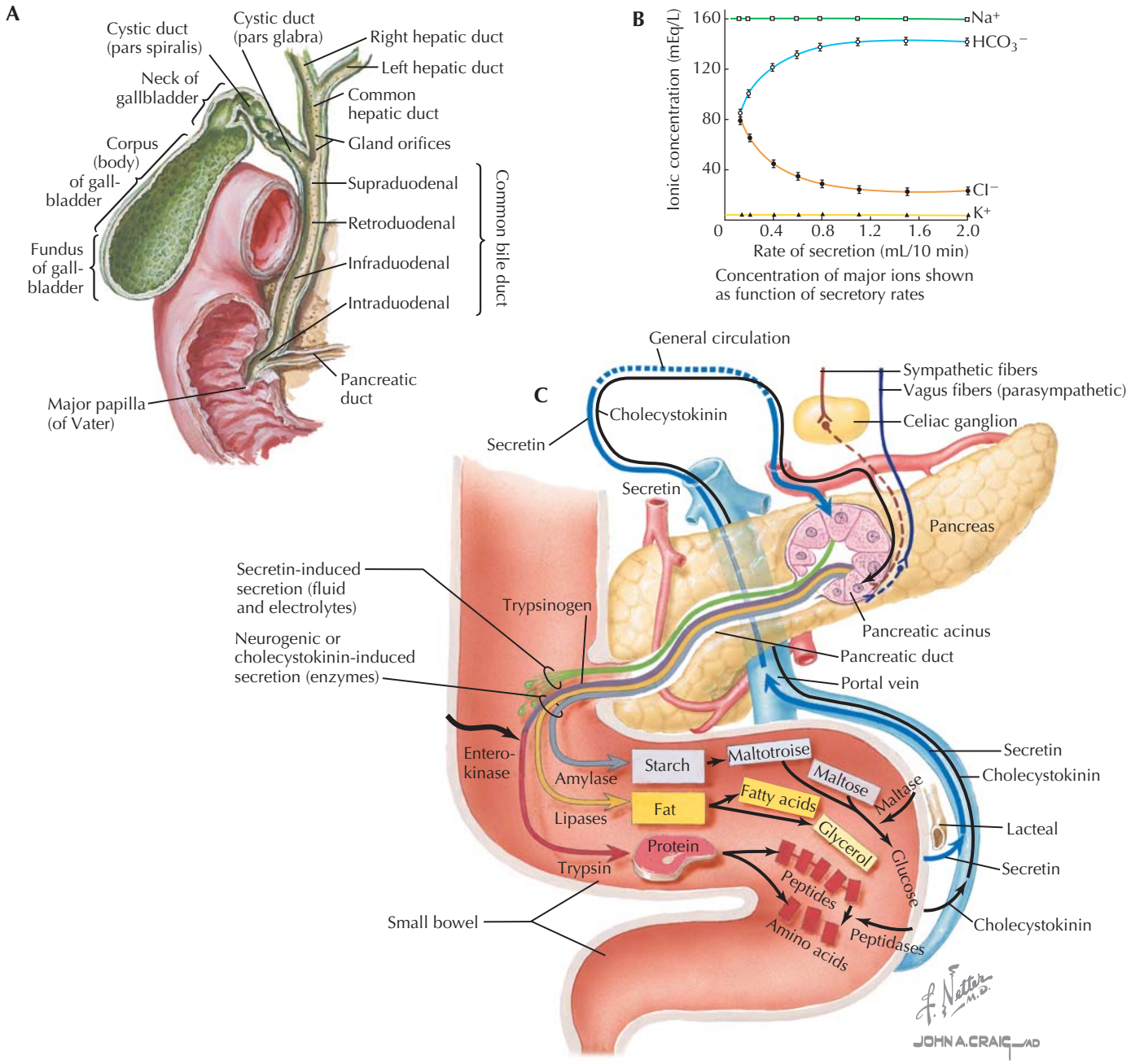


Figure 23.9 **Structure and Secretion of the Pancreas** *A*, Pancreatic, liver, and gallbladder secretions flow through the common bile duct and into the duodenum through the sphincter of Oddi at the papilla of Vater. *B*, As the rate of pancreatic secretions increases, the concentration of electrolytes changes, producing high sodium bicarbonate buffer. *C*, In response to food/chyme in the stomach and duodenum, vagal efferents and hormones stimulate pancreatic buffer and enzyme secretions.

Secretin, released in to the blood from duodenal S-cells in response to acidic chyme, binds to its receptors on the pancreatic centroacinar cells and stimulates **electrolyte and fluid secretion** (for buffering) (see Fig. 23.9*C*). As with the salivary glands, as the secretion goes through the ducts, there is modification of electrolytes. As the rate of secretion increases, the composition of the fluid changes, becoming rich in HCO_3^- (see Fig. 23.9*B*).

Cholecystokinin (CCK) is released into the blood from the duodenal I-cells and acts on the pancreatic acinar cells. Along with the vagus, CCK stimulates **pancreatic enzyme secretions,** which include:

- **Pancreatic proteases:** Trypsin, chymotrypsin, and elastase, the major proteases, are stored and released as inactive zymogens (trypsinogen, chymotrypsinogen,

and proelastase). This protects the pancreas and ducts from digestion. When the zymogens enter the duodenum, **enterokinase** (in the duodenal brush border) cleaves trypsinogen to trypsin, and then trypsin can activate additional trypsinogen (autoactivation), as well as the other proteases.

- **Pancreatic α-amylase:** Starch digestion begins in the mouth with salivary α-amylase. Digestion continues in the small intestine by pancreatic α-amylase, which hydrolyzes the starch molecules to maltose, maltotriose, and isomaltose. The amylase is activated by Cl^-.
- **Pancreatic lipase** and **colipase:** Pancreatic lipase hydrolyzes triglycerides to monoglycerides and free fatty acids; colipase is a cofactor for this process. Other lipases convert cholesterol esters to cholesterol and fatty acid, and phospholipids to lysophospholipids and fatty acid. However, pancreatic lipase cannot readily access the lipids in the small intestine because of the presence of bile. Colipase is released as precolipase and is activated in the duodenum by trypsin. The colipase binds to bile and allows the pancreatic lipase to access the lipids (see Chapter 25).

GALLBLADDER FUNCTION

The function of the gallbladder is to store bile. The sphincter of Oddi relaxes early in feeding, via vagal stimulation, releasing the contents of the bile duct (bile, electrolytes) into the duodenum. When chyme enters the duodenum, CCK is released. CCK opens the sphincter and causes gallbladder contraction. The stored bile enters the duodenum and begins lipid emulsification (see Chapter 25).

COLONIC SECRETIONS

In the colon, there is secretion of mucus, HCO_3^-, H^+, and K^+. The mucus is required to lubricate chyme as it is dehydrated and formed into feces. With colonic reabsorption of sodium (through Na^+/H^+ exchangers), H^+ is secreted into the lumen. Cl^- is also absorbed, in part through lumenal Cl^-/HCO_3^- exchangers. Thus, H^+ and HCO_3^- are secreted into the lumen of the colon. In addition, a concentration gradient develops for K^+, which then diffuses into the lumen. Potassium secretion can also occur when aldosterone is elevated (during volume contraction), because aldosterone increases Na^+/K^+ antiporters on the lumenal membrane, reclaiming additional sodium in exchange for K^+. Because of the relatively high HCO_3^- content of feces, chronic diarrhea can cause metabolic acidosis (see Chapter 20).

Gasses are formed throughout the GI tract, diffusing in and out of cells, and for the most part we are unaware of the fluxes. CO_2 is constantly produced, but in addition, bacterial action can produce H_2, N_2, and methane, for example. Typically, a person produces and expels (as flatus) about 200 milliliters (mL) of colonic gas each day. This can change, with diets high in carbohydrates and meat protein increasing gas production.

CLINICAL CORRELATE
Zollinger-Ellison Syndrome

Gastrinomas are tumors (usually pancreatic) that secrete gastrin, but do not have any of the normal feedback systems that control gastrin release. These tumors cause **Zollinger-Ellison syndrome,** in which the constant secretion of gastrin causes uncontrolled, high levels of gastric HCl release and ulcerations of the stomach mucosa. In addition, the high acid secretion acidifies the duodenum and early jejunum, impeding the actions of digestive enzymes and precipitating bile. This especially affects lipid digestion and absorption, because the low duodenal pH denatures pancreatic lipase, significantly reducing lipid digestion. This results in steatorrhea and excess bile salts in the feces. Treatment is by removal of the tumor and the use of PPIs to further reduce acid secretion, allowing ulcerations to heal.

CHAPTER 24 Hepatobiliary Function

OVERVIEW OF LIVER FUNCTIONS

The liver has a myriad of functions that revolve around vascular, metabolic, and secretory aspects. The **hepatocytes** are the cells making up the parenchyma of the liver. The basic functions of the liver include:

- Regulation of carbohydrate, lipid, and protein metabolism: The liver receives newly absorbed nutrients through the portal vein, as well as contents of systemic blood, and processes them according to need. It produces albumin, fibrinogen, immunoglobulins, binding proteins, cholesterol, lipoproteins, and other important molecules.
- Regulation of cholesterol production and excretion: The body requires cholesterol, which the liver is able to synthesize.
- β-Oxidation of fatty acids: While many tissues use β-oxidation as an alternate energy source when glucose is not present, the liver has a high rate of β-oxidation during the interdigestive period.
- Bile acid production and secretion: Bile is necessary for efficient lipid absorption. Bile is polar, allowing it to incorporate lipids into a **micelle,** and then taxi the lipids through the unstirred water layer adjacent to the enterocytes (see Chapter 25). Without bile, the bulk of the hydrophobic lipids cannot get near the brush border.
- Endocrine functions: The hepatocytes produce and secrete hormones into blood, including insulin-like growth factor-1 (IGF-1), hepatocyte growth factor, angiotensinogen, and cytokines. It converts thyroxine (T4) to active triiodothyronine (T_3) and participates in activation of vitamin D.
- Detoxification: The liver contains reticuloendothelial cells, the **Kupffer cells,** which are fixed macrophages in the endothelial lining of hepatic sinusoids. As blood passes through the liver, old and damaged erythrocytes undergo phagocytosis by the Kupffer cells. Hormones, drugs, and other chemicals are metabolized by the hepatocytes.
- Vitamin and iron storage: The liver stores several elements crucial to normal body functions (B12, folic acid, iron). Vitamins can be stored for weeks to months, and in the case of essential vitamins like B12 (cobalamin), this provides a source of the vitamin if the dietary supply is depleted. The liver is also the site of large iron stores, bound to the protein **ferritin** (containing 25% of the body's iron). When needed, the iron (bound to transferrin) is released into the blood and enters the bone marrow for production of hemoglobin.

This great variety of functions makes the liver a crucial organ for maintaining immune cell function and proper blood glucose levels, excreting waste products, processing proteins, and even indirectly regulating blood pressure and fluid homeostasis (through synthesis of plasma proteins) (Fig. 24.1). When part of the liver is damaged, it has the ability to regenerate functional hepatocytes, and this compensatory action allows it to maintain adequate metabolic function. In addition, the ability of the liver to achieve a high level of metabolic activity is dependent on the blood flow.

LIVER STRUCTURE AND BLOOD FLOW

The liver is like a sponge. The hepatocytes are surrounded by sinusoidal capillaries and lymph vessels (Fig. 24.2). This allows for the free flow of blood to the cells, and the cellular products secreted into the perisinusoidal **space of Disse** can be released back into blood, or into the lymphatic vessels. **Kupffer cells** are affixed to the sinusoidal membranes and are present throughout the liver. These cells phagocytose bacteria and damaged red blood cells. The hepatocytes metabolize hormones and drugs and clear the waste, "detoxifying" the blood. The heptocytes also produce bile and electrolyte solutions that drain into the **bile canaliculi,** which lead to the bile duct.

Under normal conditions, the liver contains ~400 milliliters (mL) of blood, which is ~8% of the total blood volume. This illustrates the "blood storage" aspect of the liver. Two key factors that make the system work properly are that hepatic vein pressure is very low, near 1 mm Hg, and that there is no obstruction of blood flow through the liver sinusoids. This allows the free flow of blood through and out of the liver into the vena cava. If there is obstruction of flow through the liver (cirrhosis, hepatitis) or increased hepatic vein pressure (congestive heart failure), blood will back up and pressure will rise, causing **portal hypertension.** The volume of blood associated with the liver can also increase to 1 liter (L), causing **hepatomegaly** (enlarged liver).

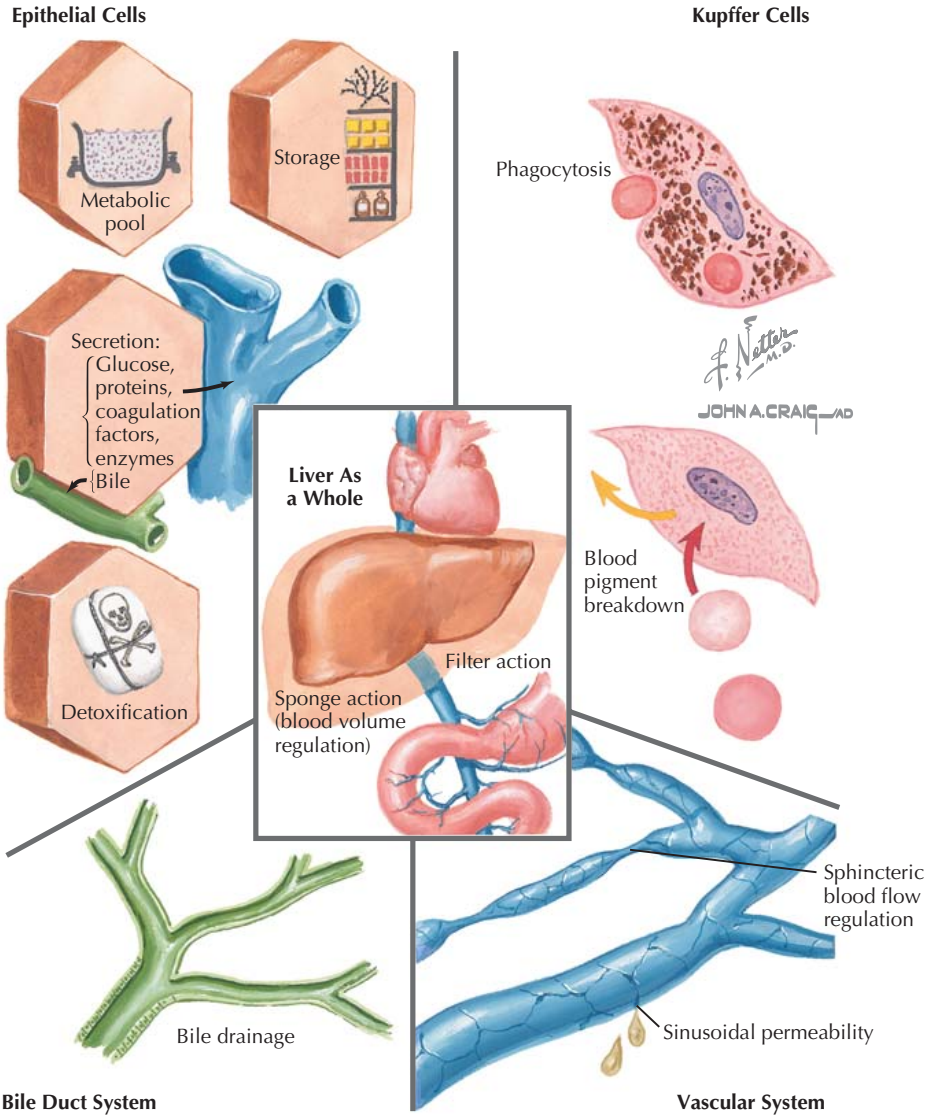


Figure 24.1 Overview of Liver Function The liver performs many functions, including metabolism of carbohydrates, proteins, and lipids; phagocytosis and removal of waste and bacteria; detoxification; synthesis of bile; blood volume control; and vitamin storage.

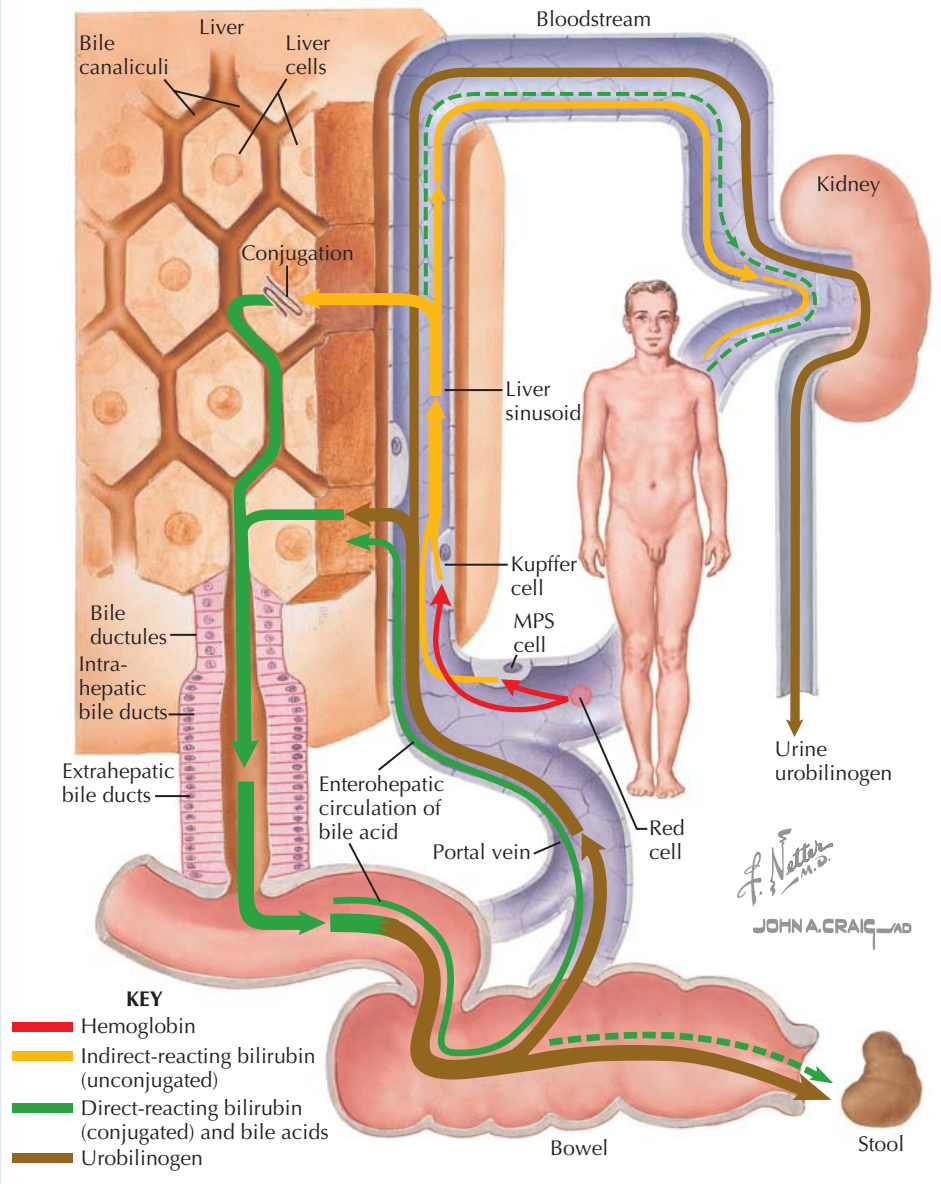
The blood supply to the liver comes from the hepatic artery and portal vein. The systemic blood from the hepatic artery enters the liver at a rate of ~450 mL per minute. The portal vein carries the blood from the intestines (~1 L per minute), and the arterial and venous blood intermingles in the sinusoidal capillaries. This amount represents about 30% of the cardiac output. As the blood from the portal vein enters the liver, nutrients, bacteria, and foreign bodies are processed—this is the "first pass" effect, which allows the absorbed materials to be "cleared" by the liver before the blood leaves through the hepatic vein into the systemic circulation. Although not all such substances will be cleared or metabolized in one pass, the bulk of the substances will be handled.

Ascites is fluid in the peritoneal cavity of the abdomen. This can be caused by increased vascular pressure within the liver. Because the liver capillaries have a high permeability, when the pressure increases, fluid is forced out of the space of Disse and lymphatics, into the peritoneal space. Increased venous pressure, as in congestive heart failure, can cause ascites as well as peripheral **edema**. Edema results from elevated capillary hydrostatic pressure, increasing the Starling forces pushing fluid out of the capillaries into the interstitial space (in the lower extremities).

CLINICAL CORRELATE
Bilirubin and Jaundice

Red blood cells (RBCs) are viable for about 120 days, and new cells are continually being produced to replace damaged old cells. Phagocytic mononuclear cells throughout the body (especially Kupffer cells in the liver) remove and break down the old red blood cells, so that the iron can be recycled and waste eliminated. **Bilirubin** is a by-product of RBC degradation and is eliminated from the body by incorporation into bile (and subsequent loss in feces) and by urinary excretion as urobilinogen. The addition of bilirubin to bile, and its excretion in feces, contributes to the pigmentation of the feces. The bile pathway of excretion is important for ridding the body of excess bilirubin.

Jaundice occurs when plasma bilirubin is elevated. In patients it is observed as a yellowing tinge in the whites of the eyes and in skin tone and nail beds; stool is pale. **Primary jaundice** arises from hepatic dysfunction, as seen with obstructive liver disease (cirrhosis), blockage of bile ducts (by tumor or gallstones), or inflammation (hepatitis C). **Secondary jaundice** occurs from extrahepatic sources, such as abnormal lysis of RBCs (hemolytic disease). In most cases, when the primary cause of the jaundice is treated, the jaundice will abate as the excess bilirubin eventually clears (through bile and urinary excretion). An important distinction is that with secondary jaundice liver function is normal.



Bilirubin Production and Excretion

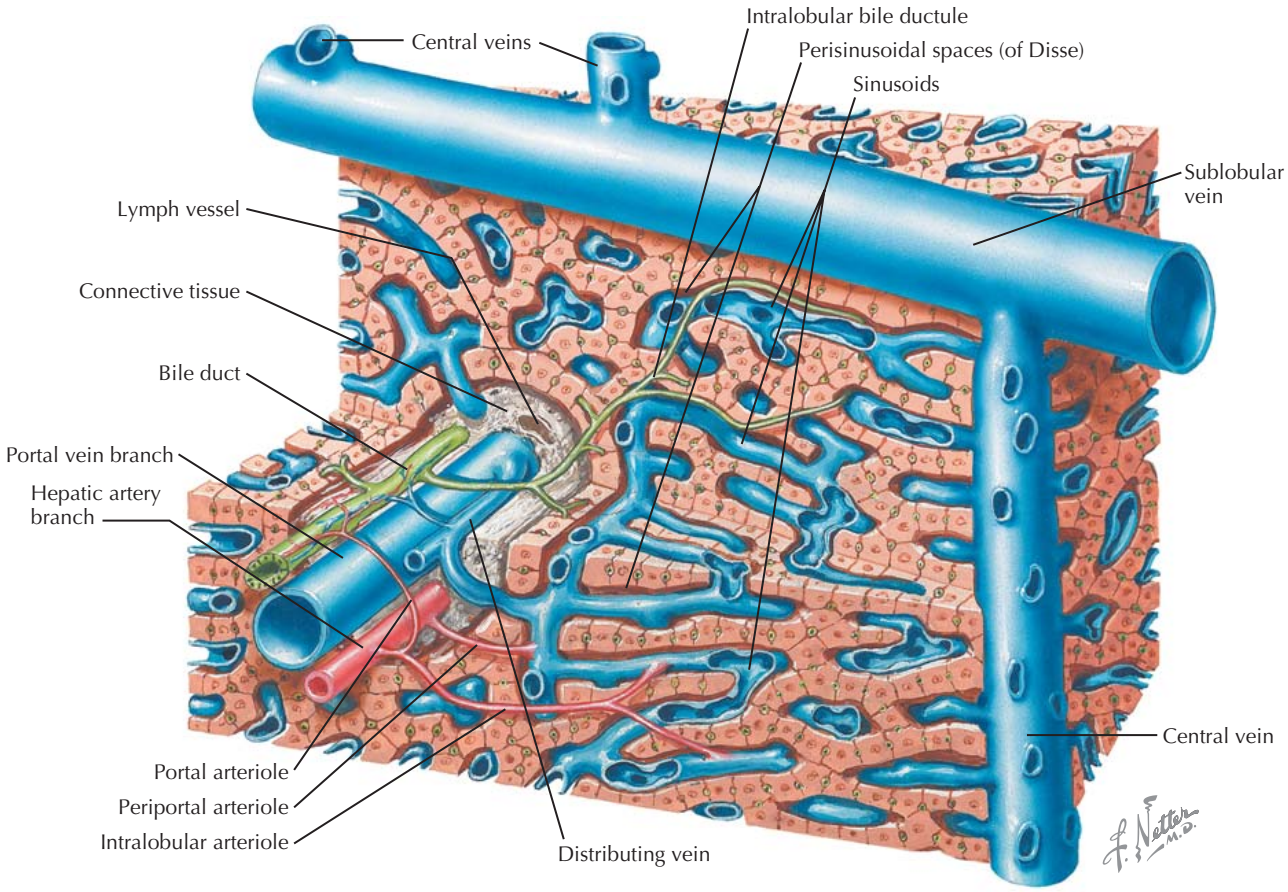


Figure 24.2 Structure of the Liver The liver is highly vascularized to accomplish its primary function of filtering portal and systemic blood. The capillary sinusoids surround the liver cells (hepatocytes), allowing efficient access of blood to the cells and transfer of products back into the blood. The sinusoids also contain the Kupffer cells, which are fixed macrophages that phagocytose damaged or aged red blood cells.

BASIC METABOLISM OF CARBOHYDRATES, LIPIDS, AND PROTEINS

Carbohydrates

The liver acts as a blood glucose monitor, storing glucose as glycogen and releasing it when blood levels are low. Carbohydrates are absorbed in the intestine as monosaccharides and are carried in the portal blood to the liver. Most of the glucose passes through the liver rapidly and is released into the systemic blood, where elevated insulin will facilitate its entry into tissues. In the liver, excess monosaccharides are handled by:

- **Conversion of other monosaccharides to glucose:** Fructose and galactose can be converted into glucose.
- **Glycogen synthesis and storage:** Excess glucose is polymerized and stored as glycogen. Stored glycogen can provide glucose for 17 to 24 hours during fasting. When blood glucose levels are low, glucagon (and other hyperglycemic hormones like epinephrine and growth hormone) stimulates glycolysis to break down glycogen and release glucose into the blood. If the glycogen stores are not used, excess glucose (not released into the blood) will eventually be converted to triglycerides (TG) and transported to adipose tissue for storage (see "Lipids").
- **Gluconeogenesis:** The liver (and to a lesser extent, the kidney) has the ability to make glucose from substrates such as glycerol, pyruvate, and the amino acids glutamine and alanine. This provides an alternate energy



The ingestion of carbohydrates raises blood glucose levels; the **glycemic index** of a specific carbohydrate refers to the degree to which it raises blood glucose. Diets that produce high glycemic indices are believed to be associated with development of type II diabetes. High-fructose corn syrup is used in many foods, and because of its low glycemic index, has been recommended for people with diabetes. However, some studies suggest that elevated blood fructose levels may actually contribute to insulin resistance and hyperlipidemia, which, along with elevated blood pressure, are components of metabolic syndrome.

source and occurs primarily during fasting and starvation.
- **Formation of chemical compounds:** Excess glucose can also be converted into other chemical compounds (pyruvic acid, lactic acid, acetyl CoA) that can be used in metabolic pathways such as the citric acid cycle.

Lipids

Most lipids are packaged into **chylomicrons** in the enterocytes (see Chapter 25). The chylomicrons enter the lymph lacteals in the small intestine, entering the systemic blood in the large vessels in the thoracic cavity. Thus the first entry of absorbed lipid into the liver is from the systemic, not portal, circulation. Liver lipid metabolism includes the following:

- **β-Oxidation of fatty acids:** Although many tissues use β-oxidation as a source of energy when needed, the rate is very high in the liver.
- **Formation of most lipoproteins:** Very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) are formed in the liver. VLDL and LDL transport TG and cholesterol to tissues. LDL is implicated in development of cardiovascular disease because it is incorporated into atherosclerotic plaques. HDL transports lipids from tissues to the liver and is considered beneficial.
- **Synthesis of cholesterol and phospholipids:** These substrates are necessary for making membranes, and cholesterol is also the precursor for steroid hormones and bile. Because of these important functions, the liver ensures a supply of these substrates by forming them from other lipids. A liver enzyme, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, is the rate-limiting step in cholesterol synthesis, and pharmacologic intervention by **statins** (cholesterol-lowering drugs) inhibits this enzyme.
- **Conversion of unused glycogen to TGs:** If liver glycogen is not used, it is converted to TGs, which are transported to adipose tissues in VLDLs.

Proteins

Protein metabolism in the liver is essential for survival; the liver processes dietary amino acids and participates in the processing of nitrogen wastes for excretion. The major functions of the liver in this regard are:

- **Deamination of amino acids:** This prevents toxin buildup, because aminotransferases remove the amino group from the amino acids, creating ammonia (NH_3).
- **Production of urea:** The NH_3 combines with CO_2 to form urea, thereby buffering NH_3 and allowing urinary excretion.
- **Synthesis of plasma proteins:** About 90% of plasma proteins are made in the liver. This includes:
  - albumin, which contributes to oncotic pressure
  - immunoglobulins, which contribute to immune functions
  - fibrinogen, which is necessary for blood clotting
- **Interconversion of amino acids:** Needed amino acids are synthesized from other available amino acids.

PRODUCTION AND SECRETION OF BILE

Bile is critical for transport of lipids through the **unstirred water layer** to the enterocytes. The unstirred water layer is the area in the gut lumen that is closest to the villous lining. There is little flow near the cells, and the water and mucus create a barrier that impedes access of the hydrophobic lipids to the enterocytes (carbohydrates and proteins have no trouble passing through this area). This challenge is met by bile, which is amphipathic (has both hydrophilic and hydrophobic regions) and thus is able to move lipids across the unstirred water. Bile and lipids form **micelles,** which act like taxis to shuttle the lipids through the unstirred water layer to the enterocytes (discussed further in Chapter 25). **Bile solids** are composed of bile salts (50%), phospholipids (40%), and smaller amounts of cholesterol (~4%), bilirubin (~2%), and water and electrolytes. Secreted bile is composed of the bile solids, water, and electrolytes.

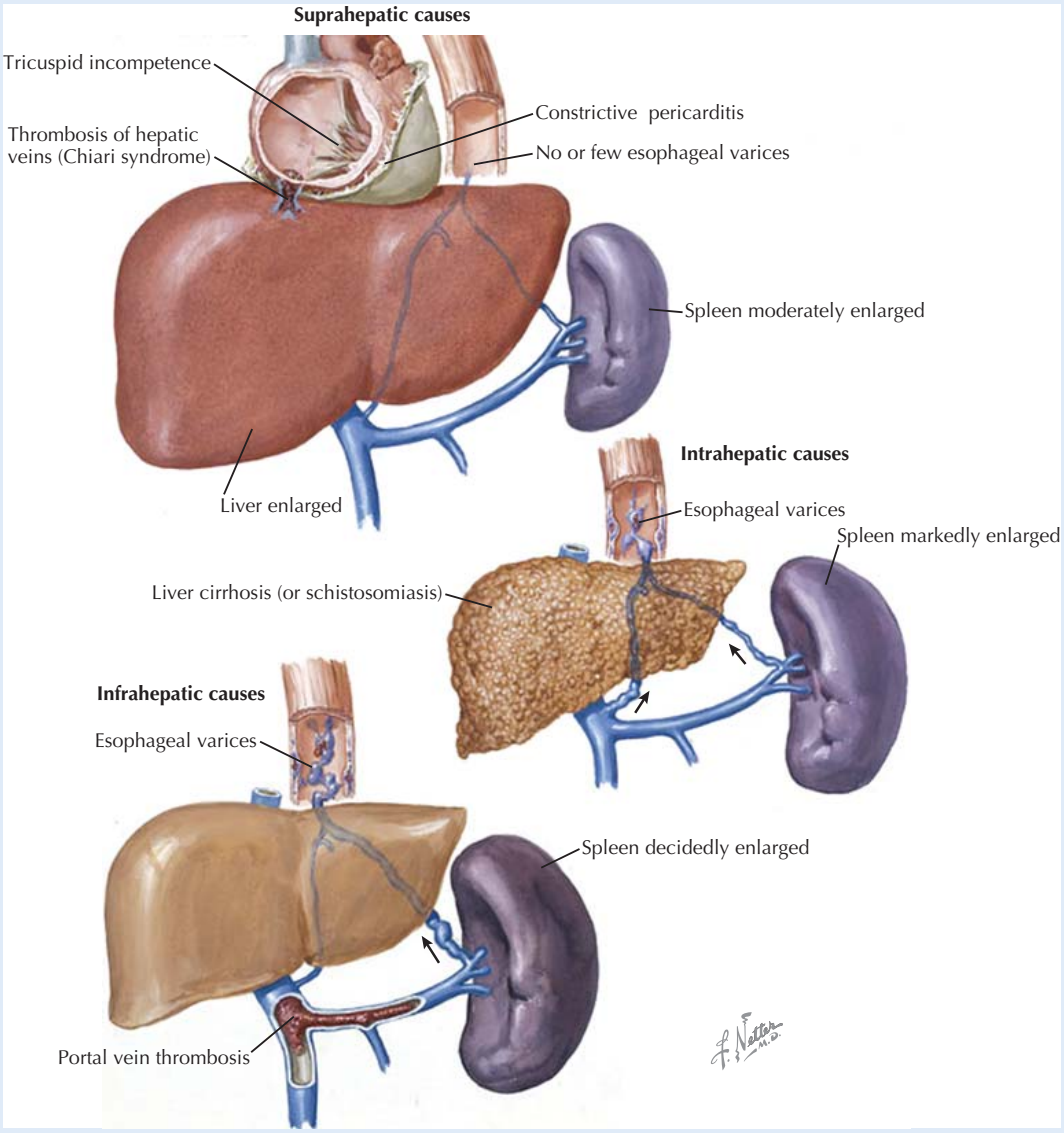
In the liver, primary **bile acids** (cholic, chenodeoxycholic acids) are synthesized in the hepatocytes from sterol rings (from cholesterol). There are several important aspects of bile synthesis and secretion:

- In the liver, one side of the primary bile acid is conjugated with an amino acid (either taurine or glycine), forming a **bile salt.** This conjugation increases the water solubility of bile in the lower pH found in the duodenum. The primary bile salts are secreted into the bile canaliculi, or ductules, and into the common bile duct (see Fig. 24.2).
- Bile salts are osmotic, and their secretion will draw water, and then solvents (sodium chloride, HCO_3^-) from the cells—this is called **solvent drag** and contributes to the buffering capacity of the bile when it enters the duodenum.
- After micelles are formed and the lipids are dropped off at the enterocytes, the majority of the bile remains in the lumen of the small intestine until the terminal ileum, where Na^+-dependent transporters recycle the primary bile into the portal vein back to the liver. This bile recycling will occur three to five times for each meal and allows for efficient absorption of the lipids without synthesis of large amounts of bile, because it is reused.
- However, with each cycle, about 10% of the bile is not absorbed but is lost in the feces. This is the major pathway by which cholesterol is removed from the system; other substances including bilirubin are also excreted. The synthesis of bile acids is under feedback control by bile salts entering the liver from the portal

CLINICAL CORRELATE
Portal Hypertension and Esophageal Varices in Obstructive Liver Disease

Increased blood pressure in the portal vein can result from suprahepatic pathology (e.g., increase in systemic venous pressures, as with congestive heart failure) or hepatic pathology (e.g., obstructive liver disease). Obstructive liver disease is most commonly a result of cirrhosis or fibrous scarring of the liver, which severely decreases the flow of blood through the organ. In the United States, alcoholism and hepatitis C infection are the most common causes of cirrhosis. Interestingly, alcoholism causes cirrhosis of the liver or pancreatitis in individual patients, but not both diseases.

In the cirrhotic liver, the obstruction of blood flow through the liver increases pressure in the portal system. This **portal hypertension** results in increased backpressure in vessels coming from the stomach and esophagus, causing enlargement and thinning of these vessel walls, forming **varices.** The thin walls, high pressure, and increased radius in the varices make them susceptible to rupture, and because of the superficial nature of the vessels serving the esophagus, rupture may cause severe bleeding into the esophageal lumen, requiring immediate medical attention. Treatment of varices is by either sclerotherapy (injecting a solution to block the vessels), or rubber-band ligation of the varices, where a band is wound around the varices, cutting off blood flow. The atrophied area sloughs off, leaving a healed scar. Portal hypertension can also result in **ascites** and **hemorrhoids,** again caused by the backup in pressure in the portal venous system.



Esophageal Varices

circulation. Reduced bile salts will increase **cholesterol 7α-hydroxylase,** which controls bile synthesis.

- In the intestines, some of the primary bile acids undergo dehydroxylation by bacteria, forming **secondary bile acids** (deoxycholic, lithocholic acids), which are less efficient at crossing the unstirred water layer, and hence are less readily absorbed.
- When the stomach is emptied and chyme is no longer present in the duodenum, the sphincter of Oddi will close. As the bile is recycled through the portal system back through the liver, it will stop at the sphincter of Oddi, and back up into the relaxed gallbladder, where it will be stored until the next meal.

BASIC ENDOCRINE FUNCTIONS

The liver produces or modifies several endocrine and paracrine substances, including the following:

- **Insulin-like growth factor-I** (IGF-I), which is released by the liver into the circulation in response to growth hormone. IGF-I mediates many of the somatic effects of growth hormone.
- **Angiotensinogen,** which is the precursor to angiotensin I and II (angiotensin II plays an important role in blood pressure regulation).
- **Thrombopoietin** (**TPO**), which stimulates stem cells in bone marrow to differentiate to megakaryocytes, which give rise to platelets. Platelets are participate in blood clotting.
- **Hepatocyte growth factor** (**HGF**), which acts locally to stimulate regeneration of liver cells and is especially important when the organ is damaged.
- **Vitamin D metabolism**: The liver hydroxylates cholecalciferol (from diet or synthesized in skin) to form 25-hydroxycholecalciferol. This is still inactive and must be further hydroxylated in the kidney to become the active form of vitamin D, 1,25-dihydroxycholecaliferol. Vitamin D is a key regulator of intestinal calcium absorption.

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CHAPTER 25
Digestion and Absorption

ANATOMY AND NUTRIENT ABSORPTION

Absorption of nutrients in the small intestine depends on an intact villous lining, which is designed to facilitate efficient nutrient uptake into the body. The lumen of the small intestine is composed of circular folds, villi, and microvilli (Fig. 25.1). This increases the surface area of the small intestine to approximately 250 square meters and dramatically increases the efficiency of the system so that most of the nutrient absorption will occur by mid- to late-jejunum. As a rule of thumb, ~25% to 30% of digestion occurs preduodenally, and ~70% to 75% occurs in the duodenum and jejunum.

The upper half of the villi is the site of membrane-bound enzymes (brush border enzymes) for final digestion of carbohydrates and proteins. This is also the site of absorption. The bottom part of the villi form the crypts of Lieberkühn, from which buffers and mucus are secreted, as previously discussed in Chapter 23. Finally, because there is laminar flow through the lumen, the slowest movement is near the enterocytes, and this is slowed even further because of the mucus secreted to protect the cells. This creates an **unstirred water layer** that molecules must pass through to access the enterocytes. This is no problem for movement of most nutrients but creates a problem for hydrophobic, lipid-based molecules.

CARBOHYDRATE DIGESTION AND ABSORPTION

Much of the carbohydrate in our diet is in the form of starch, **sucrose** (table sugar), **lactose** (milk sugar), and fructose. **Starch** is a large, branched, long-chain polysaccharide synthesized by plants; it represents a large portion of the carbohydrates consumed in most diets. The glucose moieties within the starch molecule are bound by α-1,4 glycosidic linkages, with α-1,6 linkages at branch points. **Sucrose** and **lactose** are **disaccharides.** We also ingest large quantities of the monosaccharide **fructose,** which is present in fruits and many foods using "high-fructose corn syrup" as a sweetener.

Although we ingest long-chain sugars and oligosaccharides, we can only absorb monosaccharides. Carbohydrate digestion begins in the mouth and continues through to the small intestine (Fig. 25.2):



Starch, glycogen, and cellulose are all polymers of glucose. Starch is a storage form of glucose in plants and is a major source of energy in our diet. Although animals store glucose in their muscles in the form of glycogen, the meat we consume contains little or no glycogen, because it is broken down after animals are slaughtered. Cellulose is the structural component of the cell walls of green plants and has no caloric value to humans. Cellulose is plant fiber and is composed of glucose molecules bound by β-1,4 linkages in large, straight chains. Humans do not have an enzyme that can digest β-linkages, so this "fiber" remains in the gastrointestinal (GI) lumen. Fibers attract water, loosening stools and adding bulk. High-fiber diets have other health-related advantages, including a blood cholesterol–lowering effect and enhanced glucose tolerance (antidiabetogenic effect). In contrast to other mammals, ruminants such as cows are able to digest cellulose due to the presence of symbiotic prokaryotic organisms in their GI tracts.

- **Mouth: Salivary α-amylase** begins starch digestion, breaking α-1,4 linkages and creating smaller oligosaccharides (maltose and isomaltose, both disaccharides consisting of two linked glucose molecules, as well as larger oligosaccharides and polysaccharides). It is inactivated by the acid pH in the stomach.
- **Small intestine: Pancreatic α-amylase** continues the digestion, forming more maltose and isomaltose.
- **Small intestine brush border:** As the chyme contacts the villous brush border, specific **brush border saccharidases** digest the maltose, isomaltose, sucrose, and lactose to their constitutive monosaccharides (Table 25.1).

In the small intestine, glucose and galactose are transported into the enterocytes with sodium via SGLT-1 transporters (secondary active transport); fructose has its own transport protein, GLUT-5 (through facilitated transport). The monosaccharides leave the basolateral membranes by facilitated transport through GLUT-2, diffuse through the interstitial space into the capillary, and are transported through the portal vein to the liver for processing and release into the systemic circulation. Carbohydrates are efficiently digested and quickly absorbed.

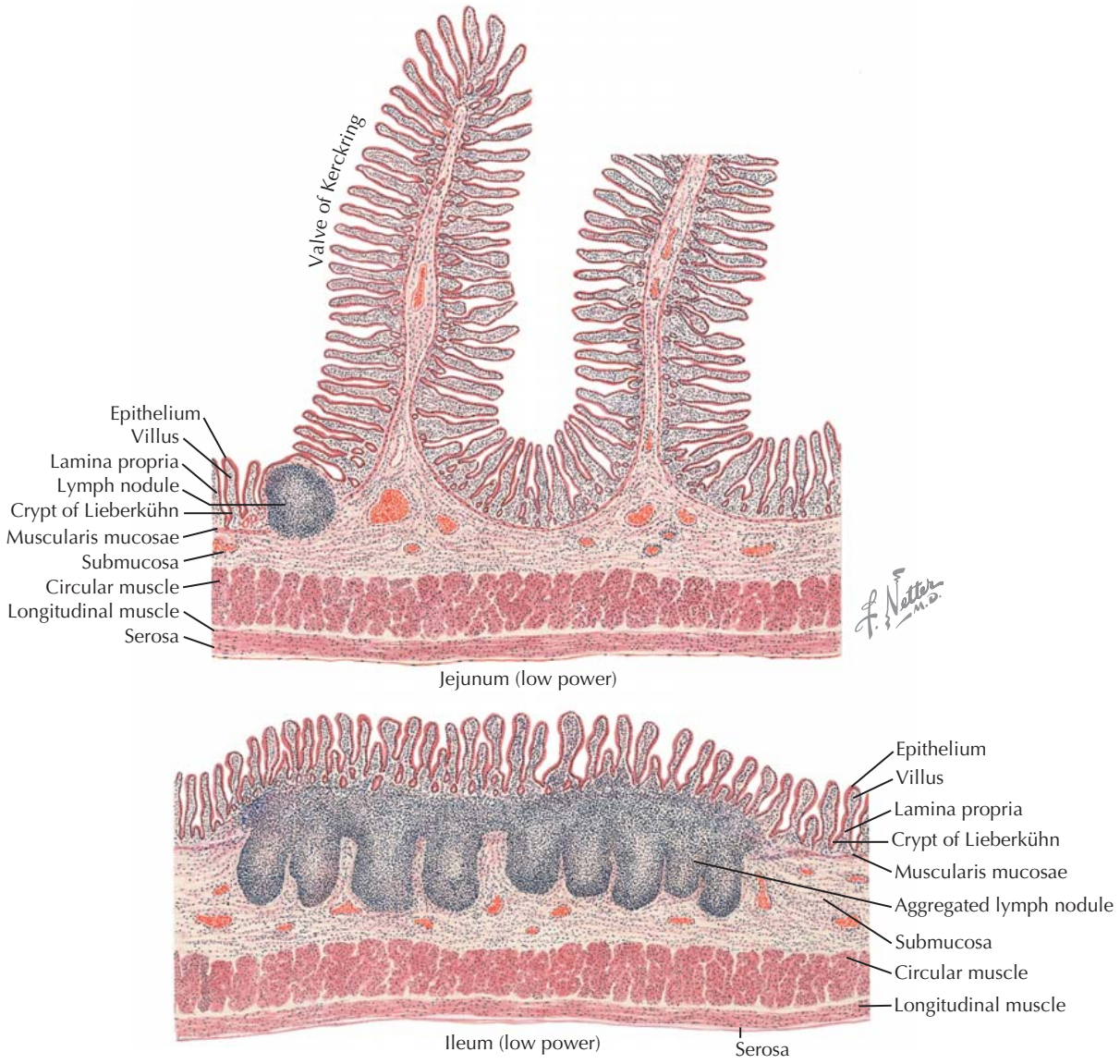


Figure 25.1 Small Intestine Surface Area The small intestine has circular folds, villi, and microvilli (hairlike projections on villi), which increase the surface area for absorption to about 600 times the area of a straight tube. This allows efficient absorption of nutrients. The upper half of the villi are the site of the brush border saccharidases and proteases (for final digestion of carbohydrates and proteins), and the upper half is also where absorption occurs.

Table 25.1 Brush Border Saccharidases and Products

Brush Border Enzyme	Substrate	Product(s)
Maltase	Maltose	Glucose
Isomaltase	Isomaltose	Glucose
Sucrase	Sucrose	Glucose + Fructose
Lactase	Lactose	Glucose + Galactose

Because glucose is absorbed into the enterocytes by SGLT-1 transporters, the rapid absorption of glucose facilitates sodium absorption, and hence chloride and water absorption. This is the principle behind **oral rehydration therapy** (ORT) for dehydration or enteric diseases such as cholera.

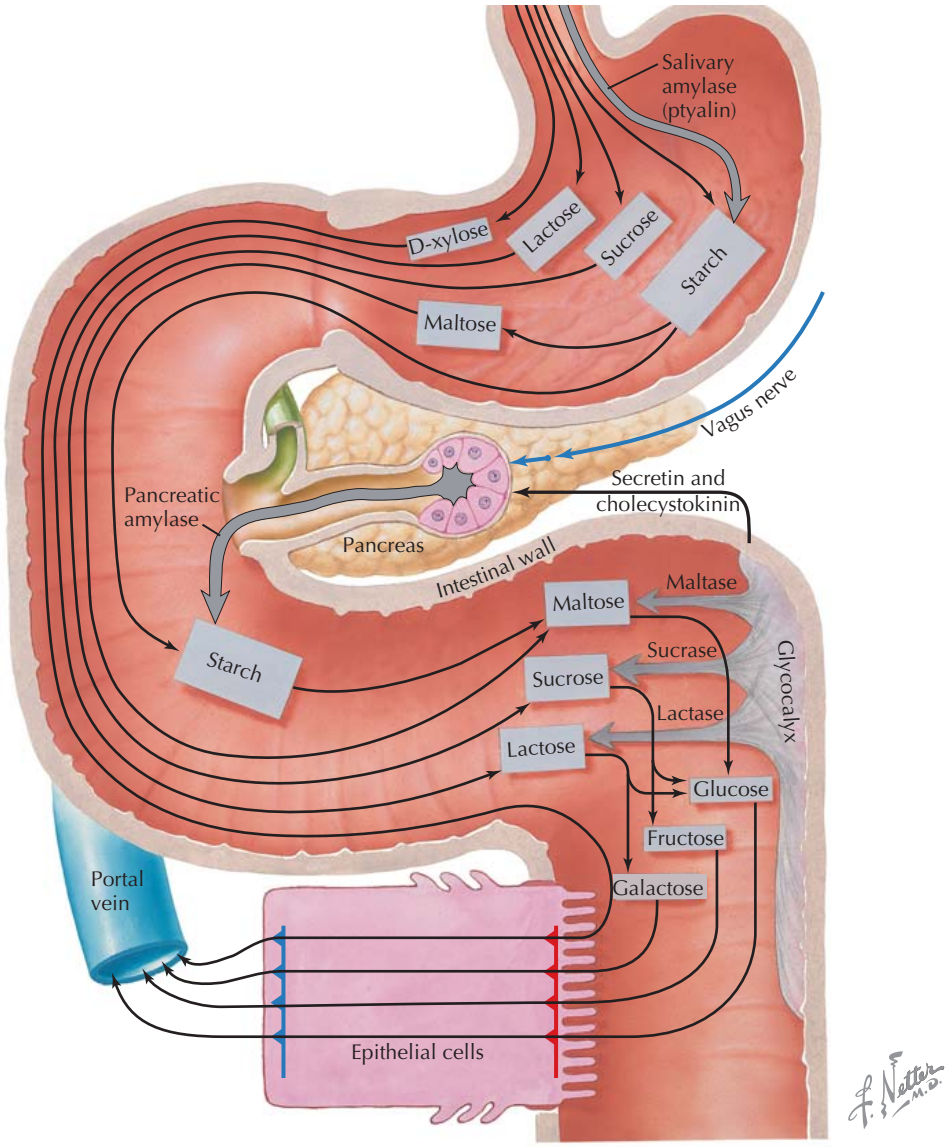


Figure 25.2 Carbohydrate Digestion and Absorption Starch digestion begins in the mouth with salivary α-amylase, which produces smaller malto-oligosaccharides. In the small intestine lumen, pancreatic α-amylase continues to digest the starches. At the same time, brush border saccharidases perform the final digestion of maltose and isomaltose (by maltase and isomaltase, producing glucose molecules), and the disaccharides sucrose (by sucrase, producing glucose and fructose) and lactose (by lactase, producing glucose and galactose). The monosaccharides then are transported into the enterocytes by secondary active transport with sodium (glucose and galactose) and facilitated transport (fructose; not shown on diagram).

PROTEIN DIGESTION AND ABSORPTION

Dietary protein digestion begins in the stomach and continues in the small intestine:

- **Stomach: Pepsinogens** are secreted from the gastric chief cells and are activated to pepsins by stomach acid. Pepsins are endopeptidases (such as trypsin and chymotrypsin) and hydrolyze inner peptide bonds, creating smaller oligopeptides. Pepsins are inactivated in the higher pH of the duodenum.
- **Small intestine: Pancreatic proteases** are responsible for digesting the oligopeptides down to smaller peptides. As stated in Chapter 23, the pancreatic proteases are released as zymogens into the duodenum primarily in response to cholecystokinin (CCK). The brush border enzyme **enterokinase** activates trypsinogen to **trypsin,** and the trypsin activates the other endopeptidases (chymotrypsin, elastase) and the exopeptidases (carboxypeptidase A and carboxypeptidase B). Once activated, trypsin can also activate trypsinogen. The pancreatic proteases

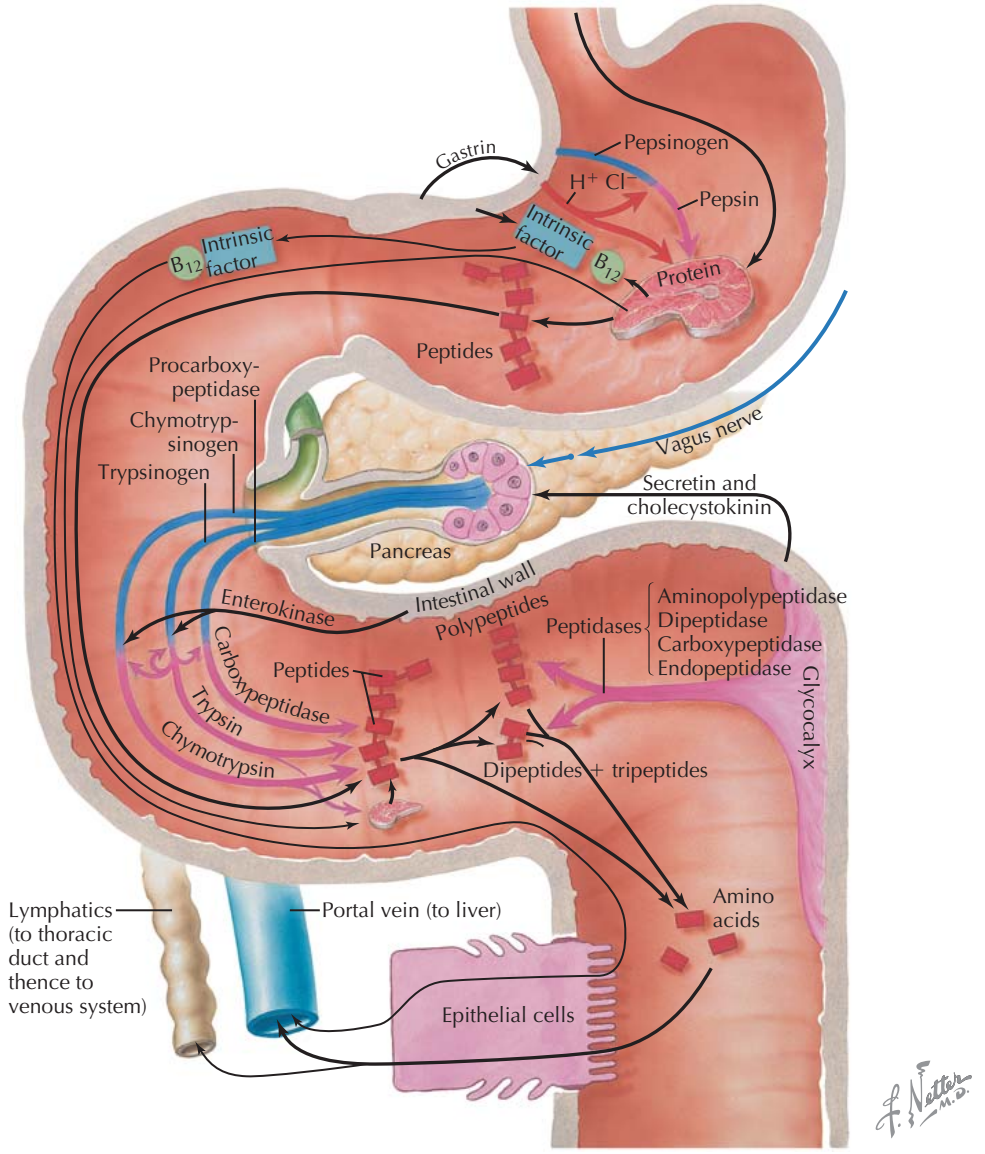


Figure 25.3 Protein Digestion and Absorption Protein digestion begins in the stomach with HCl and pepsins, which break protein down to smaller polypeptides. In the lumen of the small intestine, pancreatic proteases (trypsin, chymotrypsin, carboxypeptidase) are activated and continue the digestion to smaller peptide chains. Final digestion occurs by the brush border proteases, which produce dipeptides, tripeptides, and single amino acids. These molecules are transported into the cells via secondary active transport with sodium (amino acids), or coupled with H^+ (dipeptides and tripeptides). In the cells, the dipeptides and tripeptides are digested to amino acids by cytoplasmic peptidases.

continue hydrolysis of peptide bonds, making smaller oligopeptides (Fig. 25.3).

- **Small intestine brush border:** A variety of **brush border peptidases** hydrolyze the peptides to amino acids and dipeptides and tripeptides, which can then be absorbed.
- **Enterocytes: Cytoplasmic peptidases** digest the dipeptides and tripeptides to amino acids, which can exit the cells.

In the small intestine, most of the proteins are absorbed into the enterocytes in dipeptide and tripeptide form, via H^+



As previously stated, storing and secreting the pancreatic proteolytic enzymes as zymogens helps prevent digestion of the pancreatic tissue. However, because trypsin can autoactivate itself, the pancreas also produces **trypsin inhibitor,** which deactivates trypsin in the pancreas and ducts. In the small intestine, the large amount of active trypsin is also prevented from damaging the intestinal mucosa by the presence of other trypsin inhibitors (PSTI, pancreatic secretory trypsin inhibitors), which can compete with proteins for trypsin. The PSTI have also been shown to stimulate growth of intestinal epithelial cells.

symporters that are specific for the peptides. Amino acids have different Na^+-dependent transporters for basic, acidic, neutral, and imino acids. Once inside the intestinal cells, the cytoplasmic peptidases hydrolyze the dipeptides and tripeptides to amino acids, which leave the cells by facilitated transport into the capillaries. A small amount of the dipeptides and tripeptides can be transported through the cell and into the blood, but the mechanism is unclear.

LIPID DIGESTION AND ABSORPTION

Almost all (98%) of dietary lipids are triglycerides (TG), with the remainder cholesterol esters and phospholipids (PL). Lipids are easily hydrolyzed to molecules that can be absorbed; however, their hydrophobicity does not allow easy access to the absorptive cells of the small intestine brush border. As a result, there is a complex mechanism for efficiently moving lipids through the unstirred water layer to the enterocytes. It should be noted that although there is not a lot of lipid digestion in the upper GI tract in adults, lingual and gastric lipases do have a role in hydrolysis of lipids in the neonate:

- **Mouth: Lingual lipase** is secreted from Von Ebner's glands of the tongue into the saliva and begins hydrolysis of TGs to diglycerides and free fatty acids (FFA). The enzyme remains active in the stomach.
- **Stomach: Gastric lipase** is secreted from the chief cells of the gastric pits and also hydrolyzes TGs to diglycerides and FFA. Again, in the adult this appears to be a minor factor in lipid digestion.
- **Small intestine:** Various **lipases** are secreted in active form from the pancreas in response to the action of CCK on the pancreatic acinar cells. **Pancreatic lipase** hydrolyzes TGs to monoglycerides (MG) and FFA; **procolipase** is also secreted and is activated in the lumen of the duodenum by trypsin, forming colipase, which facilitates the enzymatic action of pancreatic lipase; **cholesterol ester hydrolase** hydrolyzes cholesterol esters to cholesterol and FFA; **phospholipase A_2** hydrolyzes PL to lysophospholipids and FFA. These cleavage products are all able to diffuse into the enterocytes; however, they must first be incorporated into micelles to traverse the unstirred water layer.

Micelle Formation

Micelles are aggregates of bile salts and small lipids. The polar (hydrophilic) ends of the bile are oriented outward, and the hydrophobic core allows incorporation of small lipids. The micelles function to move lipids through the unstirred water layer, allowing lipids access to the enterocytes.

Most lipids are in the last portion of chyme entering the small intestine. In the duodenum, the lipids are surrounded by bile and exposed to pancreatic lipases. However, although the pancreatic lipase can readily hydrolyze triglycerides, lipase access to lipids is blocked by bile. The colipase is critical for lipase action. It displaces the bile from the lipids, allowing the lipase to hydrolyze the lipids.

These are the steps for micelle formation (Fig. 25.4):

1. The detergent action of bile emulsifies the fat globules, forming smaller fat droplets, which increases the surface area for digestion.
2. Colipase displaces the bile from the lipids.
3. Pancreatic lipase binds to colipase and hydrolyzes the TGs to monoglycerides and FFA. Cholesterol ester hydrolase and phospholipase A_2 hydrolyze cholesterol esters and phospholipids (these enzymes are not affected by bile).
4. When there is a critical amount of bile and digested lipids, they form a **micelle,** with the hydrophilic ends of bile salts on the outside, and lipophilic ends inside surrounding the lipid products.
5. The micelles diffuse through the unstirred water layer to the enterocytes, and the lipids are released from the micelle and diffuse through the enterocyte membrane, leaving the bile salts in the lumen.
6. The bile salts continue down the small intestine to the terminal ileum, where most primary bile salts enter the intestinal cells through Na^+-dependent transporters. The bile diffuses out of the cell into the portal circulation back to the liver.

Intracellular Lipid Processing

Once the lipids diffuse into the enterocytes, they are re-esterified with FFA in the smooth endoplasmic reticulum to reform triglycerides, cholesterol esters, and phospholipids (see Fig. 25.4). The lipids are surrounded by a β-lipoprotein (ApoB) coat forming **chylomicrons.** The chylomicrons are packaged into secretory vesicles and leave the cell by exocytosis. The chylomicrons enter the lymph lacteals; they are too large to enter capillaries. They enter the systemic blood in the large vessels in the thorax, and return to the liver for processing through the systemic circulation. A small amount of short-chain fatty acids are not incorporated into chylomicrons and are able to diffuse into the portal blood to the liver. This is a minor pathway.



β-Lipoprotein is critical for **chylomicron** formation. When it is absent, lipids will not be able to exit the intestinal cells and enter the lymph. Fat builds up in the enterocytes. As the villous cells are replaced and sloughed off into the lumen, the lipid is excreted. This condition of **abetalipoproteinemia** results in the inability to absorb lipids.

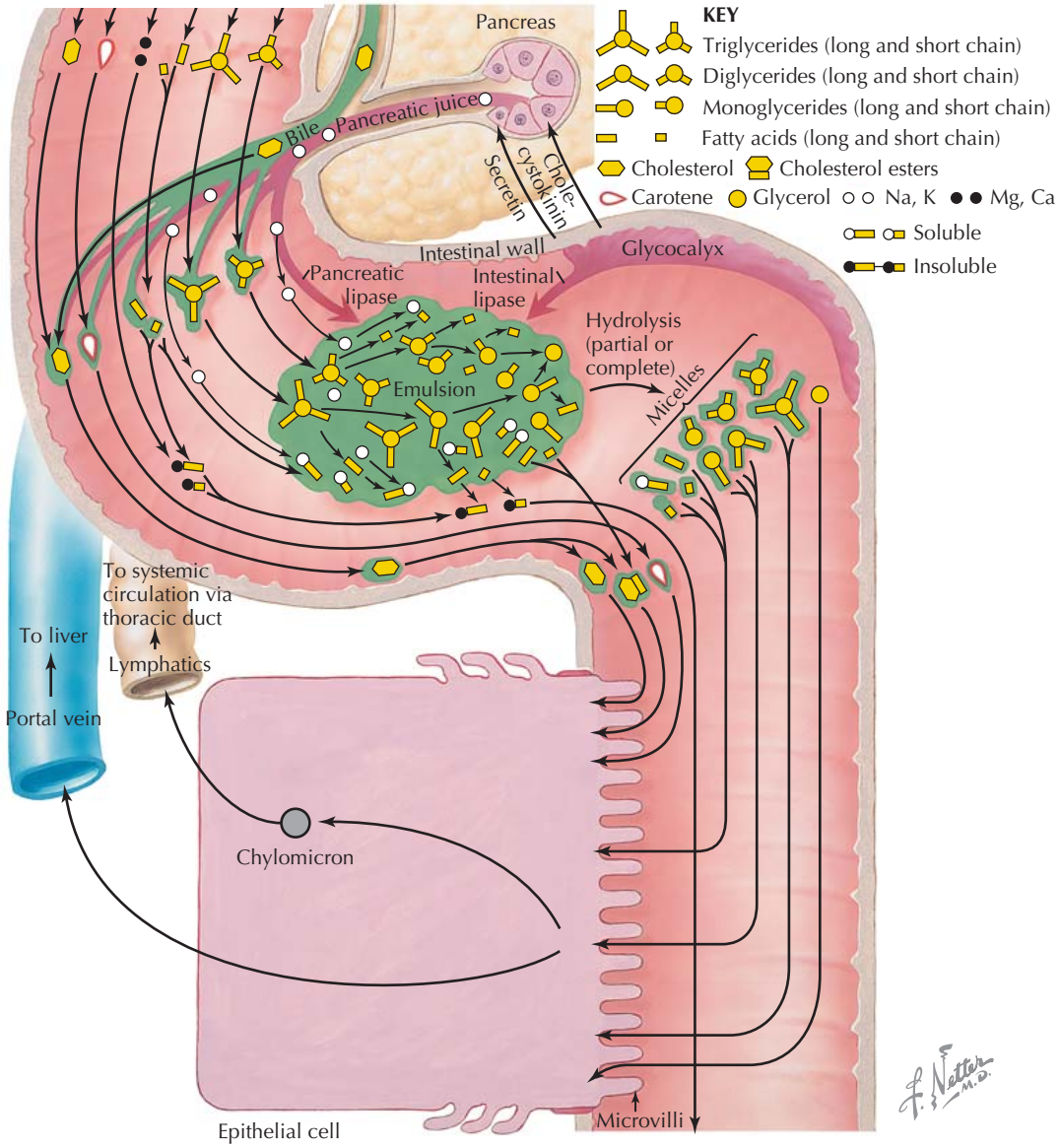
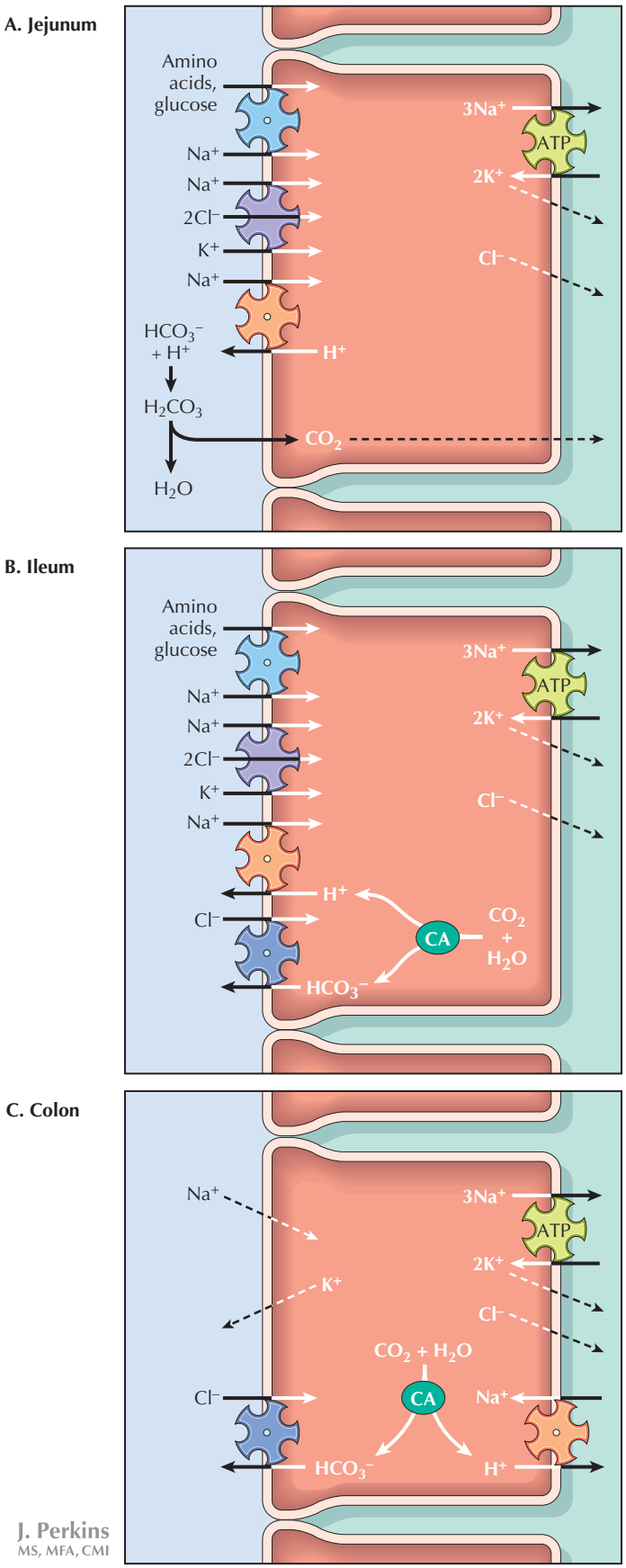


Figure 25.4 Lipid Digestion and Absorption Although some lipid digestion occurs preduodenally by lingual and gastric lipases, most digestion occurs in the lumen of the small intestine by pancreatic lipase. The overall process of digestion and absorption is complex, because the lipids must first be incorporated with bile into micelles and shuttled through the unstirred water layer to the enterocytes. The lipids diffuse into the enterocytes and are re-esterified with free fatty acids in the smooth endoplasmic reticulum and packaged into chylomicrons for transport into the lymph, eventually passing through the thoracic duct into venous circulation. Some soluble fats (glycerol and short-chain and medium-chain fatty acids) can access the enterocytes without micelles and are small enough to be taken up into the portal circulation.

ELECTROLYTE AND WATER ABSORPTION

In addition to the ~2 liters (L) of fluid ingested each day, approximately 7 or more additional liters are added to the GI tract in various segments to facilitate digestion and absorption of the nutrients. Absorption of the 9 L of fluid occurs as nutrients and electrolytes are absorbed. Within the small intestine, several mechanisms of absorption occur in various segments (Fig. 25.5):

- **Jejunum:** The large surface area in the small intestine makes digestion and absorption extremely efficient. The bulk of the nutrients, fluid, and electrolytes is absorbed by mid- to late-jejunum, although there is significant electrolyte and fluid absorption in the ileum.
- **Sodium** absorption is a driving force for nutrient and water absorption, and the basolateral Na^+/K^+ ATPase



J. Perkins
MS, MFA, CMI

Figure 25.5 Electrolyte and Fluid Transport *A*, Sodium absorption in the jejunum and ileum occurs though a variety of mechanisms, with sodium movement facilitating entry of other molecules such as glucose, galactose, amino acids, and chloride. This also creates an osmotic gradient for water absorption. *B*, The ileum secretes HCO_3^- into the gut lumen in exchange for Cl^-, and the Cl^- exits through the basolateral membrane by facilitated transport. *C*, The colon is sensitive to the effects of aldosterone, which will enhance sodium absorption and potassium secretion. The water follows the osmotic gradient, dehydrating the chyme and producing feces.

maintains the low intracellular concentration necessary for the lumenal Na^+ to enter the cells.

- **Bicarbonate** is formed by the intracellular CO_2 metabolism and exits the cell through the basolateral membrane by facilitated transport. The **water** follows the osmotic gradient created by the electrolyte movement (see Fig. 25.5*A*).
- **Ileum**: As noted, the Na^+-dependent transporters for sugars and amino acids are also present in the ileum, and this redundancy helps ensure nutrient absorption if absorption is reduced in the jejunum. **Sodium** is absorbed in the same manner as in the jejunum; however, in the ileum and colon, the bicarbonate formed in the cells is *secreted* into the lumen via HCO_3^-/Cl^- antiporters, and the **chloride** leaves the basolateral side via facilitated transport (see Fig. 25.5*B*).
- **Colon:** Aldosterone stimulates lumenal sodium absorption by Na^+/K^+ and Na^+/H^+ exchangers. As water follows the sodium, the chyme is dehydrated, producing feces. The colon usually absorbs ~400 to 500 milliliters of water per day, which follows sodium absorption, and water absorption in the colon can increase to ~1 L per day, when aldosterone is elevated (see Fig. 25.5*C*).

DIVALENT CATION ABSORPTION

Calcium and iron are absorbed early in the small intestine, from the duodenum through early- to mid-jejunum (first half of the jejunum). Because the early part of the small intestine has a lower pH, it favors the reduced (Fe^{2+}) form of iron and keeps the cations from forming insoluble salts.

Calcium

Calcium absorption is regulated by active **vitamin D** (1,25-dihydroxycholecalciferol), which increases the calcium channels (TRPV-6) at the lumenal membrane, as well as the cytosolic binding protein **calbindin**. Calbindin binds Ca^{2+}, keeping the intracellular free Ca^{2+} levels very low (10^{-6} M), maintaining a gradient for Ca^{2+} entry into the cell, and allowing Ca^{2+}-dependent messenger systems to function properly. The Ca^{2+} exits the basolateral side through active Ca^{2+} ATPase pumps and Na^+/Ca^{2+} antiporters (Fig. 25.6*A*). The activity of the Ca^{2+} ATPase is also increased by vitamin D.

Iron

Free iron is toxic to cells, and in the body iron is always bound to proteins. Ingested iron is either in organic (hemoglobin or myoglobin from meats) or free (from vegetables) forms.

Organic forms can diffuse into the enterocytes, and intracellular xanthine oxidase frees the iron, which is then bound in ferritin in the cell or is transported out of the cell into the blood, where it is bound to transferrin (TF).

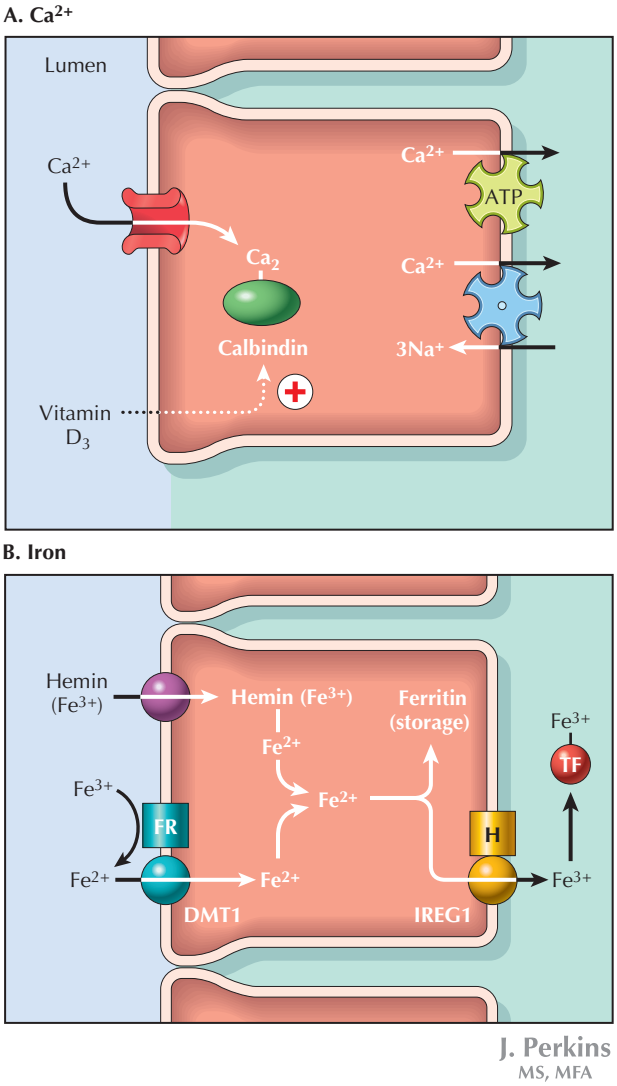


Figure 25.6 Calcium and Iron Absorption *A*, Calcium entering the enterocytes through the TRPV-6 Ca^{2+} channel is bound by cytosolic calbindin. Transport out of the cell is via Ca^{2+} ATPase pumps and Na^+/Ca^{2+} exchangers. Active vitamin D enhances Ca^{2+} absorption by increasing calbindin production and Ca^{2+} pump activity. *B*, Ingested iron is in both organic (heme) and inorganic forms. Heme can enter enterocytes, and intracellular heme oxygenase releases the iron (Fe^{2+}), which is then bound in ferritin stores or shuttled out of the cell through the transmembrane protein hephaestin (H) and bound to transferrin (TF) in the blood. It is transported to the liver for storage, or the bone marrow for hemoglobin and red blood cell production. Inorganic iron in the ferric form (Fe^{3+}) can be reduced to Fe^{2+} by ferrireductase (FR) in the lumenal membrane, and then the Fe^{2+} can enter the enterocytes through the divalent metal transporter 1 (DMT-1), and be handled as described above.

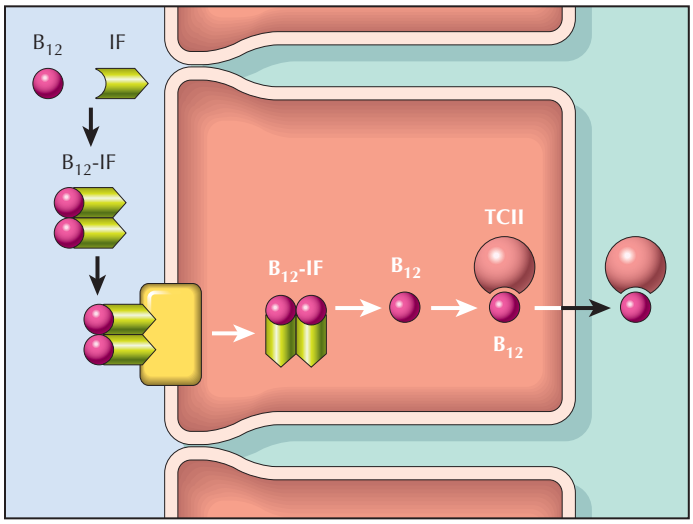
The lumenal membranes in the jejunum have divalent metal transport proteins (DMT-1), which transport **free Fe^{2+}** into the cell, where it is bound in ferritin. The iron can also be transported out of the cell into the blood, where it is bound to transferrin (TF) (see Fig. 25.6*B*).

In the blood, the transferrin-bound iron is transported to the bone marrow for hemoglobin and red blood cell synthesis, or

Table 25.2 Vitamin Absorption

Vitamin	Site of Absorption	Mechanism
WATER SOLUBLE VITAMINS		
Vitamin C	Ileum	Na^+-coupled/2° active
Thiamin (B1)	Jejunum	Na^+-coupled/2° active
Riboflavin (B2)	Jejunum	Na^+-coupled/2° active
Biotin	Jejunum	Na^+-coupled/2° active
Vitamin B12	Ileum	Facilitated diffusion
Pyridoxine (B6)	Jejunum and ileum	Passive diffusion
FAT-SOLUBLE VITAMINS		
Vitamin A	Jejunum and ileum	Passive diffusion
Vitamin D	Jejunum and ileum	Passive diffusion
Vitamin E	Jejunum and ileum	Passive diffusion
Vitamin K	Jejunum and ileum	Passive diffusion

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Vitamin B_{12} J. Perkins MS, MFA

Figure 25.7 Vitamin B12 Absorption Vitamin B12 (cobalamin) is protected from digestion in the small intestine by binding to intrinsic factor (IF) released from the gastric parietal cells. B12/IF dimers are recognized by receptors on the enterocytes in the terminal ileum, and the complex is internalized. The B12 is bound to transcobalamin II (TCII) for transport through the blood to the liver for storage, or bone marrow for red blood cell maturation.

to the liver and spleen for storage. Typically, ~1 milligram (mg) of iron is absorbed daily, which balances the ~1 mg loss of iron (from intracellular ferritin stores) that occurs when enterocytes slough off each day. If iron utilization increases (such as in growing children and menstruating women), iron intake must increase, or anemia will result.

VITAMIN ABSORPTION

Fat soluble vitamins A, D, E, and K are transported in micelles to the enterocytes, although vitamin A and D are less hydrophobic, and are also able to access the enterocytes independently. Table 25.2 details the sites and mechanism of vitamin absorption in the small intestine.

Vitamin B12 Absorption

Vitamin B12 (cobalamin) is an essential vitamin and is protected from digestion until it is absorbed in the terminal ileum. The process of protecting B12 begins in the mouth:

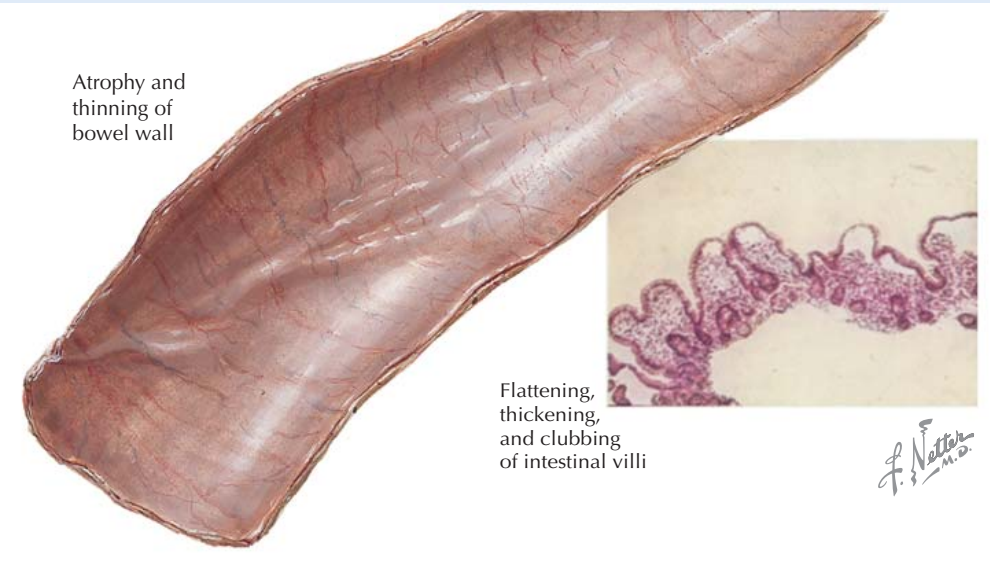
- In the saliva, vitamin B12 is bound by **R-proteins.**
- **Intrinsic factor** is secreted by gastric parietal cells. It does not bind B12 until it reaches the duodenum, where the R-proteins are cleaved by trypsin.
- The **B12-intrinsic factor complex dimerizes** and continues down the small intestine to the terminal ileum, where the complex binds to a transport protein and enters the cell. The B12 binds to **transcobalamin II** in the cytosol, exits the cell, and is transported to the bone marrow (where it promotes red blood cell maturation) or to the liver for storage (Fig. 25.7).

Surgical removal of the **terminal ileum** causes multiple problems, including loss of both bile recycling and vitamin B12 absorption. In this circumstance, bile production by the liver is upregulated, but production is not sufficient for absorption of fat contained in a normal meal, and some steatorrhea may result. To treat vitamin B12 deficiency, injections are administered every few months (infrequent injections are sufficient because excess B12 will be stored in the liver).

CLINICAL CORRELATE
Gluten Enteropathy and Celiac Disease

Celiac sprue is an autoimmune "allergic" reaction to **gluten proteins** in wheat and results from the plasma cell production of antibodies (IgA and IgG) against the intestinal epithelium. The α-gliadin (part of gluten proteins) is deaminated in the enterocytes, increasing the immunogenicity of gliadin. The antibodies cross-react with the intestinal tissue, producing inflammation; this results in flattening of the villous lining and crypt hyperplasia. The surface area for absorption is diminished, and brush border enzyme activity is impaired. The loss of brush border enzymes with villous atrophy will reduce final digestion of carbohydrates and protein and cause general malabsorption of micronutrients and macronutrients. The presence of undigested nutrients lower in the GI tract facilitates bacterial production of gasses, causing cramps, odiferous gas, and feces. Diarrhea, weight loss, anemia, and vitamin deficiency can occur.

Although it is suggested that 1 in 250 persons have some degree of gluten enteropathy, most cases are considered "silent" sprue, with little or no GI symptoms. In addition to GI complications, the immune reaction to wheat can also cause respiratory (rhinitis, asthma) and skin (eczema, dermatitis herpetiformis, and/or hives) problems. Primary treatment involves complete avoidance of gluten in the diet.



Gluten Enteropathy (Celiac Disease)

Review Questions

CHAPTER 21: OVERVIEW OF THE GASTROINTESTINAL TRACT

1. All of the following are functions of the gastrointestinal tract **EXCEPT:**

A. secretion of endocrine hormones.
B. secretion of digestive enzymes.
C. absorption of nutrients from chyme.
D. regulation of systemic blood flow.
E. storage of chyme.

2. Motility and secretion through the gastrointestinal tract is regulated by all of the following factors **EXCEPT:**

A. duodenal hormones.
B. chemoreceptors.
C. autonomic nerves.
D. enteric nerves.
E. growth hormone.

3. In the absence of *extrinsic* innervation to the gastrointestinal tract,

A. propulsive movements would not occur in the small intestine.
B. propulsive movements would occur in the small intestine, but secretion into the small intestine would be abolished.
C. secretion would be abolished in the entire GI tract.
D. motility and secretion throughout the tract would be stimulated by local mechanoreceptors, chemoreceptors, and osmoreceptors, as well as hormones.
E. motility and secretion would be affected only in the large intestine.

4. Input from vagal efferent nerves to the gastrointestinal tract regulates the following actions **EXCEPT:**

A. lower intestinal motility.
B. primary esophageal peristalsis.
C. the cephalic phase of gastric acid secretion.
D. receptive relaxation in the stomach.
E. stimulation of hepatic bile production.

CHAPTER 22: MOTILITY THROUGH THE GASTROINTESTINAL TRACT

5. Action potentials in the GI smooth muscle:

A. occur only in the upper GI tract.
B. are stimulated when the slow waves are depolarized above –40 mV.
C. occur only in the lower GI tract.
D. result from influx of sodium ions into the smooth muscle cells.
E. are only stimulated by extrinsic nerves.

6. Slow waves constituting the basal electrical rhythm:

A. are hyperpolarized by stretch, ACh, and gastrin.
B. occur at a consistent rate throughout the GI tract.
C. are undulations in the resting membrane potential resulting from Na^+/K^+ ATPase activity.
D. are depolarized by sympathetic nerve stimulation.
E. are absent in the colon.

7. In the small intestine, peristalsis:

A. occurs primarily in response to the chemical composition in the chyme.
B. proceeds in both forward and backward directions from the site of contraction.
C. involves receptive relaxation of the muscle proximal (toward the mouth) to the bolus of chyme.
D. involves contraction of the muscle proximal to the bolus of chyme.
E. is dependent on parasympathetic innervation.

8. Select the **FALSE** answer about the migrating myoelectric complex (MMC).

A. The MMC is a series of contractions that "sweep" undigested fibers and bacteria into the colon.
B. The parasympathetic nervous system controls the MMC contractions.
C. In each cycle, the main contractions of the MMC occur during phase III.
D. The hormone motilin stimulates phase III contractions.
E. The MMC occurs during fasting, and stops upon feeding.

CHAPTER 23: GASTROINTESTINAL SECRETIONS

9. Secretions entering the lumen of the stomach include all of the following substances **EXCEPT:**

A. HCl.
B. lipase.
C. mucus.
D. gastric inhibitory peptide.
E. intrinsic factor.

10. Parietal cell gastric acid secretion is regulated:

A. directly by secretin.
B. directly by peptide YY.
C. directly and indirectly by the vagus nerve.
D. indirectly by somatostatin.
E. indirectly by gastrin.

11. Select the **TRUE** statement about gastric acid secretion.

A. Histamine suppresses acid secretion.
B. Blocking the H^+/K^+ ATPase pump increases alkaline tide.
C. Basolateral HCO_3^-/Cl^- exchangers decrease intracellular Cl^- in parietal cells.
D. Parasympathetic stimulation of acid secretion is limited to the cephalic phase of acid secretion.
E. Proton pump (H^+/K^+ ATPase) activity is the rate-limiting step in acid secretion.

12. Which of the following is **NOT** a mechanism by which sodium ions enter the intestinal epithelial cells from the lumenal membrane?

A. Diffusion down the sodium concentration gradient
B. Active transport via Na^+/K^+ ATPase
C. Co-transport with certain amino acids
D. Co-transport with monosaccharides
E. In exchange for H^+

13. Select the **TRUE** statement about pancreatic secretions.

A. The release of pancreatic enzymes into the duodenum is primarily stimulated by gastrin.
B. The release of pancreatic enzymes into the duodenum is primarily stimulated by the sympathetic nerves.
C. Secretin is released in response to low duodenal pH and acts at the pancreas to stimulate the release of electrolyte buffer solution.
D. Pancreatic proteases are released in active form.
E. Pancreatic lipase digests all lipids.

CHAPTER 24: HEPATOBILIARY FUNCTION

14. The liver performs all of the following functions **EXCEPT:**

A. synthesis of cholesterol.
B. vitamin production.
C. β-oxidation of fatty acids.
D. bile acid production.
E. metabolism of proteins.

15. Obstruction of blood flow through the liver (from cirrhosis or hepatitis) will

A. have no effect on gastrointestinal digestion or absorption.
B. have no effect on bile secretion.
C. increase bile secretion.
D. increase portal vein pressure.
E. reduce hepatic blood content.

16. Metabolism of lipids within the hepatocytes includes:

A. formation of most lipoproteins, including very low and low density lipoproteins.
B. net breakdown of phospholipids.
C. net breakdown of cholesterol.
D. formation of steroid hormones.
E. None of the above.

17. Bile salts:

A. hydrolyze dietary fats.
B. are essential for creating micelles.
C. are efficiently absorbed into the portal blood all along the small intestine.
D. do not contribute to intestinal buffering of acidic chyme.
E. production is not affected by loss of the terminal ileum.

CHAPTER 25: DIGESTION AND ABSORPTION

18. Which of the following would delay or diminish the absorption of proteins?

A. Inhibition of gastric somatostatin release
B. An increase in Na^+/K^+ ATPase activity in the basolateral membranes of the enterocytes
C. Stimulation of gastric pepsinogen release
D. pH of 3 in the duodenum and jejunum
E. Secretion of cholecystokinin

19. Select the **TRUE** statement about carbohydrate digestion.

A. Digestion of carbohydrates begins in the intestines.
B. Loss of the intestinal brush border has no effect on carbohydrate digestion.
C. Disaccharidases are secreted into the duodenum from the crypts of Lieberkühn.
D. Starch digestion is initiated by α-amylase.
E. The majority of carbohydrate digestion occurs before the duodenum.

20. When chyme is present in the stomach and duodenum, all of the following actions occur **EXCEPT:**

A. stimulation of intestinal buffers by gastrin.
B. stimulation of hepatic bile production by vagal afferents.
C. stimulation of pancreatic enzyme secretion by cholecystokinin.
D. stimulation of intestinal buffer secretion by secretin.
E. conversion of trypsinogen to trypsin by enterokinase.

21. In a patient with celiac sprue,

A. gastric ulcerations are common.
B. fibrosis decreases intestinal absorption and reduces portal blood flow.
C. flattening of intestinal villi decreases enzymatic digestion and reduces the area for absorption.
D. hypersecretion of mucus obstructs absorption.
E. hyposecretion of mucus allows acidification of the intestinal lumen, decreasing enzymatic digestion.

22. The absorption of vitamin B12 (cobalamin) is dependent on all of the following **EXCEPT:**

A. the integrity of the terminal ileum.
B. the concentration of B12 in the enterocytes.
C. the presence of R-protein in saliva.
D. the presence of intrinsic factor in gastric juice.
E. the presence of vitamin B12/intrinsic factor binding sites in the ileum.

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Section 7

ENDOCRINE PHYSIOLOGY

The endocrine system, along with the nervous system, is responsible for maintenance of the internal environment and has a central role in growth, development, and propagation of the species. It consists of a number of endocrine glands as well as regions of the brain and other organs not typically thought of as endocrine glands, all of which secrete hormones into the bloodstream as a mechanism for regulation of function in target tissues. An understanding of normal physiological function requires knowledge of this complex system, and appreciation of the consequences of dysfunction of the endocrine system is essential to the practice of medicine. Nearly all physiological processes are affected by hormones, and many of the diseases or dysfunctions of the endocrine system are commonly encountered by medical practitioners; examples of the more common endocrine disorders include diabetes, thyroid diseases, and some forms of infertility.

Chapter 26 **General Principles of Endocrinology and Pituitary and Hypothalamic Hormones**

Chapter 27 **Thyroid Hormones**

Chapter 28 **Adrenal Hormones**

Chapter 29 **The Endocrine Pancreas**

Chapter 30 **Calcium-Regulating Hormones**

Chapter 31 **Hormones of the Reproductive System**

Review Questions

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CHAPTER 26

General Principles of Endocrinology and Pituitary and Hypothalamic Hormones

HORMONE SYNTHESIS

Hormones are substances that are secreted by a gland or tissue into the blood and bind to receptors in other tissues, where they affect specific physiological processes. The organization of the endocrine system is illustrated in Figure 26.1. Chemically, hormones are **peptides** (e.g., insulin, growth hormone), **steroids** (e.g., estrogen, testosterone, cortisol), or **amines** or their derivatives (e.g., epinephrine, thyroxine). Neurohormones are a subclass of hormones secreted by neurons (e.g., vasopressin, oxytocin).

Peptide Synthesis

Genes encoding peptide hormones are transcribed to produce specific messenger ribonucleotides (mRNAs) that are subsequently translated on ribosomes to form a preprohormone. The preprohormone is a protein hormone precursor that includes a "signal peptide" that directs its transport to the endoplasmic reticulum, where the signal peptide is cleaved, leaving a prohormone. The prohormone is transported to the Golgi apparatus, where it is sequestered into secretory vesicles. Within these vesicles, the prohormone is further cleaved to create the final active form of the hormone. Secretion of peptide hormones occurs when the contents of these vesicles are released.

Steroid Synthesis

Steroid hormones are synthesized from the precursor cholesterol, which is derived from dietary sources or synthesized *de novo* from acetyl-coA (acetyl coenzyme A). The steroidogenic pathways involved in synthesis of steroid hormones from cholesterol are considered in Chapters 28 and 31. The major steroid hormones are:

- cortisol
- aldosterone
- testosterone and other androgens
- estradiol and other estrogens
- progesterone

Cortisol and aldosterone are synthesized in the adrenal cortex (Chapter 28), which also produces adrenal androgens. Testosterone is produced by the testes, and estradiol and progesterone are synthesized in the ovaries (Chapter 31).

MECHANISMS OF HORMONE ACTION

Hormones are secreted into the blood by endocrine glands or tissues. When they reach their target tissues, they bind to membrane or nuclear receptors, initiating a chain of events that ultimately results in the physiologic effects of the hormone.

Steroid hormones (e.g., testosterone, estradiol, progesterone), thyroid hormone, and vitamin D are lipophilic and therefore readily enter into the target cell, where they bind to nuclear receptors and initiate gene transcription. The mRNA produced is translated into proteins that regulate biochemical and physiologic processes (Fig. 26.2).

Most peptide hormones and catecholamines bind to membrane receptors linked to heteromeric G proteins, initiating a cascade of events involving generation (or inhibition of production) of second messengers such as cAMP, cGMP, and IP_3 that ultimately regulate cellular function. The second messengers can directly act on existing enzymes and other proteins or may activate or induce transcription factors and more indirectly affect cellular function. Growth hormone binds to a membrane receptor that associates with a monomeric G protein; subsequently, tyrosine kinase activity and various transcription factors are involved in its action.

By definition, hormones (endocrine secretions) are substances that are carried by the blood and act on distal tissues but are part of a larger group of regulatory secretions that also includes **autocrine, paracrine,** and **neuroendocrine** secretions (see Fig. 26.2). The common feature of these substances is that they are secreted and have effects on the same cell type (autocrine secretion) or other cell types.

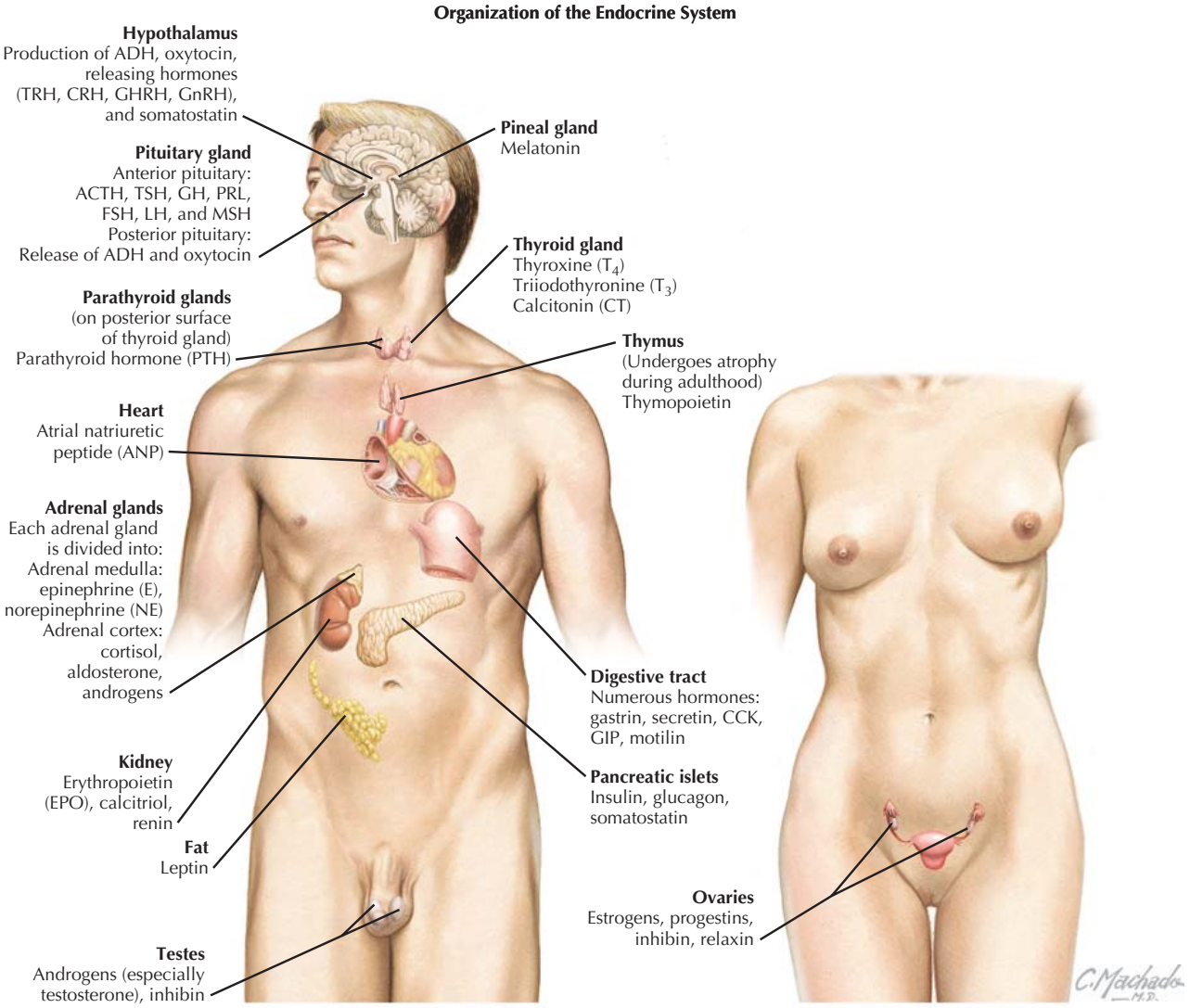


Figure 26.1 Organization of the Endocrine System Hormones are secreted into the blood by endocrine organs throughout the body, affecting physiological function at various target sites. ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GIP, gastric inhibitory peptide; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; MSH, melanocyte-stimulating hormone; PRL, prolactin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

GENERAL ENDOCRINE ROLES OF THE HYPOTHALAMUS AND PITUITARY GLAND

The **hypothalamus** and **pituitary gland** regulate the function of much of the endocrine system (Figs. 26.3 and 26.4). The hypothalamus is located in the ventral diencephalon and is connected by the pituitary stalk to the pituitary gland (**hypophysis**), which resides in the **sella turcica,** a cavity in the sphenoid bone. The pituitary consists of two lobes, known as the **anterior pituitary** (**adenohypophysis**) and the **posterior pituitary** (**neurohypophysis**).

The posterior pituitary is continuous with the hypothalamus, connected to it by the pituitary stalk, which contains axons originating in hypothalamic nuclei. The posterior pituitary stores and secretes the neurohormones **antidiuretic hormone** (**ADH;** also known as **vasopressin**) and **oxytocin.** These hormones are synthesized mainly in the supraoptic nucleus and paraventricular nucleus of the hypothalamus and are carried by axonal transport to the posterior pituitary.

The anterior pituitary (unlike the posterior pituitary) is not directly connected with the hypothalamus but is connected to it by the vessels of the hypophyseal portal circulation. In addition to synthesizing vasopressin and oxytocin, the hypothalamus synthesizes and releases **hypothalamic releasing and inhibitory hormones** that are carried through the **hypophy-**

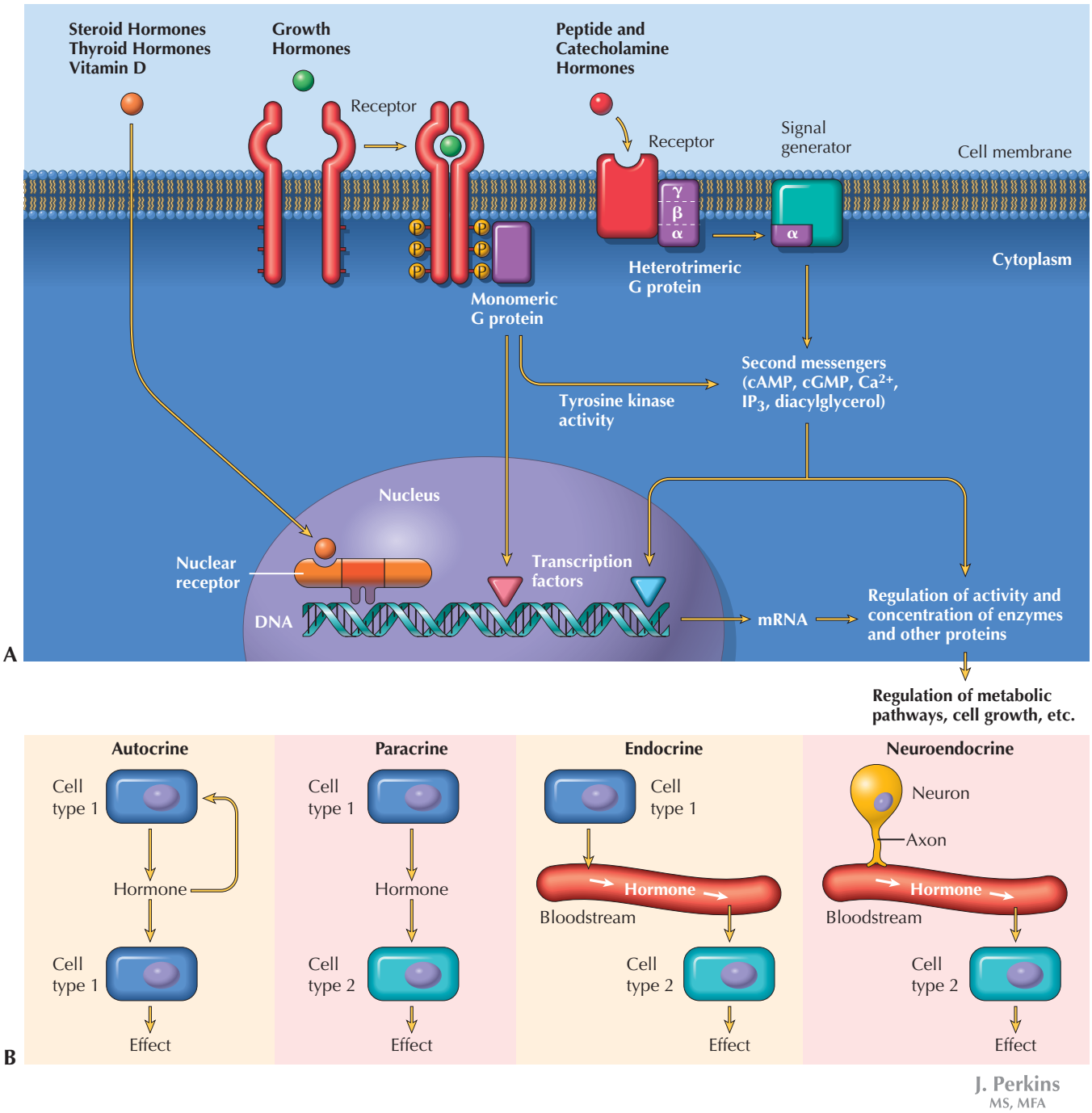


Figure 26.2 **Overview of Hormone Action** Hormones act at target cells by binding to specific cell membrane or cytosolic receptors, initiating a cascade of events that produces a physiological change *(A)*. Binding to the receptor may result in generation of second messengers (e.g., cAMP, cGMP, IP_3) or regulation of gene transcription. True hormones (endocrine secretions) are released by "ductless glands" and are carried by the bloodstream to their sites of action. They are part of a larger group of substances that includes autocrine, paracrine, and neuroendocrine secretions *(B)*.

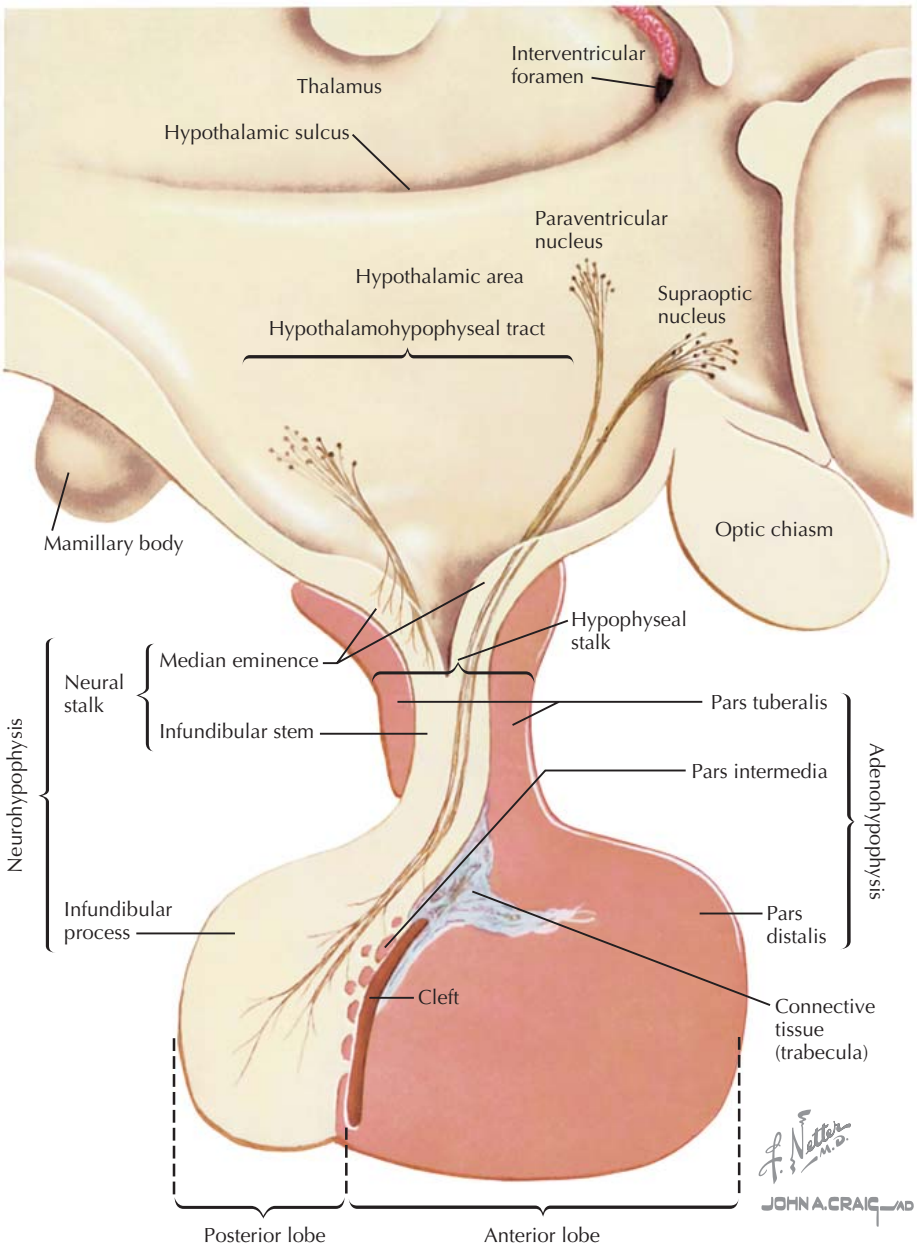


Figure 26.3 Structure of Hypothalamus and Pituitary The anterior pituitary (adenohypophysis) and posterior pituitary (neurohypophysis) are derived from different embryonic tissues and function as separate glands. Axons from hypothalamic nuclei extend to the posterior pituitary, where hormones (oxytocin and vasopressin) are stored until released into the systemic bloodstream; other axons from hypothalamic nuclei extend to the median eminence, where they release hormones into the hypophyseal portal circulation, which carries them directly to the anterior pituitary. At the anterior pituitary, these hormones inhibit or stimulate the release of various trophic hormones into the systemic blood.

seal portal veins to the anterior pituitary and regulate the secretion of trophic hormones (see Fig. 26.4). This portal circulation allows direct transport of these hypothalamic hormones to the pituitary, without dilution in the general circulation. The major hormones secreted by the anterior pituitary are as follows:

- **Thyroid-stimulating hormone** (TSH), which stimulates thyroid hormone synthesis and release by the thyroid gland.
- **Adrenocorticotropic hormone** (ACTH), which stimulates synthesis of adrenocortical steroids.
- **Gonadotropins** (LH and FSH), which promote steroidogenesis and gametogenesis by the testes and ovaries.
- **Prolactin,** which stimulates milk production by the breasts.
- **Growth hormone** (GH), which promotes the synthesis of **insulin-like growth factors** (IGFs) by the liver and other target tissues. IGFs produced by the liver are

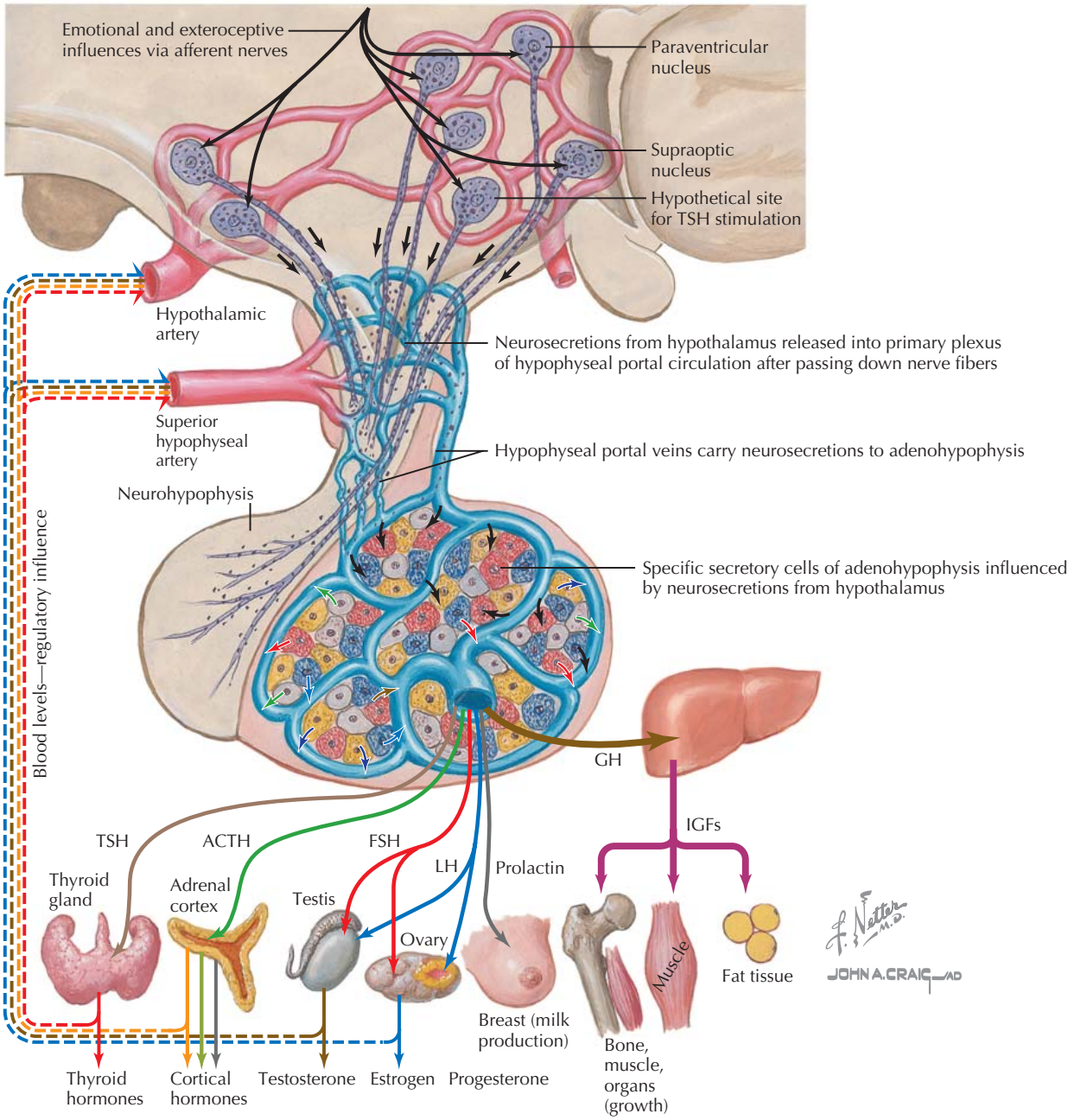


Figure 26.4 Overview of Anterior Pituitary Function The anterior pituitary gland is controlled by releasing and inhibitory hormones secreted into the hypophyseal portal circulation; these hormones reach the anterior pituitary directly through this portal circulation without entering the general circulation. Under control of these factors, specific secretory cell types of the anterior pituitary secrete six major trophic hormones (TSH, ACTH, FSH, LH, prolactin, and GH), which act on distal endocrine glands. Trophic hormones and the target gland hormones have feedback effects on these endocrine systems, designed to regulate blood levels of the target gland hormone. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

released into the circulation, whereas IGFs produced in other tissues act locally, in an autocrine manner. Growth hormone has growth-promoting and anabolic effects.

Various anterior pituitary hormones are often referred to as *trophic hormones*, because they stimulate secretion of *target gland hormones* (for example, gonadotropins stimulate steroid synthesis and secretion by the gonads).

FEEDBACK SYSTEMS AND RECEPTOR REGULATION IN THE ENDOCRINE SYSTEM

Feedback systems control blood hormone levels within normal ranges, often with cyclic variations in levels. These feedback systems are an important aspect of homeostasis, providing for regulation of hormone levels and their physiological effects. The cyclic variations in secretion that occur for many

hormones are important in regulating complex processes such as menstrual cycles and in the homeostatic responses to diurnal cycles in activity levels. Furthermore, many hypothalamic and pituitary hormones are released in a pulsatile manner that allows for further fine-tuning of hormone release and action.

Negative Feedback

Blood levels of endocrine secretions are controlled within relatively narrow ranges, with normal, often cyclic, variations. Typically, **negative feedback systems** control levels of hormones, whereby increased blood levels of a hormone inhibit its synthesis, maintaining the normal level (see Figs. 26.4 and 26.5). For example, synthesis of the major male sex hormone, **testosterone,** is stimulated by the pituitary hormone **luteinizing hormone (LH),** which is released in response to a hypothalamic hormone, **gonadotropin-releasing hormone (GnRH)** (Fig. 26.5). The normal adult male level of testosterone is maintained by negative feedback of testosterone on the production of LH and GnRH, as well as shorter feedback loops. In endocrine systems consisting of the hypothalamus, pituitary, and a target endocrine gland, feedback loops are classified as follows:

- **Long-loop feedback**, in which hypothalamic and pituitary hormones in an endocrine axis are inhibited by the target gland hormone, as in the case of testosterone inhibition of GnRH and LH (as well as **follicle-stimulating hormone, FSH**).
- **Short-loop feedback,** whereby an anterior pituitary hormone inhibits the release of its associated hypothalamic hormone (e.g., inhibition of GnRH by LH).
- **Ultrashort-loop feedback,** in which secretion of a hypothalamic hormone is inhibited by that same hormone.

These multiple feedback systems allow for the fine-tuning of hormone levels and participate in the generation of the cyclic variations observed in levels of many hormones.

Positive Feedback

Although negative feedback is the primary homeostatic mechanism in the endocrine system, there are rare examples of **positive feedback.** These positive feedback mechanisms are, by nature, self-limited, as dictated by the need for homeostasis in physiologic systems. The prime example of positive feedback occurs during the menstrual cycle (see Fig. 26.5). In the late follicular phase of the cycle, **estradiol** levels rise above a critical point, above which positive feedback occurs. The high estradiol concentration results in a surge in hypothalamic secretion of GnRH and pituitary secretion of LH and **follicle-stimulating hormone (FSH),** inducing ovulation. Ovulation and transformation of ovarian follicular cells into the **corpus luteum** signals the end of positive feedback.

Receptor Regulation

The cellular response to a hormone is dependent on the presence of specific receptors for the hormone. Although the response to a hormone is dependent on the concentration of the hormone, regulation in the endocrine system can also occur at the level of hormone receptors, by altering the number of receptors or their binding affinity for a hormone. In some cases, hormones induce **down-regulation** (reduction) of the number of their receptors or of the binding affinity of their receptors, as a type of negative feedback. For example, exposure of the ovary to increased levels of LH will result in reduced membrane LH receptors. Hormones may also produce receptor **up-regulation,** in which the number or affinity of receptors is increased. As an example, growth hormone increases the number of its receptors in some target tissues. When a hormone affects the number of its own receptors, the process is called **homologous regulation.** In other cases, hormones may affect (upward or downward) the number of receptors for a different hormone. This process is known as **heterologous regulation.**

POSTERIOR PITUITARY HORMONES

ADH and **oxytocin** are both nonapeptides (nine amino acid peptides) derived from preprohormones synthesized by hypothalamic nuclei. Cleavage of the preprohormones produces **neurophysins** along with ADH and oxytocin. The neurophysins function as carrier proteins as ADH and oxytocin are transported in vesicles down the axons of the neurons in which they are synthesized and into the posterior pituitary. The hormone-containing vesicles are stored in nerve endings within the posterior lobe of the pituitary. When the hypothalamic neuron is depolarized, the action potential is propagated along the axon to the nerve terminal, where Ca^{2+} influx occurs and results in exocytosis of vesicular contents.

Antidiuretic Hormone (ADH)

As implied by its name, ADH is secreted during conditions in which water retention ("antidiuresis") is required for homeostasis. The synthesis, release, and physiological actions of ADH are illustrated in Figure 26.6 and described further in Chapters 12 and 18. In addition to its antidiuretic effect, it is also a vasopressor, causing contraction of vascular smooth muscle (thus, the name "vasopressin"). Therefore, ADH is released mainly in response to one of two stimuli:

- **Hyperosmolarity of plasma,** detected by osmoreceptors within the hypothalamus.
- **Hypovolemia and hypotension,** detected by arterial and atrial baroreceptors.

Hyperosmolarity (caused, for example, by fluid deprivation or dehydration) is normally much more important than hypovolemia or hypotension in terms of stimulation of ADH secretion. Although normal variation of blood pressure is not

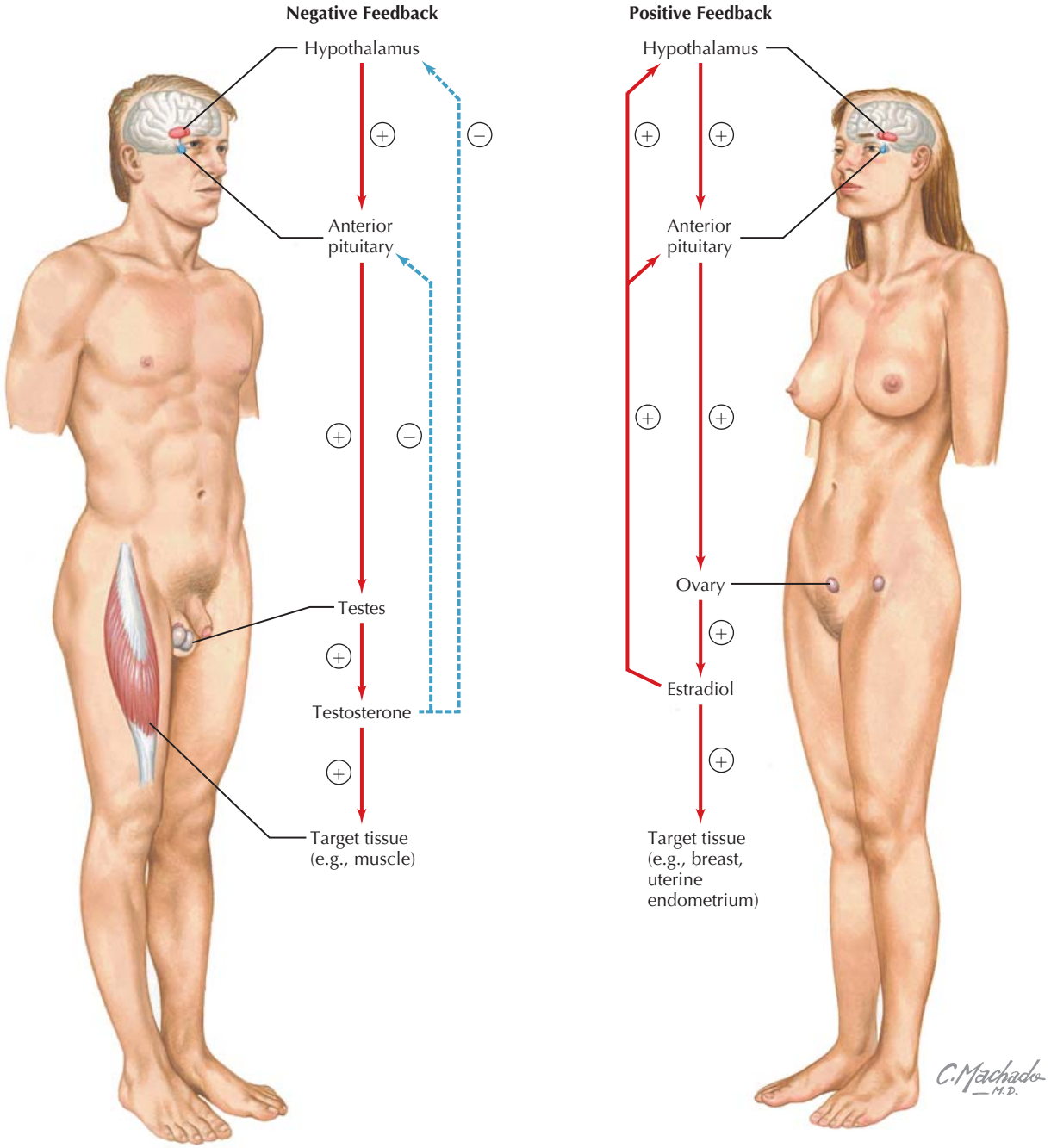


Figure 26.5 **Negative and Positive Feedback Regulation** In most cases, a hypothalamic-pituitary-target gland axis is regulated by negative feedback, whereby the trophic hormone of the anterior pituitary gland has negative feedback effects on the hypothalamus, and the target gland hormone has negative feedback effects on both the hypothalamus and the anterior pituitary. Through these mechanisms, illustrated for the hypothalamus-pituitary-testes axis, levels of the target gland hormone are maintained within the normal physiological range. In a few specific cases, positive feedback can also occur. For example, during the late follicular and ovulatory phases of the menstrual cycle, high levels of estradiol actually cause greater secretion of the hypothalamic releasing hormone and trophic hormones in that system, resulting in the surge in pituitary hormone release that is responsible for ovulation at midcycle.

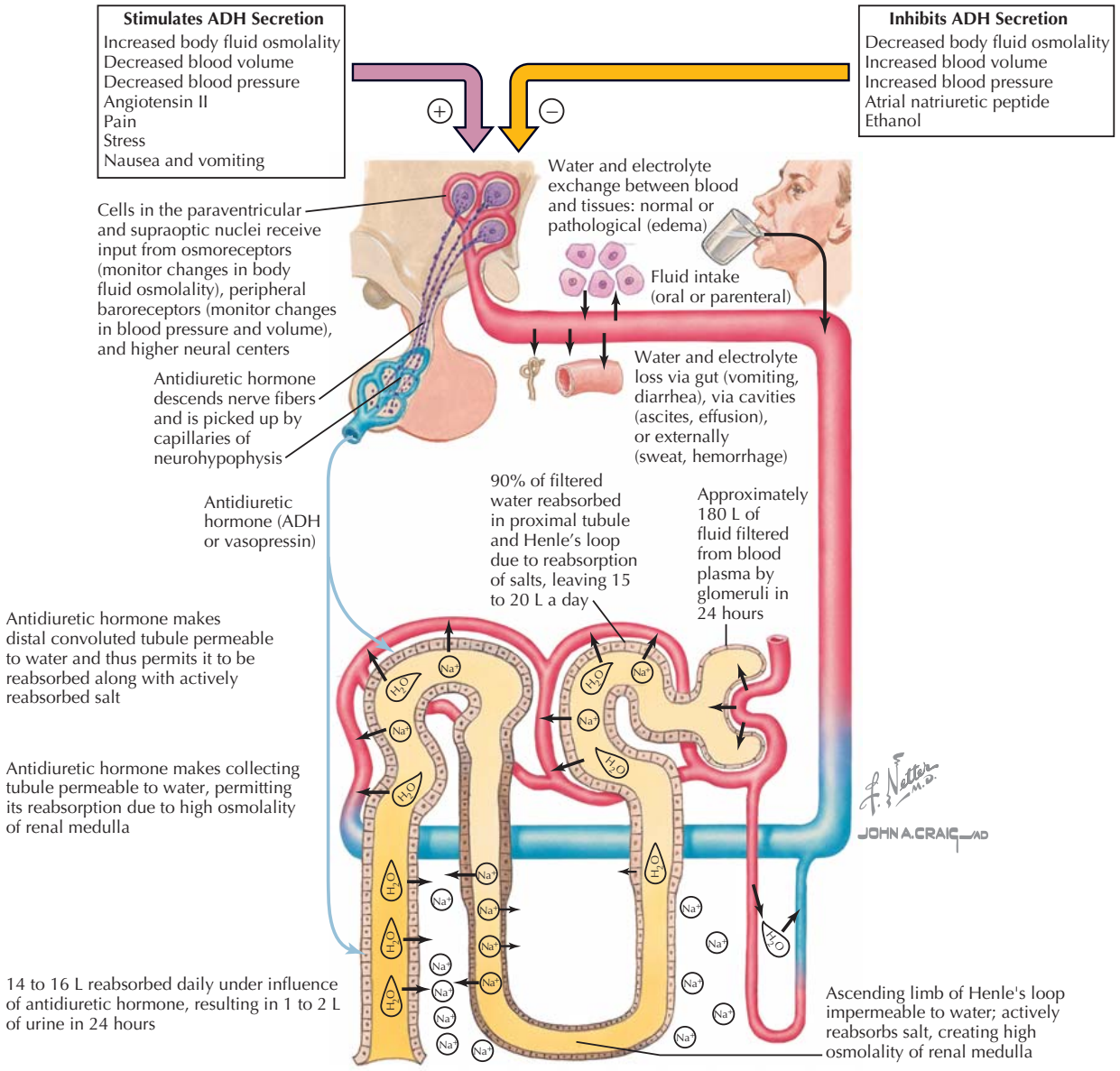


Figure 26.6 Posterior Pituitary Function (ADH) Antidiuretic hormone (ADH; also known as vasopressin) is synthesized mainly in the supraoptic nuclei (and also the paraventricular nuclei) of the hypothalamus and is stored and released at the posterior pituitary. Its main function is in water balance; it is released in response to increased osmolarity of extracellular fluid and decreased blood pressure and has the major effect of promoting water reabsorption by the kidney. When ADH levels in plasma are high, a low volume of concentrated urine is produced.

a significant stimulus for ADH release, significant loss of blood volume (for example, during hemorrhage) causes secretion of the hormone, which participates in blood pressure homeostasis and fluid replenishment under those conditions by stimulating water retention in the kidney and contraction of vascular smooth muscle.

Physiological actions of the hormone are covered in greater detail in Chapter 18. To summarize (see Fig. 26.6), the actions of ADH include effects on renal handling of water, specifically, increased permeability of the distal convoluted tubule and collecting tubule to water, and thus increased water reabsorption, by the kidney.

Oxytocin

Oxytocin, the other hormone released by the posterior pituitary, has a role in breastfeeding and in childbirth (Fig. 26.7). Thus, it is released in response to:

- breastfeeding
- cervical and vaginal stimulation

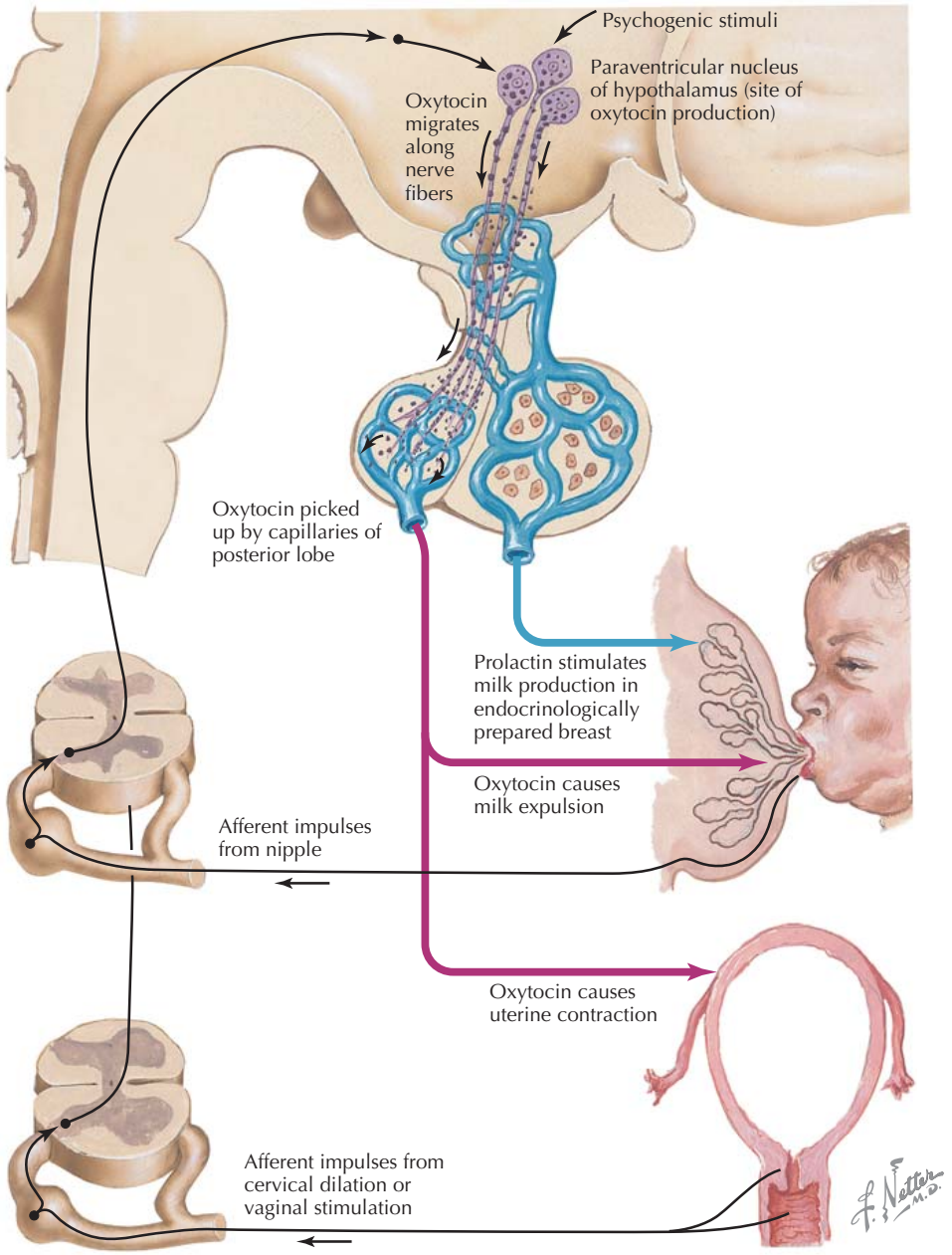


Figure 26.7 Posterior Pituitary Function (Oxytocin) Oxytocin is synthesized mainly in the paraventricular nuclei (and also the supraoptic nuclei) of the hypothalamus and is stored and released at the posterior pituitary. Its main functions are to stimulate milk let-down and uterine contraction.

During breastfeeding, oxytocin released by the neurohypophysis causes **"let-down"** or **expulsion of milk** from the mammary glands of the breasts. The actual production of milk is stimulated specifically by a different hormone, prolactin. Distension of the cervix and vagina also stimulates the release of oxytocin, and the hormone stimulates **uterine contractions.** However, its actual physiological role in induction or progression of labor is not well established. Oxytocin is also released during orgasm in both sexes and might have a role in sperm transport during ejaculation of the male, as well as transport of sperm within the female reproductive tract. Furthermore, oxytocin

CLINICAL CORRELATE
Induction of Labor by Synthetic Oxytocin

Although a physiological role for oxytocin in humans in induction or progression of labor is not well established, it stimulates strong uterine contractions when used at high doses as a drug. Thus, synthetic oxytocin is often used in clinical situations in which artificial induction or stimulation of the progression of labor is medically required. As is generally the case for peptide drugs, it is not effective orally due to cleavage in the gastrointestinal tract, and it is administered by intravenous infusion.

appears to stimulate pair-bonding in mammals, including humans, through its central nervous system effects.

ANTERIOR PITUITARY HORMONES

The six anterior pituitary hormones are peptides, proteins, or glycoproteins and are synthesized and secreted by distinct cell types within the adenohypophysis:

- **Gonadotrophs** produce the two gonadotropins (LH and FSH).
- **Thyrotrophs** synthesize thyroid-stimulating hormone (TSH).
- **Corticotrophs** synthesize adrenocorticotropic hormone (ACTH).
- **Lactotrophs** produce prolactin.
- **Somatotrophs** produce growth hormone (GH).

Synthesis and secretion of these hormones is regulated by hypothalamic hormones that reach the anterior pituitary via the hypophyseal portal circulation, as well as by various feedback loops. In some cases, the hormones are mainly controlled by either a hypothalamic releasing hormone or an inhibitory hormone; in others, there is dual control by a hypothalamic releasing hormone and a hypothalamic inhibitory hormone. The anterior pituitary hormones are discussed in subsequent chapters in the context of their target gland hormones, with the exception of growth hormone and prolactin.

GROWTH HORMONE

Growth hormone (also known as **somatotropin**) is a 191 amino acid, single-chain polypeptide with structural similarities to **prolactin** and **human chorionic somatotropin** (a placental hormone with growth hormone–like effects). As implied by its name, growth hormone is the primary hormone in the human growth process. It is secreted throughout life, in a pattern that consists of basal secretion upon which several **daily pulses of secretion** are superimposed. These pulses occur during sleep and are especially pronounced and frequent during the pubertal growth spurt; basal secretion rates are highest in young children. The growth spurt in boys typically begins at about 12 years of age, and growth in height is usually concluded by about 16 or 17 years of age, although there is significant variability between individuals in both parameters. The growth spurt in girls begins about a year earlier and is concluded about 2 years earlier, again with considerable variability.

Regulation of Growth Hormone Secretion

The secretion of growth hormone by anterior pituitary somatotrophs is regulated by two hypothalamic hormones (Fig. 26.8):

- **Growth hormone–releasing hormone** (GHRH), which stimulates growth hormone release, and
- **Somatostatin,** which inhibits growth hormone release.

Most of the effects of growth hormone are not direct but are mediated by the synthesis and release of **somatomedins** by the liver and by stimulation of somatomedin production in specific target tissues. Somatomedins are also known as **insulin-like growth factors (IGFs);** the most important of these is **IGF-1,** which is produced by the liver and other tissues in response to growth hormone. IGF-1 binds to receptors on target tissues producing tyrosine kinase activation, similar to the actions of insulin on its receptor, resulting in intracellular effects.



IGF-1 is produced by the liver and secreted into the bloodstream in response to growth hormone; it is also produced directly at target tissues. Although plasma levels of IGF-1 respond to growth hormone stimulation of the liver, it is believed that local production of IGF-1 at the target tissues, as opposed to circulating IGF-1, is probably more important in mediating the effects of growth hormone on those tissues.

Both growth hormone and IGF-1 exert negative feedback effects on the hypothalamus and anterior pituitary; GHRH inhibits its own release. Metabolites also affect growth hormone release directly or indirectly: Glucose and free fatty acids inhibit GHRH release, whereas amino acids stimulate pituitary release of growth hormone.

Effects of Growth Hormone and IGF-1

The primary roles of growth hormone and IGF-1 are stimulation of growth and development of the body during childhood and adolescence and regulation of metabolism and body composition in adults (see Fig. 26.8). These general effects reflect more specific actions mediated by IGF-1:

- **Stimulation of linear growth,** through proliferative effects, amino acid uptake, and protein synthesis in bone and cartilage (in childhood and adolescence).
- **Increase in muscle mass** (anabolic effect), through increased amino acid uptake and protein synthesis in muscle.
- **Decreased adiposity** by stimulation of lipolysis.
- **Increase in organ size,** associated with proliferation and protein synthesis.

The actions of IGF-1 on growth of muscle, bone, and other organs involve stimulation of RNA and DNA synthesis as well its more direct effects on cellular amino acid uptake and synthesis of protein.

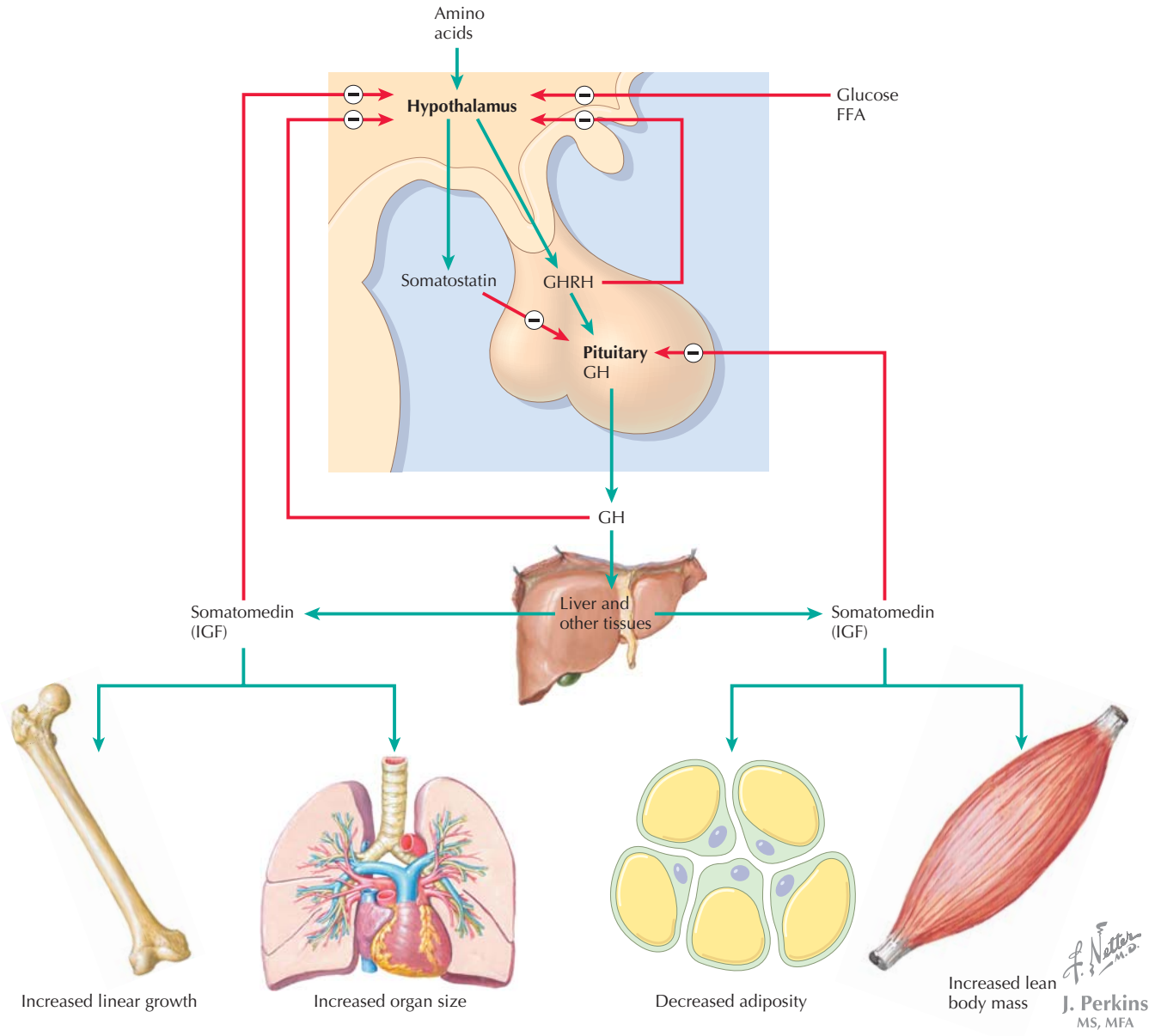


Figure 26.8 Growth Hormone Growth hormone release by the anterior pituitary is controlled by GHRH and somatostatin. Growth hormone has an important role in growth and development of children and regulation of metabolism. Its effects are mediated by somatomedins produced by the liver or by specific target tissues. AA, amino acids; FFA, free fatty acids; GH, growth hormone; GHRH, growth hormone–releasing hormone; IGF, insulin-like growth factor.

Recent studies have led to the discovery of several hormones involved in growth, appetite, and obesity. Ghrelin is a 26 amino acid, acylated peptide hormone produced by the stomach as well as the arcuate nucleus of the hypothalamus. Its actions include stimulation of hunger and release of growth hormone and may provide a link between food intake and growth stimulation. Its effects on hunger oppose the actions of leptin, a hormone produced by adipose tissue that causes satiety. Current research is focusing on the relationship of these and other hormones to obesity.

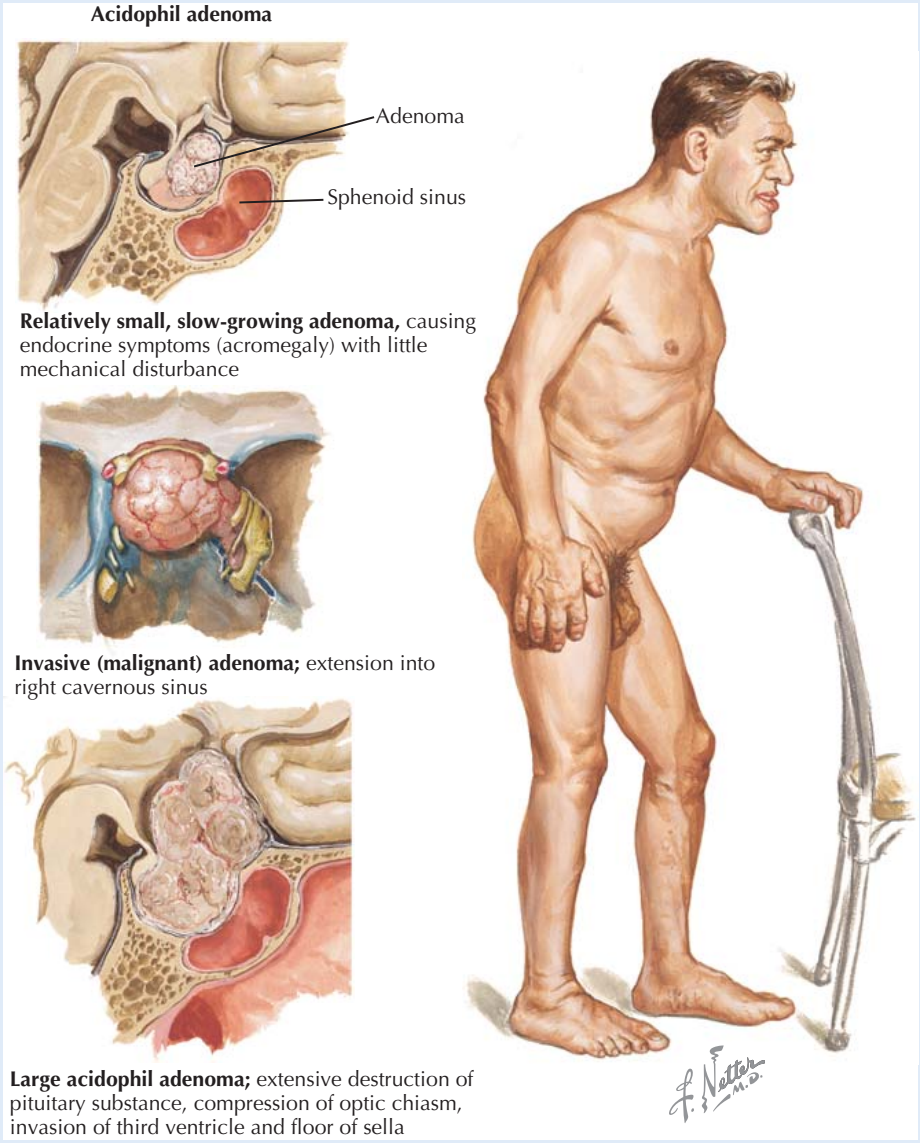
Growth hormone is often referred to as a **diabetogenic hormone** because of its metabolic effects and opposition of the actions of insulin. Growth hormone acts to:

- **Elevate blood glucose levels** through inhibition of glucose uptake by muscle and adipose tissue.
- **Elevate plasma free fatty acids** through its lipolytic action in adipose tissue.
- **Induce insulin resistance** and **elevate plasma insulin levels.**

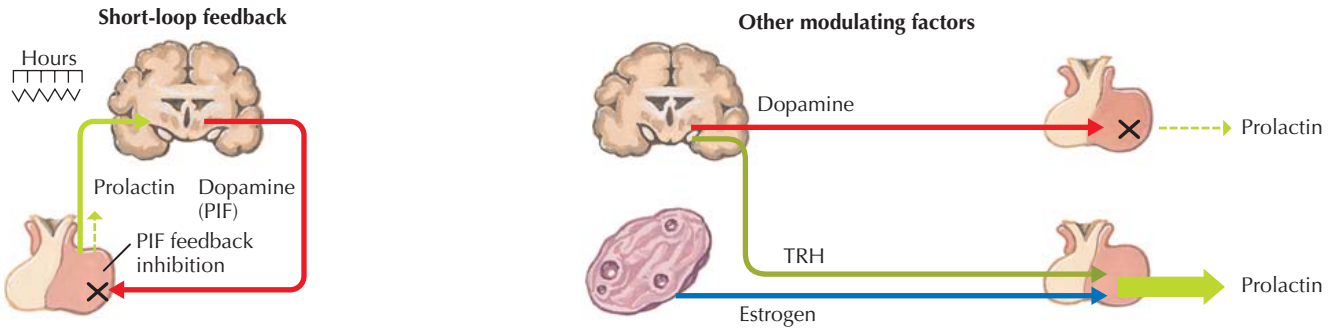
CLINICAL CORRELATE
Growth Hormone Excess and Deficiency

Deficiency of growth hormone in prepubertal children results in short stature and may delay the onset of puberty. Deficiency may result from a variety of causes, including primary failure to secrete growth hormone, low GHRH production, pituitary or hypothalamic damage, and deficiency in IGF production. Affected children are treated with recombinant human growth hormone therapy. Deficiency in growth hormone can also occur in adults, often as a result of a pituitary tumor. Such deficiency can have multiple manifestations, including loss of muscle mass, weight gain, and psychosocial effects; human growth hormone therapy is beneficial in some cases.

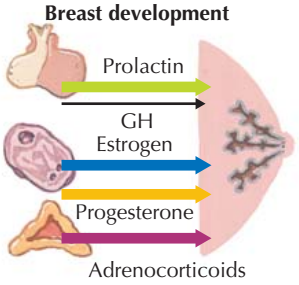
The most common cause of excess growth hormone is a growth hormone–secreting adenoma. These are slowly growing tumors that are usually diagnosed in midlife; surgery is the most common treatment. Growth hormone excess in adulthood produces acromegaly, a condition characterized by thickening of the bones of the hands, feet, and jaw; protrusion of the jaw and brow; and enlargement of the tongue (macroglossia), as well as cardiovascular and renal complications, diabetes, and other effects. Prepubertal growth hormone excess is rare and causes pituitary gigantism.



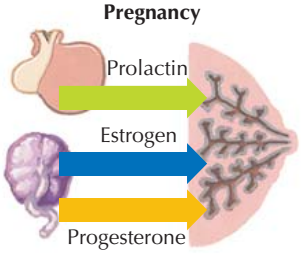
Growth Hormone–Secreting Adenomas The effects of growth hormone–secreting adenomas vary depending on size and growth rate as well as invasiveness. Large tumors cause destruction of the pituitary and deficiency of other pituitary hormones and may affect the optic chiasm and vision. Growth hormone excess produces acromegaly in adults (right panel), with protrusion of the jaw, macroglossia, and other effects.



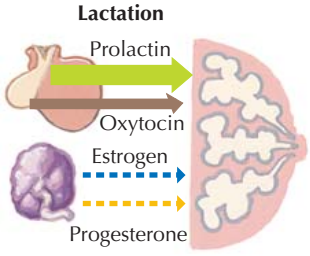
Prolactin-inhibiting factor (PIF), thought to be dopamine, modulates prolactin secretion. Elevated prolactin levels increase PIF secretion and cause feedback inhibition of prolactin secretion (short-loop feedback inhibition). Estrogen and TRH stimulate prolactin secretion.



Prolactin, along with GH, estrogen, progesterone, and adrenocorticoids, is necessary for breast development.



In pregnancy, elevated prolactin, estrogen and progesterone increase alveolobular development. High estrogen levels inhibit lactation.



Sudden decrease in estrogen and progesterone in presence of prolactin results in milk production. Oxytocin stimulates milk release.

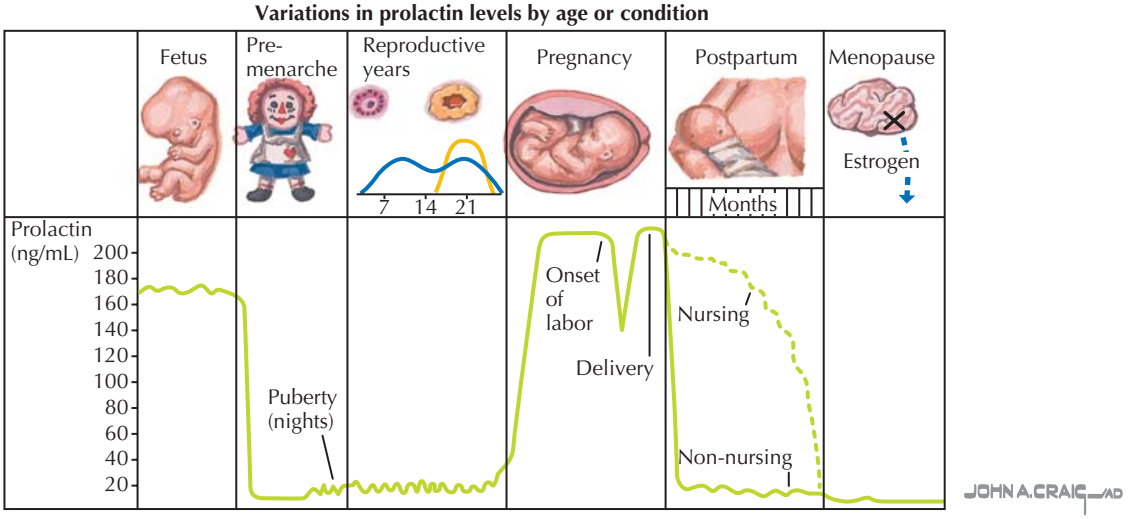


Figure 26.9 **Prolactin** Prolactin synthesis and release by the anterior pituitary is mainly under tonic negative control by dopamine (prolactin inhibitory factor, PIF). Its major functions are in breast development, pregnancy, and lactation. Its levels are elevated during fetal development, pregnancy, and the postpartum period (if the woman is breastfeeding). TRH, thyrotropin-releasing hormone.

PROLACTIN

Prolactin is a 198 amino acid, single-chain polypeptide structurally related to growth hormone. It is secreted at low levels except in pregnant and lactating women, in whom the number of lactotrophs in the anterior pituitary is increased and plasma prolactin is elevated. The hormone's main actions are to stimulate breast development and milk production, as suggested by its name.

Regulation of Prolactin Secretion

The hypothalamic hormones involved in the regulation of prolactin secretion by the anterior pituitary are (Fig. 26.9):

- **Dopamine** (also referred to as **prolactin inhibitory factor** in this context), which inhibits prolactin release, and

- **Thyrotropin-releasing hormone** (TRH), which stimulates release of prolactin in addition to thyroid-stimulating hormone.

Prolactin exerts negative feedback effects on its own release by stimulating secretion of dopamine by the hypothalamus.

Effects of Prolactin

In most instances, prolactin synthesis and release is primarily under the inhibitory influence of dopamine. During puberty, prolactin stimulates **breast development,** acting in concert with other hormones. In pregnancy, the final **alveolar and ductal development** of breasts is stimulated by prolactin, estrogen, and progesterone. The high prolactin levels during pregnancy are promoted by estrogen, which is not a direct prolactin secretagogue, but rather, enhances prolactin secretion in response to other factors.

After parturition, **suckling** promotes prolactin synthesis and release. Whereas the high levels of estrogen inhibit lactation during pregnancy, after parturition, estrogen levels are reduced and the lactogenic action of prolactin is unopposed. Binding of prolactin to its receptors in the mammary glands results in tyrosine kinase activation, transcriptional regulation, and ultimately, synthesis of milk proteins. One of the actions of prolactin is inhibition of **gonadotropin-releasing hormone** and therefore suppression of the female reproductive cycle, which accounts for the reduced likelihood of another conception during breastfeeding.



Breastfeeding acts as a partially effective contraceptive measure in the first 6 months after parturition because of its inhibitory effects on the reproductive endocrine axis of the mother. If the baby is fed exclusively by breastfeeding, conception is unlikely during this period as long as the mother has not had a menstrual period. In developing nations, birthrates have sometimes risen early in the process of industrialization, due to an increase in formula feeding of infants.

CHAPTER 27 Thyroid Hormones

Thyroid hormones (TH) have biologic actions in every organ in the body and are critical to proper fetal, postnatal, and pubertal growth and development. In addition, the action of thyroid hormones to maintain basal metabolic rate (BMR) makes states of thyroid excess and deficiency in adults readily evident—this is one reason that treatment for "enlarged neck," or goiter (hypothyroid-induced), was described in Chinese herbal medicine almost 5000 years ago.

Reverse T_3 (rT_3) is also synthesized in the thyroid gland, but in small amounts. It differs from T_3 by the position of the iodine moiety. rT_3 has little biologic activity; there is little rT_3 present under normal conditions, but high amounts are present in chronic diseases, in the fetus, and during starvation. rT_3 is made in larger amounts when T_4 is processed at end organ tissues.

STRUCTURE OF THE THYROID GLAND

The thyroid is a shield-shaped gland located on the anterior side of the trachea, below the thyroid cricoid cartilages (Fig. 27.1). It is composed of right and left lobes and an isthmus and weighs ~20 grams. As with all endocrine glands, it is highly vascularized to supply nutrients for hormone synthesis and blood flow for hormone transport. The functional units of the gland are the **follicles,** which are filled with thyroglobulin (Tg). Tg is the glycoprotein precursor to thyroid hormones, and modified Tg is collectively known as **colloid.** The follicle cells are surrounded by an epithelial cell layer. Scattered between the follicles are parafollicular cells, which are **calcitonin**-producing cells (see "Main Areas of Calcium Regulation" in Chapter 30). On the follicular cell basal membrane, there are G protein–coupled receptors for thyroid-stimulating hormone (TSH).

SYNTHESIS OF THYROID HORMONES

The thyroid gland synthesizes two main types of TH: **triiodothyronine (T_3)** and **thyroxine (T_4)** (Fig. 27.2). Although T_3 is about four times more biologically active than T_4, the amount of T_4 produced and secreted is about 20 times *greater* than the more potent T_3. When T_4 is secreted and enters a tissue, it is then converted to T_3, and thus, T_4 acts as a prohormone. This is an important concept to understand—because thyroid hormone is active in most organs, the amount available for immediate biologic action is regulated by several different mechanisms (discussed in detail later). Limiting the amount of highly active T_3 released into the blood is one of the safety mechanisms.

Steps in Thyroid Hormone Synthesis

Within the follicular cells, the elements necessary for thyroid hormone synthesis are combined in the following steps (Fig. 27.3):

1. **Thyroglobulin** molecules rich in tyrosine are produced in the endoplasmic reticulum, packaged in vesicles by the Golgi, and exocytosed into the lumen of the follicle.
2. **Iodide** (I^-) enters the follicle cell via basolateral Na^+/I^- cotransporters (the I-trap). The iodide exits the cell on the apical side into the lumen via I^-/Cl^- antiporters.
3. In the follicular lumen, I^- is oxidized to iodine by **thyroid peroxidase** and substituted for H^+ on the benzene ring of tyrosine residues of thyroglobulin.
4. Binding of one iodine will form **monoiodotyrosine (MIT),** and binding of two iodine moieties will form **diiodotyrosine (DIT).** This reaction is termed **organification. Thyroid peroxidase** also catalyzes the binding of DIT to another DIT, forming **T_4**. Some DIT will also bind to an MIT, forming **T_3**. These products remain linked to the Tg.
5. The mature thyroglobulin, containing MIT, DIT, T_4, and T_3 (in order of greater to lesser abundance), is endocytosed back into the follicle cell and can be stored as colloid until secreted. TH can be stored *several weeks* while bound to Tg—this is different than seen with other hormones.
6. Proteolysis of the colloid is stimulated by TSH and releases the constituent molecules. MIT and DIT reenter the synthetic pool, and T_3 and T_4 exit the basolateral membrane into the blood.

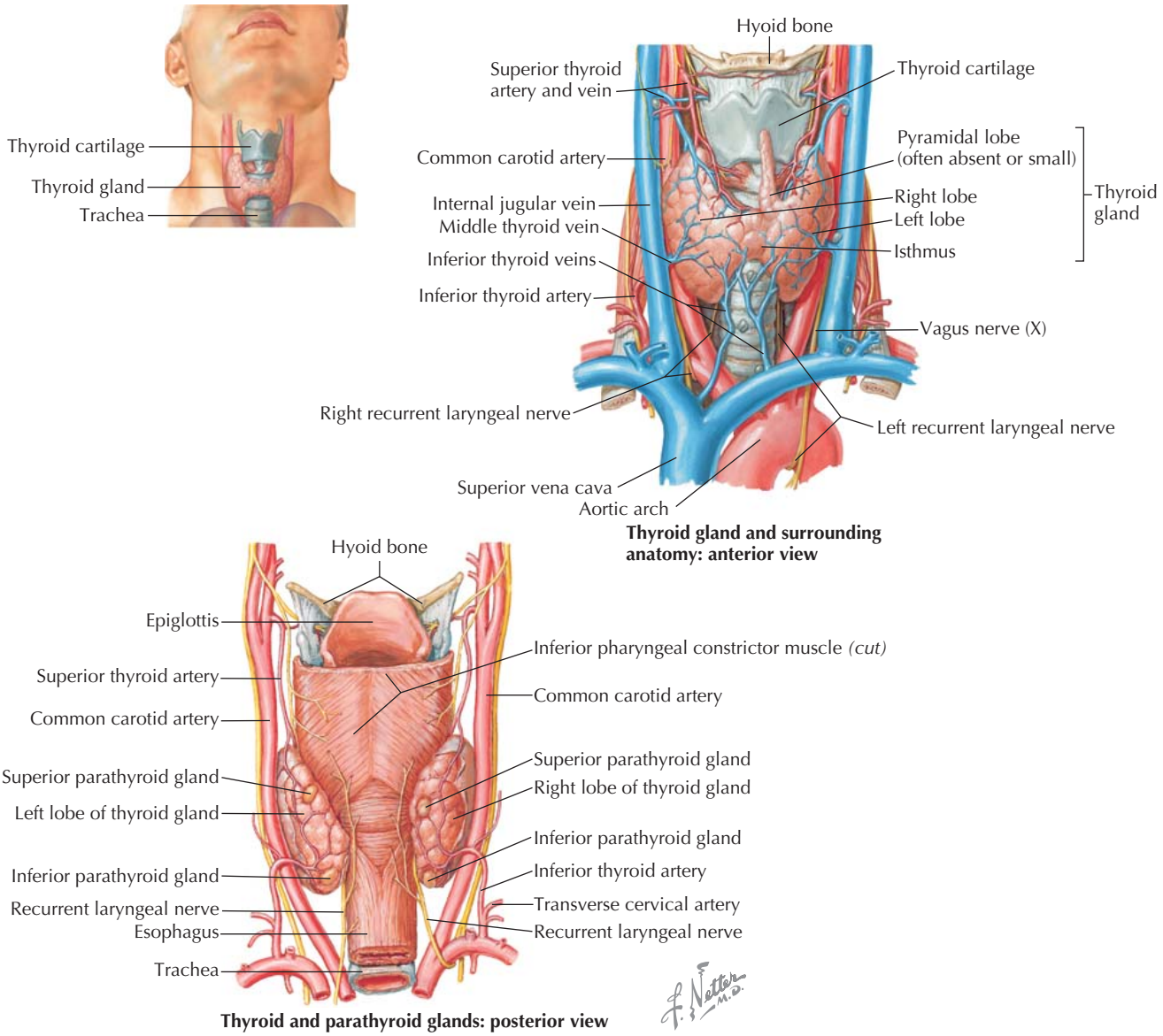


Figure 27.1 **Thyroid Gland Structure** The thyroid gland is a highly vascularized structure located anterior to the trachea and inferior to the cricoid cartilage. In about 15% of the population, a small pyramidal lobe is present (as seen).

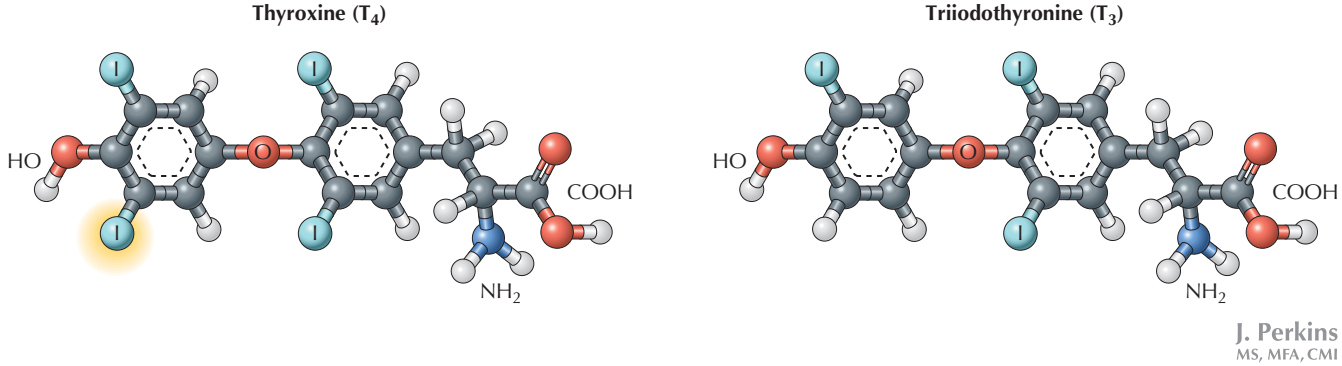


Figure 27.2 **Structure of T_3 and T_4** The two main types of thyroid hormones (TH), thyroxine (T_4) and triiodothyronine (T_3), differ from each other by the addition of one iodine in T_4. The majority of circulating TH is T_4, and almost all of the circulating TH is bound to a thyroxine-binding protein.

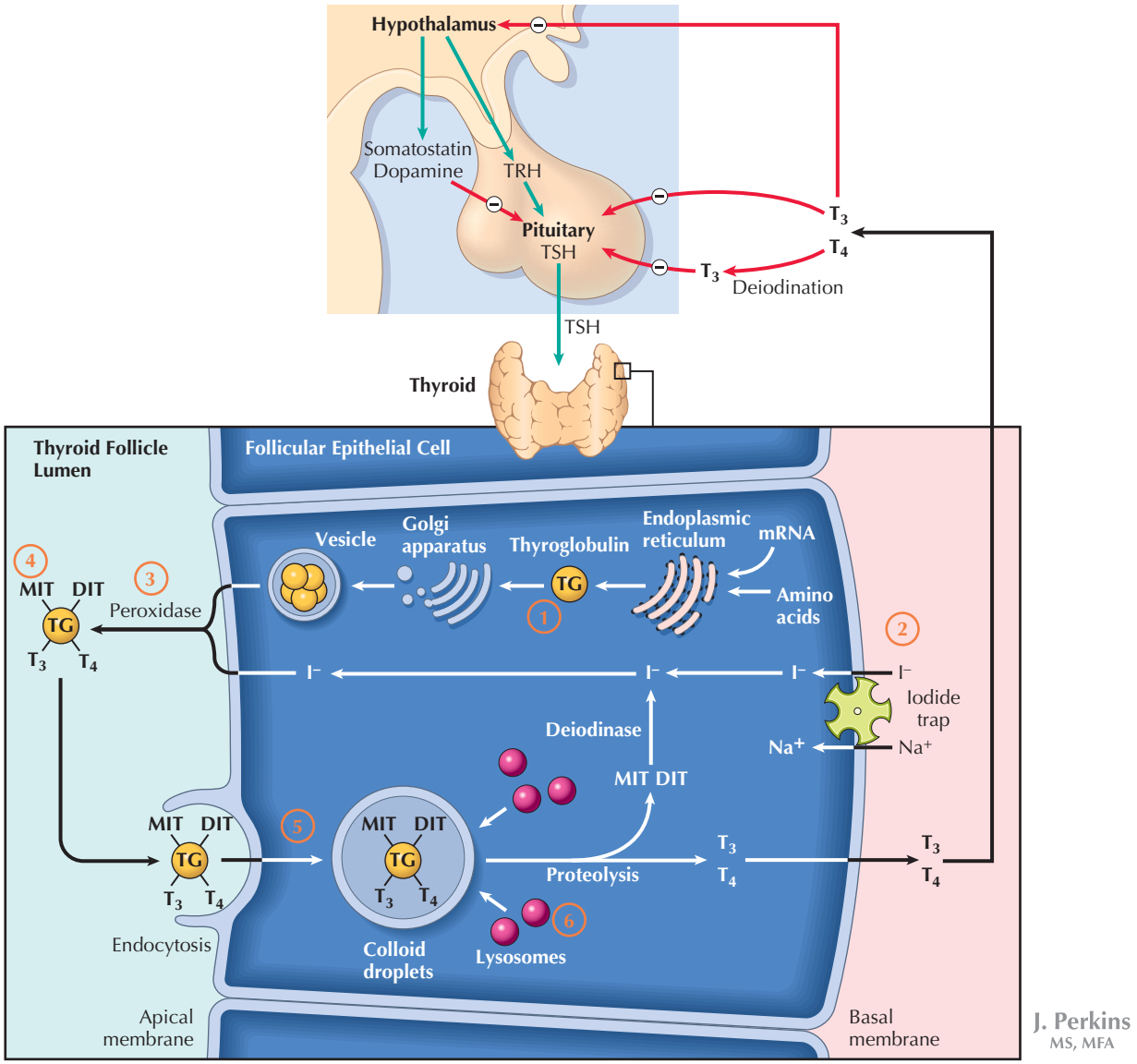


Figure 27.3 Synthesis and Regulation of Thyroid Hormones The thyroid gland is composed of follicular epithelial cells that synthesize and store thyroxine (T_4) and triiodothyronine (T_3) and release these hormones into the circulation. The synthesis is controlled by release of thyroid-stimulating hormone (TSH), which is under negative feedback control by the thyroid hormones. Synthesis and storage of the thyroid hormones is outlined here and in the figure: *(1)* In the endoplasmic reticulum, thyroglobulin molecules are produced, packaged in vesicles by the Golgi, and exocytosed into the lumen of the follicle. *(2)* Iodide (I^-) (from the diet) enters the follicle cell via basolateral Na^+/I^- cotransporters (the I-trap). The iodide exits the cell on the apical side into the lumen via I^-/Cl^- antiporters. *(3)* In the follicular lumen, I^- is oxidized to iodine by thyroid peroxidase and substituted for H^+ on the benzene ring of tyrosine residues of thyroglobulin. *(4)* Binding of one iodine will form monoiodotyrosine (MIT), and binding of two iodine moieties will form diiodotyrosine (DIT). This reaction is termed organification. Thyroid peroxidase also catalyzes the binding of DIT to another DIT, forming T_4. Some DIT will also bind to an MIT, forming T_3. These products remain linked to the thyroglobulin (Tg). *(5)* The mature Tg, containing MIT, DIT, T_4, and T_3 (in order of greater to lesser abundance), is endocytosed back into the follicle cell and can be stored as colloid until secreted. *(6)* Proteolysis of the colloid is stimulated by TSH and releases the constituent molecules. MIT and DIT reenters the synthetic pool, and T_3 and T_4 exit the basolateral membrane into the blood. TRH, thyrotropin-releasing hormone.



Propylthiouracil (**PTU**) is used to treat hyperthyroidism, because it blocks **thyroid peroxidase** and acts at all biosynthetic steps of TH production, from **organification** of iodine to conversion of T_4 to T_3 in the peripheral tissues.

About one third of the iodine needed for T_3 and T_4 synthesis comes from dietary sources. Although several tissues, including salivary glands, mammary glands, and stomach, can absorb iodine, oxidation can take place only in the thyroid gland, because of the presence of thyroid peroxidase.

SYNTHESIS, RELEASE, AND UPTAKE OF THYROID HORMONES

Synthesis and Release of Thyroid Hormones

The synthesis and release of TH is regulated by the secretion of TSH from the anterior pituitary gland (see Chapter 26). TSH binds to its G protein–coupled receptor on the thyroid gland, stimulating cAMP, which acts *at each biosynthetic step* (see Fig. 27.3). If TSH is elevated for extended periods of time, it can also exert a trophic effect on the thyrocytes, causing hypertrophy of the thyroid tissue and **hyperthyroidism.**

- TSH secretion is stimulated by thyroid-releasing hormone (TRH), estrogen, and low circulating T_3 or T_4.
- TSH secretion is inhibited by somatostatin, growth hormone, cortisol, and high circulating T_3 or T_4.

TSH ultimately releases T_3 and T_4 into the blood, with 20 times the amount of T_4 (thyroxine) secreted compared with T_3. In the blood, most of the T_3 and T_4 is bound to proteins including albumin and **thyroxine-binding globulin** (TBG). The TBG acts as a plasma reservoir for T_4, because T_4 will only be active when it is released from the plasma proteins and enters the target cells. Thus, because of the high affinity for binding to plasma proteins, there is relatively little "free" circulating T_3 and T_4, but this is the fraction that is the physiologically and clinically relevant fraction.

Circulating free T_3 and T_4 provides feedback to both the hypothalamus and pituitary gland to decrease TRH and TSH, respectively (see Fig. 27.3). This feedback system is critical to maintaining appropriate levels of TH secretion.

Thyroid Hormone Uptake at Target Tissues

Free T_4 and T_3 diffuse into target cells, and within the cells the T_4 is converted to T_3 by **5′-deiodinase,** producing approximately the same concentrations of T_3 and rT_3. The active T_3 then binds the intracellular thyroid hormone receptor in the nucleus, which forms a complex with the **thyroid hormone response element** (TRE) in the nucleus and stimulates gene transcription (Fig. 27.4). TREs are found on a variety of genes, including the growth hormone receptor gene, cardiac and sarcoplasmic reticulum Ca^{2+}-ATPase genes, and genes that encode Na^+/K^+ ATPase subunits. Thus, TH can control diverse functions like growth, heart rate, and general metabolic rate. In general, low to normal levels of TH have anabolic effects and lead to synthesis of other hormones, and high levels of TH have catabolic effects, causing breakdown of proteins and hormones.

ACTIONS OF THYROID HORMONES

TH affects virtually all systems and can act at cellular and whole tissue levels, generally to increase metabolism and growth processes (see Fig. 27.4). Within cells, TH promotes production of proteins, enzymes, and other hormones; increases Na+/K+ ATPase; and increases the number of mitochondria, which increases O_2 consumption. These actions of TH are seen in:

- bone and tissues—contributing to normal growth and development; bone cell proliferation
- brain and nervous system—contributing to normal growth and development
- lungs—increasing ventilation
- heart—increasing cardiac output
- kidneys—increasing renal function
- metabolism—increasing food intake; increasing lipolytic effect on adipose cells, releasing free fatty acids into circulation; decreasing adipose tissue; decreasing muscle mass; increasing body temperature

Thus, TH has major effects on metabolism and growth, and disruptions in its normal secretion can have dramatic consequences.

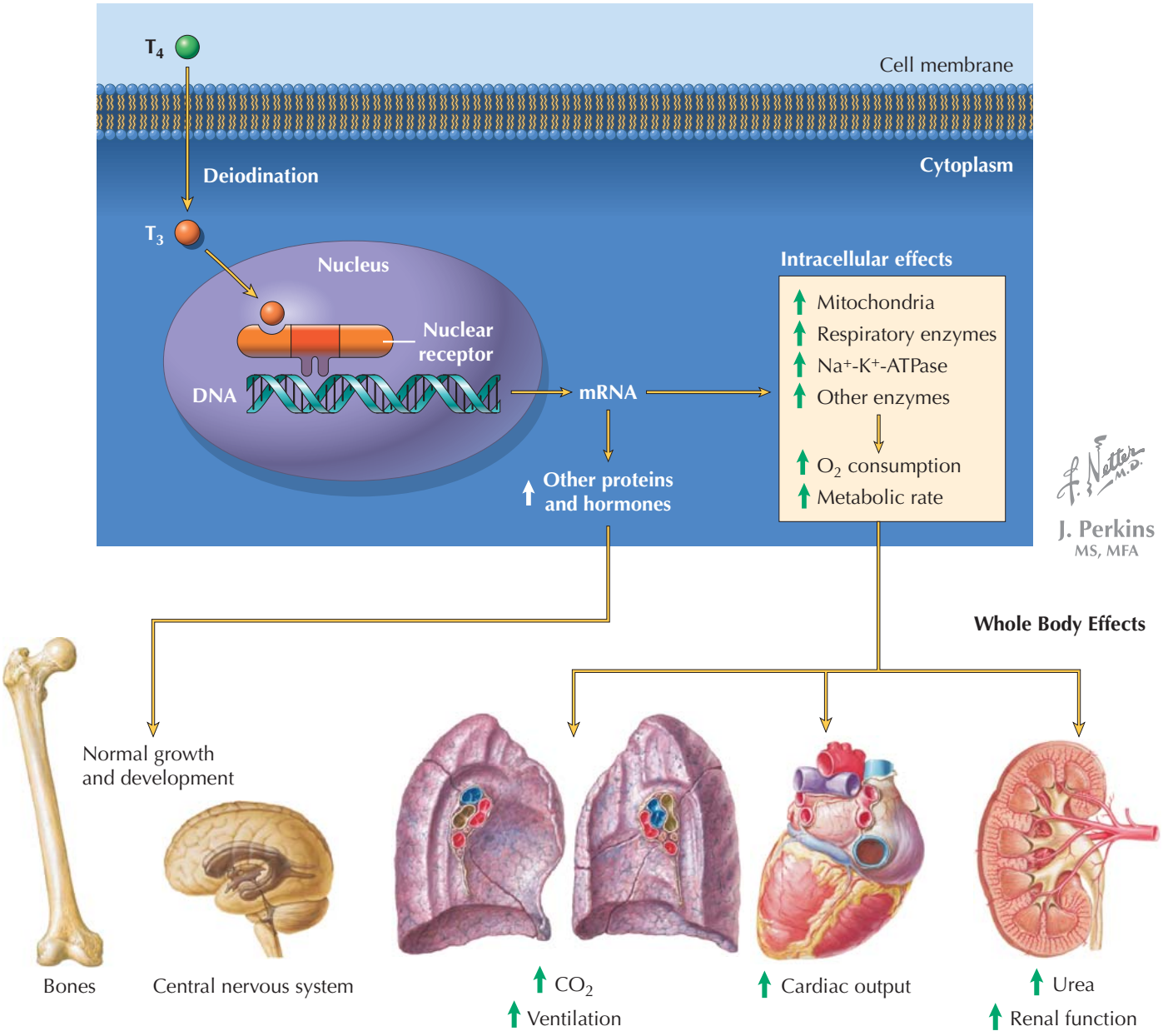
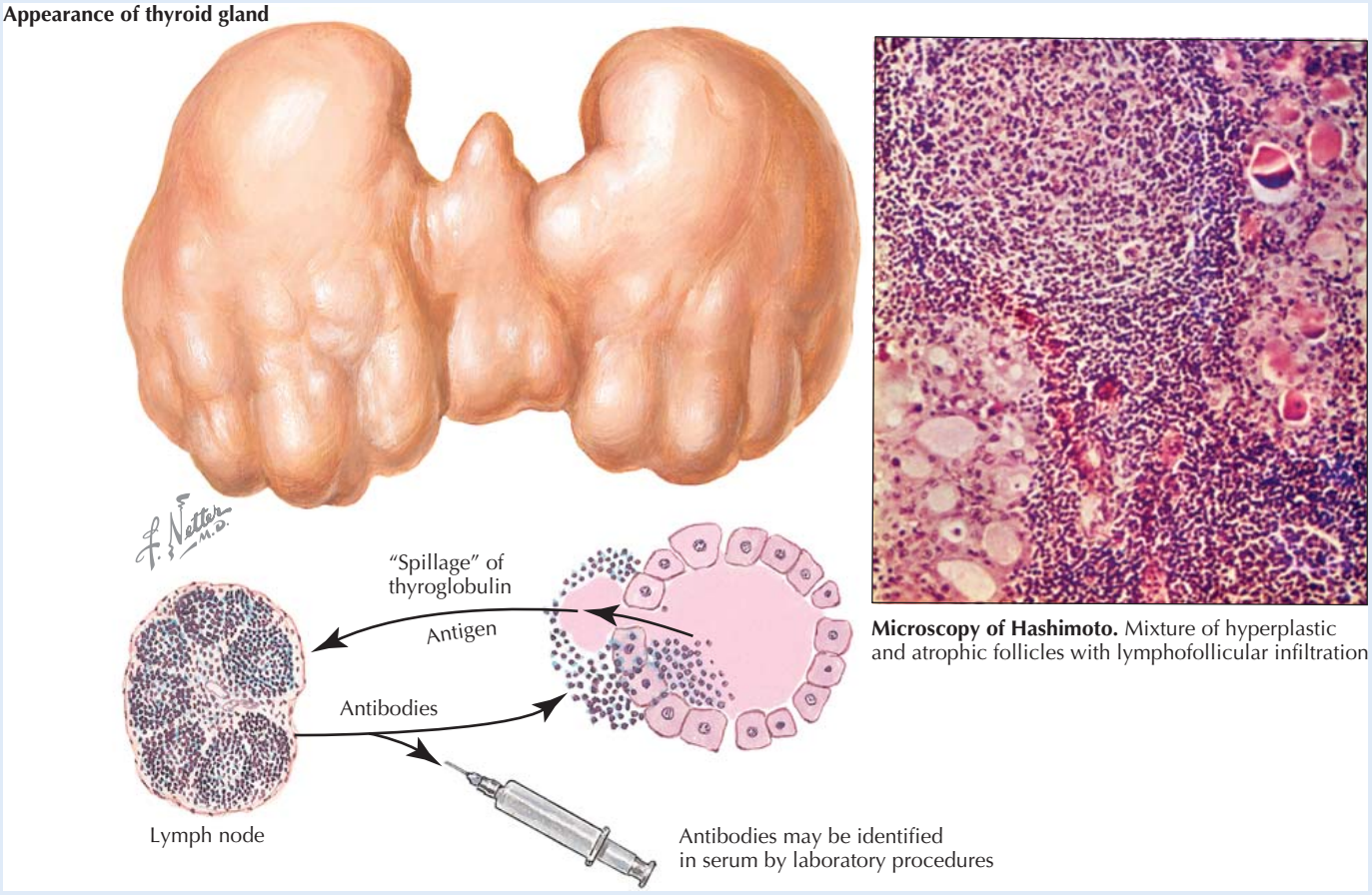


Figure 27.4 **Thyroid Hormone Action** T_4 is converted to active T_3 at target tissue by 5′-deiodinase action. The T_3 binds to nuclear receptors, initiating transcription of a variety of proteins and enzymes. The overall effects of thyroid hormone are to increase metabolic rate and O_2 consumption, and the general effects in target organs are illustrated.

CLINICAL CORRELATE
Diseases of Thyroid Function: Hypothyroidism

Hypothyroidism, or reduced TH, can result from lack of iodine, as well as autoimmune disease. Although there is dietary supplementation of iodine in the Western hemisphere, iodine deficiency is a health problem in many countries. **Iodine deficiency** severely reduces organification of Tg, and thus TH synthesis. Immune system dysfunction accounts for most cases of thyroid disease in the Western hemisphere. The most common cause of low TH is production of antibodies to thyroglobulin or thyroid peroxidase (TPO) (**Hashimoto's thyroiditis**). These antibodies act at the thyroid gland to inhibit the production and secretion of TH, and eventually destroy the gland.

- In children, untreated congenital hypothyroidism can result in **cretinism,** which is associated with stunted growth, mental retardation, impaired motor neuron function, and constipation.
- In adults, hypothyroidism results in **myxedema,** which is associated with increased fat deposition, nonpitting edema, cold intolerance, constipation, hypotension, fatigue, and depression, among other symptoms.
- Whether hypothyroidism is caused by iodine deficiency or immune cells, the low circulating TH feeds back to the pituitary and hypothalamus, causing *high levels of circulating TSH*. Treatment of hypothyroidism is with synthetic thyroxine.



Microscopy of Hashimoto. Mixture of hyperplastic and atrophic follicles with lymphofollicular infiltration

Hashimoto's Thyroiditis Hashimoto's thyroiditis is a common form of hypothyroidism and is caused by autoimmune antibodies directed against thyroglobulin or thyroid peroxidase. This results in low TH production (and high circulating TSH) and eventual destruction of the thyroid gland.

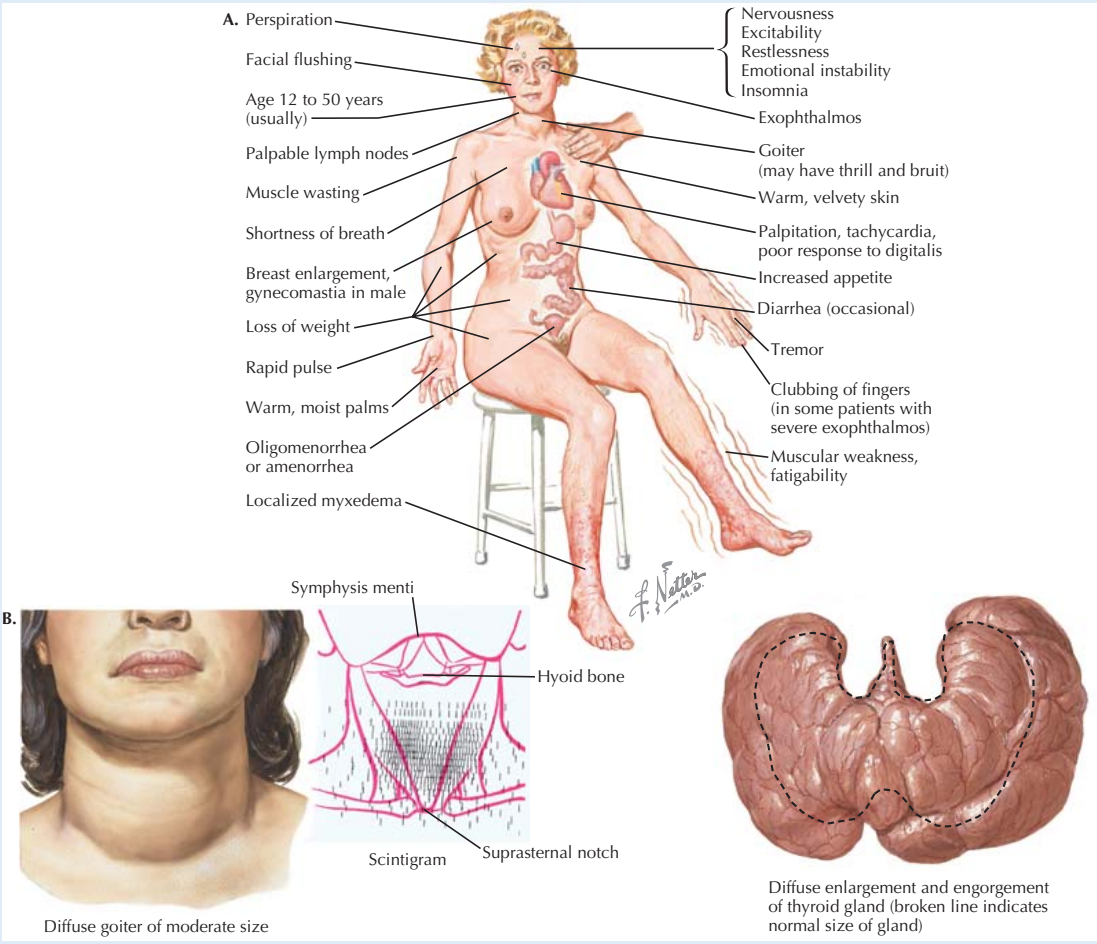
CLINICAL CORRELATE
Diseases of Thyroid Function: Hyperthyroidism

Hyperthyroidism, or overproduction of TH, is associated with high metabolic rate (30% to 60% above normal), weight loss, increased appetite, tachycardia, hyper-reactive bowels, and muscle weakness. Again, the most common cause is from immune cells targeting the thyrocytes.

- **Thyroid-stimulating immunoglobulins** can bind to the TSH receptors on the thyroid gland and produce the same biologic actions as TSH. However, while the elevated circulating TH suppresses pituitary TSH, there is no feedback regulation of the thyroid-stimulating immunoglobulins, so synthesis and release of TH continues. The gland becomes hypertrophied, forming a **goiter,** due to the trophic effect of immunoglobulin on the thyrocytes. These immunoglobulins are the cause of **hyperthyroidism** in **Graves' disease,** which is characterized by elevated circulating TH but *reduced* TSH. Exophthalmus (protruding eyes) is a symptom of Graves' disease and is caused by deposition of glycoproteins and water behind the eyes.
- In contrast to Graves' disease, the **hyperthyroidism** resulting from a **TSH-secreting pituitary tumor** is characterized by *elevated TH and TSH*. Although rare, **thyroid storms** can occur when TH levels increase to toxic levels, creating acute awareness of discomfort in the patient. These symptoms can include tachycardia, sleeplessness, dramatic mood swings, and hyperkinesis. If untreated, it can rapidly (within days) progress to congestive heart failure, circulatory collapse, and death. Treatment of hyperthyroidism is by propylthiouracil (PTU), radiation, or thyroidectomy and then thyroxine replacement.

Many people with autoimmune thyroid disease have antibodies to both the TSH receptor *and* thyroid peroxidase and have a mix of Graves' disease and Hashimoto's thyroiditis. Initially, the patient will be hyperthyroid, and then hypothyroid. Approximately 70% of people with Graves' disease have Hashimoto's.

Goiter (enlarged thyroid gland) can occur in hypothyroid and hyperthyroid conditions. For example, in both iodine deficiency and TSH-secreting tumor, elevated TSH levels stimulate thyroid growth. This is because, in both cases, elevated TSH has a growth effect on the thyrocytes. In each case, it takes years to develop goiter.



Clinical Symptoms of Hyperthyroidism *A*, Hyperthyroidism, such as is seen in Graves' disease, affects most physiologic systems and can increase metabolic rate by 30% to 60% over normal. The elevated thyroid hormone causes a wide variety of symptoms as illustrated above. *B,* Goiter. Enlargement of the thyroid gland (goiter) can be caused by both hypothyroid and hyperthyroid conditions and results from TSH, or immunoglobulin-mediated stimulation of hyperplastic growth of the thyrocytes.

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CHAPTER 28
Adrenal Hormones

The paired **adrenal glands** are also known as the **suprarenal glands,** due to their location above the kidneys in the retroperitoneal space (Fig. 28.1). The two adrenal glands (right and left) consist of an inner medullary and outer cortical layer, which produce catecholamines and steroid hormones, respectively. The adrenal medulla and adrenal cortex are derived from embryologically distinct tissues (ectodermal neural crest and endoderm, respectively), and can functionally be considered distinct organs. As a whole, however, the adrenals are sometimes discussed in terms of their role in the stress response, during which both medullary catecholamines and cortical steroids are released; this is a narrow view of the adrenals, though, which actually participate in a wide array of physiological processes.

ADRENAL GLAND STRUCTURE

The human **adrenal cortex** consists of three distinct histological layers (Fig. 28.2):

- The outer **zona glomerulosa,** which synthesizes mineralocorticoid hormones, mainly **aldosterone.**
- The middle **zona fasciculata,** which produces the glucocorticoid hormone **cortisol.**
- The inner **zona reticularis,** which produces male sex hormones (androgens), mainly **dehydroepiandrosterone** (**DHEA**) and **androstenedione.**

The **adrenal medulla** is found beneath the cortex, at the center of the gland; it contains **chromaffin cells** that function as postganglionic cells of the sympathetic nervous system, secreting mainly epinephrine, and in lesser amounts, norepinephrine into the bloodstream.

SYNTHESIS AND REGULATION OF ADRENAL CORTICAL STEROID HORMONES

The pathways for biosynthesis of adrenal steroids are depicted in Figure 26.3. Cholesterol, either produced *de novo* in the adrenal cortex or transported to the cortex in the form of LDL cholesterol, is the precursor of these products. Although illustrated in Figure 28.3 as a single, complex pathway, only portions of the pathway exist in each of the layers of the cortex. For example, the cells of the zona glomerulosa contain the enzymes involved in synthesis of aldosterone, and cells of the zona fasciculata have the enzymes necessary to produce cortisol.

The hypothalamic-pituitary-adrenal axis (HPA axis) (see Fig. 28.3) is affected by various physiological states including stress and anxiety (which activate the axis) and sleep/wake cycles. **Corticotropin-releasing hormone** (**CRH**), a 41 amino acid peptide produced by the hypothalamus and secreted into the hypothalamic-hypophyseal portal circulation, stimulates the anterior pituitary corticotrophs to release as well as synthesize **adrenocorticotrophic hormone** (**ACTH**). ACTH stimulates the **conversion of cholesterol to pregnenolone** in the adrenal cortex. This stimulation results in:

- Increased cortisol synthesis by the zona fasciculata.
- Higher androgen production by the zona reticularis (although androgen production is also probably affected by other factors as well).
- *Permissive* effects on aldosterone production by the zona glomerulosa. ACTH is necessary but not by itself sufficient stimulus for aldosterone synthesis, which is under primary control by other factors.



The 39 amino acid polypeptide hormone ACTH is first synthesized as a 241 amino acid prohormone called **pro-opiomelanocortin** (**POMC**). Although ACTH is the main physiologically relevant product of POMC in corticotrophs of the anterior pituitary, POMC is produced in various other sites, including the hypothalamus and brainstem. The multiple products of POMC include ACTH, **β-lipotropin, α-melanocyte-stimulating hormone** (**α-MSH**), **β-MSH,** and the endogenous opioid **β-endorphin,** among others. The relevance of endogenous production of some of the products in humans is limited or not well-defined in some cases. For example, α-MSH is produced by the pituitary's pars intermedia (see Fig. 26.3) and promotes pigmentation of skin. However, although the pars intermedia produces α-MSH in the fetus, there is little or no intermedia present in adults. Interestingly, because α-MSH consists of the first 13 amino acids of ACTH, when ACTH is produced in excess (for example, by an ACTH-secreting tumor), increased skin pigmentation can occur.

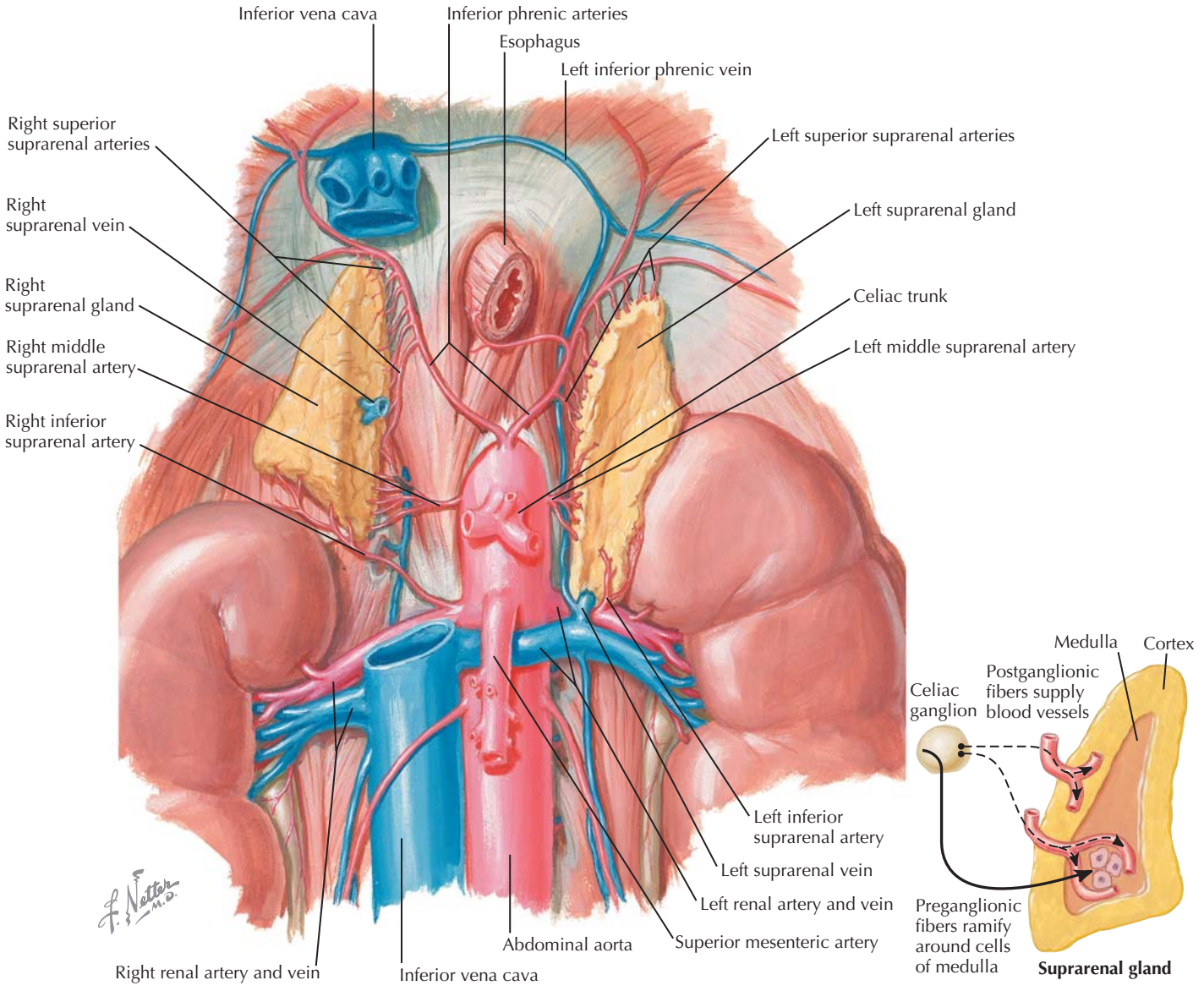


Figure 28.1 **Adrenal Gland Structure** The two adrenal glands are located above the kidneys and below the diaphragm in the retroperitoneal space. The outer cortex of the adrenal gland produces steroid hormones, whereas the inner medulla synthesizes and releases catecholamines.

The predominant adrenal effect of activation of the HPA axis is release of cortisol. ACTH is secreted in a pulsatile manner in response to variations in CRH release, with peak secretion early in the morning, in the hours before awakening, and lowest secretion just before sleep. Stress (e.g., hypoglycemia, heavy exercise, severe pain, surgery, trauma, and infection) is a major stimulus for activation of the HPA axis and therefore cortisol release.

Negative feedback regulation in the HPA axis involves long-loop feedback by cortisol on the pituitary gland and hypothalamus and short-loop feedback of ACTH on hypothalamic CRH release (see Fig. 28.3).

ACTIONS OF CORTISOL

Cortisol, secreted in response to HPA activation, has a wide array of physiological effects (Fig. 28.4). Like other steroid hormones, it binds to specific cytoplasmic receptors in target cells. The receptor-hormone complex is translocated to the nucleus, where it affects the transcription of specific genes. The term **glucocorticoid** stems from the fact that cortisol raises blood glucose levels; some of the other products of the steroid synthesis pathways, notably **corticosterone,** also have glucocorticoid activity. Notably, many of the effects of cortisol are **permissive,** meaning that the hormone does not directly cause a particular effect but is necessary for that effect to occur

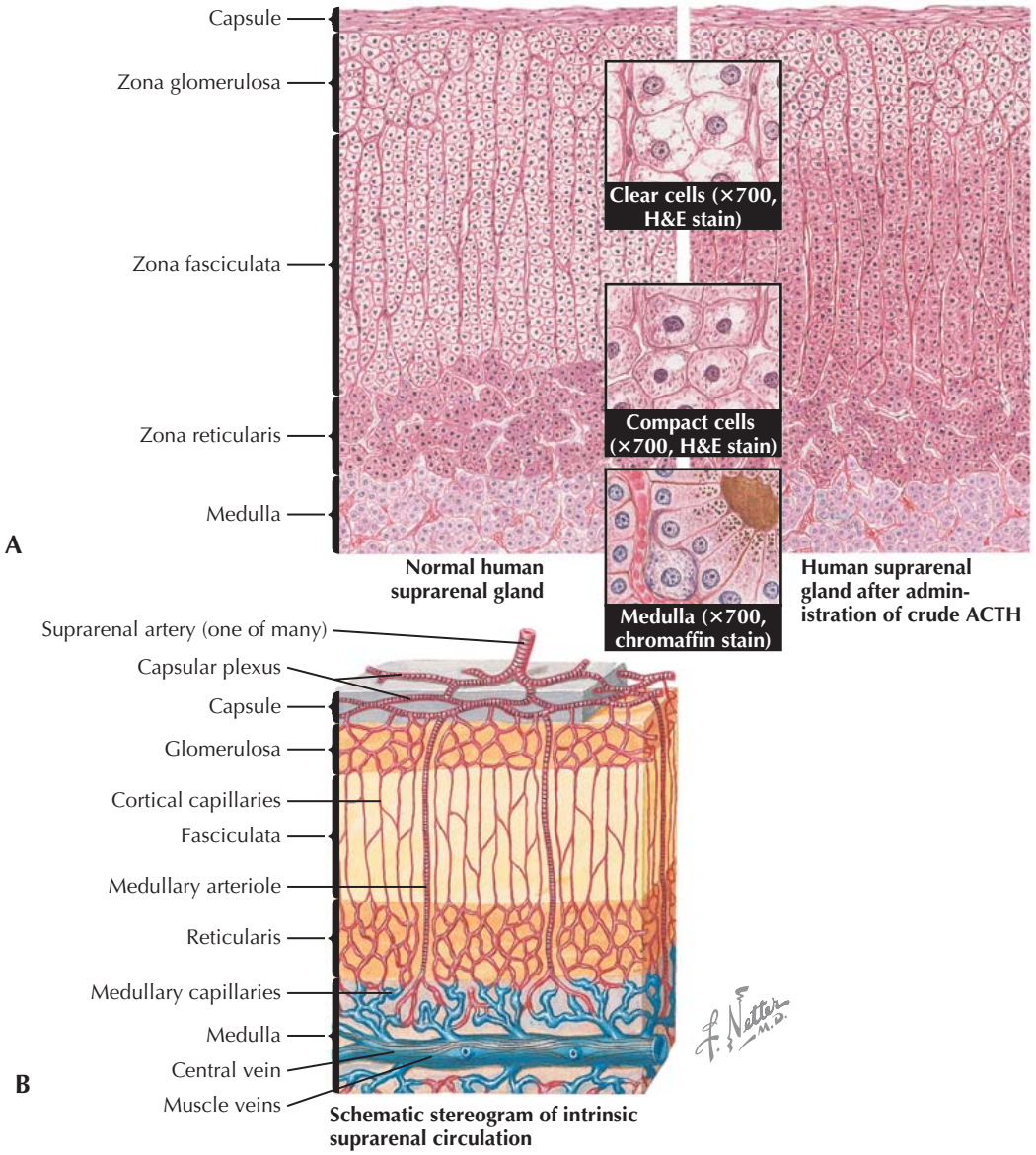


Figure 28.2 Adrenal Gland Histology The highly vascularized adrenal (suprarenal) glands comprise an outer cortex and inner medulla. The cortex synthesizes the steroid hormones aldosterone, cortisol, and androgens, respectively, in its zona glomerulosa, zona fasciculata, and zona reticularis. ACTH administration results in increased cell size and steroid biosynthetic activity mainly in the zona fasciculata but also in the zona reticularis *(A)*. The medullary chromaffin cells synthesize and release catecholamines (mainly epinephrine) into the bloodstream in response to sympathetic nervous system activation. The blood supply to the adrenal gland is provided by the suprarenal arteries *(B)*. ACTH, adrenocorticotropic hormone.

in response to another stimulus. For example, cortisol stimulates the *synthesis* of enzymes involved in gluconeogenesis (synthesis of glucose from specific gluconeogenic amino acids or from lactate, pyruvate, or glycerol). In general, the effects of glucocorticoids can be categorized as **metabolic, anti-inflammatory, and immunosuppressive** (see Fig. 28.4).

Metabolic Effects of Glucocorticoids

The major metabolic effects of cortisol at **normal** levels are:

- Stimulation of **gluconeogenesis.** As noted, this is a permissive action of cortisol, which induces synthesis of enzymes involved in hepatic gluconeogenesis.
- **Protein catabolism** to provide substrate (amino acids) for gluconeogenesis.
- **Lipolysis** in adipose tissue.
- **Inhibition of insulin-stimulated glucose uptake** by muscle and adipose tissue. Because of this action, as well as stimulation of gluconeogenesis, cortisol is considered a **diabetogenic** hormone.

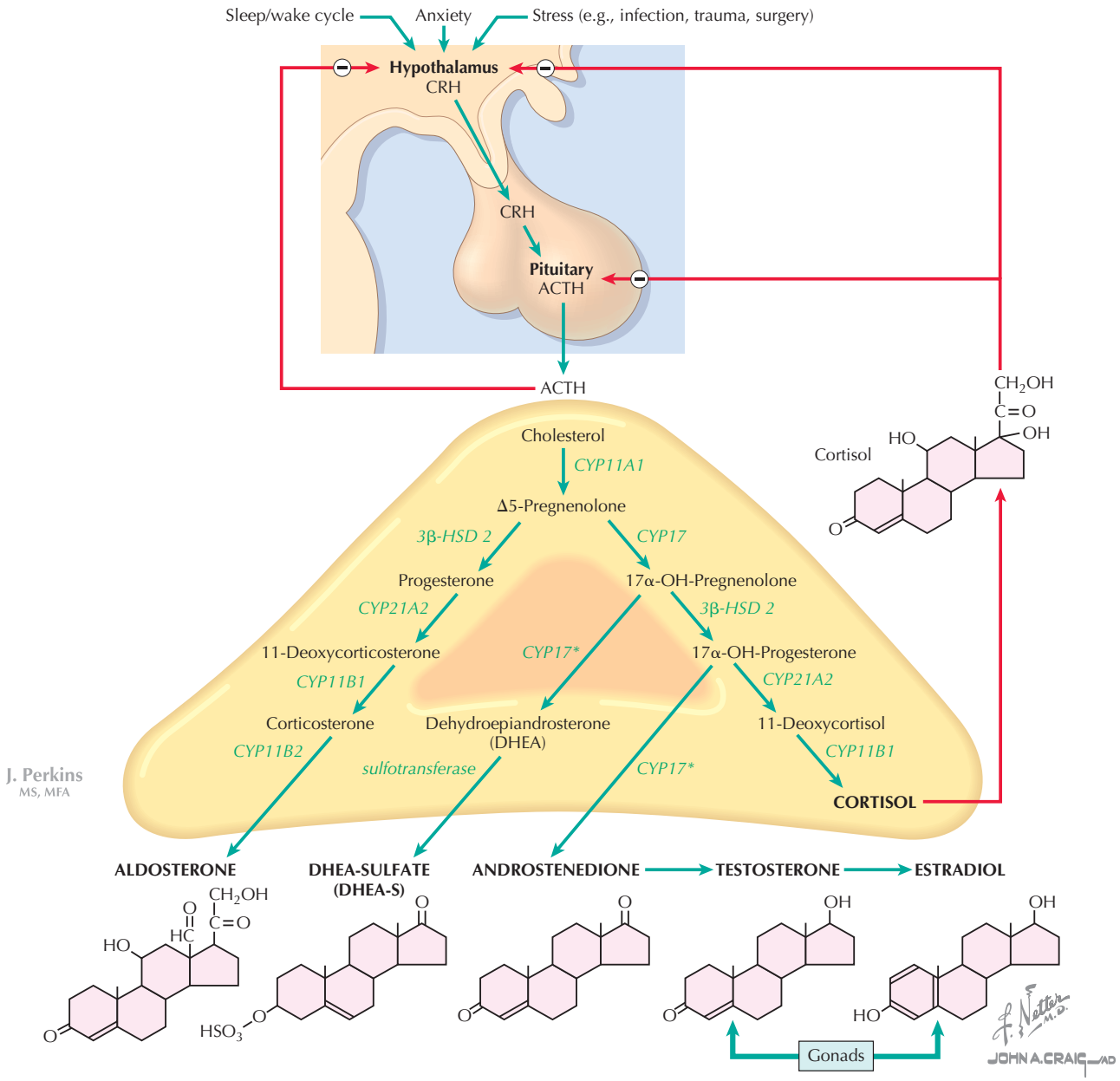


Figure 28.3 Adrenal Cortical Hormones Adrenal mineralocorticoid (aldosterone), glucocorticoid (cortisol), and androgens (dehydroepiandrosterone and androstenedione) are synthesized from cholesterol through the biosynthetic pathways illustrated. ACTH stimulates the conversion of cholesterol to Δ5-pregnenolone by the enzyme CYP11A1; the conversion of Δ5-pregnenolone to various products is dependent on additional enzymes in the various zones of the adrenal cortex. The adrenal gland also synthesizes small amounts of other steroids (e.g., testosterone and estradiol). Negative feedback on ACTH and the hypothalamic-releasing hormone CRH is accomplished by cortisol. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

As a result of these various effects, normal levels of glucocorticoids stimulate gluconeogenesis and, in the well-fed state, storage of glucose in the liver in the form of glycogen. These actions become extremely important in maintaining blood glucose levels during periods of fasting.

As is the case for many hormones, the consequences of excess glucocorticoids are in part, but not wholly, predictable based on their normal actions. The metabolic effects of excess glucocorticoids include:

- **Muscle wasting** and **thinning of skin,** due to protein catabolism and inhibition of protein synthesis. In **excess,** cortisol is a **catabolic hormone.**
- **Bone resorption,** due to imbalance between osteoclastic and osteoblastic activity.

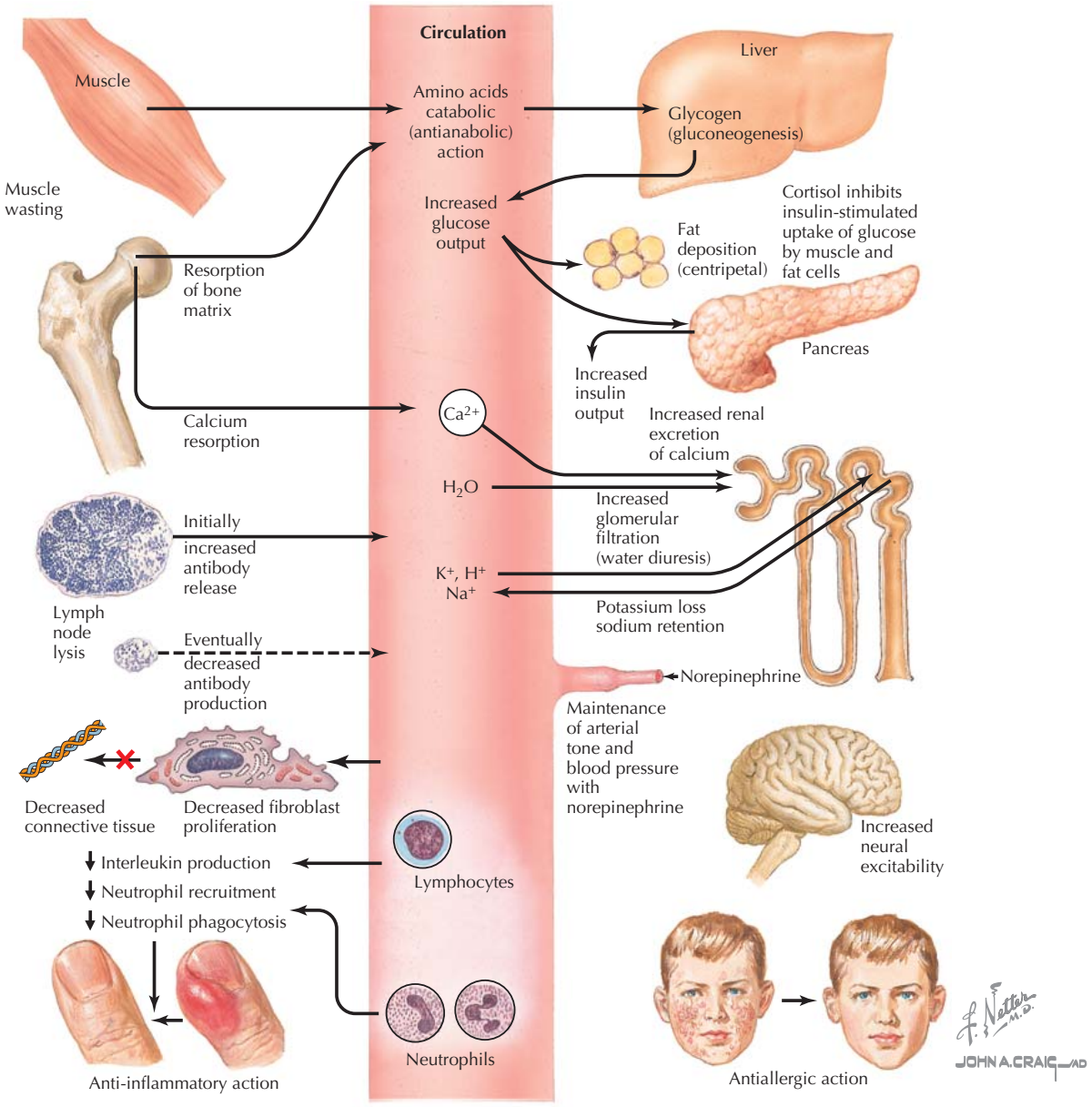


Figure 28.4 **Actions of Cortisol** Cortisol has a wide array of actions, including muscle wasting, gluconeogenesis, hyperglycemia, anti-inflammatory and anti-immune effects, and insulin resistance. It also has mineralocorticoid-like effects on the kidney at high concentrations.

- Deposition of centripetal (truncal) fat, and therefore, **centripetal obesity.**
- Renal **sodium retention** and **potassium loss**. Cortisol binds to mineralocorticoid receptors in addition to glucocorticoid receptors. It is ordinarily converted by the kidney to cortisone, limiting its effects on the renal tubules, but in cortisol excess, mineralocorticoid activity is observed.

Other Effects of Glucocorticoids

Other important actions of glucocorticoids include **anti-inflammatory, immunosuppressive,** and **vascular effects.** These include:

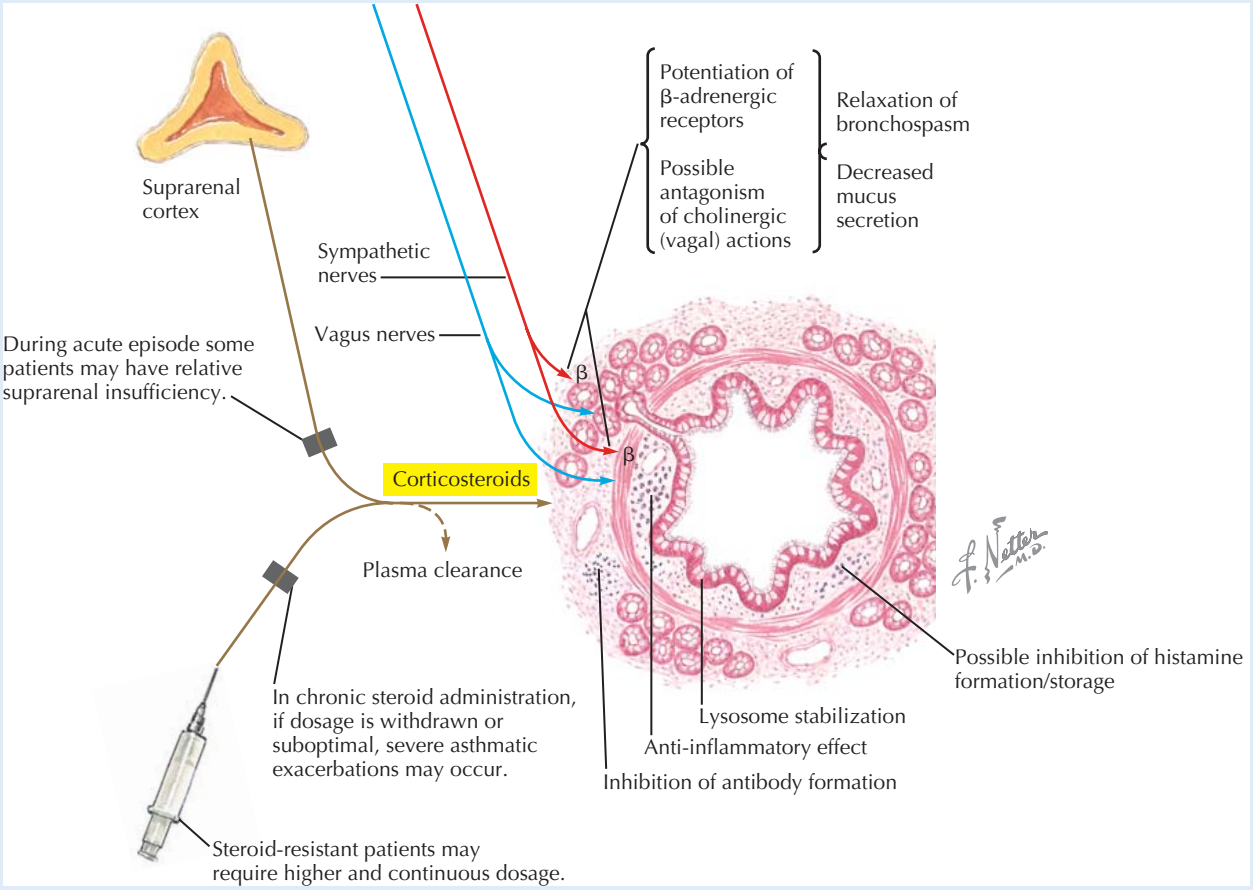
- Inhibition of the production of **arachidonic acid metabolites** (e.g., prostaglandin, thromboxane, and leukotrienes) and **platelet-activating factor.**
- Reduction in T-lymphocytes and their production of **interleukins, interferon,** and **tumor necrosis factor.**
- Decreased fibroblast production and their deposition of connective tissue.
- An initial increase in **antibody production,** but eventually decreased production.
- Increased responsiveness of vascular smooth muscle to norepinephrine. Cortisol is important in maintaining normal vascular responses to adrenergic stimulation and, thus, normal blood pressure regulation.

ACTIONS OF ADRENAL ANDROGENS

ACTH stimulates the zona reticularis of the adrenal cortex to synthesize and release androgens, although additional factors are likely involved. The adrenal androgens, dehydroepiandrosterone (DHEA) and androstenedione, have notable effects in females, because the adrenal gland is normally the only significant source of androgens in women. Effects of adrenal androgens in females include development of pubic hair, hypertrophy of sebaceous glands (acne), stimulation of libido, and possibly, inhibition of osteoporosis. They have only a minor role in men, in whom testosterone produced by the testes is the major androgen. However, in both sexes, adrenal androgen production rises in mid childhood, and thus the hormones may contribute to early pubertal changes in boys as well as girls (Chapter 31). **Adrenarche** is the maturation of the adrenal cortex, which occurs between 6 and 10 years of age and results in the three distinct zones of the cortex, and subsequently, production of adrenal androgens. Adrenal androgen levels reach a peak at about 20 years of age and decline through adulthood.

CLINICAL CORRELATE
Glucocorticoids as Anti-inflammatory and Immunosuppressive Drugs

Based on their anti-inflammatory and immunosuppressive properties, cortisol and various synthetic glucocorticoids (for example, dexamethasone) are used therapeutically to suppress serious inflammation and allergic reactions, autoimmune responses, and transplant rejection. However, systemic treatment with steroids is avoided when possible, due to a wide array of potentially serious side effects, including immunosuppression, muscle wasting, osteoporosis, hyperglycemia, neural excitability and associated psychiatric effects, and, ultimately, adrenal insufficiency (due to negative feedback on the HPA axis). When an anti-inflammatory steroid is used systemically, the patient is gradually weaned from the drug, to prevent sudden withdrawal before endogenous cortisol production can resume.



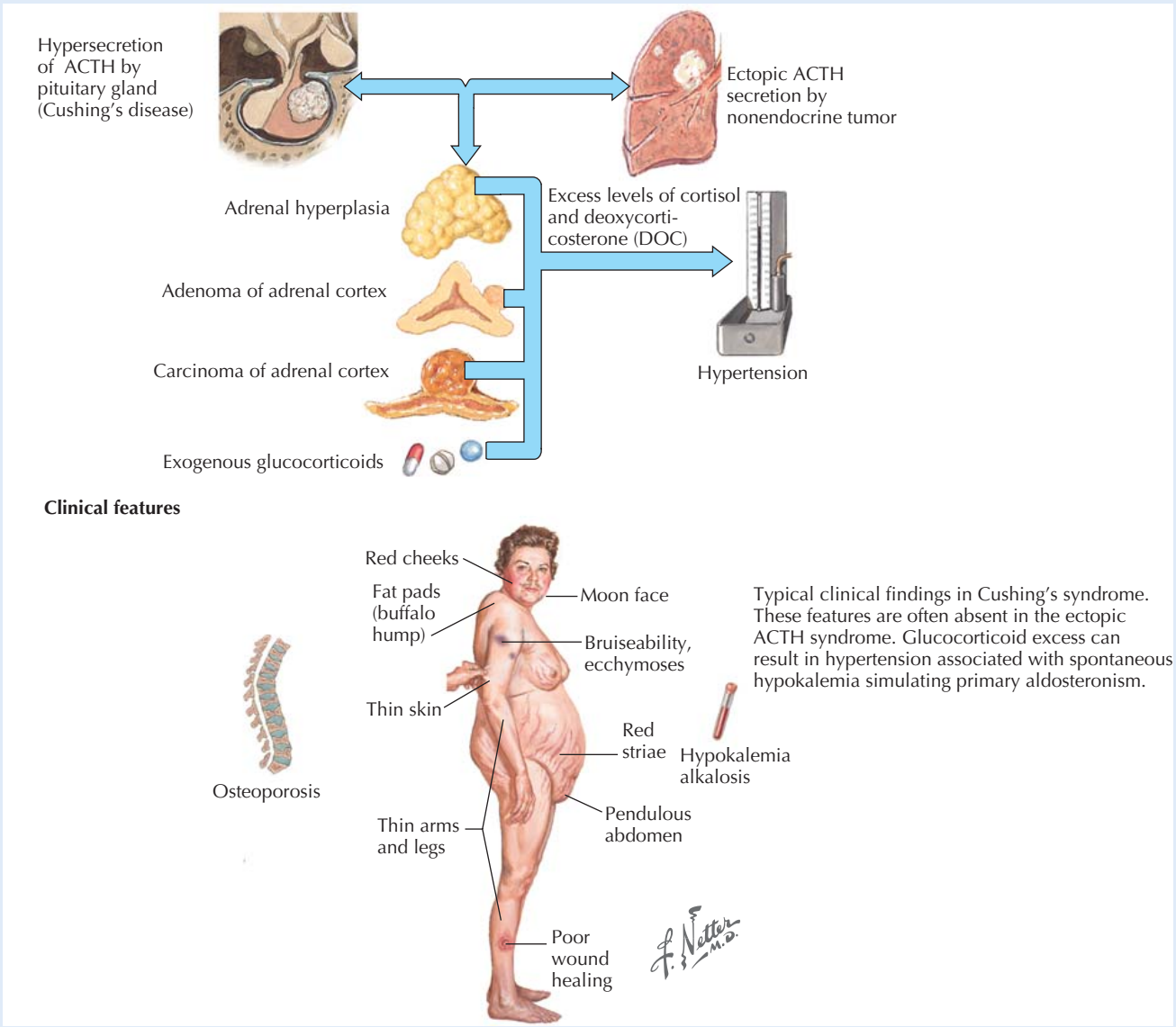
Corticosteroid Actions in Bronchial Asthma Anti-inflammatory effects are the basis for use of inhaled corticosteroids as preventive medication in patients who suffer frequent or severe asthma attacks.

CLINICAL CORRELATE
Cushing's Syndrome

Cushing's syndrome is an endocrine disease caused by high levels of blood cortisol. Its etiology may be due to a pituitary or ectopic ACTH-secreting tumor, hyperplasia or tumor of the adrenal gland, or use of glucocorticoid drugs. The symptoms and signs of Cushing's syndrome, which might be predicted based on the effects of adrenal steroids, include:

- centripetal obesity, accompanied by muscle wasting in the extremities
- "moon face" (a rounding of the face)
- thinning and bruising of the skin
- skin hyperpigmentation (if ACTH is elevated; see earlier in the chapter)
- hypertension
- hyperglycemia and insulin resistance
- osteoporosis

The dexamethasone suppression test may be useful in diagnosing the cause of hypercortisolism. Although secretion of ACTH by the pituitary (and thus, adrenal cortisol production by the adrenal gland) is normally suppressed by administration of dexamethasone (a glucocorticoid drug), pituitary ACTH-secreting tumors have reduced sensitivity to such inhibition. When hypercortisolism is the result of an adrenal tumor, cortisol production is unaffected by exogenous glucocorticoid (dexamethasone) administration. Once the cause of glucocorticoid excess is identified and appropriately addressed (often by surgery), treatment with replacement steroids is usually necessary.



Causes of Cushing's Syndrome Cushing's syndrome may result from a variety of causes, all of which result in elevated plasma glucocorticoid level. ACTH, adrenocorticotropic hormone.

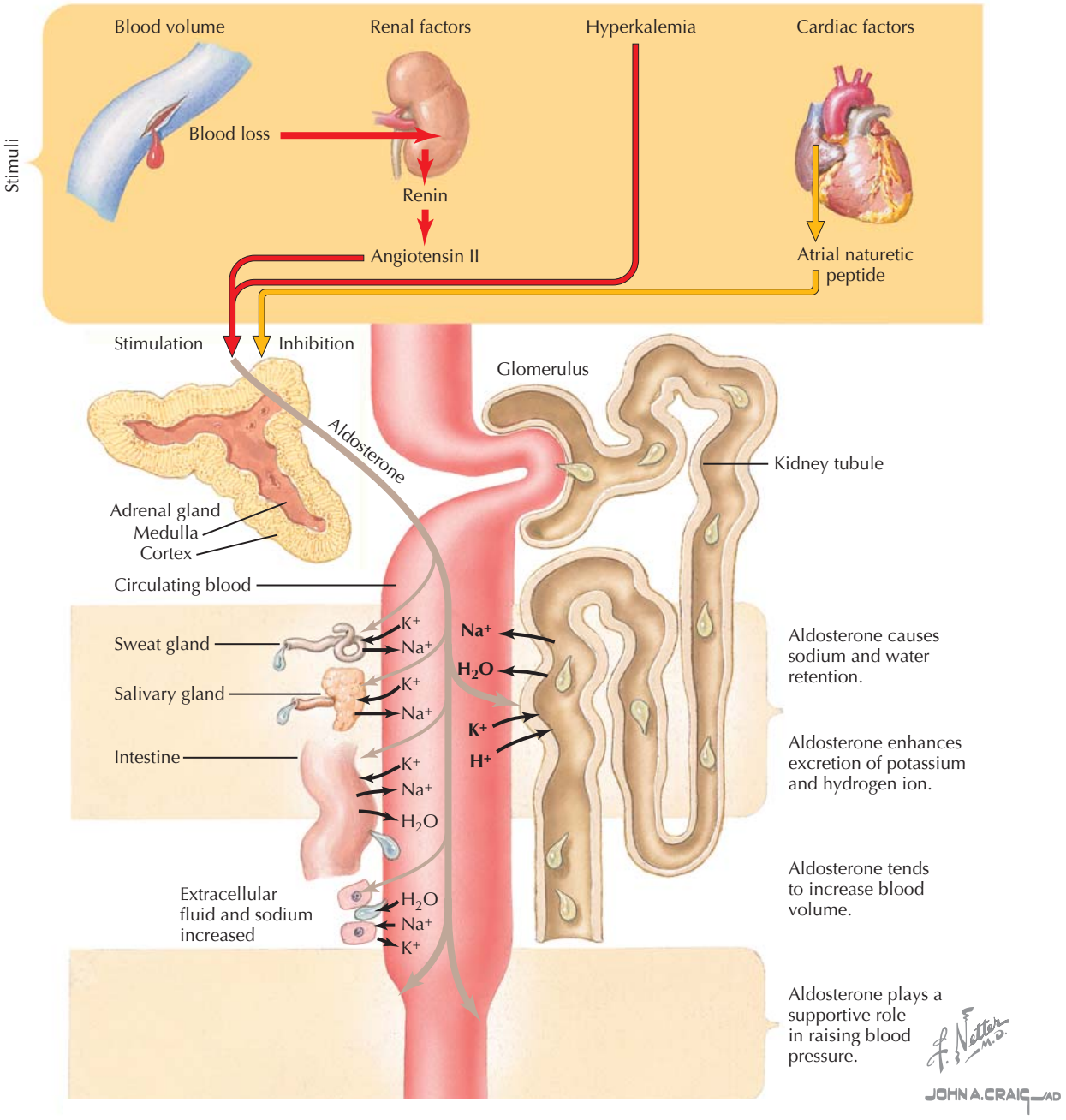


Figure 28.5 **Actions of Aldosterone** The steroid hormone aldosterone has the important functions of regulating extracellular fluid volume and K^+ levels. Synthesis and release of aldosterone is promoted by angiotensin II and hyperkalemia and is inhibited by atrial natriuretic peptide. Its action results in water and Na^+ retention and K^+ and H^+ excretion by the kidney; it has similar effects on the intestine, sweat glands, and salivary glands.

REGULATION AND ACTIONS OF ALDOSTERONE

The mineralocorticoid aldosterone is a regulator of **extracellular fluid volume** and **K^+ homeostasis** (Fig. 28.5). Its actions are accomplished mainly by effects on the collecting ducts and late distal tubules of the kidney, where it stimulates:

- **Na^+ reabsorption,** and as a result, water retention and **expansion of extracellular fluid volume;** in excess, hypertension results.
- **K^+ excretion;** excess aldosterone will cause hypokalemia.
- **H^+ excretion;** in excess, aldosterone causes metabolic alkalosis.

In addition to the renal tubules, aldosterone also affects Na^+ and K^+ handling by the intestines, salivary glands, and sweat glands.

The primary stimuli for secretion of aldosterone by cells of the adrenal zona glomerulosa are (see Fig. 28.5):

- **Hyperkalemia** (elevated plasma K^+), which directly acts on the adrenal gland to increase aldosterone secretion; aldosterone reduces plasma K^+ through its renal actions.
- **Angiotensin II,** which stimulates aldosterone secretion. Reduction of blood volume results in renin release by the kidney, which cleaves the plasma protein angiotensinogen to angiotensin I, which is subsequently cleaved by angiotensin-converting enzyme (ACE) to form angiotensin II (see Section 5, "Renal Physiology"). Aldosterone, by promoting Na^+ and water retention, increases blood volume.
- **Atrial natriuretic peptide (ANP),** which inhibits aldosterone secretion. ANP is released by cardiac myocytes when blood volume is elevated, for example, in congestive heart failure. Inhibition of aldosterone secretion results in reduction of blood volume.

While ACTH is required for synthesis of aldosterone, the above listed factors play a more important regulatory role in its synthesis and release. Release of aldosterone, like release of cortisol and adrenal androgens, is greatest in the early morning hours. The physiology of aldosterone is discussed in greater detail in Section 5, "Renal Physiology."

THE ADRENAL MEDULLA

In addition to the following discussion, physiological effects of adrenal catecholamines are discussed throughout the various chapters of this book in relation to the physiology of various target systems and in the specific context of the autonomic nervous system as a whole in Chapter 7.

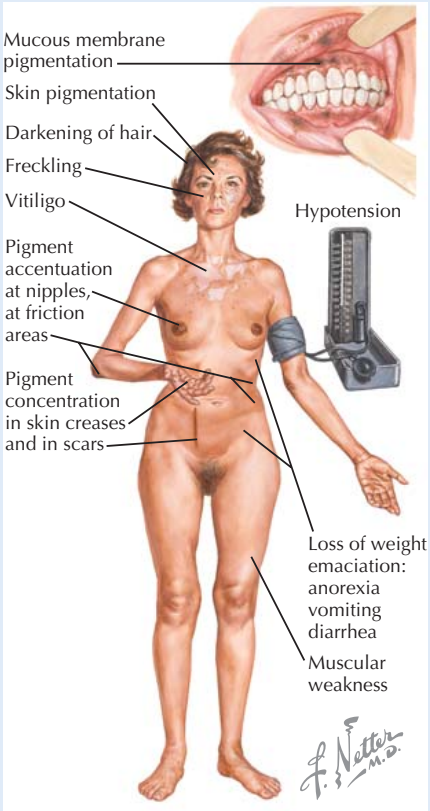
The adrenal medulla, the central portion of the adrenal gland, is functionally distinct from the cortex, acting as a postganglionic effector of the sympathetic nervous system. Its **chromaffin cells** synthesize and release catecholamines into the bloodstream in response to sympathetic nervous system activation. Whereas sympathetic postganglionic nerves mainly release **norepinephrine,** 70% to 80% of the catecholamine release from chromaffin cells is **epinephrine.** As is the case for postganglionic neurons, a number of sympathetic cotransmitters, including **neuropeptide Y,** are also synthesized and released. Release of adrenal catecholamines results in a spectrum of physiological actions throughout the body, with effects differing somewhat in degree compared with effects of norepinephrine released from sympathetic nerves, owing to the differences in binding affinity of epinephrine and norepinephrine at subtypes of adrenergic receptors (Fig. 28.6).

CLINICAL CORRELATE
Addison's Disease

Addison's disease is an uncommon endocrine disease characterized by failure of steroid synthesis by the adrenal gland, due to various causes including autoimmune or tubercular destruction of the gland and rare genetic disorders. As is the case for Cushing's syndrome, effects of deficiency of adrenal steroids might be predicted based on the normal actions of the hormones. Symptoms and signs of adrenal insufficiency include:

- poor stress tolerance
- hypoglycemia
- fatigue and weight loss
- hyperpigmentation of skin (due to ACTH elevation; see earlier in the chapter)
- low blood pressure
- salt appetite

An Addisonian crisis, caused by a severe deficiency of adrenal hormones, is a medical emergency, sometimes marking the onset of the disease. Vomiting and diarrhea, low blood pressure, fainting, loss of consciousness, convulsions, and hypoglycemia are among the signs and symptoms. Addisonian patients require long-term glucocorticoid replacement therapy, and sometimes mineralocorticoid treatment as well.



Chronic Primary Adrenocortical Insufficiency (Addison's Disease) In primary adrenocortical insufficiency, adrenocortical steroid production is low, due to adrenal atrophy, tubercular destruction of the adrenal, or other causes, and ACTH level is elevated (due to lack of negative feedback). Symptoms reflect deficiency of corticosteroids but also reflect excess of ACTH, which causes pigmentation due to its sequence homology with α-melanocyte-stimulating hormone (MSH). ACTH, adrenocorticotropic hormone.

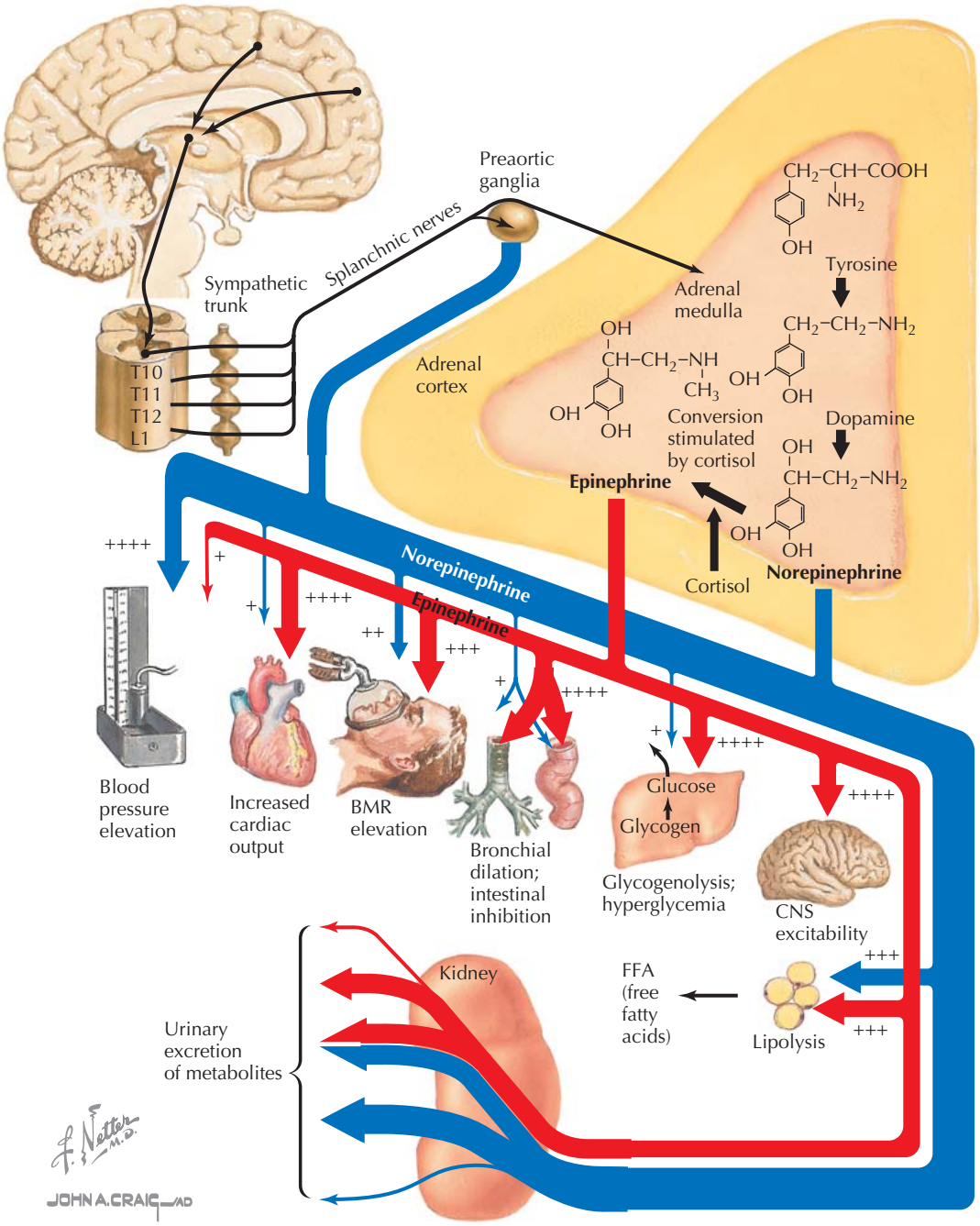


Figure 28.6 **Function of the Adrenal Medulla** The adrenal medulla releases epinephrine (80%) and norepinephrine (20%) into the bloodstream during activation of the sympathetic nervous system. The effects of epinephrine and norepinephrine, including relative magnitude, are illustrated for various sites. BMR, basal metabolic rate.

CHAPTER 29 The Endocrine Pancreas

The pancreas has key roles in both gastrointestinal function and modulation of blood glucose levels. Because the products of the exocrine pancreas (enzymes and buffers) allow digestion and absorption of carbohydrates into the blood, and the products of the endocrine pancreas (insulin, glucagon, and somatostatin) regulate the blood glucose levels, the pancreas can be viewed as a total processing unit for glucose entry into the body and the cells.

STRUCTURE OF THE PANCREAS

As noted in Section 6, the exocrine pancreas performs crucial digestive and buffering functions. The exocrine pancreas makes up about 99% of the functional cells, with the remainder serving the endocrine function (Fig. 29.1). The primary endocrine portion is composed of the islet of Langerhans cells, which are made up of three cell types:

- α-Cells produce **glucagon,** which mobilizes glucose stores *into the blood*.
- β-Cells produce **insulin,** which stimulates glucose transport *into the cells*.
- δ-Cells produce **somatostatin,** which inhibits both insulin and glucagon secretion.

In the islets, the cells are organized with the α-cells surrounding the β-cells. There are many more insulin-producing β-cells than α and δ cells. There is a fourth cell type (F-cell) within the islets, which produce pancreatic polypeptide, which inhibits exocrine secretions (buffers and enzymes).

There are also important paracrine (cell-to-cell) interactions within the islets. Because the blood forms a capillary network in the islets, insulin (from β-cells) is carried to the glucagon-producing α-cells in a paracrine manner. Insulin can inhibit its own secretion, as well as glucagon secretion, whereas somatostatin inhibits both insulin and glucagon. This allows paracrine modulation of the pancreatic response to blood glucose levels.



Because both insulin and the **C-peptide fragments** are secreted when contents of the insulin-containing granules are released, the amount of C-peptide in the blood is a reflection of insulin production. Clinically, C-peptide is used to determine endogenous insulin secretion in diabetic patients receiving insulin injections.

SYNTHESIS OF INSULIN, GLUCAGON, AND SOMATOSTATIN

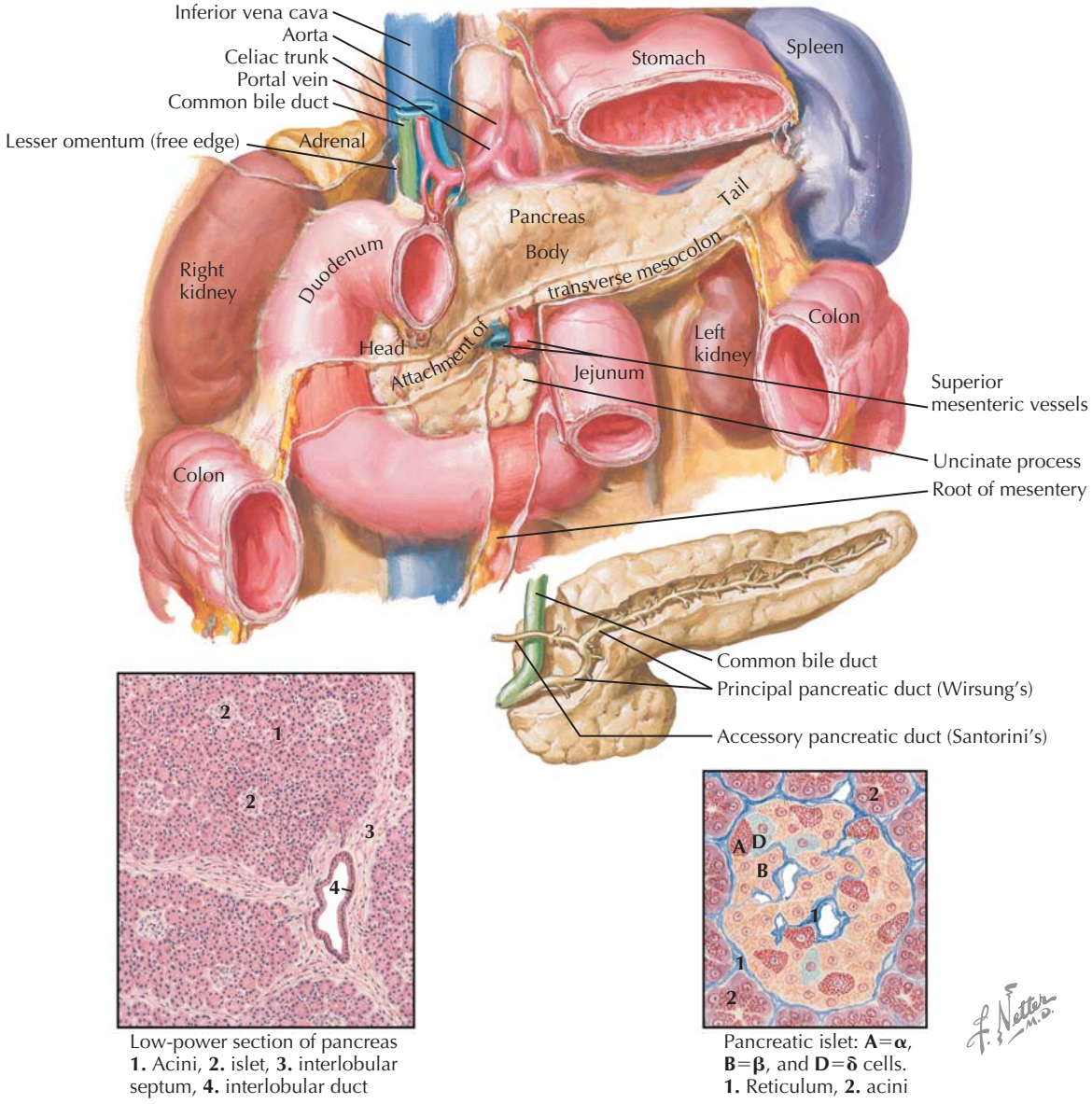
Insulin

The major control of blood glucose levels occurs through the production and secretion and action of **insulin,** which is a 51 amino acid peptide hormone formed in the β-cells from a prohormone that contains three peptides: the A and B chains of the active insulin molecule and the connecting "C"-peptide (Fig. 29.2). In the endoplasmic reticulum, disulfide bridges are formed between the A and B chains of the proinsulin, which are still connected by the C-peptide chain. In the Golgi apparatus, the C-peptide is cleaved from the proinsulin, forming active insulin. Both the insulin and C-peptide are packaged in granules for secretion into blood.

Glucose (GLUT) Transporters

Secretion of insulin is stimulated directly by blood glucose levels, as well as by gut peptides. The glucose enters cells through a variety of facilitated glucose transporters (GLUT). Although many GLUT transporters have been identified (more than 10), the function of several of the newly discovered isoforms is not clear. Of the main transporters:

- **GLUT1** is in all adult cell membranes and is responsible for allowing enough glucose into cells to maintain cellular respiration and viability. It is also found in high concentration in the membranes of the blood-brain barrier, and the transporters are under positive control by circulating glucose (increased glucose increases GLUT1 transporters). **SGLUT1** are secondary active transporters, which carry glucose with sodium, and these are found in *apical* membranes of renal proximal tubules, choroid plexus, and small intestine along with **SGLUT2**.
- **GLUT2** is located in the membranes of the small intestine (basolateral side), brain, liver, and pancreas, and these transporters facilitate easy entry of glucose to those tissues. SGLUT2 are secondary active transporters,



Low-power section of pancreas **1.** Acini, **2.** islet, **3.** interlobular septum, **4.** interlobular duct

Pancreatic islet: **A**=**α**, **B**=**β**, and **D**=**δ** cells. **1.** Reticulum, **2.** acini

Figure 29.1 Structure of the Endocrine Pancreas The pancreas is a key component of the gastrointestinal (GI) tract because of its exocrine function; it also provides the primary control of blood glucose because of its production of endocrine hormones. The vast majority of the pancreas (~99%) is composed of acinar cells, which produce and secrete the buffers and enzymes through ducts into the GI tract (exocrine function) *(micrograph on left).* The endocrine pancreas is composed of cells that form the islets of Langerhans. The cells of the islets produce insulin (β-cells), glucagon (α-cells), and somatostatin (δ-cells).

which carry glucose with sodium, and these are found in *apical* membranes of renal proximal tubules, choroid plexus, and small intestine along with SGLUT1.

- **GLUT3** is mainly in neurons and placenta.
- **GLUT4** is expressed in skeletal and cardiac muscle and adipose tissue and is the **insulin-stimulated glucose transporter.**
- **GLUT5** is the fructose transporter.

Mechanism of Insulin Secretion

When blood glucose increases (see Fig. 29.3*A*):

- Glucose enters the pancreatic β-cells via **GLUT2** transporters.
- Intracellular glucose metabolism increases adenosine triphosphate (ATP), which inhibits K^+ efflux. This depolarizes the β-cells and opens voltage-gated Ca^{2+} channels.
- The Ca^{2+} influx stimulates secretion of the insulin and C-peptide into the blood.

In addition to blood glucose, the gut-derived **incretins** (glucose insulinotropic peptide [GIP] and glucagon-like peptide-1 [GLP-1]) and increased blood amino acids, fatty acids, and

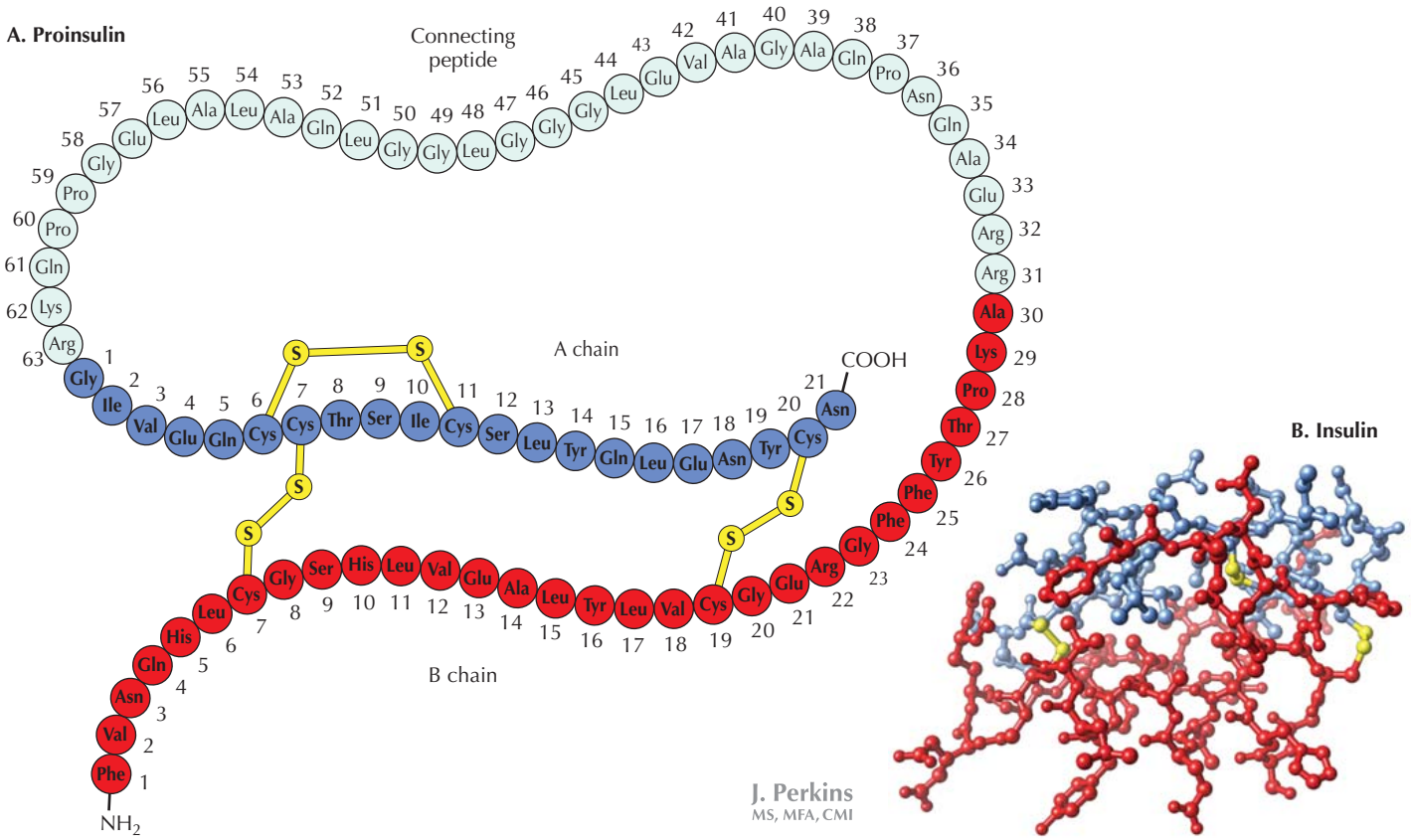


Figure 29.2 **Insulin Structure** *A* illustrates the proinsulin molecule, which is composed of an A *(blue)* and B *(red)* chain of insulin, connected by two disulfide bridges *(yellow).* In the endoplasmic reticulum, the insulin chains are attached to the connecting "C"-peptide, which is cleaved in the Golgi apparatus to yield the insulin and C-peptide and then packaged in secretory granules; the three-dimensional structure of active insulin is illustrated in *B.*

acetylcholine also promote insulin secretion (Fig. 29.3*B*). A common theme is that all of these elements reflect the fed state as a stimulus for elevating insulin. Lastly, glucagon can also stimulate insulin secretion by increasing intracellular Ca^{2+} (via phospholipase C). This modulates the hyperglycemic effects of glucagon.

Insulin secretion is suppressed when blood glucose is low, when the sympathetic nervous system is stimulated (elevated norepinephrine and epinephrine), and when local somatostatin is elevated.

Glucagon

Glucagon is a 29 amino acid peptide hormone produced as a prohormone in the α-cells of the islets of Langerhans. As with insulin, intracellular processing results in packaging of active glucagon molecules in dense core granules.

Glucagon acts to mobilize glucose into blood (actions opposite of insulin); the secretion of glucagon is stimulated primarily by low blood glucose. Insulin inhibits glucagon secretion in a paracrine manner. Thus, modulation of glucagon is observed with ingestion of amino acids, which increases both insulin and glucagon. Glucagon secretion is also inhibited by high glucose and fatty acids in the blood.

Somatostatin

Although not well understood, **somatostatin** plays a lesser role in control of blood glucose. It is a 14 amino acid peptide produced in the δ-cells of the islets and acts in a paracrine manner to suppress *both* insulin and glucagon. This adds one more level of control in modulating blood glucose levels. The somatostatin produced in the pancreas is the same hormone that is produced in the brain and gut, and as in these other tissues, it acts locally on adjacent cells.



Pancreatic polypeptide is another endocrine hormone secreted from F-cells in the pancreatic islets. Although the function is not clear, it is released in response to meals high in protein, and it appears to decrease secretion of gastric and intestinal enzymes, modulating the effects of cholecystokinin (see Chapter 23).

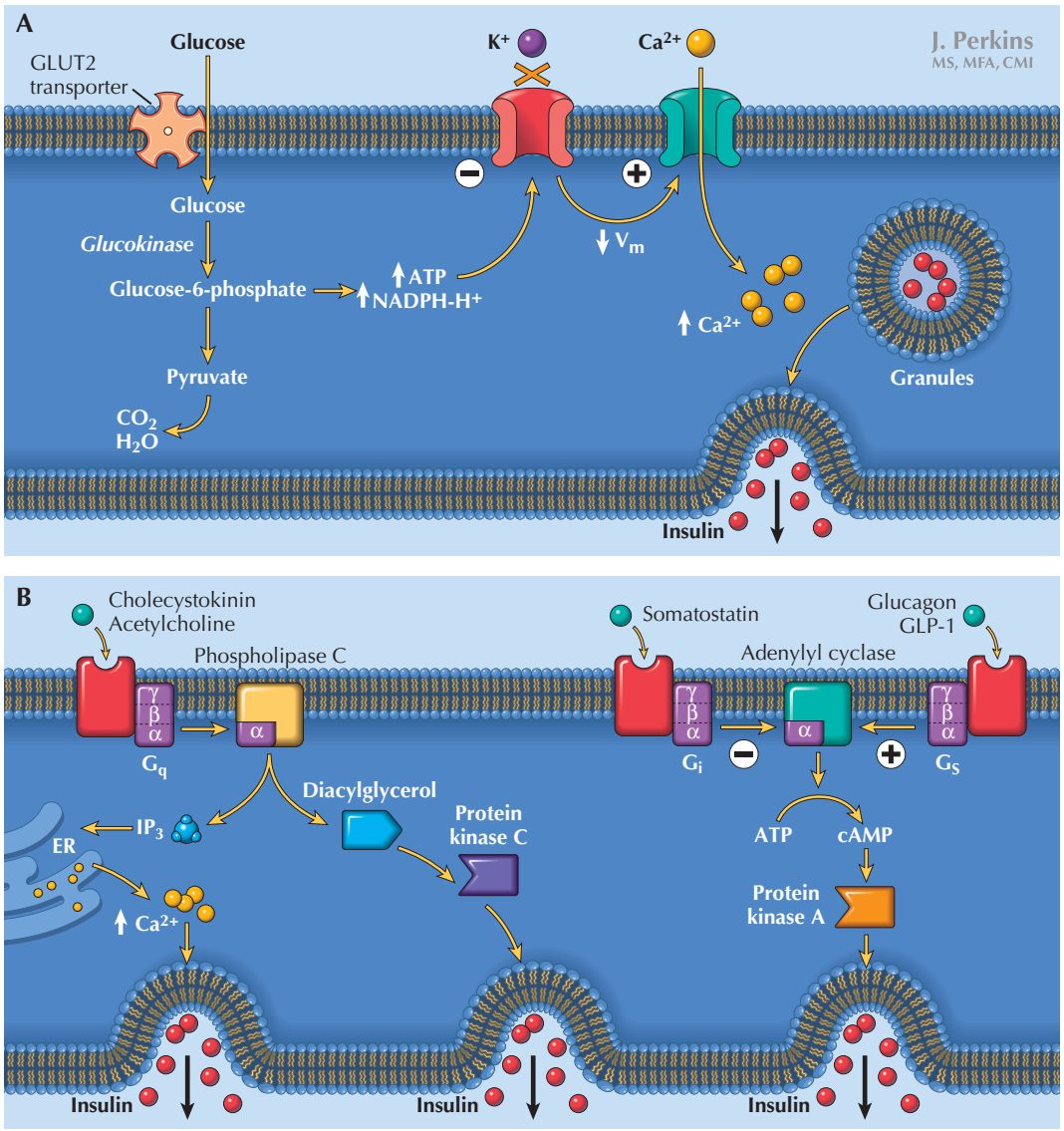


Figure 29.3 **Insulin Synthesis and Release** Glucose is the most important factor regulating insulin synthesis and secretion, although gastrointestinal peptides and local glucagon and somatostatin also contribute to modulation of release. *A* depicts the action of glucose to increase Ca^{2+} influx, which stimulates insulin secretion. *B* illustrates the receptor-mediated *stimulation* of insulin secretion by local glucagon, gut peptides (CCK and GLP-1), and ACh, and *inhibition* of insulin by local somatostatin. ACh, acetylcholine; CCK, cholecystokinin; GLP, glucagon-like peptide.

ACTIONS OF PANCREATIC HORMONES

The primary role of the pancreatic hormones is to maintain an appropriate basal level of glucose in the blood, which in humans is 70 to 90 mg%. To accomplish this, the hormones sequester glucose into cells when there is an influx during feeding—the hypoglycemic effect of insulin—and mobilize glucose out of cells during fasting—the hyperglycemic effect of glucagon. This overall balance is accomplished by the integration of glucose metabolic activity primarily within liver, muscle, and adipose tissues, all orchestrated by the pancreatic hormones.

Insulin

As discussed earlier, elevation of blood glucose level will stimulate insulin secretion. Overall, insulin promotes entry of glucose into cells, synthesis of glycogen stores, and reduced lipolysis (Fig. 29.4). These anabolic functions ensure that nutrients are stored and thus available to tissues between meals (fasting).

Whereas the insulin receptor is expressed on most tissues, the receptor concentration is high in liver, muscle, and adipose tissue. The insulin receptor consists of two extracellular

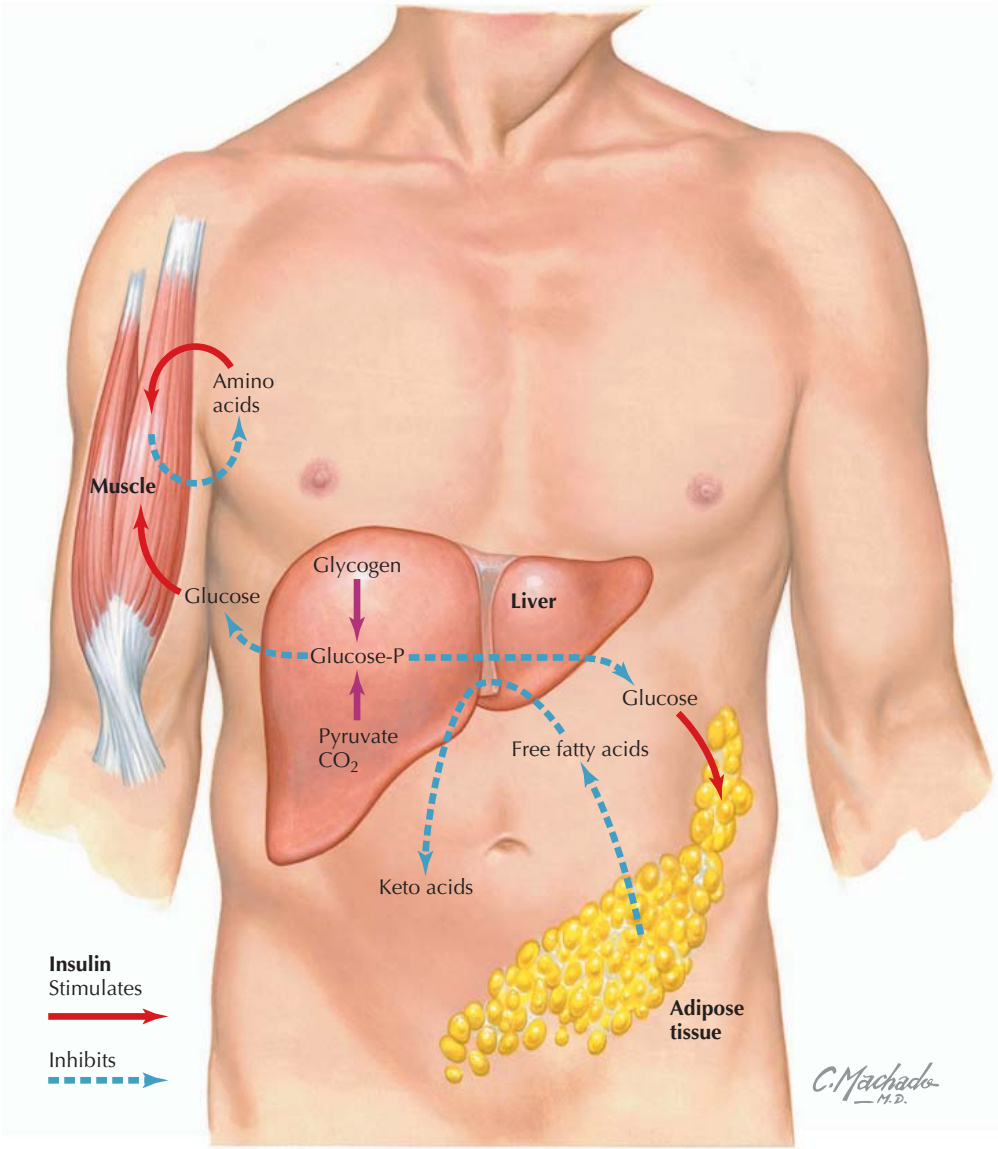


Figure 29.4 Actions of Insulin Insulin is considered a "fuel storage" hormone, and therefore insulin promotes the storage of glucose (as glycogen) and fatty acids (as triglycerides [TG] in adipose tissue). Insulin stimulates the uptake of glucose into cells via GLUT4 transporters, and the glucose is used or stored as glycogen. The major glycogen stores are in muscle and liver. Insulin also stimulates fat synthesis and inhibition of lipolysis in adipose tissue, which maintains stores of TGs and reduces keto acid production. Lastly, insulin stimulates uptake of amino acids into skeletal muscle and storage as protein. The overall result is that insulin decreases plasma glucose, fatty acids, and keto acids.

α-subunits and two β-subunits (transmembrane). Insulin binds to the α-subunits and stimulates phosphorylation of the β-subunits, as well as phosphorylation of other intracellular proteins. Thus, the ability of insulin to phosphorylate various intracellular proteins causes its hypoglycemic effect by:

- Increasing GLUT4 transporters in membranes, allowing efficient glucose entry into cells.
- Increasing glycogen production from excess glucose, to facilitate storage.
- Inhibiting glycogenolysis, to maintain the glycogen storage.
- Inhibiting gluconeogenesis, to prevent production and release of glucose back into the blood.

All of these factors rapidly reduce the blood glucose concentration when insulin is present. Furthermore, insulin also has effects on lipid metabolism by:

- Inhibiting hormone-sensitive lipase in adipose tissue, which decreases lipolysis and reduces the amount of circulating free fatty acids.
- Inhibiting oxidation of fatty acids (especially in the liver), which decreases keto acid formation.

Once the receptor phosphorylation occurs, the entire receptor complex is internalized and then is degraded, stored, or reinserted in the membrane. Insulin also has the ability to down-regulate its receptors through increased degradation and decreased synthesis.

Insulin is a critical metabolic hormone; without it most cells cannot take up glucose. The exception is in brain, liver, and exercising muscle, which have adequate normal glucose uptake due to the presence of GLUT2 transporters (and up-regulation of GLUT4 in exercising muscle). Until the discovery of insulin, type 1 diabetes was a fatal disease.

Glucagon

When blood glucose levels fall during periods of fasting, glucagon is released. In opposition to insulin, glucagon promotes the use of the cellular energy stores, releasing glucose into the blood (Fig. 29.5). The glucagon receptor is a G protein–coupled receptor and is a member of the secretin-glucagon family of receptors, sharing homology with secretin and GIP receptors. Unlike insulin receptors, glucagon receptors are mainly on the cell membranes in the liver and kidney. The liver has stores of glycogen as well as the ability to oxidize fatty acids at a high rate, and glucagon stimulates gluconeogenesis in both organs.

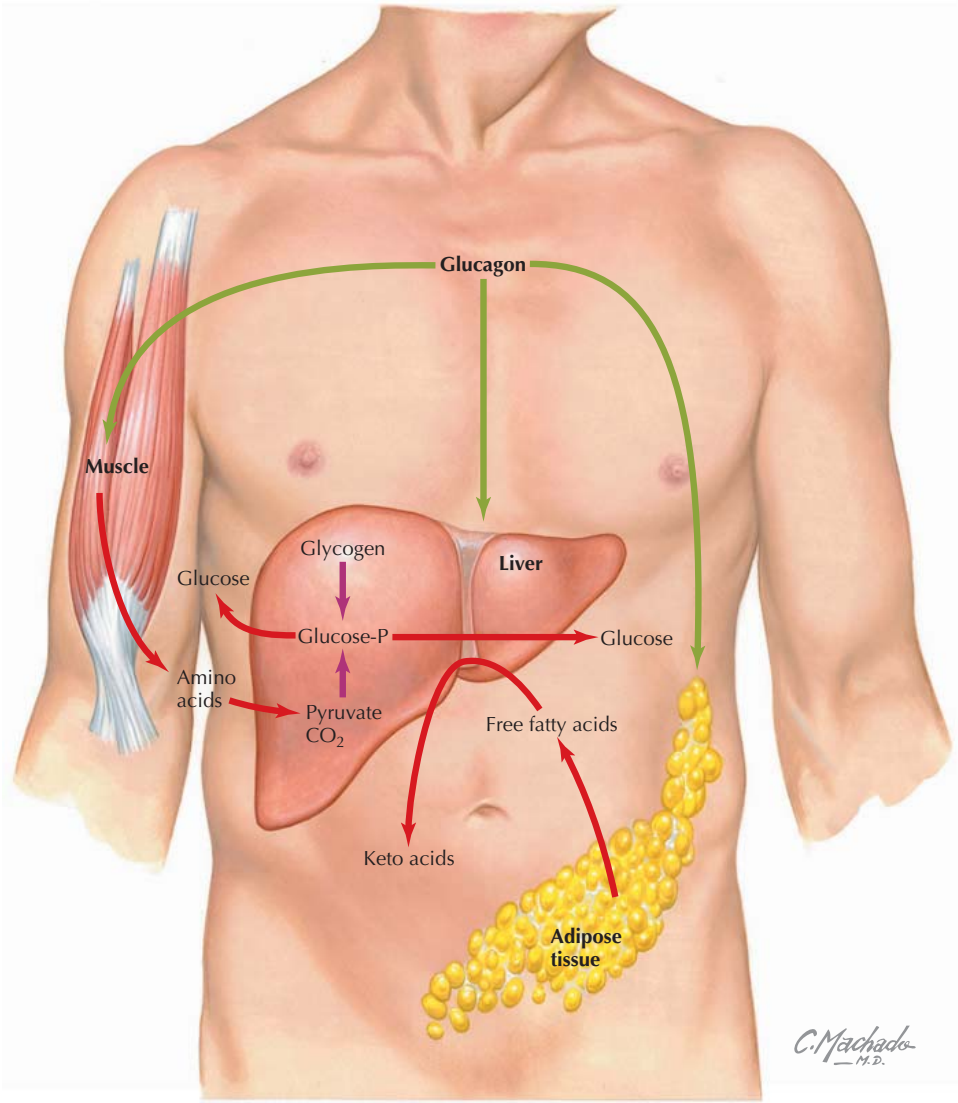


Figure 29.5 Actions of Glucagon Glucagon is considered the "fuel mobilization" hormone, because it breaks down glycogen, protein, and lipids, releasing glucose, amino acids, fatty acids, and keto acids into the blood to serve metabolic demand. Glucagon is stimulated by low blood glucose and promotes glycogenolysis and gluconeogenesis in the liver, increasing blood glucose. Glucagon also stimulates lipolysis and release of fatty acids from adipose tissue, which are oxidized to keto acids in the liver. Lastly, in muscle, glucagon inhibits protein synthesis providing amino acids for conversion to glucose via gluconeogenesis in the liver.

Binding of glucagon with its receptor stimulates cAMP, which then activates kinases that phosphorylate various enzymes. These enzymes contribute to the hyperglycemic effect of glucagon by:

- inhibiting glycolysis
- increasing gluconeogenesis
- increasing glycogenolysis, breaking down glycogen stores, and releasing the glucose into the blood

These factors produce a rapid increase in blood glucose levels. In addition, glucagon has effects on lipid metabolism by increasing β-oxidation of fatty acids.

In normal fasting between meals, there is a balance between glucagon mobilizing glucose and insulin replenishing cellular glucose. However, with prolonged fasting, the glucagon effect predominates, and following depletion of glycogen stores, there are high rates of gluconeogenesis and fatty acid oxidation. The increased oxidation of fatty acids to acetyl coenzyme A (acetyl-CoA) produces **ketone bodies** (acetoacetate and hydroxybutyrate), which can contribute to the acid load of the body (Chapter 20).



Both insulin and glucagon are stimulated by certain **amino acids.** Although this may seem counterintuitive, if a meal is high in protein, but low in carbohydrates, insulin will be increased, stimulating both amino acid and glucose uptake into cells—this lowers the plasma glucose concentrations and would produce hypoglycemia, *if not for the increase in glucagon*. Thus, glucagon is modulating the insulin response.

In addition, although both insulin and glucagon reduce plasma amino acid concentrations by increasing uptake into the hepatocytes, their objectives are different. Insulin promotes peptide synthesis; glucagon uses the amino acids for gluconeogenesis. Thus, amino acids contribute to the mobilization of glucose in the fasted state.

Somatostatin

Somatostatin is secreted in response to all ingested nutrients, as well as glucagon, and is inhibited by insulin. Somatostatin's role in the pancreas is to suppress insulin and glucagon secretion. The apparent disconnection between these actions suggests that somatostatin acts to modulate the secretion of the major hormones.

CLINICAL CORRELATE
Diabetes Mellitus

Diabetes mellitus is a disease of impaired insulin function, resulting in hyperglycemia. There are two classifications of diabetes, which relate to their etiology. **Type 1 diabetes** (T1D) is what used to be called juvenile diabetes or insulin-dependent diabetes mellitus (IDDM); **type 2 diabetes** (T2D) was known as adult-onset diabetes or non–insulin-dependent diabetes mellitus (NIDDM).

T1D is caused by progressive destruction of the pancreatic β-cells by autoimmune attack, eventually resulting in minimal release of insulin and hyperglycemia. The autoimmune (T-lymphocyte) destruction may be caused by viral infection, but the exact causes are not well understood. The onset of hyperglycemia occurs rapidly and usually becomes evident before the person reaches 20 years old. The lack of insulin creates two immediate problems: (1) the glucose cannot enter the cells efficiently, and (2) the lack of glucose in adipose cells decreases fat synthesis and increases fat breakdown, releasing fatty acids into the blood—they get oxidized to ketone bodies by the liver and can result in ketoacidosis (see Chapter 20). Treatment is to stabilize the acid–base balance and start insulin injections. Careful monitoring of blood glucose levels and insulin injections are needed throughout life.

In contrast, **T2D** appears to be a form of **insulin resistance,** resulting from a reduction in the insulin receptors on target tissues. If insulin is not present (T1D), or the receptors are reduced (T2D), the GLUT4 receptors will not be increased at the target cells, and glucose will not efficiently enter the cells and will be elevated in the blood. Although insulin resistance is hereditary, the down-regulation of receptors is also exacerbated with obesity. There are several ethnic groups that have strong genetic predisposition for T2D, including Mexican Americans, Native Americans in the Southwest, and African Americans. There is also a higher incidence of T2D in African American and Native American women than in men of the same ethnicity, suggesting a further role of sex hormones in the insulin resistance. Whether or not the person with T2D is obese or lean, prior to an increase in basal blood glucose levels, there is a loss of sensitivity to insulin so that the β-cells secrete more insulin to maintain euglycemia. Thus, in response to an oral glucose load, the prediabetic person will display up to twice the insulin secretion, and have secretion occur over a prolonged period, compared with a nondiabetic person. As the diabetes becomes more pronounced (basal hyperglycemia), insulin secretion can decrease, further compounding the hyperglycemia. In cases where T2D is precipitated by obesity, reduction in weight and increased exercise can control the hyperglycemia.

Symptoms of uncontrolled hyperglycemia include the following:

- polyuria, from the osmotic effect of glucose in the urine
- polydipsia, to compensate for urinary fluid losses
- polyphagia, because glucose cannot enter the tissues, so the tissues are "starved" and hunger is stimulated
- metabolic ketoacidosis (primarily in T1D)

Long-term uncontrolled or poorly controlled diabetes can lead to or be associated with:

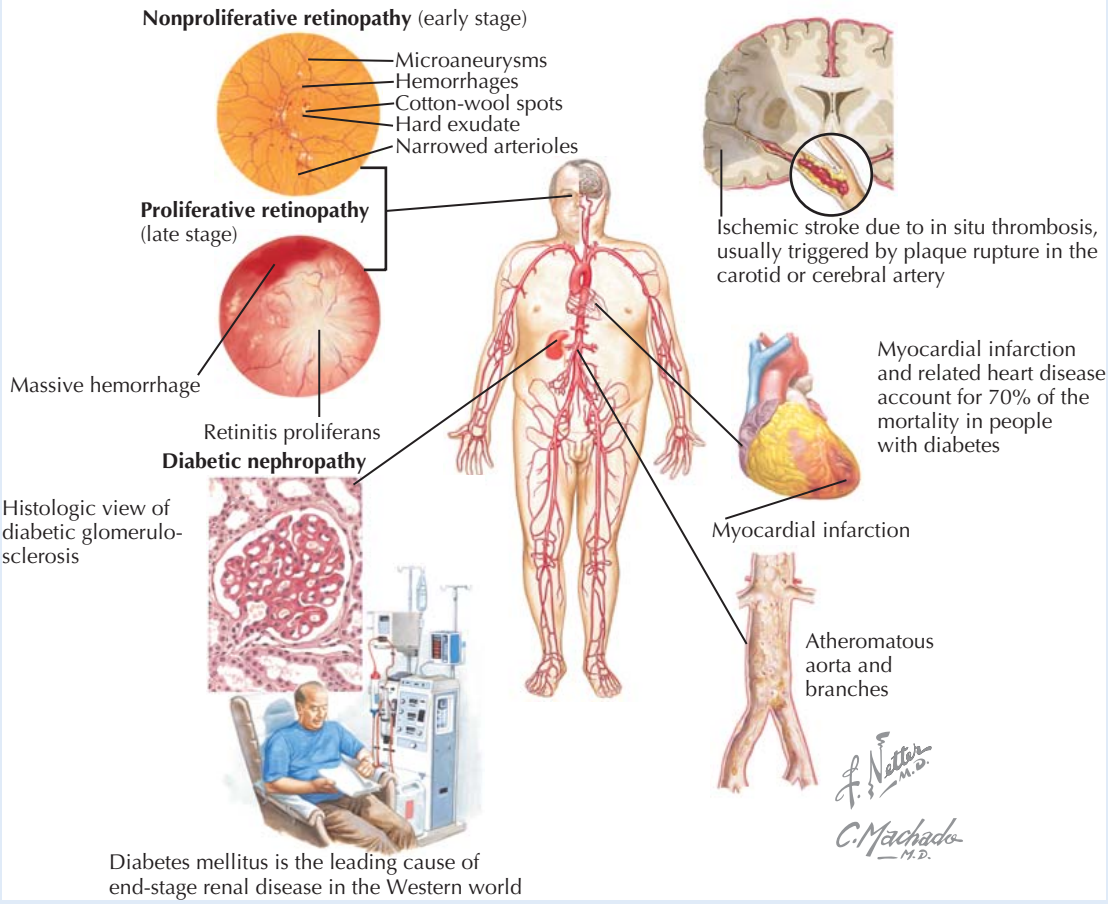
- retinopathy and blindness
- nephropathy and renal failure
- hypertension
- cerebrovascular disease
- peripheral vascular pathology

(Cont'd)

CLINICAL CORRELATE—cont'd

Whereas treatment of T1D is primarily with insulin injection (along with diet and exercise), treatment of T2D includes:

- diet and exercise, because exercise increases GLUT4 transporters in cell membranes
- insulin
- sulfonylureas and meglitinides (taken orally), which increase β-cell insulin secretion
- thiazolidinediones, which increase the sensitivity of muscle and fat tissue to insulin and decrease glucose production in the liver



Microvascular and Macrovascular Complications of Diabetes Vascular complications can occur with either type 1 or type 2 diabetes and include retinopathy (which can lead to blindness), cardiovascular disease, cerebrovascular disease, and diabetic nephropathy. These complications are responsible for the high morbidity in diabetes.

CHAPTER 30 Calcium-Regulating Hormones

OVERVIEW OF CALCIUM HOMEOSTASIS

As previously discussed in Sections 5 and 6, calcium and phosphate homeostasis are closely linked, primarily because of their roles in bone metabolism. Although several hormones regulate both minerals, this chapter will focus on calcium and its regulation. Plasma calcium concentrations are under tight control, with regulatory systems keeping normal levels ~2.4 mEq/L (or 9.4 mg/dL) of ionized calcium. Calcium is critical to a myriad of functions, including contraction of cardiac, skeletal, and smooth muscle; bone mineralization; transmission of nerve impulses; and blood clotting. Thus, alterations in plasma levels (higher or lower) can cause severe consequences (see Clinical Correlates).

Main Areas of Calcium Regulation

The intestines, kidneys, and bone are integral to calcium homeostasis:

- **In the GI tract:** In an average diet, adults ingest ~1000 mg of calcium daily. The intestines absorb one third of this, but because additional calcium is lost through salivary and gastrointestinal (GI) secretions, there is only about 100 to 200 mg of net calcium absorption into the blood. **1,25-dihydroxycholecalciferol** (the active form of **vitamin D**) and **parathyroid hormone** (**PTH**) facilitate intestinal calcium absorption.
- **In the bone:** The majority of the body's calcium (~99%) is stored in the skeletal bone, with much of the unmineralized calcium in the **osteoid,** which is an extracellular pool that is available for transport into bone or plasma. Thus, calcium readily moves between bone and plasma as part of homeostatic regulation. To a great extent, daily plasma calcium homeostasis is regulated through the effect of PTH to stimulate bone resorption, which adds calcium to the plasma. In contrast, vitamin D stimulates entry of calcium into the bone calcium pool, providing substrate for bone deposition.
- **In the kidney:** To maintain balance, because 100 to 200 mg of calcium is absorbed daily, 100 to 200 mg must be excreted by the kidneys. This represents about 2% of the filtered load of calcium to the kidneys, so 98% of the calcium is reabsorbed, in part because of stimulation by PTH.



Bone remodeling is a constant process involving deposition and resorption of minerals from the exchangeable calcium-phosphate mineral pool. In the bone, **osteoblasts** promote bone deposition. **Osteoclasts** are phagocytic cells that promote bone resorption (absorption of minerals out of bone and into the extracellular fluid). The activity of these two cell types are typically in balance, with bone deposition equaling bone resorption. The ability to continually remodel bone is important and contributes to increasing bone strength when bones and muscles are stressed or exercised and keeping up with bone development in growing children. When this remodeling activity decreases, as seen in the elderly, brittle bones can result.

Factors That Alter Plasma Calcium Concentration

Forty percent of plasma calcium is bound to calcium-binding proteins, mainly albumin. About 10% is bound to other anions (including bicarbonate, phosphate, and citrate), so only 50% of the calcium is free (ionized) and biologically active. The plasma provides the calcium reservoir for bone and tissue and is under tight control by calcium regulatory hormones; vitamin D; PTH; and to some extent, calcitonin. Hormone-independent changes in plasma calcium concentration can be caused by:

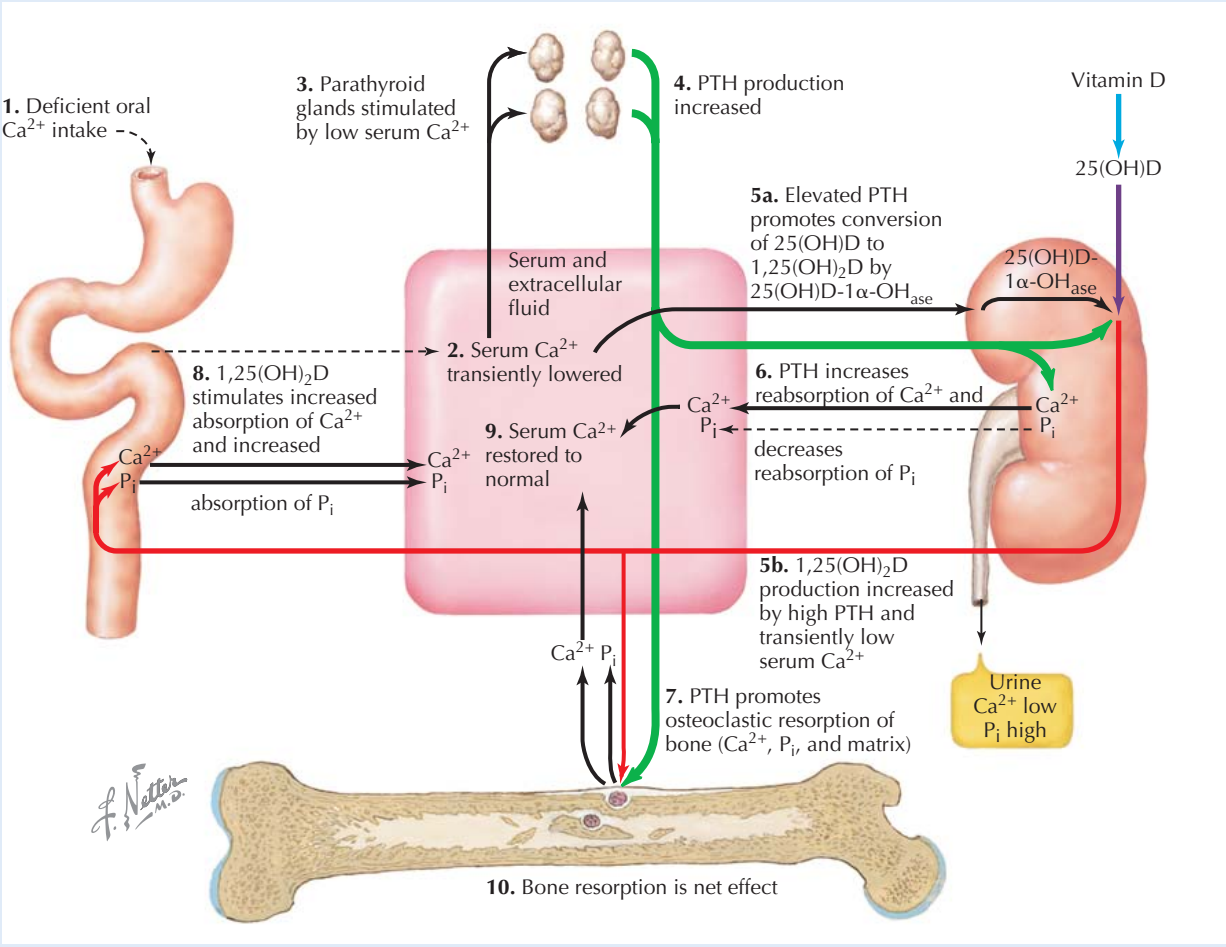
- **Acid–base disorders:** In acidosis, albumin will be used to buffer excess H^+ in exchange for Ca^{2+}, which increases free Ca^{2+} in the plasma; conversely, in alkalosis, H^+ will be released from albumin in exchange for Ca^{2+}, and plasma free Ca^{2+} will increase.
- **Changes in plasma protein concentrations:** Because 40% of plasma calcium is bound to proteins, changes in plasma proteins relate directly to total calcium: Decreases in protein will decrease total calcium, and increases in protein will increase total plasma calcium.
- **Changes in plasma anion concentrations:** This is especially relevant with plasma phosphate levels. If phosphate increases, the calcium-phosphate complexes increase, reducing ionized calcium, and vice versa. Because of this relationship, the hormone PTH regulates both calcium and phosphate.

CLINICAL CORRELATE
Effects of Altered Plasma Calcium Concentration

Hypercalcemia is an increase in plasma calcium concentration, which can have profound effects to depress nervous system activity. A 30% rise in plasma calcium (to ~12 mg/dL) will affect the nervous system, causing symptoms that can include increased urination, constipation, and important neurologic complications resulting in hyporeflexia. If plasma calcium continues to rise (above 15 to 17 mg/dL), coma and death can result.

Conversely, **hypocalcemia,** or decreased plasma calcium, will cause hyperexcitability of sensory and motor nerve and muscle cells, resulting in numbness and tingling, as well as muscle twitching and tetany. **Tetany** can occur when plasma calcium falls about 30% (to ~6 mg/dL), and death can occur if levels fall to 4 mg/dL. Hypocalcemia can result from changes in regulatory hormones, as well as dietary calcium deficiency. The effects of inadequate calcium intake are depicted in the illustration.

Changes in plasma calcium can be manifested in disorders involving parathyroid hormone and vitamin D (see "Calcium-Related Pathophysiology" Clinical Correlate).



Dietary Calcium Deficiency Inadequate dietary calcium intake *(1)* reduces plasma calcium concentration *(2),* which stimulates parathyroid hormone (PTH) secretion *(3 and 4).* PTH increases the renal production of active vitamin D *(5)* (which increases gut absorption of calcium) *(8),* increases renal calcium reabsorption and decreases renal phosphate reabsorption *(6),* and increases bone resorption of calcium and phosphate *(7).* All of these mechanisms serve to increase the plasma calcium concentration to normal *(9).* When there is a sustained calcium deficiency, the plasma calcium is maintained at a cost of severe bone demineralization *(10).*

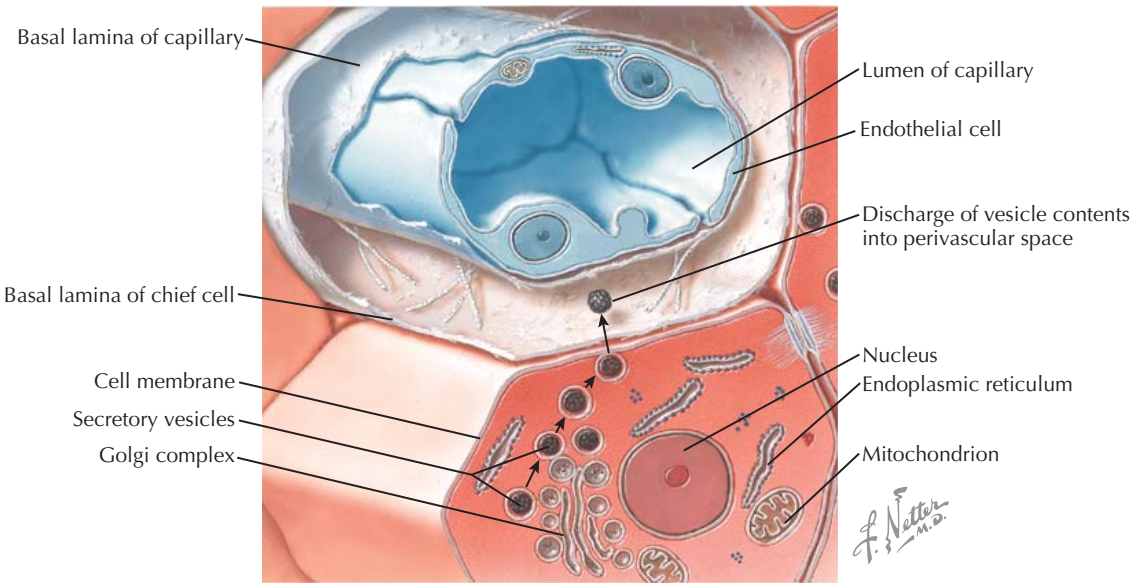


Figure 30.1 Parathyroid Hormone Secretion Parathyroid hormone is synthesized in the chief cells of the parathyroid glands. The active hormone is packaged in vesicles and stored in the cytoplasm until released. PTH secretion is stimulated by small decreases in plasma calcium levels and provides rapid mobilization of calcium into the extracellular fluid.

SYNTHESIS AND ACTIONS OF CALCIUM-REGULATING HORMONES

Parathyroid Hormone

Synthesis of Parathyroid Hormone

Parathyroid hormone (**PTH**) is the primary hormone regulating plasma calcium concentration. PTH is synthesized by the chief cells of the parathyroid glands as a 110 amino acid preprohormone (see Fig. 27.1). It is then cleaved to a prohormone in the endoplasmic reticulum and to the active 84 amino acid peptide hormone in the Golgi apparatus. It is then packaged into secretory vesicles in the cytoplasm, and the vesicles stored until needed (Fig. 30.1).

Actions of Parathyroid Hormone

The hormone is continually synthesized, and there is constant low-level release of PTH into the blood. In response to small decreases in ionized calcium in the plasma, additional PTH is released into the blood and acts at the intestines, bone, and kidney to restore plasma calcium to normal levels (Fig. 30.2). PTH stimulates cAMP through its G protein–coupled receptors:

- **At the kidney:** (1) to increase calcium reabsorption at the *distal tubule,* and to inhibit phosphate reabsorption at both the proximal and distal tubules; and (2) to increase the synthesis of 1,25-dihydroxycholecalciferol, the active metabolite of vitamin D. This conversion is critical to producing active vitamin D, and loss of PTH or loss of kidney function can impair vitamin D metabolism and function. The actions at the kidney are rapid and are a main avenue for the rapid restoration of plasma calcium levels.
- **At the bone:** To increase bone resorption, freeing calcium into the blood. This occurs by **osteocytic osteolysis,** which rapidly (within 1 to 2 hours) mobilizes calcium from the unmineralized calcium phosphate pool, and by **osteoclastic osteolysis,** which breaks down mineralized bone over about 12 hours. In response to more severe, prolonged decreases in plasma calcium (days to weeks), PTH can stimulate the proliferation of osteoclasts, to further break down mineralized bone. The end result is increased calcium and phosphate in the plasma, at the expense of loss of mineralization of bone.

The chief cells of the parathyroid gland have calcium sensors, which monitor plasma calcium concentration. This allows rapid response when plasma calcium decreases, and PTH can quickly mobilize calcium from bone and stimulate vitamin D production. Thus, PTH is crucial to the maintenance of calcium homeostasis.



Parathyroid hormone–related protein (**PTHrp**) is a protein that mimics the calcium-mobilizing effects of PTH. It is present in a variety of tissues including smooth muscle, breast, and the central nervous system and is believed to act in a paracrine manner. Although its normal actions are still being investigated, PTHrp is also secreted from certain tumors, such as breast cancers and renal cell and squamous cell carcinomas.

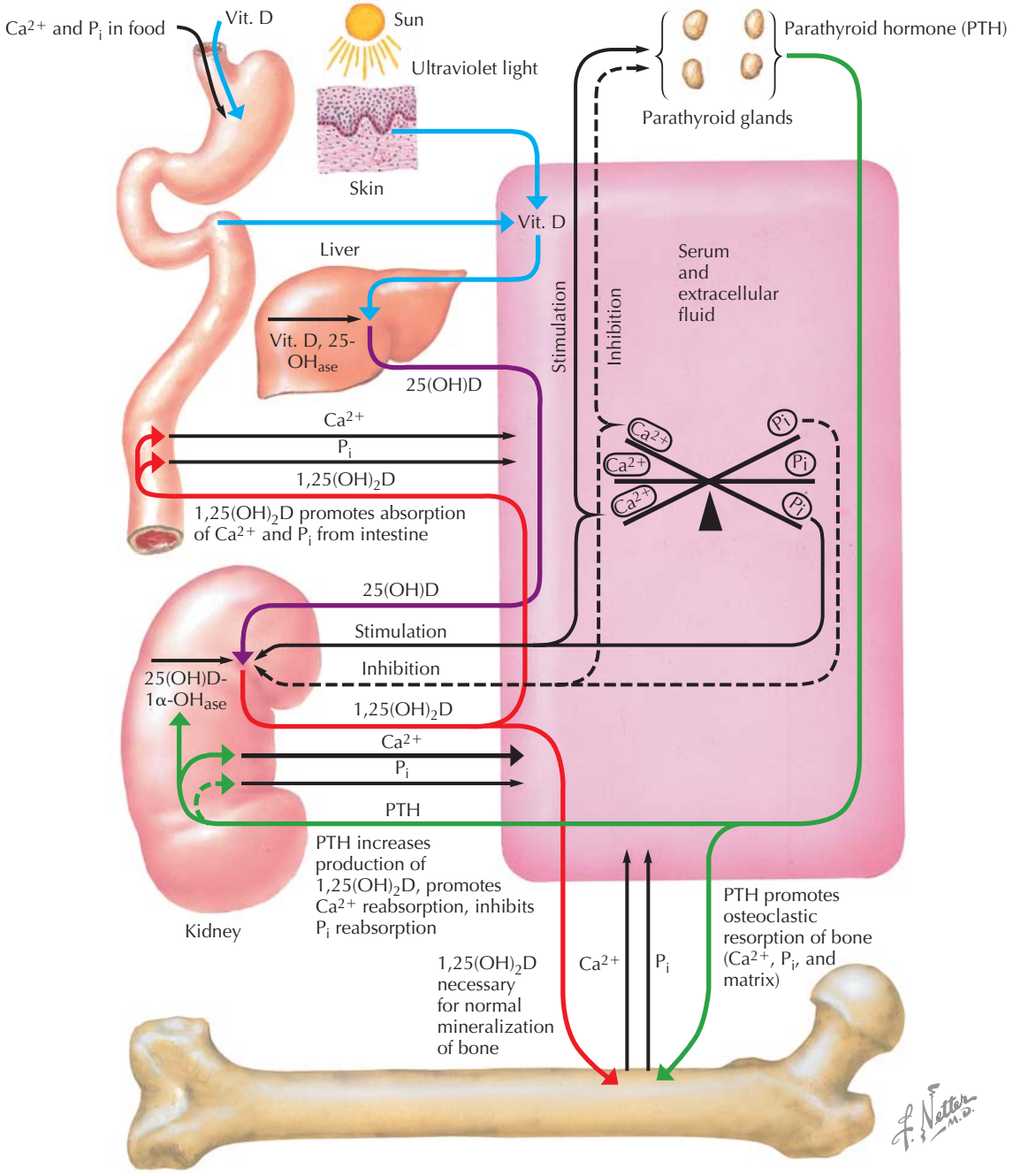


Figure 30.2 Parathyroid Hormone and Vitamin D Actions on Plasma Calcium Concentrations Parathyroid hormone (PTH) is secreted from the parathyroid glands in response to a decrease in plasma ionized Ca^{2+}. PTH acts rapidly (1) on bone to cause resorption and increase plasma Ca^{2+}; and (2) on the kidney to increase Ca^{2+} reabsorption and decrease phosphate reabsorption *and* increase production of active vitamin D. The increase in vitamin D increases Ca^{2+} absorption in the gut and promotes bone mineralization. Overall, the rapid effects of PTH increase Ca^{2+} in the blood, restoring homeostasis.

Vitamin D

Synthesis of Vitamin D

Vitamin D, or **cholecalciferol,** is a sterol that enters the blood and extracellular fluid (ECF) from dietary sources and from the action of ultraviolet light on 7-dehydroxycholesterol in skin cells. The initial form of vitamin D is converted to 25-hydroxycholecalciferol in the liver and then undergoes final hydroxylation to the active form, **1,25- dihydroxycholecalciferol,** in the kidneys. Active vitamin D is bound to plasma proteins and acts to increase plasma calcium concentration and promote bone mineralization.

Actions of Vitamin D

When plasma calcium levels decrease, PTH increases and stimulates renal 1-α-hydroxylase to increase formation of active vitamin D. The PTH will also increase resorption of calcium-phosphate from bone and increase renal calcium reabsorption, with the total effect of increasing plasma calcium levels. Active vitamin D binds to its intracellular steroid receptor and acts:

- **At the small intestine:** To increase calcium absorption by increasing apical **calbindin** (Ca^{2+}-binding proteins) and increasing the basolateral Ca^{2+} ATPases. This enhances intestinal absorption of calcium. Vitamin D also increases phosphate absorption, and excess plasma phosphate is excreted by the kidneys (by PTH action).
- **At the bone:** To increase bone remodeling and mineralization through effects on both osteoblasts and osteoclasts. At high concentrations, vitamin D can cause bone demineralization.

The synthesis and actions of vitamin D take time, but they act to increase the supply of calcium from the diet. Thus, whereas in the short-term plasma calcium levels are regulated by PTH, the activation of vitamin D by PTH is important in long-term calcium homeostasis. When calcium levels are stabilized, calcium can be restored to the bone by the vitamin D.

Active vitamin D levels in the blood are tightly regulated by feedback control. Under normal conditions, 25-hydroxycholecalciferol concentrations in the plasma will remain constant, despite large increases in dietary vitamin D intake. In addition, the 25-hydroxycholecalciferol form can be stored in the liver for several months and released and converted to active vitamin D when needed, allowing another layer of regulation for plasma levels of vitamin D. This overall control of vitamin D levels is important, because overproduction of active vitamin D can actually cause bone resorption, instead of deposition.

Calcitonin

Calcitonin is a 32 amino acid peptide hormone that is produced in the parafollicular cells of the thyroid gland, and although it appears to have effects on calcium handling, it does not contribute to the rapid regulation of calcium. It is released in response to elevated plasma calcium levels and acts on G protein–coupled receptors:

- **At the kidney:** To increase both calcium and phosphate excretion.
- **At the bone:** To decrease bone resorption by reducing osteoclastic activity.

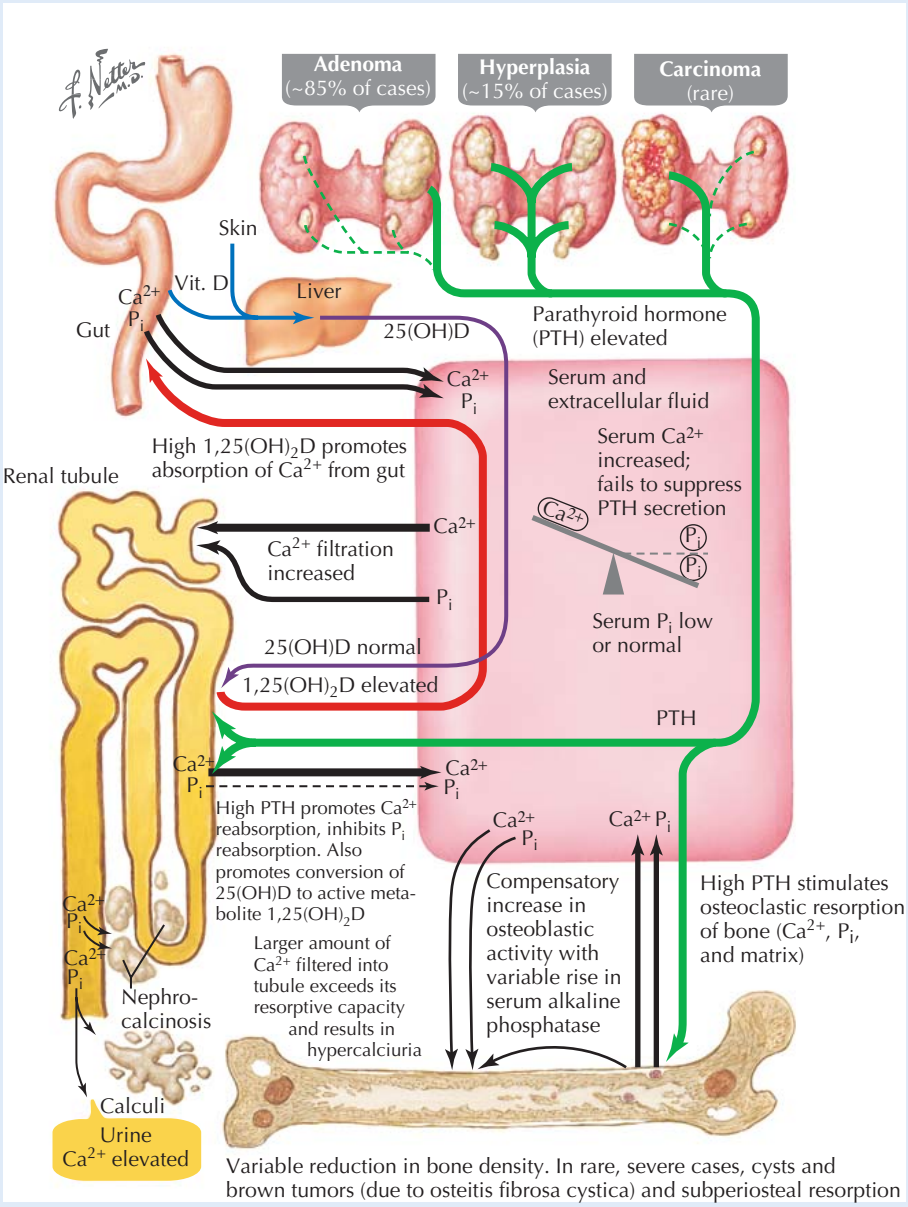
It is not clear whether the physiologic effects of calcitonin are important in humans, because removal of the parafollicular cells has no dramatic effect on calcium homeostasis.

CLINICAL CORRELATE
Calcium-Related Pathophysiology: Hyperparathyroidism

Hyperparathyroidism is associated with excessive PTH secretion and results in hypercalcemia (high plasma calcium) and hypophosphatemia (low plasma phosphate).

Primary hyperparathyroidism is usually caused by parathyroid tumors that produce PTH but do not have feedback regulation. The elevated PTH increases the renal activation of vitamin D; increases plasma calcium through increasing intestinal absorption, kidney reabsorption, and bone resorption; and decreases plasma phosphate by reducing renal phosphate reabsorption. Although renal calcium reabsorption is elevated, the significantly increased filtered calcium load results in elevated urinary calcium and phosphate excretion, increasing the chance of kidney stone formation. Though many patients are asymptomatic, the elevation in plasma calcium can cause some or all of the following "stones," "bones," "groans," and "moans": kidney stones from calcium-phosphate and calcium-oxalate formation in urine, bone pain from excessive resorption, groans from constipation due to reduced fecal calcium, and moans from generally not feeling well and fatigue. Treatment is surgical removal of the tumor.

Secondary hyperparathyroidism is caused in response to the primary problem of low plasma calcium levels. In secondary hyperparathyroidism, the low plasma calcium levels are usually caused by vitamin D deficiency and/or chronic renal failure, and the parathyroid glands secrete PTH to correct this problem. Thus, PTH levels will be high, but plasma calcium will be low or normal. Treatment is with vitamin D, when indicated.

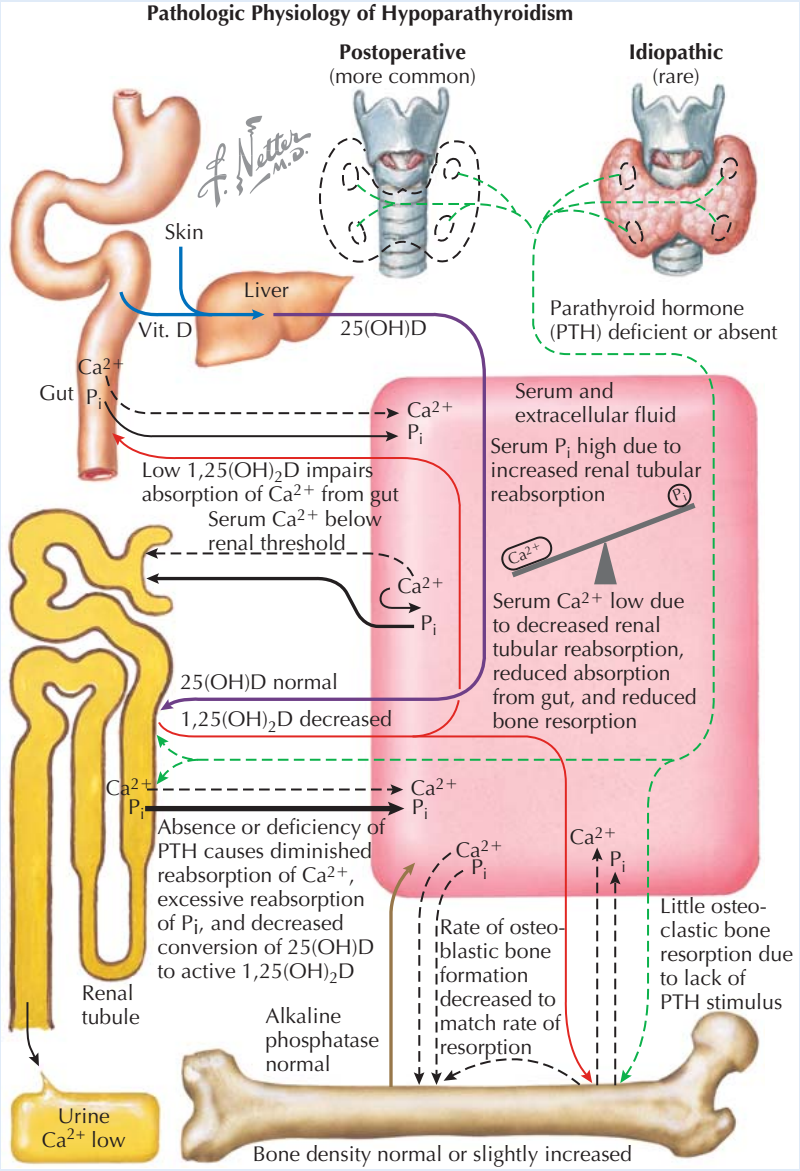


Pathophysiology of Hyperparathyroidism Most cases of hyperparathyroidism arise from parathyroid tumors that cause hypersecretion of parathyroid hormone (PTH). The elevated PTH increases bone resorption, renal calcium reabsorption, and active vitamin D production (which increases intestinal calcium absorption). This causes hypercalcemia, which can result in multiple symptoms ("stones," "bones," "groans," and "moans").

CLINICAL CORRELATE
Calcium-Related Pathophysiology: Hypoparathyroidism

Hypoparathyroidism is a deficiency of PTH, and results in hypocalcemia (low plasma calcium) and hyperphosphatemia (high plasma phosphate). This is a fairly common occurrence following thyroid or parathyroid surgery, and the decreased extracellular fluid calcium increases the excitability of sensory and motor neurons and muscle cells. This excitability can cause sensory effects such as tingling or numbness in the lips and fingers, as well as motor effects including cramping and twitching. Severe hypocalcemia can lead to tetanic muscle spasms and seizures, so treatment is initiated when first symptoms are noted. Initial treatment can include intravenous calcium (if plasma levels are dangerously low), followed by oral calcium supplements with active vitamin D. Untreated, chronic hypoparathyroidism can result in cataracts, alopecia (hair loss), and weakened tooth enamel, in addition to the muscle spasms and seizures. Although rare, sustained low (4 mg/dL) plasma calcium concentrations can lead to coma and death. If life-threatening, treatment is with intravenous calcium; otherwise, active vitamin D and oral calcium is effective in maintaining plasma calcium levels.

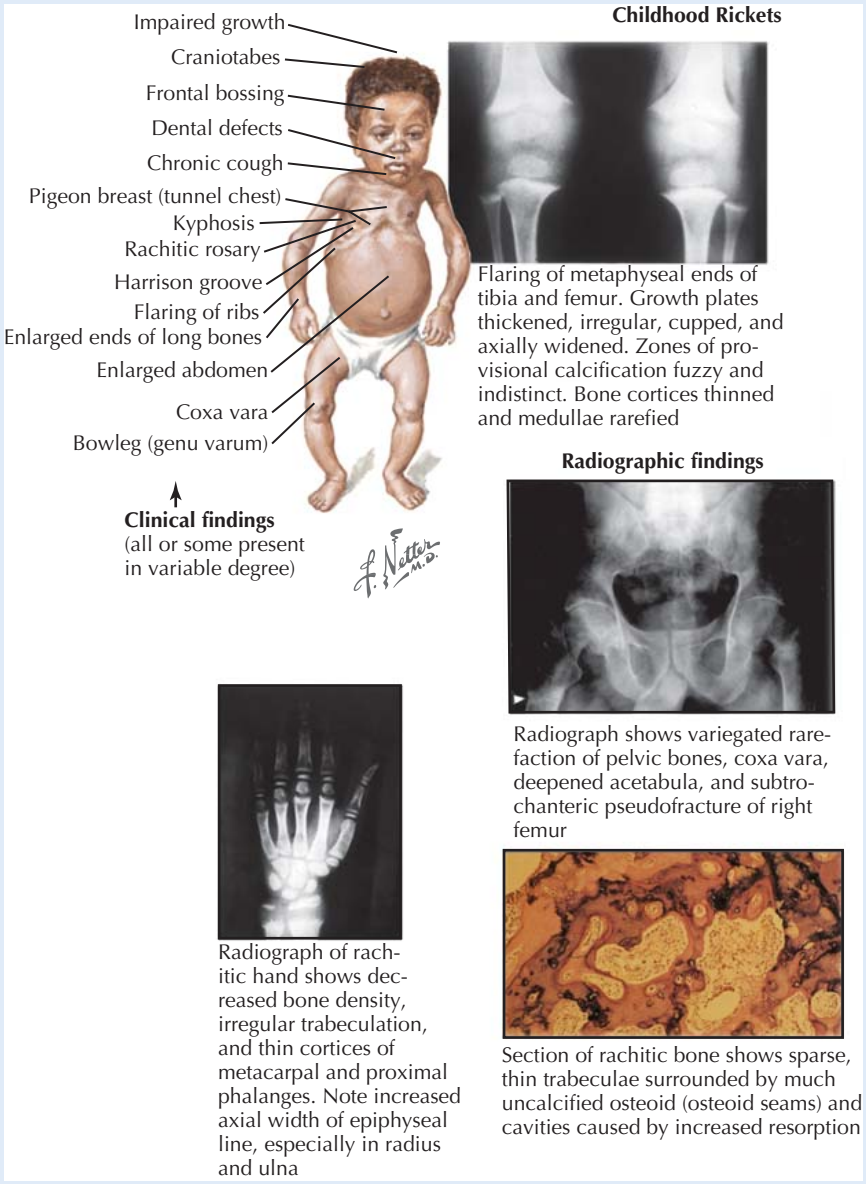
Pseudohypoparathyroidism has the same overall effect as hypoparathyroidism, reducing plasma calcium and increasing plasma phosphate—however, the cause is a primary defect in the G_s protein of the PTH receptors in bone and kidney. Although PTH can bind, the cAMP-pathway cannot be activated, and thus while PTH levels are *elevated*, renal and bone calcium transport is not activated.



Pathophysiology of Hypoparathyroidism Hypoparathyroidism is usually a result of thyroid or parathyroid surgery, and the lack of parathyroid hormone reduces the formation of active vitamin D, decreases renal calcium reabsorption, and alters bone resorption activity. Hypocalcemia develops, and the low plasma calcium levels increase neuronal and muscle cell excitation, causing twitching, cramping, and in extreme cases tetany.

CLINICAL CORRELATE
Calcium-Related Pathophysiology: Vitamin D Deficiency

Vitamin D deficiency is rarely found in areas where vitamin D is supplemented in the diet and there is regular exposure to sunlight. **Rickets** is a disease caused by insufficient vitamin D during childhood. The lack of vitamin D prevents adequate calcium and phosphate for bone mineralization, resulting in stunted growth and malformed bones. In adults, prolonged vitamin D deficiency will decrease new bone mineralization, resulting in bone deformation (**osteomalacia**). This is especially evident in weight-bearing bones, and can cause severe bow-legged stance. Although it is rare to see this in adults, it can result from chronic steatorrhea, because vitamin D is fat-soluble, and most will be lost in the feces. Renal rickets is a specific form of osteomalacia caused by chronic renal damage. This limits the production of vitamin D, because the kidney tissue is either damaged or absent, and PTH cannot convert 25-hydroxycholecalciferol to active 1,25-dihydroxycholecalciferol.



Rickets The main manifestation of vitamin D deficiency is in bone mineralization. As depicted in the illustration, in children, this results in rickets. In adults, vitamin D deficiency leads to osteomalacia.

CHAPTER 31 Hormones of the Reproductive System

Sex hormones are involved in fetal development and sexual differentiation, pubertal somatic changes, and reproductive physiology. Although the term **sex hormone** refers to sex steroids (primarily estrogen, progesterone, testosterone, and adrenal androgens), a wider array of hypothalamic, pituitary, gonadal, and placental hormones have important roles in the reproductive system. Endocrine problems involving the reproductive system are relatively common. For example, infertility, often a result of an endocrine abnormality, affects approximately 10% of the population.



Synthesis and secretion of testosterone by the fetal testes is stimulated initially by a placental hormone known as **chorionic gonadotropin,** the same hormone that is essential in maintaining maternal ovarian progesterone production during pregnancy. After the first trimester, fetal pituitary **luteinizing hormone** (**LH**) is required to maintain androgen production in a male fetus. Similarly, in a female fetus, estrogens are secreted by the ovaries in response to pituitary LH. After birth, the pituitary gonadotrophs become quiescent until puberty. The role of gonadotropins in pubertal development, reproductive function, and pregnancy is discussed below.

FETAL DEVELOPMENT OF THE REPRODUCTIVE ORGANS AND DIFFERENTIATION OF GENITALIA

An individual's sex can be characterized in terms of genetics (the male XY genotype vs. the female XX genotype), gonads (testes vs. ovaries), and phenotype (external appearance of "maleness" vs. "femaleness"). Although genetic sex is determined at the time of conception, the fetus remains undifferentiated in terms of gonadal sex for the first 5 weeks of development (Fig. 31.1).

Development of Gonadal Sex

Under the control of the **SRY gene** on the Y chromosome, the undifferentiated gonads develop into **testes;** full development of gonadal sex requires several other genes on the Y chromosome and various autosomal chromosomes. By 8 to 9 weeks of development, the **Leydig cells** of the testes begin to secrete **testosterone.** Development of **ovaries,** on the other hand, begins at week 9 of gestation and requires the presence of two X chromosomes. Germ cells within the ovaries give rise to **oogonia,** which proliferate and soon enter meiosis, leading to the **primary oocyte stage,** at which meiosis is arrested until activated during sexual cycles after puberty. The developing ovary produces the **estrogens.**

During the undifferentiated stage of fetal development, two pairs of ducts, the **wolffian ducts** and the **müllerian ducts,** develop in both sexes (see Fig. 31.1). Under the influence of testosterone, the wolffian ducts develop into male structures including the epididymis, vas deferens, and seminal vesicles. Meanwhile, **müllerian inhibitory factor,** a dimeric glycoprotein hormone secreted by the **Sertoli cells** of the fetal testes, causes regression of the müllerian ducts. The combination of these two series of events leads to the development of the male system. In the absence of testes and their secretions, the müllerian ducts persist and develop, forming the fallopian tubes, uterus, and the upper vagina, whereas the wolffian ducts degenerate.

Development of Genital Sex

The external genitalia are also present in an undifferentiated form during early development (Fig. 31.2). Differentiation begins at 9 to 10 weeks of gestation. In the absence of androgens, female genitalia are produced. In the male fetus, testosterone produced by the testes and secreted into the circulation is converted to **dihydrotestosterone** (**DHT**) in the primitive genital structures; DHT stimulates the formation of the male genitalia (conversion of testosterone to DHT is not involved in the actions of testosterone on wolffian duct differentiation).

Phenotypic Sex

Phenotypic sex is the outward appearance of maleness or femaleness. Whereas genetic sex is based on the presence of the XY or XX genotype, and gonadal sex is determined by specific genes on the X chromosome as well as several autosomal genes, phenotypic sex develops in response to gonadal hormones. In the presence of testosterone, male genitalia develop; in its absence, the female form of genitalia prevail. Other phenotypic characteristics of femaleness are promoted

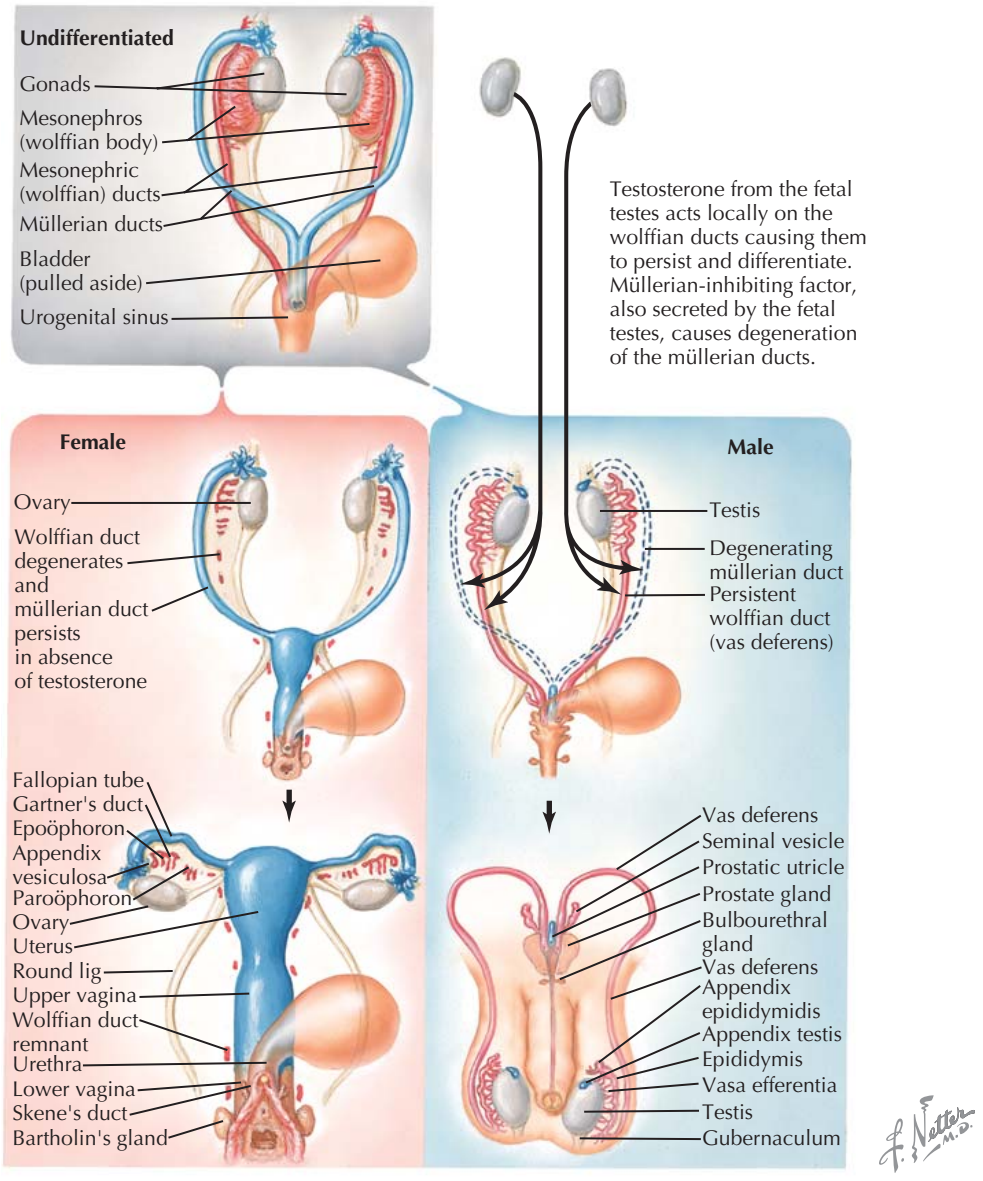


Figure 31.1 Gonad and Genital Duct Formation The undifferentiated gonads and ducts of the early embryo differentiate into the male or female gonads and duct systems under the influence of various products encoded by the X and Y chromosomes. Notably, a product of the SRY gene of the Y chromosome results in differentiation of the gonads into testes. Production of testosterone by the testes results in persistence and differentiation of the wolffian ducts. Müllerian-inhibiting factor secreted by the testes causes müllerian duct degeneration. In the female fetus, in the absence of testosterone the gonads develop into ovaries and the wolffian ducts degenerate.

by the absence of androgens and presence of estrogen. In androgen insensitivity syndrome, for example, androgen receptors are absent, and the female phenotype prevails.

PUBERTY

Beginning a year or two before the onset of puberty, production of androgens by the zona reticularis of the adrenal glands commences. The major adrenal androgens are **dehydroepiandrosterone** (DHEA) and **androstenedione.** This event is known as **adrenarche** and is distinct from puberty. Secretion of adrenal androgens results in:

- appearance of pubic and axillary hair
- adult body odor
- acne and oiliness of skin

Hormonal Regulation of Puberty

The actual process of **puberty** is associated with maturation of the hypothalamus and anterior pituitary gland. The hypo-

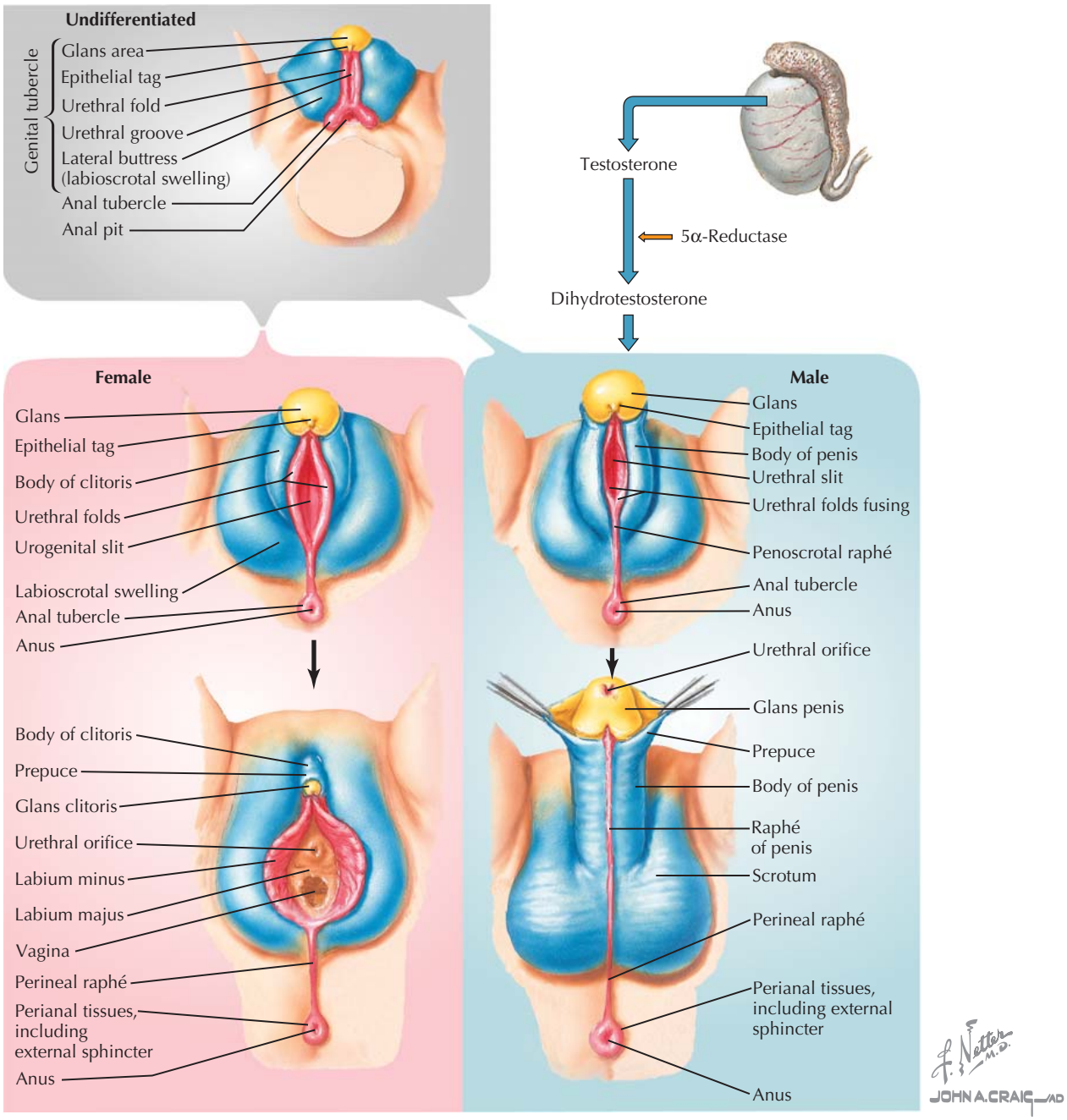


Figure 31.2 **Differentiation of the External Genitalia** In the absence of testosterone, the undifferentiated external genitalia develop into the female structures. Testosterone, after conversion to dihydrotestosterone, stimulates the formation of male external genitalia from the undifferentiated structures. Homologies between male and female genital structures are color-coded.

thalamic secretion of the decapeptide **gonadotropin-releasing hormone** (**GnRH**) increases and becomes pulsatile, as the hypothalamus becomes less sensitive to negative feedback by sex steroids. Thus, a pulsatile pituitary secretion of the gonadotropins **follicle-stimulating hormone** (**FSH**) and **luteinizing hormone** (**LH**) is established, stimulating gonadal maturation and sex hormone synthesis. **Estradiol** (the major estrogen or "estrogenic hormone") and **progesterone** are the predominant sex hormones produced in women, whereas **testosterone** is the main sex steroid of men (the details of the hypothalamic-pituitary-gonadal axis are discussed later in the chapter). Adrenal androgens continue to have a physiological role in puberty and beyond in women (effects of adrenal androgens are overshadowed by those of testosterone in men). In males, some testosterone is converted to estradiol, and the latter hormone has important functions in male puberty. The

The pubertal growth spurt typically begins earlier in girls than in boys. Previously, it was believed that androgens (testosterone and adrenal androgens) were responsible for the rapid increase in height. Recent studies, however, have demonstrated that although testosterone increases bone mass and density, estradiol is the hormone primarily responsible for the growth spurt in both sexes. Estradiol stimulates long bone growth but also promotes closure of the growth plates. Females, who enter puberty earlier, attain less adult height than males.

physiological and anatomical changes occurring at puberty are the result of various hormone actions and include:

- Gonadal maturation and sex steroid synthesis and release, as a result of increased gonadotropin secretion.
- Maturation of other sex organs and genitalia, mainly stimulated by estradiol in females and testosterone in males.
- Development of secondary sexual characteristics (characteristics of "maleness" or "femaleness" not directly associated with reproduction). These include gender-specific changes in distribution of body and facial hair, breast development, body fat distribution, muscle development, and pitch of voice. Estrogen is primarily responsible for female characteristics, whereas testosterone is the major stimulus for development of male secondary sexual characteristics.
- The linear growth spurt. This event is attributed mainly to estradiol in both sexes; estrogenic hormones cause accelerated growth of long bones but also promote the eventual closure of the epiphyseal plates of these bones, and thus the end of growth in height.

THE MENSTRUAL CYCLE AND FEMALE REPRODUCTIVE ENDOCRINOLOGY

In late puberty, adolescent girls experience their first menstruation, an event known as **menarche,** and **menstrual cycles** commence, continuing until **menopause** (unless interrupted by pregnancy). These cycles last an average of 28 days and consist of three phases (Fig. 31.3):

- The **follicular phase,** characterized by proliferation of the endometrium of the uterus and development of ovarian follicles.
- The **ovulatory phase,** during which one follicle that has fully matured ruptures and releases an ovum.
- The **luteal phase,** characterized by transformation of follicular cells into a **corpus luteum** and further proliferation of the endometrium. Unless implantation of a fertilized ovum takes place, the corpus luteum regresses and menses follows, during which the proliferated endothelium is sloughed off and bleeding occurs for a period of 3 to 5 days.

Follicular Phase

The development of follicles within the ovary is illustrated in Figure 31.4. During each cycle, after the onset of menses (by convention, "day 1" of the cycle), several primordial ovarian follicles begin to undergo further development under the influence of FSH, and hence, the term **follicular phase** is used to describe the first half of the cycle. Within the developing follicles, **theca interna** cells secrete **androgens,** which are converted to **estradiol** by the **granulosa cells** of the follicles. This conversion is stimulated by LH. Estradiol causes endometrial proliferation, as well as development of glands and growth of spiral arteries within the endometrium, in preparation for possible implantation of a fertilized egg. For this reason, the follicular phase is also called the **proliferative phase.** In addition, estradiol promotes secretion of watery cervical mucus, through which sperm can enter the uterus. Ultimately, one of the developing follicles predominates and becomes a **mature follicle** (graafian follicle), and the others regress.

Ovulatory Phase

Estradiol exerts negative feedback on the hypothalamic secretion of GnRH and anterior pituitary secretion of FSH (LH is not suppressed during this period) through much of the follicular phase. Additionally, granulosa cells of developing follicles secrete a peptide hormone, **inhibin,** which has negative feedback effects specifically on FSH. Toward the end of the follicular phase, estradiol rises to a level at which **positive feedback** is triggered (Fig. 31.5). A surge in LH, and to a lesser extent, FSH, takes place and produces **ovulation** at midcycle, releasing a mature ovum, which is carried by ciliary action into the fallopian tube (see Fig. 31.3). Interestingly, a mature ovum is produced in alternating ovaries from month-to-month, but if a woman has only one functional ovary, that one ovary will normally produce a mature ovum monthly.

Luteal Phase

In the ensuing luteal phase of the cycle, the ruptured follicle undergoes involution, forming the **corpus luteum.** Progesterone and inhibin production by the corpus luteum rise, as does estradiol production to a lesser degree. Estrogens, progesterone, and inhibin now contribute to negative feedback on the hypothalamus and anterior pituitary (see Fig. 31.5). Further proliferative and secretory changes take place in the endometrium, stimulated by progesterone; the luteal phase is also called the **secretory phase** for this reason. In the cervix, secretions become thicker, making passage of sperm into the uterus more difficult. Conception must take place within a day or two of ovulation, because the ovum is viable for only a short period after release from the graafian follicle (normally, conception takes place while the egg is in transport within a fallopian tube). Toward the end of the luteal phase, unless pregnancy occurs, steroid and inhibin secretion fall, and menses results.

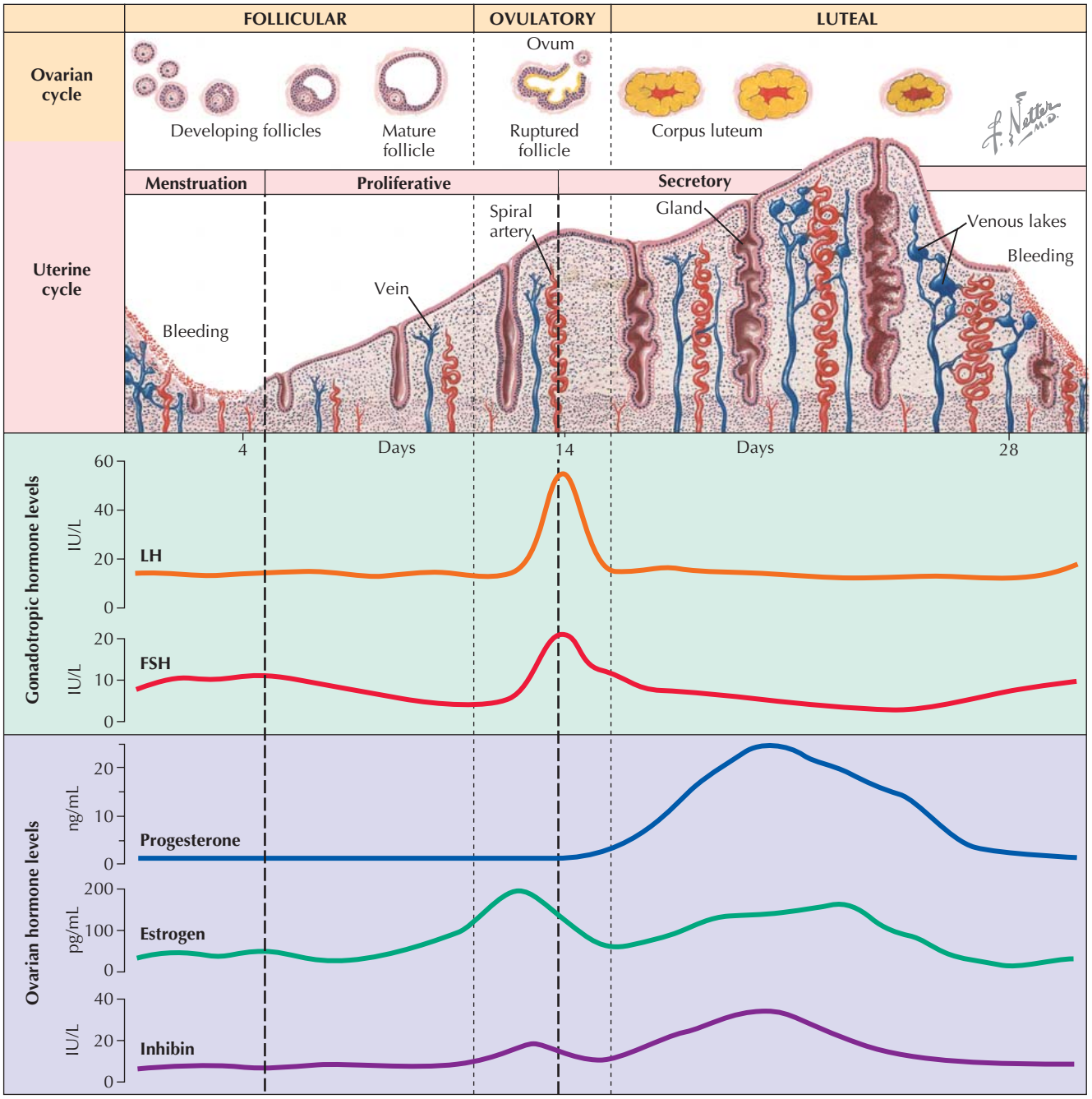


Figure 31.3 Menstrual Cycle During the female menstrual cycle, changes take place in the ovaries and uterus, under the control of the hypothalamus and anterior pituitary gland. During the follicular phase, several primary follicles undergo further development in response to FSH and synthesize androgens, which are converted to estradiol under the influence of LH. Ultimately, one follicle fully matures and the others regress. The uterine endometrium proliferates in response to estradiol. Near midcyle, estradiol rises to a level that initiates *positive feedback*, and thus a surge in LH and FSH release by the anterior pituitary, which results in ovulation. During the ensuing luteal phase, the mature follicle becomes the corpus luteum, which secretes progesterone and estradiol. The uterus undergoes further proliferative and secretory changes. Unless pregnancy occurs, endometrial sloughing and menstruation eventually occur, marking the beginning of a new cycle. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

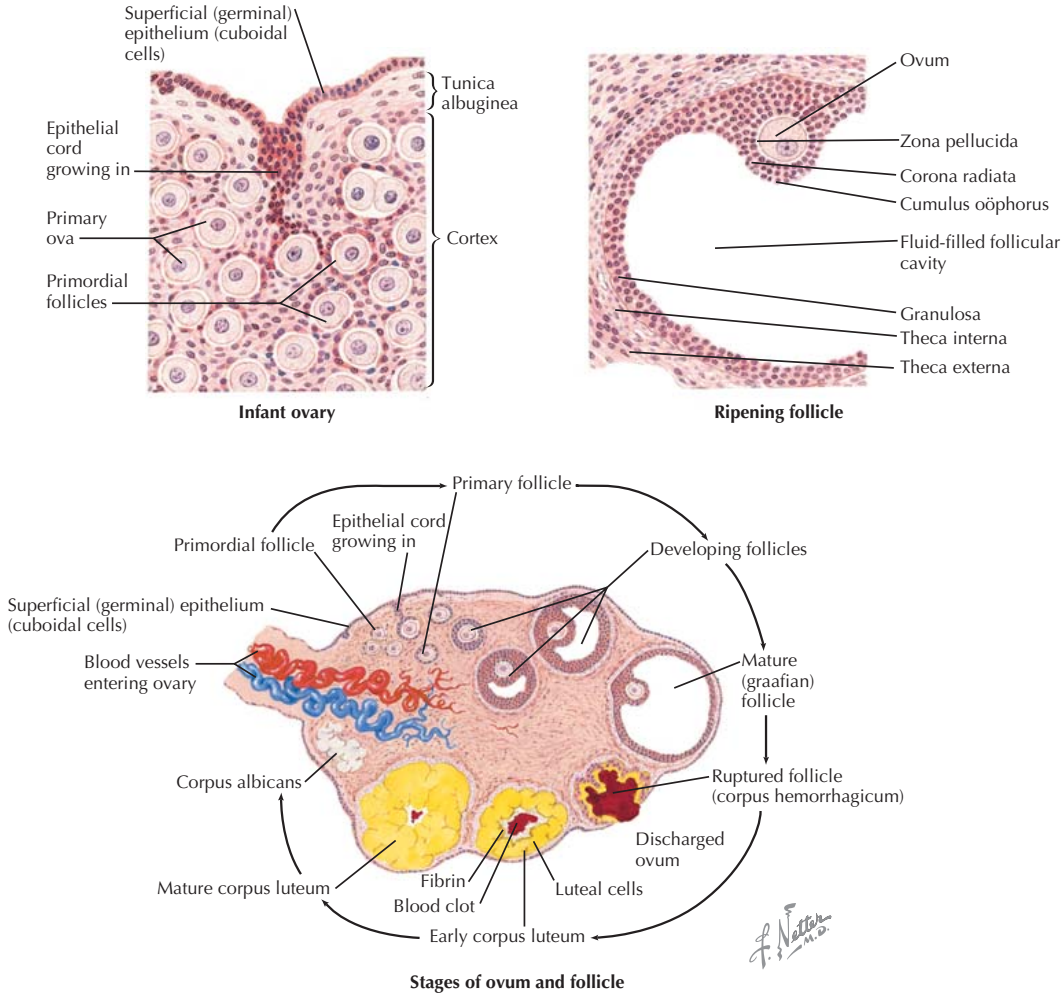


Figure 31.4 **Ovary, Ova, and Follicles** Until puberty, the ovary contains numerous primordial follicles that remain in a dormant state. After puberty, several follicles begin ripening with each menstrual cycle, in stages illustrated in the bottom panel. Only one follicle becomes a mature follicle; the others ultimately regress. After ovulation and release of the ovum, the mature follicle involutes to form the corpus luteum, which persists to the end of the cycle.

CLINICAL CORRELATE
The Rhythm Method and Oral Contraceptives

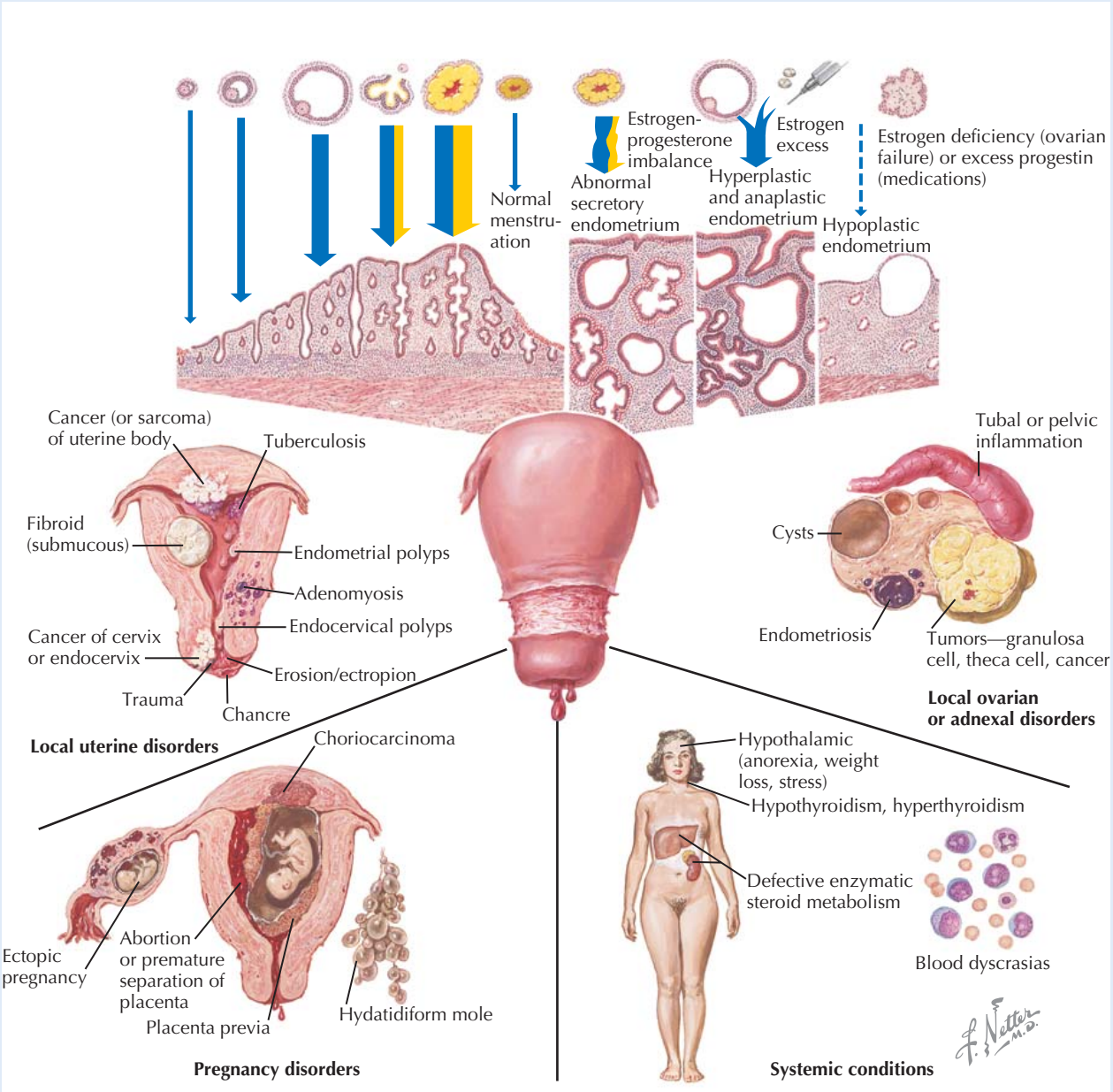
The average menstrual cycle is 28 days in length (beginning with the first day of menses), but this may vary both between women and for an individual woman. Ovulation takes place at about midcycle, but more precisely, it occurs *14 days before the onset of the next menses*. In other words, in a 26-day cycle, ovulation takes place on day 12, but in a 30-day cycle, ovulation takes place on day 16. Sperm are viable in the female reproductive tract for a few days, while mature ova are viable for only a short time after release.

For pregnancy to occur, intercourse needs to take place between approximately 5 days before ovulation and at most a day after ovulation. However, because it is not possible to predict exactly when ovulation will take place (because the date of onset of the next menses cannot be predicted with certainty), "rhythm methods" of contraception have low reliability compared with most forms of birth control. In various rhythm methods, intercourse is avoided for several days before and after the predicted date of ovulation. For example, in the Standard Days Method, women whose cycles are between 26 and 32 days in length avoid intercourse between days 8 and 19 of their cycles. In general, the rhythm method has a failure rate of several percent annually when used perfectly, and up to 25% otherwise.

With the use of oral contraceptives, most commonly a combination of an estrogen and a progestin (progesterone-like drug), cycles are controlled by the drug. Typically, hormone-containing pills are taken for 21 days, followed by a week of no pills or daily sugar pills. Pregnancy is prevented primarily by inhibition of ovulation, due to inhibition of gonadotropin release by the oral hormones. Bleeding (menstruation) occurs upon withdrawal from the hormones after 21 days. With perfect use, the annual rate of conception is 0.3%, although the failure rate is actually several percent annually.

CLINICAL CORRELATE
Abnormal Uterine Bleeding

Normal menstrual bleeding follows the luteal phase of the cycle and is caused by the fall in gonadal hormone levels. Heavy bleeding during menses (menorrhagia) or irregular bleeding during the cycle may be caused by hormonal imbalance. Abnormal uterine bleeding can also be caused by a variety of uterine or adnexal disorders as well as systemic disorders in nonpregnant, reproductive-age women. In pregnant women, bleeding may be caused by rupture of a placental blood vessel or may foreshadow an impending miscarriage. Placenta previa, in which the placenta extends over the cervix, is often associated with bleeding after the first trimester of pregnancy. Various causes of abnormal uterine bleeding are illustrated.



Causes of Abnormal Uterine Bleeding Abnormal uterine bleeding is associated with a variety of disease processes and disorders.

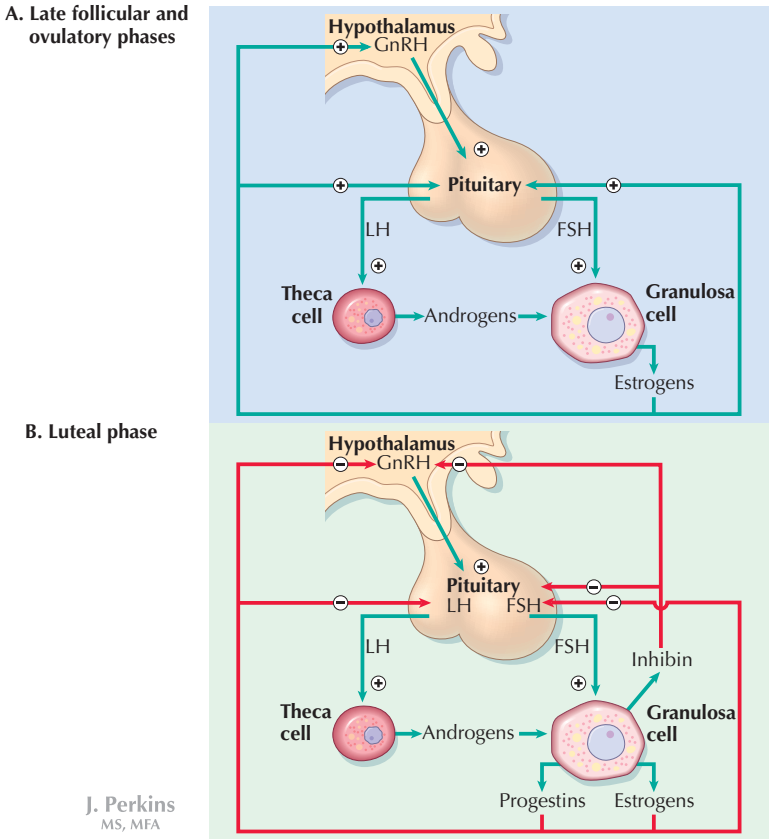


Figure 31.5 Hormonal Regulation of the Menstrual Cycle The hypothalamic-pituitary-ovarian axis is characterized by both positive and negative feedback over the course of a menstrual cycle. Initially, GnRH stimulates release of LH and FSH by the pituitary; estrogen synthesized by developing ovarian follicles has negative feedback effects on the axis. However, in the late follicular phase *(A),* blood estradiol reaches a high level that initiates positive feedback and a surge in LH and FSH release, provoking ovulation. In the luteal phase, the system is characterized by negative feedback *(B).* Estradiol, progesterone, and inhibin produced by the corpus luteum have negative feedback actions on gonadotropin release. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

IMPLANTATION AND PREGNANCY

As discussed, fertilization of the ovum takes place within the fallopian tube. Once the sperm penetrates the ovum, the second meiotic division is completed (all oocytes are arrested in the first meiotic division until a woman reaches puberty; the "mature ovum" released during each cycle has undergone further development and is arrested in the second meiotic division until sperm penetration). Subsequently, mitotic division of the fertilized egg begins and a blastocyst is formed. About 5 days after ovulation, the blastocyst begins to implant in the endometrial lining of the uterus. The sequence of events from follicular maturation to implantation of the blastocyst is illustrated in Figure 31.6.

The **placenta** is formed from **trophoblast** cells of the blastocyst and **decidual cells** of the endometrial lining. **Trophoblasts** secrete a hormone known as **human chorionic gonadotropin (HCG),** which has LH-like actions. HCG "rescues" the corpus luteum from the regression that would otherwise occur at the end of the menstrual cycle, such that synthesis of estradiol and progesterone continues, and thus, the proliferated, secretory state of the endometrium is maintained to support the pregnancy. HCG is important in this regard for the first trimester of pregnancy. By the second trimester, the placenta itself secretes large quantities of **progesterone** and **estrogens** (primarily **estriol**) to support the uterus.

CLINICAL CORRELATE
Measurement of HCG

Most pregnancy tests, including the widely available self-administered tests, are based on measurement of HCG. Although blood tests are more sensitive and may detect pregnancy earlier, urine tests are capable of detecting HCG within a few days of implantation of the blastocyst. Serial measurement of HCG also can be useful in monitoring early progress of a pregnancy when risk of ectopic pregnancy or miscarriage is an issue, because HCG normally rises rapidly following successful implantation.

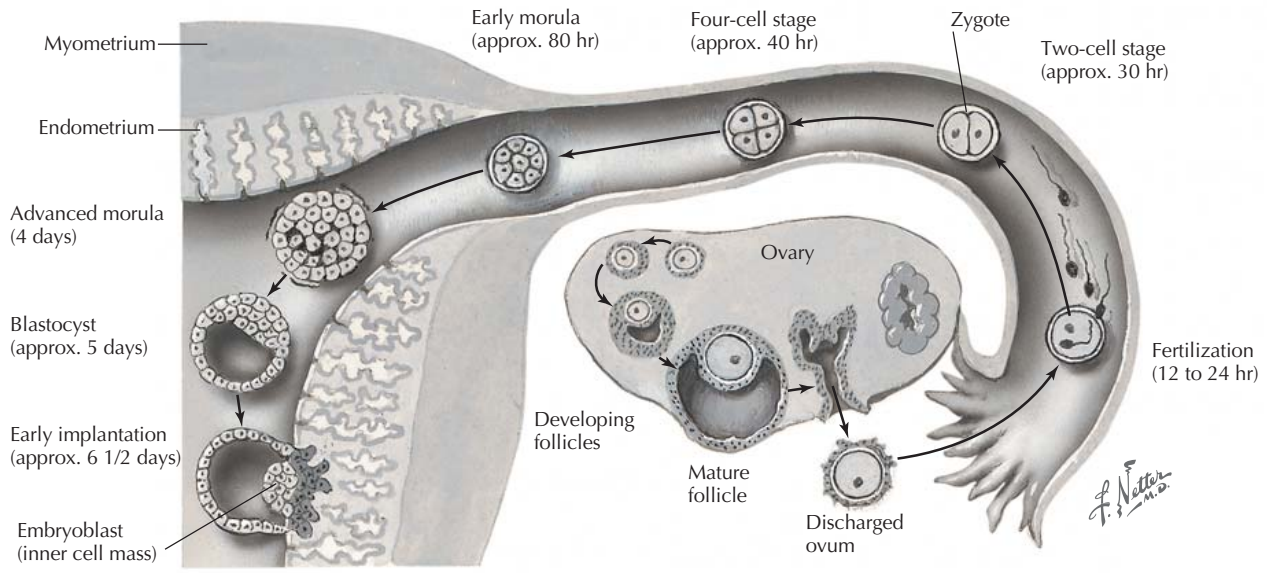


Figure 31.6 Fertilization and Implantation Upon rupture of the graafian follicle, the ovum enters the fallopian tube. If fertilization occurs, it takes place within the fallopian tube, which transports the ovum or zygote to the uterus. A zygote will have reached the blastocyst stage by day 5 and will implant in the endometrial lining at that time.

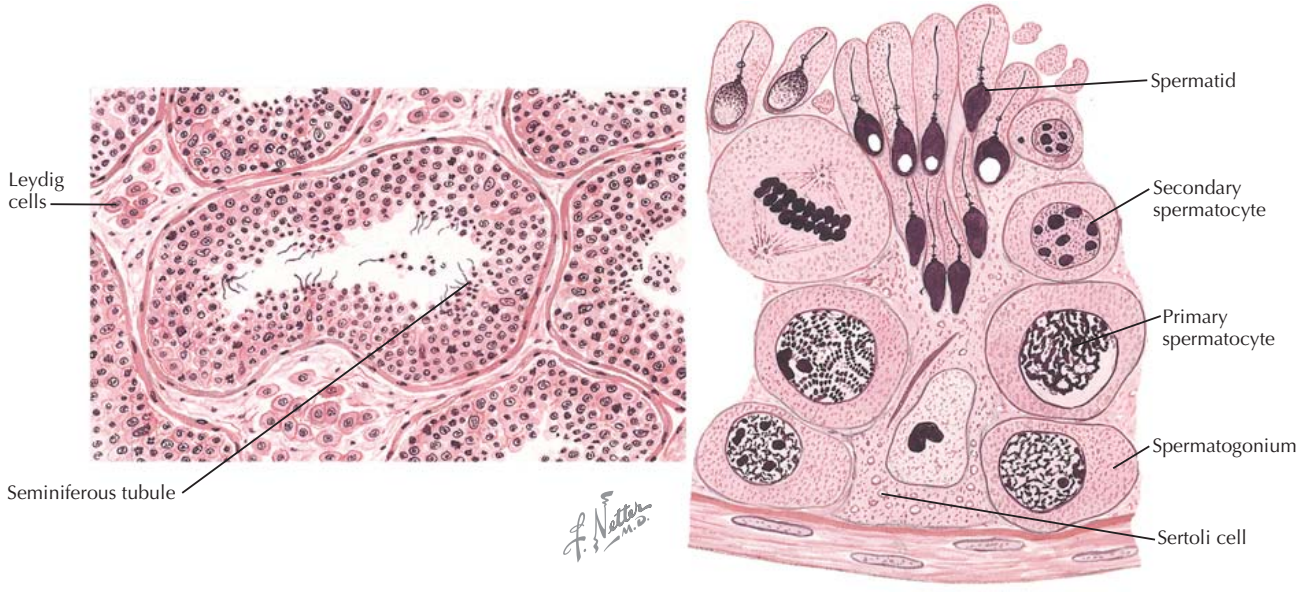
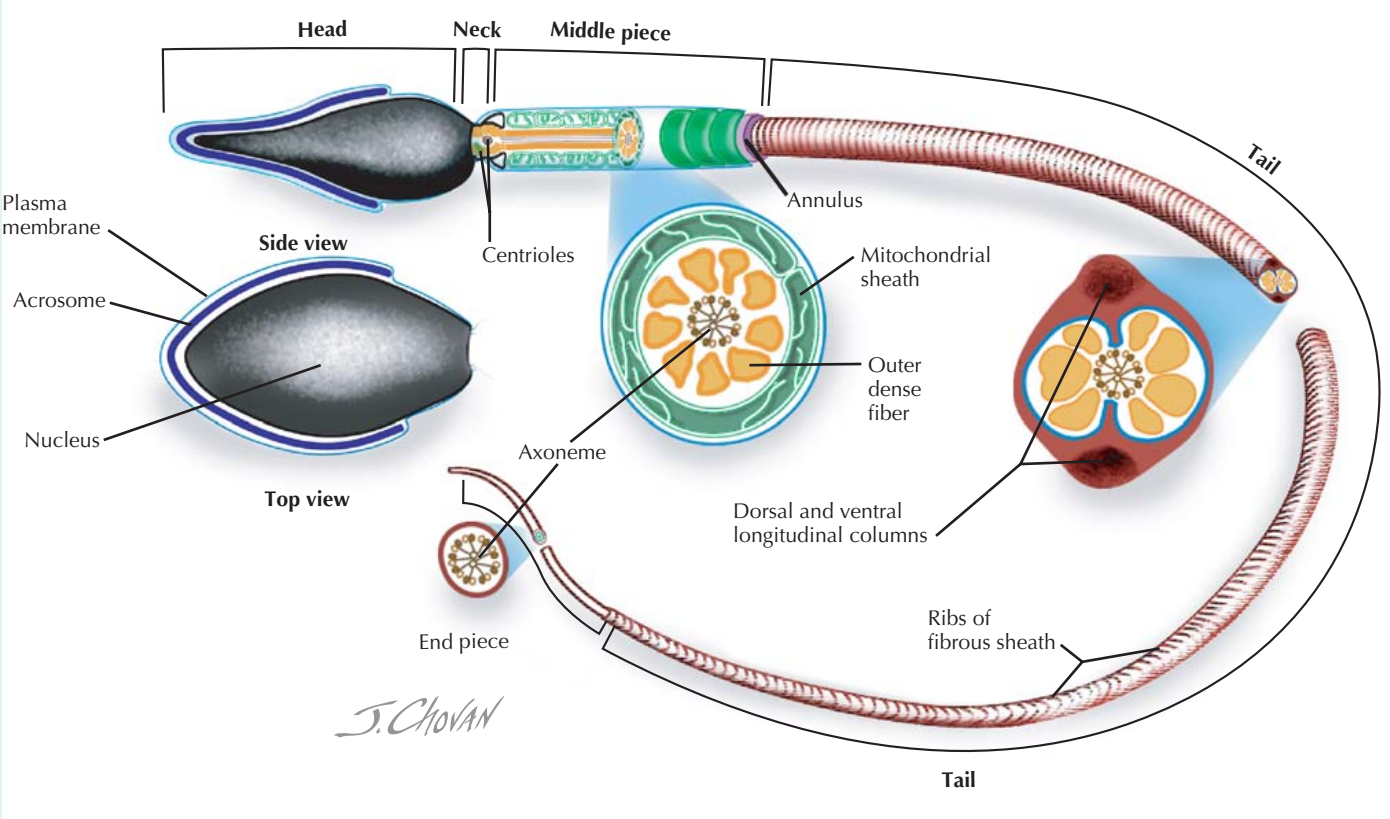


Figure 31.7 The Testes and Spermatogenesis The testes contain convoluted seminiferous tubules, where spermatogenesis takes place, and, between the tubules, Leydig cells, which synthesize testosterone in the mature male *(left panel)*. Sertoli cells constitute the epithelium of the tubules *(right panel)*. Differentiation of primary spermatocytes to sperm cells begins between the Sertoli cells and is completed in the epididymis.

MALE REPRODUCTIVE ENDOCRINOLOGY

The testes are the site of gametogenesis and steroidogenesis in males. Spermatogenesis takes place within the convoluted seminiferous tubules of the testes, whereas the **Leydig cells** located between tubules produce testosterone (Fig. 31.7). The hormone **inhibin** is synthesized and released by Sertoli cells in the lining of the seminiferous tubules. Sertoli cells provide the structure upon which male germ cells develop and secrete fluid that supports flow of sperm through the seminiferous tubules to the epididymis, where further sperm maturation takes place, and sperm are stored until

Spermatogenesis is a complex process that begins with mitotic division of spermatogonia to form primary spermatocytes, along with additional spermatogonia (unlike women, in whom there are a fixed number of primary oocytes by the time of birth, the number of germ cells in men is not fixed). Meiosis of primary spermatocytes produces secondary spermatocytes, and subsequently, haploid spermatids, which undergo further differentiation to become spermatozoa. The final product, the mature spermatozoon, includes a head piece, a mitochondria-rich middle section for energy production, and a motile tail section. The head piece has a prominent acrosome containing proteolytic enzymes necessary for penetration of an ovum.



Mature Spermatozoon The morphology of mature spermatozoa reflect their motility and ovum-penetrating functions.

ejaculation. Sertoli cell processes form tight junctions that provide a "blood-testis" barrier, sheltering the developing spermatocytes from potential damage by blood-borne substances.

Endocrine Regulation of Testicular Function

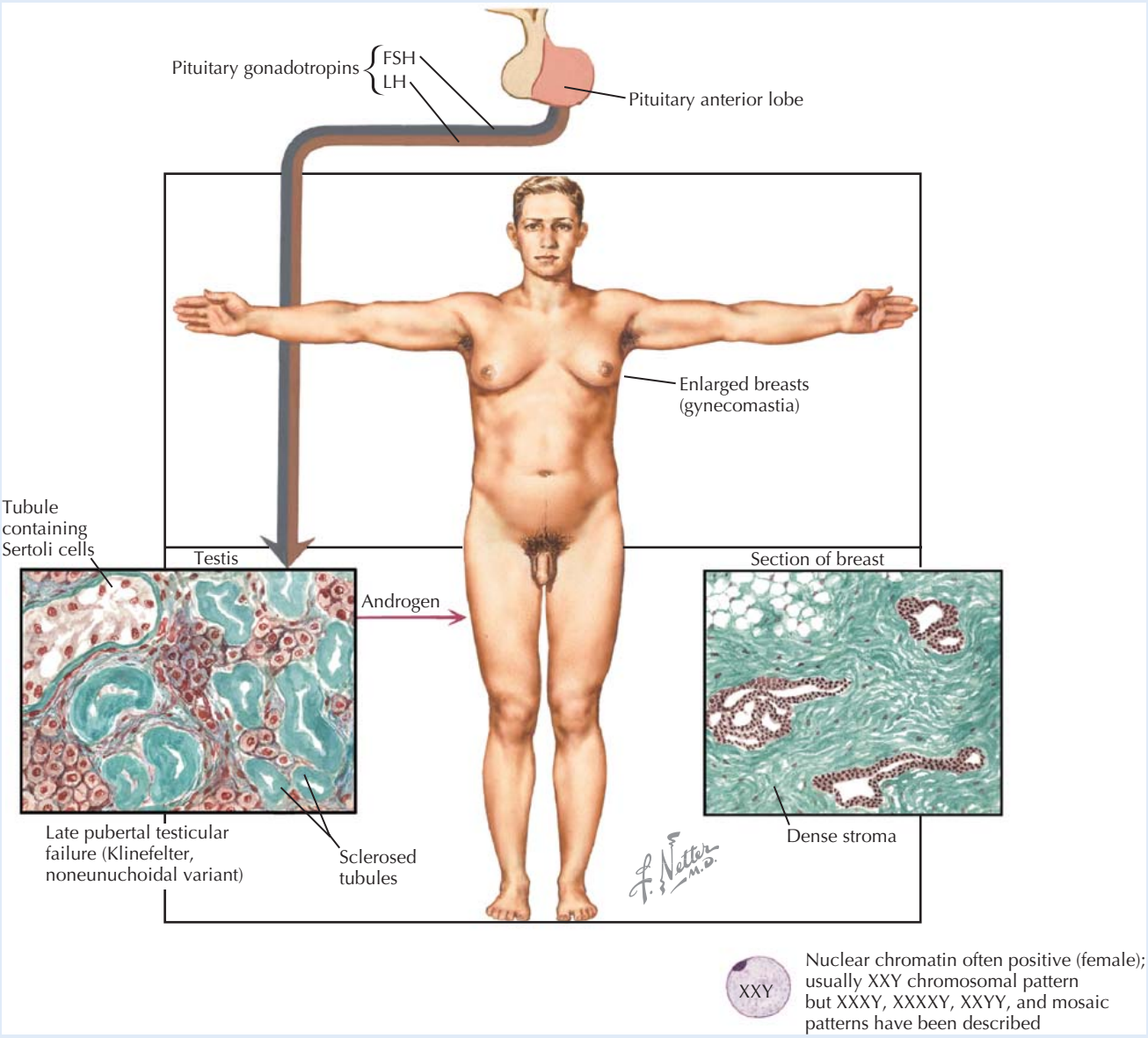
Testicular function (both gametogenesis and steroidogenesis) is regulated by the hypothalamus and pituitary gland (Fig. 31.8). GnRH is secreted by hypothalamic nuclei into the hypophyseal portal circulation (as in females, GnRH release is pulsatile in males), and subsequently stimulates the release of LH and FSH by anterior pituitary gonadotrophs. LH stimulates the first step in testosterone synthesis (conversion of cholesterol to Δ5-pregnenolone by CYP11A10, whereas FSH acts on Sertoli cells, stimulating the synthesis of **androgen-binding protein,** which subsequently binds testosterone, promoting spermatogenesis in the seminiferous tubules (see Fig. 31.7). Negative feedback in the hypothalamic-pituitary-testis axis is effected by inhibition of GnRH and LH release by testosterone and by inhibition of FSH secretion via inhibin produced by Sertoli cells.

Nonreproductive Actions of Testosterone

In addition to the nonreproductive actions of testosterone at puberty discussed, increased muscle mass, development of the male pattern of hair distribution and baldness, and deep-

CLINICIAL CORRELATE
Klinefelter's Syndrome

Male infertility has a large number of causes, including blockage of the vas deferens due to infection or injury; low sperm count (oligospermia) due to infections such as mumps and some sexually transmitted diseases; lack of sperm production as a result of chronic disease, hormonal problems, or injury to the testes; impotence; and exposure to toxins. In some cases, infertility may have a genetic basis. For example, Klinefelter's syndrome is characterized by the genotype 47, XXY. Patients with this syndrome are phenotypic males but have some identifiable physical characteristics including gynecomastia (breast enlargement) and are nearly always infertile (see illustration). They are hypogonadal, meaning that gonadal hormone levels are low, and as a result, gonadotropin levels are elevated and testicular size is reduced. Klinefelter's syndrome affects one to two men per 1000.



Testicular Failure in Klinefelter's Syndrome The presence of two X chromosomes (47, XXY genotype) results in seminiferous tubular dysgenesis and infertility, as well as primary hypogonadism (low testicular hormone levels, and as a result, high gonadotropin levels).

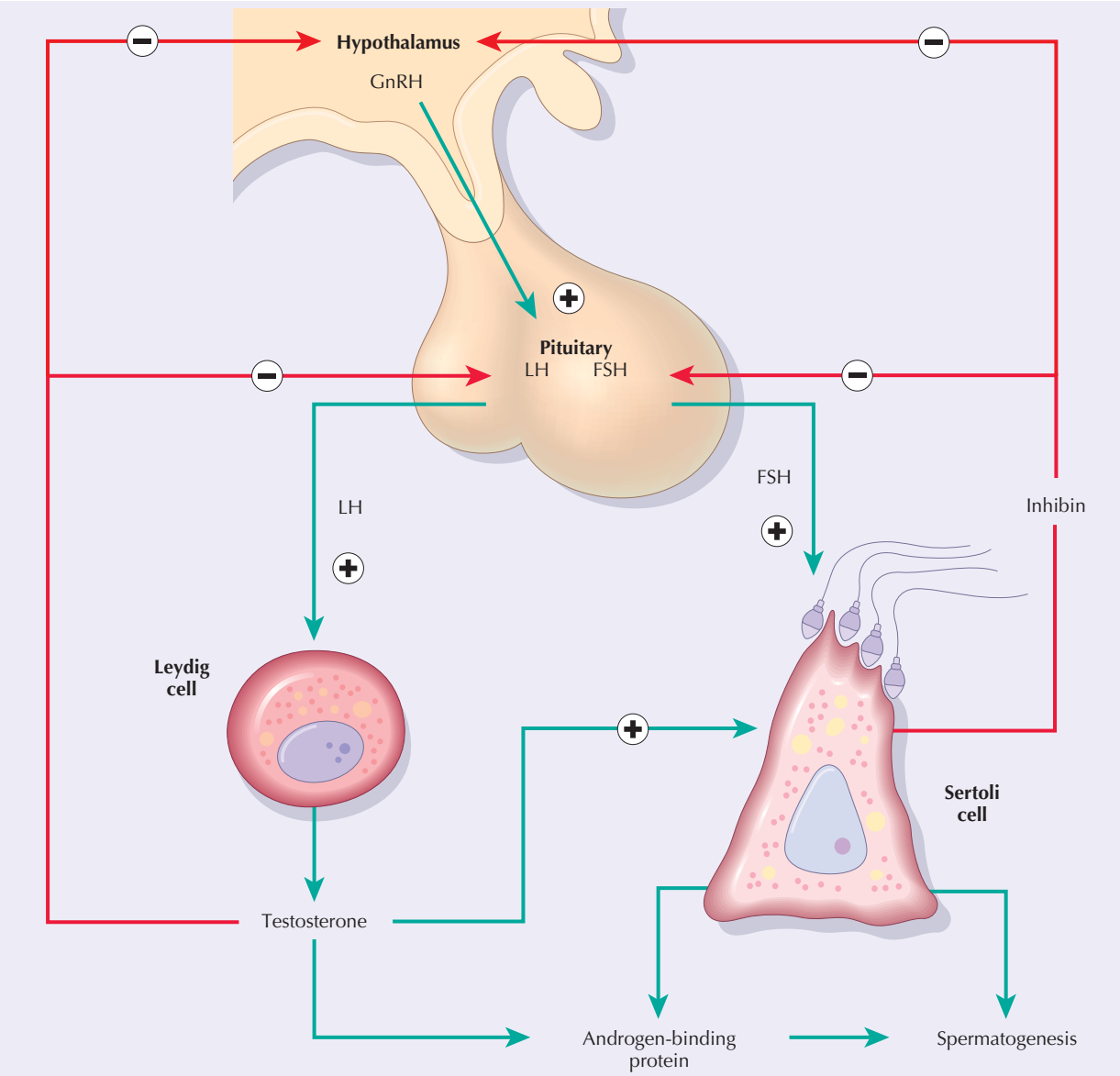


Figure 31.8 Control of Testicular Function GnRH secreted by the hypothalamus stimulates LH and FSH secretion by the anterior pituitary. LH stimulates testosterone synthesis by the Leydig cells of the testes, whereas testosterone and FSH are required for spermatogenesis. FSH induces production of androgen-binding protein (ABG); androgen is concentrated in the tubules by binding to ABG, promoting spermatogenesis. Sertoli cells also produce inhibin, which, along with testosterone, exerts negative feedback effects on the axis (inhibin specifically inhibits FSH secretion). FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Sex hormone-binding globulin (SHBG) and **androgen-binding protein** (ABG) are identical proteins, produced in the liver and testes, respectively. SHBG circulates in the bloodstream and is the major carrier for testosterone and estradiol in the blood (only a small fraction of sex hormones circulates as free hormone). ABG is produced by the testes and serves to concentrate testosterone within the seminiferous tubules, where androgens promote spermatogenesis.

ening of the voice are also actions of testosterone. Some of the actions of testosterone are dependent on its conversion to **dihydrotestosterone** (genital differentiation, prostate development and growth, male hair distribution, and baldness, for example), while others are direct effects of testosterone.

Review Questions

CHAPTER 26: GENERAL PRINCIPLES OF ENDOCRINOLOGY AND PITUITARY AND HYPOTHALAMIC HORMONES

1. Which of the following hormones initiates its actions at target tissues by binding to nuclear receptors?

A. ACTH
B. Vasopressin
C. Epinephrine
D. IGF-1
E. Thyroid hormone

2. Hormonal actions are regulated by:

A. affinity of receptors for the hormone.
B. the number of receptors for the hormone.
C. the degree of binding of hormone to plasma proteins.
D. the concentration of hormone in the blood.
E. All of the above.

3. Vasopressin (ADH) secretion by the posterior pituitary is stimulated by:

A. decreased body fluid osmolarity.
B. decreased blood volume.
C. atrial natriuretic peptide.
D. ethanol.
E. high blood pressure.

4. The hormone oxytocin:

A. is released directly into the general circulation.
B. is synthesized in the posterior pituitary gland.
C. promotes uterine quiescence.
D. has a well-established physiological role in induction and progression of labor.
E. is a 191 amino acid peptide.

5. Growth hormone secretion:

A. occurs in pulses, mainly during sleep.
B. is stimulated by a specific hypothalamic neurohormone.
C. is inhibited by somatostatin.
D. results in synthesis of insulin-like growth factor in a variety of target tissues.
E. All of the above.

CHAPTER 27: THYROID HORMONES

6. Thyroid hormone secretion is:

A. inhibited by elevated plasma estrogen levels.
B. stimulated by high plasma T_3.
C. inhibited by high thyroxine-binding globulin (TBG).
D. stimulated by high plasma T_4.
E. stimulated by TSH.

7. In adults, hypothyroidism is associated with which of the phenotypes listed below?

A. Hypertension, cold intolerance, diarrhea
B. Hypertension, nonpitting edema, cold intolerance
C. Hypotension, higher than normal temperature, diarrhea
D. Hypotension, higher than normal temperature, nonpitting edema
E. Hypotension, nonpitting edema, cold intolerance

8. In the plasma, thyroid hormone:

A. is present primarily in the T_3 form.
B. is present primarily in the T_3 form and is bound to proteins.
C. is completely bound to thyroxine-binding globulin (TBG).
D. is present primarily in the T_4 form and is mostly bound to proteins, including TBG.
E. is present only as free T_3 and T_4.

9. Feedback regulation of thyroid hormone is illustrated by:

A. high circulating levels of free T_3 and T_4, which elevate TRH.
B. high circulating levels of free T_3 and T_4, which elevate TSH.
C. high circulating levels of free T_3 and T_4, which reduce TRH.
D. reduced TRH, which elevates TSH.
E. reduced TSH, which elevates TRH.

CHAPTER 28: ADRENAL HORMONES

10. Stimulation of the adrenal gland by ACTH has the most direct effect on release of:

A. epinephrine.
B. norepinephrine.
C. cortisol.
D. androgens.
E. aldosterone.

11. Which portion of the adrenal gland secretes a hormone with anti-inflammatory actions?

A. The medulla
B. The zona reticularis
C. The zona fasciculata
D. The zona glomerulosa
E. None of the above.

12. Which of the following is a significant action of adrenal androgens in females?

A. Stimulation of libido
B. Hypertrophy of sebaceous glands
C. Development of pubic hair
D. Development of axillary hair
E. All of the above.

13. Aldosterone secretion by the adrenal gland is stimulated by:

A. hypokalemia.
B. high plasma Na^+ concentration.
C. angiotensin II.
D. atrial natriuretic peptide.
E. All of the above.

CHAPTER 29: THE ENDOCRINE PANCREAS

14. Insulin is necessary for:

A. entry of glucose into tissues via the GLUT1 transporter.
B. entry of glucose into all tissues.
C. entry of glucose into the brain.
D. entry of glucose into the pancreas.
E. entry of glucose into tissues via GLUT4 transporters.

15. Regulation of insulin release by increased plasma glucose involves which of the following sequence of steps?

A. Entry of glucose into pancreatic β-cells through GLUT1 transporters; increased ATP, which decreases K^+ efflux; depolarization of the β-cell; Ca^{2+} influx; insulin granule release
B. Entry of glucose into pancreatic β-cells through GLUT1 transporters; hyperpolarization of the β-cell; Ca^{2+} efflux; insulin granule release
C. Entry of glucose into pancreatic β-cells through GLUT2 transporters; increased ATP, which decreases K^+ efflux; depolarization of the β-cell; Ca^{2+} influx; insulin granule release
D. Entry of glucose into pancreatic β-cells through GLUT2 transporters; hyperpolarization of the β-cell; Ca^{2+} efflux; insulin granule release
E. Entry of glucose into pancreatic β-cells through GLUT4 transporters; depolarization of the β-cell; Ca^{2+} influx; insulin granule release

16. Factors that stimulate insulin secretion include:

A. glucagon-like peptide-1 (GLP-1).
B. amino acids.
C. glucose insulinotropic peptide (GIP).
D. fatty acids.
E. All of the above.

17. Insulin is a hypoglycemic hormone because of its ability to:

A. increase gluconeogenesis.
B. reduce glycogen storage in muscle.
C. increase glycogenolysis.
D. increase GLUT1 transporters in brain tissue membranes.
E. increase GLUT4 transporters in adipose tissue and skeletal and cardiac muscle membranes.

CHAPTER 30: CALCIUM-REGULATING HORMONES

18. Decreased plasma calcium levels result in:

A. reduced production of 1,25-dihydroxycholecalciferol.
B. reduced production of 25-hydroxycholecalciferol.
C. increased bone mineralization.
D. increased bone resorption.
E. increased plasma calcitonin.

19. Parathyroid hormone (PTH):

A. is released into plasma in response to increases in plasma calcium.
B. acts at the kidneys to increase calcium reabsorption and decrease phosphate reabsorption.
C. acts at the kidneys to decrease calcium reabsorption at the distal tubule.
D. acts at the bone to increase bone mineralization.
E. acts at the bone to decrease osteoclastic osteolysis.

20. Primary hyperparathyroidism is often associated with:

A. development of renal calculi.
B. bone pain.
C. constipation.
D. fatigue.
E. All of the above.

CHAPTER 31: HORMONES OF THE REPRODUCTIVE SYSTEM

21. During fetal development, the formation of male genitalia is directly stimulated by:

A. testosterone.
B. dihydrotestosterone.

C. dehydroepiandrosterone.
D. androstenedione.
E. estrone.

22. The pubertal growth spurt is mainly stimulated by the hormone:

A. calcitonin.
B. vitamin D.
C. estradiol.
D. testosterone.
E. dihydrotestosterone.

23. Conversion of androgens to estradiol by the follicular granulosa cells is stimulated by the hormone:

A. LH.
B. FSH.
C. oxytocin.
D. growth hormone.
E. prolactin.

24. During the prepubertal period, germ cells in women are arrested at which stage of gametogenesis?

A. Oogonia
B. Primary oocyte
C. Secondary oocyte
D. Ovum
E. Zygote

25. The hormone inhibin has direct negative feedback effects on the release of:

A. prolactin.
B. FSH.
C. LH.
D. testosterone.
E. GnRH.

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Answers

Section 1: Cell Physiology, Fluid Homeostasis, and Membrane Transport

1. **B.** Antipyrine diffuses throughout the body water and can be used to measure the volume of total body water; inulin does not enter cells and can be used to measure the extracellular fluid (ECF) volume. Using the indicator-dilution formula, the amount of indicator injected divided by the plasma concentration will result in the volume of the compartment. By this method, the total water (indicated by antipyrine) is 36 L, and the ECF (indicated by inulin) is 12 L; the intracellular fluid (ICF) is 24 L. The ECF (12 L) is one-fourth plasma (3 L) and three-fourths interstitial fluid (ISF) (8 L).
2. **D.** The Starling forces favoring movement out of the capillaries are the capillary hydrostatic pressure (HP_c) and interstitial oncotic pressure (π_i), while the forces favoring movement into the capillaries are the interstitial hydrostatic pressure (HP_i) and capillary oncotic pressure (π_c). Thus, $(30 + 8) - (3 + 28) = 7$ mm Hg out of the capillary.
3. **D.** Water will distribute through all compartments, and thus, both ECF and ICF volumes will increase. With the additional volume, the osmolarity of the compartments will decrease.
4. **C.** Voltage-gated channels are highly selective, and gating is dependent on membrane voltage.
5. **D.** The basolateral Na^+/K^+ ATPase, or "sodium pump," uses primary active transport to pump three sodium ions out of cells in exchange for two K^+ ions. The low intracellular Na^+ concentration facilitates apical sodium entry down its concentration gradient through several different secondary active transport symporters (e.g., Na^+-amino acid, Na^+-glucose) and antiporters (e.g., Na^+/Ca^{2+}, Na^+/H^+).
6. **B.** Ouabain (digoxin) is a cardiac glycoside that irreversibly blocks Na^+/K^+ ATPase, allowing equilibration of sodium and potassium across the cell membrane. This stops sodium-dependent transport processes and depolarizes the membrane potential.

Section 2: The Nervous System and Muscle

1. **A.** Reduced permeability of sodium ion will result in hyperpolarization of the cell. Ordinarily, sodium leakage into the cell contributes to the actual resting membrane potential, making it less negative than would be predicted on the basis of potassium concentration and permeability. Reduction in potassium ion permeability, on the other hand, would cause depolarization of the cell, as would influx of calcium ion or increased extracellular concentration of sodium or potassium ion.
2. **C.** Neuronal action potentials result when the threshold potential is reached and voltage-gated sodium channels open. Although action potentials are evoked in some excitable cells by opening of Ca^{2+} channels, opening of voltage-gated Na^+ channels is responsible for the phase 0 upstroke of the neuronal action potential.
3. **D.** Myelination of an axon results in decreased capacitance and increased membrane resistance. As a result, current travels through the interior of the axon but not through the membrane. Myelination produces a large increase in conduction velocity.
4. **A.** When axonal depolarization reaches the synaptic bouton, voltage-gated Ca^{2+} channels are opened, resulting in influx of Ca^{2+} and vesicular release of neurotransmitter into the synaptic cleft.
5. **D.** A single, large Na^+ and K^+ channel conducts the depolarizing charge during an endplate potential while the neuronal action potential involves multiple ion channels and depolarization is mainly produced by Na^+ influx. Depolarization is rapid in both endplate and action potentials. Depolarization to +40 mV, causation by voltage-gated channels, and repolarization associated with increased K^+ conductance are all characteristics of neuronal action potentials but not endplate potentials.
6. **E.** The neural tissue of the spinal cord is covered by three membranes (meninges). These are the inner pia mater, the middle arachnoid membrane, and the outer dura mater.
7. **B.** CSF is produced by the choroid plexus and is reabsorbed at the arachnoid granulations into the venous system, as well as into the capillaries of the CNS and pia mater.
8. **E.** Association pathways functionally and anatomically linking the two cerebral hemispheres include the corpus callosum and anterior, posterior, and hippocampal commissures.
9. **C.** While the pons is also involved in regulation of breathing, the medulla is the major site of autonomic regulation, including regulation and integration of cardiovascular and respiratory functions. The thalamus and hypothalamus are not part of the brainstem.
10. **A.** Meissner's corpuscles, located in the dermal papillae, especially in fingertips, palms, soles, lips, face, tongue, and genital skin (nonhairy skin), are rapidly adapting receptors with small receptive fields that allow point discrimination and detection of low-frequency stimuli such as flutter. Pacinian corpuscles respond to rapid changes in pressure and vibration, Merkel's disks respond to pressure and touch, especially indentation of the skin; hair follicle receptors respond to movement across the skin surface; and Ruffini's corpuscles respond to stretch of skin and joints.
11. **B.** Photoreceptors respond to light reception through a sequence of events that ultimately results in reduced Na^+ permeability and hyperpolarization of their cell membranes, which inhibits neurotransmitter release by the photoreceptors.
12. **E.** The three ducts of the membranous labyrinth of the cochlea of the inner ear are the scala vestibuli, scala tympani, and scala media. The scala media contains endolymph, which resembles intracellular fluid in its composition. The other two ducts contain perilymph, which resembles extracellular fluid in its composition.
13. **E.** The pattern of pressure changes between the three perpendicularly oriented semicircular canals during angular acceleration of the head is dependent on the direction of head movement. The bending of cilia as a result of these pressure changes produces hyperpolarization or depolarization and changes in neurotransmitter release by hair cells. As a result, the firing rate of afferent nerve fibers ending on the hair cells is altered. These signals are carried through cranial nerve VIII to the vestibular nuclei of the pons.
14. **A.** When the patellar tendon of the knee is tapped, muscle spindles in the quadriceps muscle are stretched, producing a reflex in which type Ia afferent nerves are depolarized, and conduct the signal to the spinal cord. The nerves synapse with α-motor neurons, which conduct the signal back to the quadriceps, causing contraction. This stretch reflex is a monosynaptic reflex. Golgi tendon reflex is a bisynaptic reflex involved in preventing muscle damage when muscle tension is excessive. The flexor withdrawal reflex is a polysynaptic reflex that occurs in response to painful stimuli.
15. **E.** The corticospinal tract carries fibers that originate in the primary motor cortex, premotor and supplemental motor areas, and somatosensory areas posterior to the motor cortex. It is the most important pathway for fine motor activity controlled by the cortex. The other

tracts mentioned are involved in other aspects of motor function, including brainstem control of balance and posture.

16. **C.** The cerebellum coordinates and fine-tunes motion. All of the efferent signals from the cerebellar cortex are inhibitory, originating from the Purkinje cells. This inhibitory output is regulated by excitatory input from climbing fibers and mossy fibers by way of the granule cells, and inhibitory input from interneurons in the cerebellar cortex.
17. **B.** Like the cerebellum, the basal ganglia have an accessory role to the motor cortex. With input from the motor cortex and output to the motor cortex through the thalamus, the basal ganglia function to produce smooth movement and regulate posture.
18. **B.** Preganglionic nerves of the sympathetic nervous system originate in the intermediolateral and intermediomedial cell columns of the thoracolumbar spinal cord (T1 to L3). Their axons extend to the chain ganglia, where they synapse with postganglionic nerves. Preganglionic nerves of the parasympathetic nervous system have cell bodies in the brainstem.
19. **D.** Postganglionic neurons of the parasympathetic nervous system (PNS) release acetylcholine, which acts at muscarinic receptors at the neuroeffector junction. Postganglionic neurons of the sympathetic nervous system (SNS) primarily release norepinephrine and epinephrine, which act at a variety of adrenergic receptors on effector organs and tissues. Both sympathetic and parasympathetic preganglionic nerves achieve ganglionic neurotransmission by release of acetylcholine, which acts at nicotinic receptors.
20. **C.** β_2-adrenergic receptors mediate sympathetic bronchial dilation. Constriction of vascular smooth muscle and mydriasis are produced by norepinephrine and epinephrine release by postganglionic sympathetic nerves and subsequent binding to α_1 receptors; increased contractility is mediated by β_2 receptors. Sweat gland secretion is stimulated by atypical sympathetic postganglionic nerve fibers that secrete acetylcholine.

Section 3: Cardiovascular Physiology

1. **B.** The systemic veins normally contain more than 60% of the blood volume and can act as a reservoir for blood. Blood can be mobilized from veins during hemorrhage or dehydration as a compensatory measure to help maintain blood pressure until blood volume can be restored.
2. **C.** Contraction of the left ventricle consists of powerful constriction of the chamber with shortening of the heart from base to apex, resulting in the high pressures required to pump blood through the high resistance systemic circulation.
3. **A.** The coronary circulation receives approximately 4% of the cardiac output at rest, while the other listed parts of the circulation each receive approximately 15% (brain) to 24% (liver and GI tract) of the circulation.
4. **E.** Following the plateau of the action potential, gradual inactivation of L-type Ca^{2+} channels leads to activation of K^+ channels and rapid repolarization. Opening of Na^+ channels is responsible for the phase 0 upstroke; this is accompanied by reduced conductance of the inwardly rectified K^+ current. Opening of L-type Ca^{2+} channels is mainly responsible for the plateau (phase 2); inactivation of Na^+ channels and opening of voltage sensitive K^+ channels cause the rapid repolarization to the plateau (phase 1).
5. **E.** A multiple-lead electrocardiogram can yield information on cardiac rhythm and conduction; presence, location, and extent of ischemia; orientation of the heart and chamber size; and abnormalities resulting from altered electrolyte levels or drugs. It does not yield direct information regarding cardiac output, stroke volume, ejection fraction, or other flow-related parameters.
6. **B.** Conduction velocity is a function of the slope of the phase 0 upstroke of the action potential. Velocity is slowed in the AV node, resulting in a pause between atrial and ventricular depolarization. As a result, there is a pause between atrial and ventricular contraction, allowing atrial contraction to produce the final filling of the ventricles before they contract.
7. **B.** Mean arterial pressure is not simply the arithmetic mean of diastolic and systolic arterial pressure, because the arterial pressure curve is complex in morphology and because diastole is longer in duration than systole. As a rule of thumb, at normal heart rates, mean arterial pressure is approximately equal to the diastolic pressure plus one third the pulse pressure. In this problem, the diastolic pressure is 80 and one third of pulse pressure is 16.7; therefore, the mean arterial pressure is predicted to be approximately 97 mm Hg.
8. **A.** The highest pulse pressure is observed in the left ventricle, where normal resting pressure is approximately 120/0 mm Hg. High systolic pressure is required to pump blood through the high resistance systemic circulation, while low diastolic pressure allows filling during diastole. Within the pulmonary circuit, the highest pulse pressure occurs in the right ventricle (approximately 25/0 mm Hg at rest).
9. **E.** According to Poiseuille's law, flow is proportional to the fourth power of the radius of a tube. Thus, doubling the radius of the tube will result in an increase in flow by a factor of 16, if other variables are held constant. Doubling the pressure gradient, halving the viscosity of the fluid, or halving the length of the tube will double the flow; doubling the viscosity will reduce flow by 50%.
10. **C.** High viscosity of fluid favors laminar flow. When the hematocrit is reduced, resulting in low blood viscosity, flow may be turbulent, resulting in audible murmurs. Wide tube diameter, rapid velocity of fluid flow, high density of fluid, and pulsatility of flow all increase Reynolds number and favor development of turbulent flow.
11. **C.** Wall tension (T) is defined by Laplace's law, $T = P_t r$, where P_t is the transmural pressure and r is vessel radius. Reduction of interstitial pressure will result in increased transmural pressure, and thus, increased wall tension. Reduced radius, vascular hydrostatic pressure, or transmural pressure will be associated with lower wall tension.
12. **D.** The isovolumetric contraction period begins when ventricular contraction results in ventricular pressure rising to exceed atrial pressure, causing the atrioventricular valve to close. Thus, the beginning of the isovolumetric contraction period for the right ventricle is marked by closure of the tricuspid valve.
13. **A.** During the cardiac cycle, valves on the left side of the heart close before the corresponding valves on the right side (mitral valve closes before the tricuspid, and aortic valve closes before the pulmonic), whereas valves on the right side open before the corresponding valves on the left side (pulmonic valve opens before the aortic, and tricuspid valve opens before the mitral valve).
14. **E.** In respiratory sinus arrhythmia, which occurs primarily in infants and children, heart rate is increased during inspiration and reduced during expiration. This is caused by increased venous return during inspiration, causing stretch of low pressure atrial baroreceptors and reflexive increase in heart rate.
15. **E.** Activation of the sympathetic nervous system (SNS) will produce all of the listed effects. Effects on the heart (increased heart rate and contractility) involve binding of adrenergic neurotransmitter to β_1 receptors; constriction of arteries and veins is produced by binding of the adrenergic transmitter to α_1 receptors.
16. **B.** The force–velocity relationship for cardiac muscle reveals an inverse relationship between velocity of contraction and afterload (force of contraction). With increased contractility, the maximum velocity of contraction (V_m, which occurs at zero afterload), is increased, as is the maximum force of contraction. Maximum force of contraction occurs during isometric contraction, at the x-intercept of the force–velocity relationship, where velocity is zero.

17. **B.** The vascular function curve represents the relationship between central venous pressure and cardiac output when central venous pressure is the dependent variable; the cardiac function curve represents the relationship when cardiac output is the dependent variable. The intersection of the two curves is at the normal, resting cardiac output and central venous pressure at equilibrium (approximately 5 L/min cardiac output and central venous pressure (CVP) of approximately 2 mm Hg).
18. **C.** Nitric oxide release by endothelial cells produces vasodilation of the vessel by relaxing underlying smooth muscle. This effect is mediated by the second messenger cGMP, which reduces free intracellular Ca^{2+}, producing the smooth muscle relaxation. Dilation of arterial vessels results in higher capillary hydrostatic pressure downstream. Nitric oxide also inhibits adhesion of platelets to the vascular wall.
19. **A.** In many tissues and organs, if blood flow is increased due to higher perfusion pressure, the expected elevation in flow will be followed by a return in blood flow toward the basal rate. According to the myogenic hypothesis, this autoregulation involves smooth muscle constriction in response to elevated transmural pressure (in other words, in response to stretch).
20. **D.** β_2 receptor binding produces vasodilation, whereas α_1 and α_2 receptor binding are associated with vasoconstriction. β_1 receptors are found in the heart, where the main effects mediated by these receptors are increased heart rate, contractility, and conduction velocity.
21. **A.** Arterial baroreceptors respond to high arterial pressure (and thus, stretch) by sending afferent nerve impulses to the central cardiovascular center, resulting in reduced sympathetic efferent activity and increased parasympathetic activity. In addition to high pressures, the baroreceptors also respond to pulse pressure.
22. **C.** Left coronary artery flow is highest during early diastole. Flow is low during systole, due to compression of myocardial vessels by the contracting myocardium. As the heart relaxes, this compression is released, and this, combined with the effects of vasodilator metabolites which build up in the myocardium during the low flow of systole, results in a large increase in left coronary artery blood flow in early diastole.

Section 4: Respiratory Physiology

1. **A.** A rise in pulmonary artery pressure produces passive distension of vessels in the pulmonary microcirculation and opening of some vessels that were previously collapsed (recruitment).
2. **D.** Spirometry measures changes in lung volume (tidal volume, expiratory reserve volume, inspiratory reserve volume, vital capacity, inspiratory capacity), but cannot measure total lung capacity, residual volume, or functional residual capacity. To determine these three values, one of them must be measured indirectly, for example by nitrogen washout, helium dilution, or body plethysmography.
3. **C.** In the standing position, both ventilation and perfusion of the lung are greatest in the bottom portion and poorest in the upper portion of the organ. However, the vertical gradient for perfusion is much greater than the gradient for ventilation. Therefore, the ventilation-to-perfusion ratio is highest toward the top of the lung. The ratio approaches infinity in areas of dead space and zero in areas of shunt.
4. **B.** Diffusion of a gas through a membrane is a passive process that follows Fick's law. It is directly related to the partial pressure gradient, directly related to surface area, directly related to the diffusion constant of the gas, and inversely related to membrane thickness.
5. **C.** In the middle portion of the lung, zone 2, alveolar pressure falls between pulmonary arterial and venous pressures, and the ventilation and perfusion are approximately balanced, resulting in a ratio of approximately 1.
6. **B.** Functional residual capacity (FRC) is lung volume after expiration in normal, quiet breathing. At this point, mechanical forces are in balance, with outward elastic recoil pressure of the chest wall balancing the inward elastic recoil pressure of the lung.
7. **C.** In the respiratory system as a whole, the greatest resistance to flow occurs in the medium-sized airways (fourth to eighth generation). Proceeding down the airways, the diameter of airways decreases while the number of tubes increases rapidly. Taking into consideration both factors, the resistance is greatest in the medium-sized bronchi (in aggregate).
8. **A.** With progressively greater effort, peak air flow is increased during expiration, but along the downward slope of the expiratory flow-volume curves, airflow is effort-independent.
9. **B.** Severe COPD is characterized by emphysema, with increased compliance of the lung and decreased elastic recoil of the lung. As a result of the decreased elastic recoil, the equal pressure point forms early during expiration, resulting in trapping of air, and ultimately causing increased total lung capacity, functional residual capacity, and residual volume. In pulmonary function tests, expiratory flow rate and FEV_1 are reduced as a result.
10. **A.** The presence of surfactant at the air-fluid interface of alveoli and small airways results in lower surface tension and therefore increased pulmonary compliance, reducing the work of breathing. Surfactant contains the phospholipid dipalmitoyl phosphatidyl choline. Surfactant deficiency is responsible for respiratory distress syndrome of the newborn.
11. **A.** An increase in hematocrit will result in a proportional rise in the amount of oxygen bound to hemoglobin in blood. At 100 mm Hg P_{O_2}, hemoglobin is saturated with oxygen, and an increase in P_{O_2} will only result in a minor rise in oxygen content by raising the small amount of dissolved oxygen. Likewise, because hemoglobin in arterial blood is normally nearly saturated with oxygen, increased alveolar ventilation will have very little effect on oxygen content. An increase in 2,3-DPG or a fall in blood pH will shift the oxyhemoglobin dissociation curve to the right, resulting in a fall in bound oxygen.
12. **C.** The pH is below the normal level of 7.4, indicating acidosis; because P_{CO_2} is elevated, this is a case of respiratory acidosis (high P_{CO_2} is the cause of the low pH).
13. **D.** In acute adaptation to high altitude, hypoxemia stimulates respiratory rate. Heart rate is also elevated. 2,3-DPG is elevated in blood, resulting in right-shift of the oxyhemoglobin dissociation curve, causing oxygen to more readily dissociate from hemoglobin at the tissue level. Renal compensation will result in elevated plasma bicarbonate level. In the long term, however, increased hematocrit (higher red blood count [RBC] and hemoglobin concentration in blood) is an important compensatory mechanism, resulting in increased oxygen carrying capacity of blood.
14. **B.** Central chemoreceptors respond mainly to changes in arterial P_{CO_2}, which diffuses readily into the cerebrospinal fluid (CSF) and alters CSF pH, resulting in stimulation of respiration when arterial P_{CO_2} is elevated. The blood-brain barrier is largely impermeable to HCO_3^- or H^+. Peripheral chemoreceptors respond to changes in arterial P_{O_2} and also pH and P_{CO_2}.
15. **D.** The initial, rapid adjustment of respiration during exercise is caused by input from proprioceptive afferents from joint receptors to the respiratory center in the brain, collaterals to the respiratory center from motor pathways for muscle activation, as well as additional, undefined factors. The additional elevation of respiration during continuing exercise is caused by feedback systems involving chemoreceptors and changes in body temperature.

Section 5: Renal Physiology

1. **C.** The clearance of inulin (C_{in}) is equated with the glomerular filtration rate, because inulin is freely filtered, is not reabsorbed or

secreted, and all filtered inulin is excreted. Thus, if the clearance of a freely filtered substance is less than C_{in}, it means that overall there was reabsorption (however, it does not determine whether secretion might also have occurred).

2. **C.** Increased extracellular matrix proteins thicken the glomerular basement membrane, increasing the filtration barrier, thus reducing the permeability to plasma.
3. **A.** Aldosterone is produced in the zona glomerulosa of the adrenal cortex.
4. **B.** Filtration fraction is defined as the glomerular filtration rate (GFR) divided by the renal plasma flow (RPF). The renal plasma flow equals [RBF × (1-hematocrit)], or 600 mL/min. Because C_{in} is equated with the GFR, the filtration fraction is 125 mL/min ÷ 600 mL/min, or ~20%.
5. **A.** Glucose is 100% reabsorbed in the proximal convoluted tubule, via Na^+-glucose cotransporters.
6. **D.** Plasma antidiuretic hormone has no direct effect on renal potassium handling, while the other conditions cause either secretion (high dietary or plasma potassium and aldosterone) or enhanced reabsorption (low dietary or plasma potassium and acidosis).
7. **D.** Loop diuretics target the Na^+-K^+-$2Cl^-$ cotransporters on the thick ascending limb of Henle. When the transporters are blocked, the solutes are carried distally (where there is little sodium reabsorption in the absence of aldosterone) and most of the fluid is excreted as urine. Because this transporter is a key factor in the countercurrent multiplier system, an additional result of the use of loop diuretics is the washing out of the medullary interstitial concentration gradient, which contributes to the sustained diuresis.
8. **E.** In the collecting duct cells, binding of ADH to V2 receptors stimulates the insertion of aquaporins into the apical membranes. This causes sodium-free water reabsorption.
9. **A.** Distal sodium reabsorption has no effect on the medullary concentration gradient, whereas the other factors all play significant roles in creating and maintaining the gradient.
10. **D.** Free water clearance (C_{H2O}) = V − [(U_{osm}/P_{osm}) × V], or +1. The positive value implies that water was cleared in excess of the amount required for iso-osmotic excretion of solutes present in the urine.
11. **C.** Angiotensin II has two direct actions on the kidneys, to increase proximal tubular sodium reabsorption and to constrict renal afferent and efferent arterioles. These actions increase sodium and water reabsorption. Renin is secreted from the juxtaglomerular cells in response to *low* sodium concentration and *low* tubular fluid flow rate in the distal tubule. Aldosterone stimulates sodium reabsorption in the late distal tubules and collecting ducts.
12. **A.** The reduction in vascular volume will stimulate sympathetic vasoconstriction and elevate sodium and fluid-retaining systems. Atrial natriuretic peptide is released from cardiac myocytes in response to *increased* atrial stretch during volume expansion. Thus, during dehydration, circulating ANP will be low.
13. **E.** Diabetes insipidus (DI) is usually of central origin (nephrogenic DI is rare), following trauma, disease, or surgery affecting the pituitary gland. Central DI involves the loss of ADH, so water channels are not present in the apical membranes of the collecting ducts, and urine cannot be concentrated. This leads to massive excretion (3 to 18 L/day) of hypotonic urine.
14. **C.** Plasma bicarbonate is low in metabolic acidosis, and the α-intercalated cells of the collecting ducts will increase H^+ secretion.
15. **C.** NAE is determined by the sum of urinary ammonium and titratable acids, minus any excreted bicarbonate. It does not depend on sodium excretion.
16. **B.** The pH is <7.4, and therefore the condition is acidosis. Because the low plasma bicarbonate (<24 mEq/L) also reflects acidosis, the disorder is metabolic in origin. The anion gap can be used to determine whether the acidosis is from acid loading or base loss; AG = $Na^+ - (Cl^- + HCO_3^-)$, or 136 − 114 = 22. The usual anion gap is ~8 to 12, and an increase in the gap reflects the addition of acid. Base loss (as found with diarrhea) would show no change in AG, because the loss of HCO_3^- in the stool would be matched by an increase in plasma Cl^-.
17. **D.** In respiratory alkalosis, the high pH will be matched by low P_{CO_2} (indicating a reduction in plasma "acid" as the primary disturbance). In *uncompensated* respiratory alkalosis, the plasma HCO_3 will be normal.
18. **A.** Phosphoric acid ($H_2PO_4^-$) is the primary TA excreted in the urine. Phosphates make very good buffers in urine because their pK is near the urine pH and there is a large amount (~25% of the filtered phosphate load) of dibasic phosphate (HPO_4^{2-}) available for conversion to TA and excretion.

Section 6: Gastrointestinal Physiology

1. **D.** The GI tract does not directly regulate systemic blood flow.
2. **E.** Growth hormone has no apparent effect on motility or secretion in the GI tract.
3. **D.** The GI tract has an intrinsic nervous system (enteric nerves), which responds to signals from lumenal receptors and hormones, as well as extrinsic nerves. When the extrinsic nerve input is severed, motility and secretion continues, but not as efficiently.
4. **B.** Vagal afferent nerves regulate all of the actions EXCEPT primary esophageal peristalsis, which is mediated by the swallowing center in the medulla. The vagus does participate in secondary esophageal peristalsis, in conjunction with local enteric nerves.
5. **B.** Action (or spike) potentials in the GI tract are caused by the influx of calcium into the smooth muscle when the slow waves are depolarized above −40 mV. This mechanism is active throughout the tract, and depolarization can result from local stretch (mechanoreceptors acting on enteric nerves), extrinsic nerves, and peptides.
6. **C.** The undulations are a result of small changes in membrane potential due to the activity of the basolateral Na^+/K^+ ATPase. The slow waves occur at different rates from the mid-stomach through the colon.
7. **D.** Peristalsis follows the law of the intestines, where muscle is contracted proximal to the bolus and relaxed distal to the bolus, producing aboral movement of the chyme.
8. **B.** There is no evidence for involvement of the parasympathetic nervous system in the MMC.
9. **D.** Gastric inhibitory peptide (GIP) is an endocrine hormone secreted from cells in the duodenum and jejunum of the small intestine. The other substances are secreted directly into the gastric lumen.
10. **C.** Vagal afferent nerves stimulate gastric acid secretion directly at the parietal cell, and indirectly by increasing gastrin-releasing peptide (GRP) (and thus, gastrin release) and inhibiting somatostatin release.
11. **E.** Proton pump activity drives acid secretion and is the target for regulatory hormones, peptides, and nerves.
12. **B.** Sodium enters the lumenal membrane by all of the mechanisms except the Na^+ pump (Na^+/K^+ ATPase), which is located on the *basolateral* membrane, and maintains the low intracellular Na^+ concentrations that drive the lumenal Na^+ transport mechanisms.
13. **C.** Secretin is a hormone released from S-cells in the duodenum and early jejunum in response to acidic chyme. The secretin binds to receptors on the pancreatic acinar cells and stimulates release of electrolyte buffers into the pancreatic duct.
14. **B.** The liver performs all of the functions noted, except vitamin production. It does store a variety of important vitamins and minerals, including vitamin B12 and iron.
15. **D.** Obstruction of blood flow through the liver increases the pressure in the portal vein, which brings blood from the intestines to

the liver. This eventually results in portal hypertension. The obstruction also reduces bile secretion.

16. **A.** The hepatocytes are the primary site of formation of lipoproteins, which carry fats, protein, and cholesterol to different tissues for processing and storage.
17. **B.** Bile is amphipathic and essential for carrying the hydrophobic lipids through the unstirred water layer adjacent to the enterocytes. The ability to form micelles, with hydrophilic ends of bile oriented outward, and lipophilic ends oriented inward and associated with the lipids, allows the efficient transport of lipids to the intestinal cells.
18. **D.** Efficient digestion of proteins in the small intestine depends on the pancreatic proteases, which have optimal catalytic activity near physiologic pH (between pH 7 to 8). Low lumenal pH will significantly decrease catalytic activity and reduce the amount of proteins digested to constituents that can be absorbed.
19. **D.** Starch is the primary dietary carbohydrate, and digestion begins in the mouth with salivary α-amylase. Only around 25% of digestion occurs preduodenally: pancreatic α-amylase digests the remaining starch to malto-oligosaccharides, and then intestinal brush border saccharidases (maltase, isomaltase, sucrose, and lactase) digest oligosaccharides and disaccharides (sucrose and lactose) to monosaccharides (glucose, galactose, and fructose).
20. **A.** The presence of chyme in the antrum of the stomach and the duodenum stimulates release of gastrin, which is a potent stimulator of gastric acid secretion. It does not promote buffer secretion.
21. **C.** Celiac sprue is an autoimmune reaction initiated by gluten proteins in wheat, resulting in the flattening of the villus lining and expansion of the crypts. The reduction in the upper villi severely decreases the brush border enzyme digestion of carbohydrates and proteins and reduces the surface area for absorption.
22. **B.** B12 is an essential nutrient and has multiple mechanisms protecting it from protease activity and facilitating entry into the intestinal cells. There is no limitation to absorption posed by intracellular B12 concentrations.

Section 7: Endocrine Physiology

1. **E.** Thyroid hormone, vitamin D, and steroid hormones are lipophilic and readily diffuse into target cells, where they are bound by nuclear receptors, initiating gene transcription. Peptide hormones and catecholamines are bound by membrane receptors, initiating an intracellular signaling cascade that ultimately leads to regulation of cellular function.
2. **E.** The cellular action of hormones is dependent on the concentration of hormone in the blood, as well as the number and affinity of hormone receptors in the cell or on the cell membrane. In addition, some hormones (particularly lipophilic hormones such as steroids) are carried in the blood by binding proteins, and it is specifically the free fraction of hormones in the blood that is available for binding by cellular receptors.
3. **B.** Vasopressin promotes increased water absorption by the kidney, and its release is stimulated by decreased blood volume, increased body fluid osmolality, and decreased blood pressure.
4. **A.** Oxytocin, a 9 amino acid peptide, is released directly into the general circulation by the posterior pituitary gland but is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. It is carried by axonal transport to nerve endings in the posterior pituitary. Its actions include milk expulsion during breastfeeding and uterine contraction, although a physiological role in induction or progression of labor is not well-established.
5. **E.** Growth hormone is released by the anterior pituitary somatotrophs, with several pulses occurring during sleep, as well as a basal level of secretion. Its release is stimulated by hypothalamic growth hormone–releasing hormone and inhibited by somatostatin. At the tissues, it acts by stimulating the synthesis of insulin-like growth factor.
6. **E.** Pituitary thyroid-stimulating hormone (TSH) is a primary stimulus for thyroid hormone (TH) release.
7. **E.** Hypothyroidism in adults results in myxedema, which is associated with nonpitting edema, hypotension, fat deposition, cold intolerance, and depression, among other symptoms.
8. **D.** Both T_3 and T_4 are released from the thyroid gland, but 20 times the amount of T_4 is released compared to T_3. Most of the T_3 and T_4 is bound to proteins including albumin and thyroxine-binding globulin.
9. **C.** Feedback control of TH production is illustrated by elevated circulating free T_3 and T_4, which reduces both pituitary thyroid-stimulating hormone (TSH) and hypothalamic thyrotropin-releasing hormone (TRH), resulting in reduced TH production.
10. **C.** Cortisol synthesis and release by the adrenal cortex is regulated by the anterior pituitary hormone ACTH. Although ACTH is required for synthesis of all adrenal steroids, androgen and aldosterone synthesis and release are primarily controlled by other mechanisms. Release of catecholamines by the adrenal medulla is controlled by the sympathetic nervous system.
11. **C.** The zona fasciculata secretes cortisol, which has anti-inflammatory and anti-immune effects among its many actions. The zona reticularis secretes androgens and the zona glomerulosa secretes aldosterone. The adrenal medulla secretes catecholamines.
12. **E.** Dehydroepiandrosterone and androstenedione are the major adrenal androgens. In females, for whom the adrenal gland is the only significant source of circulating androgens, all of the listed effects are stimulated by these hormones.
13. **C.** The primary stimuli for aldosterone secretion by the adrenal zona glomerulosa are hyperkalemia and angiotensin II. Aldosterone synthesis and secretion is inhibited by atrial natriuretic peptide.
14. **E.** The GLUT4 transporters are the insulin-sensitive transporters present on most cell membranes, and insertion of these transporters facilitates glucose entry.
15. **C.** GLUT2 transporters are prominent on the pancreas, small intestine, brain, and liver and facilitate entry of glucose into the cells. In the β-cell of the pancreas, glucose metabolism increases ATP and reduces K^+ efflux. This depolarizes the β-cell, causing Ca^{2+} influx and release of the insulin (and C-peptide).
16. **E.** All of the factors listed will stimulate insulin secretion.
17. **E.** Insulin has a hypoglycemic effect on the plasma by increasing GLUT4 transporters, which facilitate glucose entry into adipose tissue and cardiac and skeletal muscle, while it decreases gluconeogenesis and glycogenolysis and increases glycogen storage.
18. **D.** Decreased plasma calcium concentrations will stimulate the release of parathyroid hormone (PTH), which acts at bone to increase resorption, releasing calcium into the blood. PTH also acts at the kidney to increase calcium reabsorption.
19. **B.** PTH is released into plasma in response to reduced plasma calcium levels. At the kidneys it increases distal calcium reabsorption and reduces phosphate reabsorption. It also stimulates the renal conversion of 25-hydroxycholecalciferol to active vitamin D (1,25-dihydroxycholecalciferol), which increases intestinal absorption of calcium.
20. **E.** Primary hyperparathyroidism typically results from parathyroid tumors that have no negative feedback mechanisms and ultimately increases plasma calcium concentrations. The elevated PTH increases the renal conversion of 25-hydroxyvitamin D to active vitamin D, increasing intestinal calcium absorption; the reduction in fecal calcium can cause constipation. In addition, the PTH increases bone resorption (can cause bone pain), and the elevated filtered load of calcium to the kidney can cause stone formation (calculi). Overall, these symptoms can cause fatigue and general

malaise. These "stones, bones, moans, and groans" can be characteristic symptoms of hyperparathyroidism.

21. **B.** Differentiation of the external genitalia produces female genitalia in the absence of androgens. In the male fetus, the testes produce testosterone, which is converted to dihydrotesterone (DHT) in the primitive genital structures. DHT stimulates formation of male genitalia.
22. **C.** The linear growth spurt that occurs during puberty is mainly attributed to estradiol in both boys and girls. Estrogenic hormones increase linear growth of long bones and also promote the eventual closure of the epiphyseal plates.
23. **A.** In developing follicles, androgen is synthesized and secreted by theca interna cells. The conversion of androgens to estradiol by the follicular granulosa cells is stimulated by luteinizing hormone (LH).
24. **B.** During fetal development, germ cells in the ovaries give rise to oogonia, which proliferate and begin meiosis. They become primary oocytes and are arrested at this stage.
25. **B.** FSH acts on Sertoli cells of the seminiferous tubules, stimulating androgen-binding protein synthesis. This protein binds testosterone, which promotes spermatogenesis. The Sertoli cells also synthesize inhibin, which inhibits follicle-stimulating hormone (FSH) secretion by the anterior pituitary gland.

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