

• THE BIG PICTURE •

# PHYSIOLOGY

MEDICAL COURSE & STEP 1 REVIEW

JONATHAN D. KIBBLE

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# THE BIG PICTURE Physiology

*Medical Course & Step 1 Review*

Second Edition

a LANGE medical book

**Jonathan D. Kibble, PhD**

Professor of Physiology  
Assistant Dean for Students  
College of Medicine  
University of Central Florida  
Orlando, Florida



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## **DEDICATION**

In loving memory of my brother Gary.

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# Preface

The goal of this textbook is to help medical students to efficiently learn and review physiology. The text offers a complete yet concise treatment of the major topics in medical physiology. Several design features are included to make the text easy to use.

- High-yield clinical pearls ▼ are integrated throughout to the text; and clinical examples highlight the relevance and application of physiologic concepts.
- *Key concepts* are highlighted using italics, and **basic terms** are shown in bold when first used.
- Full-color figures illustrate essential processes; explanatory figure legends allow figures to be used for review.
- Bullets and numbering are used to break down complex processes.

Study questions and answers are provided at the end of each chapter. A final examination is also provided, which is organized by body system to allow either comprehensive testing or focused review.

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# Acknowledgments

Particular thanks to my first edition coauthor Colby Halsey and artist Matt Chansky; to the second edition editorial team from McGraw-Hill, especially Touseen Qadri and Kirti Sharma Kaistha; and to the project leader Michael Weitz for his patience and support.

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# About the Author

Jonathan Kibble is a professor of physiology at the University of Central Florida, College of Medicine in Orlando. He was recognized by the American Physiological Society in 2018 as the Arthur C. Guyton Physiology Educator of the Year and also received the Alpha Omega Alpha, Robert J. Glaser Distinguished Teacher Award in 2015 from the Association of American Medical Colleges. Jon trained in the United Kingdom in the early 1990s and also worked in the Caribbean and Canada before moving to the United States in 2008. Dr. Kibble brings 25 years of experience in teaching medical physiology to write a text that is both accessible and relevant for students of medicine.

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# General Physiology

## Homeostasis

1. Medical physiology is about how the body systems function and how they are controlled.
2. **Homeostasis** is the *maintenance of a stable internal environment* and requires integration of organ system functions (Table 1-1).
3. Negative feedback control.
  - a. The stability of the body's internal environment is defined by the maintenance of **physiologic controlled variables** within narrow normal ranges (Table 1-2).
  - b. Minimal variation in a controlled variable is explained by the presence of negative feedback control mechanisms.
  - c. Negative feedback responses counter deviations of a controlled variable from its normal range; *this is the major control process used to maintain homeostasis.*

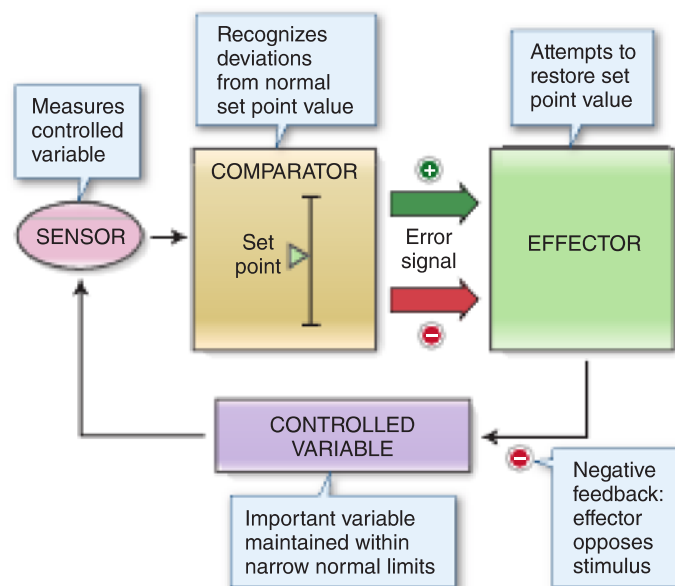
**Table 1-1.** Major Components and Functions of the Body Systems

Body System	Components	Major Function(s)
<b>Cardiovascular</b>	Heart, blood vessels, blood	Transport of materials throughout the body
<b>Digestive</b>	Gastrointestinal tract, liver, pancreas	Assimilation of nutrients; elimination of some wastes
<b>Endocrine</b>	Endocrine glands	Coordination of body functions through release of regulatory molecules
<b>Immune</b>	Thymus, spleen, lymphatic system, white blood cells	Defense against pathogens
<b>Integumentary</b>	Skin	Protection against external environment
<b>Musculoskeletal</b>	Skeletal muscle and bones	Movement and support
<b>Nervous</b>	Brain, spinal cord, peripheral nerves	Coordination of body functions through electrical signals and release of regulatory molecules; cognition
<b>Reproductive</b>	Gonads, penis, vagina, uterus	Procreation
<b>Respiratory</b>	Lungs	Oxygen and carbon dioxide and exchange with external environment
<b>Urinary</b>	Kidneys, bladder	Homeostasis of ion concentrations in internal environment; elimination of wastes

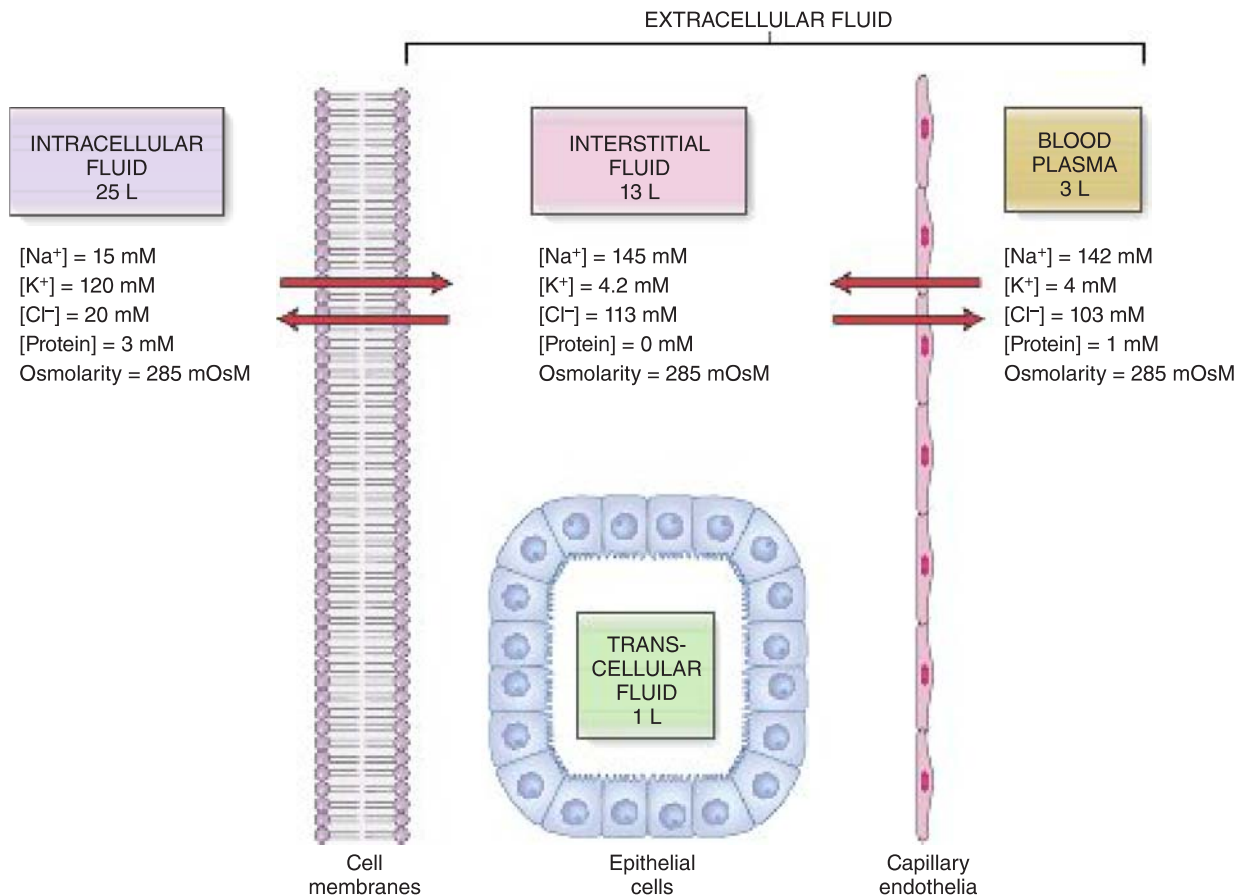
**Table 1-2.** Some Examples of Physiologic Controlled Variables

Controlled Variable (Arterial Blood Sample)	Typical Set Point Value
Arterial O <sub>2</sub> partial pressure	100 mm Hg
Arterial CO <sub>2</sub> partial pressure	40 mm Hg
Arterial blood pH	7.4
Glucose	90 mg/dL (5 mM)
Core body temperature	98.4°F (37°C)
Serum Na <sup>+</sup>	140 mM
Serum K <sup>+</sup>	4.0 mM
Serum Ca <sup>2+</sup>	2.5 mM
Mean arterial blood pressure	90 mm Hg
Glomerular filtration rate	120 mL/min

- d. A negative feedback control system has the following elements (Figure 1-1):
- i. A **set point** value, which is at the center of the normal range and is treated by the control system as the target value.
  - ii. **Sensors** that monitor the controlled variable.
  - iii. A **comparator**, which interprets input from the sensors to determine when deviations from the set point have occurred. The comparator initiates a counter response.
  - iv. **Effectors** are the mechanisms that restore the set point.
- e. Using the control of blood pressure as an example:
- i. The controlled variable is mean arterial blood pressure (MAP).
  - ii. The normal set point for MAP is approximately 95 mm Hg.
  - iii. Pressure sensors are located in the carotid sinus and relay information to a comparator located in the central nervous system.

**Figure 1-1.** Components of a negative feedback control system.

- iv. If MAP suddenly changes, the activity of effectors (e.g., cardiac contractility, vascular tone, and urinary fluid excretion) is altered to restore normal blood pressure.
4. The internal environment.
- The purpose of homeostasis is to provide an optimal fluid environment for cellular function.*
  - The body fluids are divided into two major functional **compartments**:
    - Intracellular fluid (ICF)** is the fluid inside cells.
    - Extracellular fluid (ECF)** is the fluid outside cells, which is subdivided into the **interstitial fluid** and the blood **plasma**.
  - The concept of an internal environment in the body correlates with the interstitial fluid bathing cells.
  - There is free exchange of water and small solutes in the ECF between interstitial fluid and plasma across the blood capillaries.
  - Exchange between interstitial fluid and ICF is highly regulated and occurs across cell membranes.
  - The volume of **total body water** is approximately 60% of the body weight in men and 50% in women.
    - About 60% of the total body water is ICF and 40% is ECF (Figure 1-2).

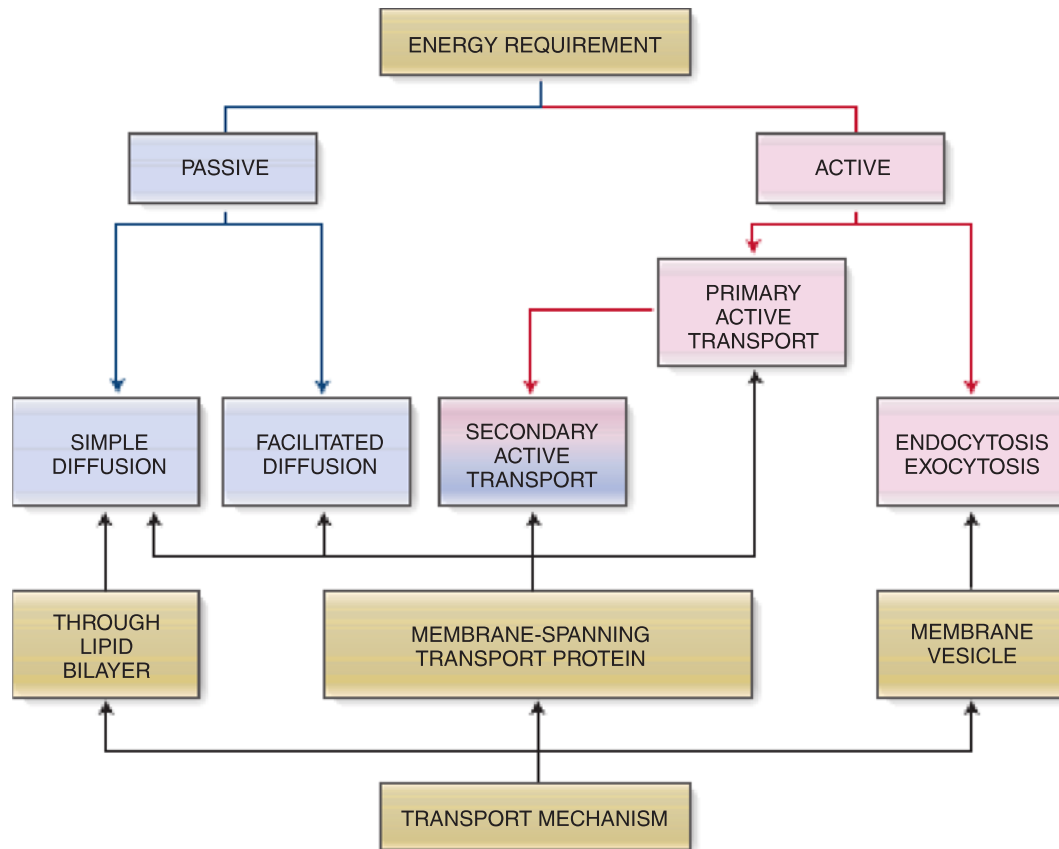


**Figure 1-2.** Body fluid compartments. Intracellular fluid (ICF) is separated from extracellular fluid (ECF) by cell membranes. ECF is composed of the interstitial fluid bathing cells and the blood plasma within the vascular system. Interstitial fluid is separated from plasma by capillary endothelia. Transcellular fluid is part of the ECF and includes epithelial secretions such as the cerebrospinal and extraocular fluids. ECF has a high [Na<sup>+</sup>] and a low [K<sup>+</sup>], whereas the opposite is true of ICF. All compartments have the same osmolarity at steady state.

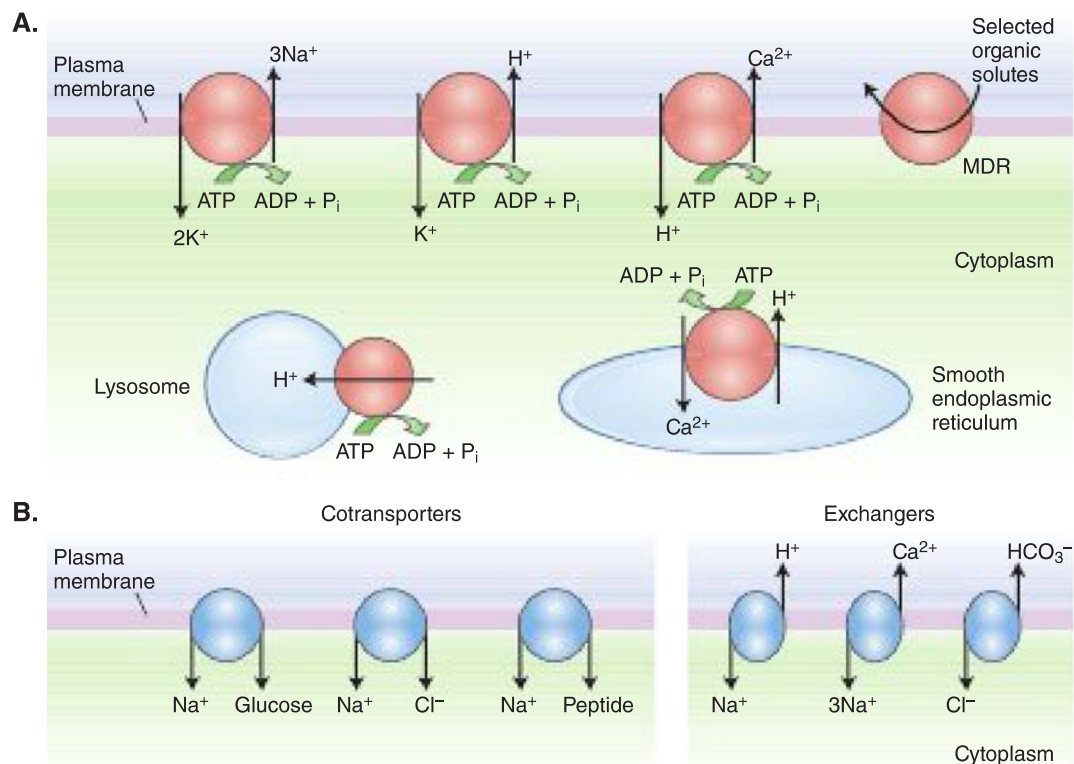
- ii. Approximately 80% of the ECF is interstitial fluid and the remaining 20% is blood plasma.
- iii. ECF is high in NaCl and low in  $K^+$ , whereas ICF is high in  $K^+$  and low in NaCl.
- iv. Interstitial fluid is similar in composition to plasma, except that *interstitial fluid has almost no protein.*
- v. Osmolarity is the same in all compartments.
- g. ▼ Fluid can move freely from the interstitial to plasma compartments and helps to maintain blood volume during **hemorrhage**.
  - i. Because approximately 80% of the ECF is interstitial fluid and 20% is blood plasma, a hemorrhaging patient must lose about 5 L of ECF before the plasma volume is decreased by 1 L.
  - ii. The reverse is also true; to replace 1 L of plasma volume, approximately 5 L of intravascular isotonic saline must be infused. ▼

### Membrane Transport Mechanisms

1. The transport of solutes across cell membranes is fundamental to the survival of all cells. Specializations in membrane transport mechanisms often underlie tissue function. For example, voltage-sensitive ion channels account for the ability to generate electrical signals.
2. Cell membranes separate the cytosol from the ECF.
  - a. Cell membranes are formed from phospholipids that are an effective barrier against the free movement of most water-soluble solutes.
  - b. Most biologically important substances require a protein-mediated pathway to cross cell membranes.
3. **Solute transport** can be categorized based on the use of cellular energy or the type of transport pathway (Figure 1-3):
  - a. **Active transport** requires adenosine triphosphate (ATP) hydrolysis.
    - i. **Primary active transport** occurs via membrane proteins that *directly couple ATP hydrolysis to solute movement.*
    - ii. **Secondary active transport** couples the transport of two or more solutes together. Energy is used to develop a favorable electrochemical driving force for one solute, which is then used to power the transport of other solutes (e.g., the inwardly directed  $Na^+$  gradient is used to drive glucose uptake from the intestine).
  - b. **Passive transport** does not require ATP hydrolysis or coupling to another solute.
  - c. Primary active transporters (Figure 1-4A):
    - i. **The  $Na^+/K^+$ -ATPase** (known as the “sodium pump”) is present in all cells and transports  $3Na^+$  out of a cell in exchange for  $2K^+$ , using 1 ATP molecule in each transport cycle. *The action of sodium pumps accounts for high  $Na^+$  concentration in ECF and high  $K^+$  concentration in ICF.*
    - ii.  **$Ca^{2+}$ -ATPases** are located in the plasma membrane and endoplasmic reticulum membrane and function to maintain very low intracellular  $[Ca^{2+}]$ .
    - iii.  **$H^+/K^+$ -ATPases** pump  $H^+$  out of cells in exchange for  $K^+$  and are present in several epithelia.  $H^+/K^+$ -ATPase is responsible for the secretion of acidic gastric juice in the stomach.



**Figure 1-3.** Classification of membrane transport systems.



**Figure 1-4.** Active transport. **A.** Examples of primary active transporters (ATPases) in the plasma membrane and in organelles. **B.** Examples of secondary active transporters; cotransporters transport solutes in the same direction, and exchangers transport solutes in opposite directions. ADP, adenosine diphosphate; ATP, adenosine triphosphate; MDR, multidrug resistance.

- iv. **H<sup>+</sup>-ATPases** are mainly expressed inside cells, including the vacuolar H<sup>+</sup>-ATPase, which acidifies lysosomes; **ATP synthase** is a form of H<sup>+</sup>-ATPase, which operates in reverse to synthesize ATP in mitochondria.
- v. The **multidrug resistance (MDR) transporters** are ATPases that extrude a wide variety of organic molecules from cells. MDRs are physiologically expressed in the liver, kidney, and blood-brain barrier.
  - ▼ The expression of **MDR transporters** (e.g., P-glycoprotein) is one mechanism by which bacteria and cancer cells can become drug resistant. The effectiveness of a drug will be reduced if it is transported out of the target cell by MDR transporters. ▼
- d. There are many examples of secondary active transporters (Figure 1-4B):
  - i. **Cotransporters (symporters)** couple the movement of two or more solutes in the same direction.
    - Examples of Na<sup>+</sup>-driven cotransporters include Na<sup>+</sup>/glucose uptake in the intestine and diuretic-sensitive Na<sup>+</sup>/K<sup>+</sup>/Cl<sup>-</sup> and Na<sup>+</sup>/Cl<sup>-</sup> uptake in the kidney.
    - H<sup>+</sup>/peptide cotransport in the intestine is an example of Na<sup>+</sup>-independent cotransport.
  - ii. **Exchangers (antiporters)** couple the movement of two solutes in the opposite direction.
    - Na<sup>+</sup>-driven antiporters include Na<sup>+</sup>/Ca<sup>2+</sup> and Na<sup>+</sup>/H<sup>+</sup> exchange, which are important for maintaining low intracellular [Ca<sup>2+</sup>] and [H<sup>+</sup>], respectively.
    - Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchange is an example of an anion exchanger. It is widely expressed, for example, in red blood cells, where it assists in HCO<sub>3</sub><sup>-</sup> transport into and out of the cell as part of the blood-CO<sub>2</sub> transport system.
- e. Passive transport can only occur along a favorable electrochemical gradient.
- f. **Simple passive transport** is characterized by a linear relationship between the transport rate and the electrochemical driving force.
- g. Pathways for simple passive transport include diffusion through the lipid bilayer or via pores or channels in the membrane (Figure 1-5A).
- h. **Fick's law of diffusion** describes the simple diffusion of an uncharged solute (s):

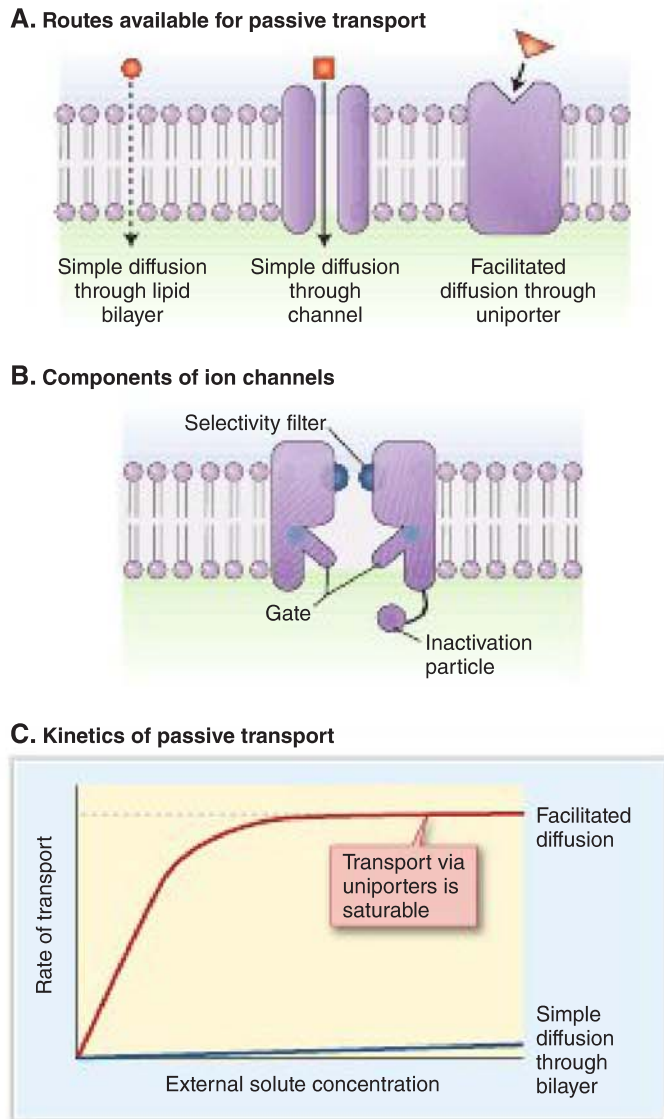
$$J_s = -P_s \Delta C_s \quad \text{Equation 1-1}$$

$J_s$  = Net flux per unit area

$P_s$  = Permeability

$\Delta C_s$  = Concentration difference of *s* across the membrane

- i. **Permeability** is a single coefficient relating the driving force for diffusion to net flux.
  - i. The membrane permeability to a solute is proportional to the lipid solubility of the solute and inversely proportional to its molecular size.
  - ii. *Gases are an example of molecules that are able to move through the lipid bilayer of cell membranes by simple diffusion because they are small and lipid soluble.*

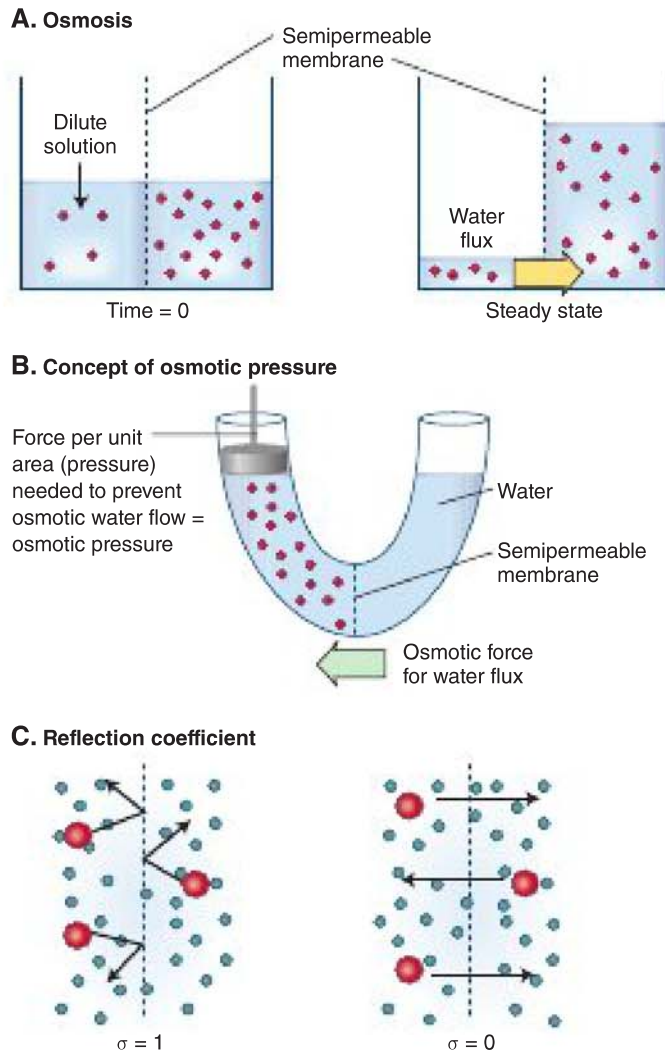


**Figure 1-5.** **A.** Passive transport pathways. **B.** General components of ion channels components. **C.** Kinetics of passive transport. Note the linear relationship between simple diffusion and flux; facilitated diffusion via uniporters is faster than simple diffusion but is saturable.

- j. The passive transport of ions and other small water-soluble molecules across a cell membrane requires transport proteins that span the membrane.
- k. **Ion channels** are the most numerous example of passive transporters. Ion channels have the following **general components** (Figure 1-5B):
  - i. A **pore region**, through which ions diffuse.
  - ii. A **selectivity filter** within the pore, causing the channel to be highly selective for a particular ion (e.g.,  $\text{Na}^+$  channels).
  - iii. A **gating mechanism** that opens and closes the channel; gates may be controlled by membrane voltage (**voltage-gated channels**), chemicals (**ligand-gated channels**), or mechanical forces in the membrane (e.g., **stretch-activated channels**).
- l. Passive transport can also occur via **uniporters**, which selectively bind a single solute at one side of the membrane and undergo a conformational change to deliver it to the other side.

- i. Solute transport via uniporters is called **facilitated diffusion** because it is faster than simple diffusion (Figure 1-5C).
    - ii. A characteristic feature of facilitated diffusion is the saturation of the transport rate at high solute concentrations.
    - iii. The **GLUT family** are examples of uniporters for glucose transport that are expressed in many tissues.
  - m. *Macromolecules are transported between the ICF and the ECF using membrane-limited vesicles.*
    - i. **Endocytosis** is the ingestion of extracellular material to form endocytic vesicles inside a cell. There are three **types of endocytosis**:
      - **Pinocytosis** is the ingestion of small particles and ECF that occurs constitutively in most cells.
      - **Phagocytosis** is the uptake of large particles (e.g., microorganisms) that occurs in specialized immune cells.
      - **Receptor-mediated endocytosis** allows uptake of specific molecules and occurs at specialized areas of membrane called **clathrin-coated pits** (e.g., uptake of cholesterol from low-density lipoproteins).
    - ii. **Exocytosis** is export of soluble proteins into the extracellular space by vesicular transport. When vesicles containing proteins fuse with the plasma membrane, the soluble proteins are secreted and the vesicle membrane is incorporated in the plasma membrane. There are two **pathways for exocytosis**:
      - The **constitutive pathway** is present in most cells and is used to export extracellular matrix proteins.
      - The **regulated pathway** is present in cells that are specialized for the secretion of proteins such as hormones, neurotransmitters, and digestive enzymes. *An increase in the intracellular  $Ca^{2+}$  concentration is a key event that triggers regulated exocytosis.*
      - ▼ **Lambert-Eaton syndrome** is a neurologic condition resulting from autoantibodies that bind to and block  $Ca^{2+}$  channels on the presynaptic motor nerve terminals. By blocking the  $Ca^{2+}$  channels, the  $Ca^{2+}$ -dependent exocytosis of vesicles filled with acetylcholine (a neurotransmitter needed for muscle contraction) is inhibited, resulting in muscle weakness. ▼
4. **Osmosis.**
- a. *Water transport across a barrier is always passive, driven either by a diffusion gradient or by a hydrostatic pressure gradient.*
  - b. Osmosis is water movement that is driven by a **water concentration gradient** across a membrane (Figure 1-6A).
  - c. Water concentration is expressed in terms of total solute concentration; the more dilute a solution, the lower its solute concentration and the higher its water concentration.
  - d. When two solutions are separated by a **semipermeable membrane** (i.e., one that allows the transport of water but not solutes), *water moves by osmosis away from the more dilute solution.*
  - e. **Osmolarity** is an expression of the osmotic strength of a solution and is the **total solute concentration**.
    - i. Osmolarity is the product of the molar solute concentration and the number of particles that the solute dissociates into when dissolved. For example:





**Figure 1-6.** Osmosis. **A.** Illustration of osmotic water movement across a semipermeable membrane. **B.** The concept of osmotic pressure. **C.** Reflection coefficients: Solutes that do not permeate the membrane exert all their osmotic pressure ( $\sigma = 1$ ); freely permeable solutes ( $\sigma = 0$ ) do not exert any osmotic pressure.

- 1 mol of glucose dissolved in 1 L of water produces a solution of 1 Osm/L.
  - 1 mol of NaCl dissolved in 1 L of water produces a solution of approximately 2 Osm/L.
- ii. Two solutions of the same osmolarity are termed **isosmotic**. A solution with a greater osmolarity than a reference solution is said to be **hyperosmotic**, and a solution of lower osmolarity is described as **hyposmotic**.
  - iii. Osmolarity can be converted into units of pressure, which allow osmotic and hydrostatic pressure gradients to be mathematically combined; for example, when considering fluid filtration across capillary walls (see Chapter 4).
  - iv. The concept of osmotic pressure ( $\pi$ ) is illustrated in Figure 1-6B and is calculated by **van't Hoff law**:

$$\pi = g \times C \times RT$$

**Equation 1-2**

$g$  = Number of particles produced when the solute dissociates in solution

$C$  = Molar solute concentration

$R$  = Gas constant

$T$  = Temperature

- f. Although blood plasma contains many solutes, a simplified **clinical estimate of plasma osmolarity** can be obtained by considering only the  $\text{Na}^+$ , glucose, and urea concentrations:

$$P_{\text{Osm}} = 2P_{\text{Na}} + (P_{\text{glucose}} / 18) + (P_{\text{urea}} / 2.8) \quad \text{Equation 1-3}$$

$P_{\text{Osm}}$  = Plasma osmolarity (mOsm/L)

$P_{\text{Na}}$  = Plasma [Na] (mEq/L)

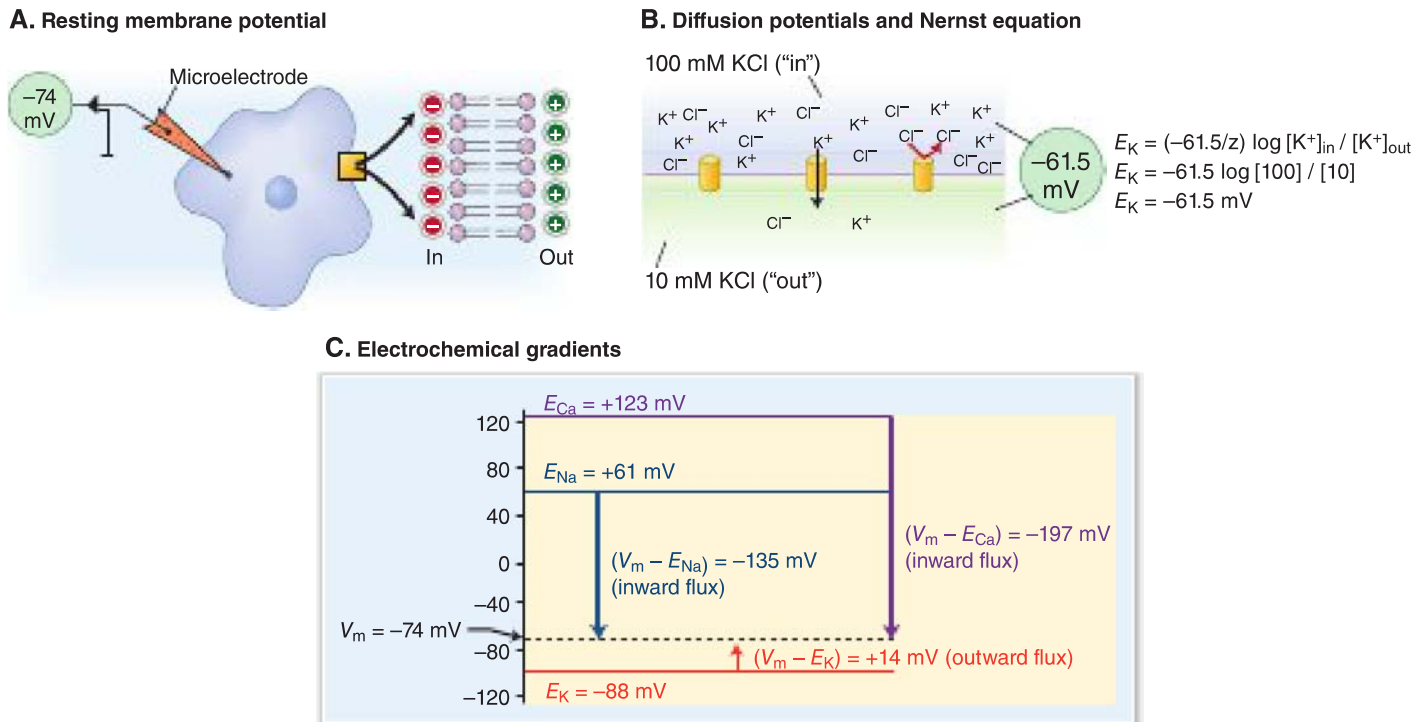
$P_{\text{glucose}}$  = Plasma [glucose] (mg/dL)

$P_{\text{urea}}$  = Plasma [urea] (mg/dL)

- g. A difference between the measured and estimated osmolarity is called an **osmolar gap** and is *caused by the presence of additional solutes in plasma*.
- i. ▼ Patients with **alcohol intoxication** or **ethylene glycol poisoning** will have an increased osmolar gap. ▼
- h. The concept of effective osmolarity (tonicity) includes the effect of solute permeation through membranes (Figure 1-6C).
- i. Most biologic membranes are not completely semipermeable.
  - ii. *When the membrane is permeated by the solute, the observed osmotic pressure gradient is reduced.*
  - iii. The **reflection coefficient** ( $\sigma$ ) is the fraction of the measured osmolarity actually applied:
    - $\sigma = 1.0$  for solutes that do not permeate a membrane.
    - $\sigma = 0$  when the membrane is freely permeable to the solute.
    - The effective osmolarity of a solution is calculated as the product of the osmolarity and the reflection coefficient (e.g., if  $\sigma = 0.5$ , the effective osmolarity exerted is only 50% of the measured osmolarity).
  - iv. The terms **isotonic**, **hypotonic**, and **hypertonic** are used to describe the effective osmolarity of a solution relative to a cell:
    - An **isotonic solution** has the same effective osmolarity as the cell and causes *no net water movement*.
    - A **hypotonic solution** has a smaller effective osmolarity and *causes cells to swell*.
    - A **hypertonic solution** has a larger effective osmolarity and *causes cells to shrink*.
  - v. ▼ *At steady state the ECF is isotonic with respect to the ICF because water moves freely across most cell membranes.* When the steady state is temporarily disrupted, water moves until ICF and ECF tonicity again becomes equal. For example, if a patient is intravenously infused with a **hypotonic saline solution**, the ECF tonicity is initially decreased and some water moves into the ICF by osmosis (i.e., cells swell). ▼

## Membrane Potentials

1. All living cells have a membrane potential difference in which the cytoplasm is negative with respect to the ECF (Figure 1-7A).



**Figure 1-7. A.** The resting membrane potential; all cells have a negative intracellular potential. **B.** Generation of a  $K^+$  diffusion potential. In this example,  $K^+$  is the only permeable ion; a small amount of  $K^+$  diffuses to the lower compartment, creating a negative potential in the upper compartment. The Nernst equation predicts the equilibrium potential (voltage), based on the size of the  $K^+$  concentration ratio between compartments. **C.** Electrochemical gradients. Membrane potential ( $V_m$ ) is shown by the dashed line. Downward arrows indicate gradients for cation flux into the cell; the upward arrow indicates a gradient for cation efflux.

2. *Membrane potentials arise because there are stable ion diffusion gradients across the membrane and because cell membranes contain ion channels that provide selective ion permeability.*
3. The following steps are involved in the development of a **diffusion potential**:
  - a. In the example in Figure 1-7B, two potassium chloride (KCl) solutions are separated by a membrane that is permeable to  $K^+$  but not to  $Cl^-$ .
  - b.  $K^+$  **diffuses** from the upper to the lower compartment, down its concentration gradient. In this case,  $Cl^-$  cannot follow.
  - c. A **voltage difference** develops as the  $K^+$  ions leave the upper compartment, leaving a net negative charge behind. *A very slight separation of KCl ion pairs is enough to generate physiologic voltages.*
  - d. The negative potential in the upper compartment attracts  $K^+$  ions and opposes the  $K^+$  concentration gradient.
  - e. An **equilibrium potential** is established when the voltage difference and the concentration gradient are equal but opposite driving forces. *At the equilibrium potential, there is no net movement of  $K^+$ .*
  - f. This simulated example is analogous to most resting cells, which contain a high  $[K^+]$  and have numerous open  $K^+$  channels at rest (note, however, that the major intracellular anion in cells is protein, not  $Cl^-$ ).
4. The equilibrium potential is a function of the size of the ion concentration gradient (Table 1-3) and is calculated using the **Nernst equation**:

**Table 1-3.** Ion Concentrations and Equilibrium Potentials

Ion	[Intracellular] mM	[Extracellular] mM	$E_{\text{Nernst}}$ mV
<b>Excitable cells (nerve and muscle)</b>			
$\text{Na}^+$	12	145	+67
$\text{K}^+$	155	4.5	-95
$\text{Ca}^{2+}$	$10^{-4}$	1.0	+123
$\text{Cl}^-$	4	115	-89
$\text{HCO}_3^-$	12	24	-19
<b>Nonexcitable cells</b>			
$\text{Na}^+$	15	145	+61
$\text{K}^+$	120	4.5	-88
$\text{Ca}^{2+}$	$10^{-4}$	1.0	+123
$\text{Cl}^-$	20	115	-47
$\text{HCO}_3^-$	16	24	-13

$$E_x = \frac{-61.5}{z} \log \frac{[X]_i}{[X]_o} \quad \text{Equation 1-4}$$

$E_x$  = Equilibrium potential for ion x

$z$  = Ion valence (+1 for  $\text{K}^+$ , -1 for  $\text{Cl}^-$ , +2 for  $\text{Ca}^{2+}$ , and so on)

$[X]_i$  = Intracellular concentration of X

$[X]_o$  = Extracellular concentration of X

- a. **Example.** The only ion channels that open in a resting cell are  $\text{K}^+$  channels. If the intracellular  $[\text{K}^+] = 155 \text{ mM/L}$  and the ECF  $[\text{K}^+] = 4.5 \text{ mM/L}$ , predict the resting membrane potential.
- i. The magnitude of the  $\text{K}^+$  diffusion potential that develops is calculated using Equation 1-4:

$$E_x = \frac{-61.5}{z} \log \frac{[\text{K}]_i}{[\text{K}]_o} \text{ mV}$$

$$E_x = \frac{-61.5}{z} \log \frac{[155]_i}{[4.5]_o} \text{ mV}$$

$$E_x = -94.5 \text{ mV}$$

5. Resting membrane potential.
- a. The measured membrane potential ( $V_m$ ) will usually be a composite of several diffusion potentials because the membrane is usually permeable to more than one ion.
- b. Ion permeability is best expressed in terms of electrical **conductance** to reflect ion movement through channels.
- c.  $V_m$  can be expressed as the weighted average of ion equilibrium potentials for permeable ions. For example, in the case of a cell with permeability to  $\text{K}^+$ ,  $\text{Na}^+$ , and  $\text{Cl}^-$ :

$$V_m = (g_K/g_m)E_K + (g_{\text{Na}}/g_m)E_{\text{Na}} + (g_{\text{Cl}}/g_m)E_{\text{Cl}} \quad \text{Equation 1-5}$$

$g_x/g_m$  = Fractional conductance of ion x  
 $E_x$  = Equilibrium potential for ion x

- i. **Example.** Estimate the membrane potential that will arise, using data in Table 1-3, for a nonexcitable cell and assuming that 80% of the total membrane conductance is due to  $K^+$  channels, 5% is due to  $Na^+$  channels, and 15% is due to  $Cl^-$  channels:

$$\begin{aligned} V_m &= (0.80)E_K + (0.05)E_{Na} + (0.15)E_{Cl} \\ &= (0.80 \times -88) + (0.05 \times 61) + (0.15 \times -47) \\ &= -74.4 \text{ mV} \end{aligned}$$

- d. In most cells,  $V_m$  is primarily a function of ECF  $[K^+]$  because  $K^+$  conductance predominates in most cells at rest.
- e. Although the  $Na^+/K^+$ -ATPase is electrogenic (i.e.,  $3Na^+$  are pumped out for every  $2K^+$  pumped into the cell), its direct contribution to the membrane potential is small. *The importance of the  $Na^+/K^+$ -ATPase in the development of resting membrane potentials is to maintain resting ion concentration gradients.*
- f. According to Equation 1-5,  $V_m$  will only change if equilibrium potentials are disturbed (i.e., if ion concentration gradients change), or if the membrane conductance to an ion changes because ion channels open or close.
- g. The following terms are used to describe **changes in the membrane potential**:
- Depolarization** is a change to a less negative membrane potential (membrane potential difference is decreased).
  - Hyperpolarization** occurs when the membrane potential becomes more negative (membrane potential difference is increased).
  - Repolarization** is the return of the membrane potential toward  $V_m$  following either depolarization or hyperpolarization.
- h. **Hyperkalemia** is a potentially fatal condition in which the serum  $[K^+]$  is increased. According to the Nernst equation, an increase in the serum  $[K^+]$  will decrease  $E_K$  and therefore will depolarize  $V_m$ , which can cause fatal cardiac arrhythmias. Using the following example, consider the effects on the heart when a normal serum  $[K^+]$  of 4.5 mM is doubled to 9.0 mM.
- Part 1.** Calculate the expected resting membrane potential for cardiac cells using the data in Table 1-3 for excitable cells (note  $[K^+] = 4.5$  mM) and assuming the following fractional membrane conductance values:  
 $g_K/g_m = 0.90$ ,  $g_{Na}/g_m = 0.05$ ,  $g_{Cl}/g_m = 0.05$ .  

$$\begin{aligned} V_m &= (0.90)E_K + (0.05)E_{Na} + (0.05)E_{Cl} \\ &= (0.90 \times -95 \text{ mV}) + (0.05 \times 67 \text{ mV}) + (0.05 \times -89 \text{ mV}) \\ &= -87.0 \text{ mV} \end{aligned}$$
  - Part 2.** Calculate the expected change in the resting membrane potential when the serum  $[K^+]$  is doubled to 9.0 mM. Assume all other variables are unchanged.
  - The first step is to calculate the new equilibrium potential based on Equation 1-4 (the Nernst equation):

$$E_x = \frac{-61.5}{z} \log \frac{[K]_i}{[K]_o} \text{ mV}$$

$$E_x = \frac{-61.5}{z} \log \frac{[155]_i}{[9]_o} \text{ mV}$$

$$E_x = -76 \text{ mV}$$

Recalculating the resting membrane potential, using the new value for  $E_K$ :

$$\begin{aligned} V_m &= (0.90)E_K + (0.05)E_{Na} + (0.05)E_{Cl} \\ &= (0.90 \times -76) + (0.05 \times 67) + (0.05 \times -89) \\ &= -69.5 \text{ mV} \end{aligned}$$

- iv. Depolarizing excitable cardiac myocytes from a membrane potential of  $-87 \text{ mV}$  to  $-69.5 \text{ mV}$  may be enough to trigger extra cardiac action potentials, which may lead to a fatal arrhythmia. ▼
6. The **electrochemical gradient** for an ion is the *net* driving force for ion flux, which is a combination of the membrane voltage and the ion concentration gradient (Figure 1-7C).
- The Nernst equation converts the ion concentration gradient into mV units for combination with the membrane voltage; the electrochemical gradient is defined as  $(V_m - E_x)$ .
    - A positive value represents a driving force for outward cation flux or inward anion flux.
    - A negative value represents a driving force for inward cation flux or outward anion flux.

### Action Potential

- Excitable tissues (i.e., neurons and muscle) can respond to a stimulus by rapidly generating and propagating electrical signals.
- An action potential is a constant electrical signal that can be propagated over long distances without decay.
- Action potentials are an **all-or-none impulse** that occurs when an excitable cell membrane is depolarized beyond a **threshold voltage**.
  - Once the threshold has been exceeded, there is a phase of rapid depolarization, which ends abruptly at a **peak voltage** greater than  $0 \text{ mV}$ .
  - The **overshoot** is the amount that the peak voltage exceeds  $0 \text{ mV}$ .
  - A slower **repolarizing phase** returns membrane potential toward  $V_m$ .
  - An **afterhyperpolarization** (undershoot) is observed in nerves (but not in muscle), in which the membrane potential is transiently more negative than the resting membrane potential.
- The phases of an action potential are explained by changes in membrane  $\text{Na}^+$  and  $\text{K}^+$  conductance with time* (Figure 1-8A):
  - Rapid depolarization** after threshold voltage is exceeded is due to the opening of **voltage-gated  $\text{Na}^+$  channels**.
  - The **peak voltage** where rapid depolarization abruptly ends and the membrane enters the repolarizing phase has two components:
    - Closure of **inactivation gates** on  $\text{Na}^+$  channels.
    - Opening of **voltage-gated  $\text{K}^+$  channels**.
  - Repolarization** of the membrane potential progresses due to the decreasing  $\text{Na}^+$  conductance and the increasing  $\text{K}^+$  conductance.