

**BOARD  
REVIEW  
SERIES**

**INCLUDES**  
Online Access to  
Questions and  
Images from  
the Book!

# PHYSIOLOGY

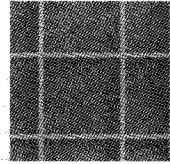
**4TH EDITION**

**Linda S. Costanzo**

- All questions and images provided both in print and online!
- Approximately 350 USMLE-type questions with explanations
- Numerous illustrations, tables, and equations
- Easy-to-follow outline covering all USMLE-tested topics

 Lippincott Williams & Wilkins  
a Wolters Kluwer business

thePoint 



# Preface

---

The subject matter of physiology is the foundation of the practice of medicine, and a firm grasp of its principles is essential for the physician. This book is intended to aid the student preparing for the United States Medical Licensing Examination (USMLE) Step 1. It is a concise review of key physiologic principles and is intended to help the student recall material taught during the first and second years of medical school. It is not intended to substitute for comprehensive textbooks or for course syllabi, although the student may find it a useful adjunct to physiology and pathophysiology courses.

The material is organized by organ system into seven chapters. The first chapter reviews general principles of cellular physiology. The remaining six chapters review the major organ systems—neurophysiology, cardiovascular, respiratory, renal and acid–base, gastrointestinal, and endocrine physiology.

Difficult concepts are explained stepwise, concisely, and clearly, with appropriate illustrative examples and sample problems. Numerous clinical correlations are included so that the student can understand physiology in relation to medicine. An integrative approach is used, when possible, to demonstrate how the organ systems work together to maintain homeostasis. More than 130 illustrations and flow diagrams and more than 50 tables help the student visualize the material quickly and aid in long-term retention. The inside front cover contains “Key Physiology Topics for USMLE Step 1.” The inside back cover contains “Key Physiology Equations for USMLE Step 1.”

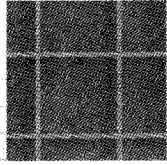
Questions reflecting the content and format of USMLE Step 1 are included at the end of each chapter and in a Comprehensive Examination at the end of the book. These questions, many with clinical relevance, require problem-solving skills rather than straight recall. Clear, concise explanations accompany the questions and guide the student through the correct steps of reasoning. The questions can be used as a pretest to identify areas of weakness or as a post-test to determine mastery. Special attention should be given to the Comprehensive Examination, because its questions integrate several areas of physiology and related concepts of pathophysiology and pharmacology.

New to this edition:

- Addition of new figures
- Updated organization and text and the addition of color
- Expanded coverage of cellular, respiratory, renal, gastrointestinal, and endocrine physiology
- Increased emphasis on pathophysiology

Best of luck in your preparation for USMLE Step 1!

*Linda S. Costanzo, Ph.D.*



# Contents

---

Preface vii

Acknowledgments ix

## **1 Cell Physiology** ..... 1

- I.** Cell Membranes 1
- II.** Transport Across Cell Membranes 2
- III.** Osmosis 5
- IV.** Diffusion Potential, Resting Membrane Potential, and Action Potential 7
- V.** Neuromuscular and Synaptic Transmission 13
- VI.** Skeletal Muscle 17
- VII.** Smooth Muscle 21
- VIII.** Comparison of Skeletal Muscle, Smooth Muscle, and Cardiac Muscle 22
- Review Test** 23

## **2 Neurophysiology** ..... 33

- I.** Autonomic Nervous System 33
- II.** Sensory Systems 37
- III.** Motor Systems 49
- IV.** Higher Functions of the Cerebral Cortex 56
- V.** Blood-Brain Barrier and Cerebrospinal Fluid 57
- VI.** Temperature Regulation 58
- Review Test** 60

## **3 Cardiovascular Physiology** ..... 68

- I.** Circuitry of the Cardiovascular System 68
- II.** Hemodynamics 68
- III.** Cardiac Electrophysiology 73
- IV.** Cardiac Muscle and Cardiac Output 78
- V.** Cardiac Cycle 88
- VI.** Regulation of Arterial Pressure 90
- VII.** Microcirculation and Lymph 94
- VIII.** Special Circulations 97
- IX.** Integrative Functions of the Cardiovascular System: Gravity, Exercise, and Hemorrhage 100
- Review Test** 105

<b>4 Respiratory Physiology</b> .....	<b>119</b>
I. Lung Volumes and Capacities	119
II. Mechanics of Breathing	121
III. Gas Exchange	128
IV. Oxygen Transport	130
V. CO <sub>2</sub> Transport	135
VI. Pulmonary Circulation	136
VII. Ventilation/Perfusion Defects	137
VIII. Control of Breathing	139
IX. Integrated Responses of the Respiratory System	141
<b>Review Test</b>	<b>143</b>
<b>5 Renal and Acid–Base Physiology</b> .....	<b>151</b>
I. Body Fluids	151
II. Renal Clearance, Renal Blood Flow, and Glomerular Filtration Rate	155
III. Reabsorption and Secretion	159
IV. NaCl Regulation	163
V. K <sup>+</sup> Regulation	167
VI. Renal Regulation of Urea, Phosphate, Calcium, and Magnesium	170
VII. Concentration and Dilution of Urine	171
VIII. Renal Hormones	176
IX. Acid–Base Balance	176
X. Diuretics	186
XI. Integrative Examples	186
<b>Review Test</b>	<b>189</b>
<b>6 Gastrointestinal Physiology</b> .....	<b>201</b>
I. Structure and Innervation of the Gastrointestinal Tract	201
II. Regulatory Substances in the Gastrointestinal Tract	202
III. Gastrointestinal Motility	206
IV. Gastrointestinal Secretion	211
V. Digestion and Absorption	221
<b>Review Test</b>	<b>228</b>
<b>7 Endocrine Physiology</b> .....	<b>234</b>
I. Overview of Hormones	234
II. Cell Mechanisms and Second Messengers	236
III. Pituitary Gland (Hypophysis)	240
IV. Thyroid Gland	245
V. Adrenal Cortex and Adrenal Medulla	248
VI. Endocrine Pancreas—Glucagon and Insulin	255
VII. Calcium Metabolism (Parathyroid Hormone, Vitamin D, Calcitonin)	259
VIII. Sexual Differentiation	263
IX. Male Reproduction	264
X. Female Reproduction	267
<b>Review Test</b>	<b>272</b>
<b>Comprehensive Examination</b> .....	<b>280</b>
<b>Index</b> .....	<b>305</b>

<b>4 Respiratory Physiology</b> .....	<b>119</b>
I. Lung Volumes and Capacities	119
II. Mechanics of Breathing	121
III. Gas Exchange	128
IV. Oxygen Transport	130
V. CO <sub>2</sub> Transport	135
VI. Pulmonary Circulation	136
VII. Ventilation/Perfusion Defects	137
VIII. Control of Breathing	139
IX. Integrated Responses of the Respiratory System	141
<b>Review Test</b>	<b>143</b>
<b>5 Renal and Acid–Base Physiology</b> .....	<b>151</b>
I. Body Fluids	151
II. Renal Clearance, Renal Blood Flow, and Glomerular Filtration Rate	155
III. Reabsorption and Secretion	159
IV. NaCl Regulation	163
V. K <sup>+</sup> Regulation	167
VI. Renal Regulation of Urea, Phosphate, Calcium, and Magnesium	170
VII. Concentration and Dilution of Urine	171
VIII. Renal Hormones	176
IX. Acid–Base Balance	176
X. Diuretics	186
XI. Integrative Examples	186
<b>Review Test</b>	<b>189</b>
<b>6 Gastrointestinal Physiology</b> .....	<b>201</b>
I. Structure and Innervation of the Gastrointestinal Tract	201
II. Regulatory Substances in the Gastrointestinal Tract	202
III. Gastrointestinal Motility	206
IV. Gastrointestinal Secretion	211
V. Digestion and Absorption	221
<b>Review Test</b>	<b>228</b>
<b>7 Endocrine Physiology</b> .....	<b>234</b>
I. Overview of Hormones	234
II. Cell Mechanisms and Second Messengers	236
III. Pituitary Gland (Hypophysis)	240
IV. Thyroid Gland	245
V. Adrenal Cortex and Adrenal Medulla	248
VI. Endocrine Pancreas—Glucagon and Insulin	255
VII. Calcium Metabolism (Parathyroid Hormone, Vitamin D, Calcitonin)	259
VIII. Sexual Differentiation	263
IX. Male Reproduction	264
X. Female Reproduction	267
<b>Review Test</b>	<b>272</b>
<b>Comprehensive Examination</b> .....	<b>280</b>
<b>Index</b> .....	<b>305</b>

# Cell Physiology

## Cell Membranes

---

- are composed primarily of phospholipids and proteins.

### A. Lipid bilayer

1. **Phospholipids** have a **glycerol backbone**, which is the hydrophilic (water-soluble) head, and two **fatty acid tails**, which are hydrophobic (water-insoluble). The hydrophobic tails face each other and form a bilayer.
2. **Lipid-soluble substances** (e.g., O<sub>2</sub>, CO<sub>2</sub>, steroid hormones) cross cell membranes because they can dissolve in the hydrophobic lipid bilayer.
3. **Water-soluble substances** (e.g., Na<sup>+</sup>, Cl<sup>-</sup>, glucose, H<sub>2</sub>O) cannot dissolve in the lipid of the membrane, but may cross through water-filled channels, or pores, or may be transported by carriers.

### B. Proteins

#### 1. *Integral proteins*

- are anchored to, and imbedded in, the cell membrane through **hydrophobic** interactions.
- may span the cell membrane.
- include ion channels, transport proteins, receptors, and guanosine 5'-triphosphate (GTP)-binding proteins (G proteins).

#### 2. *Peripheral proteins*

- are *not* imbedded in the cell membrane.
- are *not* covalently bound to membrane components.
- are loosely attached to the cell membrane by **electrostatic** interactions.

### C. Intercellular connections

#### 1. *Tight junctions (zonula occludens)*

- are the attachments between cells (often epithelial cells).
- may be an intercellular pathway for solutes, depending on the size, charge, and characteristics of the tight junction.
- may be "**tight**" (impermeable), as in the renal distal tubule, or "**leaky**" (permeable), as in the renal proximal tubule and gallbladder.

#### 2. *Gap junctions*

- are the attachments between cells that permit intercellular communication.
- for example, permit current flow and electrical **coupling between myocardial cells**.

## II. Transport Across Cell Membranes (Table 1-1)

### A. Simple diffusion

#### 1. Characteristics of simple diffusion

- is the only form of transport that is **not carrier-mediated**.
- occurs **down an electrochemical gradient** ("downhill").
- does not require metabolic energy and therefore is passive.

#### 2. Diffusion can be measured using the following equation:

$$J = -PA (C_1 - C_2)$$

where:

J = flux (flow) [mmol/sec]

P = permeability (cm/sec)

A = area (cm<sup>2</sup>)

C<sub>1</sub> = concentration<sub>1</sub> (mmol/L)

C<sub>2</sub> = concentration<sub>2</sub> (mmol/L)

#### 3. Sample calculation for diffusion

- The urea concentration of blood is 10 mg/100 mL. The urea concentration of proximal tubular fluid is 20 mg/100 mL. If the permeability to urea is  $1 \times 10^{-5}$  cm/sec and the surface area is 100 cm<sup>2</sup>, what are the magnitude and direction of the urea flux?

$$\begin{aligned} \text{Flux} &= \left( \frac{1 \times 10^{-5} \text{ cm}}{\text{sec}} \right) (100 \text{ cm}^2) \left( \frac{20 \text{ mg}}{100 \text{ mL}} \right) - \left( \frac{10 \text{ mg}}{100 \text{ mL}} \right) \\ &= \left( \frac{1 \times 10^{-5} \text{ cm}}{\text{sec}} \right) (100 \text{ cm}^2) \left( \frac{10 \text{ mg}}{100 \text{ mL}} \right) \\ &= \left( \frac{1 \times 10^{-5} \text{ cm}}{\text{sec}} \right) (100 \text{ cm}^2) \left( \frac{0.1 \text{ mg}}{\text{cm}^3} \right) \\ &= 1 \times 10^{-4} \text{ mg/sec from lumen to blood (high to low concentration)} \end{aligned}$$

**Note:** The minus sign preceding the diffusion equation indicates that the direction of flux, or flow, is from high to low concentration. It can be ignored if the higher concentration is called C<sub>1</sub> and the lower concentration is called C<sub>2</sub>.

**Also note:** 1 mL = 1 cm<sup>3</sup>.

TABLE 1-1

Characteristics of Different Types of Transport

Type	Electrochemical Gradient	Carrier-mediated	Metabolic Energy	Na <sup>+</sup> Gradient	Inhibition of Na <sup>+</sup> -K <sup>+</sup> Pump
Simple diffusion	Downhill	No	No	No	—
Facilitated diffusion	Downhill	Yes	No	No	—
Primary active transport	Uphill	Yes	Yes	—	Inhibits (if Na <sup>+</sup> -K <sup>+</sup> pump)
Cotransport	Uphill*	Yes	Indirect	Yes, same direction	Inhibits
Countertransport	Uphill*	Yes	Indirect	Yes, opposite direction	Inhibits

\*One or more solutes are transported uphill; Na<sup>+</sup> is transported downhill.

#### 4. Permeability

- is the P in the equation for diffusion.
  - describes the ease with which a solute diffuses through a membrane.
  - depends on the characteristics of the solute and the membrane.
- a. **Factors that increase permeability:**
    - $\uparrow$  **Oil/water partition coefficient** of the solute increases solubility in the lipid of the membrane.
    - $\downarrow$  **Radius (size) of the solute** increases the speed of diffusion.
    - $\downarrow$  **Membrane thickness** decreases the diffusion distance.
  - b. Small hydrophobic solutes have the highest permeabilities in lipid membranes.
  - c. Hydrophilic solutes must cross cell membranes through water-filled channels, or pores. If the solute is an ion (is charged), then its flux will depend on both the concentration difference and the potential difference across the membrane.

#### B. Carrier-mediated transport

- includes facilitated diffusion and primary and secondary active transport.
- The **characteristics** of carrier-mediated transport are:
  1. **Stereospecificity.** For example, D-glucose (the natural isomer) is transported by facilitated diffusion, but the L-isomer is not. Simple diffusion, in contrast, would not distinguish between the two isomers because it does not involve a carrier.
  2. **Saturation.** The transport rate increases as the concentration of the solute increases, until the carriers are saturated. The **transport maximum** ( $T_m$ ) is analogous to the maximum velocity ( $V_{max}$ ) in enzyme kinetics.
  3. **Competition.** Structurally related solutes compete for transport sites on carrier molecules. For example, galactose is a competitive inhibitor of glucose transport in the small intestine.

#### C. Facilitated diffusion

##### 1. Characteristics of facilitated diffusion

- occurs **down an electrochemical gradient** ("downhill"), similar to simple diffusion.
- does not require metabolic energy and therefore is **passive**.
- is more **rapid** than simple diffusion.
- is **carrier-mediated** and therefore exhibits stereospecificity, saturation, and competition.

##### 2. Example of facilitated diffusion

- Glucose transport in muscle and adipose cells is "downhill," is carrier-mediated, and is inhibited by sugars such as galactose; therefore, it is categorized as facilitated diffusion. In **diabetes mellitus**, glucose uptake by muscle and adipose cells is impaired because the carriers for facilitated diffusion of glucose require **insulin**.

#### D. Primary active transport

##### 1. Characteristics of primary active transport

- occurs **against an electrochemical gradient** ("uphill").
- requires **direct input of metabolic energy** in the form of adenosine triphosphate (ATP) and therefore is **active**.
- is **carrier-mediated** and therefore exhibits stereospecificity, saturation, and competition.

2. *Examples of primary active transport*

- a. ***Na<sup>+</sup>,K<sup>+</sup>-ATPase (or Na<sup>+</sup>-K<sup>+</sup> pump)*** in cell membranes transports Na<sup>+</sup> from intracellular to extracellular fluid and K<sup>+</sup> from extracellular to intracellular fluid; it maintains low intracellular [Na<sup>+</sup>] and high intracellular [K<sup>+</sup>].
  - Both Na<sup>+</sup> and K<sup>+</sup> are transported against their electrochemical gradients.
  - Energy is provided from the terminal phosphate bond of ATP.
  - The **usual stoichiometry is 3 Na<sup>+</sup>/2 K<sup>+</sup>**.
  - Specific inhibitors of Na<sup>+</sup>,K<sup>+</sup>-ATPase are the cardiac glycoside drugs **ouabain** and **digitalis**.
- b. ***Ca<sup>2+</sup>-ATPase (or Ca<sup>2+</sup> pump)*** in the sarcoplasmic reticulum (SR) or cell membranes transports Ca<sup>2+</sup> against an electrochemical gradient.
  - Sarcoplasmic and endoplasmic reticulum Ca<sup>2+</sup>-ATPase is called **SERCA**.
- c. ***H<sup>+</sup>,K<sup>+</sup>-ATPase (or proton pump)*** in gastric parietal cells transports H<sup>+</sup> into the lumen of the stomach against its electrochemical gradient.
  - It is inhibited by **omeprazole**.

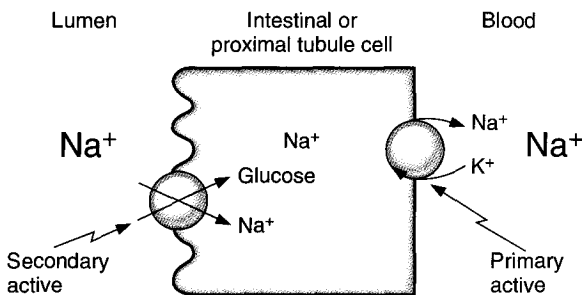
## E. Secondary active transport

1. *Characteristics of secondary active transport*

- a. The transport of two or more solutes is **coupled**.
- b. One of the solutes (usually Na<sup>+</sup>) is transported “downhill” and provides energy for the “uphill” transport of the other solute(s).
- c. Metabolic energy is not provided directly, but indirectly from the **Na<sup>+</sup> gradient** that is maintained across cell membranes. Thus, inhibition of Na<sup>+</sup>,K<sup>+</sup>-ATPase will decrease transport of Na<sup>+</sup> out of the cell, decrease the transmembrane Na<sup>+</sup> gradient, and eventually inhibit secondary active transport.
- d. If the solutes move in the same direction across the cell membrane, it is called **cotransport**, or **symport**.
  - Examples are **Na<sup>+</sup>-glucose cotransport** in the small intestine and **Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransport** in the renal thick ascending limb.
- e. If the solutes move in opposite directions across the cell membranes, it is called **countertransport**, **exchange**, or **antiport**.
  - Examples are **Na<sup>+</sup>-Ca<sup>2+</sup> exchange** and **Na<sup>+</sup>-H<sup>+</sup> exchange**.

2. *Example of Na<sup>+</sup>-glucose cotransport (Figure 1-1)*

- a. The carrier for Na<sup>+</sup>-glucose cotransport is located in the luminal membrane of intestinal mucosal and renal proximal tubule cells.
- b. Glucose is transported “uphill”; Na<sup>+</sup> is transported “downhill.”
- c. Energy is derived from the “downhill” movement of Na<sup>+</sup>. The inwardly directed Na<sup>+</sup> gradient is maintained by the Na<sup>+</sup>-K<sup>+</sup> pump on the basolateral (blood side) membrane. Poisoning the Na<sup>+</sup>-K<sup>+</sup> pump decreases the transmembrane Na<sup>+</sup> gradient and consequently inhibits Na<sup>+</sup>-glucose cotransport.



**Figure 1-1** Na<sup>+</sup>-glucose cotransport (symport) in intestinal or proximal tubule epithelial cell.

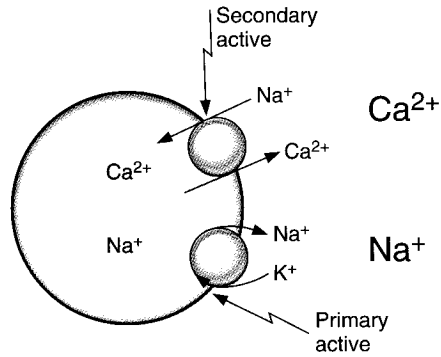


Figure 1-2  $\text{Na}^+$ - $\text{Ca}^+$  countertransport (antiport).

### 3. Example of $\text{Na}^+$ - $\text{Ca}^{2+}$ countertransport or exchange (Figure 1-2)

- Many cell membranes contain a  $\text{Na}^+$ - $\text{Ca}^{2+}$  exchanger that transports  $\text{Ca}^{2+}$  "uphill" from low intracellular  $[\text{Ca}^{2+}]$  to high extracellular  $[\text{Ca}^{2+}]$ .  $\text{Ca}^{2+}$  and  $\text{Na}^+$  move in opposite directions across the cell membrane.
- The energy is derived from the "downhill" movement of  $\text{Na}^+$ . As with cotransport, the inwardly directed  $\text{Na}^+$  gradient is maintained by the  $\text{Na}^+$ - $\text{K}^+$  pump. Poisoning the  $\text{Na}^+$ - $\text{K}^+$  pump therefore inhibits  $\text{Na}^+$ - $\text{Ca}^{2+}$  exchange.

## III. Osmosis

### A. Osmolarity

- is the concentration of osmotically active particles in a solution.
- is a colligative property that can be measured by freezing point depression.
- can be calculated using the following equation:

$$\text{Osmolarity} = g \times C$$

where:

Osmolarity = concentration of particles (osm/L)

$g$  = number of particles in solution (osm/mol)

[e.g.,  $g_{\text{NaCl}} = 2$ ;  $g_{\text{glucose}} = 1$ ]

$C$  = concentration (mol/L)

- Two solutions that have the same calculated osmolarity are **isosmotic**. If two solutions have different calculated osmolarities, the solution with the higher osmolarity is **hyperosmotic** and the solution with the lower osmolarity is **hyposmotic**.
- Sample calculation:** What is the osmolarity of a 1 M NaCl solution?

$$\begin{aligned} \text{Osmolarity} &= g \times C \\ &= 2 \text{ osm/mol} \times 1\text{M} \\ &= 2\text{osm/L} \end{aligned}$$

### B. Osmosis and osmotic pressure

- Osmosis** is the **flow of water** across a semipermeable membrane from a solution with low solute concentration to a solution with high solute concentration.

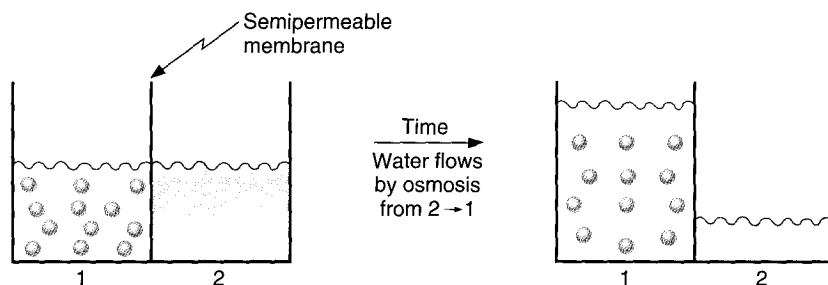


Figure 1-3 Osmosis of H<sub>2</sub>O across a semipermeable membrane.

1. *Example of osmosis* (Figure 1-3)

- Solutions 1 and 2 are separated by a semipermeable membrane. Solution 1 contains a solute that is too large to cross the membrane. Solution 2 is pure water. The presence of the solute in solution 1 produces an **osmotic pressure**.
- The osmotic pressure difference across the membrane causes water to flow from solution 2 (which has no solute and the lower osmotic pressure) to solution 1 (which has the solute and the higher osmotic pressure).
- With time, the volume of solution 1 increases and the volume of solution 2 decreases.

2. *Calculating osmotic pressure (van't Hoff's law)*

- The **osmotic pressure** of solution 1 (see Figure 1-3) can be calculated by van't Hoff's law, which states that osmotic pressure depends on the concentration of osmotically active particles. The concentration of particles is converted to pressure according to the following **equation**:

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

where:

$\pi$  = osmotic pressure (mm Hg or atm)

$g$  = number of particles in solution (osm/mol)

$C$  = concentration (mol/L)

$R$  = gas constant (0.082 L—atm/mol—K)

$T$  = absolute temperature (K)

- The osmotic pressure increases when the solute concentration increases.** A solution of 1 M CaCl<sub>2</sub> has a higher osmotic pressure than a solution of 1 M KCl because the concentration of particles is higher.
  - The higher the osmotic pressure of a solution, the greater the water flow into it.
  - Two solutions having the same effective osmotic pressure are **isotonic** because no water flows across a semipermeable membrane separating them. If two solutions separated by a semipermeable membrane have different effective osmotic pressures, the solution with the higher effective osmotic pressure is **hypertonic** and the solution with the lower effective osmotic pressure is **hypotonic**. Water flows from the hypotonic to the hypertonic solution.
  - Colloid osmotic pressure**, or **oncotic pressure**, is the osmotic pressure created by proteins (e.g., plasma proteins).
3. *Reflection coefficient ( $\sigma$ )*
- is a number between zero and one that describes the ease with which a solute permeates a membrane.

- a. *If the reflection coefficient is one*, the solute is impermeable. Therefore, it is retained in the original solution, it creates an osmotic pressure, and it causes water flow. **Serum albumin** (a large solute) has a reflection coefficient of nearly one.
  - b. *If the reflection coefficient is zero*, the solute is completely permeable. Therefore, it will not exert any osmotic effect, and it will not cause water flow. **Urea** (a small solute) has a reflection coefficient of close to zero and it is, therefore, an **ineffective osmole**.
4. *Calculating effective osmotic pressure*
- Effective osmotic pressure is the osmotic pressure (calculated by van't Hoff's law) multiplied by the reflection coefficient.
  - If the reflection coefficient is one, the solute will exert maximal effective osmotic pressure. If the reflection coefficient is zero, the solute will exert no osmotic pressure.

## V. Diffusion Potential, Resting Membrane Potential, and Action Potential

---

### A. Ion channels

- are **integral proteins** that span the membrane and, when open, permit the passage of certain ions.
1. *Ion channels are selective*; they permit the passage of some ions, but not others. Selectivity is based on the size of the channel and the distribution of charges that line it.
    - For example, a small channel lined with negatively charged groups will be selective for small cations and exclude large solutes and anions. Conversely, a small channel lined with positively charged groups will be selective for small anions and exclude large solutes and cations.
  2. *Ion channels may be open or closed*. When the channel is open, the ion(s) for which it is selective can flow through. When the channel is closed, ions cannot flow through.
  3. *The conductance of a channel* depends on the probability that the channel is open. The higher the probability that a channel is open, the higher the conductance, or **permeability**. Opening and closing of channels are controlled by **gates**.
    - a. *Voltage-gated channels* are opened or closed by changes in membrane potential.
      - The **activation gate of the Na<sup>+</sup> channel** in nerve is opened by depolarization; when open, the nerve membrane is permeable to Na<sup>+</sup> (e.g., during the upstroke of the nerve action potential).
      - The **inactivation gate of the Na<sup>+</sup> channel** in nerve is closed by depolarization; when closed, the nerve membrane is impermeable to Na<sup>+</sup> (e.g., during the repolarization phase of the nerve action potential).
    - b. *Ligand-gated channels* are opened or closed by hormones, second messengers, or neurotransmitters.
      - For example, the **nicotinic receptor** for acetylcholine (ACh) at the motor end plate is an ion channel that opens when ACh binds to it. When open, it is permeable to Na<sup>+</sup> and K<sup>+</sup>, causing the motor end plate to depolarize.