TRANSPORT ACROSS CELL MEMBRANES

Dr. MUNAZA KHATTAK

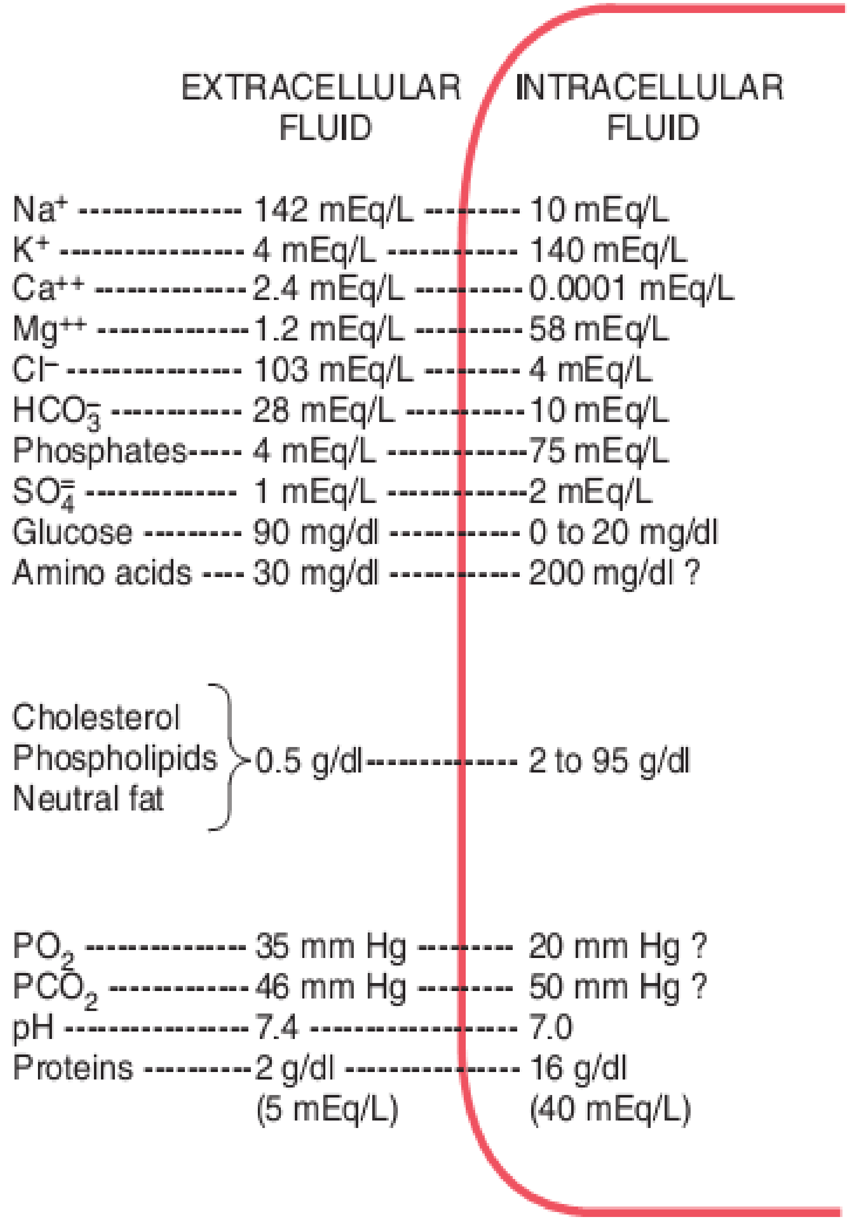
- THE CELL MEMBRANE CONSISTS OF A LIPID BILAYER WITH CELL MEMBRANE TRANSPORT PROTEINS.

Diffusion & Active Transport

- Transport through the cell membrane, either directly through the lipid bilayer or through the proteins, occurs via one of two basic processes:
- diffusion or active transport

- Diffusion means random molecular movement of substances molecule by molecule, either through inter-molecular spaces in the membrane or in combination with a carrier protein.
- The energy that causes diffusion is the energy of the normal kinetic motion of matter.

- **Active transport** means movement of ions or other substances across the membrane in com-bination with a carrier protein in such a way that the carrier protein causes the substance to move against an energy gradient, such as from a low-concentration state to a high-concentration state.



	EXTRACELLULAR FLUID	INTRACELLULAR FLUID
Na^+	142 mEq/L	10 mEq/L
K^+	4 mEq/L	140 mEq/L
Ca^{++}	2.4 mEq/L	0.0001 mEq/L
Mg^{++}	1.2 mEq/L	58 mEq/L
Cl^-	103 mEq/L	4 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L
Phosphates	4 mEq/L	75 mEq/L
$SO_4^=$	1 mEq/L	2 mEq/L
Glucose	90 mg/dl	0 to 20 mg/dl
Amino acids	30 mg/dl	200 mg/dl ?
Cholesterol Phospholipids Neutral fat	0.5 g/dl	2 to 95 g/dl
PO_2	35 mm Hg	20 mm Hg ?
PCO_2	46 mm Hg	50 mm Hg ?
pH	7.4	7.0
Proteins	2 g/dl (5 mEq/L)	16 g/dl (40 mEq/L)

Figure 4-1. Chemical compositions of extracellular and intracellular fluids. The question mark indicates that precise values for intracellular fluid are unknown. The red line indicates the cell membrane.

- Diffusion through the cell membrane is divided into two subtypes,

- Simple diffusion

- Facilitated diffusion.

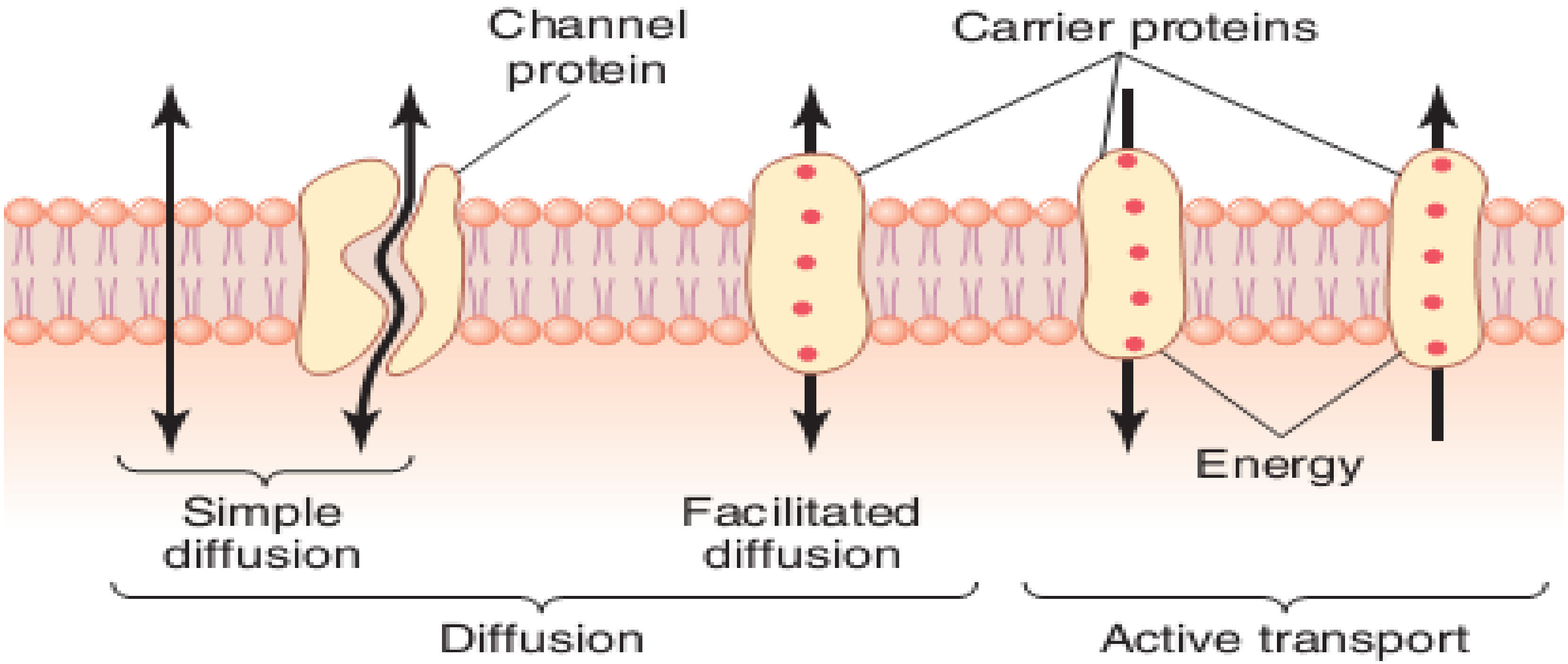


Figure 4-2. Transport pathways through the cell membrane and the basic mechanisms of transport.

- **Simple diffusion** means that kinetic movement of molecules or ions occurs through a membrane opening or through intermolecular spaces without any interaction with carrier proteins in the membrane.

- The rate of diffusion is determined by
- Amount of substance available
- Velocity of kinetic motion
- Number and sizes of openings in the membrane through which the molecules or ions can move.

- Simple diffusion can occur through the cell membrane by two pathways:

- (1) through the interstices of the lipid bilayer if the diffusing substance is lipid soluble

- (2) through watery channels that penetrate all the way through some of the large transport proteins

- Facilitated diffusion requires interaction of a carrier protein.

- The carrier protein aids passage of the molecules or ions through the membrane by binding chemically with them and shuttling them through the membrane in this form.

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.

- 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 (cm2)
- C1= concentration1(mmol/L)
- C2= concentration2(mmol/L

- **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:**
- ■↑Oil/water partition coefficient* of the solute increases solubility in the lipid of the membrane.
- ■↓Radius (size) of the solute increases the diffusion coefficient and speed of diffusion.
- ■↓Membrane thickness decreases the diffusion distance.
- b. Small hydrophobic solutes (e.g., O2) have the highest permeabilities in lipid membranes.
- c. Hydrophilic solutes (e.g., Na+) 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.
- *** Partition coefficient** (***P***) is the ratio of concentrations of a compound in a mixture of two immiscible solvents at equilibrium. This ratio is therefore a comparison of the solubilities of the solute in these two liquids.

Carrier-mediated transport

- ■Includes facilitated diffusion and primary and secondary active transport.

- ■The characteristicsof 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.
- **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

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

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(ATP)and therefore is active.
- ■is carrier-mediated and therefore exhibits stereospecificity, saturation, and competition.

2. Examples of primary active transport

- a. Na+K+ATPase (or Na+-K+ pump) in cell membranes transports Na+ from intracellular to extracellular fluid and K+ from extracellular to intracellular fluid; it maintains low intracellular [Na+] and high intracellular [K+].
- ■Both Na+and K+are transported against their electrochemical gradients.
- ■Energy is provided from the terminal phosphate bond of ATP.
- ■The usual stoichiometry is 3 Na+/2 K+
- ■Specific inhibitors of Na+,K+-ATPase are the cardiac glycoside drugs ouabain and digitalis.

- Ca2+-ATPase (or Ca2+pump) in the sarcoplasmic reticulum (SR) or cell membranes transports Ca2+ against an electrochemical gradient
- H+,K+-ATPase (or proton pump) in gastric parietal cells transports H+ into the lumen of the stomach against its electrochemical gradient

Secondary active transport

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- 1. Characteristics of secondary active transport
- a. The transport of two or more solutes is coupled.
- b. One of the solutes (usually Na+) 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+ gradient that is maintained across cell membranes. Thus, inhibition of Na+,K+-ATPase will decrease transport of Na+ out of the cell, decrease the transmembrane Na+ 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+–glucose co transport in the small intestine
  - Na+–K+–2Cl–cotransport in the renal thick ascending limb.

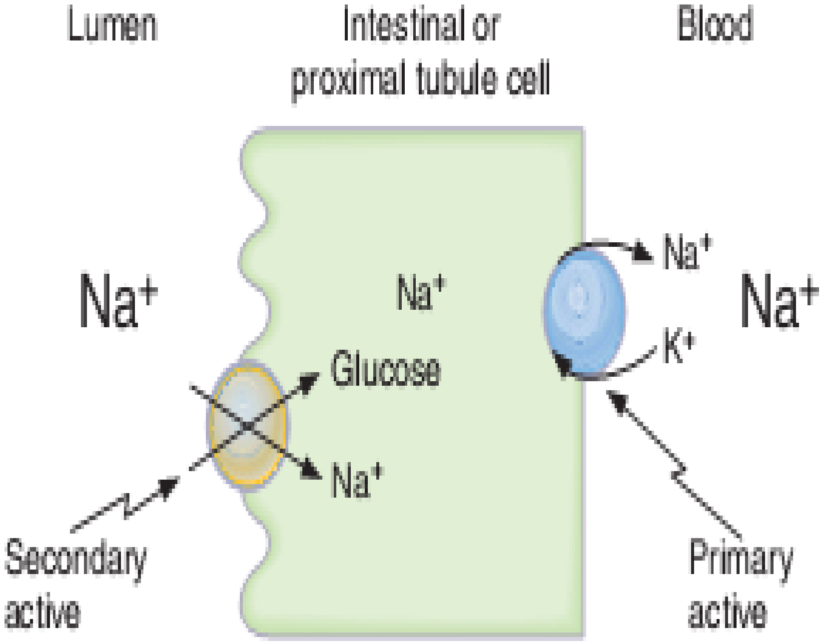
Example of Na+–glucose co transport

- a. The carrier for Na+-glucose co transport is located in the luminal membrane of intestinal mucosal and renal proximal tubule cells.

- b. Glucose is transported “uphill”; Na+ is transported “downhill.”

- c. Energy is derived from the “downhill” movement of Na+. The inwardly directed Na+ gradient is maintained by the Na+–K+ pump on the basolateral membrane.

- Poisoning the Na+–K+ pump decrease the transmembrane Na+gradient and consequently inhibits Na+–glucose cotransport.



- e. If the solutes move in opposite direction across the cell membranes, it is called counter -transport, exchange, or antiport.

- ■Examples are
  - Na+–Ca2+ exchange
  - Na+–H+ exchange.

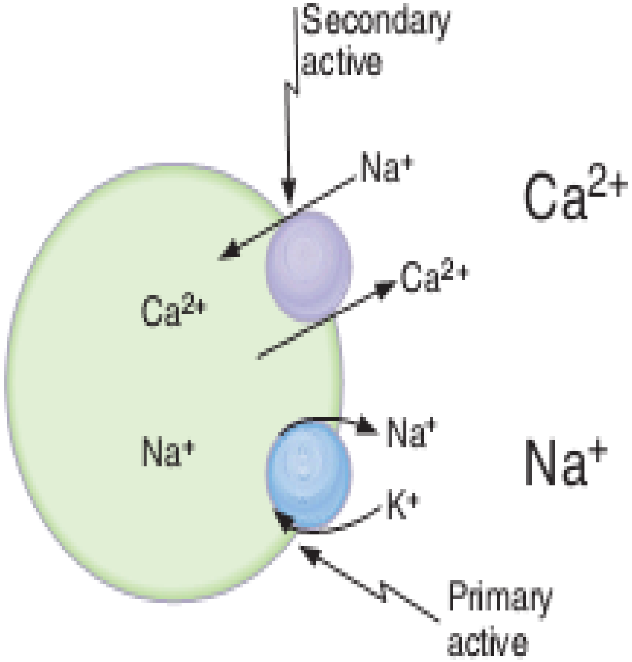
3. Example of Na+ –Ca2+ countertransport or exchange

- a. Many cell membranes contain a Na+–Ca2+exchanger that transports Ca2+“uphill” from low intracellular [Ca2+] to high extracellular [Ca2+].

- Ca2+and Na+ move in opposite directions across the cell membrane.

- b. The energy is derived from the “downhill” movement of Na+. As with cotransport, the inwardly directed Na+ gradient is maintained by the Na+–K+pump.

- Poisoning the Na+–K+pump therefore inhibits Na+–Ca2+ exchange



OSMOSIS

- **Osmolarity**
- ■is the concentration of osmotically active particles in a solution.

- ■can be calculated using the following equation:
- where:
- **Osmolarity = g × C**

- Osmolarity = concentration of particles (osm/L)
- g = number of particles in solution (osm/mol) [e.g., g NaCl= 2; g 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 semi permeable membrane from a solution with low solute concentration to a solution with high solute concentration.

Example of osmosis

- a. Solutions 1 and 2 are separated by a semi permeable 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.

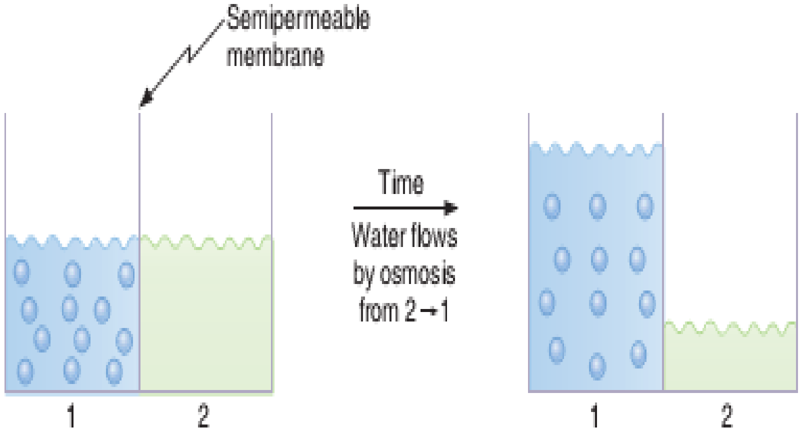


FIGURE 1-3 Osmosis of H_2O across a semipermeable membrane.

- 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).

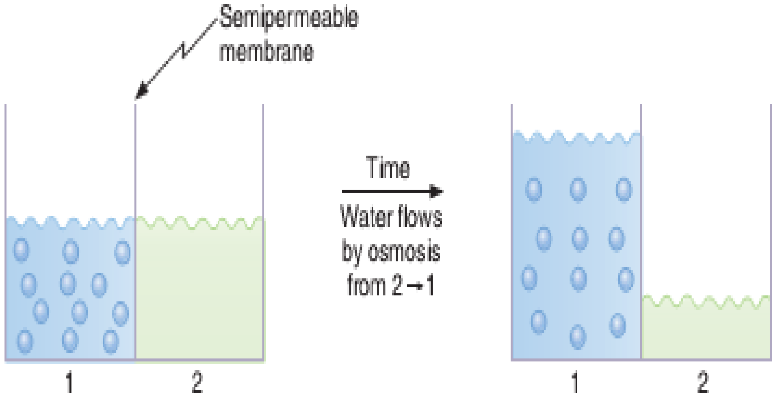
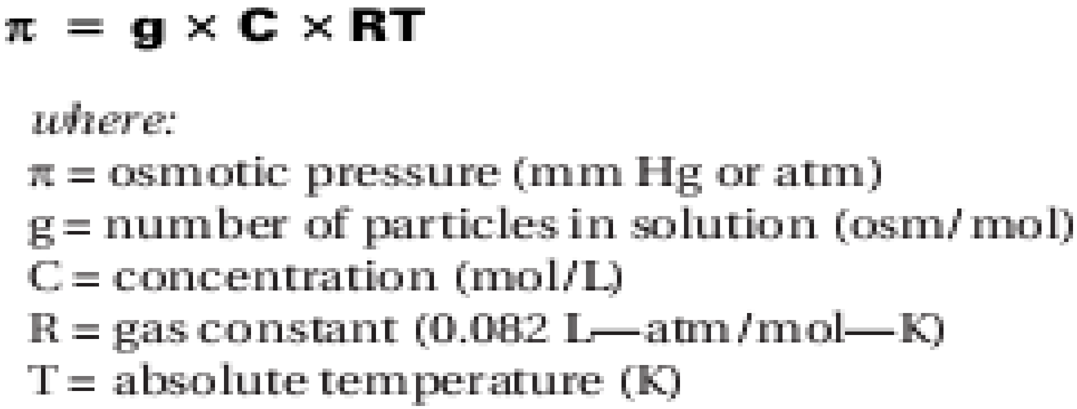


FIGURE 1-3 Osmosis of H_2O across a semipermeable membrane.

- c. With time, the volume of solution 1 increases and the volume of solution 2 decreases.

Calculating osmotic pressure (van’t Hoff’s law)

- The osmotic pressure of solution 1 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:

π = 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)

- b. The osmotic pressure increases when the solute concentration increases. A solution of 1 M CaCl2 has a higher osmotic pressure than a solution of 1 M KCl because the concentration of particles is higher.

- c. The higher the osmotic pressure of a solution, the greater the water flow into it

- d. Two solutions having the same effective osmotic pressure are isotonic because no water flows across a semi permeable membrane separating them.

- If two solutions separated by a semi permeable 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.

- e. Colloid osmotic pressure, or oncotic pressure, is the osmotic pressure created by proteins (e.g., plasma proteins).

Reflection coefficient (σ)

- ■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 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.

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.

- Osmotic pressure is the pressure of a solution against a semi permeable membrane to prevent water from flowing inward across the membrane.

- Tonicity is the measure of this pressure.