

# BODY FLUIDS PHYSIOLOGY

**Objectives after studying this chapter, you should be able to . . .**

1. Know the composition of extracellular and intracellular body fluids.
2. Explain osmosis, osmolarity and osmotic pressure, and tonicity of the body fluids.
3. Know the forces producing movement of substances between compartments.
4. Describe the process of endocytosis and exocytosis.
5. Describe the primary factors (Starling forces) that determine fluid movement through the capillary membrane and the formation of interstitial fluid and lymph.
6. Describe the intake versus output of water.

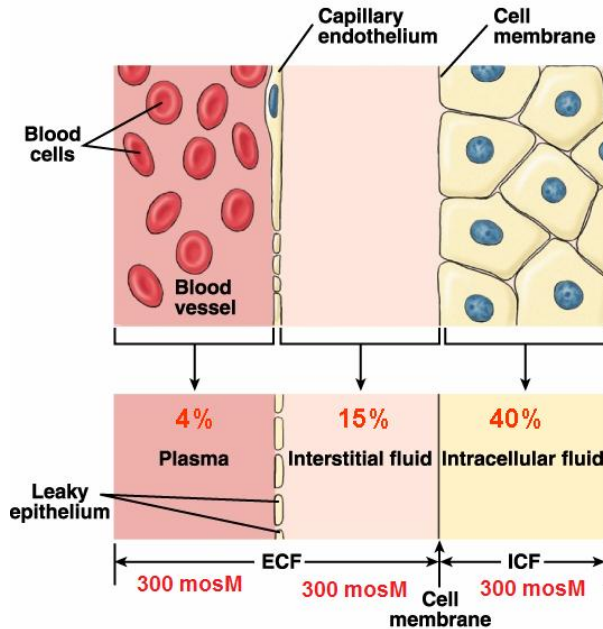
Water is by far the most abundant components of the body, constituting about **60%** in young males and about **50%** in young women of the total body weight (TBW) (lower level in fat, upper level in thin, 80% in infants). The percentage of body water varies inversely with the body's fat content and age.

The total body water in males is larger than in females because the latter have a somewhat larger amount of subcutaneous fat. In both sexes, the percentage of body water decreases with age, which can be attributed primarily to an increase of adipose tissue.

The body water is distributed into two major fluid compartments, **extracellular fluid (ECF)** (figure 2.1), which contains approximately **20%** of TBW, and **intracellular fluid (ICF)**, which contains approximately **40%** of the TBW.

**Extra cellular fluid (20% of the TBW):**

1. **The interstitial fluid** (the fluids between cells and in lymphatic) which constitutes about **15%** of the TBW.
2. **Plasma** constitutes about **4%** of the TBW.
3. **Transcellular fluids** (include fluid in the gastrointestinal, biliary, and urinary tracts, the intraocular and cerebrospinal fluids, and fluid in the serosal spaces, such as the pleural, peritoneal, and pericardial fluid) constitutes about **1%** of the TBW.



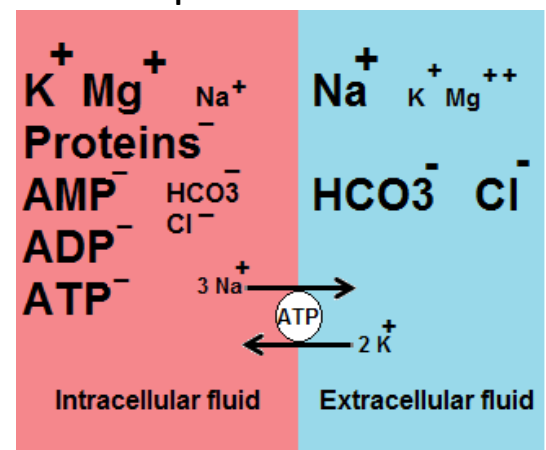
**Figure 2.1: Water distribution between body compartments.**

**Plasma and interstitial fluid:** Have very similar composition, with **Na<sup>+</sup>** as the predominant cation and **Cl<sup>-</sup>** and **HCO<sub>3</sub><sup>-</sup>** as the predominant anions (figure 2.2). However an important difference between plasma and interstitial fluid is the larger concentration of proteins in the plasma. This difference exists because the capillary endothelium is freely permeable to water and to small solutes (the so-called crystalloids), such as inorganic ions, glucose, and urea, but has limited permeability to larger solutes (colloidal particles), such as large proteins and lipids. Thus, interstitial fluid is an ultra filtrate of plasma.

In spite of the differences in ion concentrations and the total concentration of the similar charges, electrical neutrality is maintained within each compartment, i.e., the total number of cationic charges equals the total number of anionic charges.

**Intracellular fluid (40% of the TBW):** In contrast to ECF, the intracellular fluid (ICF) contains relatively low concentration of Na<sup>+</sup>, Cl<sup>-</sup>, and HCO<sub>3</sub><sup>-</sup>. Instead, the predominant cation in ICF is **K<sup>+</sup>** and **Mg<sup>++</sup>**, while the predominant anions are **organic phosphates** (e.g. ATP, ADP, and AMP) and **proteins**.

These striking composition differences between ICF and ECF can be attributed mainly to presence of the Na<sup>+</sup>-K<sup>+</sup> ATPase pump in cell membranes which actively transports three sodium ions from and two potassium ions into cells, thereby accounting for the high sodium ion and low potassium ion concentrations in ECF and the opposite picture inside ICF.



**Figure 2.2: Relative concentration of various anions and cations between ECF and ICF.**

### Osmosis, osmotic pressure and osmolarity of the body fluids:

The **Osmosis** is the diffusion or flow of water (solvent) molecules across a semipermeable membrane (through channel proteins called **aquaporins**) into a region in which there is a high concentration of a solute to which the membrane is impermeable (figure 2.3). In another word; is the diffusion or flow of water molecules from region of high concentration of water molecules across a semipermeable membrane (through channel proteins called **aquaporins**) into a region of low concentration of water molecules.

Cells can regulate the rate of osmosis by adding aquaporins to the plasma membrane or removing them. Certain cells of the kidneys, for example, install or take away aquaporins to regulate the rate of water loss from the body in the urine

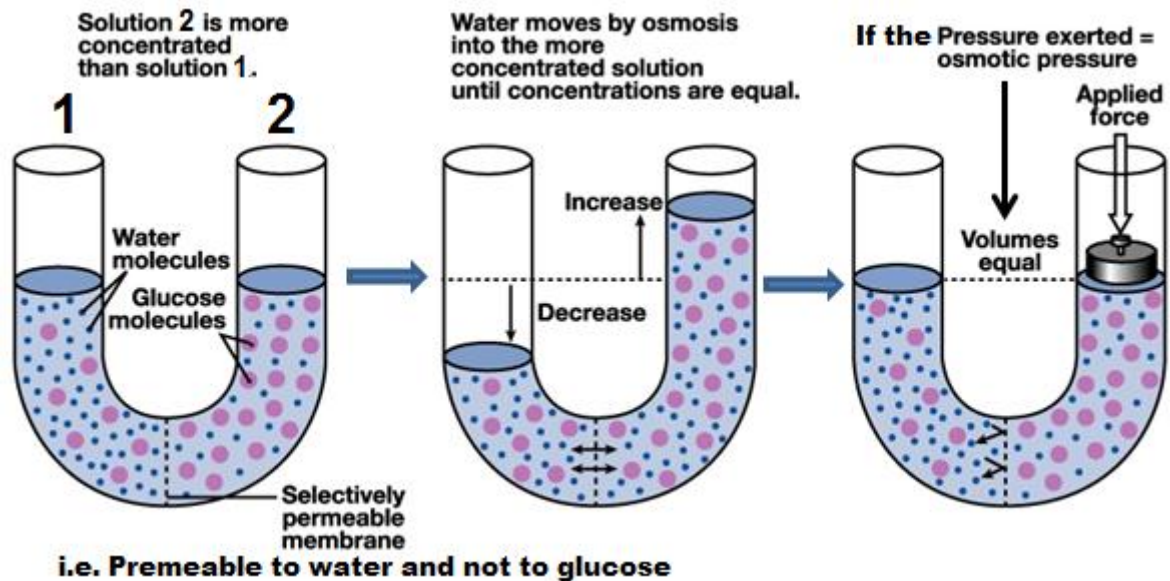


Figure 2.3: Osmosis through semipermeable membrane.

The **osmotic pressure** is an attractive force of the solute particles to water molecules that drives water molecules to move from solution 1 to solution 2 as a result of the presence of solute in solution 2. Consequently, the osmotic pressure difference across the membrane causes water to flow from solution 1 (which has no or less solute concentration and consequently lower osmotic pressure) to solution 2 (which has a higher solute concentration and a higher osmotic pressure) (figure 2.3). The number of the solute particles determines the magnitude of the osmotic pressure of the solution in which it is dissolved. **Oncotic pressure, or colloid osmotic pressure,** is a form of osmotic pressure exerted by large molecules such as **proteins** (notably albumin), in a blood vessel's plasma or interstitial fluid that usually tends to pull water toward these molecules.

- Each mole of a substance contains Avogadro's constant ( $6.022 \times 10^{23}$ ) of molecules.
- **Molarity** of a substance is the concentration of non-dissociated substance (in moles) per one L (kg) of water.
- The **osmolarity** (osmole) is the concentration of osmotically active particles (the molecules or the particles which attract water to it) in one liter of a solution (**mol/L H<sub>2</sub>O**).
- The **osmolality** (osmole) is the concentration of osmotically active particles (the molecules or the particles which attract water to it) in one kg of a solution (**mol/Kg H<sub>2</sub>O**).
- The number of osmotically active particles in any fluid is determined by: The number of moles per liter (or kg) of water **X** the numbers of osmotically active particles released into solution when the solute is dissolved.

Therefore;

**One Avogadro's constant molecules of a substance/L H<sub>2</sub>O = 1 Mole of substance/L H<sub>2</sub>O (MOLARITY) = 1 Mole X the numbers of osmotically active particles released into solution when the solute is dissolved (OSMOLARITY, Osmole of substance /L H<sub>2</sub>O).**

**Examples:**

⊙ 5% of glucose in water has a molarity of 300 mMoles/L H<sub>2</sub>O, and because the glucose molecules in water do not dissociate, it has an osmolarity of 300 mOsmol/L H<sub>2</sub>O.

⊙ 0.9% NaCl in water has a molarity of 150 mMoles/L H<sub>2</sub>O, and because each NaCl molecule in water is dissociated into two osmotically active particles (Na<sup>+</sup> and Cl<sup>-</sup> ions); it has an osmolarity of 300 mOsmol/L H<sub>2</sub>O.

Therefore, 5% of glucose in water and 0.9% NaCl in water have different molarity but identical osmolarity and consequently identical osmotic pressure.

**Therefore, osmolality of the plasma and ECF is mainly due to sodium ions, chloride ions, bicarbonate ions, and to less extent due to other ions, urea, glucose, and proteins. The osmolality of the ICF is mainly due to potassium ions, magnesium ions, organic phosphates, proteins and other nitrogen containing solutes. In spite of the differences in composition, these fluids have essentially identical total osmolality.**

**In spite of the differences in composition of the body fluids, they have essentially identical total osmolalities of about of about 290-300 mOsmol/ kg H<sub>2</sub>O.** This is because the capillary endothelium and cell membranes are freely permeable to water, allowing the plasma, interstitial fluid, and ICF to be isosmotic (iso-osmotic). It should be noted that the iso-osmolality principle applies primarily to the main body fluid compartments. Other body fluids can differ significantly from 290 mOsmol/kg H<sub>2</sub>O, including the peritubular interstitial fluid of the renal medulla (as much as 1200 mOsmol / Kg H<sub>2</sub>O) and certain transcellular fluids such as urine whose osmolality can vary from 70-1200 mOsmol/ Kg H<sub>2</sub>O.

The term **tonicity** is used to describe the effective osmotic pressure of a solution relative to plasma in which the normal body cells can be placed without causing either swelling or shrinking. A solution with effective osmotic pressure as plasma is said to be **isotonic** which corresponds to 0.9 % solution of NaCl or a 5% glucose solution. Those solutions with greater pressure are **hypertonic** in which the normal body cells shrink when they are placed in it. Those solutions with lesser pressure are **hypotonic** in which the normal body cells swell when they are placed in it. Osmolarity and tonicity are related, but different concepts. The terms are different because osmolarity takes into account the total concentration of penetrating solutes (solutes that can diffuse through cell membrane easily such as urea) and non-penetrating solute (solutes that cannot diffuse through cell membranes such as NaCl); whereas tonicity takes into account the total concentration of **only** non-penetrating solutes. For example, if a solution had 150 mMol/L of NaCl and 100 mMol/L of Urea the tonicity of the solution would be 300 mOsmol/L for only the NaCl (non-penetrating solutes). The osmolarity of the solution, however, would be both NaCl and Urea and would therefore be 400 mOsmol/L. If we were to compare the osmolarity and tonicity of this solution to that of a typical cell (300 mOsmol/L), then it would be isotonic (both have tonicities of 300 mOsmol/L) but hyperosmotic (the solution has an osmolarity of 400 mOsmol/L while the cell has an osmolarity of 300 mOsmol/L).

If water is added to the extracellular fluid by injection into the blood stream, by injection beneath the skin, or by ingesting water followed by absorption from gastrointestinal tract into the blood, the water dilutes the extracellular fluids, causing it to become hypotonic with respect to the interstitial and to the intracellular fluids, osmosis begins immediately at the capillary and cells

membranes, with large amounts of water passing to the interstitial and to the interiors of the cells, within a few minutes the water becomes distributed almost evenly amongst all the extracellular and intracellular fluid compartments, and all compartments will have the same osmolalities (i.e. the same tonicity). Excess water intake and dilution of extracellular fluid called **overhydration** or **water intoxication**.

If water is lost from the body by evaporation from the skin, lungs, or excretion of a very dilute urine as in diabetes insipidus, or loss in feces as in diarrhea, the water will leave the extracellular fluid compartment causing this compartment to have a hypertonic fluid in respect to the fluids in the intracellular compartments. Osmosis begins immediately at the cell membrane with water passing to the interstitium and plasma and distributed uniformly between the three compartments, so that all the three compartments will have the same osmolalities. The overall effect is called **dehydration**.

A principal laboratory test that indicates fluid deficit or excess is the urine **specific gravity**, which measures urine osmolality. Normal range = 1.015-1.025. As fluid volume in the blood increases, the water excreted in the urine increases, making it more dilute and causing the specific gravity of the urine to decrease (below 1.015). Conversely, as the fluid volume in the blood decreases, as occurs in dehydration, the water excreted in the urine decreases, making it more concentrated and causing the specific gravity of the urine to increase (above 1.025).

**Hematocrit levels** also can indirectly indicate fluid volume in the blood. Since the test measures the number of blood cells per volume of blood, increased fluid in the blood, that is, hypervolemia will dilute the blood cells and cause the hematocrit level to decrease. Consequently, too little fluid in the blood, that is, hypovolemia, will cause hemoconcentration and result in a high hematocrit level. It is therefore important to consider the patient's hydration level when interpreting laboratory values.

The test for **serum osmolality** measures the concentration of osmotically active particles dissolved in blood. Sodium is a major contributor to osmolality in extracellular fluid. Serum osmolality generally ranges from 290 to 300 mOsmol/kg of H<sub>2</sub>O. When fluid volume decreases, as in dehydration, serum osmolality increases and vice versa.

### Forces producing movement of substances between Compartments

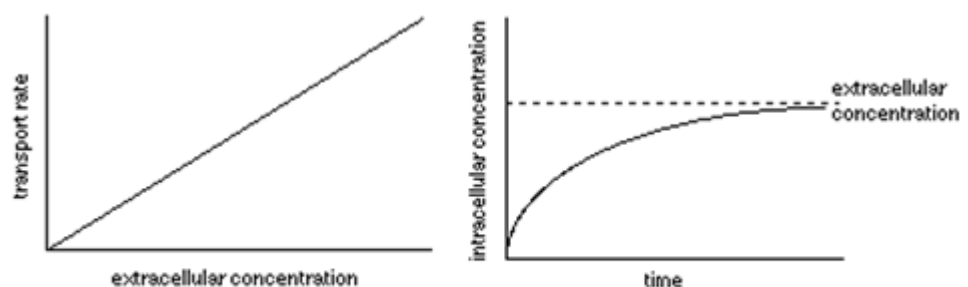
**[1] Simple diffusion:** In which the molecules or ions tend to spread from regions to another regions according to electro-chemical gradients through the **cell membrane lipid bilayer** (for lipid soluble substances such as oxygen, nitrogen, CO<sub>2</sub>, anesthetic gases, and alcohol) or through **cell membrane channel proteins** (for water and water soluble substances such as ions) until the concentration is uniform across the membrane. It does not require metabolic energy and therefore, it is passive.

Diffusion from one region to another is affected by:

(a) The concentration gradient. Diffusion of substances through cell membrane is directly proportional to the concentration gradient of that substance across the membrane.

(b) The electrical gradient. Whenever there is a potential difference between two regions, positively charged ions move along this electrical gradient to the more negative charged region, negatively charged ions move in the opposite direction.

(c) The thickness of the boundary. Diffusion of substances through cell membrane is inversely proportional to the



**kinetic behavior of simple diffusion**

thickness of the membrane

**(d)** The cross sectional area of the boundary across which diffusion is taking place. Diffusion of substances through cell membrane is directly proportional to the cross sectional area of the boundary across which diffusion is taking place.

**(e)** Temperature. Diffusion is driven by the kinetic energy of the particles, and temperature is a measure of that kinetic energy. The warmer a substance is, the more rapidly its particles diffuse. This is why sugar diffuses more quickly through hot tea than through iced tea.

**(f)** Membrane permeability. Diffusion through a membrane depends on how permeable it is to the particles. Cells can adjust their permeability to such a substance by adding channel proteins to the membrane or taking them away. Kidney tubules, for example, do this as a way of controlling the amount of water eliminated from the body.

**(g)** The diffusion coefficient of the gas in the substance of the membrane.

**[2] Filtration:** Filtration is the process by which **water** and **water soluble substances** is forced through an **epithelial layer** or other barrier due to a difference in hydrostatic pressure on the two sides. Filtration is affected by

- (a)** The pressure gradient across the membrane,
- (b)** The surface area of the membrane,
- (c)** The diameter of the membrane pores,
- (d)** The size of the filtered molecules.

In physiology, the most important case of filtration is seen in the blood capillaries, where blood pressure forces fluid through gaps in the capillary wall. This is how water and water soluble substances (salts, nutrients, and other solutes) are transferred from the bloodstream to the tissue fluid and how the kidneys filter wastes from the blood.

**[3] Osmosis.**

**[4] Carrier-mediated transport:** It is the transport of substances across the cell membrane mediated by a carrier protein.

**This type of transport is characterized by the following:**

**[i] Stereospecificity:** For example, D-glucose is transported by facilitated diffusion, but the L-isomer is not.

**[ii] Saturation:** The transport rate increases as the concentration of the solute increases, until the carriers are saturated (the transport maximum, or  $T_m$ ) then no more increase in transport in spite of increase in concentration of solute, for example, renal  $T_m$  of glucose..

**[iii] 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.

**The direction of the carrier-mediated transport is:**

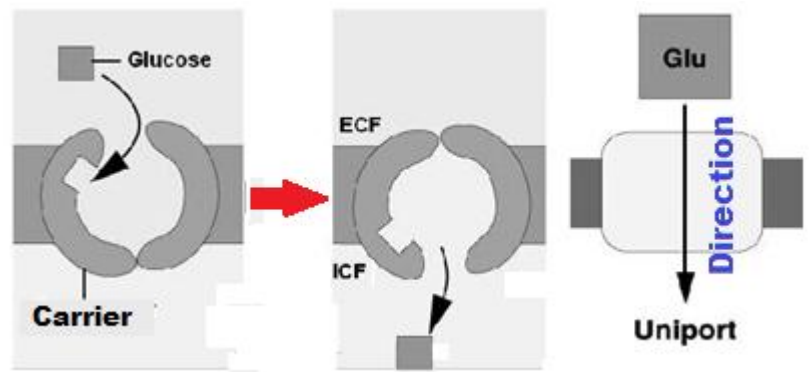
**[a] Uniport transport:** If one transported substance is moving in one direction and without an associated transport of another substance (as in the facilitated diffusion of glucose).

**[b] Co-transport or symport:** If two or more of the transported substances are moving in the same direction (as  $\text{Na}^+$ -glucose co-transport,  $\text{Na}^+$ -amino acids co-transport, and  $\text{Na}^+$ - $\text{K}^+$ - $2\text{Cl}^-$  co-transport).

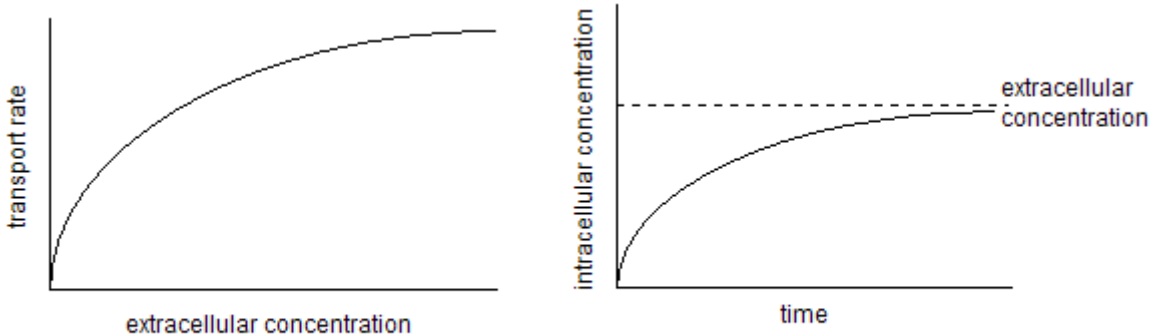
**[c] Counter-transport or antiport:** If two or more of the transported substances are moving in the opposite direction (as  $\text{Na}^+$ - $\text{Ca}^{2+}$  counter-transport and  $\text{Na}^+$ - $\text{H}^+$  counter transport).

**Carrier-mediated transports are of two main types:**

**[A] Facilitated diffusion:** When the carrier-mediated transport occurs according to electrochemical gradient and the **energy is not required** (passive), the process is called facilitated diffusion (figure 2.5). It is also called a **uniport transport**. Example of facilitated diffusion is glucose transport in muscle and adipose cells is carrier-mediated, according to the electrochemical gradient, and is inhibited by sugars such as galactose. Therefore, it is categorized as facilitated diffusion. In diabetes mellitus, glucose uptake by the muscles and adipose cells is impaired because the carriers for facilitated diffusion of glucose require insulin.



**Figure 2.5: Facilitated diffusion.**



**kinetic behavior of facilitated diffusion**

Simple diffusion	Facilitated diffusion
Diffusion according to electrochemical gradient	Same
Energy is not required	Same
Does not require a carrier protein	Requires a carrier protein
Simple diffusion is not saturable	Have saturation limited ( $T_m$ )
Bidirectional transport	Uniport transport



**[B] Active transport:** When the carrier-mediated transport occurs against electrochemical gradient, the process **requires energy** and is referred to as active transport. Active transport can be divided into two types:

**(i) Primary active transport:** In which high energy phosphate compound, ATP, **provides directly** the energy required for the transport process (figure 2.6). Such transports are  $\text{Na}^+$ - $\text{K}^+$ -ATPase pump,  $\text{H}^+$ -ATPase pump (proton pump),  $\text{H}^+$ /  $\text{K}^+$ -ATPases, and  $\text{Ca}^{2+}$ -ATPase pump.

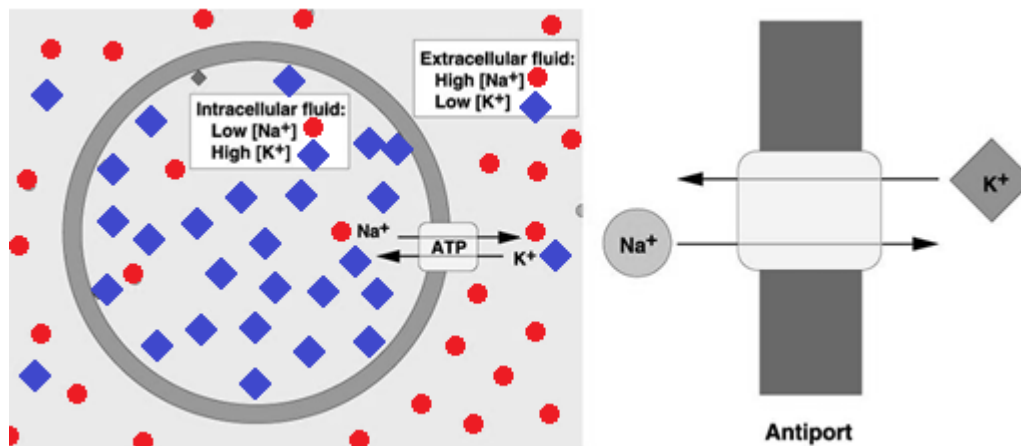


Figure 2.6: Primary active transport.

**(ii) Secondary active transport:** In which the transport of one substance (e.g.  $\text{Na}^+$ ) according to electrochemical gradient provides the energy to transport another substance against its electrochemical gradient (figure 2.7). The metabolic energy is **not provided directly**, but indirectly from the  $\text{Na}^+$  gradient, which is maintained across cell membranes by  $\text{Na}^+$ - $\text{K}^+$  ATPase pump. Thus, inhibition of  $\text{Na}^+$ - $\text{K}^+$  ATPase

pump will decrease transport of  $\text{Na}^+$  out of cell, decrease the transmembrane  $\text{Na}^+$  gradient, and eventually inhibit secondary active transport.

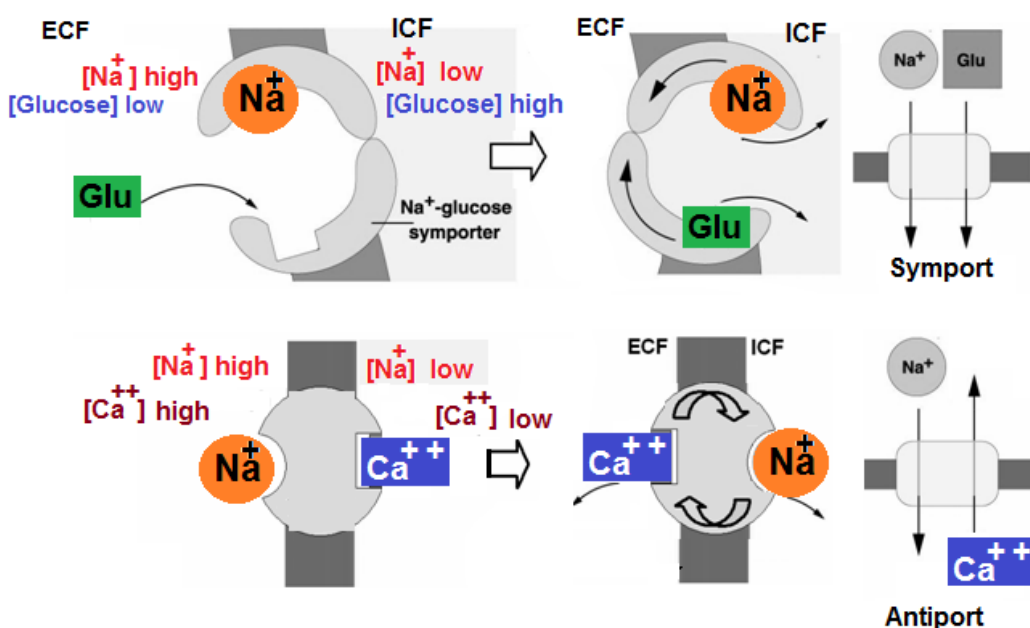
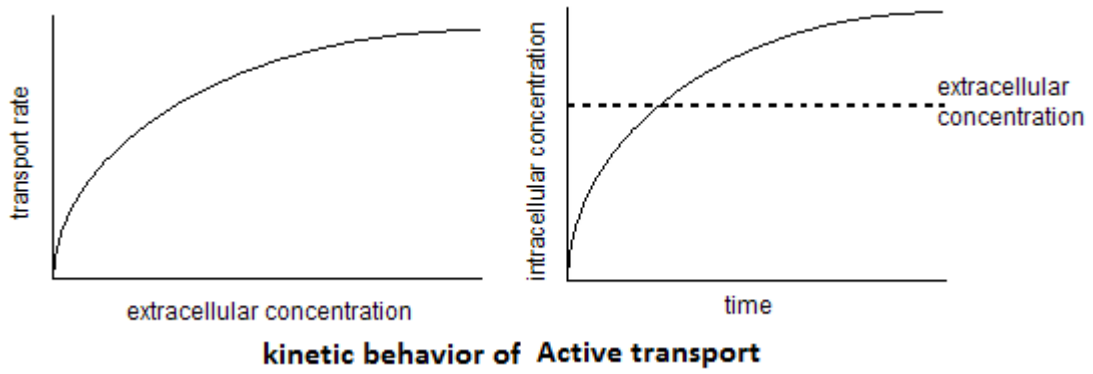
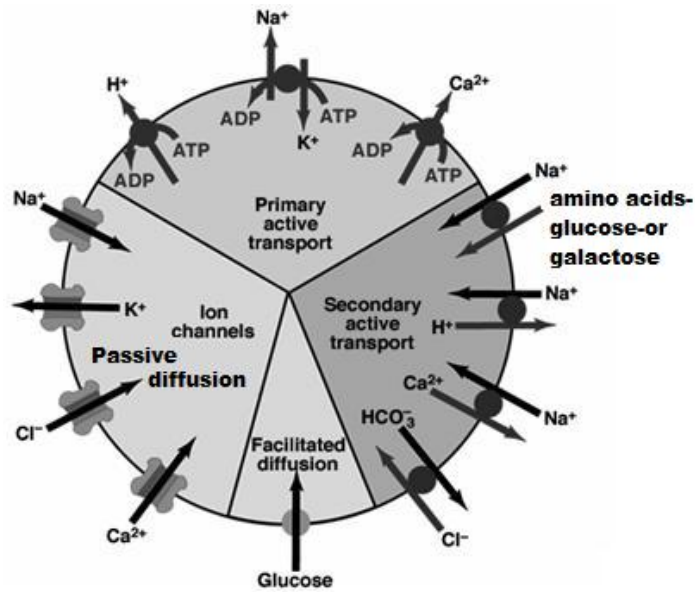


Figure 2.7: Secondary active transport.





The following figure 2.8 summarizes the main types of transport of substances across the cell membrane:

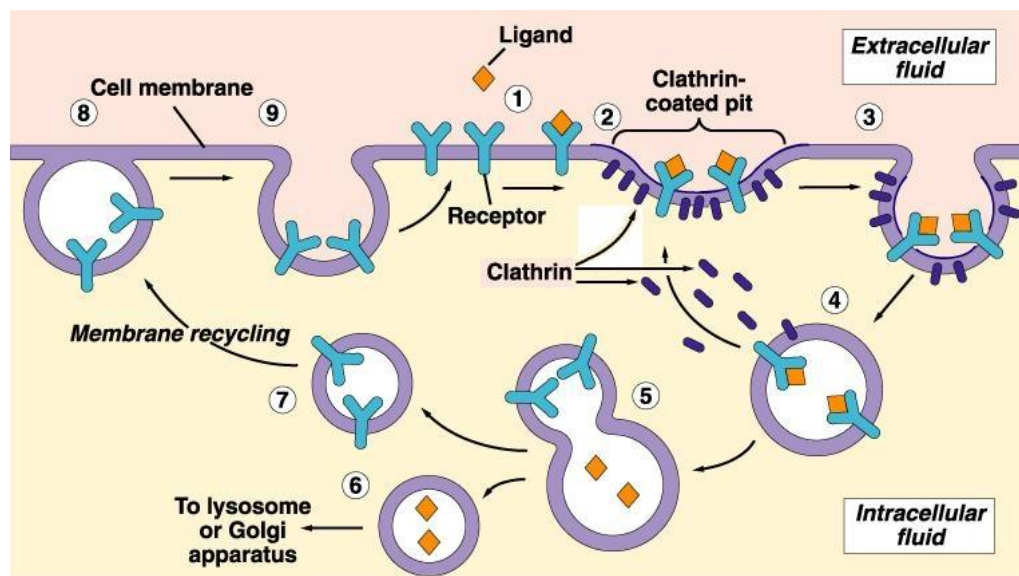


**Figure 2.8: The main types of transport of substances across the cell membrane.**

**[5] Transport of proteins and other large molecules by cytosis:** Cytosis is a completely different type of active transport involving the formation of membrane-bound vesicles with a diameter of 50–400 nm. **Vesicles** are either pinched off from the plasma membrane (**exocytosis**) or incorporated into it by invagination (**endocytosis**). Cytosis in general has three characteristics:

1. It is associated with the expenditure of ATP (active processes).
2. All forms of cytosin involve the formation of protein-coated vesicles with some exceptions.
3. All are mediated by membrane receptors.

Protein-coated vesicles provide the main route for endocytosis of solids, macromolecules, and fluids. The surface receptors accumulate at specific depressions at the cell membrane where its cytosolic surface of it is covered with a coat of protein called **clathrin** (figure 2.9). This cell membrane depression is known as **coated pits**. The coated pits progressively encloses the substance to be taken into the cell and pinch off continually to form endocytic vesicles, providing the cell with a mechanism for rapid internalization of a large amount of a specific molecule without the need to endocytose large volumes of extracellular fluid.



**Figure 2.9: Receptor-mediated endocytosis.**

**Endocytosis is of three types:** Based on the nature and quantity of material taken up and the means of uptake, three types of endocytosis that use clathrin coated vesicles are recognized: phagocytosis, pinocytosis, and receptor-mediated endocytosis.

**[A] Phagocytosis (cell eating)** is the ingestion of large particles or microorganisms that occurs in specialized immune cells. An important function of macrophages in humans is to remove invading bacteria. It occurs only after the extracellular particle has bound to the extracellular surface receptors. The particle is then enveloped by expansion of the cell membrane around it. This vesicle then fuses with many lysosomes, whereupon lysosomal enzymes digest its contents.

**[B] Pinocytosis (cell drinking)** is a general term for a nonspecific process in which a region of the plasma membrane is pinched off to form an endocytic vesicle inside the cell. During vesicle formation, some fluid and dissolved solutes from the extracellular medium are trapped inside the vesicle and internalized by the cell. It occurs in almost all cells and it occurs continually and specific stimuli are not required.

**[C] Receptor-mediated endocytosis** Receptor-mediated endocytosis is a highly selective mechanism by which cells take up a variety of important molecules, including hormones; growth factors; and serum transport proteins, such as transferrin (an iron carrier). Foreign substances, such as

diphtheria toxin and certain viruses, also enter cells by this pathway. The receptors-mediated endocytosis also aids the cellular uptake of molecules present at low concentrations outside the cell.

**Familial Hypercholesterolemia:** The significance of LDL receptors and receptor-mediated endocytosis is illustrated by a hereditary disease called familial hypercholesterolemia. People with this disease have an abnormally low number of LDL receptors. Their cells therefore absorb less cholesterol than normal, and the cholesterol remains in the blood. Their blood cholesterol levels may be as high as 1,200 mg/dL, compared to a normal level of about 200 mg/dL. People who inherit the gene from both parents typically have heart attacks before the age of 20 (sometimes even in infancy) and seldom survive beyond the age of 30.

**Exocytosis** refers to a process reverse to endocytosis. Many cells synthesize important macromolecules that are exported from the cell. These molecules are synthesized in the endoplasmic reticulum, modified in the Golgi apparatus, and packed inside transport vesicles. The vesicles move to the cell surface, fuse with the cell membrane, and release their contents outside the cell. During exocytosis, the vesicular membrane is incorporated into the plasma membrane. In this way, cell membranes can be conserved and reused. An **increase in the intracellular  $\text{Ca}^{2+}$  concentration** (as a result of cell surface signal such as binding of a hormone to a membrane receptor or a change in membrane voltage) is a key event that triggers regulated exocytosis. Exocytosis accounts for hormone secretion, neurotransmitter release, mucus secretion, and in some cases, ejection of wastes.

**The  $\text{Na}^+\text{-K}^+\text{-ATPase}$  pump:** The  $\text{Na}^+\text{-K}^+\text{-ATPase}$  is a highly-conserved integral membrane protein that is expressed in virtually all cells of higher organisms. As one measure of their importance, it has been estimated that roughly 25% of all cytoplasmic ATP is hydrolyzed by sodium pumps in resting humans. In nerve cells, approximately 70% of the ATP is consumed to fuel sodium pumps.

#### The functions of $\text{Na}^+\text{/K}^+\text{-ATPase}$ :

**1. Helps in maintaining resting membrane potential:** The sodium-potassium pump moves 3 sodium ions out and moves 2 potassium ions in, thus, in total, removing one positive charge carrier from the intracellular space. Decreasing the activity of  $\text{Na}^+\text{/K}^+\text{-ATPase}$  leads to  $\text{Na}^+$  enters the cell and  $\text{K}^+$  leaves the cell, the concentration gradients across the cell membrane are dissipated and the cell membrane loses its polarized state.

**2. Helps in transport of ions and substances through cell membrane:** Export of sodium from the cell provides the driving force for several secondary active transporters membrane transport proteins, which import glucose, amino acids, and other nutrients into the cell by use of the sodium gradient. Therefore,  $\text{Na}^+\text{-K}^+$  pump provides a  $\text{Na}^+$  gradient that is used by certain carrier processes.

**3. Regulate cellular volume:** The sodium-potassium pump ( $\text{Na}^+\text{/K}^+\text{-ATPase}$ ) maintains a low intracellular  $\text{Na}^+$  concentration. Decreasing the activity of  $\text{Na}^+\text{/K}^+\text{-ATPase}$  leads to an accumulation of intracellular  $\text{Na}^+$ . The osmotic activity of the increased intracellular  $\text{Na}^+$  pulls water into the cell, causing the cell to swell.

#### Regulation of $\text{Na}^+\text{/K}^+\text{-ATPase}$ :

**1. cAMP:** The  $\text{Na}^+\text{/K}^+\text{-ATPase}$  is up-regulated by cAMP. Thus, substances causing an increase in cAMP up-regulate the  $\text{Na}^+\text{/K}^+\text{-ATPase}$ . In contrast, substances causing a decrease in cAMP down-regulate the  $\text{Na}^+\text{/K}^+\text{-ATPase}$ . Activation of protein kinase A by cAMP directly phosphorylates the pump and causes a conformational change of the pump and increases its affinity for intracellular sodium.

**2.  $[\text{Na}]_i$  and  $[\text{K}]_o$ :** The activity of  $\text{Na}^+\text{/K}^+\text{-ATPase}$  pump is stimulated by its own substrate, i.e. by increased intracellular sodium and extracellular potassium concentrations.

**3. Exogenous substances:** The  $\text{Na}^+\text{-K}^+\text{-ATPase}$  can be pharmacologically modified by administering drugs exogenously. For instance,  $\text{Na}^+\text{-K}^+\text{-ATPase}$  found in the membrane of heart cells is an important target of cardiac glycosides (for example digoxin and ouabain), inotropic drugs used to improve heart

performance by increasing its force of contraction. Muscle contraction is dependent on the  $\text{Ca}^{2+}$  release from the muscle cells' sarcoplasmic reticulum. Immediately after muscle contraction, intracellular  $\text{Ca}^{2+}$  is quickly returned to its normal concentration by a carrier enzyme in the plasma membrane, and a calcium pump in sarcoplasmic reticulum, causing the muscle to relax. Since this carrier enzyme ( $\text{Na}^+$ - $\text{Ca}^{2+}$  counter-transport, exchanger) uses the  $\text{Na}$  gradient generated by the  $\text{Na}^+$ - $\text{K}^+$  pump to remove  $\text{Ca}^{2+}$  from the intracellular space, slowing down the  $\text{Na}^+$ - $\text{K}^+$  pump results in a permanently elevated  $\text{Ca}^{2+}$  level in the muscle, which may be the mechanism of the long-term inotropic effect of cardiac glycosides such as digoxin.

**4. Muscle inactivity and low dietary potassium intake:** Muscle inactivity and low dietary potassium intake decrease the abundance of pump in skeletal muscle, and vice versa. Accumulation of potassium in the interstitium of skeletal muscle during repetitive action potential depolarizes membrane potentials and contributes to muscle fatigue. Up-regulation of  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase will enhance muscle potassium uptake and reduce potassium accumulation in the interstitium during exercise, and explain why physical training increases exercise endurance. Up- and down-regulation of  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase are important in maintaining extracellular potassium homeostasis in response to high and low dietary potassium intake, respectively.

**5. Hormones:** Major hormonal controls over pump activity can be summarized as follows:

- **Thyroid hormones** appear to be a major player in maintaining steady-state numbers of pumps in most tissues. This effect appears to result from stimulation of gene transcription.
- **Aldosterone** is a steroid hormone with major effects on sodium homeostasis. It stimulates both rapid and sustained increases in pump numbers within several tissues. The sustained effect is due to enhanced transcription of the genes.
- **Catecholamines** have varied effects, depending on the specific hormone and tissue. For example, dopamine inhibits  $\text{Na}^+$ - $\text{K}^+$ -ATPase activity in kidney, while epinephrine stimulates pump activity in skeletal muscle. These effects seem to be mediated via phosphorylation or dephosphorylation of the pumps.
- **Insulin** has multiple effects on sodium pump activity. Within minutes of elevated insulin secretion, pumps have increased affinity for sodium, up-regulation of pump activity through activation of adenylate cyclase to produce cAMP. In skeletal muscle, insulin may also recruit pumps stored in the cytoplasm or activate latent pumps already present in the membrane.

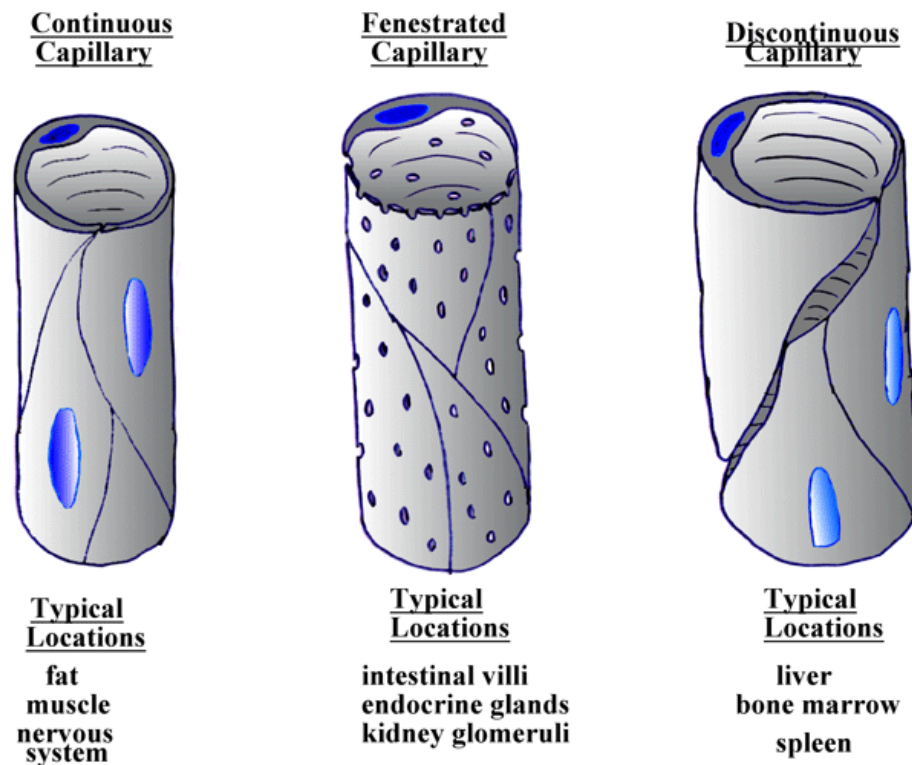
## Formation of Interstitial Fluid and Lymph

**Formation of interstitial fluid:** Exchange of water and dissolved substances through capillary wall depends upon the type of capillary. In general, three types of capillaries have been described.

**Type 1 or Continuous capillaries:** These capillaries have uninterrupted membranes and they only allow smaller molecules, such as water and ions to pass through their intercellular clefts. However lipid-soluble molecules can passively diffuse through the endothelial cell membranes along concentration gradients. They occur in skin, muscle, pulmonary circulation, nervous system, connective and adipose tissue.

**Type 2 or Fenestrated capillaries:** These capillaries have fenestrated membranes. Fenestrations are being of the order of 0.1 micrometer. The extremely thin fenestral membrane confers a very high permeability to water and to small lipophobic solutes, and limited amounts of protein. They are found in tissues specialized for water exchange, including all the exocrine glands, e.g. salivary glands, pancreas. Typical sites are glomeruli of the kidneys and intestinal epithelium.

**Type 3 or Discontinuous (sinusoidal) capillaries:** Capillaries have discontinuous membranes. They are interrupted by large intercellular spaces through which fluids and cells can pass. These capillaries are found in the bone marrow, spleen and liver.



**The primary factors (Starling forces) that determine fluid movement through the capillary membrane:** Starling proposed that fluid exchange across the capillary wall between plasma and interstitial fluid was achieved by a balance between four forces, in addition to capillary permeability. These forces include (figure 2.10):

**[1] The capillary hydrostatic pressure**, which tends to move or to filter the fluid outward through capillary membrane. The capillary pressure at the arteriolar end is about **35 mm Hg** and it is about **15 mm Hg** at the venous side (except in glomerular capillaries, where it is higher and nearly constant of about 50-60 mm Hg). The filtration is greater at the arteriolar side than at the venous side.

**[2] The interstitial fluid hydrostatic pressure**, which tends to move fluid outward through the capillary membrane when interstitial fluid pressure is negative. It is about **- 4 to - 5 mm Hg**. The interstitial pressure can be affected by lymphatic drainage and by the tissue tension. If the lymphatic drainage is blocked, the interstitial fluid pressure is increased. Moreover, in palms of the hands and in the muscles, the interstitial fluid is less able to expand its volume because of the anatomical arrangement of its connective tissues and therefore is likely to cause an increase in the interstitial fluid pressure. On the other hand, the loose texture of the connective tissue below the eyes and behind the wrists is less resistance to an increase in volume of the interstitial fluid.

**[3] The plasma colloid osmotic pressure**, which tends to cause osmosis of fluid inward through the membrane. The colloid osmotic (oncotic) pressure of normal human plasma averages approximately **25 mm Hg** mainly is caused by the dissolved protein (6-8 g/dL). About 75% of the total colloid osmotic pressure of the plasma result from the albumin fraction, 25% from globulin, and almost non from the fibrinogen. This is because albumin has a smaller M.W. than others, so there are more molecules per gm of albumin than molecules per gm of globulin. Moreover, albumin is more dissociated in plasma than globulin.

[4] The interstitial fluid colloid osmotic pressure due to protein (about 2 g/dL) which tends to cause osmosis of fluid outward through the membrane. It is about 6 mm Hg. The protein concentration is influenced, in part, by the amount of fluid filtration into the interstitium. For example, increased capillary filtration into the interstitium decreases interstitial protein concentration and reduces the oncotic pressure.

[5] **Capillary permeability:** The capillary is completely permeable to small molecules and water, but is normally only slightly permeable to plasma protein. This permeability to colloids may be increased by a number of factors such as certain poisons, oxygen lack and bacterial toxins.

Therefore, the **Starling equation** is:  $J_v = K_f [(P_c - P_i) - (\pi_c - \pi_i)]$ .

$J_v$  = Fluid movement (ml/min)

$K_f$  = Capillary permeability (ml/min/mm Hg)

$P_c$  = Capillary hydrostatic pressure (mm Hg)

$P_i$  = Interstitial hydrostatic pressure

$\pi_c$  = Capillary oncotic pressure (mm Hg)

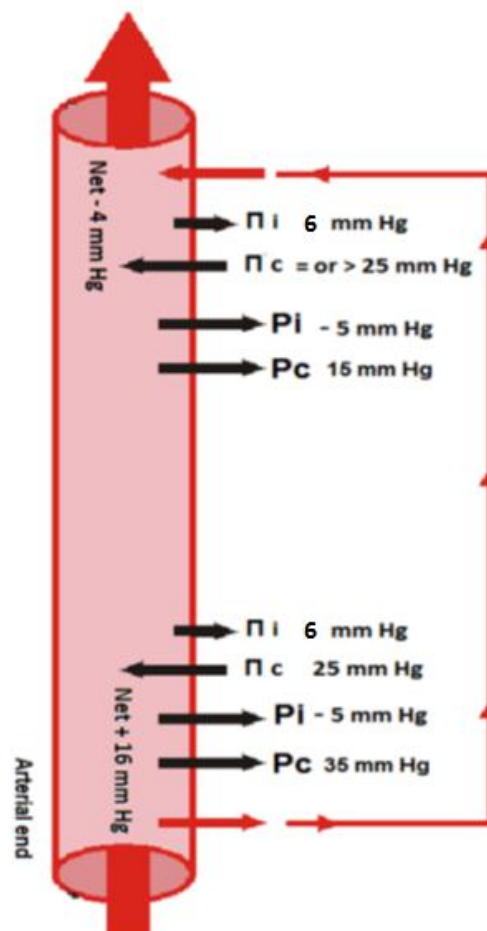
$\pi_i$  = Interstitial oncotic pressure.

**Example:** At the arteriolar end of a capillary,  $P_c$  is 35 mm Hg,  $\pi_c$  is 28 mm Hg,  $P_i$  is -4 mm Hg, and  $\pi_i$  is 1 mm Hg. Will filtration or absorption occur?

Net pressure ( $J_v$ )  $(35 - [-4]) - (28 - 6) = +17$  mm Hg. **Because the net pressure is positive, filtration will occur. If the net pressure is negative, absorption will occur.**

The hydrostatic pressure is greater at the arteriolar end than that at the venous end. The effect of the plasma proteins is to withdraw fluid from the more dilute interstitial fluid into the highly concentrated plasma. Therefore, at the arteriolar end the hydrostatic pressure is greater than the osmotic pressure and water and salts pass from the plasma to the interstitial fluid, while at the venous end the hydrostatic pressure is lower than the osmotic pressure and water and salts pass from interstitial fluid to the plasma. In this way a dynamic equilibrium is set up by water passing from the plasma to the lymphatic.

**Formation of lymph:** Lymphatics form a closed system of tubes consisting of endothelial lining supported by fibrous tissue. Out of the filtered fluid from the capillary 10% enters in these lymphatics whereas 90% is reabsorbed at the venous end. Lymphatics are much more permeable to proteins than capillaries. The proteins leaked from plasma into interstitial space cannot return to capillary because of adverse concentration gradient. Their accumulation in interstitial space will upset Starling equilibrium and proteins diffuse into the very permeable lymphatic capillaries together with large molecules produced by cells such (as hormones, enzymes, lipoproteins, chylomicrons). Large lymphatics have muscle fibers in their walls, lymphatic vessels possess numerous valves and the flow of lymph from periphery to thoracic duct and right lymphatic duct is brought about by muscular and respiratory movement in the same way as blood flows in the veins. Right lymphatic duct opens in right subclavian vein and thoracic duct opens in left subclavian vein. The lymphatics of intestine (lacteals) show rhythmic



**Figure 2.10: The primary factors (Starling forces) that determine fluid movement through the capillary membrane.**

contraction which, because of the many valves propel lymph into the thoracic duct. This contractile activity is an intrinsic property of the lymphatics and is not coordinated by NS.

### **Lymph:**

1. Has same concentration of salts as interstitial fluid and plasma.
2. Has lower concentration of proteins than plasma.
3. Has slightly higher concentration of proteins than interstitial fluid. This is because the lymph before reaching the blood lymph passes through at least one or more (usually 8-10) lymph nodes. During its passage through a lymph node the lymph is altered in composition by:
  - i. Newly formed antibodies (immunoglobulins) are added.
  - ii. Lymphocytes enter.

### **Main functions of Lymph:**

1. Return of proteins to blood from tissue spaces.
2. Fat from intestine are mainly absorbed through lymph.
3. Maintain fluid distribution in body.

**Edema:** Disturbance of water balance in which there is an excess of fluid in tissue spaces and serous cavities of the body is called **edema**. Edema is detectable clinically only when the interstitial fluid volume is increased by at least 10%. The factors that cause edema are:

- Increase in capillary hydrostatic pressure (at arterial or venous side).
- Decrease in plasma oncotic pressure (due to **hypoproteinemia**) or an increase in interstitial oncotic pressure (due to an increase of capillaries permeability to proteins as in case of inflammation, toxins, or other conditions).
- Obstruction of lymphatic drainage (**lymphedema, which** is an edema of a part of the body due to complete obstruction of lymphatic vessel draining from such part).

However, experimental and clinical observations indicate that edema does not occur until there is a relatively large change in one of these parameters. This is because the body has protective mechanisms against the development of edema.

### **Protection factors against edema:**

- An increase in lymphatic flow: Lymphatic flow is able to increase as the interstitial fluid volume is increased, so that the excess filtrate can initially be carried away.
- As fluid initially moves into the interstitium from capillaries, the interstitial oncotic pressure will fall (both by dilution and by the lymphatic removal of interstitial proteins), thereby minimizing the gradient for further entry of water from capillaries into the interstitium.
- The increase in interstitial fluid volume will cause the interstitial hydrostatic pressure to rise; edema cannot occur until the normally negative value of interstitial space becomes positive.

The importance of these safety factors varies from organ to organ. In skeletal muscle, for example, all three contribute. In comparison, the hepatic sinusoids are relatively open and freely permeable to proteins. As a result, there is normally no oncotic pressure gradient across the sinusoids, since the plasma and interstitial oncotic pressures are roughly equal. Thus, the hydrostatic pressure gradient is unopposed, although the intrasinusoidal pressure is relatively low because most of the hepatic perfusion derives from the low-pressure portal venous system. In this setting, it is hepatic lymph flow that is primarily responsible for preventing the accumulation of excess interstitial fluid.