5. HOMEOSTASIS

The human body is an "open system," to which variable amount of substances are added to, and, similarly, substances are lost from the body each day. The maintenance of constant volume and composition of the body fluid compartments and their temperature i.e. ensuring a **constant** internal environment (*interior milieu*) is termed ***homeostasis***. This *self-regulating process* is achieved through many complex mechanisms and is maintained by multiple systems designed to achieve homeostasis (Steady-State Balance). These processes consume a lot of energy even during sleep.

Another important concept is ***allostasis***, which involves maintaining stability through **change**, as it is also necessary for organisms to adapt to their environments. Allostasis considers the normal daily variations that exist in the internal system, i.e. it favors variability.

Some key concepts that are important to understand the steady-state balance:

- The body must have a **"set point"** so that deviations from this baseline can be monitored.
- *Sensor(s)* or detectors that continuously monitor deviations from the set point must generate **"effector signals"** that cause changes in input or output, or both, to maintain the desired set point.
- **"Effector organs"** must respond (through acceleration or inhibition) in an appropriate way to the effector signals generated by the set point monitor.
- The **sensitivity of the system** (i.e., how much of a deviation from the set point is tolerated) depends on several factors:
  - Nature of the sensor
  - Time necessary for generation of the effector signals,
  - Speed through which the effector organs respond to the effector signals.

It is important to recognize that deviations from steady-state balance do occur.
When input is greater than output, **a state of positive balance** exists.
When input is less than output, **a state of negative balance** exists.
Although transient periods of imbalance can be tolerated, prolonged states of positive or negative balance are generally incompatible with life.

Multiple systems in the body cooperate through different mechanisms to ensure this control. For example: c**hemo-sensors** in the carotid bodies and aortic body measure arterial PCO_2 and PO_2, send the information to the brainstem (**control center or integrating center**), to tell the **effectors** (the diaphragm and respiratory muscles) to alter breathing rate and tidal volume to return to balance.

Regulation of Homeostasis

Elements of homeostasis regulation depends on 3 mechanisms. All these elements work together to maintain homeostasis:

1. **Receptor**

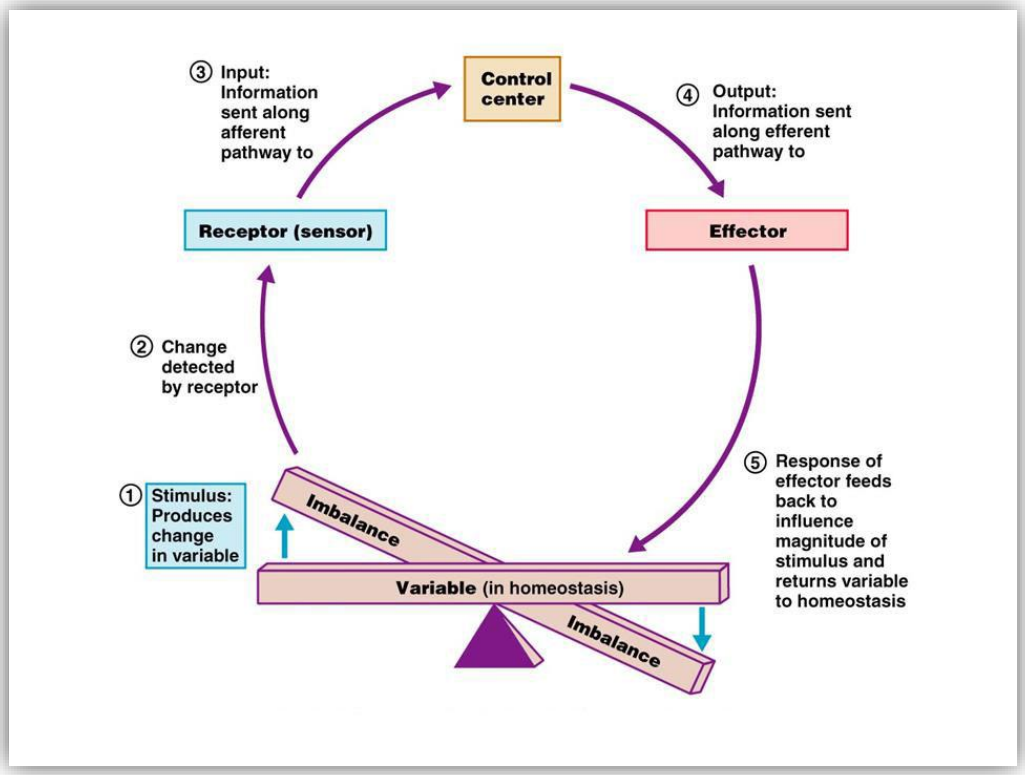
They sense the external or internal change in the surrounding and further activate the cascade to start the reactions to maintain homeostasis.

2. **Control Center** (integration center)

It receives the information from the receptor and processes it.

3. **Effector**

Effectors work according to the control center giving commands to the effector cell. According to the command, it can *enhance* or *suppress* the stimulus.



Several organs are involved in homeostasis: The CNS, Hypothalamus, the Lungs, the Liver, the Pancreas, the Skin (Integumentary system), the Skeletal & Muscular system and the Kidneys.

Example: Kidney role in *homeostasis*

- regulate fluid volume and electrolyte balance through ultrafiltration and reabsorption
- maintaining pH of body fluids through secretion of hydrogen and ammonium ions
- regulation of blood pressure via the renin–angiotensin–aldosterone system

Some other examples of Homeostasis mechanisms:

- Volume of body water homeostasis
- Blood oxygen concentration Homeostasis
- Arterial blood pressure homeostasis
- Blood glucose homeostasis
- Body temperature homeostasis
- Extracellular fluid PH homeostasis
- Blood partial pressure of CO_2 and O_2 homeostasis

5.2. FEEDBACK MECHANISMS

5.2.1. Negative Feedback Mechanism

Through the Negative feedback mechanism, systems (e.g., endocrine system) responds by *changing* or *reversing* the direction of change or action that was taken in response to an effector signal. Once an inhibitory signal received (e.g. the effect achieved the change or it exceeds the desired set-point), the system responds by stabilizing the function through either *ending* or by *reversing* the signals.

For example, thyroid stimulating hormone (TSH) released from pituitary gland stimulates thyroid gland to secretes its hormone: the thyroxine. Levels of thyroxin in blood level act as an inhibitory signal, to regulate secretion of TSH from pituitary. Normal TSH level, re-adjust the thyroid to secret thyroxin in the baseline set-point. Up- and down-regulation will follow this mechanism to keep the thyroxin in its "normal or steady-state" levels that ensure stable body functions.

5.2.2. Positive Feedback Mechanism

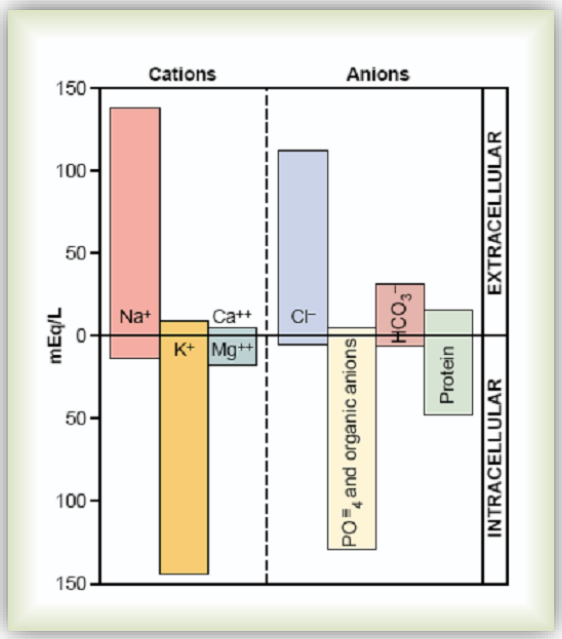
Positive feedback mechanism is less common than negative feedback mechanism in homeostasis. The body uses this mechanism to increase the intensity of the change in the same (forward) direction and this has important implications during emergency states (e.g. bleeding; child birth).

For example, blood clotting, which is the standard response to bleeding during injuries. Blood clotting occurs in three main stages:

- Formation of prothrombin activator
- Conversion of prothrombin into thrombin
- Conversion of fibrinogen into fibrin by thrombin.

5.3. Transport across cell membrane

Transport is the process through which matter and/or energy moves from one part to another.
Transport across the cell/plasma membrane is highly selective, where small size and lipid-soluble substances like O2, CO2 and steroid hormones may pass, while water-soluble substances like glucose, Na+, Cl-, water and urea may only cross through water-filled channels, or pores, or may be transported by carriers.



THREE types of transport mechanisms

1. **Diffusion** (passive)
   a. Simple diffusion
   b. Facilitated diffusion
   c. Osmosis (water only)
2. **Active transport**
3. **Vesicular transport** (active)

Factors affecting rate of diffusion

The rate of diffusion of substances through the cell membrane is ***directly*** proportional to the following factors:

- Permeability of the cell membrane
- Body temperature
- Concentration gradient or electrical gradient of the substance across the cell membrane
- Solubility of the Substance

The rate of diffusion of substances through the cell membrane is ***inversely*** proportional to the following factors:

- Thickness of the cell membrane
- Charge of the ions
- Size of the molecule

5.3.1. Diffusion (passive transport)

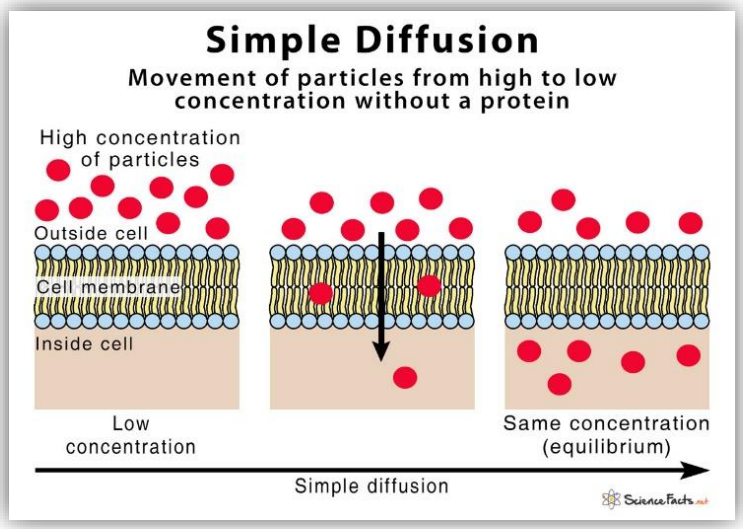
Diffusion is a process through substances cross freely and evenly through the membrane according to concentration gradient, i.e. from high to low concentrations. No energy is required to fuel this process (passive). A classic example is O_2 diffusion, which is small, lipid-soluble, non-charged molecule, therefore they diffuse into the cell freely according to a concentration gradient.

Simple diffusion allows molecules and ions to pass through:

1) phospholipid bilayer: if they are lipid-soluble like O_2, CO_2 …. or through
2) protein channels: if they are water & lipid soluble like Na^+, K^+, Ca^{++} etc.

Protein channels involved in simple diffusion are:

a) have selective permeability
b) many are gate-controlled, i.e. open and close by voltage or ligand gates.



Facilitated diffusion

Transmembrane proteins create a water-filled pore through which ions and some small hydrophilic molecules can pass by diffusion. The channels can be opened (or closed) according to the needs of the cell. It allows particular solutes or classes of solutes to cross the membrane, bi-directionally, at distinctly higher rates, driven by kinetic energy in addition to the concentration gradient of solute across the membrane.

Its a *passive* process that doesn't require energy, but some facilitated processes can be active.

Facilitated diffusion is commonly involved in the movement of *large* and *polar* molecules across a biological membrane.

Certain channel proteins are involved in facilitated diffusion, which results in the formation of particular pores for the movement of molecules.

Examples: transfer of ions like Ca++ and K+, movement of O2 in the blood with the help of hemoglobin.

Facilitated Diffusion of Ions

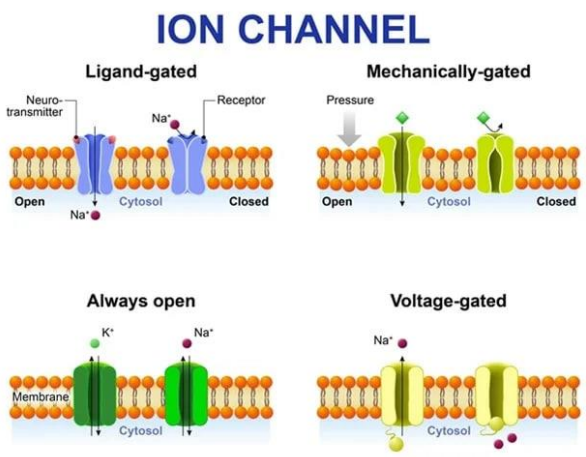
Takes place through proteins, or assemblies of proteins, embedded in the plasma membrane.

These transmembrane proteins form a water-filled channel through which the ion can pass **down** its concentration gradient.

The transmembrane channels that permit facilitated diffusion can be opened or closed.

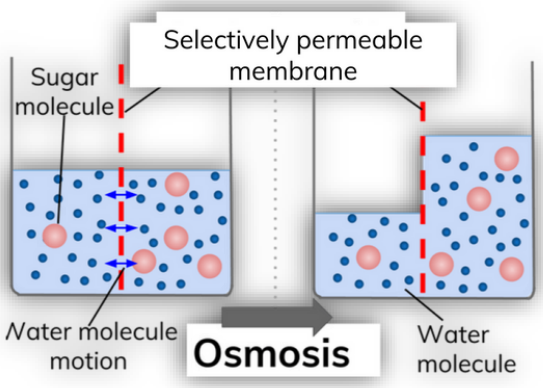
They are said to be **"gated"**; some types of gated ion channels:

a) ligand-gated
b) mechanically-gated (pressure)
c) resting channels (always open)
d) voltage-gated



Osmosis (water only)

When water molecules, but not solutes, crosses a semipermeable membrane in direction from their higher concentration (diluted solution) to their lower concentration (concentrated solution). It's a passive process, no energy is required and not affected by the small charges of water molecules.



5.3.2 Active transport

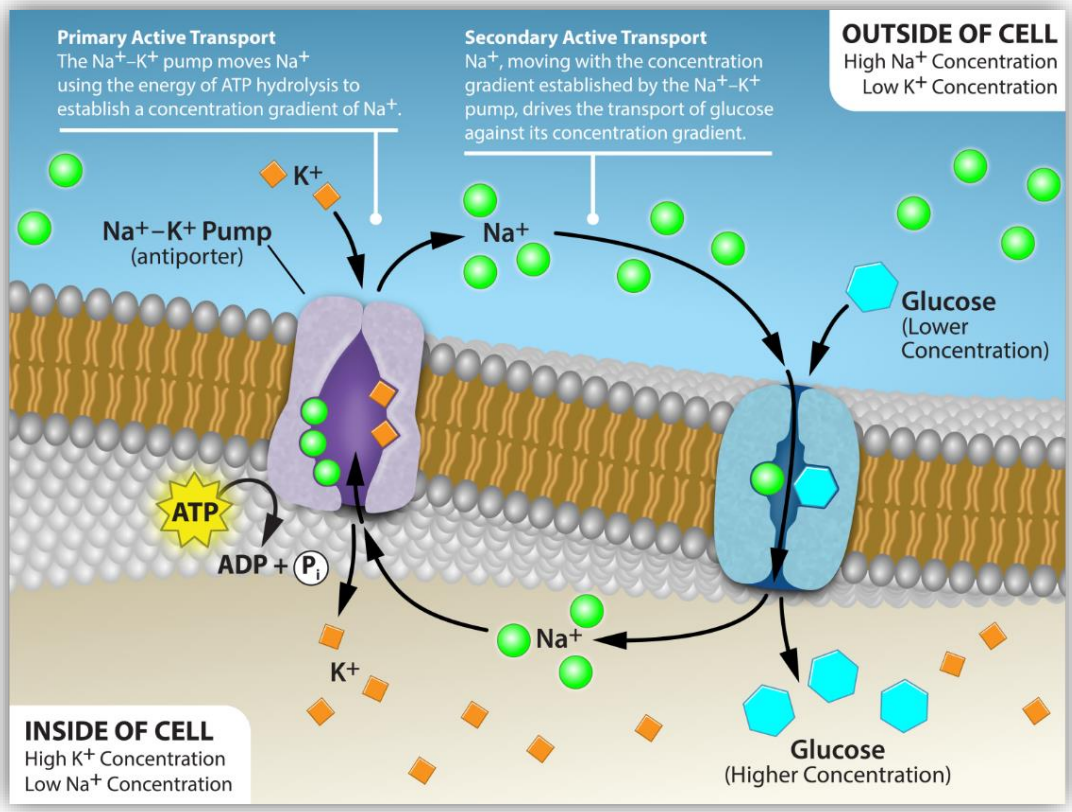
Active transport mechanisms involve moving a substance (molecule or ion) into the cell (**uphill**) against its *concentration* or an *electrical* or *pressure* gradient, and therefore, require energy, usually in the form of ATP.
Many substances require this actively transport method to be moved through some cell membranes: such as Na+, K+, Ca++, Fe++, H+, Cl- and urate ions, in addition to several sugars and most amino acids.

Active transport is divided into two types depending on the source of energy used in the active transport process:

Primary active transport (utilizes **ATP** or other high-energy phosphate compound) ... or
Secondary active transport (utilizes stored in the form of **ionic concentration differences**).

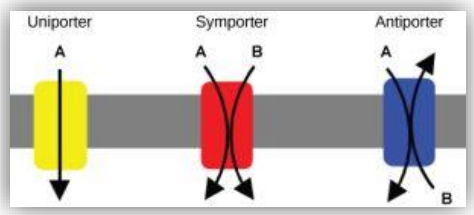
This energy in the secondary transport is stored in the form of differences in ionic concentration of secondary substances (molecules or ions) across the two faces of a cell membrane, and is originally created by a primary active transport process.

Similar to facilitated diffusion, ***carrier proteins*** that penetrate through the cell membrane, are needed in both types of active transport; primary and secondary.
Nevertheless, the carrier protein in active transport is capable of conveying energy to the transported substance to move it *against the electrochemical gradient*. The carrier protein in facilitated diffusion function through formation of particular pores for the movement of molecules.



Carrier Proteins for Active Transport

There are three protein types or transporters. A ***uniporter*** carries one specific ion or molecule. A ***symporter*** carries two different ions or molecules, both in the same direction. An ***antiporter*** also carries two different ions or molecules, but in different directions.



All these transporters can also transport small, uncharged organic molecules like glucose. These three types of carrier proteins functions also in facilitated diffusion, *but they do not require ATP to work.*
Examples of pumps for active transport (antiporter carrier proteins) are **Na^+-K^+ ATPase**, and **H^+-K^+ ATPase**. Two other carrier (uniporters) proteins are **Ca^{2+} ATPase** and **H^+ ATPase**. *Both are pumps.*

Primary Active Transport

Example: **Sodium-Potassium Pump**
One of the most important pumps in animal cells is the Na+-K+ pump.

The **Na+-K+ pump**, pumps Na+ ions *out* through the cell membrane and at pumps K+ ions *in* simultaneously. This pump maintains the Na+ and K+ concentration differences across the cell membrane, as well as for establishing a negative electrical voltage intracellularly.

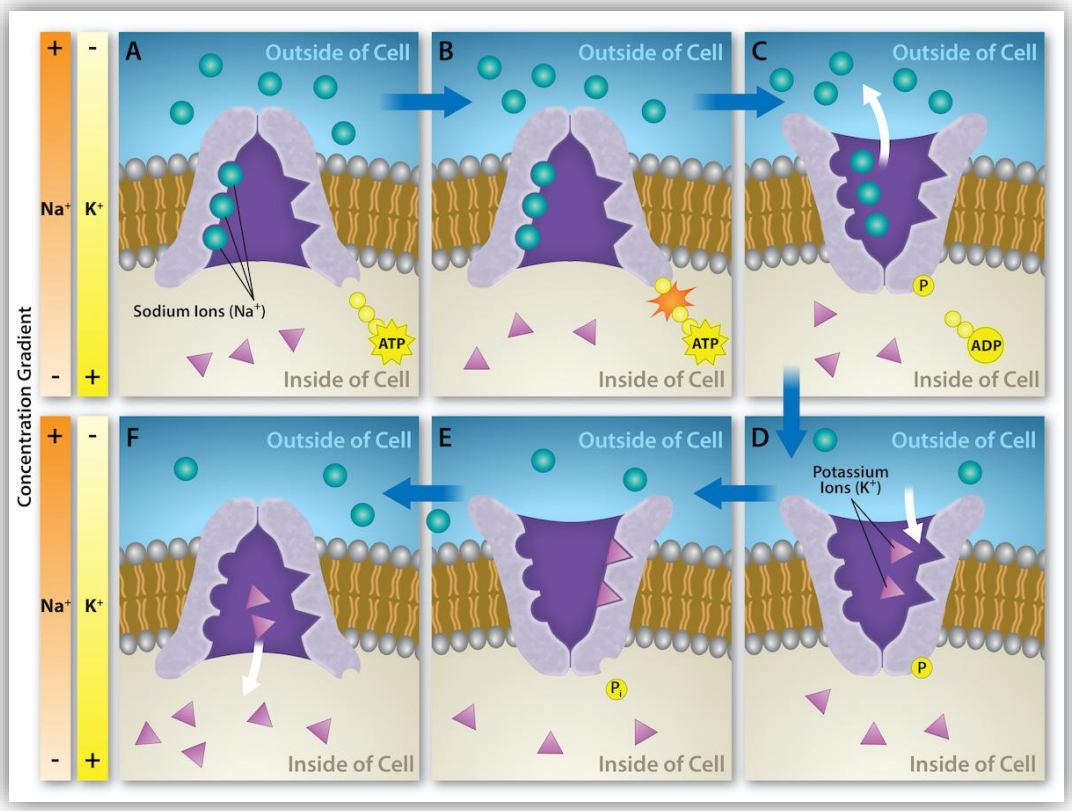
It serves as the basis of nerve function: i.e. nerve signals transmitting.
The energy is provided by the hydrolysis of ATP.
Three Na+ ions are moved out of the cell for every 2 K+ ions that are brought into the cell. This creates an electrochemical gradient that is crucial for living cells.

The carrier protein is a complex of two separate globular proteins:
a **larger (a) subunit** and a **smaller (b) subunit**.

The (a) subunit has three specific features that are functionally important for the pump:

1. The INSIDE portion of the protein protruding towards the cytoplasm has three receptor sites for binding Na+ ions.
2. This INSIDE portion has also ATPase activity near the Na+ binding sites
3. The OUTSIDE face has two receptor sites for K+ ions.

Once 2 K+ ions bind on the outside portion and 3 Na+ ions bind of the inside portion of the carrier protein, the ATPase function of the protein becomes activated. ATPase splits ATP molecule to adenosine diphosphate (ADP) releasing a high-energy phosphate bond of energy. This liberated energy induces a chemical and conformational change in the protein carrier molecule.



Secondary Active Transport

Co-Transport and Counter-Transport

Secondary active transport uses the kinetic energy of the sodium ions concentration gradient to bring other compounds, *against their concentration gradient into the cell* along with influx of Na+ ions.

As Na+ ion concentrations accumulate outside of the plasma membrane by the effect of the primary active transport process; an electrochemical gradient is created (a large concentration gradient of Na+ ions: concentrations are high outside and low inside). This gradient represents a storehouse of energy.

If a channel protein exists and is open; the Na+ ions will move down its concentration gradient across the membrane. This movement transports other substances that must be attached to the same transport protein in order for the Na+ ions to move across the membrane.

This secondary transport process also stores *high-energy H+ ions* in the mitochondria of the cells in order to produce ATP. The potential energy that accumulates in the stored H+ ions translates into kinetic energy as the ions rush through the channel protein ATP synthase, and that energy then converts ADP into ATP.

A clinically important example utilizes this method of secondary active (Co-Transport) to transport many **amino acids**, as well as **glucose**, into a cell against large concentration gradients. The transport carrier protein has two binding sites on its exterior side, one for sodium and one for glucose.

The large difference in concentration of Na+, provides energy for the transport. The transport protein has special property is that a *conformational change* that will allow sodium to enter into the cell, which will not occur until a glucose molecule is also attached to the carrier protein. Once both are attached, the conformational change takes place, and the Na+ and glucose are transported into the cell all together.

There are five specific transport proteins known to transport five subset of amino acids with specific molecular characteristics. These co-transporters of Na+ and glucose / amino acids are known to specially found through the epithelial cells of the intestinal tract and the renal tubules of the kidneys to promote their absorption into the blood. Other important co-transport mechanisms in at least some cells include co-transport of chloride ions, iodine ion.

In ***counter-transport***, Na+ ions also attempt to diffuse into the cell due to high concentration gradient. However, in this type of transport, the Na+ ion binds to the outer face of the carrier protein on the surface of plasma membrane, while the *substance to be counter-transported binds to the interior projection of the carrier protein*. When the two are bound to the two ends of carrier protein, a conformational change takes place, and the influx of Na+ into the cell releases energy the **expels** the substance outside the cell.

Tonicity of fluids

Tonicity is the *effective osmolality* and is equal to the sum of the concentrations of the solutes, which have the capacity to exert an osmotic force across the membrane.

Osmolality is the total concentration of a particle. Plasma osmolality measures the body's electrolyte–water balance.

In clinical practice, the word tonicity always refers to tonicity of a solution with respect to that of plasma (290 mOsm). This tonicity is tested across the plasma membrane of red blood cell (RBC).

Therefore:

Isotonic fluids are those which have osmolality similar to plasma. RBCs neither shrink nor swell in such solution. A solution of 0.9% NaCl is isotonic with plasma.

Hypertonic fluids have osmolality higher than the plasma. The RBCs shrink in such solutions by losing water by osmosis.

Hypotonic fluids are those whose osmolality is lower than that of plasma. The RBCs swell up in hypotonic solutions by gaining water by osmosis.

5.3.3. Vesicular transport

Vesicular transport is a mode of transport that allows the move of larger particles or macromolecules (proteins, bacteria, etc) to move into or out of the cell (between ECF & ICF) by means of vesicles, this is also called **bulk transport**.
Some cells are capable of engulfing entire unicellular microorganisms. Vesicular transport methods are active processes (require ATP), however are *not usually considered active transport.*

ENDOCYTOSIS
Endocytosis happens when a cell actively takes something in. The cell membrane folds around the substance during the process. It is not just some membrane proteins taking in a couple of molecules as in earlier forms of active transport.

It is further categorized into three types:

1. Pinocytosis,

i.e. cell drinking refers to the process of engulfing liquid substances by the enfolding of cell membrane, e.g. reabsorption by renal tubular epithelial cells.

2. Phagocytosis,

i.e. cell eating is the process of engulfing of solid particles, such as bacteria, dead tissue and for engulfing particles by the cells. The plasma membrane encloses particle and buds off to form a food vacuole. The process of phagocytosis involves three steps:
1) the attachment stage, 2) the engulfment stage and 3) killing or degradation stage.

3. Receptor-mediated endocytosis.

In this process the substance to be transported binds with the special receptor protein present on the cell surface. The receptor protein–substance complex is then engulfed by the cell membrane by the process of endocytosis. Transport of iron and cholesterol into the cells occurs by receptor-mediated endocytosis.

EXOCYTOSIS
Exocytosis is the active removal of substances from the cell *without passing through the cell membrane*.

Vacuoles, granules or vesicles from Golgi bodies or the endoplasmic reticulum (ER) fuse with the plasma membrane and expel their contents the exterior and leaving the cell membrane intact.

The process of exocytosis requires Ca++ and energy along with docking proteins. This is a common process in cells involved with secretion.