1 General Physiology

Topics Covered

HYT 1	Homeostasis
HYT 2	Cell and its organelles
HYT 3	Apoptosis
HYT 4	Transport across cell membranes
HYT 5	Body fluid compartments

Competencies

PY1.1	Describe the structure and functions of a cell, intercellular communication and their applications in clinical care and research
PY1.2	Discuss the principles of homeostasis and feedback mechanism
PY1.3	Describe apoptosis (programmed cell death), explain its mechanism of action and physiological significance
PY1.4	Describe and discuss various transport mechanisms across cell membranes
PY1.5	Describe the fluid compartments of the body, its ionic composition, and measurement methods

HYT 1 Homeostasis (PY1.2)

Q1. Define homeostasis and discuss the role of various body systems in maintaining homeostasis.

Homeostasis

Homeostasis is defined as the process of maintenance of nearly constant conditions in body's internal environment by various organ systems. Role of various organs toward homeostasis is explained in **Table 1.1**.

Q2. Explain "gain" of a homeostatic mechanism with a suitable example.

"Gain" measures degree of effectiveness of homeostatic mechanisms. Efficient mechanisms are the ones with higher "gain" values.

Formula:

$$\textit{Gain of a control system} = \frac{\textit{Correction applied}}{\textit{Error}}$$

Example: Gain of Baroreceptor Mechanism for BP Control

Baroreceptors can buffer any sudden rise/fall in BP. Normal mean arterial BP is 100 mm Hg. In person whose baroreflex is intact, over-infusion will induce a marginal rise in BP, i.e., 125 mm Hg; but if baroreceptors are non-functional, BP is substantially raised to approximately 175 mm Hg. Correction applied here is 125 − 175 = −50 mm Hg, while error is 25 mm Hg (Note: This means that BP will still rise by ~25 mm Hg despite intact baroreflex). Thus, gain of baroreflex is −2 mm Hg *(Note: Negative or positive signs denote direction of effect; and do not have any mathematical significance).*

Q3. Describe the feedback regulation of homeostasis.
(Or Differentiate between positive and negative feedback mechanisms.)

Feedback Regulation of Homeostasis

Homeostatic mechanisms are subject to two types of feedback regulation, i.e., positive and negative. Their differentiating features are given in **Table 1.2**.

Q4. Positive feedback is a "double-edged sword." Justify.
(Or Positive feedback is also called vicious cycle. Why?)

Positive feedback has both beneficial and harmful effects depending on its extent and location in the body as explained in **Table 1.3**.

Table 1.1 Mechanisms of homeostasis

Mechanism	System	Description
Addition of nutrients to extracellular fluid (ECF)	GIT	▪ Complex nutrients (polysaccharides, triglycerides, and polypeptides) in food are broken down into simpler forms (glucose, free fatty acids, amino acids) through digestion and absorption ▪ Liver further modifies these nutrients to more simpler forms
	Lungs	▪ Within pulmonary capillaries, O_2 is picked up by RBCs
	Kidneys	▪ Reabsorption of useful substances (glucose, amino acids, ions) by renal tubules
	Musculoskeletal	▪ Enables animal to "move in search of food"
Removal of toxins and wastes from ECF	GIT	▪ Removal of unwanted/undigested wastes as feces and bile
	Lungs	▪ Unloading of CO_2 by RBCs across alveolo-capillary membrane
	Kidneys	▪ Excretion of excess water, ions, and nitrogenous wastes in urine
Transport and mixing of ECF	CVS	▪ Transport function: ECF is constantly circulated within body, providing nutrients and picking up wastes from different tissues. Cardiac systole provides sufficient "pushing force" for ECF to move constantly ▪ Mixing function: Presence of capillary pores ensures diffusion of nutrients into the tissues and picking wastes out of tissue interstitium
Integration of various body activities	CNS	▪ Three major components are input (sensory component, i.e., receptors, monitors state of external environment); processor (brain and spinal cord process input signal and decide output signal); and output (effector component, i.e., muscles and glands, acts appropriately)
	Endocrine	▪ Secrete hormones that control target cell's metabolic activities
	Reproductive system	▪ Maintains continuity of life by replacing dead/decaying beings with new living ones

Table 1.2 Difference between negative and positive feedback mechanisms

Features	Negative feedback mechanisms	Positive feedback mechanisms
Other name	Servo mechanism	Vicious cycle
Basic principle	Initial event inhibited by end product	Initial event facilitated by end product
Concept **(Fig. 1.1)**	"A" produces "B"; "B" inhibits "A" from generating less of its own	"A" produces "B"; "B" stimulates "A" to generate more of its own
Overall effect on body	Usually beneficial	Usually harmful; may prove beneficial in some cases
Occurrence	Majority of homeostatic mechanisms belong to this category	Only few mechanisms are of this type
Examples	Regulation of: ▪ Hormone secretion ▪ Respiratory rate (via CO_2 removal) ▪ Blood pressure ▪ Body temperature	▪ Blood loss in hemorrhage ▪ Blood clotting ▪ Childbirth ▪ Initiation of nerve impulse ▪ LH surge

HYT 2 Cell and its Organelles (PY1.1)

Q5. Describe the structure of cell membrane. (Or Cell membrane is a fluid mosaic. Explain)

Characteristics of Fluid Mosaic Model

Fluid mosaic model (proposed by Singer and Nicholson) is based on the following two important characteristics of cell membrane.

Mosaic Arrangement of Various Substances

Membrane is an assortment of carbohydrate, lipid, and protein molecules grouped together in varying proportions.

Fluidic Nature

These molecules are not rigidly fixed, but simply "float" in ECF (like ships on water) so that their position constantly changes. This arrangement makes membrane structure very dynamic.

Membrane Components as per Fluid Mosaic Model

These are explained in **Table 1.4** and shown in **Fig. 1.2**.

Table 1.3 Beneficial and harmful effects of positive feedback

Beneficial effects	Harmful effects
Blood clotting Vascular injury activates clotting factors which then form a permanent clot **Childbirth** During parturition, cervical canal gets stretched by descent of fetus, triggering labor contractions that further push fetus downwards, leading to more stretching and more stronger uterine contractions. This ultimately results in childbirth **Nerve impulse conduction** An incoming electrical impulse causes slight Na^+ influx within neuronal cell body, which opens some more Na^+ channels. This continues until many Na^+ channels open up suddenly, resulting in action potential (nerve impulse) **Ovulation** Throughout menstrual cycle, estrogen (from ovarian cells) has negative feedback control over luteinizing hormone (LH) release from anterior pituitary. However, during midcycle, there is a "transient switch-over" whereby estrogen has positive feedback on LH secretion, leading to LH surge which causes ovulation	**Blood loss** In case of severe hemorrhage, BP falls → widespread ischemia (especially brain, heart, and kidney) → weakening of cardiac pump → multiorgan failure and death **Thromboembolism** If left unchecked, blood clotting can ultimately result in massive clot formation, thus causing vascular obstruction and embolization *Note: Due to its harmful effects, positive feedback is also called vicious cycle*

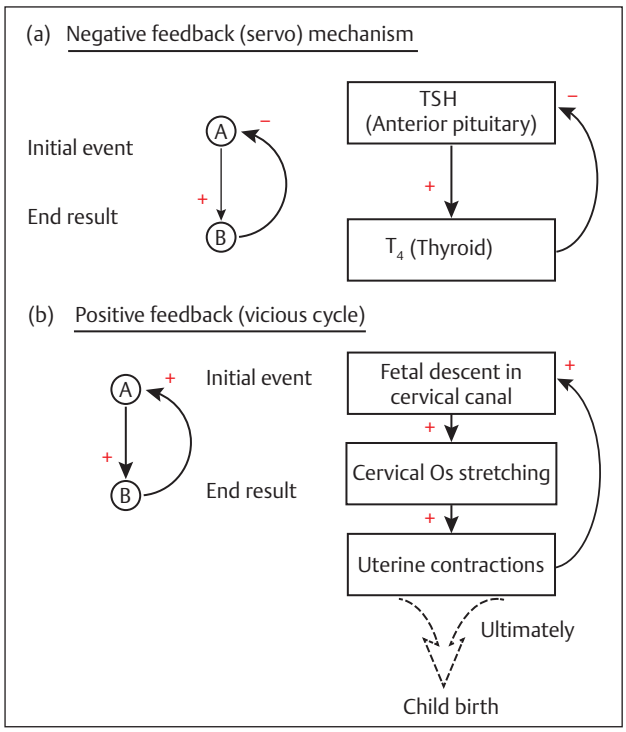


Fig. 1.1 Feedback regulation of homeostatic mechanism.

Properties of Cell Membrane

These are explained in **Table 1.5**.

Applied Aspect: Paroxysmal Nocturnal Hemoglobinuria (PNH)

This condition is characterized by hematuria (blood in urine), especially in midnight/early morning urine sample. It occurs due to a genetic defect in specific surface antigenic proteins (i.e., GPI or Glyco-Phosphatidyl-Inositol) which are peripheral proteins anchored on RBC surfaces. Due to absence of these GPI surface proteins, the immune system fails to recognize affected RBCs as "self" and starts destroying them, resulting in hemolysis.

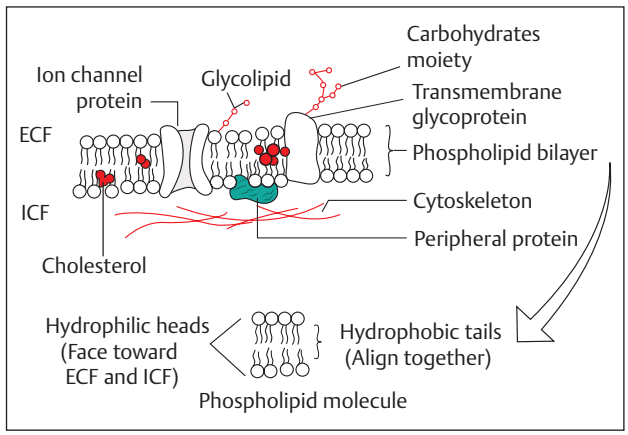


Fig. 1.2 Fluid mosaic model of cell membrane.

Q6. Write a short note on Cytoskeleton.

Cytoskeleton

Cytoskeleton refers to the interconnected network of fibers within cytoplasm that serves as "musculoskeletal framework" of cells. It includes various structures listed in **Table 1.6**.

Microtubules: Important Points

- Microtubules are **most dynamic portion** of cytoskeleton since their subunits are constantly assembled at "Plus" end and simultaneously "dissembled" at "Minus" end.
- Some **anticancer drugs** (paclitaxel, vinblastine, and colchicine) bind and interfere with microtubule subunit assembly. This interrupts cell division (mitosis) as well as movement of essential substances within cancer cells, leading to their death.

Table 1.4 Components of fluid mosaic model and their specific functions

Components		Location	Functions
Membrane proteins	Peripheral proteins	Bound to extra/intracellular membrane surface via weak glyco-phosphatidyl-insoitol (GPI) anchors	"Antigenic identity markers" that allow immune system to identify "self and non-self" cells
	Integral proteins	Lie embedded within membrane, spanning its entire width (transmembrane proteins). Bind with adjacent phospholipids via strong covalent bonds	Facilitate easy movement of water and water-soluble substances (nutrients, ions) inside cell by forming transmembrane channels
Membrane lipids	Phospholipids	Bipolar molecules spanning entire length of membrane and having hydrophilic head and hydrophobic tails. These are of four types depending on the type of "alcohol moiety" attached to "phosphatidyl" group (i.e., phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol and phosphatidylinositol). Sphingomyelins are special type found in neurons (contain sphingol) *Note: Their location keeps changing since "they constantly twirl around like skaters in a crowded rink"*	Help in formation of a "waterproof" membrane bilayer
	Cholesterol	Tucked in between phospholipid bilayer	Cholesterol content is inversely proportional to fluidity; hence, it stabilizes membrane structure
Membrane carbohydrates		▪ They are bound with proteins (proteoglycans/ glycoproteins) and/or phospholipids (glycolipids) ▪ "Glyco" portion usually dangles freely on cell surface	▪ Provide immunity by repelling negatively charged substances (usually pathogens), as they are also charged ▪ Receptors for specific hormones ▪ Antigenic identity markers ▪ Promote cell-to-cell interaction between similar types of cells; important during embryonic development ▪ Form glycocalyx sheath (slimy, fuzzy, halo-like layer outside cells). This makes cell slippery, thereby preventing stasis/adherence of platelets and WBCs within circulation. This normally keeps in check clotting and inflammatory mechanisms

Table 1.5 Properties of cell membrane

Property	Description
Thinness	Very thin *(7–10 nm)*
Pliability	Extremely elastic and flexible, allowing cells to change shape, e.g., myocytes change during contraction and RBCs while traversing through capillaries
Permeability	Selectively permeable barrier; allows controlled movement of substances. Lipid-soluble substances (e.g., alcohol and gases like O_2 and CO_2) pass easily, but water-soluble substances (e.g., nutrients, ions, urea, etc.) need pores or carriers
Fluidity	Structure changes instantaneously due to continuous change in position of its constituents. Degree of fluidity depends on cholesterol content of membrane

Table 1.6 Cytoskeleton

Structure	Diameter	Subunit	Function
Microtubules (**Fig. 1.3**)	15 nm	Tubulin (α, β)	▪ Form "rail-like tracks" for movement of molecular motors, allowing transport of various substances ▪ Spindle formation during mitosis
Intermediate filaments	7–14 nm	Various	▪ Connect nuclear membrane with cell membrane, thus maintaining nuclear integrity ▪ Form flexible internal "supportive beams" (scaffolding), imparting physical endurance to cells against shear stress and pressure. Cells can rupture very easily in their absence
Microfilaments	≤6 nm	Actin	▪ Muscle contraction ▪ Movement tracks for molecular motors (like microtubules) ▪ Facilitate amoeboid motion of cells by forming focal adhesion molecules, which allow cells to "twist and move" over membrane surfaces

Q7. Discuss in brief molecular motors.

Molecular Motors

These are a group of special transporters that "move their cargo" to different locations within cytosol. Their consignment includes proteins, vesicles, organelles, neurotransmitters, etc. (**Fig. 1.4**).

Parts of Molecular Motor

It has three parts: head, neck, and cargo binding portion. Head binds to microtubules (mostly) or microfilaments, while cargo domain binds the substance to be moved.

Types of Molecular Motors

Some molecular motors move on microtubules, e.g., kinesin and dyenins, while some others prefer microfilaments, e.g., myosin.

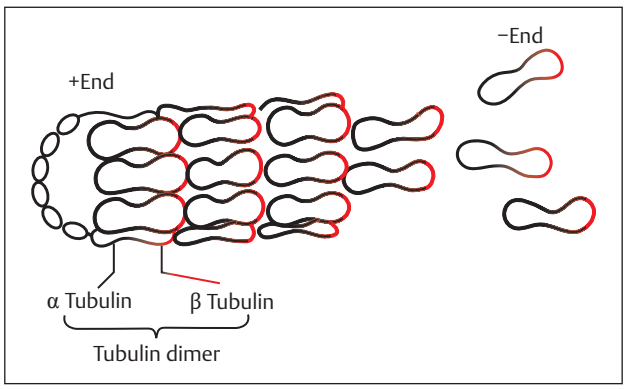


Fig. 1.3 Microtubules.

Their movement resembles that of train wagons moving over railway tracks. Energy for this comes from ATP hydrolysis in the head portion. While they are moving, new tracks are constantly laid down ahead and old ones are constantly removed from behind, all the way till final drop point.

Dynamins

These are newly discovered molecular motors having GTPase activity. They possess a unique "twisting action" which helps in "budding" of new vesicles from a portion of cell membrane and twisting it "until it gets cut off" from the rest of membrane. They facilitate clathrin-mediated endocytosis.

Q8. Write a short note on Cell adhesion molecules (CAMs).

Cell Adhesion Molecules (CAMs)

CAMs facilitate binding of cells to their basement membrane or to adjacent cells, thus maintaining structural integrity of tissue. These are explained in **Table 1.7** and in **Fig. 1.5**.

Q9. Explain the various types of intercellular connections/junctions. (Or Write a short note on Gap junctions.)

Intercellular Connections

Intercellular connections are special structures that allow cells to "firmly attach with" their basal lamina or adjacent cells. They reinforce the anchoring effect of CAMs. They are divided into three categories as explained in **Table 1.8** and in **Fig. 1.6**.

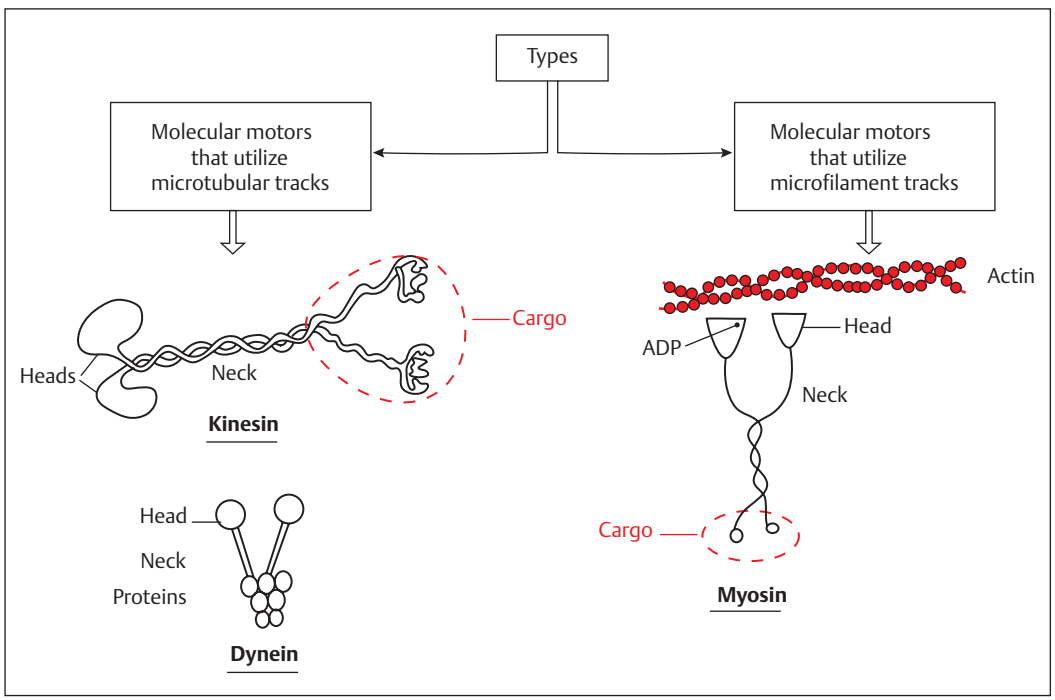


Fig. 1.4 Molecular motors.

Table 1.7 Various types of CAMs

Name	Type of binding	Function
Cadherin (act as velcro tape for cells)	Homophilic binding *(cadherin of one cell binds only to cadherin of another)*	▪ Facilitate tissue development in embryo ▪ Promote wound healing
Selectin	Heterophilic binding *(bind to glycoprotein/glycolipid of another cell)*	▪ Participate in intercellular and intracellular signalling ▪ Immune response: Facilitate aggregation and movement of WBCs at injury/infection site
Integrins and IgSF *(IgSF = Immunoglobulin Superfamily)*	Heterophilic binding *(bind to laminins in ECM or to each other)*	▪ Maintain structural integrity of cell ▪ Prevent apoptosis: Cells with defective integrins have higher rate of apoptosis

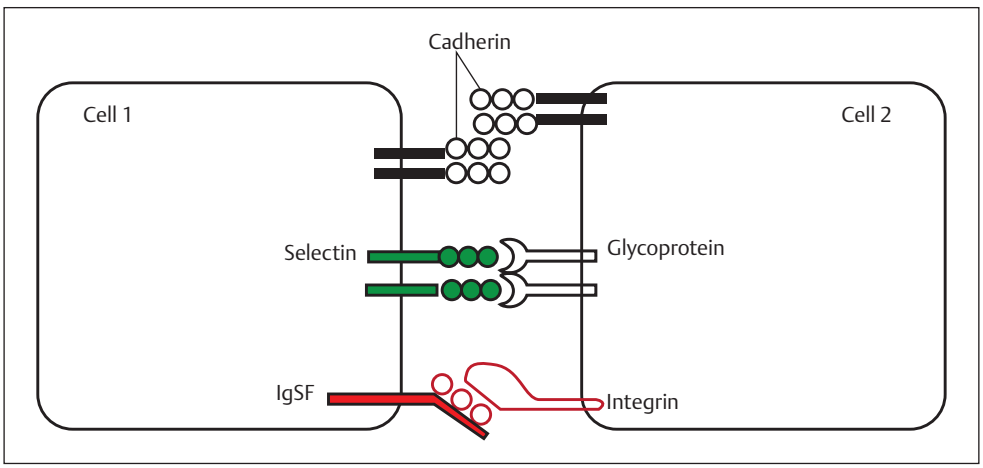


Fig. 1.5 Cell adhesion molecules.

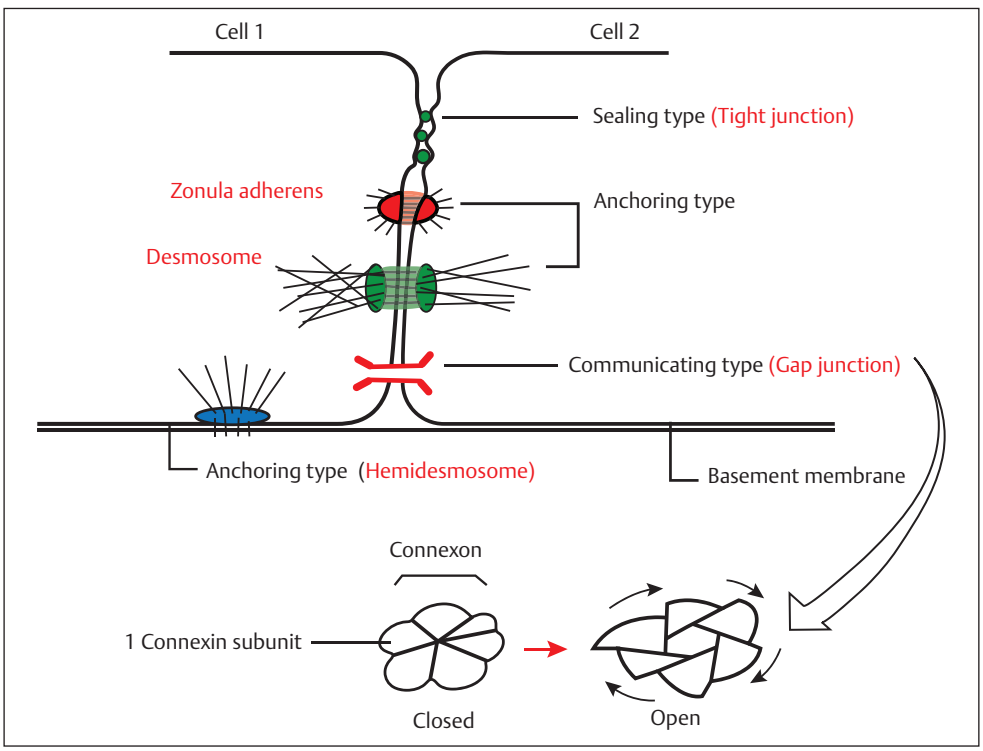


Fig. 1.6 Various types of intercellular junctions.

Table 1.8 Intercellular connections

Type	Morphology	Functions
Sealing Type *(close the gap between the adjacent cells)*		
Tight junctions (zonula occludens)	Made up of multiple strands of occludins, transcellulins, etc., that are embedded within ICF at one end and bind with similar strands from other cells in ECF	▪ Act as scaffoldings, thus providing stability to cell structure ▪ Act as physical barriers, by "sealing off" gaps between two adjacent cells and essentially "zipping up" any potential leak points between ECF and intracellular fluid (ICF). This inhibits entry of toxins and pathogens into cells *Note: Blood brain barrier and blood testes barrier are two important examples where tight junctions (between endothelial cells of brain capillaries and Sertoli cells of testis respectively) effectively seal off and protect underlying structures (neurons and sperms) from damage caused by entry of toxins and pathogens*
Anchoring Type *(firmly fix cell with its surroundings)*		
Desmosomes	Resemble rivets on jeans. Consist of button-like cytoplasmic thickenings (plaques) and intercellular filaments (thread-like structures that connect to plaques of opposite cell). Their intracellular portions are connected with keratin	▪ Act as cellular glue, provide firm cell-to-cell attachment. Especially abundant in cells exposed to constant, high degree of stretching (e.g., heart, uterus, skin epithelium) ▪ Impart considerable tensile strength to cells, protecting against tear injuries due to mechanical deformations **Applied aspect: Pemphigus** It is an autoimmune condition that results in extensive blistering (acantholysis) of skin and entire GIT mucosa and is due to destruction of desmoglein found in desmosomes
Hemidesmosomes	Look like "desmosomes split in half"	▪ Firmly anchor cells to their basal laminas **Applied aspect: Pemphigoid** Milder form of blistering due to autoimmune destruction of hemidesmosomes
Zonula adherens	Abundant in endothelium and epithelial cells. Lie immediately below tight junctions. Bind to actin filaments intracellularly and with similar molecules from other cell extracellularly	▪ Impart endurance to cell, enabling it to withstand physical stresses
Communicating Type *(allow movement of substances between adjacent cells)*		
Gap junctions (nexus)	Adjacent cells are interlinked by small tunnels (connexons) made up of smaller subunits (connexins)	Abundant in tissues where rapid communication is required between cells. Examples: ▪ In cardiac muscles, gap junctions are a part of intercalated discs. Depolarization of one cardiac cell leads to instantaneous spread of depolarization wave to all cardiac cells via ionic movement through gap junctions! This allows ventricles to contract effectively as a single unit *(functional syncytium)* ▪ Smooth muscles also undergo simultaneous contractions due to gap junctions. In intestine, this is especially helpful in moving food through entire length of gut within a short span of time. In gravid uterus, it helps in parturition **Applied aspect: Charcot Marie Tooth Disease** Hereditary condition due to mutation in connexin coding genes resulting in peripheral sensory and motor neuropathy

Q10. Explain the various ways in which cells interact with each other.
(Or Write a short note on Intercellular communications.)

Intercellular Communications

Cells communicate with each other either directly or indirectly through various modes as explained in **Table 1.9** and shown in **Fig. 1.7**.

Table 1.9 Intercellular communications

Type	Description
Direct communication	
Gap junction	Rapid means of communication. *(see Q9)*
Juxtacrine	Specific chemicals released by one cell (e.g., growth factors, cytokines, etc.) bind to their receptors on surfaces of other cells, serving as "transient communication mediums" by linking up the two cells. Cytotoxic T-cells interact with pathogens via this mechanism
Indirect communication	
Autocrine	Chemicals secreted by a cell bind to receptors on the cell surface itself. For example, interleukin I on monocytes and IL-2 on helper T-cells
Paracrine	Chemicals diffuse into ECF and affect neighboring cells lying some distance away. They do not enter blood as they are rapidly inactivated by enzymes in ECF. For example, histamine from injured/inflamed cells acts on adjacent endothelial cells to produce vasodilatation
Endocrine	Certain chemicals (hormones) are long-range messengers as they are released into blood and can thus reach far off target sites. Only the cells having specific receptors respond to them; others remain unaffected
Synaptic (neural)	Special chemicals (neurotransmitters) are released by presynaptic cells at synaptic junctions, between terminal ends of neurons and adjacently lying post synaptic cell (which can be neuron/gland cell/muscle cell)

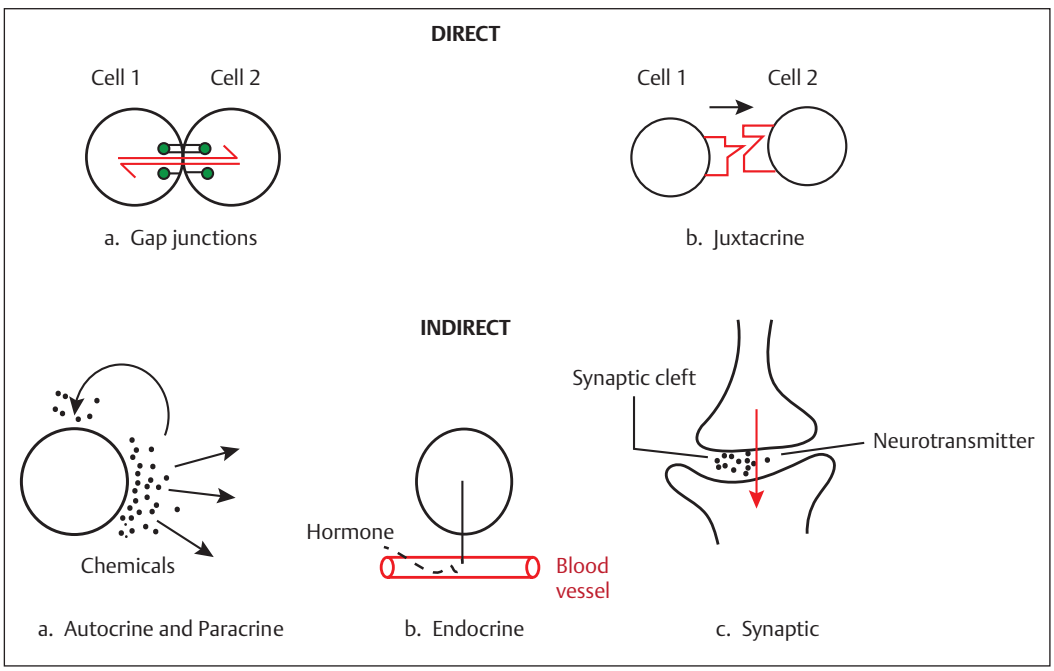


Fig. 1.7 Intercellular communications.

HYT 3 Apoptosis (PY1.3)

Q11. Write a short note on Programmed cell death. (Or Write a short note on Apoptosis and its physiological significance.)

Apoptosis

Apoptosis is a genetically pre-programmed physiological process by which cells initiate their own death. The term refers to the falling of dead leaves in autumn *(Apo = Away; Ptosis= Fall)*.

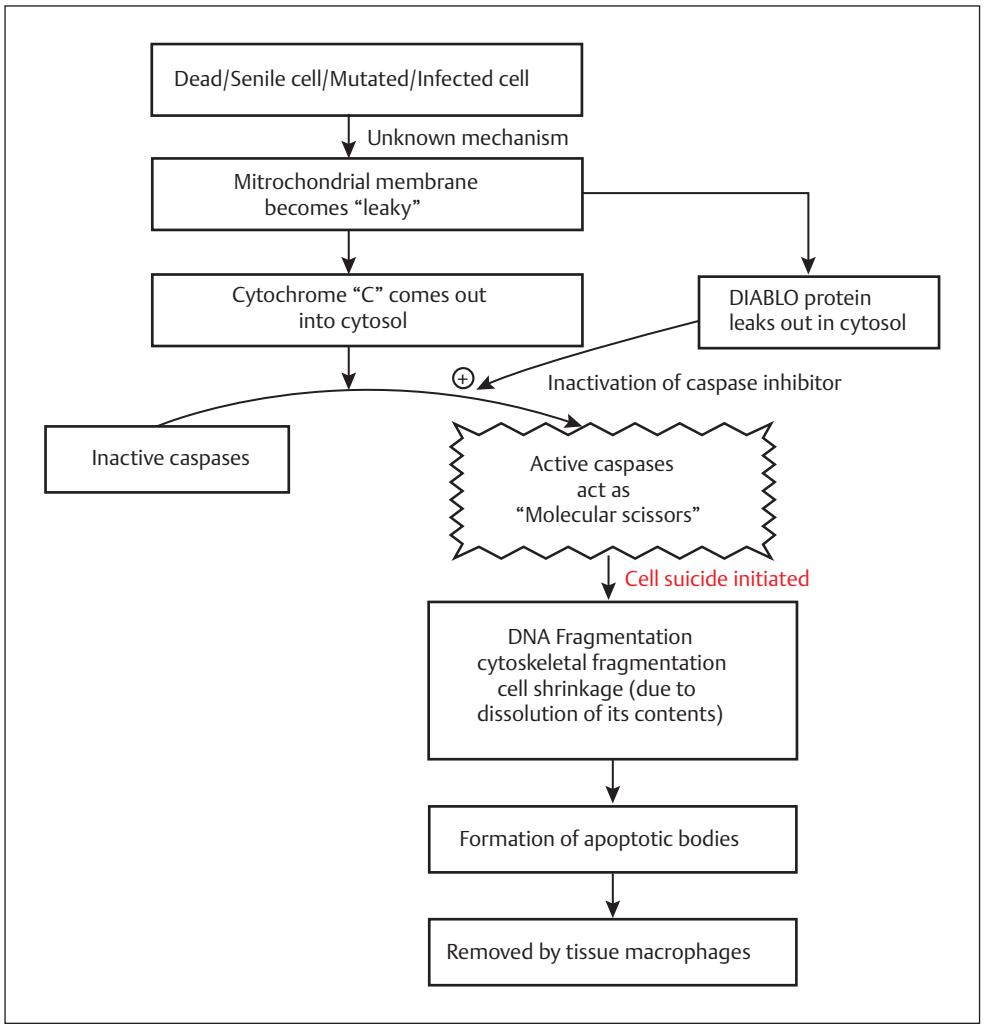
Physiological Basis

Apoptosis is initiated within any cell when a suicide signal (of unknown nature) causes leakage of cytochrome C and DIABLO protein from mitochondria into cell cytosol. This activates caspase enzyme which causes widespread destruction of cellular components. This is explained in **Flowchart 1.1**.

Note: Cells lying adjacent to those undergoing apoptosis remain totally unaffected.

Physiological Significance of Apoptosis

It is explained in **Table 1.10**.



Flowchart 1.1 Mechanism of apoptosis.

Table 1.10 Significance of apoptosis

Function	Description
Role in normal tissue growth and development	By way of apoptosis: ▪ Finger webs get removed automatically in fetus, thus gradually "carving out" the normal hand shape. Reproductive tracts get pruned in developing fetus, enabling formation of internal and external genitalia. This happens during regression of Wolffian duct in female fetus and Mullerian duct in male fetus ▪ In CNS, many old synapses are constantly removed by apoptosis to make way for new ones
Immunity	▪ Infected cells trigger their own death ▪ WBCs also auto-delete themselves after their task is finished
Homeostatic mechanism	▪ Optimum tissue health is maintained by constant removal of unwanted/dead/senile/dysfunctional cells to make way for new ones

Applied Aspect: Abnormal Apoptosis

Excessive apoptosis is associated with neuronal death in Alzheimer's and Parkinsonism; helper T cells die in AIDS due to similar reason. On the contrary, apoptosis is greatly deficient in cancerous cells, thus allowing their unchecked growth.

HYT 4 Transport Across Cell Membranes (PY1.4)

Q12. Describe the various active transport mechanisms.
(Or Write a short note on Na-K-ATPase and its physiological significance
Or Compare and contrast primary and secondary active transport
Or Explain physiological basis of inotropic effect of Digitalis
Or Explain why glucose is added to oral rehydration solution?)

Active transport is so named because it utilizes energy (from ATP lysis) to move substances against their electro-chemical gradient.

Primary Active Transport (PAT)

It is named so because energy is derived primarily (directly) from ATP breakdown. Typical example of primary active transporter is Na-K-ATPase pump.

Na-K-ATPase

It is universally present in all body cells. Lysis of a single ATP triggers ***efflux*** of three Na^+ and ***influx*** of two K^+ ions simultaneously (coupling ratio $3Na^+$:$2K^+$). Its structure and functioning are shown in **Fig. 1.8**. It is stimulated by thyroxine and inhibited by digitalis and ouabain. Physiological significance of Na-K-ATPase is explained in **Table 1.11**.

Other Primary Active Transporters

These are enlisted in **Table 1.12**.

Secondary Active Transport (SAT)

It is named so because it derives energy secondarily (indirectly) from large ionic concentration gradients (mostly Na^+) established by PAT.

Mechanism

Na-K-ATPase establishes a large concentration gradient (for Na^+) across cell membrane (due to Na^+ efflux). Consequently, Na^+ ions readily diffuse back into ICF via secondary pumps. If another substance attaches simultaneously with SAT pump,

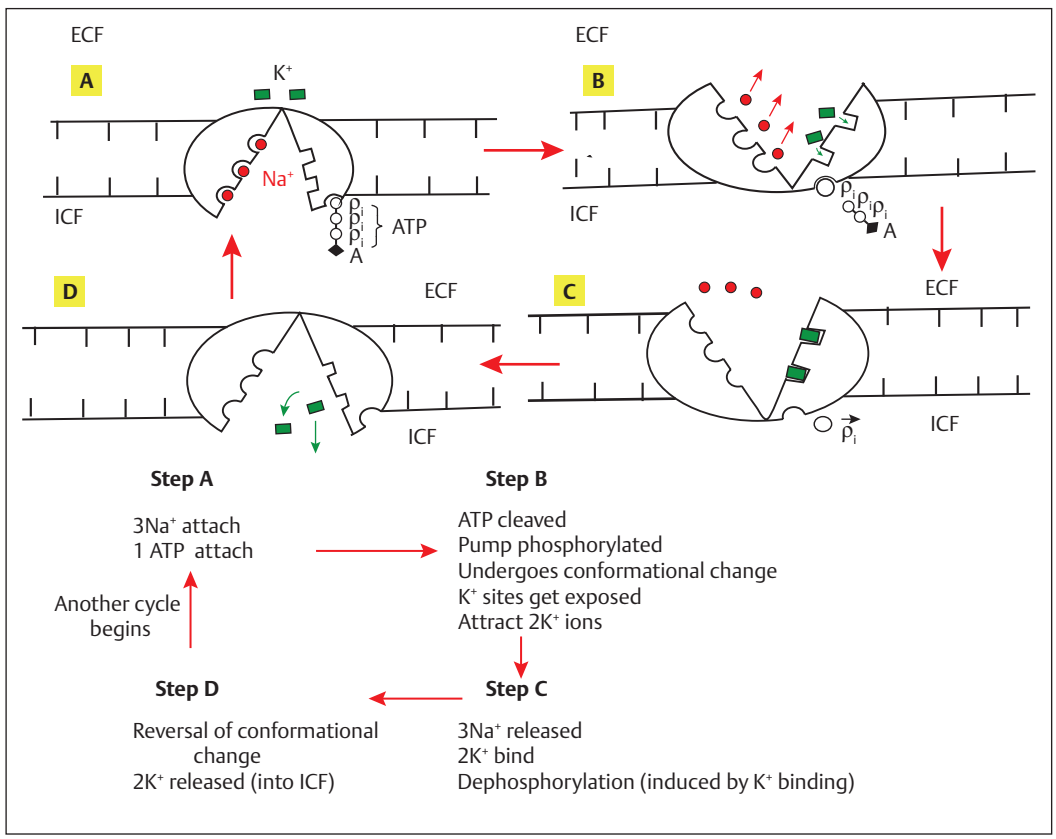


Fig. 1.8 Na-K-ATPase pump and its working mechanism.

Table 1.11 Physiological significance of Na-K-ATPase

Significance	Function
Genesis of resting membrane potential (RMP)	Electronegativity of RMP (−70 mV for neurons) is maintained by electrogenic nature of this pump. Each time this pump operates, there is net loss of 01 positive charge from inside the cell, creating negativity inside
Maintains continuity of new action potentials (APs)	After AP is over, membrane potential values attain resting value but Na^+ and K^+ ions distribution gets disturbed (i.e., Na^+ is more inside and K^+ is more outside). Na-K-ATPase restores their concentrations (Na^+ will be sent out; K^+ will be sent in), recreating resting conditions so that newer APs can occur uninterrupted. Disturbance of this pump leads to dysfunction of neurons, muscles, and gland cells
Maintains cell volume	Na-K-ATPase activity results in net loss of ions from ICF, reducing cell tonicity to some extent, thus preventing osmotic movement of excessive water from interstitium. In its absence, cells tend to swell and burst
Maintains secondary active transport	Na-K-ATPase "energizes" secondary active transport by creating a large Na^+ gradient

Table 1.12 Location and functions of other secondary active transporters

H-K-ATPase	Ca ATPase
▪ *In stomach:* Parietal cells secrete H^+ in lumen to form HCl ▪ *In nephron:* Distal tubules and collecting ducts secrete H^+ in urine	▪ *In muscle cells:* Sarcoplasmic reticulum accumulates adequate calcium for muscle contraction via these pumps ▪ *In all cells:* Ca^{2+} is an important intracellular signaling molecule whose concentration is maintained at optimum level by these pumps

Table 1.13 Types of secondary active transport

Co-Transport (Symport) of Na^+ and Substances		Counter-Transport (Antiport) of Na^+ and Substances	
Occurs in same direction (both substances move toward ICF)		Occurs in opposite directions (Na^+ toward ICF and the substance toward ECF) *Note: The antiporters are also called "exchangers"*	
Example	**Function**	**Example**	**Function**
Na-glucose linked transporter (SGLT)	In GIT and renal tubules: Glucose absorption	Na-H pump	In renal tubules: Urine acidification
Na-amino acid transporter	In GIT and renal tubules: Amino acid reabsorption	Na-Ca pump	In heart: Regulate intracellular calcium levels (calcium efflux occurs via these pumps)
Na-K-2Cl transporter	In renal tubules: Maintains counter-current mechanism in renal medulla (by absorbing all these ions)		
Na-HCO_3 transporter			

it would also "get free ride" with Na^+. Thus, SAT is dependent upon normally functioning PAT.

Types of SAT

These are explained in **Table 1.13**.

Applied Aspect: Various Drugs Affecting Active Transport

Inotropic Effect of Digitalis (Digoxin)

This plant based chemical deactivates Na-K-ATPase in all cells, including cardiac cells. This further results in secondary inhibition of Na-Ca exchanger within cardiac cells, leading to Ca^{2+} ion accumulation inside them. More calcium results in stronger cardiac contractions; thus, digitalis is used in heart failure (**Fig. 1.9**).

Note: Inotropic effect means increased cardiac contractility.

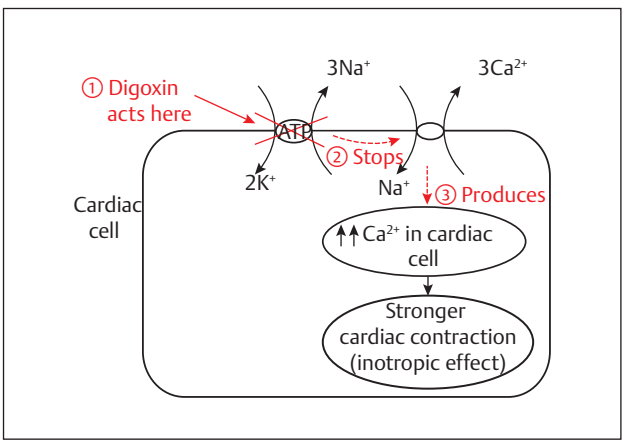


Fig. 1.9 Inotropic effect of digitalis.

Toxic Effect of Ouabain

This is another plant based chemical that is mainly used as arrowhead poison by African tribes during hunting and warfare. Its action is similar to but much stronger than digitalis. It produces fatal cardiac arrhythmias (due to strong inhibition of Na-Ca pump) along with neural dysfunction and paralysis (action potentials are interrupted in these tissues due to Na-K-ATPase pump inhibition).

Oral Rehydration Solution (ORS)

ORS (given in dehydration) contains glucose and ions (especially Na^+). The main aim of adding glucose to ORS is to promote Na^+ reabsorption via SGLT (i.e., sodium glucose linked transporter). This is because SGLT undergoes conformational change only when both Na^+ and glucose attach simultaneously to it. *Note: Providing nutrition via glucose is of secondary importance in ORS therapy* (**Fig. 1.10**).

Q13. Describe various passive transport mechanisms.
(Or Write short notes on (a) Osmosis (b) Diffusion (c) Facilitated [carrier mediated] transport.)

In passive transport, substances are transported down their concentration and/or electrical gradients; hence, no energy is used. Two types: osmosis (for solvent transport) and diffusion (for solute transport).

Osmosis

Movement of solvent (usually water) molecules from higher concentration toward lower concentration, across semipermeable membrane. This is driven by osmoles, i.e., osmotically active molecules (e.g., ions, organic molecules, etc.), which attract solvent molecules toward their own side. Magnitude of osmosis is directly proportional to osmolarity (number of osmoles in solution) (**Fig. 1.11**).

Significance: Maintenance of Cell Volume

Osmosis is the main mechanism by which water leaves/enters cells through semi-permeable cell membrane. Direction of osmotic movement depends on difference in osmolarity between cell and its surroundings.

Osmotic Pressure

Osmosis can be stopped by applying counter-pressure on the side where solute concentration is more. This is known as osmotic pressure and is calculated by the equation **P = nRT/V**; where P = osmotic pressure; n = number of solute particles, R = constant, and V = volume of solution.

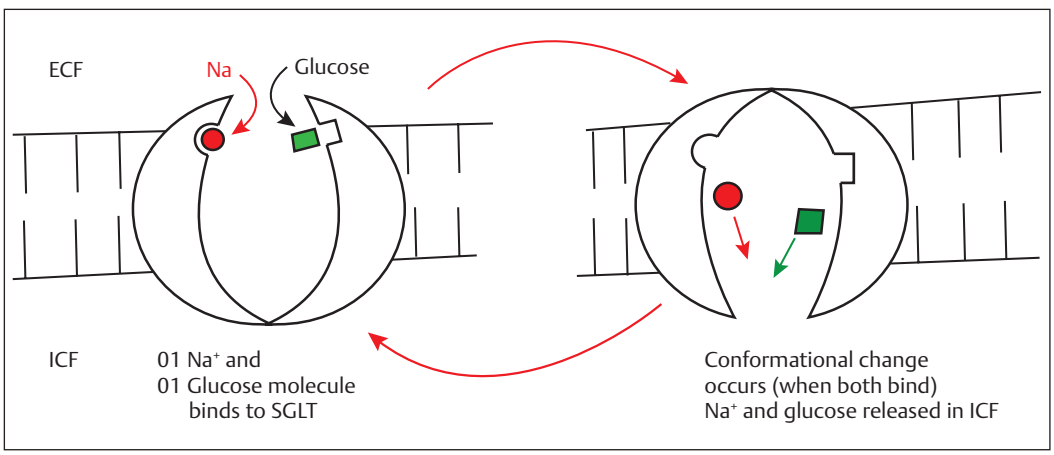


Fig. 1.10 Sodium glucose linked unit transporter.

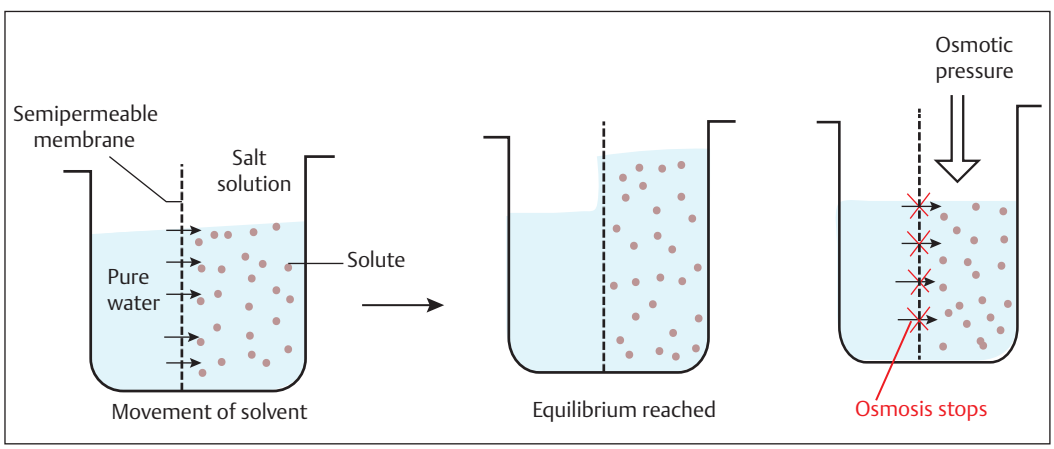


Fig. 1.11 Osmosis.

Diffusion

Continuous movement of fluid and gas molecules from higher concentration toward lower concentration is called diffusion; it achieves uniform spatial distribution of fluid/gas particles.

Types of Diffusion

Simple Diffusion

In this, the molecules move through membrane components (channel proteins/membrane lipids) without interacting with them, thereby "passing as such" through the membranes (**Fig. 1.12**).

Facilitated (Carrier Mediated) Diffusion

In this, the movement of substances is facilitated by special carrier proteins (**Fig. 1.13**). *Examples:* Urea transporter (UT) in renal tubules; glucose linked unit transporter (GLUT) in GIT, muscles, and liver. Special characteristics of facilitated transport are given in **Table 1.14**.

Kinetics of Simple and Facilitated Diffusion

Simple diffusion follows "linear kinetics," i.e., rate of transport keeps increasing as more substance becomes available.

Facilitated diffusion follows "saturation kinetics," i.e., rate of transport keeps increasing with availability of substance only initially; however, once Tm is achieved, plateau is observed (**Fig. 1.14**).

Q14. Compare secondary active transport and facilitated transport.

Both these processes are compared in **Table 1.15**.

Table 1.14 Special characteristics of carrier-mediated transport

Features	Description
Specificity	Some carriers transport only a specific substance
Competition	Some other carriers bind two or more substances that closely resemble each other, creating competition between them and diminishing each other's transfer. For example, glycine and alanine, glucose and galactose, etc.
Saturation	There exists an upper limit to both number of carriers and their rate of transport (transport maximum or Tm). Carriers continue to function optimally till Tm is reached

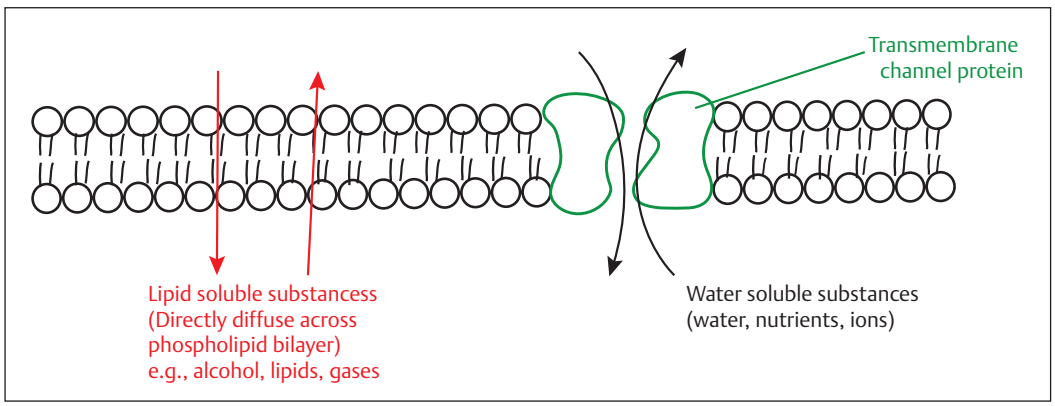


Fig. 1.12 Mechanism of simple diffusion.

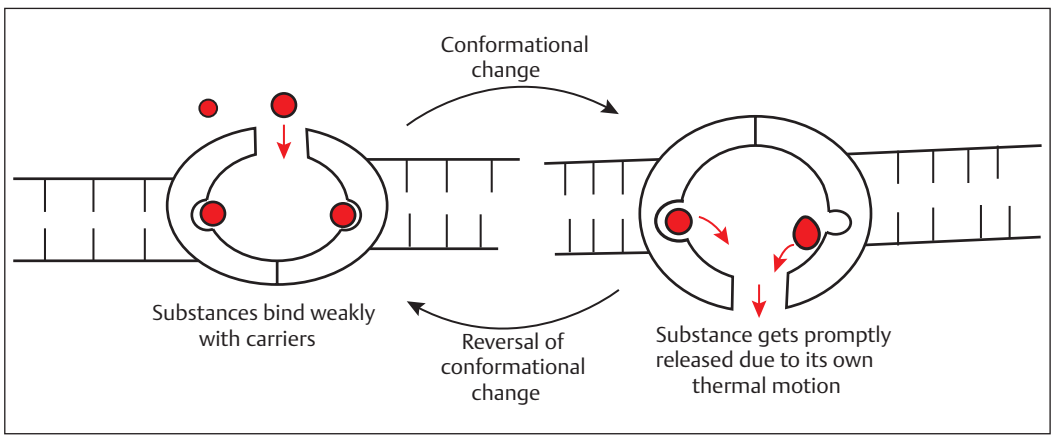


Fig. 1.13 Facilitated (carrier mediated) diffusion.

Table 1.15 Similarities and differences between secondary active transport and facilitated diffusion		
Characteristics	**Secondary active transport**	**Facilitated diffusion**
Similarities	▪ Both utilize proteins undergoing conformational change ▪ Both follow saturation kinetics	
Differences		
Proteins involved	Transporters (symporters/antiporters)	Carriers
Conformational change	Due to phosphorylation of transporters	Spontaneously; when substance binds
Energy required	Yes. Indirectly from primary active transport	No
Affinity of substrate and transport protein	Keeps changing. More when protein is active; less when inactive	Constant. Does not depend on activity

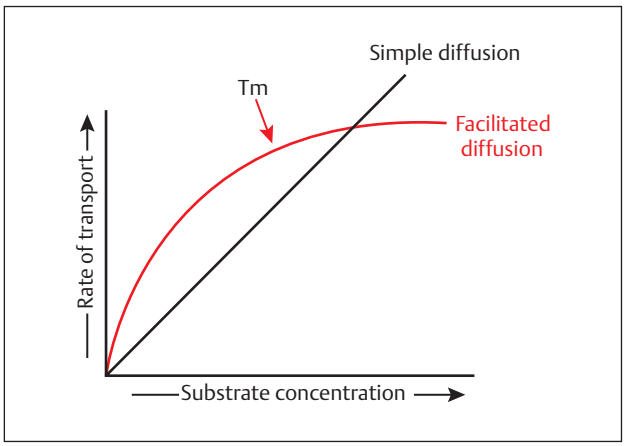


Fig. 1.14 Saturation kinetics of diffusion.

Q15. Explain vesicular transport. (Or Write a short note on Clathrin-mediated endocytosis Or Differentiate between constitutive and non-constitutive exocytosis.)

Vesicular Transport

It is a special form of active transport that involves movement of substances (that are too big for carriers/channels) within membrane-bound structures.

Endocytosis

Involves ingestion of contents by cells. It is of four types and these are explained in **Table 1.16**.

Exocytosis

Involves expulsion of cellular contents. Vesicular membrane "docks" with cell membrane at specific sites (V-snare proteins on vesicle membrane attach with T-snare proteins on cell membrane). Consequently, vesicular membrane "fuses" with cell membrane. Vesicular contents are then exposed and discharged.

Table 1.16 Types of endocytosis	
Type	**Mechanism**
Clathrin mediated *(Main mechanism)* **(Fig. 1.15)**	Substances that use this route (e.g., iron and LDL) bind to their membrane receptors. Underside (cytosolic side) of the membrane at these receptor areas is coated with clathrin molecules. As soon as ligand–receptor interaction occurs, clathrin causes membrane invagination and surrounds invaginated portion. Simultaneously "dynamin" also attaches to the neck of developing vesicle, starts "twisting" it, thereby pinching and squeezing vesicle until it gets separated from the membrane. At this point clathrin coats are shed off and recycled
Phagocytosis *(Cell eating)* **(Fig. 1.16)**	Ingestion of large, solid substances, e.g., bacteria, cell debris, dust, etc. Involves invagination of membrane for vesicle formation without clathrin. Seen in neutrophils, monocytes, and macrophages *Note: Macrophages ingest substances many times larger than themselves; hence, their membrane evaginates to wrap around substances*
Pinocytosis *(Cell drinking)*	Ingestion of small ECF packets containing substance to be ingested (e.g., nutrients) in solution form, rather than solid form
Potocytosis	Endocytosis mediated by special membrane areas called "caveolae" (small pits containing cholesterol binding proteins, i.e., caveolins) which act as "lipid rafts" to "ferry" their cargo toward ICF. Seen in adipocytes, smooth muscles, endothelium

Significance of Exocytosis

- Secretory pathway for macromolecules (e.g., polypeptides, fat droplets, etc.).
- Adds specific intracellular-specific components to cell membrane (e.g., channel proteins, glycoproteins, receptors, etc.). These are synthesized intracellularly and get attached transiently for specific function, after which they are internalized and destroyed.

Types of Exocytosis

These are explained in **Table 1.17**.

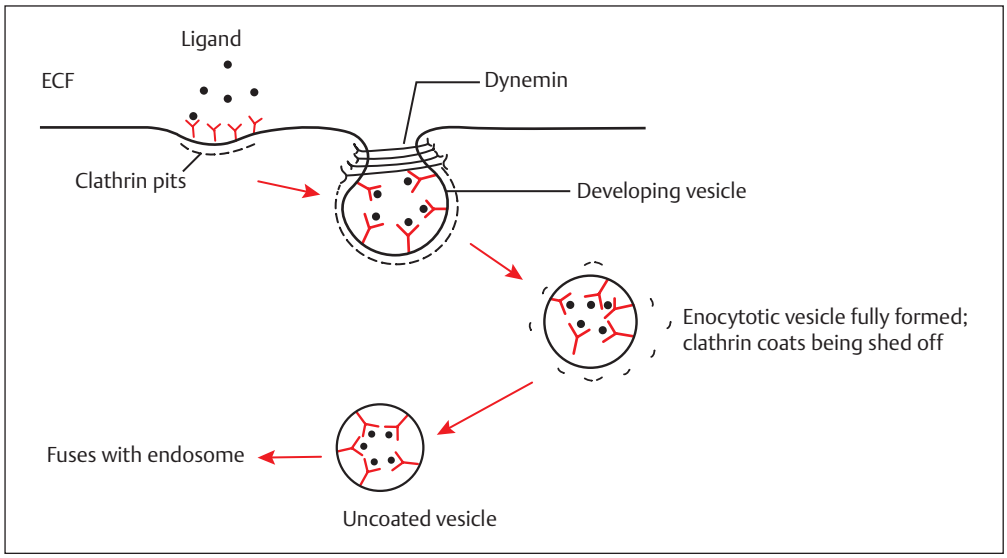


Fig. 1.15 Clathrin-mediated endocytosis.

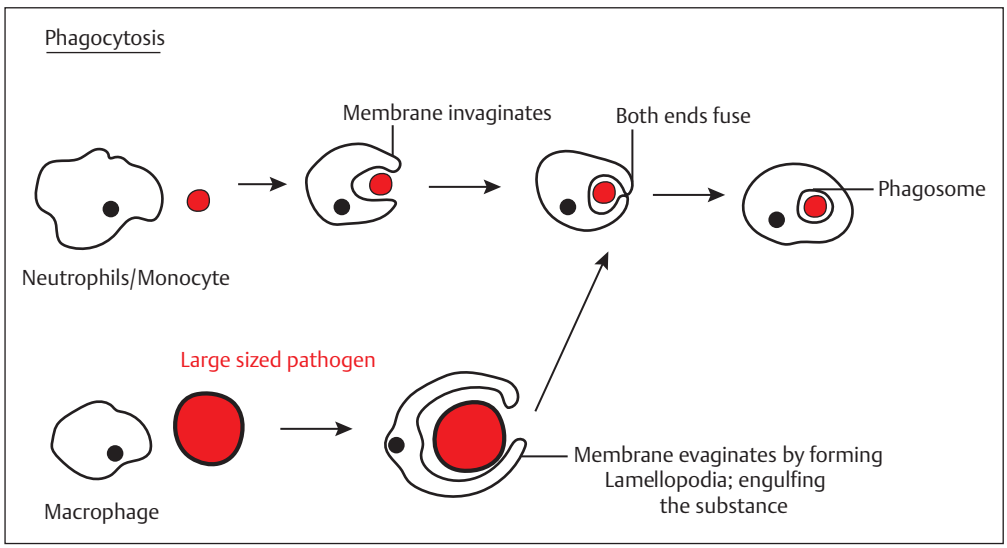


Fig. 1.16 Phagocytosis.

Table 1.17 Types of exocytosis

Feature	Constitutive exocytosis	Non-constitutive exocytosis
Constituents of vesicles	Normal membrane constituents (glycoproteins, glycolipids, lipids)	Special chemicals (e.g., histamine, autacoids, neurotransmitters, etc.)
Processing of substances within vesicles	Absent	Present
Vesicular movement	Occurs continuously, without any specific stimulus (non-regulated exocytosis)	Occurs only in response to interaction of a specific ligand with its receptor on cell surface (regulated exocytosis)

HYT 5 Body Fluid Compartments (PY1.5)

Q16. Describe various body fluid compartments. How are they measured? (Or Explain indicator dilution method used for estimation of body fluid volumes.)

Preliminary Concept: Total Body Water (TBW)

Around 60% of body weight in adult male is contributed by water and this level is maintained by a balance between water addition and water removal mechanisms as explained in **Table 1.18**.

Body Fluid Compartments

Total body water is divided into three main compartments by biological membranes **Fig. 1.17**.

Intracellular Compartment (40%)

- It is a portion of TBW that lies within cell (forms cytosol).
- It is also called intracellular fluid (ICF).
- It is separated from ECF by semi-permeable plasmalemma.

Extracellular Compartment (20%)

- It is the portion of TBW that lies outside cell.
- It is also called extracellular fluid (ECF).
- It has three subcompartments as explained in **Table 1.19**.

Measurement of Body Fluid Compartments: Indicator Dilution Method

Underlying Principle: Law of Conservation of Mass

If an indicator/dye is allowed to mix (disperse) with fluid in a compartment, then total mass of indicator before dispersion is same as that after dispersion.

Procedure

- An indicator/dye is chosen as per following selection criteria:
  - Should disperse *uniformly* and *only within* the compartment whose volume is to be estimated.
  - Should *not leave* that compartment, i.e., should neither be metabolized nor excreted.
- Predetermined quantity of dye is injected into known volume of fluid.
- After it has dispersed evenly, fluid sample is removed, and concentration of the dye is analyzed. During this time, no dye is allowed to enter/leave the fluid.
- Calculation is shown in **Fig. 1.18**.

Estimation of various body fluid compartments is done as shown in **Table 1.20**.

Q17. Explain why estimation of ECF volume is difficult?

ECF volume estimations are less accurate/difficult to estimate because:

- ECF is not stored in a single fixed compartment; instead, it is distributed within interstitium, blood vessels, and

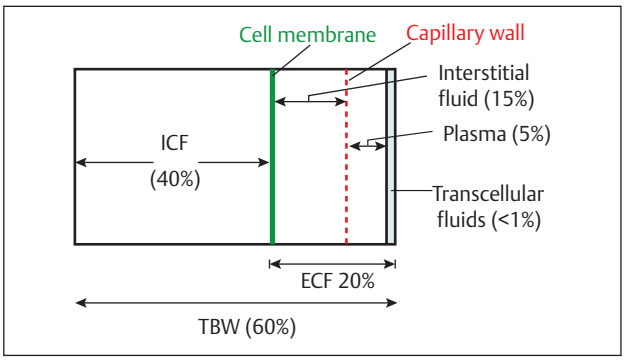


Fig. 1.17 Various body fluid compartments.

Table 1.18 Water adding and removal mechanisms

Water adding mechanisms	Water removal mechanisms
▪ Ingestion of liquids (mainly) ▪ Synthesis of metabolic water (slightly)	▪ *Insensible (non-excretory) water loss:* Animals remain unaware to constant loss of water molecules due to diffusion into atmospheric air via breath and from skin (non-evaporative loss). The loss is normally around 300 to 400 mL/day but can reach 700 mL/day in extremely dry conditions. This type of water loss is more in dry weather and in burns ▪ *Excretory water loss:* Daily loss of water is 100 mL in feces, 1,500 mL in urine, and variable in sweat

Table 1.19 Subcompartments within ECF

Interstitial fluid (15%)	Plasma (5%)	Transcellular fluids (<1%)
Lies within immediate vicinity of cells. Tissue capillaries also lie in interstitial space. Tissue cells exchange nutrients and wastes with capillaries via this fluid	"Watery component" of blood. Separated from interstitial fluid by capillary wall	They consist of small fluid "pockets" lying within specific tissues, e.g., CSF, synovial fluid, ocular fluids, lymph, inner ear fluids, digestive secretions, etc.

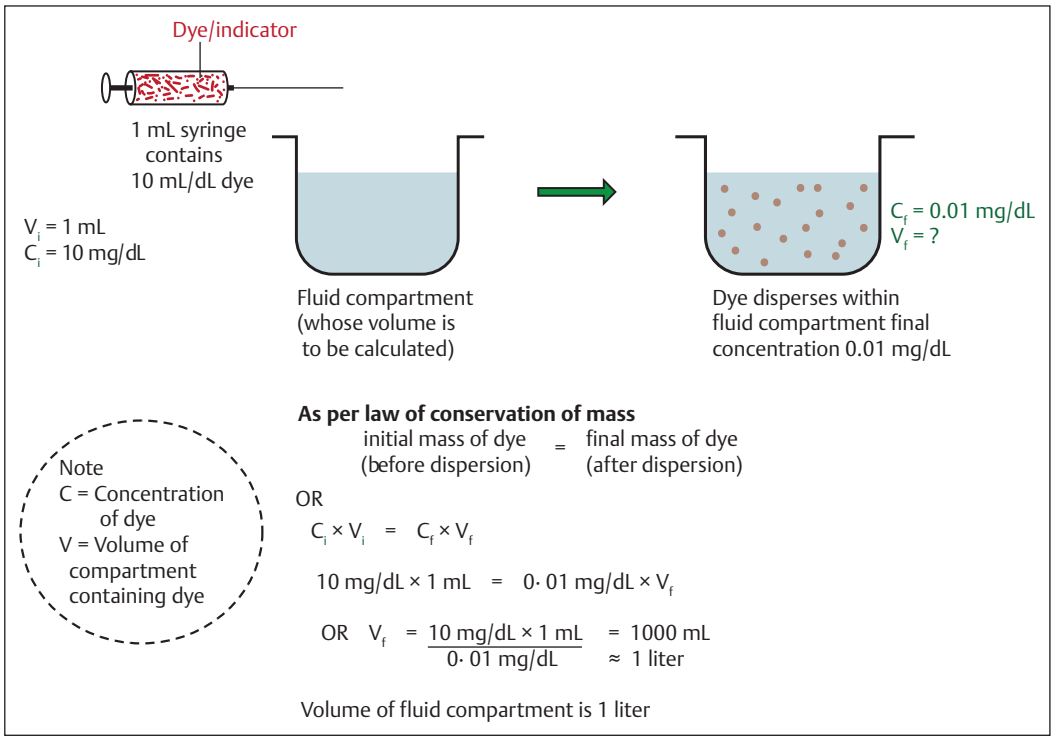


Fig. 1.18 Indicator dilution method.

Table 1.20 Estimation of various body fluid compartments

Volume	Selection criteria for indicator/dye	Indicator/dye used
Total body water (TBW)	Should spread throughout all compartments (i.e., it can cross cell and capillary membranes)	Radioactive water (^3H_2O) Heavy water (^2H_2O) Antipyrine
ECF	Should remain within ECF (i.e., crosses capillary membrane but not cell membranes)	Radioactive ions *(Na, Cl, thiosulfate)* Sugars *(inulin, mannitol, sucrose)*
Plasma volume	Should remain within plasma (i.e., can't cross capillary membrane)	Iodine-125 labelled albumin Evans blue dye *(binds proteins)*
ICF	TBW – ECF *(since TBW = ECF + ICF)*	No indicator used; Values are calculated mathematically
Interstitial fluid	ECF – Plasma *(since ECF = IF + Plasma)*	

lymphatic vessels, all of which are further separated by semi-permeable membranes.

- ECF volume constantly changes depending on salt and water intake, BP levels and hormones (e.g., ADH, angiotensin).
- ECF indicators "osmotically drag" ICF fluid, thus falsifying the results.

Q18. Explain why infants are more prone to dehydration than adults.

In infants, ECF:ICF ratio is more than adults, even though their overall ECF volume is lower. Moreover, evaporative loss of ECF is also more in infants due to:

i. Larger body surface area as compared to ECF volume.
ii. Higher metabolic rate.
iii. Inability to seek fluid/communicate thirst.

Q19. Explain why body fluids within each compartment are electrically neutral. (Or Write a short note on Gibbs Donan equilibrium.)

Gibbs Donan Equilibrium

Gibbs Donan equilibrium is a physiological process that plays a critical role in ionic distribution between ECF and ICF (**Fig. 1.19**). These compartments are separated by semi-permeable membrane, which allows certain ions to pass through while restricting others (**Fig. 1.20**).

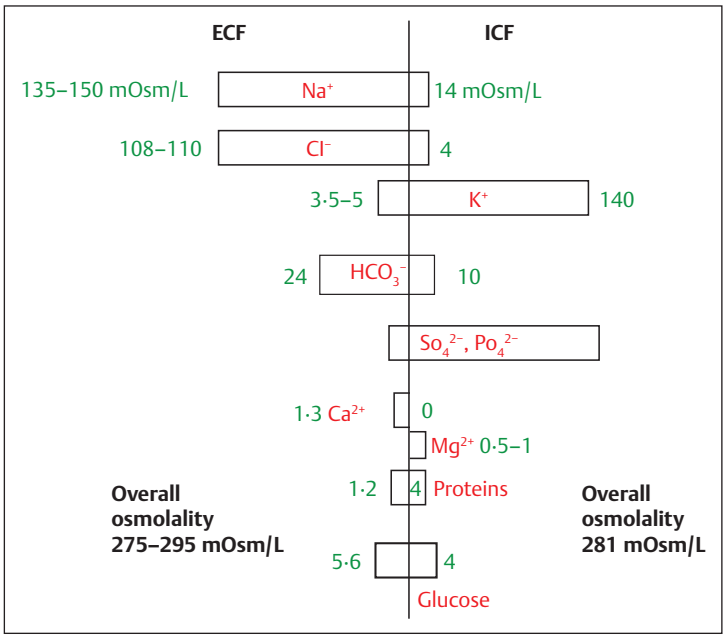


Fig. 1.19 Relative distribution of various ions across body fluids.

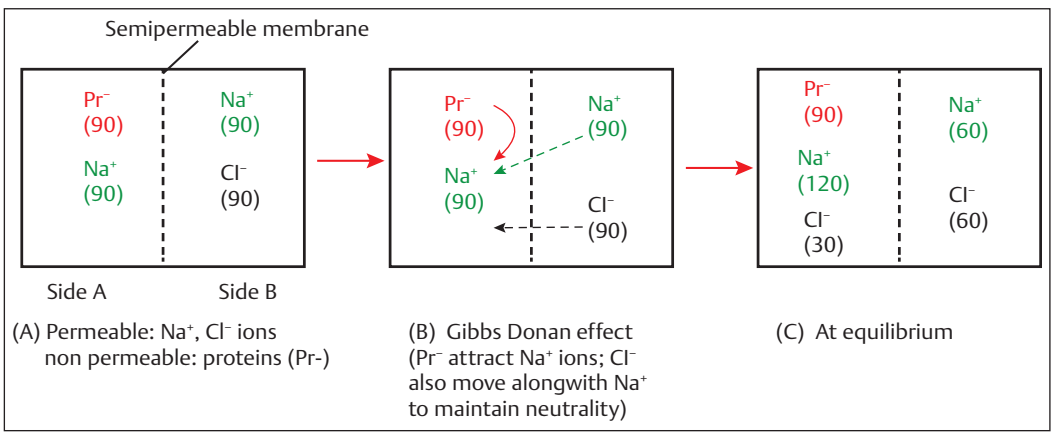


Fig. 1.20 Gibbs Donan effect.

Significance of Donan Effect

Specifically, this effect describes how non-diffusible ions (large, negatively charged plasma proteins) will cause movement of oppositely charged ions across membrane, resulting in overall ionic redistribution across both sides in such a way that at equilibrium:

- Concentration of cations is more on one side and anions on the other.
- Fluid in each compartment is electrically neutral, since cations exactly balance anions in each compartment.

Q20. Differentiate between crystalloids and colloids.
(Or Write a short note on Plasma expanders.)

Plasma Expanders

Plasma expanders are substances/solutions that increase plasma volume. They are used in hypovolemic shock, i.e., severe dehydration (diarrhea, vomiting, burns) and severe blood loss (trauma, major surgery). Its various types are differentiated in **Table 1.21**.

Q21. Explain why normal saline is preferred over 5% dextrose/glucose for initial fluid replacement in hypovolemia.

For initial resuscitation 5% glucose/dextrose is *never* used because it causes hyperglycemia and osmotic diuresis. Whereas normal saline is effectively able to restore ECF volume as 3/4th of it enters interstitium and 1/4th remains in plasma. These patients usually have hyponatremia, which also gets corrected.

Table 1.21 Various types of plasma expanders		
Features	**Crystalloids**	**Colloids**
Definition	Aqueous solutions of water-soluble substances	Aqueous suspensions of large, water-insoluble molecules
Useful to restore	All fluid volumes	Plasma volume only
Effect on plasma oncotic pressure	Decreased *(They dilute plasma proteins.)*	Increased *(They remain within plasma and "hold on to" water molecules in blood.)*
Cost	Cheaper	Expensive
Typical examples	Normal saline (0.9% NaCl), ringer lactate, 5% dextrose solution	Albumin, fresh frozen plasma, hydroxyethyl starch

Q22. Write a short note on Darrow Yannet diagrams.

Darrow Yannet Diagrams

Darrow Yannet (DY) diagrams are schematic illustrations depicting changes in volume and solute concentrations (i.e., osmolarities) of ECF and ICF in response to various conditions. Volume is represented in mL on X-axis and osmolarity is represented in mOsm/L on Y-axis. DY diagrams of normal and imbalanced hydration states are depicted in **Fig. 1.21**.

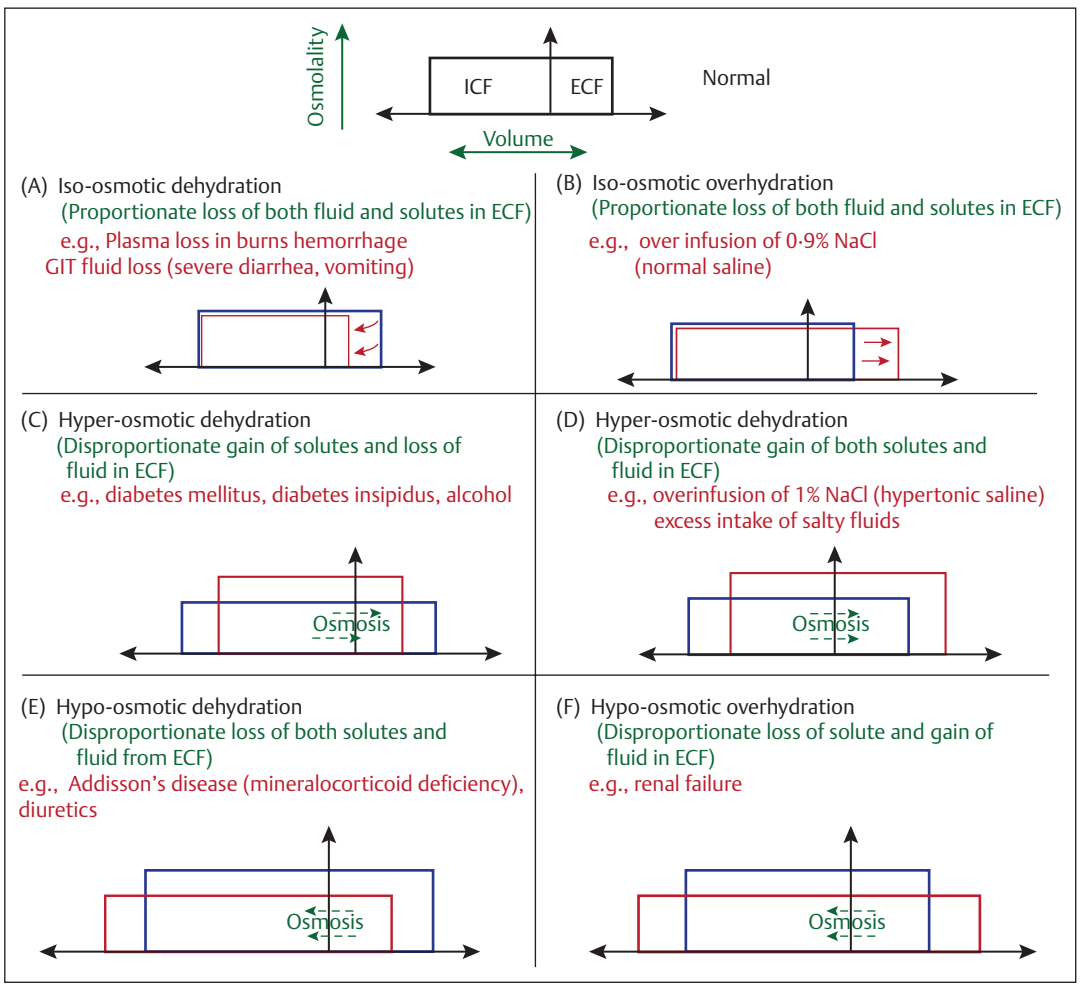


Fig. 1.21 Darrow Yannet diagrams. *Note: In each case, normal state is shown in blue while abnormal state is shown in red.*

At a Glance

- **Homeostasis** was coined by Walter Cannon; **Milieu interior** was coined by Claude Bernard.
- **Milieu interior:** It refers to internal environment (ECF) which is in constant contact with all body cells. Any change in ECF composition (ion content, pH, toxins, nutrients, etc.) also affects tissue cells. Hence, maintenance of ECF constancy (by homeostatic mechanisms) is essential for optimum cell growth and function.
- **Cytoplasmic inclusions:** Nonliving, nonmetabolic substances within cytosol. They are of three types: ***pigment granules*** (e.g., Hb, melanin, lipofuscin), ***nutrients*** (e.g., TGs, glycogen), and ***secretory products*** (e.g., hormones, neurotransmitters, digestive enzymes). Unlike organelles, they are not membrane bound.
- **Extracellular matrix (ECM):** Gelatinous mass that occupies interstitial space and "cements together" various tissue cells, thus acting as "connective tissue." Constituents are water, fibroblasts, proteins (elastin, collagen), and amorphous gel like ground substance formed by proteoglycans and fibronectins.
- **Older models of cell membrane:** ***Sandwich model*** (*Danielli and Dawson*): Lipid layer is sandwiched between two protein layers. ***Unit membrane model*** (*Robertson*): Phospholipid bilayer is sandwiched between two protein monolayers.
- **Autophagy:** Physiological process in which cells can self-regulate removal of their dysfunctional/damaged organelles, proteins, etc. (auto = self; phagos = eating). It is genetically triggered by activation of cytosolic protein kinases. Substances are initially ingested into an autophagosome which later fuses with lysosome to form phagolysosome and gets digested. Autophagy maintains optimum cell function and recycles amino acids for protein synthesis.
- **Ionophores:** Certain microorganisms synthesize lipid-soluble ion carriers (ionophores) instead of ion channel proteins. These bind reversibly with ions, make membranes more permeable, and then transport ions to target sites within cells, acting as ion carriers.
- **Patch clamping:** Technique for studying structure of ion channels, their mechanism of operation, and types of ions transported. Small areas of membrane are connected (via suction) to microelectrodes, creating "membrane patches." Ionic composition is modulated across both ends of membrane and subsequent effect on working of specific channels (within that patch) is noted.
- **Gelofusine (*4% succinyl gelatine*):** It is a newer colloid that restores not only plasma volume but also the O_2 levels in blood.