
DESTINATION
PHARMAGENS

CELL, CELLULAR SYSTEM AND TISSUE

CELLULAR ORGANELLES

1 Nucleus

Components of nucleus are: Nuclear wall, nucleoplasm, chromatin, Gene

All cells have matured nuclei, and it is the largest cellular organelle

RBC don't have nucleus, while cells having multiple nuclei are – (Polymorphonucleocytes & skeletal cells)

Inside nucleus - **chromatin** present, generated from coiling of DNA and proteins, these proteins are called as **histones**.

Chromatin - During cell division the chromatin replicates and becomes more tightly coiled forming **chromosomes**.

Gene - The **functional subunits** of chromosomes, these Controls activity, if any gene missing that activity also missing, this give rise to genetic disorders.

Resistance in bacteria

If some bacteria having gene which encodes for synthesis of efflux proteins or enzymes, such proteins may lead to either efflux or degradation of drugs. In such case, bacteria said to be resistant to given drugs. This could be inherited or acquired by bacterias during their lifetime. Mechanisms by which bacteria acquire resistance are

Conjugation – pilli formation

Transduction- through bacteriophage

Transformation – gene released into medium

2 Mitochondria

Also known as power house of cell, where **aerobic respiration** occurs and ATP get generated.

Mitochondrial also contains their sub-DNA

3 Ribosome

Tiny **granules** composed of RNA and Protein, help to synthesize **proteins.**

During the synthesis of proteins RIBOSOMAL-RNA COMPLEX generated which is inhibited by number of drugs such as

30 s RIBOSOMAL-RNA COMPLEX	50 s RIBOSOMAL-RNA COMPLEX
Tetracycline 30S	Lincosaminde (Clindamycine), Clhoramphenicol, Macrolide antibiotics (Azithromycin, Roxithromycin, Clarithromycin)

Aminoglycosides (streptomycin, kanamycin, amikacin) binds to both 30S+50S ribosmomal subunit.

4 Endoplasmic reticulum (ER)

It is a series of interconnecting membranous canals in the cytoplasm.

There are two types of ER: smooth and rough.

Smooth ER synthesizes lipids and steroid hormones, also supply intracellular Ca^{++} (This fact forms the basis of Mode Of Action of **DIGITALIS in heart**)

Rough ER is studded with ribosomes. These are the site of synthesis of **proteins** i.e. enzymes and hormones that pass out of their parent cell to be used by other cells in the body.

5 Golgi apparatus

The proteins move from the endoplasmic reticulum to the Golgi apparatus where they are 'packaged' into membrane- bound vesicles called secretory granules.

Here modifications carried out- export purpose

6 Lysosomes

Lysosomes are one type of secretory vesicle formed by the Golgi apparatus.

Lysosomes contains Cellular digestive system – collectively called as **HYDROLASES,** these includes

α-glucosidase (for glycogen)	Cathepsins (for proteins)	Lipases (for lipids)	Ribonuclease (for RNA)

Lysosomes in white blood cells contain enzymes that digest foreign material such as microbes.

In case of malaria (Mode Of Action – 4 amino quinolones ANTIMALARIALS are weakly basic nature, there these drugs raises the vacuolar pH and thereby interferes with degradation of haemoglobin by forming complex and leads to disruption of plasmodial membrane)

7 Microfilaments and microtubules

Microfilaments - These are tiny strands of protein that provide structural support and maintain the characteristic shape of the cell.

Microtubules - These are contractile protein structures in the cytoplasm involved in the movement of the cell and of organelles within the cell, the movement of cilia (small projections from the free border of some cells) and possibly the organisation of proteins in the plasma membrane.

vinca alkaloids-as an anticancers acts on microtubules protein i.e. tubuin inhibiting its function disrupting to cytoskeletal function/preventing mitotic spindle formation specifically in M Phase – cell cycle specific-excpt-vinblasitn)

8 Cell division

MEIOSIS: cell division process for germinal cells

MITOSIS: cell division process for somatic cells

Interphase: time duration between Mitosis.

C- cyclins-mitosis promoting proteins

Details of mitotic cell division phases and anticancer drugs specifically acting in that cell cycle. Such anticancer drugs are collectively called as cell cycle specific drugs

G1	Pre mitotic Gap 1 phase	synthesis of mRNA occurs , dependent on C & CDK molecule	Vinblatine
S	Synthesis Phase	Replication of nuclear DNA , dependent on C & CDK molecule	Mtx, cytarabine, fludarabine, 6-TG, 6-MP, 5-FU, hydroxyurea, mitomycin C, doxorubicin, daunorubicin. (topotecan and irinotecan here they act)
G2	Pre mitotic Gap 1 phase	Correctness of DNA assessed, C & CDK promotes it	Daunorubicin, bleomycin, etoposide (topotecan and irinotecan here they arrest growth)
M	Mitotic Phase	Daughter cells are formed (pro+meta+ana+telo)	Vinca alkaloids (Vincristine, vinblastine, vinorelbine) paclitaxel, docetaxel.
G0		Daughter cells grow and continues to divide	

P54: it stops further cell divisions, present inside cell

9 Plasma membrane

Bilayer membrane (about 100 Å thick) two layers of phospholipids and cholesterol with some Extrinsic and intrinsic protein molecules embedded in them. This composition varies according to cell to cell and organ.

The phospholipid molecules have a head which is electrically charged ***hydrophilic***

Tail which - glyceryl phosphate, has no charge and is ***hydrophobic***

Polar groups (ethanolamine/choline or hydroxyl group of cholesterol)

High electrical resistance and relative impermeability to the membrane that's why AP propogated over surface only never crosses to cell membrane

Glycoproteins or glycolipids are formed on the surface by attachment to polymeric sugars, aminosugars or sialic acids.

The proteins are able to freely float through the membrane: associate and organize or vice versa.

TRANSPORT ACROSS CELL MEMBRANE

Paracellular spaces or **channels** exist between certain epithelial/endothelial cells

Passive transport -

Diffusion –

It is the Diffusion across the membrane in the direction of its concentration gradient, where membrane doesn't play any active role in the transport process.

The rate of transport being proportional to the lipid:water partition coefficient of that molecule.

Involved in Absorption, Distribution, Metabolism, and excretion of drug (A-D-M-E)

More it get diffused across GIT more it is absorbed, more it is metabolized in liver in form of first pass metabolism, more it is reabsorbed from urine by process tubular reabsorption.

This balance of ionized and unionized form of drug decides its ADME via diffusion.

General consideration

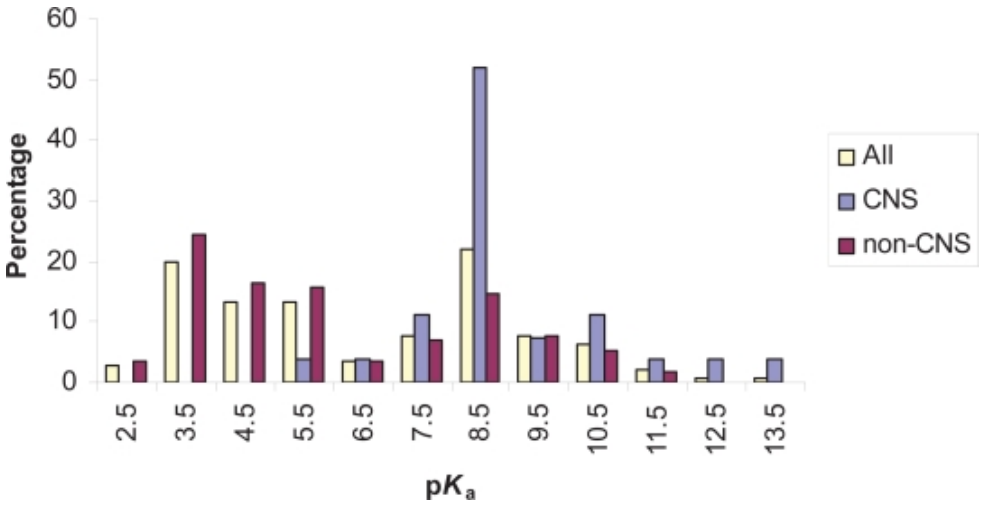
	ASORPTION	DISTRIBUTION	METABOLISM	EXCREATION	EXAMPLE
ACIDIC	Mild acidic drugs are largely unionized at acid gastric pH and are absorbed from stomach	-	-	Acidic drugs are ionized more in alkaline urine—do not back diffuse in the kidney tubules and are excreted faster	aspirin, enlist other too (pKa 3.5)
BASIC	largely ionized in stomach and are absorbed only when they reach the intestines.	Generally binds to Lipoproteins and α1-acid glycoprotein.	-	basic drugs are excreted faster if urine is acidified.	e.g. atropine, Paracetamol, omeprazole, enlist other too (pKa 10)

Basic drugs attain higher concentration intracellularly (pH 7.0 vs 7.4 of plasma).

albumin (carries mostly anionic drugs, some cationic and neutral drugs)

α_1-acid glycoprotein (AAG) (cationic and neutral drugs)

lipoproteins (cationic and neutral drugs).



This image shows distribution of drugs on the basis of pKa in CNS, non CNS parts and considering body as single part to all compartment.

Filtration

Filtration is passage of drugs through aqueous pores in the membrane or generally dependent on size, hydrostatic or blood pressure while capillaries have larger space except of BBB capillaries.

Carrier transport

All cell membranes express a host of trans-membrane proteins which serve as carriers or transporters.

Transporters combine transiently with their substrate undergo a **conformational change** carrying the substrate to the other side of the membrane where the substrate dissociates and the transporter returns back to its original state.

Carrier transport - substrate specific, saturable, follows the Michaelis-Menten kinetics.

Depending on requirement of energy, carrier transport is of two types:

a. **Facilitated diffusion** - solute carrier (SLC) transporters, operates passively without needing energy and translocates the substrate in the direction of its electrochemical gradient, i.e. from higher to lower concentration. Eg the entry of **glucose** into **muscle and fat cells** by the **glucose transporter GLUT 4 (**Part of Moa of antidaibetic drugs)
b. **Active transport**- requires energy, and transports the solute against its electrochemical gradient (low to high), resulting in selective accumulation of the substance on one side of the membrane. Active transport can be primary or secondary **depending on the source of the driving force.**

Primary active transport	Secondary active transport
Energy is obtained directly by the hydrolysis of ATP	The energy to pump one solute is derived from the downhill movement of another solute (mostly Na+)
The transporters belong to the superfamily of ATP binding cassettee (ABC) transporters whose intracellular loops have ATPase activity	Effected by another set of SLC transporters
They mediate only efflux of the solute from the cytoplasm, either to extracellular fluid or into an intracellular organelle (endoplasmic reticulum, mitochondria)	The SLC transporters mediate both uptake and efflux of drugs and metabolites.
P-gp - expressed in the intestinal mucosa, renal tubules, bile canaliculi, choroidal epithelium, astrocyte foot processes around brain capillaries (the blood-brain barrier), testicular and placental microvessels, which pumps out many drugs/ metabolites and thus limits their intestinal **absorption**	The organic anion transporting polypeptide **(OATP)** and organic cation transporter **(OCT)**, highly expressed in liver canaliculi and renal tubules, are secondary active transporters important in the **metabolism and excretion** of drugs and metabolites (especially glucuronides).
multidrug resistance associated protein 2 (MRP 2) and breast cancer resistance protein (BCRP).	neurotransmitter transporters for norepinephrine, serotonin and dopamine (NET, SERT and DAT)

Genetic polymorphism can alter both the density and affinity of the transporter protein for different substrates and thus affect the pharmacokinetics of drugs.

Pinocytosis – applicable to bigger molecules like vit B_{12}

Where ion channel stands classify them as ligand gated and voltage gated ion channels. Also point to be mentioned is moa of local anaesthetics.

Types of ca^{++} channels such as ligand gated and voltage gated (L N T type)

10 TISSUE

• epithelial tissue or epithelium

• connective tissue

• muscle tissue

• nervous tissue

10.1 epithelial tissue or epithelium

Simple: a single layer of cells. The types are named according to the shape of the cells, which differs according to their functions.

Squamous (pavement) epithelium

Heart, blood vessels, lymph vessels > where it is also known as endothelium, Alveoli in lungs.

Cuboidal (cubical) epithelium

Ciliated epithelium

Intestinal cilliary cells: why it helps to absorbs more

Stratified: several layers of cells

Stratified squamous epithelium – main function is protection of underlying tissue from mechanical wear and tear

Non-keratinized stratified epithelium - wet surfaces that may be subjected to wear and tear are protected from drying (conjunctiva, oesophagus)

Keratinised stratified epithelium - This is found on dry surfaces that are subjected to wear and tear, i.e. skin, hair and nails.

Transitional epithelium - found lining the urinary bladder, allows for stretching as the bladder fills.

10.2 Connective tissue

Types of cells involved in connective tissue

Fibroblast	Fibroblasts are large flat cells with irregular processes. They produce **collagen and elastic fibres** and a matrix of **extracellular material** like **ligaments of bones**
Adipocytes	Found in many types of connective tissue and are especially abundant in **adipose tissue**. They vary in size and shape according to the amount of fat they contain.
Macrophages	Fixed or motile, They are an important part of the body's defence mechanisms as they are actively **phagocytic, engulfing and digesting** cell debris, bacteria and other foreign bodies.
Leukocytes (WBC)	Motile & Lymphocytes synthesize and secrete specific **antibodies** into

	the blood in the presence of foreign material, such as microbes.
Mast Cells	Found in loose connective tissue and under the fibrous capsule of some organs, e.g. liver and spleen, and blood vessels. They produce **granules** containing heparin, histamine and other substances, which are released when the cells are damaged by disease or injury.

Loose (areolar) connective tissue

Adipose tissue

White adipose tissue – thermal insulator of body, mostly in adults

Brown adipose tissue - thermal insulator of body, mostly in newborns

Dense connective tissue

Fibrous tissue – forming ligaments and bone covering (osteo-cology)

Elastic tissue – found in blood vessels

Lymphoid tissue

It contains white blood cells (monocytes and lymphocytes). They are found in blood and in lymphoid tissue in the: lymph nodes, spleen, pharyngeal tonsils and aggregated nodes in the small intestine, wall of the large intestine.

Cartilage (chondrocytes)

Hyaline cartilage, Fibrocartilage, Elastic cartilage

Bone supporting and joining material it is if we have to generalize term.

Bone

Bone is a connective tissue with cells (osteocytes) surrounded by a matrix of collagen fibres that is strengthened by inorganic salts, especially calcium and phosphate. This provides bones with their characteristic strength and rigidity.

Muscle tissue

There are three types of muscle tissue, which consists of specialized contractile cells: HEART MUSCLES &

skeletal muscle	skeletal, striated, striped or **voluntary** muscle	NMJ	Skeletal muscle endplate	Muscle spastic conditions	Dantolene
smooth muscle	non-striated or **involuntary**	Ca++ channel	Actin and myosin interaction	BP	Nifedipine

11 Cellular disease: Neoplasm or tumors

Carcinogens -

Chemical carcinogens	aniline dyes, arsenic compounds, asbestos, benzene derivatives, cigarette smoke, nickel compounds, some fuel oils, vinyl chloride.
Radiation carcinogens	X-rays, radioactive isotopes, environmental radiations and ultraviolet rays in sunlight
Oncogenic carcinogens	RNA AND DNA VIRUSES

Metastasis – primary tumor dislocate and grow at another site into secondary form process is called as metastasis.

Lymphatic spread - This occurs when malignant tumours grow into lymph vessels. Groups of tumour cells break off and are carried to lymph nodes where they lodge and may grow into secondary tumours.

CELL CYCLE NON SPECIFIC: ALKYLATING AGENT, Taxanes, Bortezomib (Proteasome inhibitor), L-asparaginase, cisplatin, actinomycin D.

Cell cycle specific

G1	Vinblatine
S	Mtx, cytarabine, fludarabine, 6-TG, 6-MP, 5-FU, hydroxyurea, mitomycin C, doxorubicin, daunorubicin. (topotecan and irinotecan here they act)

G2	Daunorubicin, bleomycin, etoposide (topotecan and irinotecan here they arrest growth)
M	Vinca alkaloids (Vincristine, vinblastine, vinorelbine) paclitaxel, docetaxel.

Cancer chemotherapy toxicity occurs at:

Damage to Lympho-reticular tissue & epithelial tissue > host immune system get disturbed

Skin epithelia get damaged leading to – alopecia, dermatitis

WATER & ELECTROLYTES

Major body constituents about 60%

Intracellular fluid – 28L

Extracellular fluid – 10.5L (Interstitial fluid and plasma)

Thirst center located in hypothalamus. Increase in the **osmolality of plasma** stimulates thirst centre.

Major route of water output – urinary route and minor - by sweating

Hormonal regulation and urine production –

Water excretion by the kidney is tightly controlled by vasopressin also known as antidiuretic hormone (ADH) of the posterior pituitary gland.

The secretion of ADH is regulated by the osmotic pressure of plasma.

An increase in osmolality promotes ADH secretion that leads to an increased water reabsorption from the renal tubules (less urine output). On the other hand, a decrease in osmolality suppresses ADH secretion that results in reduced water reabsorption from the renal tubules (more urine output).

Plasma osmolality is largely dependent on the **sodium concentration**, hence sodium indirectly controls the amount of water in the body.

Diabetes insipidus is a disorder characterized by the deficiency of ADH which results in an increased loss of water from the body.

Electrolytic composition of body fluids

Extracellular fluid (plasma)				**Intracellular fluid**			
Cations		**Anions**		**Cations**		**Anions**	
Na^+	142	Cl^-	103	K^+	150	HPO_4^-	140
K^+	5	HCO_3^-	27	Na^+	10	HCO_3^-	10
Ca^{2+}	5	HPO_4^-	2	Mg^{+2}	40	Cl^-	2
Mg^{2+}	5	SO_4^-	1	Ca^{+2}	2		

Diuretics are the most important drugs altering electrolytes composition by acting on nephron subunits

Diuretic	Na^+	K^+	Cl^-	HCO_3^-	% Na^+ excreted	Diuresis efficacy
Furosemide	+++	+	++	+	25	High
Thiazide	++	+	+	+	8	Medium
Acetazolamide	+	++	+	++	5	Mild
Spironolactone	+		+	+	3	Low
Amiloride	+		+	+	3	Low
Mannitol	++	+	+	+	20	High

Regulation of plasma Sodium:

- **ADH** (hormone regulating plasma sodium levels)
  - Increased plasma osmolality stimulates
  - Increases water reabsorption by renal tubules
  - The characteristic feature of cells lining CD is their responsiveness to antidiuretic hormone (ADH).

If ADH is absent, the hypotonic fluid entering CD is passed as such → **dilute urine is produced** during water loading.

If ADH levels are high, CD cells become fully permeable to water → equilibrate with hyperosmotic medulla → **concentrated urine is passed,** as occurs during water deprivation or hypertonic saline infusion.

The CD and thin AscLH are the only segments permeable to urea.

ADH promotes insertion of urea transporter (UT1 or VRUT) into the luminal membrane of CD cells → more urea is accumulated in the medullary interstitium, reinforcing the medullary hypertonicity during water deprivation.

Free water clearance

It is defined as the volume of urine excreted per unit time in excess of that required to excrete the contained solute isoosmotically with plasma. It is **positive** when dilute urine is passed in the **absence of ADH** and **negative** when concentrated urine is passed in the **presence of ADH.** If isotonic urine is passed, regardless of its volume, free water clearance is zero.

Both positive and negative free water clearance are dependent on the production of a corticomedullary osmotic gradient; diuretics acting on medullary AscLH depress both.

- **RAS**
  - The secretion of aldosterone is controlled by renin-angiotensin system. Decrease in the blood pressure (due to a fall in ECF volume) is sensed by juxtaglomerular apparatus of the nephron which secrete renin.
  - Renin acts on angiotensinogen to produce angiotensin I. The latter is then converted to
  - angiotensin II which stimulates the release of aldosterone
  - Aldosterone retains Na^+ and water
- **Atrial natriuretic peptide**
  - This is a polypeptide hormone secreted by the right atrium of the heart. Atrial natriuretic peptide increases the urinary Na+ excretion.

Dehydration

1. The volume of the extracellular fluid (e.g. plasma) is decreased with a concomitant rise in electrolyte concentration and osmotic pressure.

2. Water is drawn from the intracellular fluid that results in shrunken cells and disturbed metabolism e.g. increased protein breakdown.

3. ADH secretion is increased. This causes increased water retention in the body and consequently urine volume is very low.

4. Plasma protein and blood urea concentrations are increased.

5. Water depletion is often accompanied by a loss of electrolytes from the body (Na+, K+ etc.).

6. The principal clinical symptoms of severe dehydration include increased pulse rate, low blood pressure sunken eyeballs, decreased skin turgor, lethargy, confusion and coma

DIARRHEA

Cholera is transmitted through water and foods, contaminated by the bacterium Vibrio cholera. This bacterium produces a toxin which stimulates the intestinal cells to secrete various ions (Cl-, Na+, K+, HCO- etc.) into the intestinal lumen. These ions collectively raise the osmotic pressure and suck the water into lumen. This results in diarrhea with a heavy loss of water (5-10 liters/day). If not treated in time, the victims of cholera will die due to dehydration and loss of dissolved salts. Thus, cholera and other forms of severe diarrhea are the major killers of young children

New formula for WHO-ORS			
CONTENT		CONCENTRATION	
NaCl	2.6g	Na^+	75mM
KCl	1.5g	K^+ & Cl^-	20mM & 65 mM
Trisod citrate	2.9g	Citratre	10 mM
Glucose	13.5g	Glucose	75 mM
Water	1Lr	-	-

Total osmolarity 245 mOsmol/Lr

Blood

It is composed of a straw-coloured transparent fluid, *plasma,* in which different types of cells are suspended. Plasma constitutes about 55% and cells about 45% of blood volume

The constituents of plasma are water (90 to 92%) and dissolved substances, including:

- plasma proteins: albumins, globulins (including antibodies), fibrinogen, clotting factors
- enzymes, e.g. certain clotting factors
- inorganic salts (mineral salts): sodium chloride, sodium bicarbonate, potassium, magnesium, phosphate, iron, calcium, copper, iodine, cobalt
- nutrients • organic waste materials • hormones • gases

1. Cellular content of blood

All blood cells originate from pluripotent stem cells and go through several developmental stages before entering the blood.

1.1. Erythrocytes (red blood cells)

The process of blood cell formation is called **haemopoiesis** and takes place within red bone marrow & characterized by following two main features:

maturation of the cell

- During this process the cell decreases in size and loses its nucleus.
- vitamin B12 and folic acid Dependent
- Deficiency of either vitamin B12 or folic acid leads to impaired red cell production.

Formation of haemoglobin

Haemoglobin is a complex protein, consisting of globin and an iron-containing substance called haem, and is synthesised inside developing erythrocytes in red bone marrow.

The process of development of red blood cells from pluripotent stem cells takes about 7 days and is called **erythropoiesis**

1 haemoglobin contains 4 (iron & oxygen)

Haemoglobin in mature erythrocytes combines with oxygen to form oxyhaemoglobin, giving arterial blood its characteristic red color.

1.2. The ABO system

A-type antigens (blood group A)

B-type antigens (blood group B)

Both A & B antigens (blood group AB)

None of A & B type antigens (blood group O).

1.3. The Rhesus system

The red blood cell membrane antigen important here is the Rhesus (Rh) antigen, or Rhesus factor.

1.4. Destruction of erythrocytes

The life span of erythrocytes is about 120 days and their breakdown, or haemolysis, is carried out by phagocytic reticuloendothelial cells.

2. Leukocytes (white blood cells)

- function in defending the body against microbes and other foreign materials.
- largest blood cells
- They contain nuclei and some have granules in their cytoplasm.

There are two main types

Granulocytes (polymorphonuclear leukocytes)	agranulocytes
(purple) neutrophils, (red) eosinophils and (blue) basophils	monocytes and lymphocytes.

2.1. Granulocytes (polymorphonuclear Leukocytes)

Neutrophils

- protection against any foreign material by their phagocytic activity
- grannules contains lysosomal enzymes
- attracted in large numbers to any area of infection by chemical substances, released by damaged cells, called **chemotaxins** and process is called as **chemotaxis**
- numbers increases in conditions such as : microbial infection / inflammation/ injury , **leukaemia**, **use of oral contraceptives**

Eosinophils

- Lesser active in phagosytosis but carry out phagocytosis of bigger invader such as worms.
- Promote inflammation by release of inflammatory chemicals

Basophils

- Basophils, which are closely associated with allergic reactions, contain cytoplasmic granules packed with **heparin** (an anticoagulant), **histamine** (an inflammatory agent) and other substances that promote inflammation.
- Usually the stimulus that causes basophils to release the contents of their granules is an allergen (an antigen that causes allergy) of some type.

2.2. Agranulocytes

large nucleus and no granules in their cytoplasm

Monocytes

Some monocytes actively motile and phagocytic while migrate into the tissues where they develop into **macrophages.**

Both monocytes and macrophages produce **interleukin 1** which:

• acts on the hypothalamus, causing the rise in body temperature associated with microbial infections

• enhances the **production of activated T-lymphocytes.**

Macrophages have important functions in inflammation and immunity. (important cell performing phagocytic activity along with monocytes & Lymphocytes)

monocyte macrophage system

This system, which is sometimes called the reticuloendothelial system, consists of the body's complement of monocytes and macrophages.

Macrophages could be fixed to one place or could be mobile

histiocytes in	connective tissues
microglia in the	Brain
Kupffer cells in the	Liver
osteoclasts in.	Bone
lymph nodes and	thymus gland

alveolar macrophages in the	Lungs
sinus-lining macrophages (reticular cells) in the	Spleen
mesangial cells in	the glomerulus of nephrons in the kidney

Lymphocytes

Lymphocytes are smaller than monocytes and have large nuclei. They circulate in the blood and are present in great numbers in lymphatic tissue such as lymph nodes and the spleen.

Lymphocytes develop from pluripotent stem cells in red bone marrow, then travel in the blood to lymphoid tissue elsewhere in the body where they are activated, i.e. they become **immunocompetent** which means they are able to respond to antigens (any foreign material having antigenic properties could be drug, virus, or microbe).

two distinct types of lymphocyte are produced — T-lymphocytes and B-lymphocytes.

T-lymphocytes

- provide cell-mediated immunity
- processed by the thymus gland, here hormone **thymosin** responsible for formation of mature, functional T-lymphocytes.
- T-lymphocyte has been programmed to recognise only one type of antigen

B-lymphocytes

- Provides humoral immunity, antibody mediated immunity
- processed in the bone marrow.

- Their role is in production of antibodies (immunoglobulins)

3. Thrombocytes (platelets)

These are very small non-nucleated discs, 2 to 4 um in diameter, derived from the cytoplasm of megakaryocytes in red bone marrow.

They contain a variety of substances that promote blood clotting, which causes haemostasis (cessation of bleeding).

The control of platelet production is not yet entirely clear but it is believed that one stimulus is a fall in platelet count and that a substance called thrombopoietin is involved.

The life span of platelets is between 8 and 11 days and those not used in haemostasis are destroyed by macrophages, mainly in the spleen.

Haemostasis

When a blood vessel is damaged, loss of blood is stopped and healing occurs in a series of overlapping processes, in which platelets play a vital part.

1. **Vasoconstriction.**

   When platelets come in contact with a damaged blood vessel, their surface becomes sticky and they adhere to the damaged wall.

   They then release **serotonin (5-hydroxytryptamine)**, which constricts (narrows) the vessel, reducing blood flow through it.

2. **Platelet plug formation.**

   The adherent platelets clump to each other and release other substances, including adenosine diphosphate (ADP), which attract more platelets to the site.

   This is a positive feedback system by which many platelets rapidly arrive at the site of vascular damage and quickly form a temporary seal — the **platelet plug**.

3. **Coagulation (blood clotting)**

Blood clotting results in formation of an insoluble thread-like mesh of fibrin which traps blood cells and is much stronger than the rapidly formed platelet plug.

In the final stages of this process prothrombin activator acts on the plasma protein prothrombin converting it to thrombin. Thrombin then acts on another plasma protein fibrinogen and converts it to fibrin

Prothrombin activator can be formed by two processes which often occur together: the **extrinsic and intrinsic pathways**

The **extrinsic pathway** occurs rapidly **(within seconds)** when there is tissue damage outside the circulation. Damaged tissue releases a complex of chemicals called thromboplastin or tissue factor, which initiates coagulation.

The **intrinsic pathway** is slower (**3-6 minutes**) and is confined to the circulation. It is triggered by damage to a blood vessel lining (endothelium) and the effects of platelets adhering to it. After a time the clot shrinks, squeezing out serum, a clear sticky fluid that consists of plasma from which clotting factors have been removed.

4. **Fibrinolysis.**

After the clot has formed the process of removing it and healing the damaged blood vessel begins. The breakdown of the clot, or fibrinolysis, is the first stage.

An inactive substance called **plasminogen** is present in the clot and is converted to the enzyme **plasmin** by activators released from the damaged endothelial cells.

Plasmin initiates the breakdown of fibrin to soluble products that are treated as waste material and removed by phagocytosis.

As the clot is removed, the healing process restores the integrity of the blood vessel wall

4. **<u>Anaemias</u>**

In anaemia there is not enough haemoglobin available to carry sufficient oxygen from the lungs to supply the needs of the tissues.

It occurs when the rate of production of mature cells entering the blood from the red bone marrow does not keep pace with the rate of haemolysis.

The classification of anaemia is based on the cause

• impaired erythrocyte production

— iron deficiency (insufficient intake of iron or loss of iron from the body)

— megaloblastic anaemias

— hypoplastic anaemia

• increased erythrocyte loss

— haemolytic anaemias

— normocytic anaemia.

Megaloblastic anaemias

Maturation of erythrocytes is impaired when deficiency of vitamin B12 and/or folic acid occurs and abnormally large **erythrocytes (megaloblasts)** are found in the blood.

Anaemia due to Vitamin B12 deficiency

Pernicious anaemia

It is an autoimmune disease in which auto-antibodies destroy intrinsic factor (IF) and parietal cells in the stomach.

Anaemia due Folic acid deficiency

Hypoplastic and aplastic anaemias

Occur due to varying degrees of bone marrow failure

Bone marrow function is reduced in hypoplastic anaemia, and absent in aplastic anaemia.

pancytopenia

Since the bone marrow produces leukocytes and platelets as well as erythrocytes, leukopenia (low white cell count) and thrombocytopenia (low platelet count) are likely to accompany diminished red cell numbers.

When all three cell types are low, the condition is called **pancytopenia**, and is accompanied by anaemia, diminished immunity and a tendency to bleed.

Haemolytic anaemias

These occur when red cells are destroyed while in circulation or are removed prematurely from the circulation because the cells are abnormal or the spleen is overactive.

Congenital haemolytic anaemias

In these diseases genetic abnormality leads to the synthesis of abnormal haemoglobin and increased red cell membrane friability, reducing cell oxygen-carrying capacity and life span. The most common forms are sickle cell anaemia and thalassaemia.

Sickle cell anaemia

The **abnormal haemoglobin molecules** become misshapen when deoxygenated, making the erythrocytes sickle shaped. A high proportion of abnormal molecules makes the sickling permanent. The life span of cells is reduced by early haemolysis. **Sickle cells** do not move smoothly through the small blood vessels. This tends to increase the **viscosity** of the blood, reducing the rate of blood flow and leading to intravascular clotting, ischaemia and infarction. The anaemia is due to early haemolysis of irreversibly sickled cells. Blacks are more affected than other races. Some affected individuals have a degree of immunity to malaria because the life span of the sickled cells is less than the time needed for the malaria parasite to mature inside the cells.

Thalassaemia

There is reduced **globin synthesis** with resultant reduced **haemoglobin production** and increased friability of the cell membrane, leading to early haemolysis.

Polycythaemia

There are an abnormally large number of erythrocytes in the blood. This increases blood viscosity, slows the rate of flow and increases the risk of intravascular clotting, ischaemia and infarction.

5. Leukocytic disorder

Leukopenia

This is the name of the condition in which the total blood leukocyte count is decreased.

Granulocytopenia (neutropenia)

This is a general term used to indicate an abnormal reduction in the numbers of circulating granulocytes (polymorphonuclear leukocytes), commonly called neutropenia because 40 to 75% of granulocytes are neutrophils. A reduction in the number of circulating granulocytes occurs when production does not keep pace with the normal removal of cells or when the life span of the cells is reduced. **Extreme shortage or the absence of granulocytes is called agmnulocytosis.** A temporary reduction occurs in response to inflammation but the numbers are usually quickly restored.

Septicaemia

It is the presence of significant numbers of active pathogens in the blood. The pathogens are commonly commensals, i.e. microbes that are normally present in the body but do not usually cause infection, such as those in the bowel.

Leukocytosis

An increase in the number of **circulating leukocytes** occurs as a normal protective reaction in a variety of pathological conditions, especially **in response to infections**.

Leukaemia

Leukaemia is a **malignant proliferation of white blood cell precursors** by the **bone marrow**. It results in the uncontrolled increase in the production of leukocytes and/or their precursors. As the tumour cells enter the blood the total leukocyte count is usually raised but in some cases it may be normal or even low.

The proliferation of immature leukaemic blast cells crowds out other blood cells formed in bone marrow, causing anaemia, thrombocytopenia and leukopenia (pancytopenia).

Types of leukaemia

Leukaemias are usually classified according to the type of cell involved, the maturity of the cells and the rate at which the disease develops

Acute	Chronic
Acute leukaemias	Chronic leukaemias
Acute myeloblastic leukaemia	Chronic granulocytic leukaemia
Acute lymphoblastic leukaemia	Chronic lymphocytic leukaemia

Types of leukaemia	Cells involved
Myloid	Granulocytes, myelocytes, myeloblasts
Lymphocytic	Lymphocyets,, lymphoblasts
Monocytic	Monocytes

IMMUNITY AND INFLAMMATION

Non-specific defence mechanisms

These protect against any of an enormous range of possible dangers.

There are four main non-specific defence mechanisms:

- defence at body surfaces
  - physical-skin barrier
  - sweat and sebum
  - hairs
  - unidirectional urine flow
- phagocytosis
  - Phagocytic defence cells such as **macrophages and neutrophils** are attracted to sites of inflammation and infection by **chemotaxis**.
  - **Macrophages** have an important role as a link between the non-specific and specific defence mechanisms. After ingestion and digestion of an antigen, they act as **antigen presenting cells**, displaying their antigen on their own cell surface to stimulate T-lymphocytes and activate the immune response.
  - TNFα is **secreted by activated macrophages and other immune cells**. TNFα **amplifies immune inflammation** by **releasing other cytokines** and enzymes like collagenases and metalloproteinases.
  - Stimulated macrophages and other mononuclear cells elaborate IL-1 which activates helper T-cells and induces production of other ILs
- natural antimicrobial substances
  - **Hydrochloric acid**
  - **Lysozyme -** This is a small molecule protein with antibacterial properties present in granulocytes, tears, and other body secretions. It is not present in sweat, urine and cerebrospinal fluid.
  - **Antibodies -** These are present in nasal secretions and saliva
  - **Saliva**
  - **Interferons -** These are substances produced by T-lymphocytes and by cells that have been invaded by viruses. They prevent viral replication within cells and spread of viruses to other cells.

- Complement
  - Complement binds to, and makes holes in, bacterial cell walls, thus destroying the microbe
  - binds to bacterial cell walls, stimulating phagocytosis by neutrophils and macrophages
  - attracts phagocytic cells such as neutrophils into an area of infection

- natural killer cells
- the inflammatory response

Acute inflammation

Episodes of acute inflammation are usually of short duration, e.g. days to a few weeks, and may range from mild to very severe. The cardinal signs of inflammation are:

redness, heat, pain, swelling, loss of function.

Following image shows summary of inflammatory substance and release conditions

Substance	Made by	Trigger for release	Main pro-inflammatory actions
Histamine	Mast cells (in most tissues), basophils (blood); stored in cytoplasmic granules	Binding of antibody to mast cells and basophils	Vasodilatation, itching, ↑vascular permeability, degranulation, smooth muscle contraction (e.g. bronchoconstriction)
Serotonin (5-HT)	Platelets Mast cells and basophils (stored in granules) Also in CNS (acts as neurotransmitter)	When platelets are activated, and when mast cells/basophils degranulate	Vasoconstriction, ↑vascular permeability
Prostaglandins (PGs)	Nearly all cells; not stored, but made from cell membranes as required	Many different stimuli, e.g. drugs, toxins, other inflammatory mediators, hormones, trauma	Diverse, sometimes opposing, e.g. fever, pain, vasodilatation or vasoconstriction, ↑vascular permeability
Heparin	Liver, mast cells, basophils (stored in cytoplasmic granules)	Released when cells degranulate	Anticoagulant (prevents blood clotting), which maintains blood supply (nutrients, O_2) to injured tissue and washes away microbes and wastes
Bradykinin	Tissues and blood	When blood clots, in trauma and inflammation	Pain Vasodilatation

Inflammatory response

The acute inflammatory response is described in a series of overlapping stages: increased blood flow, increased formation of tissue fluid and migration of leukocytes.

- **Increased blood flow**
    - arterioles and the local capillaries dilated, increasing blood flow to the site.
    - local release of a number of chemical mediators from damaged cells, e.g. histamine and serotonin.
    - Increased blood flow causes the increased temperature and reddening of an inflamed area.
- **Increased formation of tissue fluid**

  Increased permeability of small blood vessel walls.

  This is caused by **inflammatory mediators, e.g. prostaglandins, histamine and serotonin**, which are released by injured cells and cause the cells that form the single layered venule wall to pull apart from one another.

  When plasma proteins leave the blood, as in inflammation, the osmotic pressure of the blood falls and water moves from the bloodstream into the tissues.

  Increased hydrostatic pressure.

  The increased blood flow into the capillary bed forces fluid out of the vessels and into the tissues.

  Some interstitial fluid returns to the capillaries but most of the inflammatory exudate, phagocytes and cell debris are removed in lymph vessels because the pores of lymph vessels are larger, and the pressure inside is lower, than in blood capillaries.

- **Migration of leukocytes**

  In the acute stages, the most important leukocyte is the neutrophil, which adheres to the blood vessel lining, squeezes between the endothelial cells and enters the tissues, where its main function is in phagocytosis of antigens.

  Later in the inflammatory response, after about 24 hours, macrophages become the predominant cell type at the inflamed site, and they persist in the tissues if the situation is not resolved, leading to chronic inflammation.

- **Chemotaxis**

This is the chemical attraction of leukocytes to an area of inflammation.

chemo-attractants - microbial toxins, chemicals released from leukocytes, prostaglandins from damaged cells and complement proteins

Benefits of acute inflammation

- Promotion of phagocytosis by Neutrophils and macrophages
- Promotion of the immune response by antibodies and immune supporting proteins
- Toxin dilution
- Increased core temperature (interleukin 1) is released from macrophages and granulocytes
    - The increased temperature of inflamed tissues has the twin benefits of inhibiting the growth and division of microbes, whilst promoting the activity of phagocytes.
- Fibrin formation

Specific defence mechanisms

These are grouped together under the term immunity. Resistance is directed against only one particular invader. In addition, immunological memory develops, which confers long-term immunity to specific infections. An antigen is anything that stimulates an immune response.

Primary lymphoid organs - Thymus and bone marrow

This white blood cell is manufactured in the bone marrow, released into the bloodstream from the bone marrow, distinct types: the T-lymphocyte and the B-lymphocyte.

CMI

- **Memory T-cells** &**Cytotoxic T-cells**
- inactivate any cells carrying antigens.
- Remain attached to cells carrying antigens and releases powerful toxins in the vicinity of attached cells
- Performs destruction of abnormal body cells e.g. infected cells

T LYMPHOCYETS & B-LYMPHOCYTES

Helper T-cells

These are essential for correct functioning of CMI & ABI

CMI	ABI
production of **cytokines**, e.g. interleukins and interferons, (which support and promote cytotoxic T-lymphocytes and macrophages)	Production of antibodies; although B-lymphocytes are responsible for antibody manufacture, they require to be stimulated by a helper T-lymphocyte first.

When helper T-lymphocyte numbers fall significantly, the whole immune system is compromised. Their central role in immunity is emphasised in situations where they are destroyed, as by the human immunodeficiency virus (HIV).

Antibody mediated immunity

It produces two functionally distinct types of cell, plasma cells and memory B-cells.

Plasma cells

These secrete antibodies into the blood. Antibodies are carried throughout the tissues, while the B-lymphocytes themselves remain fixed in lymphoid tissue. Plasma cells live no longer than a day, and produce only one type of antibody, which targets the specific antigen that originally bound to the B-lymphocyte.

Memory B-cells

INFLAMMATION

Organ	PG	ACTION
CVS	PGE2 & PGF2α	Vasodilation (limited physiological role)
	PGF2α	Vasoconstriction (pulmonary vein and artery)
	PGI2	Vasodilator (potent hypotensive than PGE2 and possess this physiological role)
	TXA2	Vasoconstriction
Platelet aggregation activity	TXA2, (produced locally by platelets)	Potent inducer of aggregation and release reaction.
	PGG2 and PGH2	Pro-aggregatory
	PGI2 (generated by vascular endothelium)	Potent inhibitor of platelet aggregation
	PGD2	anti-aggregatory action
	PGE2	inconsistent effects
Bronchial muscle	**PGF2α, PGD2 and TXA2**	Potent bronchoconstrictors (more potent than histamine)
	PGE2	powerful bronchodilator
	PGI2	mild bronchodilatator
	Asthmatics are more sensitive to constrictor as well as dilator effects of PGs.	
	Asthma may be due to an imbalance between **constrictor PGs (F2 , PGD2, TXA2) and LTs** on one hand and **dilator ones (PGE2, PGI2)** on the other. In allergic human asthma, LTs play a more important role, and COX inhibitors are without any effect in most patients.	

CVS	**LTB4**	highly chemotactic for **neutrophils and monocytes**
	cysteinyl LTs (C4, D4)	chemotactic for **eosinophils**
Smooth muscles	**LTC4 and D4**	contract most smooth muscles. They are potent **bronchoconstrictors** and induce spastic contraction of g.i.t. at low concentrations. They also increase mucus secretion in the airways
	The cysteinyl LTs (C4 and D4) are the most important mediators of human allergic asthma.	

RSPPIRATORY SYSTEM

Bronchi and bronchioles

Structure

- The bronchi are composed of the same tissues as the trachea.
- They are lined with ciliated columnar epithelium.
- The bronchi progressively subdivide into bronchioles, terminal bronchioles, respiratory bronchioles, alveolar ducts and finally, alveoli.
- The smooth muscle in the walls of the bronchioles is responsive to autonomic nerve stimulation and irritation.

Arterial blood flow - bronchial arteries & bronchial veins

The nerve supply

- This is by parasympathetic and sympathetic nerves.
- The **vagus nerves** (parasympathetic) stimulate contraction of smooth muscle in the bronchial tree, causing bronchoconstriction**(M3 CHOLINOCEPTOR)**, and **sympathetic nerve** stimulation causes **bronchodilatation (β2 adrenoceptors)**

Infectious and inflammatory disorders

Inflammation of the upper respiratory tract can be caused by inhaling irritants, but is commonly due to infection. Such infections are usually caused by viruses that lower the resistance of the respiratory tract to other infections.

Common cold and influenza

common cold (coryza) is usually caused by the **rhinoviruses** and is a highly infectious, normally mild illness characterised mainly by a **runny nose (rhinorrhoea), sneezing, sore throat** and sometimes slight fever.

Influenza is caused by a different group of viruses and produces far more severe symptoms than a cold, including very high temperatures and muscle pains; complete recovery can take weeks and secondary bacterial infections are more common than with a simple cold.

Sinusitis: This is usually caused by spread of microbes from the nose and pharynx to the mucous membrane lining the paranasal sinuses

Pharyngitis: This usually accompanies common colds and tonsillitis. Viruses, with superimposed bacterial infection, cause acute inflammation of the mucous membrane of the pharynx, nose and sinuses.

Diphtheria: This is an infection of the pharynx, caused by Corynebacterium diphtheriae, that may extend to the nasopharynx and trachea.

Hay fever (allergic rhinitis): In this condition, atopic ('immediate') hypersensitivity develops to foreign proteins (antigens), e.g. pollen, mites in pillow feathers, animal dander. The acute nonmicrobial inflammation of nasal mucosa and conjunctiva causes rhinorrhoea (excessive watery exudate from the nose), redness of the eyes and excessive secretion of tears.

DISEASES OF THE BRONCHI

Acute bronchitis: This is usually a secondary bacterial infection of the bronchi. It is usually preceded by a common cold or influenza and it may also complicate measles and whooping cough in children. The viruses depress normal defence mechanisms, allowing bacteria already present in the respiratory tract to multiply, e.g. Streptococcus pneumoniae, Haemophilus influenzae, Streptococcus pyogenes, Staphylococcus aureus.

Chronic bronchitis: Chronic bronchitis is defined clinically when an individual has had a cough with sputum for 3 months in 2 successive years. It is a progressive inflammatory disease resulting from prolonged irritation of the bronchial epithelium.

Asthma : Asthma is an inflammatory disease of the airways in which the mucous membrane and muscle layers of the bronchi become thickened and the mucous glands enlarge, reducing airflow in the lower respiratory tract. During an asthmatic attack spasmodic contraction of bronchial muscle (bronchospasm) constricts the airway and there is excessive secretion of thick sticky mucus which further reduces the airway.

Non-specific factors that may precipitate asthma attacks include: • cold air • cigarette smoking • air pollution • upper respiratory tract infection • emotional stress • strenuous exercise.

Bronchial muscle	**PGF2α, PGD2 and TXA2**	Potent bronchoconstrictors (more potent than histamine)
	PGE2	powerful bronchodilator
	PGI2	mild bronchodilatator
	Asthmatics are more sensitive to constrictor as well as dilator effects of PGs.	
	Asthma may be due to an imbalance between **constrictor PGs (F2 , PGD2, TXA2) and LTs** on one hand and **dilator ones (PGE2, PGI2)** on the other. In allergic human asthma, LTs play a more important role, and COX inhibitors are without any effect in most patients.	
Smooth muscles	**LTC4 and D4**	contract most smooth muscles. They are potent **bronchoconstrictors** and induce spastic contraction of g.i.t. at low concentrations. They also increase mucus secretion in the airways.
	The cysteinyl LTs (C4 and D4) are the most important mediators of human allergic asthma.	

CARDIAC ELECTROPHYSIOLOGY

Transmembrane Potential

The characteristic action potential at any given stage, and it is the result of activation and inactivation of multiple ion channels, which allows the flow of **charged ions** across the sarcolemmal membrane.

The ion channels are trans-membrane proteins possessing important features:

- ion channel allows the flow of a specific cation or anion
- these trans-membrane proteins respond to chemical and transmembrane potential changes

The action potential has been divided into five phases:

- rapid depolarization **(phase 0)**
- early repolarization **(phase 1)**
- plateau **(phase 2)**
- rapid repolarization **(phase 3)**
- finally the resting phase in myocytes or slow diastolic depolarization **(phase 4)**

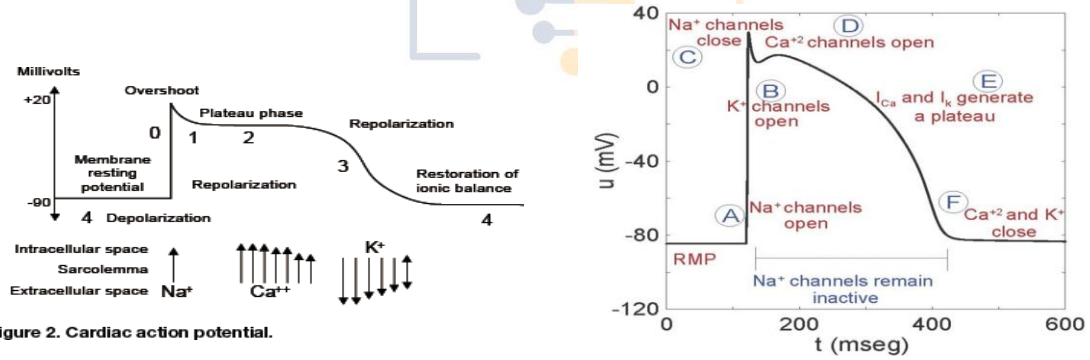
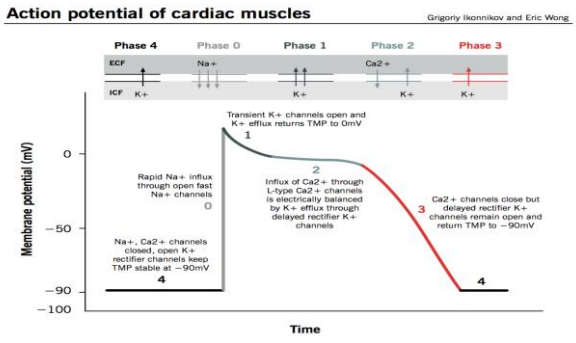
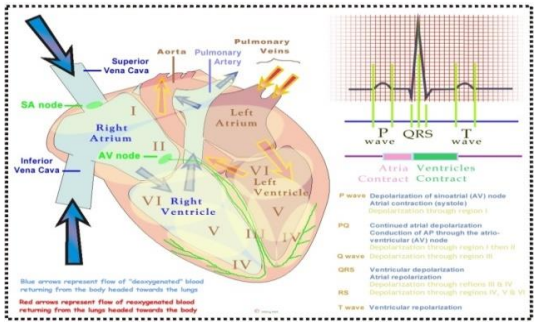


Figure 2. Cardiac action potential.





Ionic Basis for the Trans-Membrane Action Potential

Rapid Depolarization Phase 0 of the action potential

- the rapid depolarization of the myocyte induced principally by the opening of voltage gated sodium channels and closes time dependently.
- The conformation of the channels changes, and they enter an inactivated state in which they cannot be recruited to participate in generating a subsequent action potential for a defined interval. The interval during which the myocyte cannot be stimulated is the *absolute refractory period.*
- After the myocyte returns to a hyperpolarized resting potential, the channels cycle through the inactivated state back to the rested or closed conformation and again are available to open in response to a stimulus of sufficient intensity.

Phase 1

At the peak of the action potential upstroke, a short rapid period of repolarization occurs and the membrane potential returns toward 0 mV.

This produces a spike and dome configuration of the action potential and is a result of the inactivation of the **Fast inward current (I_{na})** and activation of a short-lived outward current called the **transient outward current (I_{to}). I_{to} is established by two distinct channels either potassium or chloride.**

I_{to} is present in both the atrium and the ventricular myocardium. Within the ventricle, I_{to} is present in the epicardium and absent in the endocardium.

Consequently, the epicardium repolarizes more rapidly than the endocardium; this is the basis for the QRS complex and the T-wave on the surface electrocardiogram having an identical axis as opposed to an opposite axis.

Abnormalities in the function of Ito have been resulting in ventricular tachycardia and fibrillation.

(Its treatment comes under antiarrhythmic drugs enlist)

Phase 2: Action Potential Plateau

Phase 2 is characterized by a net balance between inward (depolarizing) and outward (repolarizing) ion currents maintaining the myocyte in a depolarized state.

During this phase, Ca^{++} enters the cell, causing Ca^{++} release from intracellular stores and linking electrical depolarization with mechanical contraction.

Here your treatment of CHF Comes where drugs used to enhance cardiac performance utilizing slow but effective contractility like digitais on failing heart.

Interestingly, the current flow during the plateau phase is small

Ca^{++} enters the cell through **voltage-dependent channels highly selective for Ca^{++} (L-type calcium channel)** that open when the membrane is depolarized above -40 mV. **L-type calcium channel** possesses slow inactivation kinetics resulting in a long lasting current.

Outward repolarizing K^+ currents oppose the effect of the inward I_{Ca++} on the plateau phase. Here the end of phase 2 starts and this Ik is unopposed by Ica.

This current is carried predominantly through delayed rectifier potassium channels as delayed rectifying potassium current (I_K). These channels are voltage sensitive, with slow inactivation kinetics.

Phase 3: Late Phase of Repolarization

Termination of phase 2 of the action potential plateau occurs when time-dependent, voltage-dependent, and intracellular Ca++ dependent inactivation of I_{Ca}++ results in the unopposed repolarizing effects of the outward K^+ currents.

The combination of these effects results in rapid repolarization with a return to the hyperpolarized resting membrane potential.

Phase 4:

In normal atrial and ventricular myocytes, phase 4 is electrically stable, with the **resting membrane potential** held at approximately -90 mV and maintained by the outward potassium leak current and ion exchangers previously described.

It is during phase 4 that the Na^+ channels necessary for atrial and ventricular myocyte depolarization recover completely from inactivation.

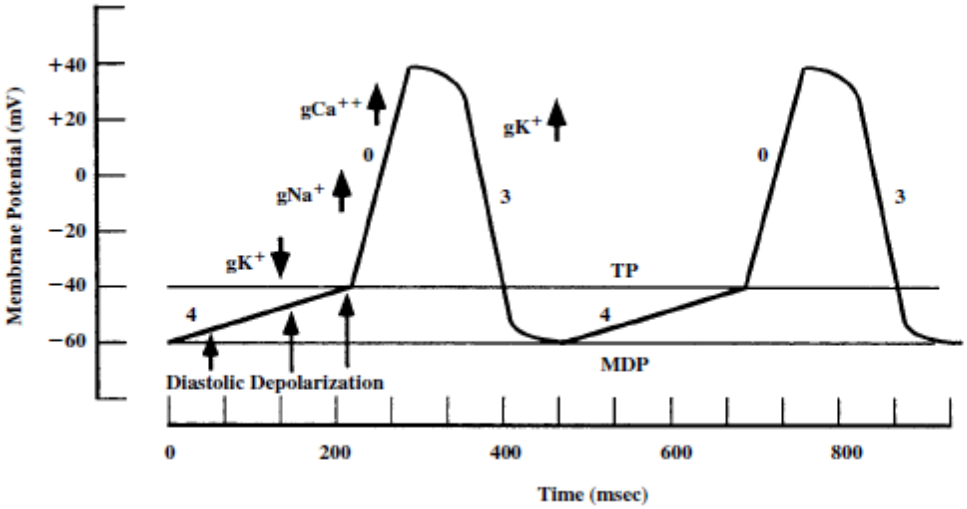
In myocytes capable of automaticity, the membrane potential slowly depolarizes during this period to initiate an action potential.

Automaticity

Automaticity can be defined as the ability of a cell to alter its resting membrane potential toward the excitation threshold without the influence of an external stimulus. Myocardial cells or Myocytes are capable of doing this. That's why these cells are known as pacemaker cells.

The characteristic feature of cells with automaticity is a slow decrease in the membrane potential during diastole (phase 4) such that the membrane potential reaches threshold.

During phase 4 in these **pacemaker cells**, the background potassium leak current decreases and an inward depolarizing current (If) is activated. In combination, this results in slow depolarization of the myocyte. If the membrane potential depolarizes above the threshold for the opening of ICa, an action potential is generated. **Myocytes within the sino-atrial node possess the most rapid intrinsic rate of automaticity or depolarization; therefore, the sinoatrial node serves as the normal pacemaker of the heart.**



Specialized cells within the atria, **atrioventricular (A-V) node, and His-Purkinje system** are capable of spontaneous depolarization, albeit at a slower rate.

The rapid rate of depolarization of the sinoatrial nodal cells capable of suppressing automaticity of all other cells. **The other cells will become pacemakers when their own intrinsic rate of depolarization becomes greater than that of the sinoatrial node or when the pacemaker cells within the sinoatrial node are depressed. This leads to generation of ectopic beats/ ectopic foci in ECG.**

When impulses fail to conduct across the A-V node to excite the ventricular myocardium (**condition is generated known as heart block**).

The rate of pacemaker discharge within these specialized myocytes is influenced by the activity of both divisions of the autonomic nervous system.

Increased sympathetic nerve activity to the heart/the release of catecholamines/the exogenous administration of adrenomimetic amines causes an increase in the **rate of pacemaker activity** through stimulation of **β1 adrenoceptors** on the **pacemaker cells**.

The parasympathetic nervous system, through the vagus nerve, inhibits the **intrinsic rate of depolarization of pacemaker cells**. The release of acetylcholine from cholinergic vagal fibers increases **potassium conductance (gK^+) in pacemaker cells**, and this enhanced **outward movement of K^+** results in a more **negative potential**, or **hyperpolarization**, of the sinoatrial cells. **Thus, during vagal stimulation, the threshold potential of the sinoatrial node pacemaker cells is achieved more slowly and the heart rate is slowed.**

Organ	PARASYMPATHETIC	SYMPATHETIC
Cardiovascular System (heart rate)	***Decreases heart rate***	***Increases contraction, heart rate***

Cardiac Conduction

The cardiac impulse begins in the sinoatrial node in the right atrium near the junction of the superior vena cava and the right atrium. Excitation leaves the sinoatrial node and spreads throughout the atrium.

After the excitatory wave has spread throughout the atrium, it enters the atrioventricular (A-V) node.

- **If additional connections exist between the atrium and ventricle (accessory pathway), the potential for arrhythmia is present (atrioventricular reciprocating tachycardia), such as occurs with the Wolff-Parkinson-White syndrome.**
- ***One common clinical cause of arrhythmic depolarization of myocardial tissue is ischemia resulting from coronary artery disease***

Refractory Period

Depolarized cardiac cells are transiently unresponsive to any activation stimuli. During this interval, most Na^+ and some Ca^{++} channels are inactivated, and the cardiac myocytes are said to be refractory period.

The refractory period is subdivided into three phases, absolute, effective, and relative.

The ***absolute refractory period*** is the time from the onset of the action potential until a stimulus is able to evoke a local nonconducted response. **During this period, the cell is completely refractory to any stimulus regardless of its intensity.**

The ***effective refractory period*** (***ERP***) begins with the onset of the action potential, incorporates the absolute refractory period, and ends when an excitatory stimulus is able to generate a conducted **Action potential**.

The ***relative refractory period*** begins with the completion of the ERP and continues through the time in which a signal may be conducted slowly, prior to obtaining normal propagation of the signal. Since the cell is not fully repolarized during the relative refractory period, a stronger than normal stimulus is needed to produce depolarization and conduction of a propagated impulse.

All these thing are site of action of antiarrhythmic drug. Antiarrhythmic drugs possess the ability to modify ARF, ERF, RRF of cardiac cells.

Mechanisms of Arrhythmias

Disturbances in the orderly formation and conduction of the cardiac impulse may result in heart rates that are either too fast (tachycardia) or too slow (bradycardia).

In general, bradyarrhythmias result from the failure of impulse generation within the sinoatrial node or failure of the excitatory wavefront to conduct from the atrium to the ventricle through the atrioventricular node.

In general, bradyarrhythmias are not amenable to long term pharmacological therapy and may require permanent cardiac pacing.

Tachyarrhythmias, conversely, frequently may be palliated with long-term medical therapy. The mechanisms supporting tachycardias may be classified broadly into three groups: (1) abnormal automaticity, (2) triggered activity, or (3) reentry.

Treatment incudes:

Basics for anti-hypertension topic

Cardiac output is the product of two variables, stroke volume and heartbeat. Heartbeat is simply a count of the number of times a heart beats per minute. Stroke volume is the amount of blood circulated or ejected by the heart with each beat. The formula for this is expressed as **CO = SV x HR**.

An increase in **cardiac output** results in increased **blood pressure**. Anything that **affects** heart rate or stroke volume **affects cardiac output** and thus **blood pressure**.

Afterload is the pressure in the wall of the left ventricle during ejection. In other words, it is the end load against which the heart contracts to eject blood. **Afterload** is readily broken into components: one factor is the aortic pressure the left ventricular muscle must overcome to eject blood. **(roughly consider pressure associated with systole for your convenience)**

Preload, also known as the left ventricular end-diastolic pressure (LVEDP), is the amount of ventricular stretch **at the end of diastole**

The **resistance** offered by the systemic circulation is known as the **systemic vascular resistance** (**SVR**) or may sometimes be called by the older term **total peripheral resistance** (**TPR**), while the **resistance** offered by the pulmonary circulation is known as the **pulmonary vascular resistance** (**PVR**).

(how drugs affect these aforementioned 3 things we will see in Antihypertensive activity profile of drugs)

A **resistance vessels** is artery (**small diameter blood vessel)** in the microcirculation that contributes significantly to the creation of the **resistance** to flow and regulation of the blood flow. **Resistance** arteries are usually **arterioles or end-points of arteries.**

The **capacitance** of blood **vessels** describes the distensibility of blood **vessels** located within the body; it is directly proportional to **elasticity**. Therefore, the greater the amount of elastic tissue in a blood **vessel**, the greater the elasticity, and the smaller the compliance.

CHF basics

Result from any functional or structural dysfunctional disorder that impairs the ventricle's ability to fill with or eject blood.

CHF indicates not only an inability of the heart to maintain adequate oxygen delivery; it is also a **systemic response attempting to compensate for the inadequacy.**

Since Cardiac output is major determinant in CHF, any drug possess beneficial effect of factor which ultimately improves Cardiac output is used for therapy of CHF.

There are 2 mechanisms of reduced cardiac output and heart failure are as follow:

systolic dysfunction and diastolic dysfunction.

- **systolic dysfunction (defined by a left-ventricular ejection fraction of lesser than 50% and ventricles are dilated and unable to develop sufficient wall tension to eject adequate quantity of blood)** the most common causes are ischemic heart disease, idiopathic dilated cardiomyopathy, hypertension, and valvular heart disease.
- **Diastolic dysfunction (defined as dysfunction of left-ventricular filling with preserved systolic function, The ventricular wall is thickened and unable to relax properly during diastole; ventricular filling is impaired because of which output is low)**. It can occur in many of the same conditions that lead to systolic dysfunction. The most common causes are hypertension, ischemic heart disease, hypertrophic cardiomyopathy, and restrictive cardiomyopathy.

Congestive heart failure (CHF) later get complicated by **generating in pulmonary vascular congestion and reduced cardiac output.**

Degenerative valve disease, idiopathic cardiomyopathy, and alcoholic cardiomyopathy are also major causes of heart failure.

Class I antiarrhythmic drugs

Class I antiarrhythmic drugs are characterized by their ability to block the voltage-gated sodium channel. The class I agents may block the channel when it is in either the open or the inactivated state.

Inhibition of the sodium channel results in a decrease in the rate of rise of phase 0 of the cardiac membrane action potential and a slowing of the conduction velocity.

Additionally, class I drugs, through inhibition of the sodium channel, require that a more hyperpolarized membrane potential (more negative) be achieved before the membrane becomes excitable and can propagate an excitatory stimulus.As a result, the ERP of fast-response fibers is prolonged.

The antiarrhythmic drugs in class I suppress both normal Purkinje fiber and His bundle automaticity in addition to abnormal automaticity resulting from myocardial damage.

Suppression of abnormal automaticity permits the sinoatrial node again to assume the role of the dominant pacemaker.

Class IA drugs slow the rate of rise of phase 0 (Vmax>) of the action potential and prolong the ventricular ERP. Members of this class impair the function of the membrane sodium channel, thereby decreasing the number of channels available for membrane depolarization. Class IA drugs do not alter the resting membrane potential. Because they decrease Vmax>, class IA drugs slow conduction velocity. Members of this class directly decrease the slope of phase 4 depolarization in pacemaker cells, especially those that arise outside of the sinoatrial node.

class IB drugs have a minimal effect on the rate of depolarization and are characterized by their ability to decrease the duration of action potential and ERP of Purkinje fibers. Members of this class have a minimal effect on conduction velocity in ventricular myocardium and are without apparent effect on refractoriness.

class IC drugs produce a marked depression in the rate of rise of the membrane action potential and have minimal effects on the duration of membrane action potential and ERP of ventricular myocardial cells.

Class II antiarrhythmic drugs

Class II antiarrhythmic drugs competitively inhibit _- adrenoceptors and inhibit catecholamine-induced stimulation of cardiac _-receptors.

In addition, some members of the group (e.g., propranolol and acebutolol) cause electrophysiological alterations in Purkinje fibers that resemble those produced by class I antiarrhythmic drugs. The latter actions have been called **membrane stabilizing effects.**

Class III antiarrhythmic drugs

Class III antiarrhythmic drugs prolong the membrane action potential by delaying repolarization without altering phase 0 of depolarization or the resting membrane potential.

Class IV antiarrhythmic drugs

Class IV drugs block the slow inward Ca__ current* (*L-type calcium channel*) *in cardiac tissue. The most pronounced electrophysiological effects are exerted on cardiac cells that depend on the Ca^{++} channel for initiating the action potential, such as those found in the sinoatrial and A-V nodes.

Tubular Reabsorption and Secretion

Two additional processes that participate in urine formation are reabsorption and secretion. **Reabsorption** defines movement of solute or water from the tubule lumen to the blood, whereas **secretion** denotes transport from the blood to the tubule lumen.

Figure 21.1 illustrates the various nephron segments, the primary sites of solute transport, and the magnitude of sodium reabsorption (that is how much sodium is reabsorbed from different sites, its percentage is given)

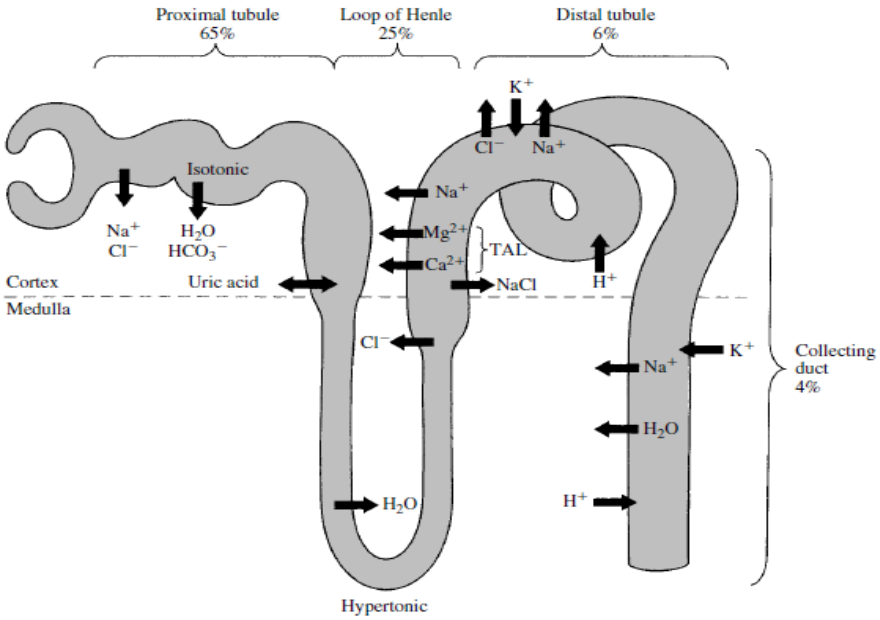


FIGURE 21.1
A nephron, showing the major sites and percentage (in braces) of sodium absorption along with other features of solute transport. The filtered load = GFR (180 L/day) ×plasma Na^+ (140 mEq/L) or 25,200 mEq/day. About 1% of this amount is excreted in voided urine. Sites where tubular fluid is isosmotic, hypertonic, or hypotonic relative to plasma are shown. PCT, proximal convoluted tubule; LH, loop of Henle; DCT, distal convoluted tubule; CCD, cortical collecting duct; TAL, thick ascending loop.

For simplification, tubular reabsorption can be divided into four sites see following figure:

Site I: Proximal tubule

Site II: Ascending limb of loop of Henle (Asc LH)

Site III: Cortical diluting segment of loop of Henle

Site IV: Distal tubule (DT) and collecting duct (CD)

Site I: Proximal tubule

Four mechanisms of Na^+ transport have been defined in this segment.

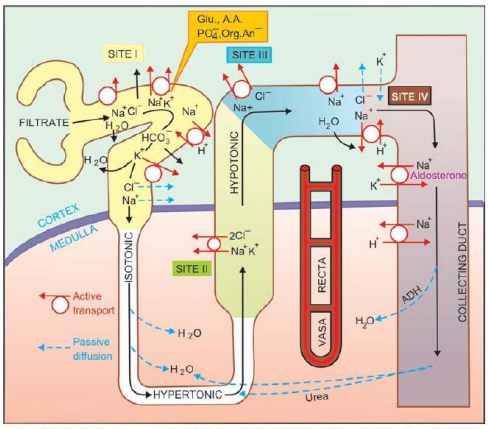


Fig. IX.1: Diagrammatic representation of nephron showing the four sites of solute reabsorption. The thick ascending limb of loop of Henle is impermeable to water; Glu.—Glucose; A.A.—Amino acid; Org. An.—Organic anions.

- **Direct entry**
  - Na^+ along a favourable electrochemical gradient. This is electrogenic.
- **Active reabsorption coupled transport**
  - Transport of Na^+ and K+ coupled to active reabsorption of glucose, amino acids, other organic anions and $(PO4)^{3-}$ through specific symporters.
  - only the glucose coupled Na^+ reabsorption is electrogenic, rest of absorption processes are active transports.
- **Exchange with H^+:**
  - The PT cells secrete H+ with the help of **carbonic anhydrase (CAase)** H+ ion exchanges with Na+ present in tubular fluid through Na^+-H^+ antiporter located in the luminal membrane and forms H2CO3 by combining with $HCO3^-$.
  - This H2CO3 is broken into H2O + CO2 by brush border CAse; both CO2 and H2O diffuse inside the cell and recombine to form H2CO3 (intracellular CAse catalysed reaction) which is the source of H+.
  - The dissociated $HCO3^-$ in the cell is transported to cortical e.c.f. by basolateral membrane Na+-$HCO3^-$ symporter resulting in net reabsorption of NaHCO3.
  - Practically all $HCO3^-$ is reabsorbed in PT by this mechanism, because tubular membrane, as such, is relatively impermeable to $HCO3^-$. This carbonic anhydrase enzyme is inhibited by **weak efficacy diuretics: CAase inhibitors**
  - The disproportionately large $HCO3^-$, acetate, $(PO4)^{3-}$, amino acid and other anion reabsorption create passive driving forces for Cl^- to diffuse through the paracellular pathway (in between tubular cells), particularly in the later PT.

This takes Na+ and water along to maintain electrical neutrality and isotonicity; reabsorption in PT is isotonic. Major part of filtered K+ is reabsorbed in the PT.

Thus, an isotonic tubular fluid with major changes in composition enters the thin descending limb of loop of Henle.

Several **additional noteworthy features** of proximal Na^+ transport are relevant to diuretic action are as follow:

First, since several transport proteins mediate proximal Na^+ reabsorption, no single diuretic would be expected to inhibit all these processes. Consequently, inhibition of any one mechanism leaves the others unaffected and able to continue to absorb the remaining Na^+.

Second, Na^+ that escapes proximal tubular transport is delivered to more distal nephron segments, where compensatory reabsorption reduces the impact of diminished upstream Na^+ recovery.

Hence, although most Na^+ is reabsorbed by proximal tubules, diuretics inhibiting its transport in this nephron segment have only a modest effect in reducing overall Na^+ reabsorption.

About K+ secretion and absorption from Proximal tubule Site I :

Most of the K^+ that is filtered at the glomerulus is reabsorbed by proximal tubules.

K^+ appearing in the voided urine was secreted by distal and terminal nephron segments

Another significant feature of the proximal tubule is that it is the **site of organic acid transport**. This is important in understanding both the **pharmacokinetics of many of the diuretics**, most of which are weak organic acids, and also certain of the **side effects induced by these drugs**. For instance, uric acid, which is the end product of purine metabolism in humans, is both reabsorbed and secreted by the organic acid transport pathway.

An important functional characteristic of the proximal tubule is that fluid reabsorption is isosmotic; that is, proximal reabsorbed tubular fluid has the same osmotic concentration as plasma. Solute and water are transported in the same proportions as in the plasma because of the high water permeability of the proximal tubule.

Thus, the total solute concentration of the fluid in the proximal convoluted tubule does not change as the fluid moves toward the descending loop of Henle. The corollary of this high water permeability is that *unabsorbable or poorly permeable solutes in the luminal fluid retard fluid absorption by proximal tubules.*

This is an important consideration for understanding the actions of osmotic diuretics

Descending thin limbs *are virtually devoid of Na_–K_–ATPase and therefore do not participate in active sodium reabsorption.* Moreover, the descending thin limb is highly impermeable to sodium and urea. Although the descending thin limb is not a site of diuretic action per se, its permeability contributes importantly to the action of osmotic agents because of its high water permeability.The presence of unabsorbable solute in the lumen retards water absorption and thereby contributes to the osmotic diuresis.

Site II: Ascending limb of loop of Henle (Asc LH)

The thick ascending limb is a major site of salt absorption and a principal locus of action of an important group of diuretics. Approximately 25% of the filtered sodium is reabsorbed by the thick ascending limb of Henle's loop.

The thick AscLH can be distinguished into two distinct portions:

(i) Medullary part lined by cuboidal cells.
(ii) Cortical part lined by flattened cells.

Both portions are relatively impermeable to water but absorb salt actively and thus dilute the tubular fluid. As the tubular fluid traverses Asc LH it progressively becomes hypotonic.

Sodium transport in this *medullary portion* segment is mediated by **Na^+–K^+–2Cl^- cotransport.** This transporter is present only on the apical, or urine, side of the tubule cells.

This is inhibited by **HIGH CEILING (LOOP) DIURETICS**

Although K^+ is taken up by the transporter, little net K^+ reabsorption occurs in the thick ascending limb because much of the absorbed K^+ is recycled across the apical cell membrane back into the urine.

The recirculation of K^+ is important to the generation of the electropositive voltage within the lumen, which serves as a driving force for passive transport of Na^+, Ca^{++}, and Mg^{++} through the tight junctions joining adjacent cells.

Hence, *although K^+ is transported by the Na^+–K^+–2Cl^- cotransporter, the primary solute absorbed into the blood is NaCl.*

Sodium reabsorption in thick ascending limbs depends on the amount, or load, of salt delivered from upstream segments.

The amount of sodium reabsorbed by the thick ascending limb increases as more is delivered.

The reabsorption of NaCl by the thick ascending limb is not accompanied by water because of the low hydraulic permeability of this nephron segment.

Consequently, *the tubular fluid becomes dilute as it passes through the thick ascending limbs.*

This process contributes to normal urinary dilution. Moreover, when Na^+ transport in thick ascending limbs is inhibited, urinary dilution will diminish.

The thick ascending limb is also an important site for the reabsorption of Ca^{++} and Mg^{++}. These cations are mostly passively reabsorbed through the paracellular pathway between adjacent cells. The driving force for their transport is the transepithelial voltage, which is established by the rate of Na^+ reabsorption.

Site III: Cortical diluting segment of loop of Henle

This segment, also impermeable to water, continues to absorb salt, but here it is through a pump known as **Na^+-Cl^- symport.** ***Tubular fluid gets further diluted.*** This symport is inhibited by **medium efficacy diuretics.**

Site IV: Distal tubule (DT) and collecting duct (CD)

In the late DT and CD, Na^+ is again actively reabsorbed; the cation-anion balance being maintained partly by passive Cl^- diffusion and partly by secretion of K^+ and H^+

Absorption of Na+ at this site occurs through a specific **amiloride sensitive Na^+ channel** and is controlled to a large extent by **aldosterone**.

This provides fine tuning to electrolyte excretion according to body needs.

In common with other cells, the DT and CD cells are rich in K^+; a chemical gradient exists for its diffusion into tubular lumen which is aided by the lumen negative transepithelial potential difference in this part of the tubule.

The luminal membrane possesses an active secretory pump for H^+ which is again governed by movement of Na+ in the reverse direction.

Any diuretic acting proximal to the aldosterone sensitive ion exchange site causes an increased delivery of Na^+ to the distal nephron—more exchange with K^+ takes place.

Thus, K+ is reabsorbed in the PT and AscLH, and is secreted in the DT and CD.

The net K+ loss is regulated by variations in the secretory process and depends on:
(i) The Na+ load delivered to distal segment
(ii) Presence or absence of aldosterone
(iii) Availability of H+
(iv) Intracellular K+ stores

The characteristic feature of cells lining CD is their responsiveness to antidiuretic hormone (ADH).

If ADH is absent, the hypotonic fluid entering CD is passed as such → **dilute urine is produced** during water loading.

If ADH levels are high, CD cells become fully permeable to water → equilibrate with hyperosmotic medulla → **concentrated urine is passed,** as occurs during water deprivation or hypertonic saline infusion.

The CD and thin AscLH are the only segments permeable to urea.

ADH promotes insertion of urea transporter (UT1 or VRUT) into the luminal membrane of CD cells → more urea is accumulated in the medullary interstitium, reinforcing the medullary hypertonicity during water deprivation.

Free water clearance

It is defined as the volume of urine excreted per unit time in excess of that required to excrete the contained solute isoosmotically with plasma.

It is **positive** when dilute urine is passed in the **absence of ADH** and **negative** when concentrated urine is passed in the **presence of ADH.**

If isotonic urine is passed, regardless of its volume, free water clearance is zero.

Both positive and negative free water clearance are dependent on the production of a corticomedullary osmotic gradient; diuretics acting on medullary AscLH depress both.

Organic ion transport

The PT has nonspecific bidirectional active transport mechanism, separately for organic acids and organic bases.

Diuretic	**Na^+**	**K^+**	**Cl^-**	**HCO_3^-**	**% Na^+ excreted**	**efficacy**
Furosemide	+++	+	++	+	25	High
Thiazide	++	+	+	+	8	Medium
Acetazolamide	+	++	+	++	5	Mild
Spironolactone	+		+	+	3	Low
Amiloride	+		+	+	3	Low
Mannitol	++	+	+	+	20	High