← Unit-2 →

"Drug used in the therapy of shock"

Shock :- → Energy is required for the process of metabolism in each and every cell.

→ And the metabolism of Glucose is occurs in the presence of oxygene.

→ When the lack of supply of oxygen takes place in our body then shock condition is occure.

→ When O_2 is insufficient to reach our the cell then this condition is called shock.

→ Mitochondria

Glucose
↓ ← O_2
energy

$C_6H_{12}O_6 + O_2 \rightarrow 6CO_2 + 6H_2O + ATP$
Glucose. Energy

Types of Shock :-

→ Shock is of four types →

(1) Hypovalemic Shock

(2) Septic Shock

(3) Cardiotonic Shock

(4) Other Shock.

(i) Hypovolemic Shock :-

⇒ Hypovalemic shock is a type of shock which is derrived from two word Hypo and valemic.

⇒ It means when the blood volume is reduce in our body then o_2 supply is also insufficient this is called Hypovalemic shock.

⇒ And it may be caused by the following reasons.

(i) Blood loss due to trauma.

(ii) Lack of blood due to Anaemia.

(iii) Hypertension.

(iv) Loss of Electrolyte and water from body due to diarrhea.

(v)

(ii) Septic Shock :-

⇒ Due to any accidental case when the bacterias like, Gram +ve, Gram,-ve, E-Coli, and Stephlococcus bacteria attack on human body then they enter into the blood and they converting blood into the pash.

⇒ In that condition the concentration of blood is reduce and the concentration of pash is increase so the o_2 supply is insufficient to the cell and this type of shock is called septic shock.

⇒ And for the treatment of this type of shock Antibiotic are given.

(iii) Cardiotonic Shock:-

→ Cardiotonic shock are arrise due to the cardiac problem like, Conjestive Heart failure, Angina Pectoris, Myocardial infraction, and Arrhythemia so the O_2 supply is insufficient to the organs and this type of shock is called cardiotonic shock.

(iv) Other Shock:-

→ Activation of Renin-Angiotensin System.
→ Reabsorption of fluid from interstitial tissue.
→ Adrenergic Discharges.
→ Renal conservation of body water and electrolyte.

Stages of Shock

(1) Initial / Non Progressive / Reversible shock

→ In this shock stage the homiostasis of body is maintained.
→ In this stage the body is contineous to respond for any action.
→ In this stage the demond and supply of O_2 is imbalance in our blood and organs

→ At this emergency stage the emergency harmone Nor-Nephrine and Epinephrine is release and they maintance the blood supply to the vital organ like brain and heart.

→ Blood supply to Non vital organ by RAS.

(2) Progressive / Partially Irreversible Shock :

- In this stage the body compensatory Mechanisms and homeostasis mechanism is failed.
- → And the oxygen perfusion rate is decrease.
- → Circulatary Volume is decrease
- → And the Hepatic level of lactic Acid and Ammonia is increase

(3) Irreversible Shock :

In the last stage of shock, it is a very dangerous stage. in this stage patients have inadiquate O_2 supply to the organ.

→ And decrease oxygene perfusion rate
→ decrease Cardiac output.
→ Lactic Acid and Ammonia accumulation are increase so the dilation in capillary and decrease blood flow.

÷ Shock Therapy ÷

(i) Hypovolemic Shock Therapy :- We know that in the hypovolemic shock volume of blood and body fluid is reduce so the improper sufficient of O_2 supply takes place into the tissues and cells.

→ In the therapy of hypovolemic shock we try to increase the blood volume and body fluid.

→ By increasing the IV fluid.

→ By increasing the blood product like WBC, RBC, Platlets

→ And by using the dextrose and saline salution like 0.91% Nacl solution, 0.45% Saline Solution, 5% Dextrose Solution and 10% Dextroose solution.

→ When the volume of blood becomes proper apropriate then the problem of hypovolemic shock it shall be recover.

(2) Septic Shock :- In the Septic shock caused by the bacteria and virus attack on the blood.

→ In the septic shock basically Antiviral and Antibiotic drugs are used to treat the viral infection.

S.No	Types of Infection	Antibiotics
(1)	Pseudomonas	Gentamicin or Cefepime
(2)	Anaerobic	Clindamycin or Metronidazole
(3)	N. Meningitidis H. Influenzae	Ceftriaxone
(4)	Neutropenic	Cefepime or Imipenem

(3) Cardiotonic Shock Therapy: In the cardiotonic shock therapy basically when the Problem of Edema is appear then the diuretics drug are given for their management.

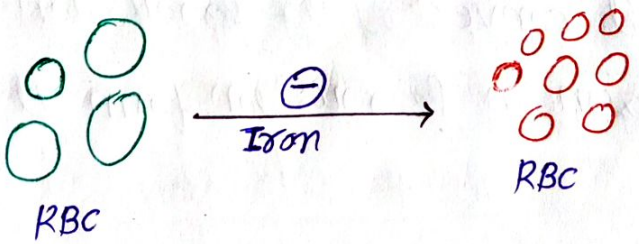
⇒ Sometimes Steroids, Vasoactive drugs and β-Blockers drugs are given for the treatment of cardiotonic shock.

→ Hematinics, Coagulants and Anticoagulants:-

Iron Dificiency of Anaemia That condition of body in which the RBC lavel in blood is decrease this is called Anaemia.

→ And The main component of RBC is haemoglobin which made by the iron. and in the deficiency of iron the heamoglobin lavel is decrease so the blood volume is decrease and this is called iron deficiency Anaemia. or Megaloblastic Anaemia.

→ When the size of RBC is reduce then this is called microcytic Hypochromic Anaemia.



Causes for Iron Deficiency:- Iron deficiency may occur due to following reasons -

(i) Excessive loss as in chronic haemorrhage
(ii) Dietary Deficiency.
(iii) Increased Demand as in Puberty and Pregnancy.
(iv) Defective absorption as in chronic diarrhoea.

Iron Requirement: The daily iron requirements are as follows -

⇒ 5 to 10 mg/day for a normal male Adult.

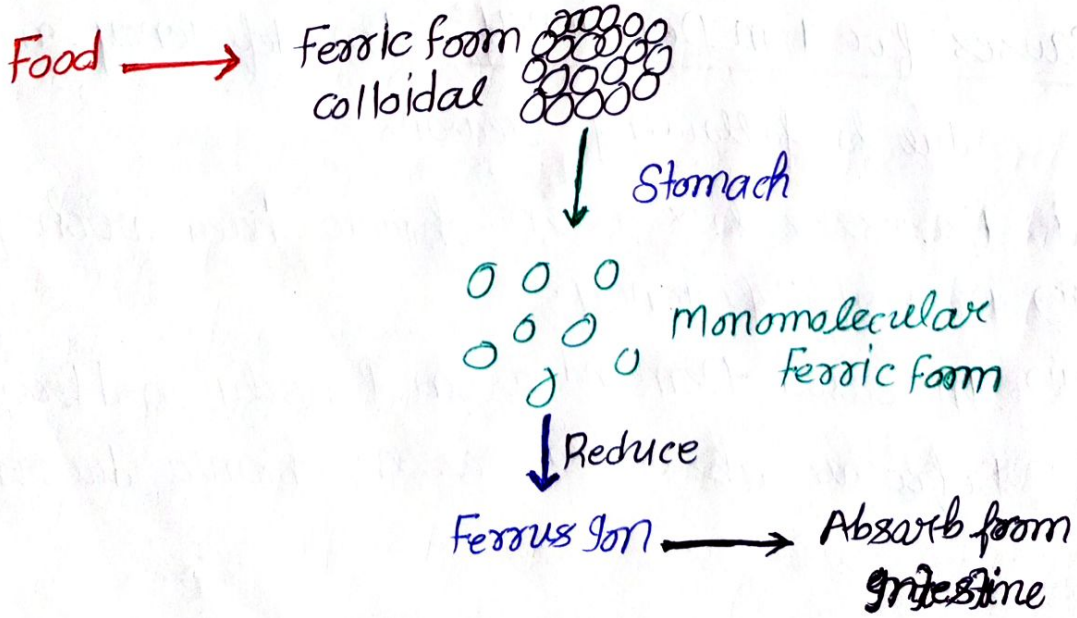
⇒ 10 to 15 mg/day for a woman upto menopausal age.

⇒ 15 to 20 mg/day for woman during pregnancy and Lactation.

Mechanism of Iron Absorption: The iron is obtain in colloidal ferric form from the food but it is absorb in stomach only Ferrous form.

→ So after come in into stomach colloidal ferric form is convert into monomolecular Ferric form and after reduction it convert into ferrous ion form

→ And after conversion in ferrous ion form it absorb in intestine.



Preparation And dose:

(a) Oral Iron: (1) Excicated Ferrous Sulphate - 600 mg daily

(2) Ferrous Gluconate - 900 mg daily

(3) Ferrous Fumarate - 600 mg daily.

(b) Intramuscular Iron: (1) Dextran - Iron combination - 50 to 250 mg. of iron.

(2) Iron - Sorbitar - citric Acid complex - 75 to 100 mg of Iron

(c) Intravenous Iron: (1) Saccharated iron oxide - 100 to 200 mg of iron.

(2) Iron - Dextran complex 30 to 100 mg of Iron

← Drugs Effective in Megaloblastic Anaemia:

(i) Vitamin B_{12} (CYANOCOBALAMIN): Vitamin B_{12} belongs to the group of cobalamins.

- It contains a cyanide group attached to the cobalt atom.

Source and Occurrence: Vitamin B_{12} is synthesised by microorganisms of the colon.

- But it is not absorbed there and so it is eliminated in feces.
- Commercially it is obtained from Streptomyces griesius as a by product of streptomycin.

It is mostly present in non vegetarian foods like liver, kidney, fish and egg.

Requirements:- The requirement of Vitamin B_{12} is about 1 microgram per day.

→ The recommended daily intake is.

→ 2 micrograms for normal adults.

→ 3 micrograms for women during pregnancy and lactation.

→ 0.3 micrograms for children.

Absorption, Distribution and Extraction:- In food, Vitamin B_{12} is present in a metabolically inactive and bound form.

→ It is released by cooking. Vitamin B_{12} is absorbed only in presence of intrinsic factor.

→ Intrinsic factor is a mucopeptide secreted by the gastric muscosa.

→ It acts a carrier for vitamin B_{12}

→ Vitamin B_{12} is stored in the liver to the extent of 99% some quantity is present in the spleen and kidneys.

→ It is excreted in bile but it is reabsorbed by enterohepatic circulation.

→ The daily urinary extraction of vitamin B_{12} is negligible.

→ The total ~~eliminated~~ body content is about 5gm of this only about 0.1 microgram is eliminated.

→ So the deficiency of Vitamin B_{12} does not occur except after 5 or 6 years of pralonged malnutrition.

(2) Folic Acid (Pteroylmonglutamic Acid):

Chemistry and Occurance: Chemically, Folic acid molecule consists of pteridine, para, amino benzoic acid and glutamic acid.

→ The rich sources of folic acid are vegetarian foods like cabbages and greens.

→ However, small quantities are found in eggs, meat, fish and dairy products. Cooking destroys folic Acid.

Absorption, distribution and excretion: In food, folic Acid is present in a conjugated form.

→ Usually, it occurs as triglutamic acid and ~~pt~~heptaglutamic acid conjugate.

→ It is broken down by enzymes known as conjugases present in the gastro intestinal tract.

→ In the absence of conjugases, folic acid is not absorbed.

→ It is absorbed mainly in the proximal portion of small intestine.

→ Folic Acid circulates in blood as N-Methyl tetrahydrofolate.

→ It is distributed in all tissues. but high concentration is found in liver. It is excreted mainly through urine

Requirement ÷ The requirement of folic acid is -

→ 100 micrograms for children.

→ 200 micrograms for adults.

→ 300 to 400 micrograms for women during pregnancy and lactation.

Metabolic Actions: Folic acid is necessary for the following metabolic Actions.

→ (i) Biosynthesis of purines and Pyrimidines.

→ (ii) Interconversion of Amino acids (like serine to glycine and homocysteine to methionine)

(iii) Incorporation of formate into purine ring.

All these reactions are needed for nucleic acid synthesis.

÷ **Preparation and dose** ÷ Folic acid tablet 5 to 20 mg. daily

Therapeutic Uses ÷ (i) Megaloblastic Anaemia due to nutritional deficiency.

(ii) Megaloblastic Anemia of Pregnancy and infancy.

(iii) Some cases of Agranulocytosis.

(3) Folinic Acid (Citrovarum Factor)

→ Folinic Acid is the formyl derivative of Folic Acid. In the body, folic acid is converted to folinic Acid.

→ folinic acid is required for thymine synthesis. It is used in the treatment of toxicity due to folic Acid Antagonists like methotrexate.

→ It is effective in megaloblastic Anaemia even at a dose of 50 micrograms.

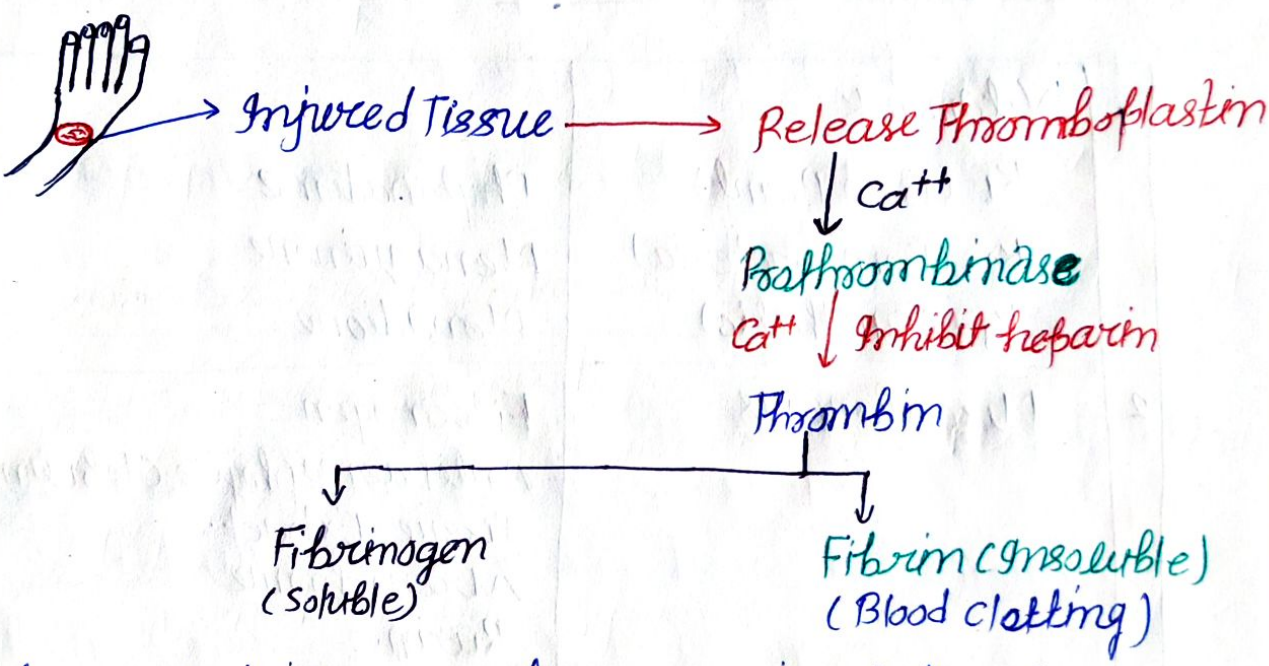
÷ Blood Clotting ÷

→ Blood clotting is a mechanism in which the flow of blood is stop after injury.

→ Platlets and calcium ion play an important role in blood clotting.

→ Fibrine are the thread like structure which cover the wound and stop the flow of blood.

Mechanism of blood Clotting



→ When any injury or cut occurs in body then Platlets aggrigate at that place and release Thrombo-plastin.

→ In the presence of calcium ion thromboplastin activate the enzyme prothrombinase and in the presence of Ca^{++} ion it change into thrombin.

→ Fibrinogen are the soluble protein present in blood and in the presence of thrombin it convert into insoluble fibrine

→ Fibrin increase the viscosity of blood and covers the wound this is called blood clotting.

→ Types of blood clotting :-

(i) Coagulants.
(ii) Local Haemostatics (Styptics)
(iii) Anti-Coagulant.

(1) Coagulants :-

- These are agents which promote coagulation.
- They are used in haemorrhagic states.

Classification of Coagulants :-

1	Vitamin K K_1 (From Plant) K_2 (From bacteria) K_3 (synthetic)	 Phytonadione Menaquinone Menadione
2	Miscellaneous	Fibrinogen Antihaemophylic Globulin Tissue Extract. Adrenochrome Rutin.

(i) Vitamin K :- It is a fat soluble vitamin.
→ It is not a single entity.

→ Naturally it occurs in the form of two distinct substances, vitamin, K_1 and K_2.

→ Vitamin K_3 (Menadione) is a lipid-soluble synthetic compound.

→ Vitamin K is necessary for the biosynthesis of Prothrombin and factors VII, IX and X.

→ Vitamin K is produced by bactericial flora of human intestine and it is absorbed in presence of bile salts.
→ It can also be absorbed on parenteral administration

Use: (1) Hypoprothrombenemia due to hepatocellular disease obstructive jaundice and chronic diarrhoea
(2) For treating toxicity of oral Anticoagulants and salicylates

(2) Fibrinogen: It is obtained from human plasma. It is used to control bleeding in hemophilia and also in the deficiency of Antihaemophilic globulin (AHG)

Dose: 0.5g as I.V. infusion.

(3) Antihaemophylic Globulin (AHG) It is highly effective in controlling bleeding.
→ It is prepared from pooled human plasma.
→ It is used in haemophilia and AHG deficiency.

(4) Tissue Extract: It acts by activating platelet aggregati
→ It can be used to control internal haemorrhages.

(5) Adrenochrome: It reduces capillary fragility.
→ It prevents bleeding from raw surfaces and micro vessels. e.g. epistaxis hematuria and retinal hemorrhage.

(6) Rutin: It is a plant glycoside. It is used to reduce capaillary bleeding. It is used with vitamin c which facilitates its action.

← (2) Local Haemostatics (Styptics) :-

→ These are substances used to stop bleeding from local sites.
→ They are effective on oozing surfaces like tooth sockets and open wounds.
→ They should never be injected.

(1) **Thrombin :-** It is obtained from bovine plasma.
⇒ It is applied on bleeding surfaces as a dry powder or as a freshly prepared solution.
- It is used in skin grafting.

(2) **Fibrin :-** It is obtained from human plasma.
⇒ It is used as sheets or foam for covering bleeding surfaces.

(3) **Gelfoam :-** It is spongy gelatin.
⇒ It is moistened with saline or thrombin solution and used for packing wounds.
→ Since it is completely absorbed within 2 months, it can be left in place after suturing a wound.

(4) **Russels Viper Venom :-** It enhance coagulation by stimulating thrombokinase.
→ It is used to stop external bleeding in haemophilics.

(5) **Vasoconstrictors :-** Cotton gauze soaked in 1% adrenaline can stop epistaxis or similar bleeding.

(6) **Astringents :-** Tannic acid can be used for bleeding gums and bleeding piles.

(3) Anticoagulants :-

→ Anticoagulants are agents which inhibit the process of clotting.

÷ Classification of Anticoagulants :-

1.	In vitro Anticoagulants.	Citrates Oxalates Fluorides EDTA
2.	In vivo Anticoagulants (oral Anticoagulants)	Coumarin derivatives Indanedione derivatives Warfarin.
3.	Both in vitro and in vivo Anticoagulants (Parenteral Anticoagulants)	Heparin.

In Vitro Anticoagulants :- These compounds are chealating agents like citrates, Fluorides and E.D.T.A (Ethylene diamine tetra Acetic Acid)

→ They act by removing calcium ions.

→ These compounds are used in vitro to preserve blood (so as to make it suitable for transfusion).

In vivo anticoagulants (Slow Acting Anticoagulants)

Coumarin Derivatives :-

→ Dicoumarol
→ Cyclocoumarol
* Phenprocoumon
* Ethyl biscoumacetate.

* Dicoumarol (Bishydroxycoumarin):- Dicoumarol was earlier isolated from spoilt sweet clover hay.

⇒ In cattle it produced sweet clover disease which is characterised by severe bleeding.

→ It is effective orally.

→ Mechanism of Action:- Dicoumarol acts by inhibiting the synthesis of prothrombin and factors VII, IX & X in the liver.

* For the synthesis of prothrombin, vitamin K is necessary.
* Dicoumarol acts as a competitive Antagonist of vitamin K.
* The anticoagulant effect of dicoumarol is Antagonised by vitamin K.

Absorption Fate and Excretion:- Dicoumarol is effective on oral and intravenous administrations.

* In blood, it is bound to albumin. High concentration is present in liver.
* It cross placental barrier and also is secreted in milk.
* It is eliminated in urine, mostly in a metabolised form.

Adverse Reactions:- Haemorrhage is the major toxicity.

* This may occur as haematuria, bloody stools, bleeding of gums etc.
* These effects can be treated by large doses of vitamin K.

Dose:- * 300 mg on the first day.
* 200 mg on the second day.
* And 50 to 100 mg on subsequent days by oral route.

Indanediones :-
* Phenindione
* Diphenadione
* Anisindione
* Chlorphenindione

* The indanediones are effective on oral and parenteral Administration.
* They act by inhibiting prothrombin synthesis like dicoumarol.
* They have a rapid onset and short duration of action.
* Toxicities of indanediones are haemorrhage, hepatitis and skin reaction.

Warfarin:- * It was orginally used as a rat poison.
* It is well soluble and so can be Administered by all routes.
* It act by the same mechanism as dicoumarol.
* It has a bronchodilator and coronary vasodilator effect.
* Haemorrhage is the important toxicity and it can be controlled by vitamin K.
* other toxicities are Alopecia urticaria and dermatitis.

* Both in vitro and in vivo Anticoagulants (Fast acting Antocoagulants) *

* Heparin

* **Source:** Heparin was first extracted from liver.
  * It is also obtained from lungs and intestinal mucosa.
  * In these tissues, it is present in mast cells.
  * Heparin is released from mast cells during anaphylactic shock.

* **Chemistry:** * Heparin is a mucopolysaccharide.
  * It consists of hexosamine and hexuronic acid molecules esterified with sulphuric acid.
  * The content of esterified sulphuric acid is very high.
  * This makes heparin the strongest acid present in the body.

* **Pharmacological Actions:**
  (i) **Anticoagulant Action:** Heparin prevents clotting both in vivo and in vitro.
  * It does not inhibit prothrombin synthesis.
  * It acts by the following mechanism
  (1) It binds to Antithrombin III (heparin co-Factor).
  ⇒ This combination inactivates serum coagulation factors.
  (2) It inhibits factor Xa mediated conversion of prothrombin to thrombin.
  (3) It also inhibits thrombin (IIa) mediated conversion of fibrinogen to fibrin.

(ii) Lipemia Clearing:- Heparin clears the turbidity of lipemic plasma.

* It occurs due to activation of the enzyme lipoprotein lipase.

Absorption, Fate and Excretion:- Heparin is ineffective orally.

* It is well absorbed after subcutaneous injection.
* On intravenous injection, it produces immediate anticoagulant effect.
* Heparin should not be used intramuscularly because it produces hematoma.
* Heparin does not cross placental barrier. also it is not secreted in milk.
* It is metabolised in the liver by an enzyme called heparinase.
* It is eliminated in urine both in an inactive and as a metabolised form.

Adverse Reactions:- (1) Danger of bleeding due to over dosage

(2) Allergic and Anaphylactic reactions.

(3) Alopecia on prolonged use.

÷ Fibrinolytic Agent and Anti Platlet drugs ÷

Fibrinolysis ÷ Fibrinolysis is a process in which the blood clot is dissolve this is called Fibrinolysis.

→ The process of Fibrinolysis (dissolution of clot) occurs as follows.

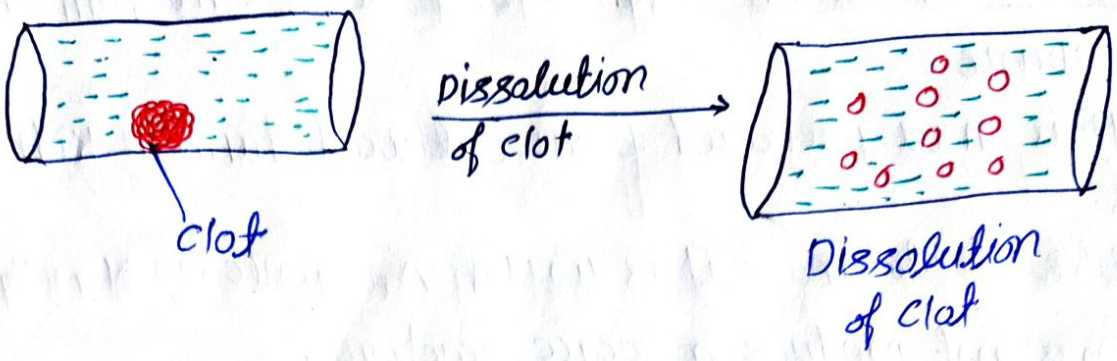
- Plasminogen is the inactive precursor present in Plasma.
- It is convered to plasmin by an activator substance Present in blood and tissues.
- Plasmin can breakdown clots.

Fibrinolytics (Thrombolytics) ÷ Fibrinolytics are those agent which dissolve the blood clot and by the activating Plasminogen activators.

* All Fibrinolytics agent currently in use act directly or indirectly as plasminogen activators.
* They produce lysis of an already formed clot.
* So they are curative rather than profphylactic.
* They can be injected (1) Intra Arterially close to a thrombus for a localised effect.

(2) Intravenously for a generalised effect in multiple thrombi.

* Incidence of bleeding is high with intravenous injection in general, venous thrombi are lysed easily than arterial thrombi. also recent thrombi respond better



Plasminogen $\xrightarrow{\text{Activate}}$ Plasmin ⟶ clot Dissolve

Indications: Fibrinolytic agents are used in -

(1) Myocardial Infraction.
(2) Pulmonary Embolism.
(3) Deep vein thrombosis.
(4) Peripheral Arterial Occlusion.

Streptokinase: It is a fibrinolytic agent obtained from β haemolytic streptococci.

* It acts as a plasminogen activator leading to Fibrinolysis.
* **Disadvantages:** (1) It is inactivated by antibodies to streptococci present in the body.
(2) It is antigenic and so produces hypersensitivity reactions.
(3) Local irritation and dangerous haemorrhage
(4) Produces Fever.
* It is used in deep vein thrombosis at a dose of 250,000 units I.V in 30 minutes.
* It is followed by 100,000 units every hour for 24 to 72 hours

Urokinase:- * It is an enzyme prepared from human Urine.

* It is now prepared from cultured human kidney cells.
* Unlike streptokinase it is (1) Non-Antigenic (2) Non-Pyrogenic (3) Does not produce allergic reactions.
* But it is expensive.

Tissue-Type Plasminogen Activator:- It is a natural protein in man.

* It is prepared by recombinant DNA technology.
* It has a selective effect on plasminogen bound to fibrin clot.
* Systemic Activation of Plasminogen and so bleeding is minimised.
* So it is safer than streptokinase.

(2) Antifibrinolytics:-

* These drugs inhibit Fibrinolysis and therefore prevent the dissolution of clot.
* They act by inhibiting plasminogen activation.

Epsilon Amino-caproic Acid (EACA) It is structurally related to lysine.

* It blocks plasminogen activation by competitive blockade.
* Thus is reduce fibrinolytic activity.
* Dose initial 5g-oral or I.V followed by 1g every one hour till bleeding stop.

* It is used to control haemorrhage like (1) Abruptio Placentae (2) Post-Partum haemorrhage (3) Traumatic and surgical bleedings.

Tranexamic Acid: It is a synthetic inhibitor of fibrinolysis.

* It is 10 times more potent than EACA.
* It binds to lysine binding site on plasminogen.
* Thus, it prevents the combination of plasminogen with fibrin. Dose - 1g orally or I.V 3 to 4 times a day.

Aprotinin: It is a polypeptide protease inhibitor.

* It is isolated from bovine tissue.
* It inhibits kallikrein, Trypsin and fibrinolysin.

***Sclerosing Agent:** These are irritating substances used to obliterate varicose veins.

* They are also used for closure of hernial rings and for fibrosing haemorrhoids.
* The preparations used are.

(1) Phenol 5% in vegetable oil.

(2) Preparations containing salts of fatty acid (like sodium linoleate or Ethanolamine oleate)

(3) Antiplatelet Drugs :-

Functions of Platelets :- Intravascular thrombosis is initiated by platelet Adhesion and aggregation.

→ Platelets stick to the damaged vessel wall ~~Adenosine~~ (Adhesion)

* Then they stick to each other (Aggregation) and release (adenosine) diphosphate (ADP) and thromboxane A_2 (TXA_2).

⇒ This promotes further aggregation and also fibrin formation (Clot)

- Antiplatelet drugs inhibit platelet aggregation. so they are useful in the prevention and treatment of thrombosis in condition like - ① Myocardial Infraction.

② Myocardial Ischemia.

③ Cerebral ischemia. Prostacyclin (PGI_2) synthesised in the blood vessel is a natural inhibitor of platelet aggegation.

(1) Aspirin :- Aspirin inhibits the release of ADP from Platelets also, it inhibits the synthesis of prostaglandins and thromboxane A_2.

→ All these mechanisms inhibit platelet aggregation.

(2) Dipyridamole :- It has no effect on the levels of thromboxane A_2 or PGI_2.

- It acts by inhibiting phosphodiesterase which inturn increases cyclic AMP.

→ This inhibits platelet aggregation.
→ Dipyridamole is also a coronary vasodilator

(3) Ticlopidine :- It is a new synthetic inhibitor of Platelet aggregation.
→ It has no effect on cyclo-oxygenase or cyclic AMP.
→ It inhibit platelet deposition, aggregation and release reaction.

(4) Clopidogrel :- → It is a congenor of ticlopidine.
→ It has similar mechanism as ticlopidine.
→ It is better tolerated.
→ It produces less neutropenia and thrombocytopenia than ticlopidine.
→ Side effects diarrhoea, epigastric pain and rashes.
→ Dose :- 75 mg once daily as tablet.

÷ Diuretics & Antidiuretics drugs ÷

Diuretics ÷

Di + Uretics
↓ ↓
Dilute. Urine

→ Diuretics are those agent which dilute the urine concentration by increasing the water, Sodium ion, Potassium ion, Ca^{++} ion, glucose ion and increase the volume of urine they are called diuretics drugs.

→ Diuretics drugs are generally given to remove the toxic material from body in the form of urine.

← As well as when the volume of urine is increase then the maximum toxic substence release outside from the body.

← Diuretics drugs are also given in the case of edema.

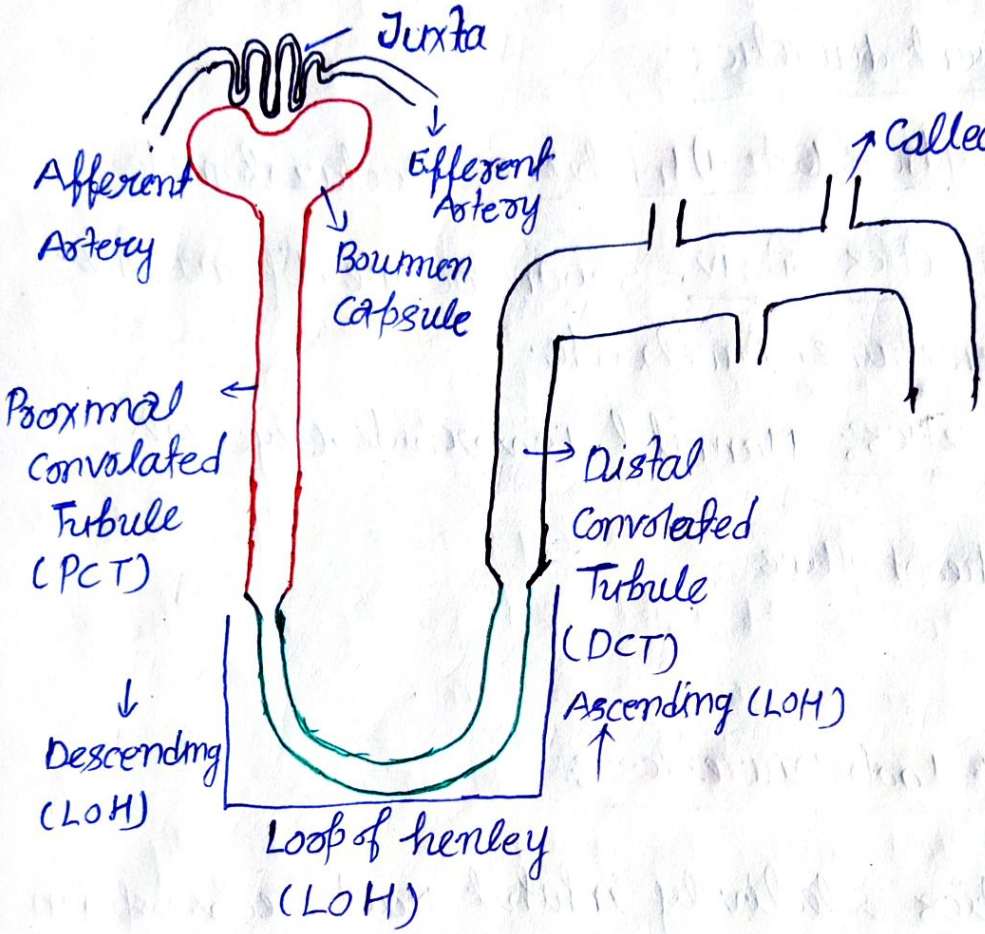
→ When the accumulation of fluid inside the lower limbs and body of any human beings takes place then by the using of diuretics this extracellular fluid can be remove in the form of urine.

⇒ In the formation of urine basically three step involve
(1) Ultrafiltration.
(2) Selective Reabsorption
(3) Tubular secretion.

⇒ Basically diuretics drugs alter the Selective Reabsorption

⇒ They act on the PCT, DCT, CT and Loop of henley.

And decrease the water reabsorption capacity so the urine volume is increase.



÷ Classification of Diuretics ÷

(1) **High Eficacy diuretics ÷ / Loop Diuretics** - Site-II $Na^+/K^+/Cl^-$

(A) Sulfhomoyl derivative ÷ Furosemide, Brumetanide.

(B) Phenoxy Acetic Acid Derivative ÷ Ethacrynic Acid

(C) Organomercurials → Merasabyl.

(2) **Medium Efficacy diuretics ÷** - Site-III Na^+/K^+

(A) Thiazide Hydrochloric thiazide, Benzathiazide, Hydroflumethazide Bendroflumethazide.

(B) Thiazide like :- Chlorthalidone, Metalazone, Xipamide
Indapamide, Clopamide

(3) Weak or Adjuent diuretics :-

(A) Carbonic Anhydrase Site-I Inhibitor :- Acetazolamide

(B) K-sparing diuretics - site iv :- Spironolactone, Eplinerone.
Triamterine, Amiloride.

(C) Osmatic Diuretics :- Mannitol, Isosorbide, Glycerol.

(D) Xanthine :- Theophylline

:- Loop Diuretics :-

→ Loop diuretics selectively inhibit Nacl reabsorption in the thick ascending limb of Henle loop.

→ Because of the large Nacl absorptive capacity of this segment and the fact the diuretic action of these drugs is not limited by development of Acidosis, as is the case with the carbonic anhydrase inhibitor, loop diuretics are the most efficacious diuretic agents currently available

→ The protatypical drugs of this group is furosemide.

→ The loop diuretics are rapidly absorbed.

→ They are eliminated by the kidney by glomerular filtration and tubular secretion

⇒ Increase in mg^{2+} and ca^{2+} excretion

→ Loop diuretics have also been shown to induce expression of one of one of the cyclooxygenases (COX-2), which participates in the synthesis of prostaglandins from Arachidonic acid

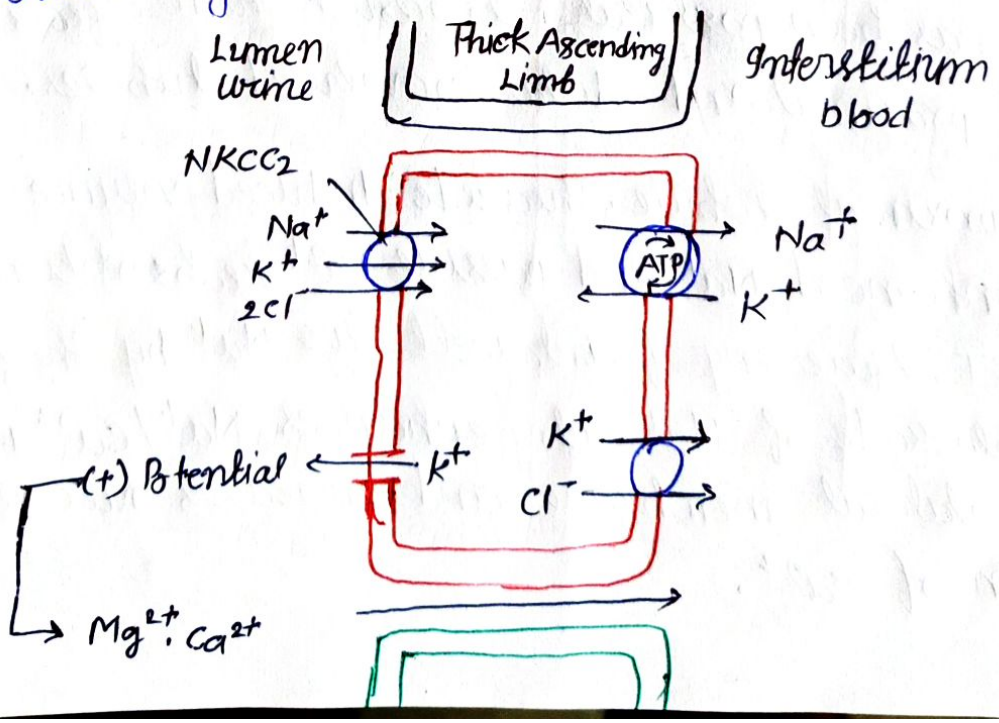
→ At least one of these prostaglandins, PGE_2, inhibits salt transport in the tal and thus participates in the renal actions of loop diurel

→ NSAIDS (Eg. indomethacin, which blunt cyclooxygenase activity, can interfere with the actions of loop diuretics

→ Furosemide increased renal blood flow via prostaglandin actions on kidney vasculature.

→ Furosemide and ethacrynic acid have also been shown to reduce pulmonary congestion and left ventricular filling pressures in heart failure before a measurable increase in urinary output occurs.

→ These effects on peripheral vascular tone are also due to release of renal prostaglandins that were induced by the diuretics.



Thiazides

→ The thiazides diuretics were discovered in 1957, as a result of efforts to synthesize more potent carbonic anhydrase inhibitors.

⇒ It subsequently became clear that the thiazides inhibit NaCl, rather than $NaHCO_3$ - Transport and that their action was predominantly in the DCT, rather than the PCT.

→ The prototypical thiazide is hydrochlorothiazide (HCTZ).

→ All thiazides can be administered orally, but there are differences in their metabolism.

→ Chlorthiazide the present of the group, is not very lipid-soluble and must be given in relatively large doses.

→ HCTZ is considerably more potent and should be used in much lower doses.

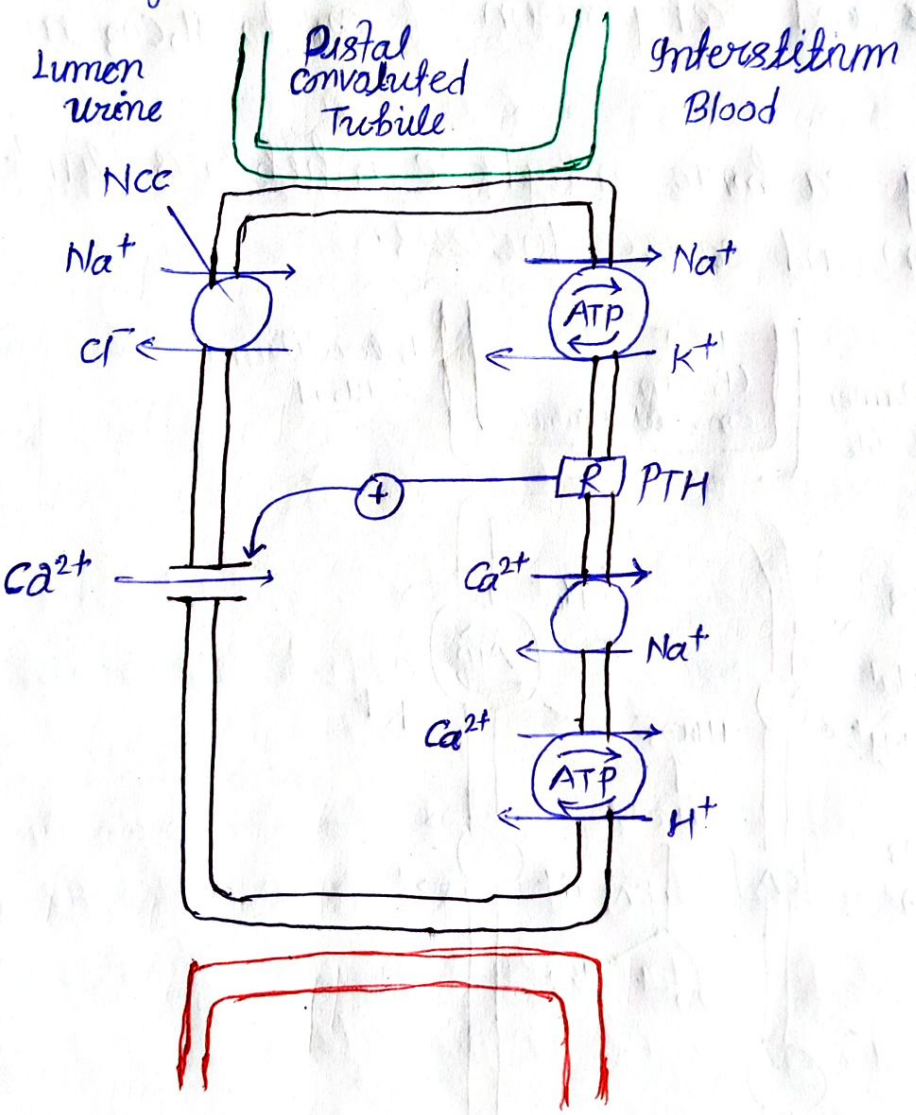
→ The enhancement in Ca^{2+} + reabsorption caused by thiazides has been postulated to result from effects in both the proximal and distal convoluted tubules.

→ In the proximal tubule, Thiazide-induced volume depletion leads to enhanced Na^+ and passive Ca^{2+} reabsorption.

→ In the DCT, lowering of intracellular Na^+ by thiazide induced blockade of Na^+ entry enhances Na^+/Ca^{2+} + exchange in the basolateral membrane and increases over all reabsorption of Ca^{2+}.

→ Although thiazides rarely cause hypercalcemia as the result of this enhanced reabsorption, they can unmask hypercalcemia due to other caused (ex- (Hyperparathyroidism, Carcinoma, Sarcoidosis)

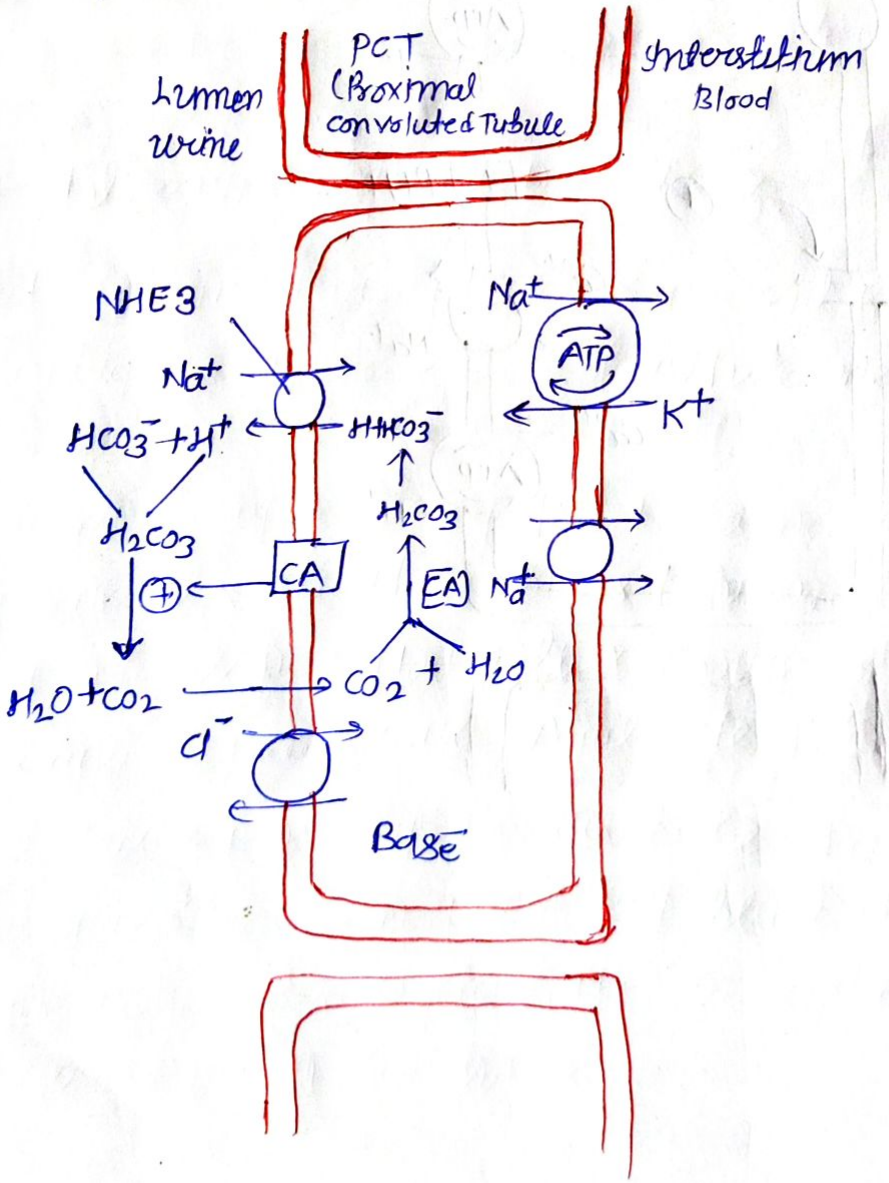
→ Thiazides are useful in the treatment of kidney stones caused by hypercalciuria.



÷ Carbonic Anhydrase Inhibitors ÷

→ Carbonic Anhydrase is present in many nephron sites but the pedominant location of this enzyme is the epithelial cells of the proximal tubule.

* Catalyzes the dehydration of H_2CO_3 to CO_2 at the luminal membrane and rehydration of CO_2 to H_2CO_3 in the cytoplasm.
* By blocking carbonic anhydrase inhibitors blunt $NaHCO_3$ reabsorption and causes diuresis.



→ With the development of newer agents, carbonic anhydrase inhibitors are now rarely used as diuretics, but they still have several specific Applications

* The prototypical carbonic anhydrase inhibitor is acetazolamide.

Pharmacokinetics :-

→ The carbonic anhydrase inhibitors are well absorbed after oral administration.

→ An increase in urine pH from the HCO_3^- diuresis is apparent within 30 minutes, is maximum at 2 hours and persists for 12 hours after a single dose.

→ Excretion of the drug is by secretion in the proximal tubule.

→ Therefore dosing must be reduced in renal insufficiency.

Pharmacodynamics :-

→ Inhibition of carbonic Anhydrase activity profoundly depresses HCO_3^- reabsorption in the PCT.,

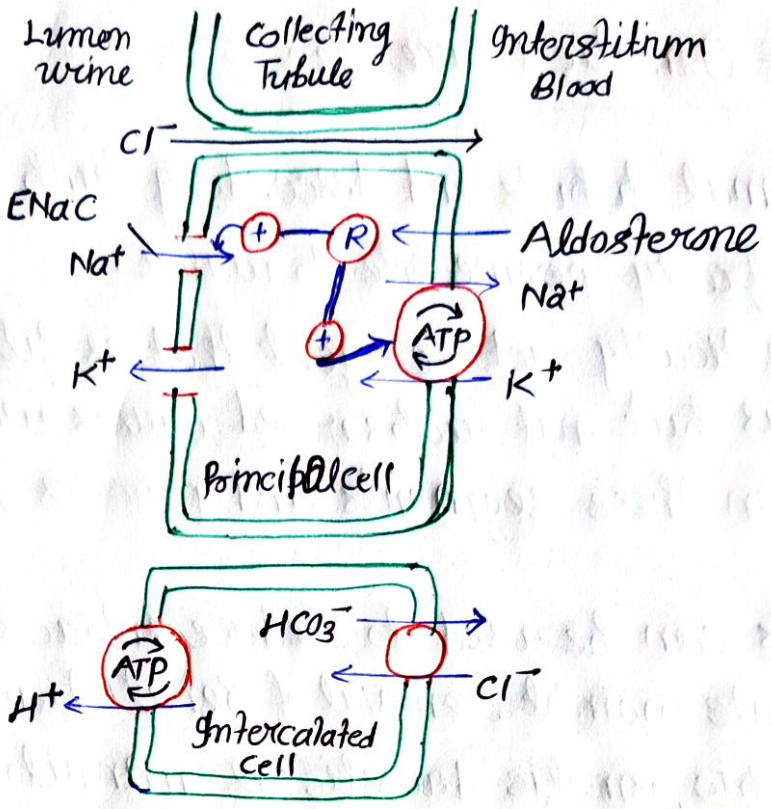
→ At maximal safe dosage, 85% of the HCO_3^- reabsorptive capacity of the superficial PCT is inhibited

→ Because of reduced HCO_3^- in the glomerular filtrate and the fact that HCO_3^- depletion leads to enhanced NaCl reabsorption by the remainder of the nephron, the diuretics efficacy of acetazolamide decreases significantly with use over several days

* At present, the major clinical Applications of Acetazolamide involve carbonic anhydrase-dependent HCO_3^- and fluid transport at sides other than the kidney
* The cilliary body of the eye secretes HCO_3 from the blood into the aqueous humar.
* Likewise formation of cerebrospinal fluid by the charaid plexus involves HCO_3^- secretion.
* Although these processes of that in the proximal tubule They are similarly inhibited by carbonic anhydrase inhibitors.

← Potassium-Sparing Diuretics →

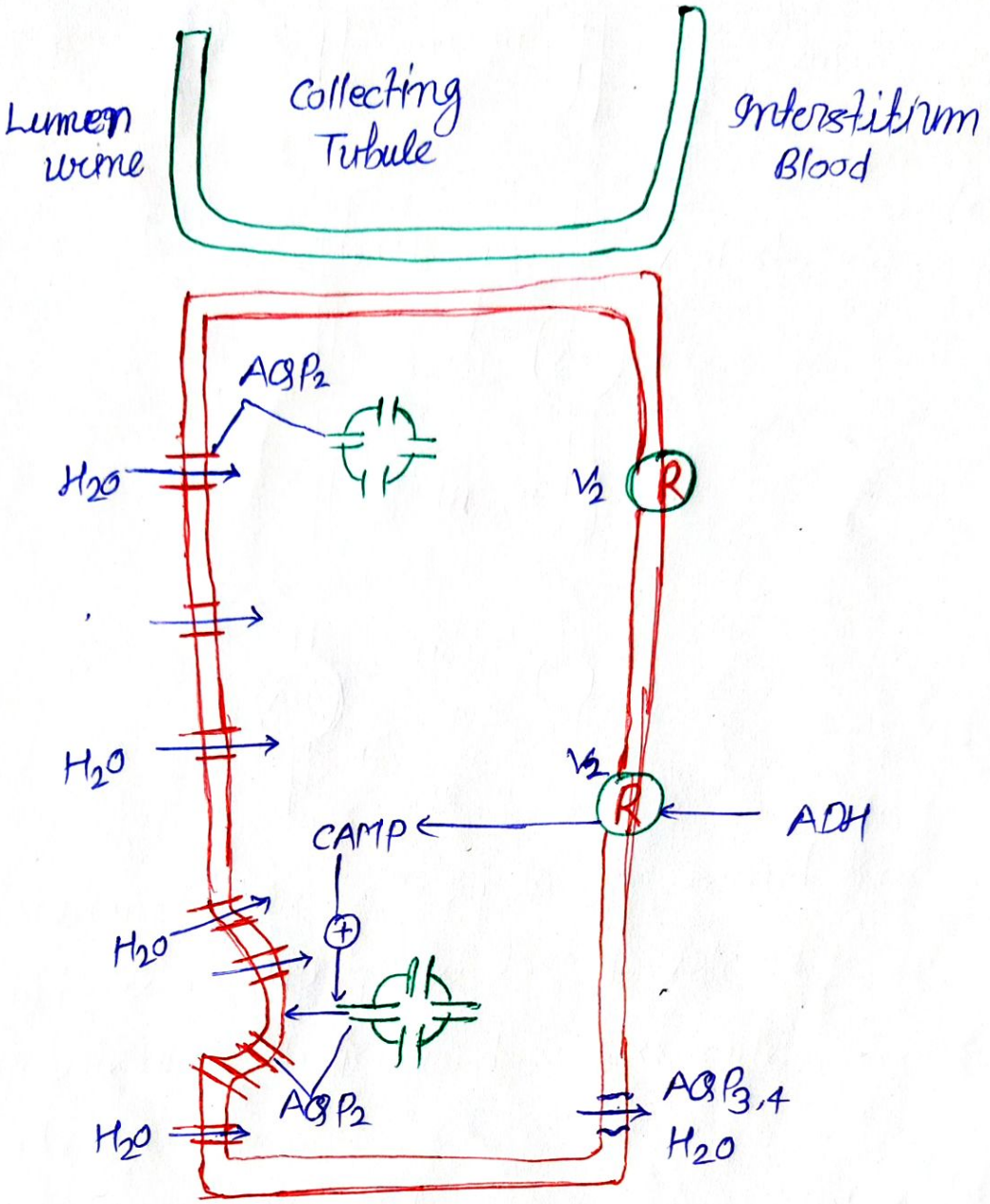
* Potassium sparing diuretics prevent K^+ secretion by antagonizing the effects of Aldosterone in collecting tubules.
* Inhibition may occur by direct pharmacologic Antagonism of mineralocorticoid receptors (Spironolactone, Eplerenone) or by inhibition of Na^+ influx through ion channels in the luminal membrane (Amiloride, Triamterene).
* This latter property appears to be shared by Adenosine antagonists, which primarily blunt Na^+ reabsorption in the PCT, but also blunt Na^+ reabsorption and K^+ secretion in collection tubules.



* Spironolactone is a synthetic steroid that acts as a competitive antagonist to aldosterone.
* Active on androgen and progesterone receptores
* Side effects -
* Potassium-sparing diuretics reduce Na^+ absorption in the collecting tubules and ducts.
* Potassium absorption (and K+ secretion) at this site is regulated by aldosterone as described above. Aldosterone antagonists interfere with this process.
* The actions of the aldosterone antagonists depend on renal prostaglandin production. The action of K+-sparing diuretics can be inhibited by NSAIDs

÷ Osmotic Diuretics ÷

* The proximal tubule and descending limb of Henle's loop are freely permeable to water.
* Any osmotically active agent that is filtered by the glomerulus but not reabsorbed causes water to be retained in these segments and promotes a water diuresis.
* Such agents can be used to reduce intracranial pressure and to promote prompt removal of renal toxins.
* The prototypic osmotic diuretic is mannitol.
* Mannitol is poorly absorbed by the GI tract, and when administered orally, it causes osmotic diarrhoea rather than diuresis.
* For systemic effect, mannitol must be given intravenously.
* Mannitol is not metabolised and is excreted by glomerular filtration within 30-60 minutes, without any imp. tubular reabsorption or secretion.
* Osmotic diuretics have their major effect in the proximal tubule and the descending limb of henle's loop.
* Through osmotic effects, They also oppose the action of ADH in the collecting tubule.


Lumen
Urine
Collecting Tubule
Interstitium
Blood
AQP2
H2O
V2
R
H2O
V2
R
cAMP
ADH
H2O
+
AQP2
H2O
AQP3,4
H2O