Biopharmaceutics & Pharmacokinetics

8th SEM

PHYSIOLOGICAL BARRIERS TO DIFFUSION OF DRUG

Dr. Praveen Khirwadkar
Institute of Pharmacy
Vikarm University
Ujjain

PHYSIOLOGICAL BARRIERS:-

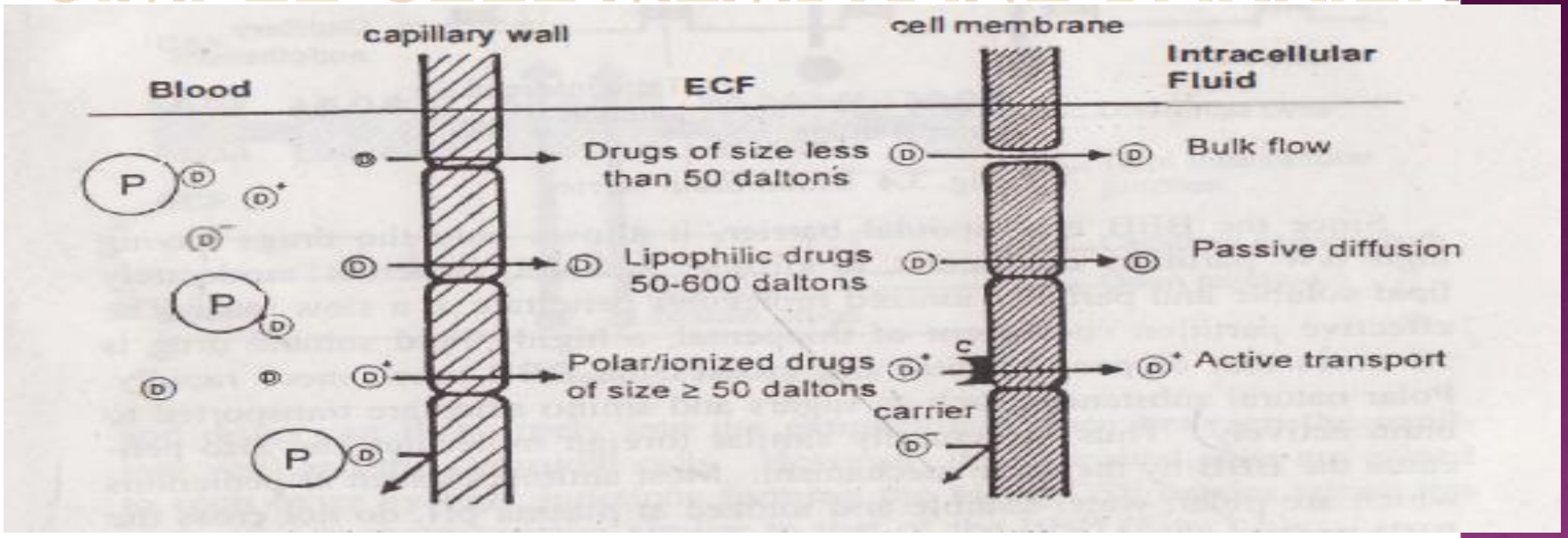
- 1-Simple capillary endothelial barrier
- 2- Simple cell membrane barrier
- 3- Blood brain barrier
- 4- Blood CSF barrier
- 5- Blood placental barrier
- 6- Blood testis barrier

SIMPLE CAPILLARY ENDOTHELIAL BARRIER

- Membrane of capillary supply blood to the most inner tissues.
- All drugs ionized or unionized, with a molecular size less than 600 daltons, diffuse through the capillary endothelium and into the interstitial fluid.
- Only drugs bound to the blood components are restricted because of the large molecular size of the complex.

- Once a drug diffuses through capillary to extracellular fluid its further entry into cells of most tissues is limited by its permeability through the membrane that lines such cells.
- Simple cell membrane is similar to lipoidal barrier (Absorption)
- Non polar & hydrophilic dugs passes through it passively.
- Lipophillic drugs with 50-600 dalton mol. Size and hydrophilic, polar drugs with< 50 dalton mol. Size will pass this membrane.

SIMPLE CELL MEMBRANE BARRIER



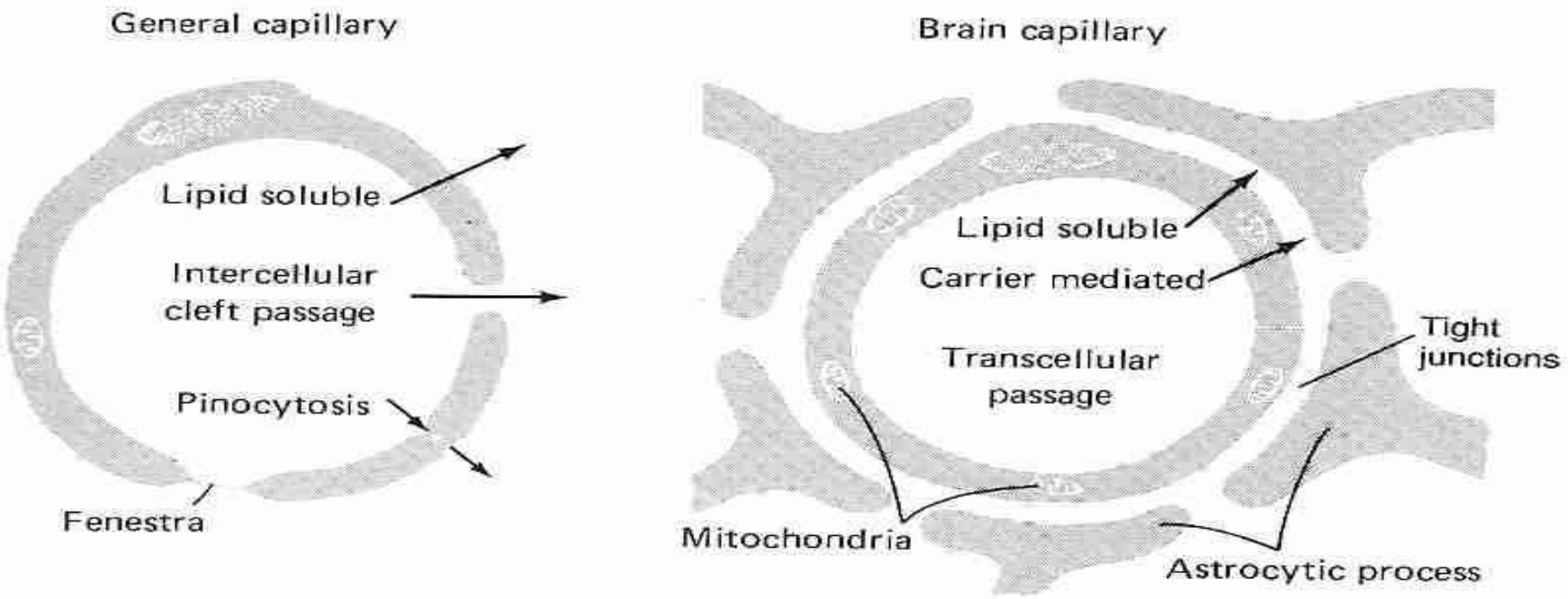
- Once a drug diffuses through capillary to extracellular fluid its further entry into cells of most tissues is limited by its permeability through the membrane that lines such cells.
- Simple cell membrane is similar to lipoidal barrierAbsorption)
- Non polar & hydrophilic dugs passes through it passively.
- Lipophillic drugs with 50-600 dalton mol. Size and hydrophilic, polar drugs with< 50 dalton mol. Size will pass this membrane.

BLOOD BRAIN BARRIER

- Capillary in brain are highly specialized & much less permeable to water soluble drugs.
- The brain capillaries consist of:-

ENDOTHELIAL CELLS:- These are joined to each other by continuous tight intercellular junction.

PERICYTES & ASTROCYTES:-These are the elements supporting tissue found at the base of endothelial membrane, form a solid envelope around the brain capillaries.



Thus the intercellular(paracellular) passage is blocked and for a drug to gain access from the capillary circulation into the brain it has to pass through the cells (transcellular) rather than between them.

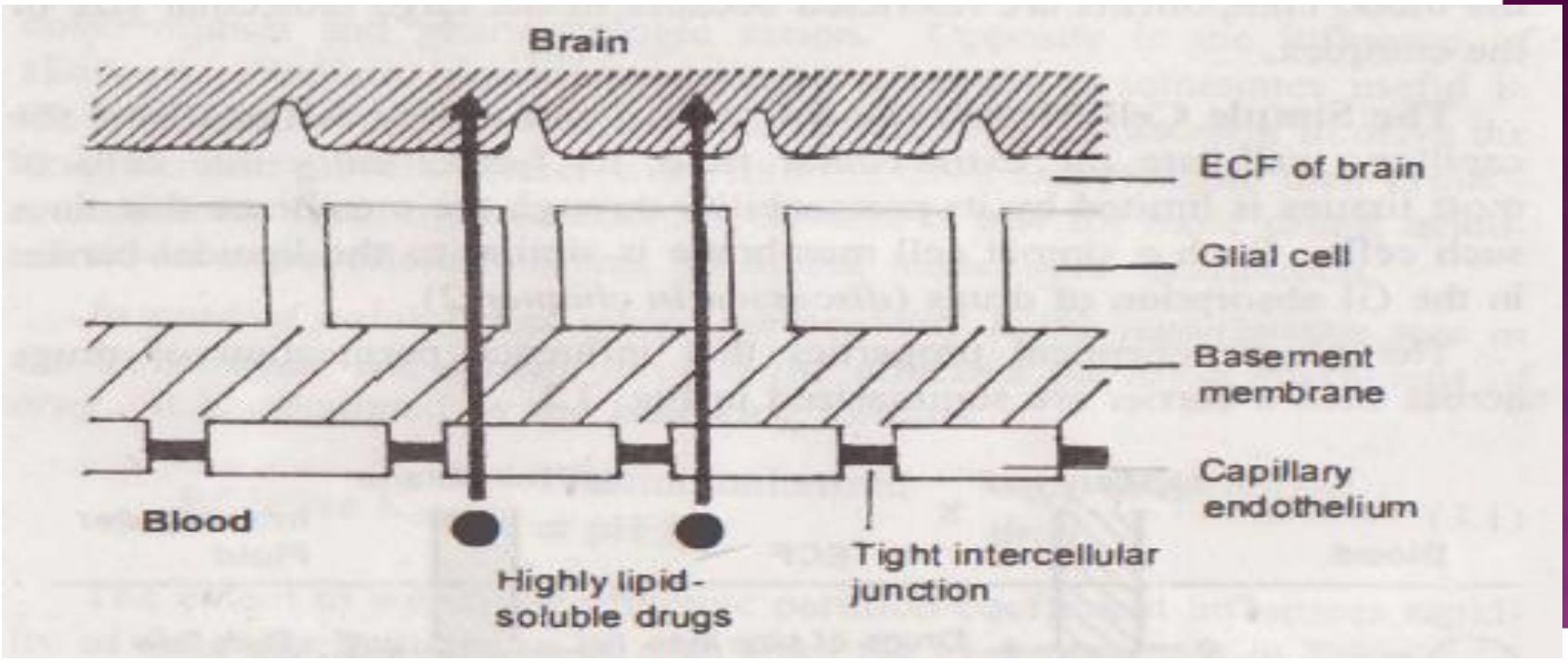
- A solute may gain access to brain via :-

1) Passive diffusion through the lipoidal barrier:-thus drugs with high o/w partition coefficient diffuse passively others (moderately lipid soluble and partially ionised molecules passes slowly.

2) Active transport of essential nutrients such as sugar and amino acid thus structurally similar foreign molecules pass through BBB by same mechanism.

DIFFERENT APPROACHES TO CROSS BBB:-

- *Permeation Enhancers* :- Dimethyl Sulfoxide
- *Osmotic disruption of the BBB* by infusing internal carotid artery with mannitol



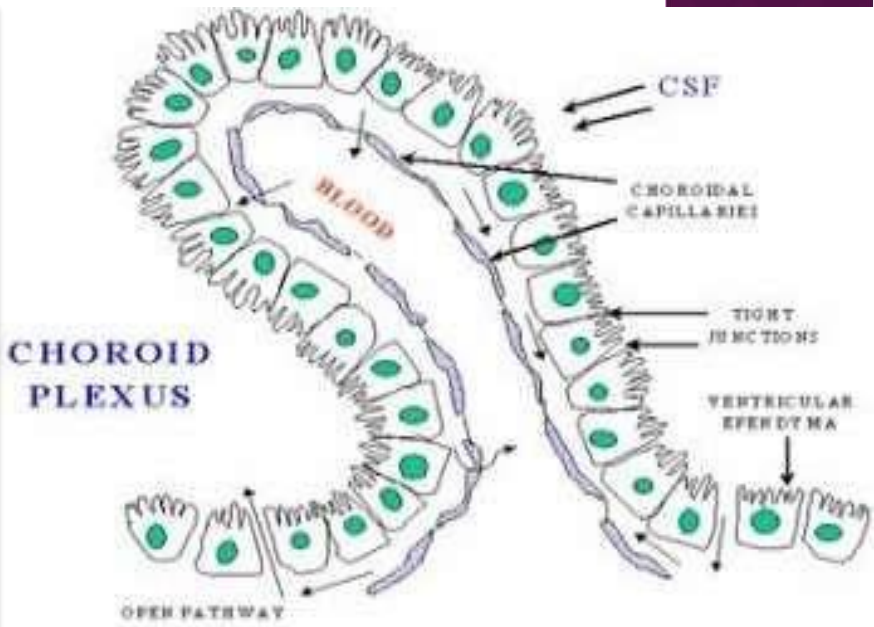
- *Carrier system* :- Dihydropyridine (Lipid soluble) moiety redox system (highly lipophilic & cross the BBB) linked as a carrier to polar drug to form a prodrug & cross BBB. After entering in brain DHP gets oxidize to polar pyridinium ion by (CNS) enzyme in brain which cannot diffuse back out from brain and drug gets trapped in side the brain.(used for steroidal drugs)

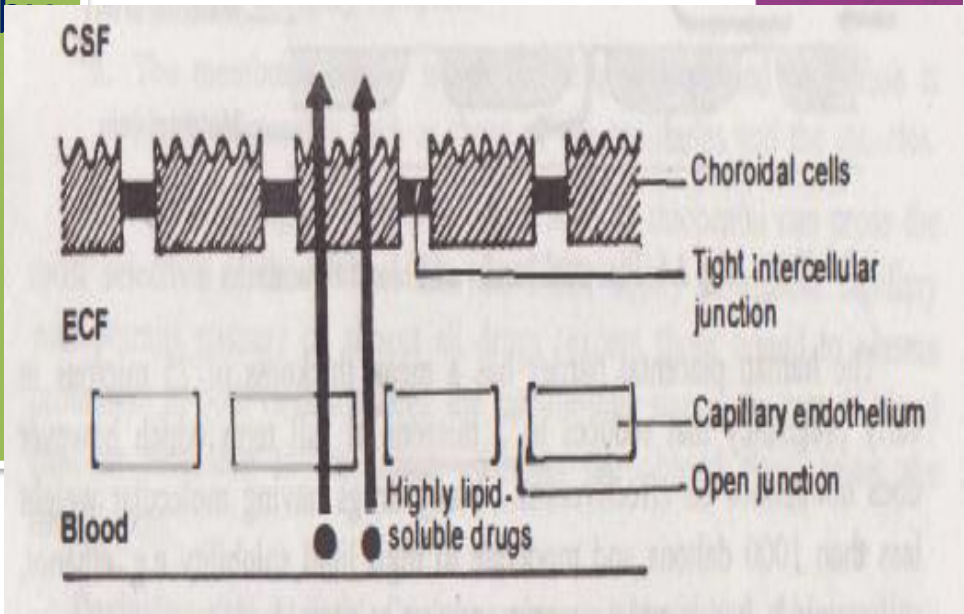
Some key points

- Concept was introduced by Paul Ehrlich .
- Consists of Endothelial cells tightly joined
- Efflux transporters like p-gp ABCC and OATP
- Lipid soluble non-ionised ions easily pass
- Inflammtory condition usually alter permiability
- Non polar compunds easily pass. Ex-ether, choloroform, & thiopentone
- Polar compunds doesn't pass. Ex- dopamine, sertonin, Ach, & Neostigmine.
- loratadine, achieve lower brain concentrations than diphenhydramine
- BBB disruption has emerged as a strategy in the treatment of certain brain tumors such as primary CNS lymphomas.

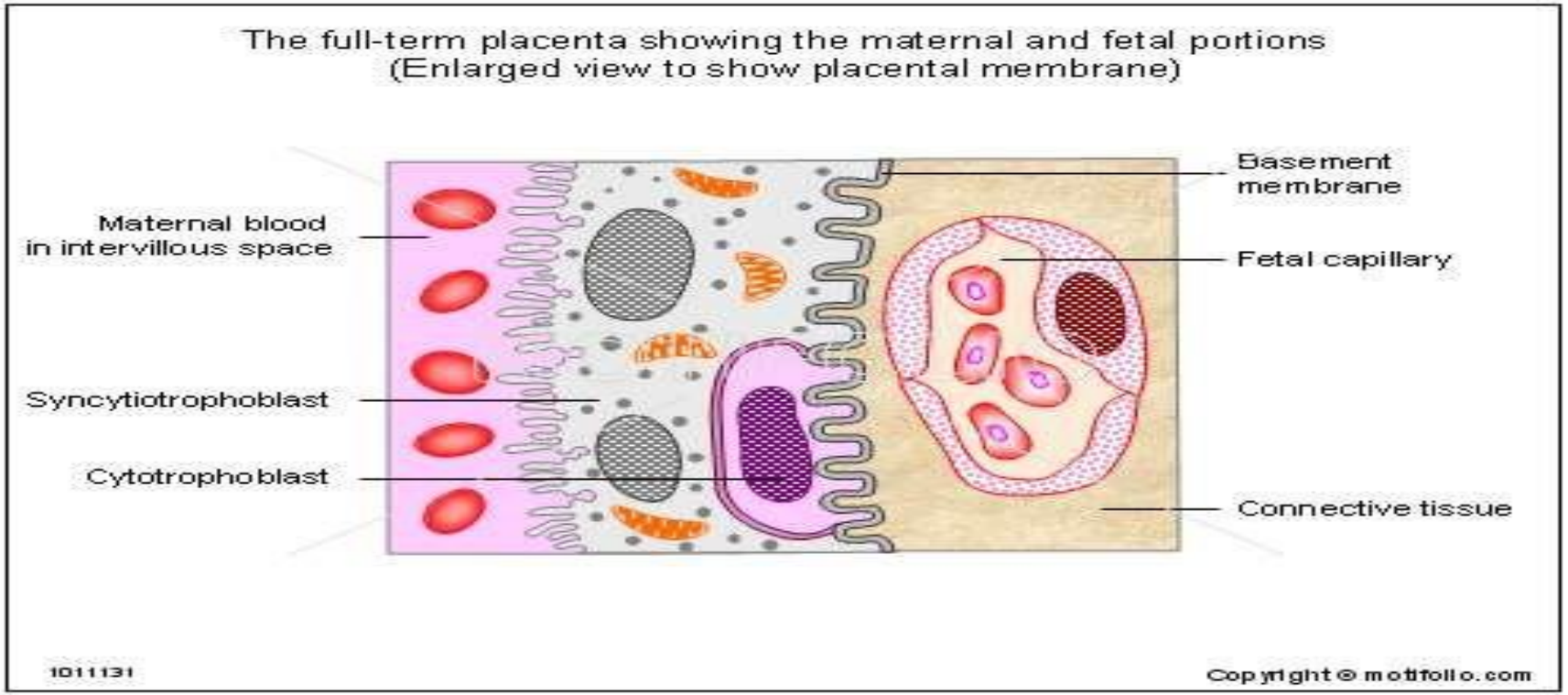
BLOOD CEREBROSPINAL FLUID BARRIER

- **Formed** mainly by the choroid plexus of the lateral, third and fourth ventricles & is similar in composition to the ECF of brain.
- The capillary endothelium that lines the choroid plexus have open junctions or gaps & drugs can flow freely into extracellular space b/w capillary wall and choroidal cells.
- Choroidal cells joined to each other by tight junctions forming blood-CSF barrier.
- Highly lipid soluble drugs can easily cross the blood- CSF Barrier but moderatly soluble & ionize drugs permeate slowly.

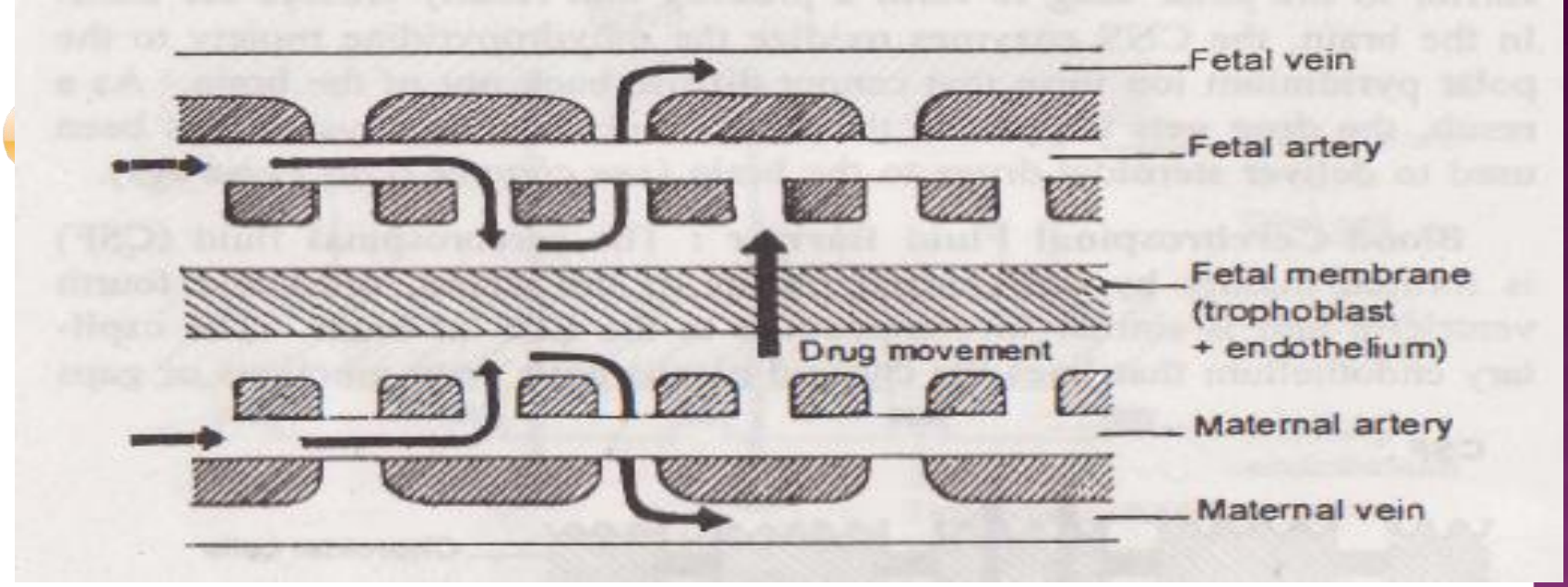




BLOOD - PLACENTAL BARRIER



It’s the barrier b/w maternal & foetal blood vessels both are separated by a no. of tissue layers made of foetal trophoblast basement membrane & endothelium together constitute placental barrier.



- Mean thickness 25µ at early pregnancy later reduce up to 2µ (even its effectiveness remain unchanged).
- M,any drugs having Mol wt <1000 Dalton & moderate to high lipid solubility drugs like (Sulphonamides, Barbiturates, Steroids, Narcotic some Antibiotics) cross the barrier by simple diffusion rapidly.

It means that placental barrier is not effective barrier as BBB.

- Essential Nutrients for fetal growth transported by carrier-mediated processes & Immunoglobulines are transported by endocytosis.

BLOOD TESTIS BARRIER

- This barrier not located at capillary endothelium level but at sertoli - sertoli cell junction. It is the tight junction b/w neighbouring sertoli cells that act as blood-testis barrier . This barrier restrict the passage of drugs to spermatocytes & spermatids.

Thank You