PHARMACOKINETICS

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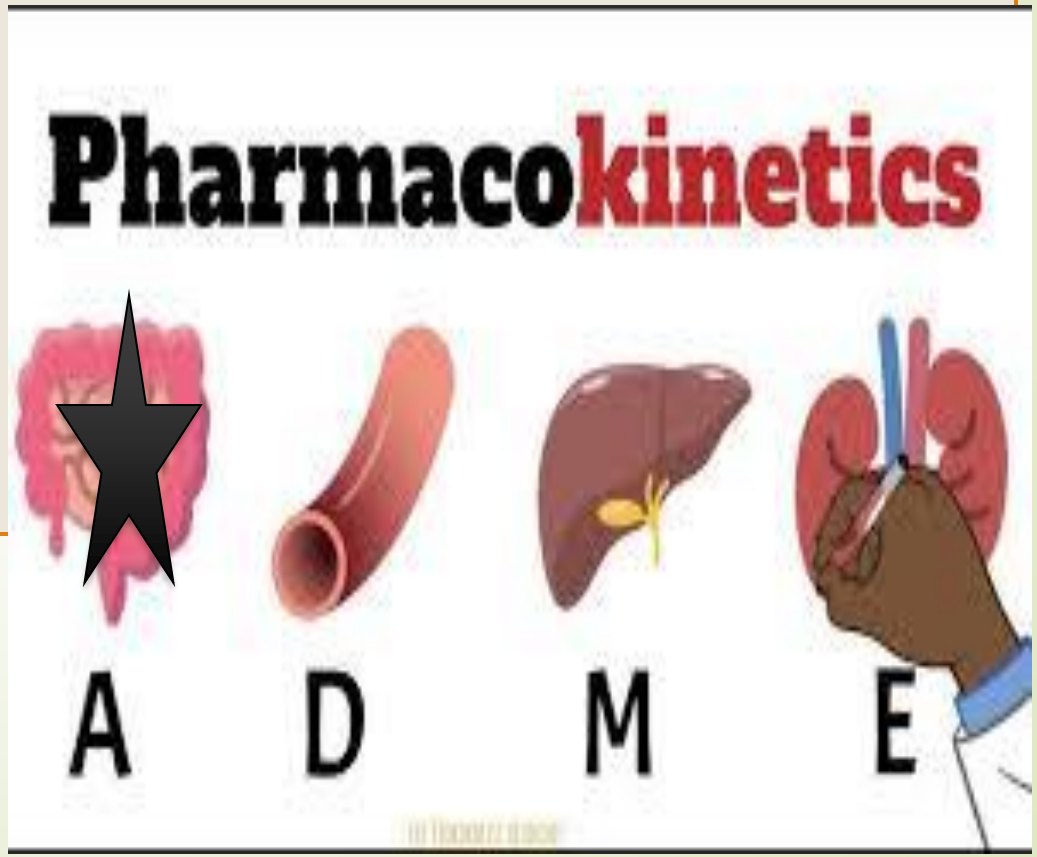
Pharmacokinetics

what the body does to the drug?

- **Absorption**
- Distribution
- Metabolism
- Excretion.



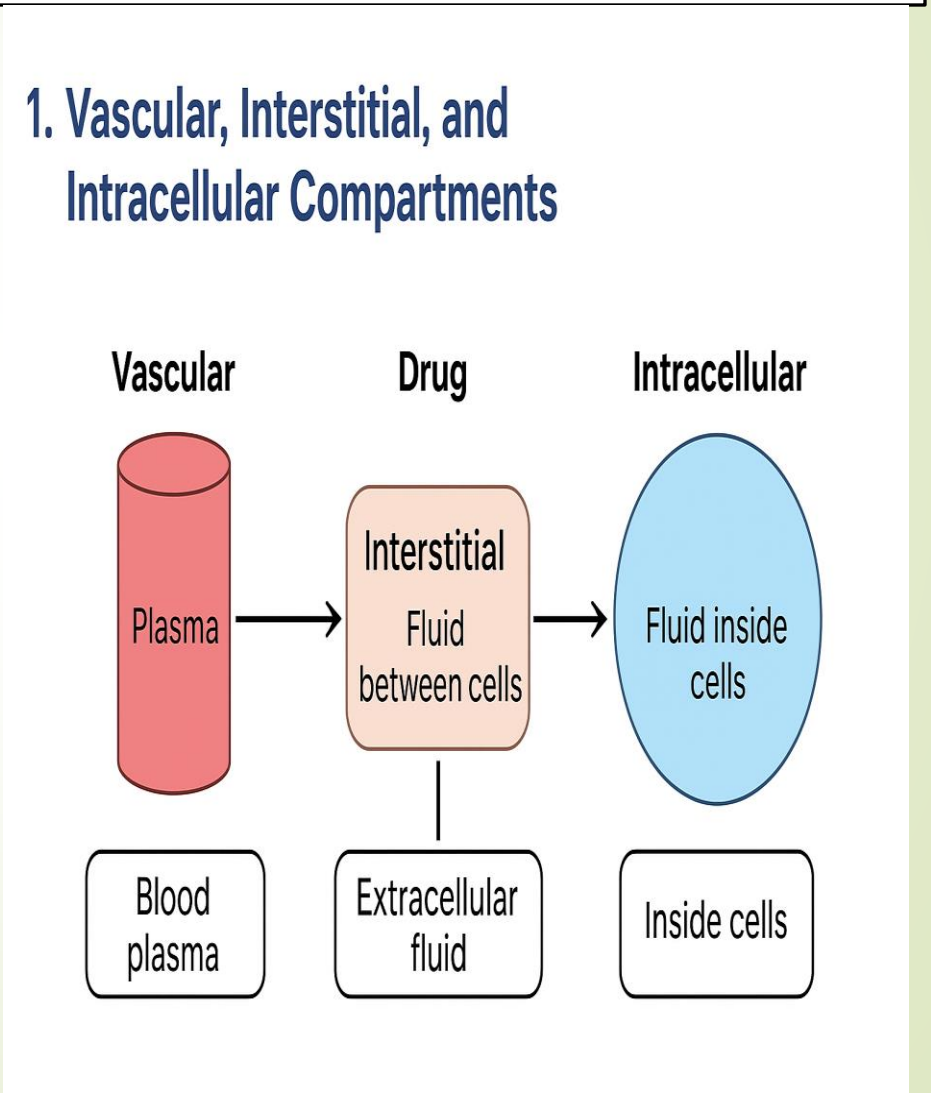
Distribution

Reversible transfer of a drug between the bloodstream (plasma) and tissues/organs after absorption

It involves the distribution of the substance throughout the body compartment

- After absorption, the drug is distributed through **3** body compartments:

1. • **Vascular**
2. • **Vascular & interstitial**
3. • **Vascular, interstitial and intracellular**



1. Vascular compartment:

Small volume of distribution

(4 Litres in 70 kg person)

- Drugs distributed in this compartment are **hydrophilic**, and most drugs are **ionized** at the plasma pH (e.g. Heparin).

2. Vascular and Interstitial compartments:

- Moderate volume of distribution (14 Litres in a 70 kg person)
- Drugs distributed in these compartments are hydrophilic, with small molecular weight and a lesser degree of ionization at plasma pH (e.g., neostigmine, aminoglycosides).

3. Vascular, interstitial and intracellular compartments:

- Large volume of distribution (40-42 litres in 70 kg person)
- Drugs distributed in these compartments are non-Ionized and lipophilic .e.g. barbiturates

Feature	Vascular	Interstitial	Intracellular
Location	Inside blood vessels (plasma)	Between tissue cells	Inside body cells
Contains	Blood plasma + plasma proteins	Tissue fluid (no plasma proteins)	Cytoplasm & cell contents
Volume (adult)	~4–5 L	~10–14 L	>25–30 L
Drug type	Large, polar, or protein-bound	Hydrophilic (water-soluble)	Lipophilic (fat-soluble)
Examples	Heparin, Warfarin	Aminoglycosides, β-lactams	Ethanol, Corticosteroids
Membrane barrier	Capillary wall	Cell membrane	None (drug already inside cell)
Movement	Limited by size and protein binding	Diffuses freely to cells	Crosses lipid membranes
Volume of Distribution (Vd)	Smallest	Moderate	Largest

Blood –brain barrier (BBB):

Special barriers

Brain capillary endothelium with tight inter-cellular pores & adjacent glial tissues).

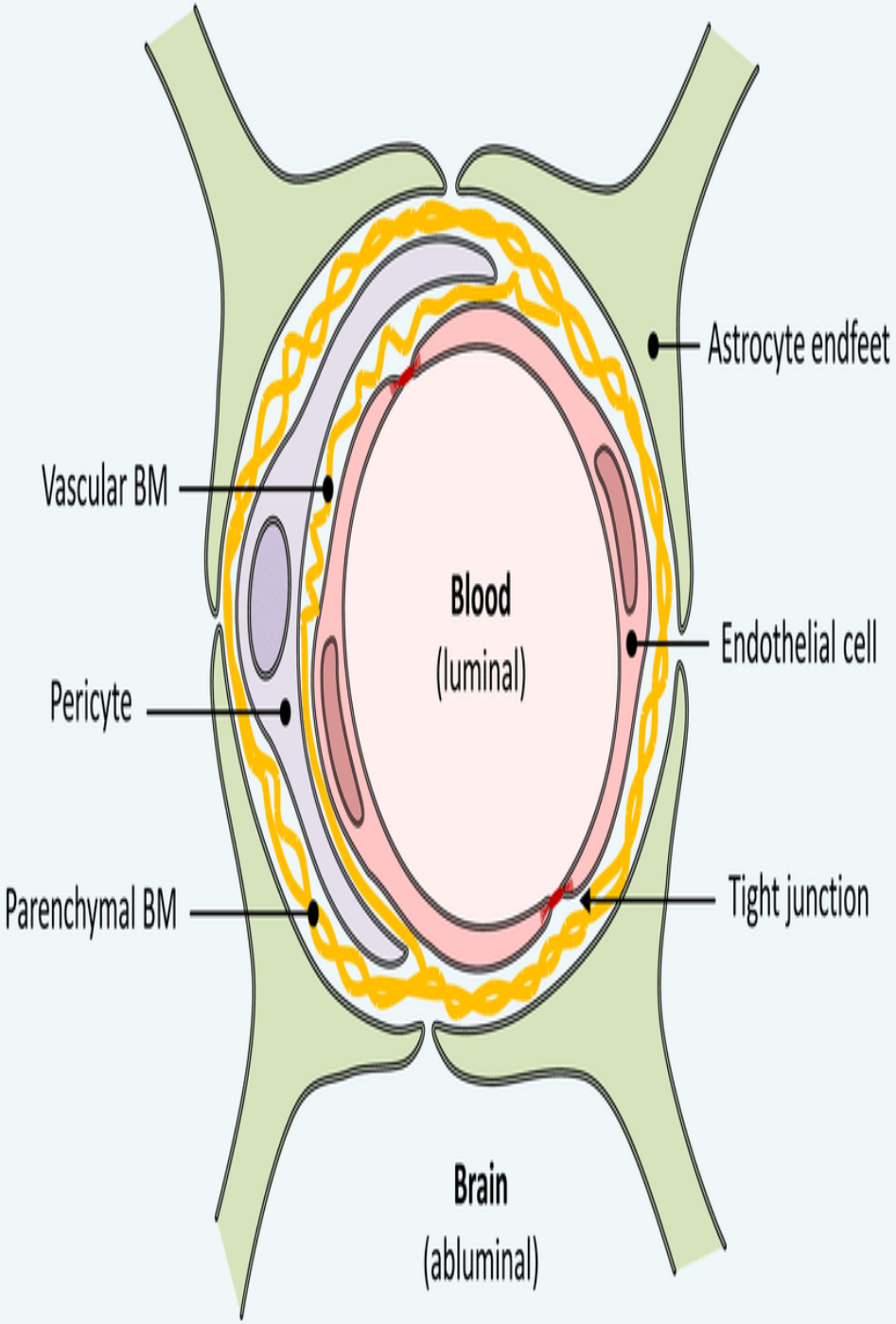
- Only lipid-soluble & non-ionized drugs can pass blood-brain barrier.
- Inflammation (meningitis) increases permeability of BBB (The concentration of penicillins & cephalosporins in the CSF of normal subjects is 0.5 -1 % of plasma level, this could increase up to 5% in case of meningitis).

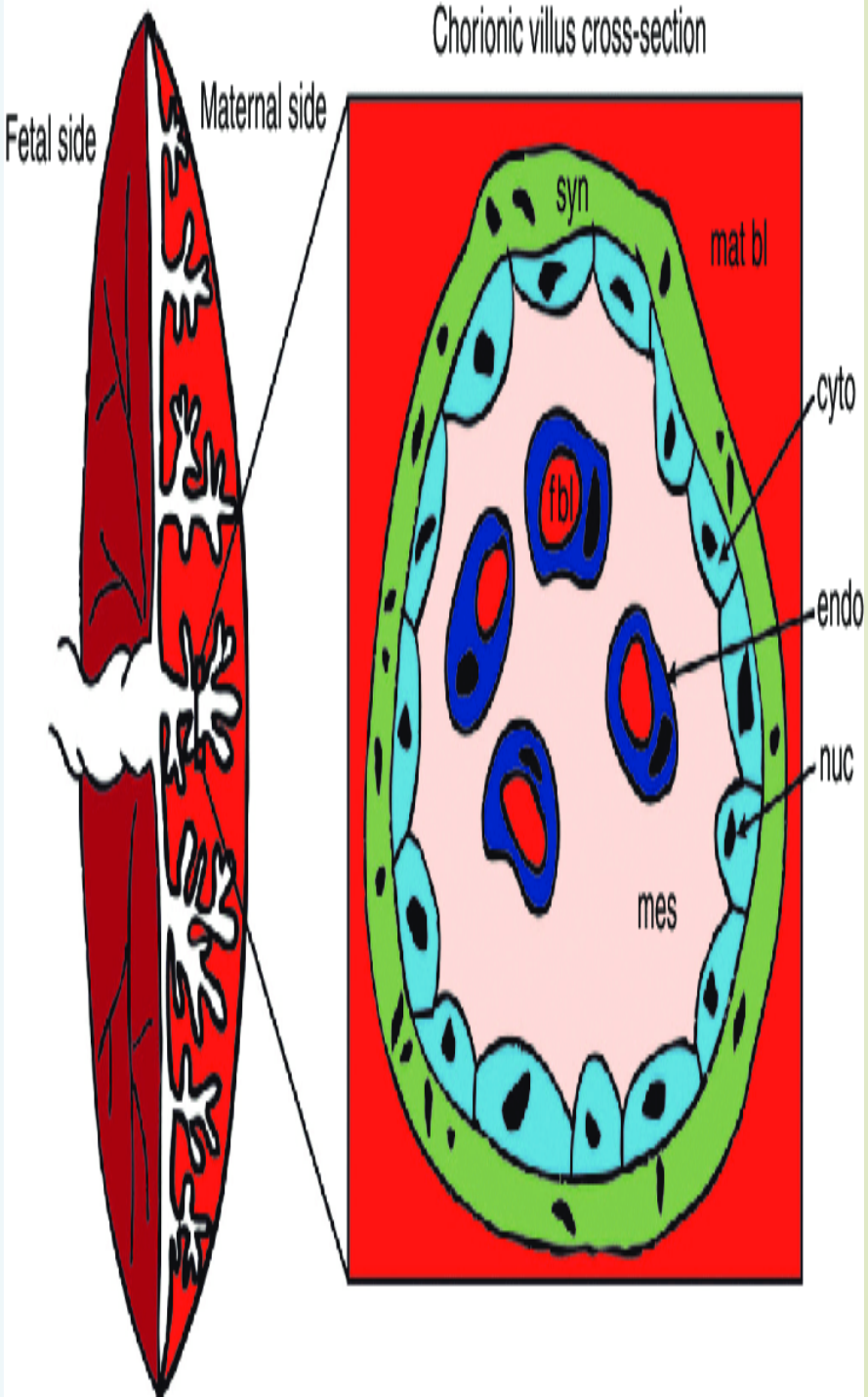
Placental barrier:

Special barriers

Drugs that pass placental barrier may cause:

- *During pregnancy* : Teratogenicity, embryotoxicity
- *During labor:* Neonatal asphyxia ,neonatal jaundice (Kernicterus)


Astrocyte endfeet
Vascular BM
Blood
(luminal)
Endothelial cell
Pericyte
Parenchymal BM
Tight junction
Brain
(abluminal)


Chorionic villus cross-section
Fetal side
Maternal side
syn
mat bl
cyto
tbl
endo
nuc
mes

Redistribution:

- Occurs with highly lipid-soluble drugs as thiopental. After initial distribution to the CNS, thiopental redistributes to less perfused tissues, e.g., skeletal muscle and fat, ending its action.
- It helps **terminate the drug's effect** even while some of the drug remains in the body.
- After IV administration, the drug rapidly reaches highly perfused organs (brain, heart, liver, and kidneys). Drug concentration in plasma then drops as it diffuses into less perfused tissues (muscle, fat). The drug leaves the CNS or other target sites and redistributes to these tissues. The clinical effect ends even though the total body drug amount hasn't decreased much (metabolism/elimination not complete).

movement of a drug from its initial site of action (usually highly perfused organs like the brain) to other tissues (like muscle or fat) **after plasma concentration falls**

Drug	Initial site of action	Redistribution site	Effect
Thiopental (barbiturate)	Brain (anesthesia)	Muscle, fat	Rapid recovery after short anesthesia
Diazepam	CNS	Fat, muscle	Sedation wears off despite presence in body
Propofol	Brain	Fat	Short duration of action

VOLUME OF DISTRIBUTION *(Vd)*

It is a theoretical expression, relates the entire amount of the drug in the body to its concentration in plasma.

$$V_d = \frac{\text{Amount of the drug in the body}}{\text{Plasma concentration}}$$

Importance of *Vd*:

Calculation of the loading dose of a drug

Calculation of the **corrective dose of a drug**

Treatment of drug toxicity

- **Calculation of the loading dose of a drug:**

  LD =target plasma concentration (Tc) x Vd.

- Calculation of the **corrective dose of a drug**

(desired plasma Css –achieved plasma level) X Vd

2. **Treatment of drug toxicity:**

- Hemodialysis is **not** useful for drugs with **high Vd** (most of the drug is in the tissues).
- Hemodialysis is useful for drugs with **low Vd** (most of the drug is in the blood).
- Peritoneal dialysis is useful for drugs with moderate Vd

Factors affecting drug distribution.

1. **Lipophilicity (Diffusion):** The ability of the drug to diffuse across cell membranes depends **on its lipophilicity.**

2. **Binding to tissue constituents (Tissue affinity):**

It is due to the affinity of drugs to some cellular constituent.

- Chloroquine is concentrated in the liver
- Iodides are concentrated in the thyroid.

3- Plasma protein binding (PPB):

Drug in blood exists in **two forms:**

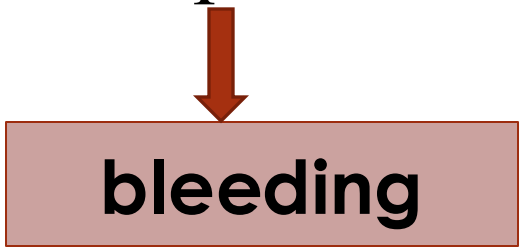
- **PP bound form:** inactive, non diffusible and cannot be metabolized or excreted.
- **Free Form:** active, diffusible and can be metabolized or excreted.

N.B The two forms exist in **equilibrium**, when fraction of the free form is metabolized or excreted similar fraction is released from plasma protein binding sites.

Characteristics of drug with high PP binding:

- PP bound fraction cannot be eliminated and acts as **reservoir**.
- Because the plasma protein binding sites are limited, drugs can displace each other clinically significant interactions.

- Displacement from PP is clinically important when the drug has high PPB capacity & small Vd (most of the drug is present in the circulation). So, minimal displacement → large increase in the free part → toxicity.
- Example: aspirin displaces warfarin (PPB: 99%)




TO BE
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