Charting New Horizons in Education

Pharmacokinetics II

04

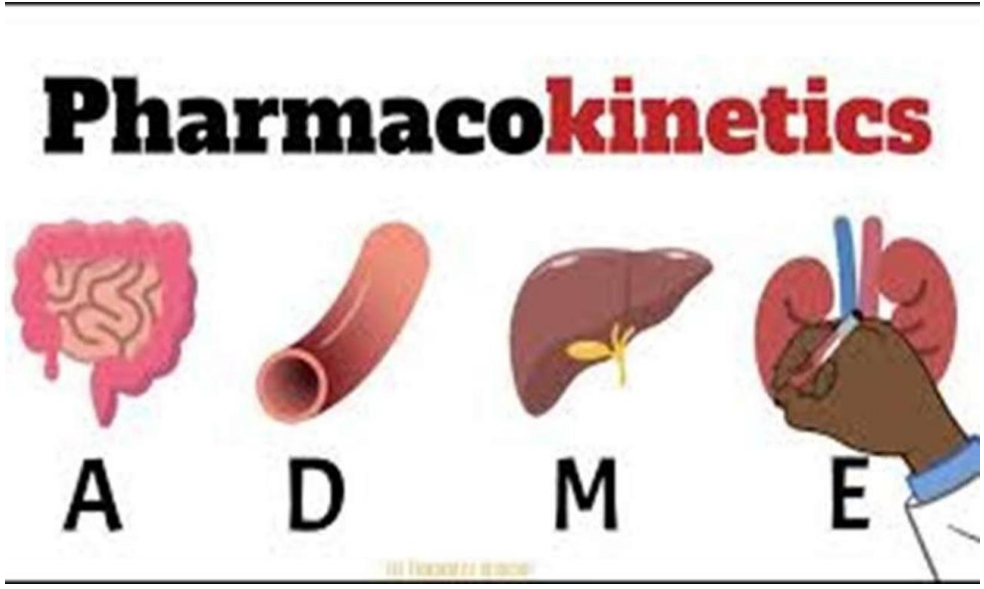
pharmacology

Created by : Dr Maya Mashal

Pharmacokinetics

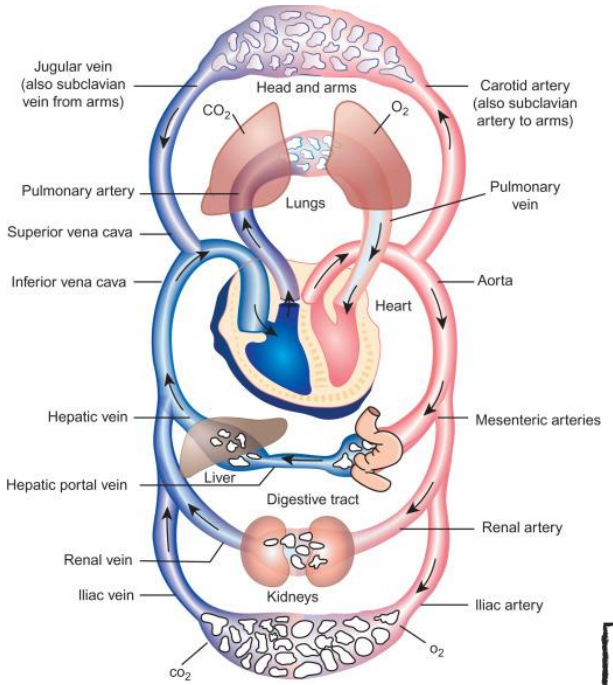
what the body does to the drug?

- Absorption
- Distribution
- Metabolism
- Excretion.



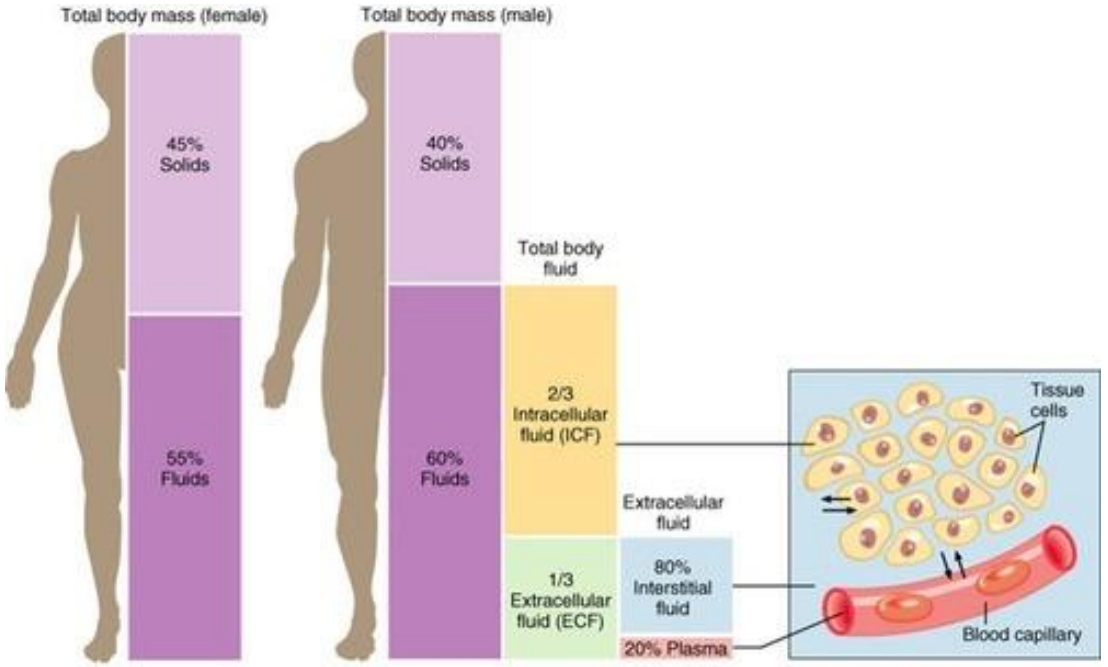
Distribution

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, with high molecular weight (e.g. Heparin)

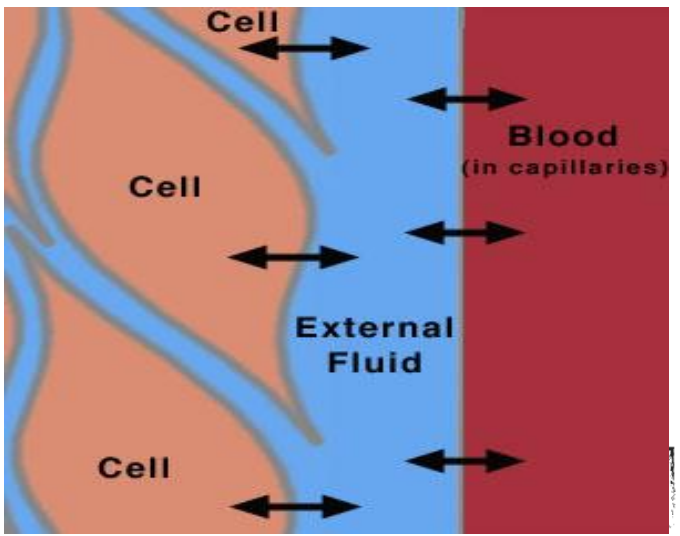
2. Vascular and Interstitial compartments:

Moderate volume of distribution (14 Liters in 70kg person)

Drugs distributed in these compartments are hydrophilic ,

with small molecular weight and lesser degree of ionization at

plasma pH(e.g.neostigmine)

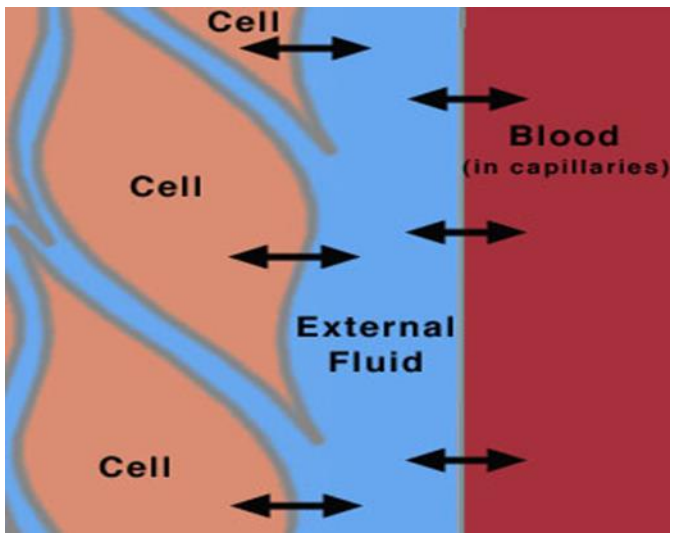


3. Vascular, interstitial and intracellular compartments:

Large volume of distribution (40-42 litres in70 kg person)

Drugs distributed in these compartments are non-Ionized and lipophilic .e.g.

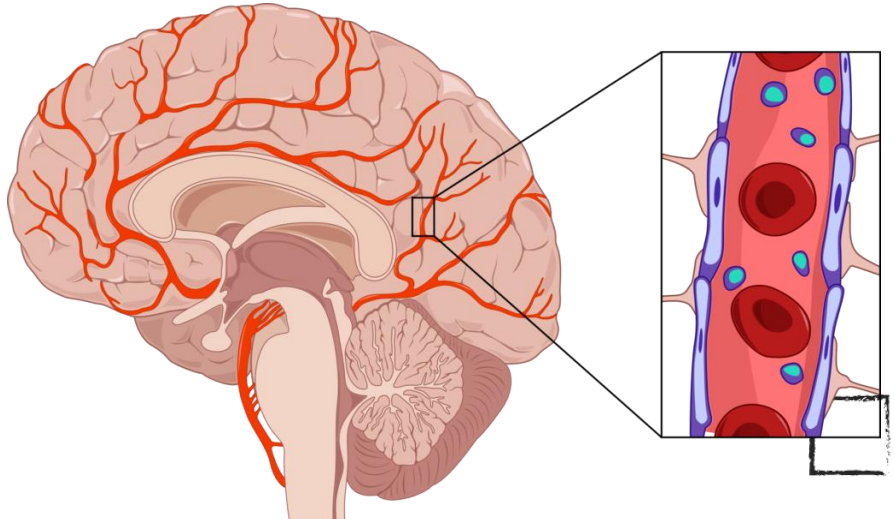
(barbiturates)



Special barriers:

Blood –brain barrier (BBB):

- 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 theCSF of normal subjects is 0.5 -1 % of plasma level, this could increase up to 5% in case of meningitis)

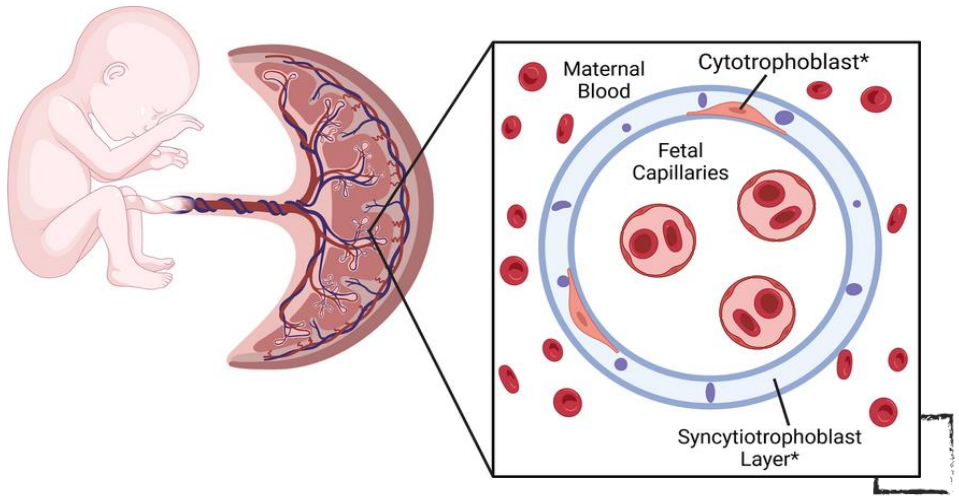


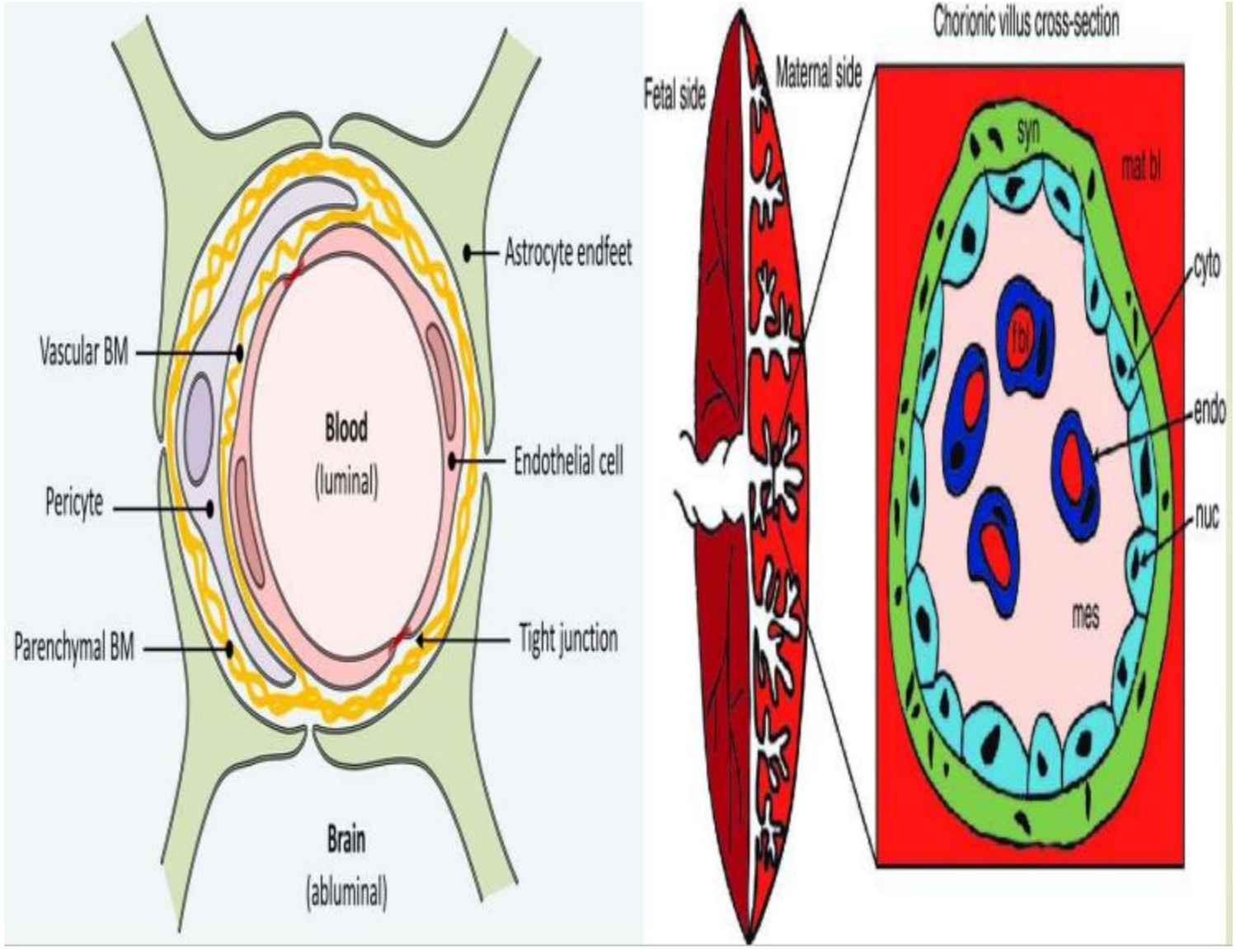
Special barriers:

Placental barrier:

Drugs that pass placental barrier may cause:

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

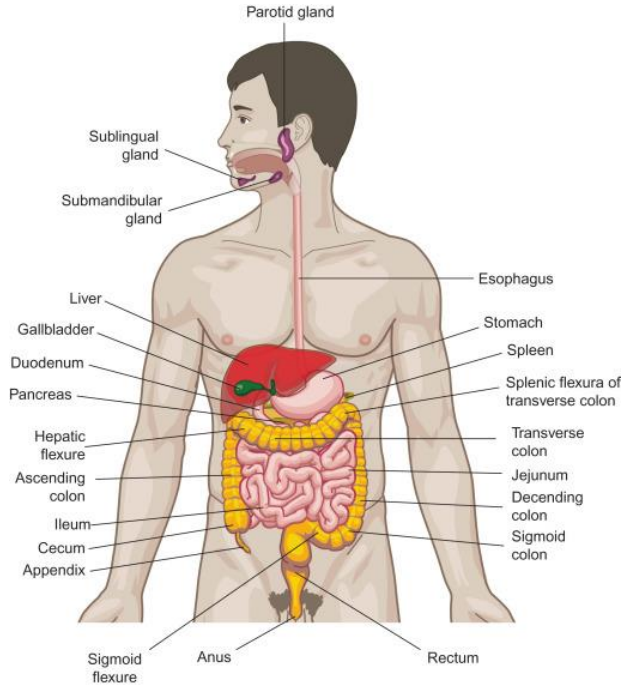



Astrocyte endfeet
Vascular BM
Blood
(luminal)
Endothelial cell
Pericyte
Parenchymal BM
Tight junction
Brain
(abluminal)
Chorionic villus cross-section
Fetal side
Maternal side
syn
mat bl
cyto
fbl
endo
nuc
mes

Redistribution:

Occurs with highly lipid-soluble drugs as thiopental.

After initial distribution to CNS, thiopental redistributes to less perfused tissues e.g. skeletal muscle and fat, ending its action



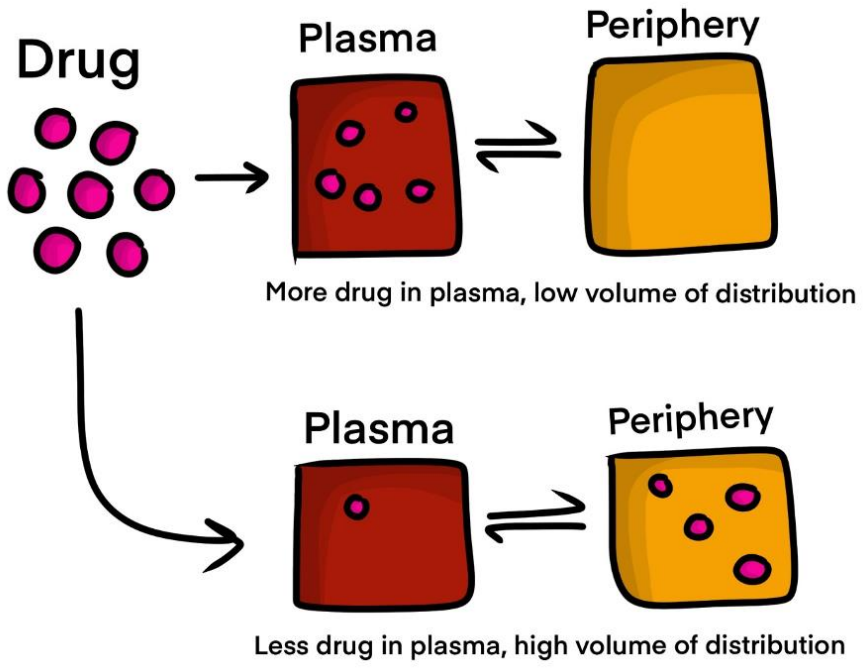
VOLUME OF DISTRIBUTION (Vd):

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:

1. Calculation of the loading dose of a drug
2. Calculation of the corrective dose of a Drug
3. Treatment of drug toxicity



Importance of Vd:

1. Calculation of the loading dose of a drug:

Loading dose= target plasma concentration (Tc) x Vd2.

2. Calculation of the corrective dose of a drug

desired plasma Css–achieved plasma level) X (Vd)

Importance of Vd:

3. Treatment of drug toxicity::

- Hemodialysis is not useful for drugs with high Vd

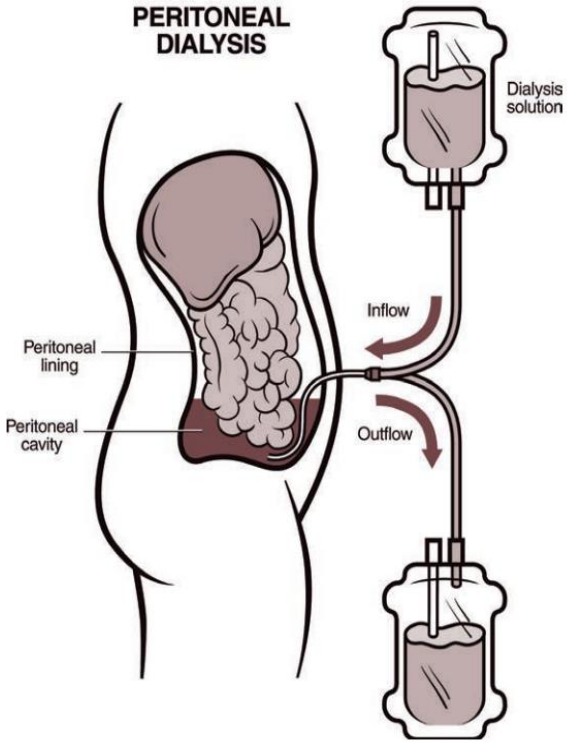
(most of the drug is in the tissues).

- 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 affinity of drugs to some cellular constituent.

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

Factors affecting drug distribution.

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 lead to large increase in the free part so it cause toxicity.

Example: aspirin displaces warfarin (PPB: 99%)

«Education is the passport to the future, for tomorrow belongs to those who prepare for it today»

- Maclom X-

Charting New Horizons in Education