Pharmacokinetics II: Bioavailability and Distribution

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By the end of the lectures, students should be able to define the following:

- **Major body fluid compartments**
- **Concept of compartments.**
- **Apparent volume of distribution (vd).**
- **Plasma protein binding.**
- **Tissue binding.**

Bioavailability

- Is the amount of <u>unchanged</u> drug that enters systemic circulation after administration and becomes available to produce pharmacological actions (rate and extent of active reaching systemic circulation)

- **Bioavailability (F) = $\dfrac{\text{AUC (oral)}}{\text{AUC (I.V.)}}$ X 100**
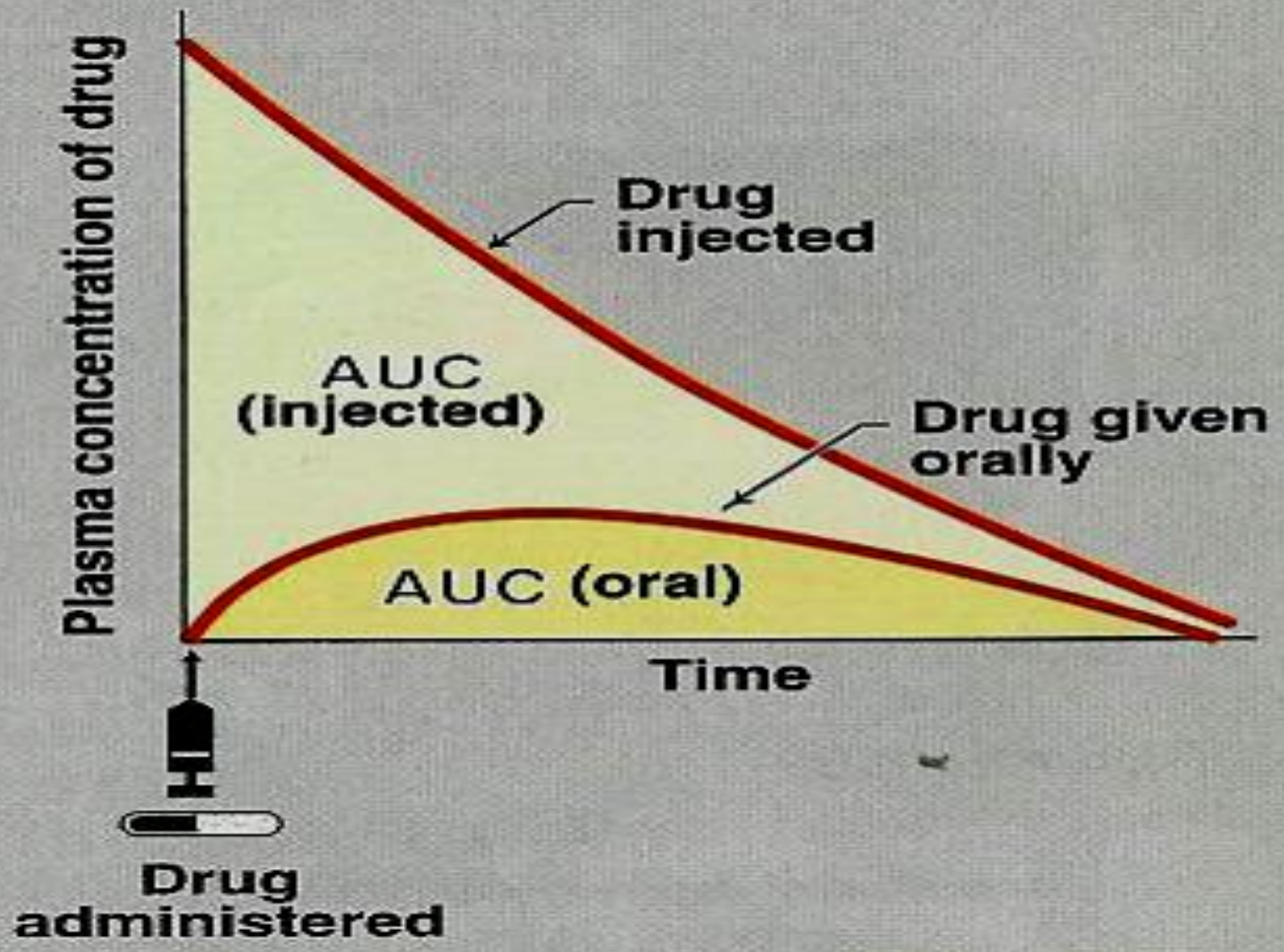
Bioavailability

- **I.V. provides 100% bioavailability i.e. F= 1.**

- Subcutaneous, intramuscular, oral, rectal, and other extra vascular routes of administration require that the drug be absorbed first, which can reduce bioavailability.

Absolute bioavailability

▸ The bioavailability of a drug after administration by any route is compared to its intravenous standard formulation.

Relative bioavailability

▸ is determined when two products are compared to each other, not to an intravenous standard.

▸ This is commonly calculated in the drug industry to determine that the generic formulation is bioequivalent to another formulation.

▸ e.g Tylenol (paracetamol 500 mg) compared to panadol (paracetamol 500 mg).

Relative bioavailability

- is important to get an idea of how **different formulations** or **routes of administration** differ in their bioavailability.

- dosage adjustment is required when changing formulations or routes of administration.

Bioequivalence

▸ Two pharmaceutically products are **bioequivalent** when the rate and extent of bioavailability of active ingredients in two products are the same.
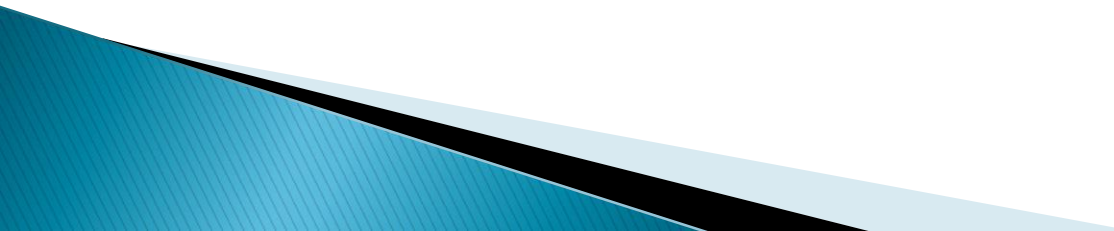
Factors affecting bioavailability:

- are the same factors controlling drug absorption

- First pass effect

Distribution

Distribution

Is the process by which drugs leave blood circulation and enters the interstitium and/or the cells of the tissues.
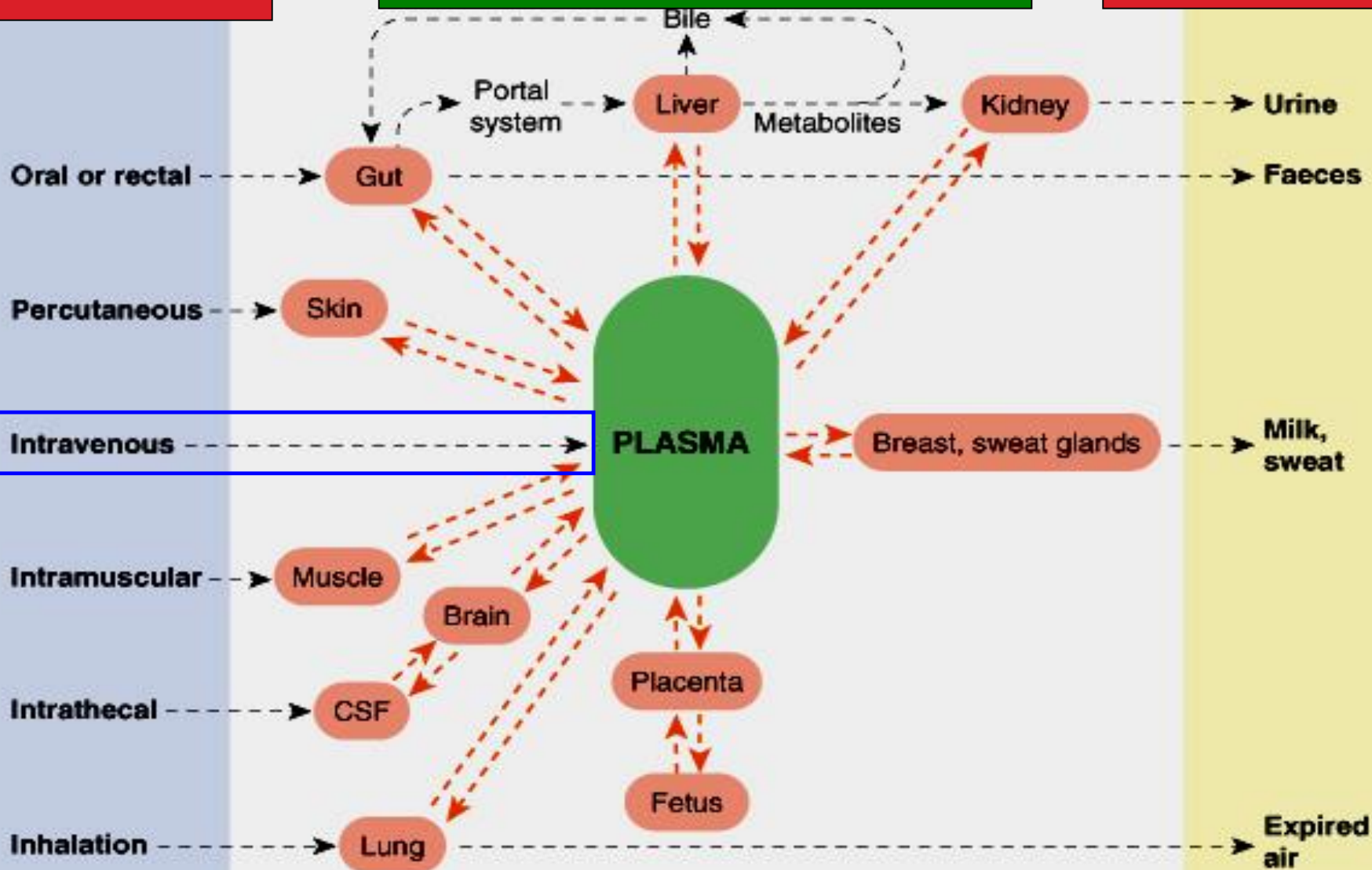
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Apparent Volume of Distribution (Vd)

is the ratio of drug amount in the body (dose) to the concentration of drug in blood.

$$Vd \, (L) = \frac{Dose \, (mg)}{plasma \, concentration \, (mg/L)}$$

Why is Vd important?

➢ To calculate loading dose

➢ Large Vd = means **long duration of action**
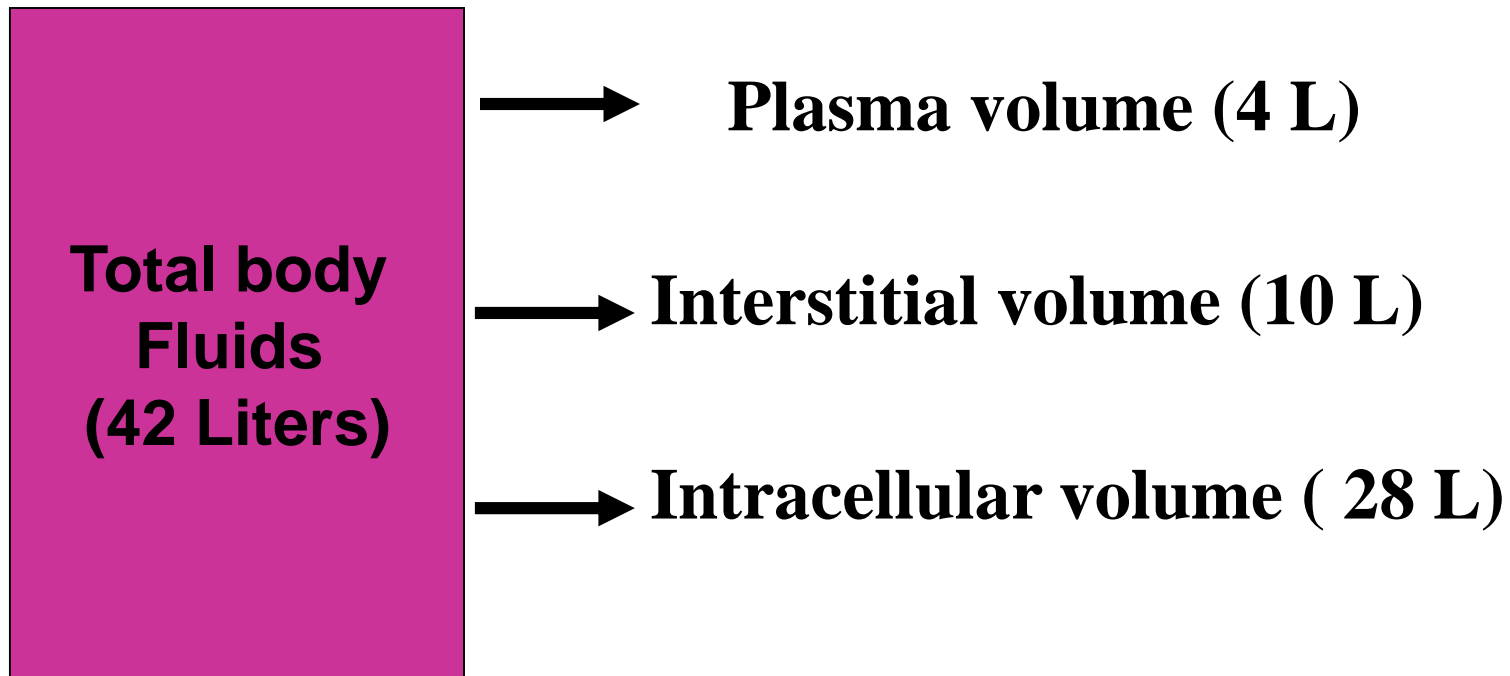
The major body fluid compartments are

Extracellular fluid (21%)
- Plasma (5 % of body weight = 4 liters).
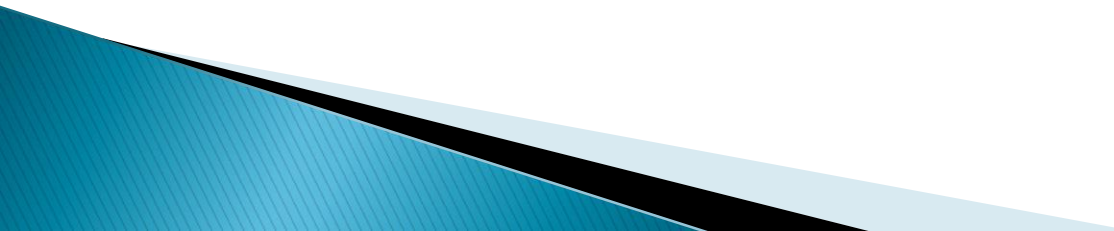- Interstitial fluid (16 % = 10 liters).

Intracellular fluid (35 %)
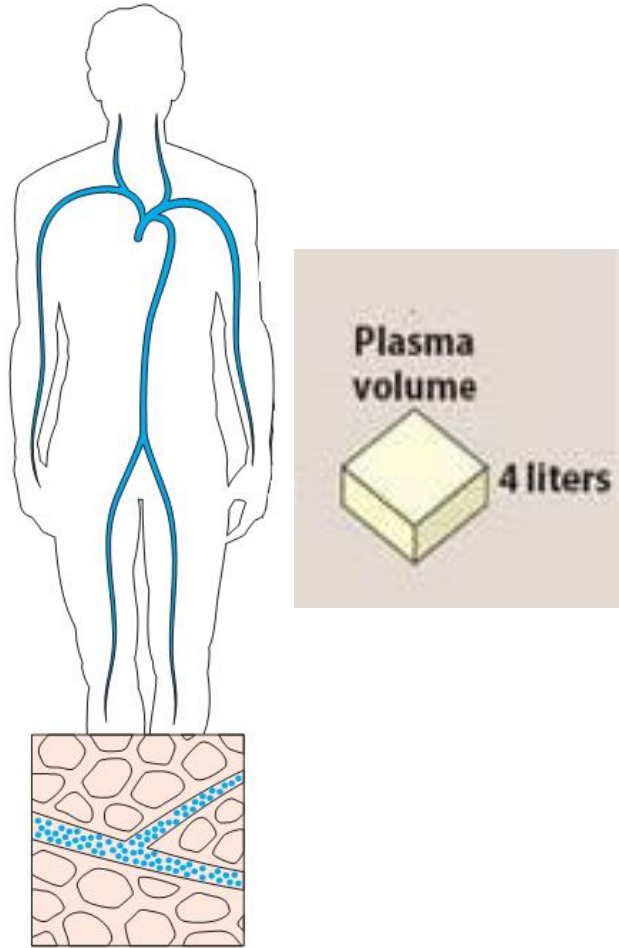fluid present inside all cells in the body (28 L).

Total body fluids
(70% of body weight in 70−kg individual)

Total body Fluids (42 Liters)

→ **Plasma volume (4 L)**

→ **Interstitial volume (10 L)**

→ **Intracellular volume (28 L)**

Drugs may distribute through:

- One compartment
- Two compartments
- Multi-compartments

Plasma compartment

Plasma volume
4 liters

- Vd: around 4 L.

- Very high molecular weight drugs, or drugs that bind to plasma proteins

- Can not moves across endotelial cells of capillaries

- Drugs are trapped in blood

- Example: heparin 4L

Extracellular fluid

Interstitial volume

Plasma volume

10 liters

4 liters
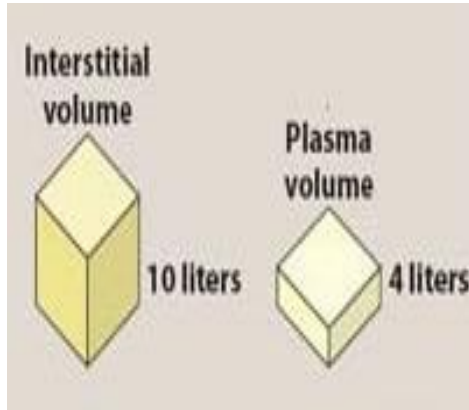
▸ Distribute through extracellular fluids.

▸ Pass endothelium into interstitial fluids BUT can not cross cell membranes to intracellular fluids.

▸ Drugs that have a low molecular weight but are hydrophilic.

▸ Vd: between 4 and 14 L.

  ➢ E.g. atracuronium 11 L

Total body water (extracellular and intracellular)

- Diffusion to intracelullar fluid

- For lipid soluble drugs

- Vd equal to total body water.

  ◦ Ethanol 38 L

  ◦ Drug that binds strongly to tissues. Vd higher than total body water.

  ◦ Digoxin:385 L
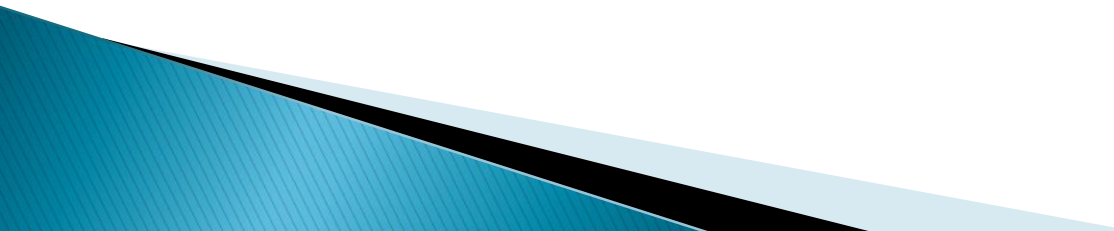
Volume of Distribution (Vd)

Drugs with low Vd

- **distributed in extracellular compartments (plasma & interstitial fluid).**

- **Polar comp or lipid insoluble drugs. e.g. gentamycin, atracurium**

- **High MW e.g. heparin – insulin.**

- **High plasma protein binding e.g. warfarin (anticoagulant).**

- **Do not cross BBB or placental barriers.**

Drugs with high Vd

- Have higher concentrations in tissues than in plasma.
- Lipid soluble.
- Distributed intracellularly
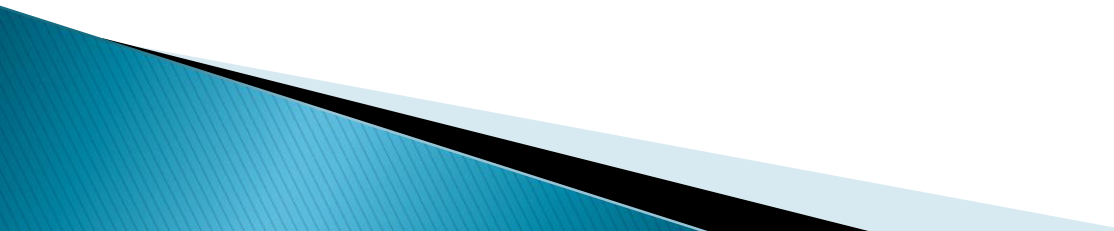- e.g. digoxin, phenytion, morphine

FACTORS AFFECTING DISTRIBUTION

1.Cardiac output and blood flow.

2. **Physical and chemical properties of the drug**.

   ◦ Molecular weight

   ◦ Pka.

   ◦ Lipid solubility.

3. Capillary Permeability

4. Plasma protein binding

5. Tissue binding.

Blood flow to organs

- The greater the blood flow to tissues, the more distribution that occurs from plasma to interstitial fluids.

- Drugs distribute more rapidly to brain, liver and kidney > more than skeletal muscles & fat.

Physical and chemical properties of drug

- Most lipid soluble drugs (unionized, uncharged, nonpolar) cross biological membranes

- Hydrophilic drugs (ionized, charged, polar) do not readily cross membranes but go through slit junctions in endothelial cells of capillaries.

Capillary permeability

- Endothelial cells of capillaries in tissues other than brain have wide slit junctions allowing easy movement, permeation and distribution.

- Brain has tight junction Blood Brain Barrier (BBB).

Blood brain barrier (BBB):

▶ Only lipid soluble drugs or actively transported drugs can cross BBB.

▶ Hydrophilic drugs (ionized or polar drugs) can not cross BBB.

▶ Inflammation as in **<u>meningitis</u>** increase permeability to hydrophilic drugs
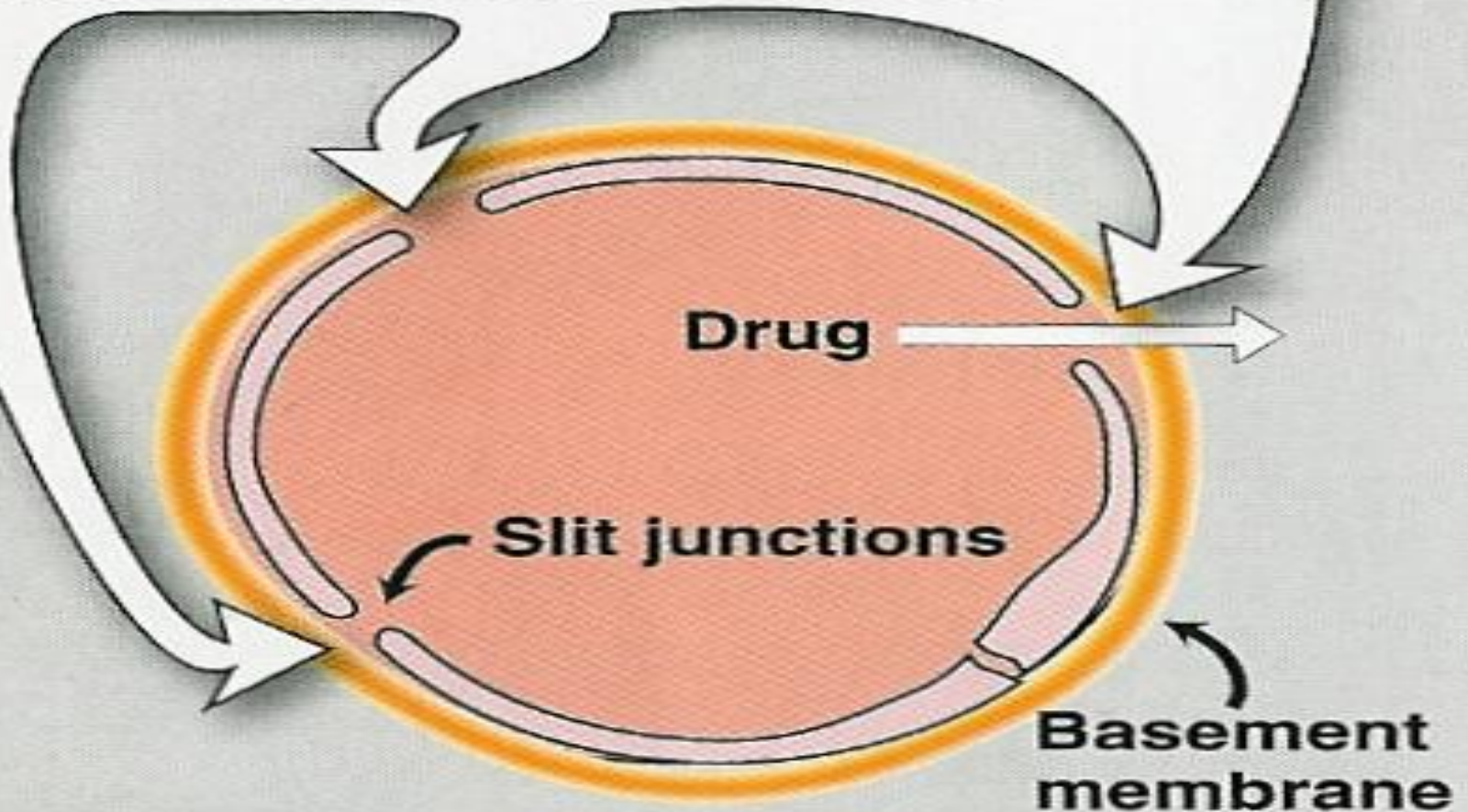
▶ e.g. penicillin & gentamycin

Placental barrier

▶ Lipid soluble drugs can cross placental barrier and enter the fetal blood.
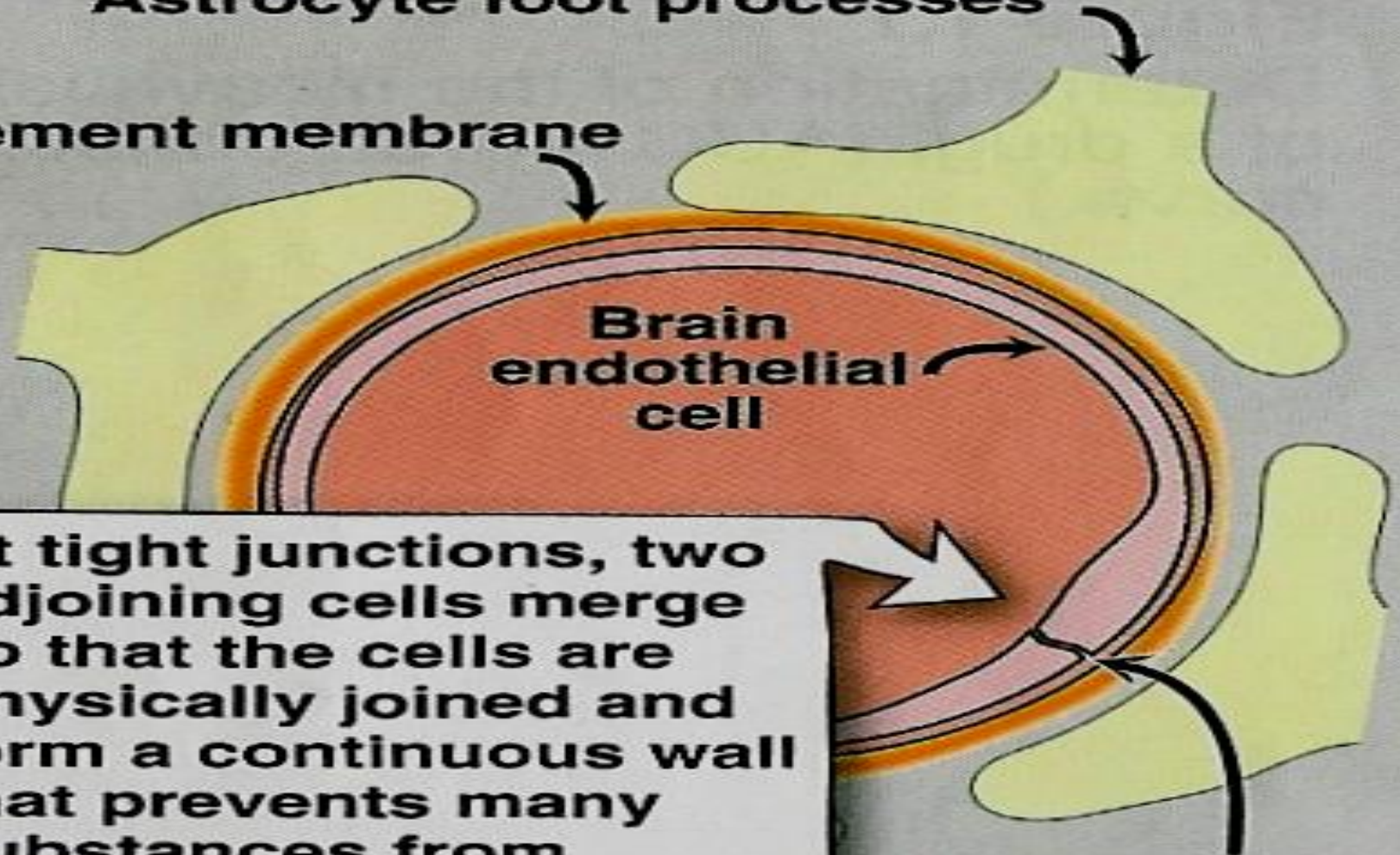
B Structure of a brain capillary

Astrocyte foot processes

Basement membrane
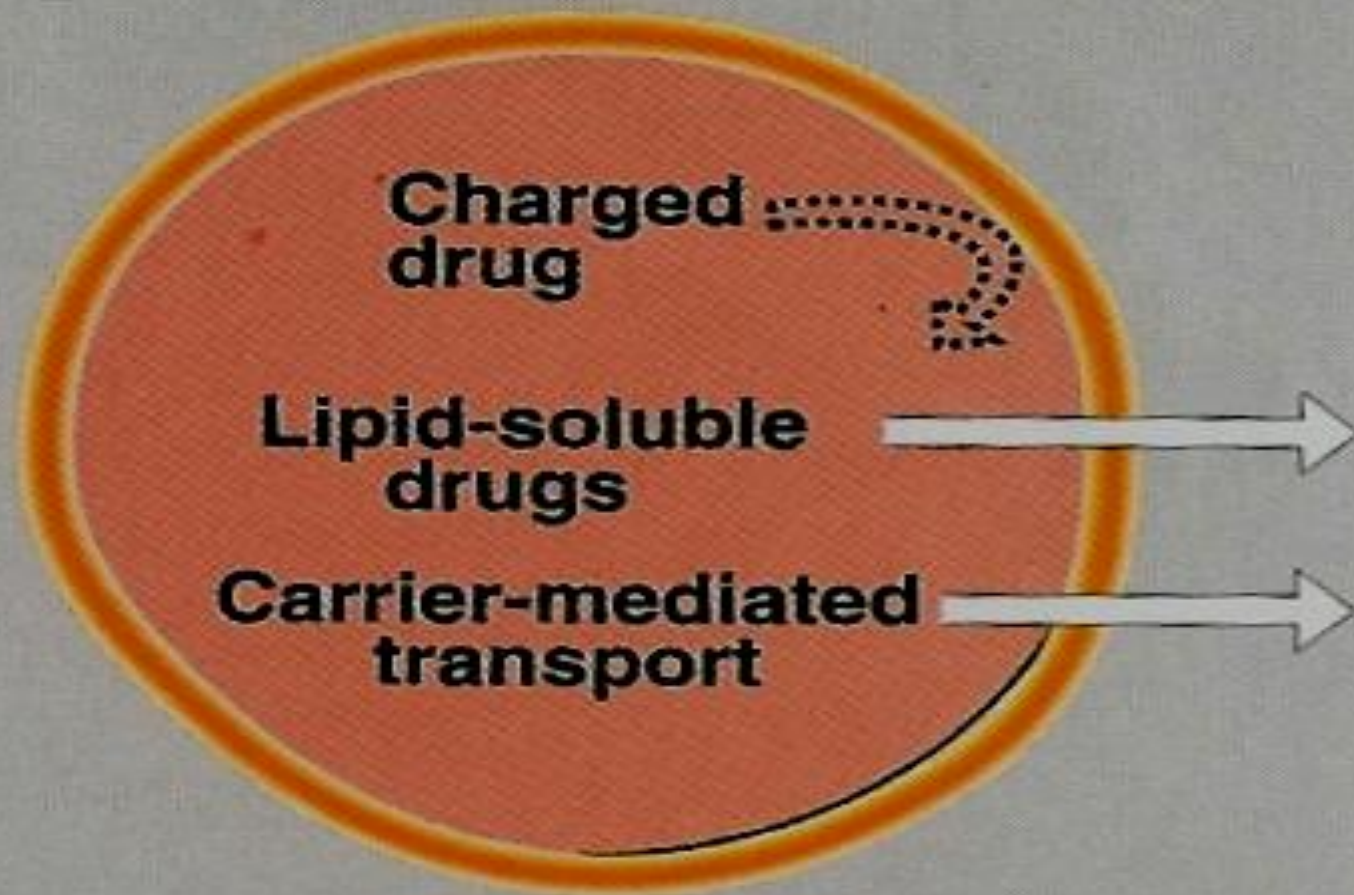
Brain endothelial cell

At tight junctions, two adjoining cells merge so that the cells are physically joined and form a continuous wall that prevents many substances from entering the brain.

Tight junction

C Permeability of a brain capillary

Charged drug

Lipid-soluble drugs

Carrier-mediated transport

Binding of Drugs

- Plasma proteins binding.

- Tissue proteins binding.

Plasma protein binding:

◦ Extensive plasma protein binding will cause more drug to stay in the blood compartment .

◦ Therefore, drugs which bind strongly to plasma protein tend to have lower distribution (Vd).

Plasma Proteins

Albumin

Has affinity for **acidic drugs** as warfarin, phenytoin, aspirin

alpha 1 -acid glycoproteins

Has affinity for **basic drugs** (cationic) as diazepam, quinidine.

Plasma protein binding

▸ drugs which bind strongly to plasma protein tend to have lower distribution (Vd).

▸ In blood, drugs exist in two forms bound and unbound forms in equilibrium

Unbound drug (free) ⇌ **bound drug**

Tissues Binding

Drugs can bind to specific tissues and will have high volume of distribution (Vd)
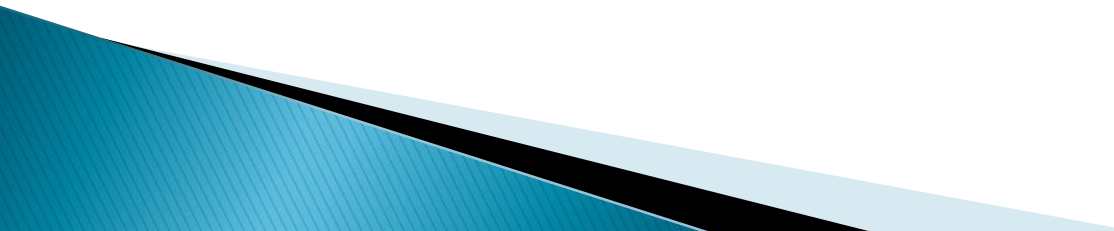
Tetracycline bind to bone

Bound form of drug

- non diffusible form
- can not cross endothelial barrier
- can not combine with receptors
- inactive

- not available for metabolism & excretion

- has long duration of action (t ½).

Unbound form of drug

- diffusible form
- cross endothelial barrier
- combine with receptors

- active

- available for metabolism & excretion

- has short duration of action (t ½).

Characters & consequences of Binding

- Usually reversible.

- determines volume of distribution (vd)

- Slows drug metabolism & excretion.

- Prolongs duration of drug action (t1/2).

- Result in clinically important drug interactions

Displacement

▸ Competition for the same binding site on the plasma proteins may occur between two drugs ⟶ displacement of one drug & increasing its concentrations & effects.

▸ Aspirin + Albumin–warfarin ⟶

Albumin–aspirin + free warfarin ⟶ bleeding.