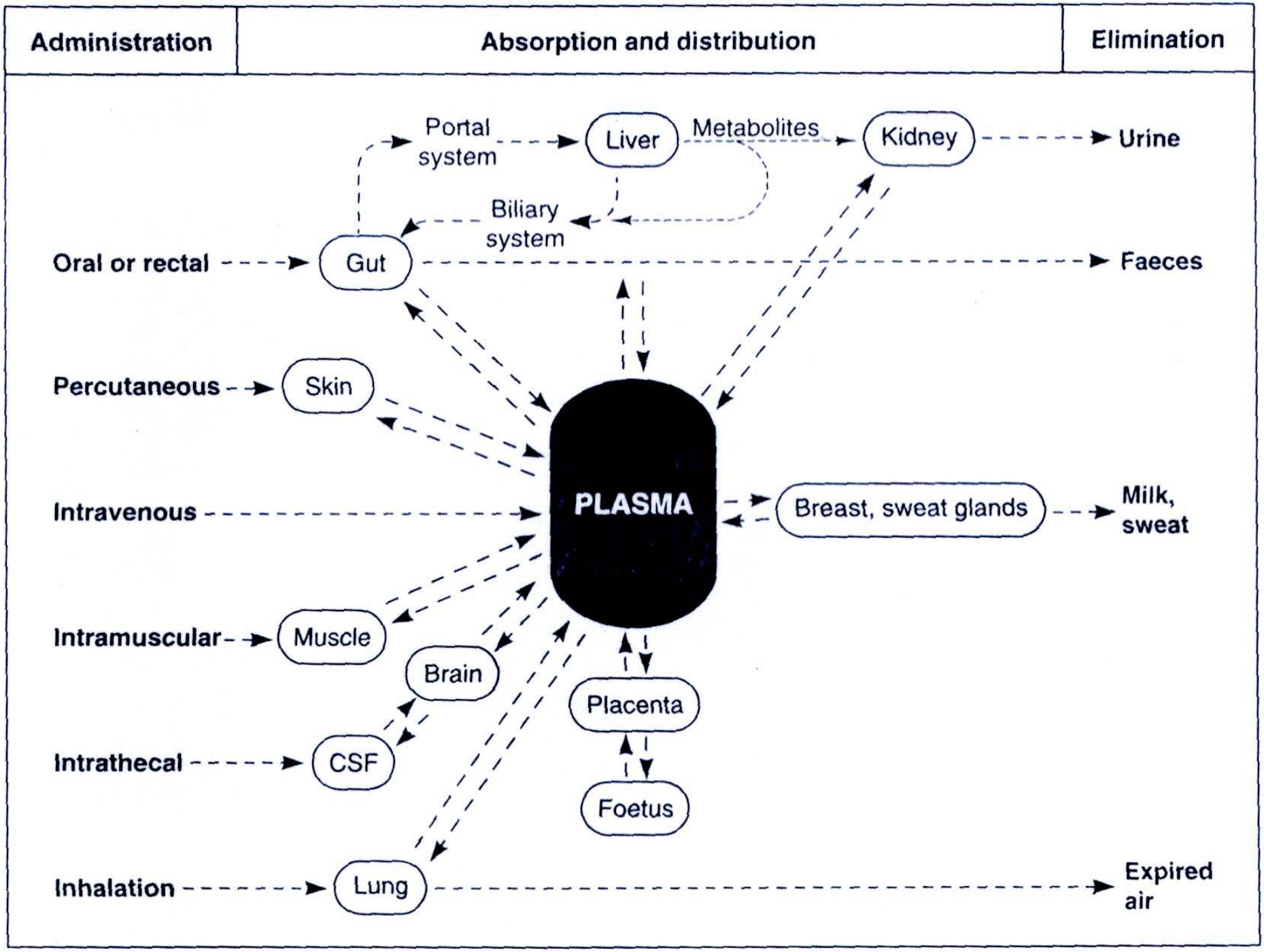
Distribution of drugs

OUTLINE

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

Distribution

Is the process by which drugs leave blood and enters the interstitium and/or the cells of the tissues.


Administration
Absorption and distribution
Elimination
Portal system
Liver
Metabolites
Kidney
Urine
Biliary system
Oral or rectal
Gut
Faeces
Percutaneous
Skin
PLASMA
Intravenous
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Placenta
Intrathecal
CSF
Foetus
Inhalation
Lung
Expired air

The major body fluid compartments are

1. **Extracellular fluid (22%)**
   - Plasma (5 % of body weight = 4 L).
   - Interstitial fluid (10 L).

2. **Intracellular fluid (35 %)**

Fluids present inside all cells in the body. (28L)

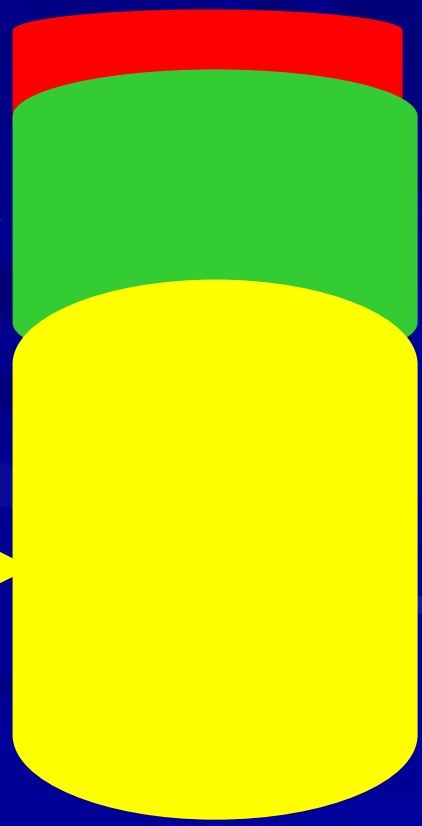
Body fluids compartments

Total body fluids = 60% of body weight in 70-kg individual

Plasma (4L)

Interstitial fluids (10 L)

Intracellular fluid (28 L)



Drugs may distribute into

1. **Plasma (vascular) compartments**

- Drug binds to plasma proteins
- Has high MW e.g. heparin
- can not move across endothelial junctions of capillaries

2. **Interstitial fluids**

- Drug has low MW but hydrophilic
- Pass endothelium into interstitial fluids

BUT will not cross cell membranes to intracellular water.

- Can not enter inside the cells e.g. aminoglycosides

3. Intracellular fluids

- Pass endothelium and cell membranes
- Enter cells
- Distribute through plasma, interstitial fluids and intracellular fluids (total body water) (42 L).
- Has low MW and hydrophobic (lipophilic)

e.g. Physostigmine, ethanol

Apparent Volume of Distribution (Vd)

is the ratio of drug amount in the body to the concentration of drug in plasma.

$$Vd = \frac{\text{total amount of drug in body}}{\text{concentration in plasma}}$$

Units: L and L/kg

Large Vd means prolonged duration of action (t ½).

Volume of Distribution (Vd)

Drugs with high Vd

- lipid soluble
- Distributed intracellularly
- e.g. phenytion, morphine, digoxin, tricyclic anti-depressants.

Volume of Distribution (Vd)

Drugs with low Vd

- Distributed only in plasma & interstitial fluid (extracellular ly) but not intracellularly).
- Polar comp (lipid insoluble drugs)
- High MW e.g. heparin
- High plasma protein binding e.g. warfarin.
- Do not cross blood brain barrier or placental barriers.

FACTORS AFFECTING DISTRIBUTION

1.Cardiac output and blood flow to organs.

2. Physiochemical properties of the drug.
   - PH.
   - Pka.
   - Lipid solubility (Fat : Water partition).

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

Physiochemical properties

- Lipid soluble drugs crosses most biological membranes
- Hydrophilic drugs
  - do not readily cross membranes
  - Go through the slit junction

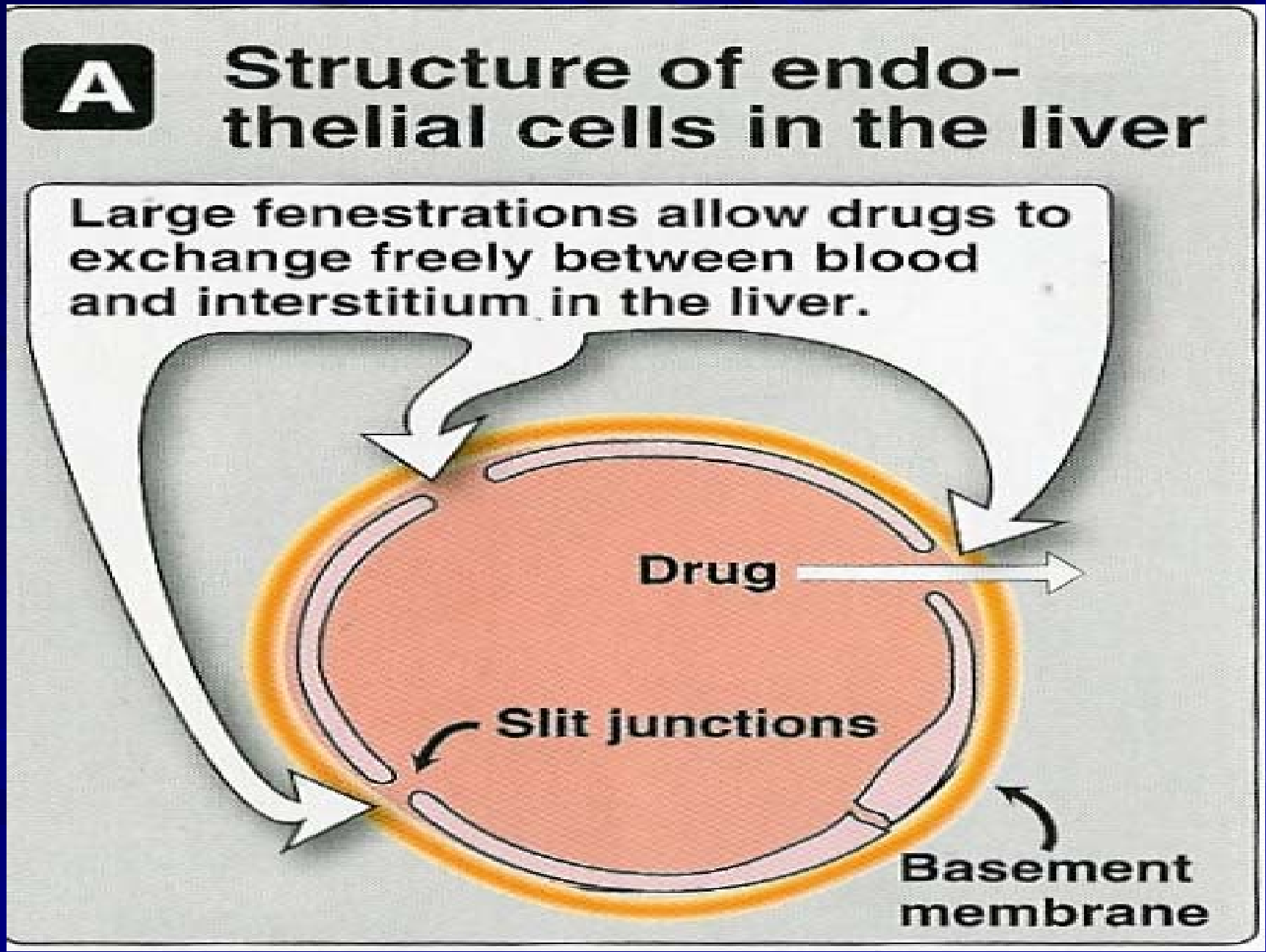
Capillary permeability

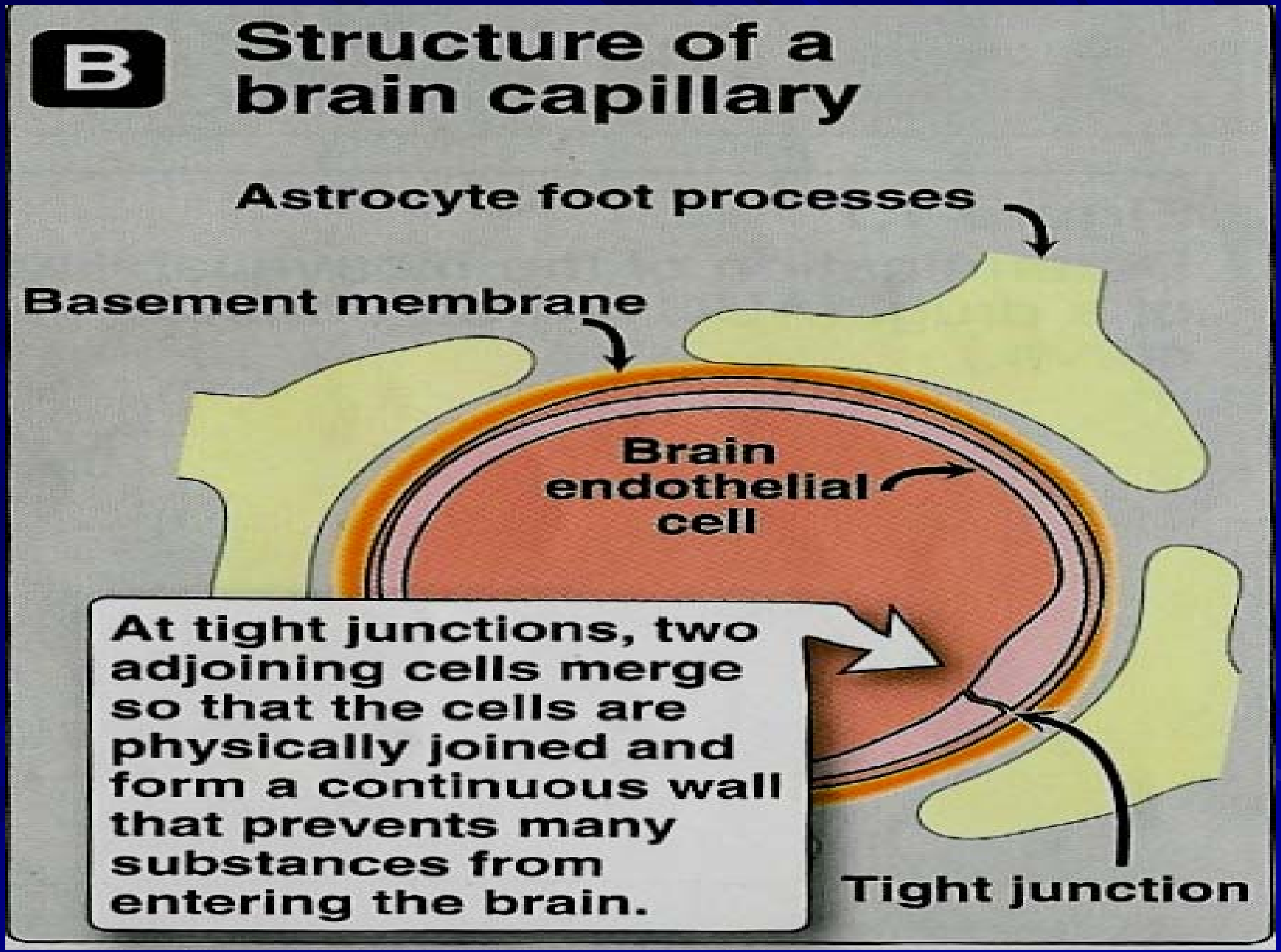
Endothelial cells of ca other capillaries in tissues other than brain have wide slit junctions allowing easy movement & distribution

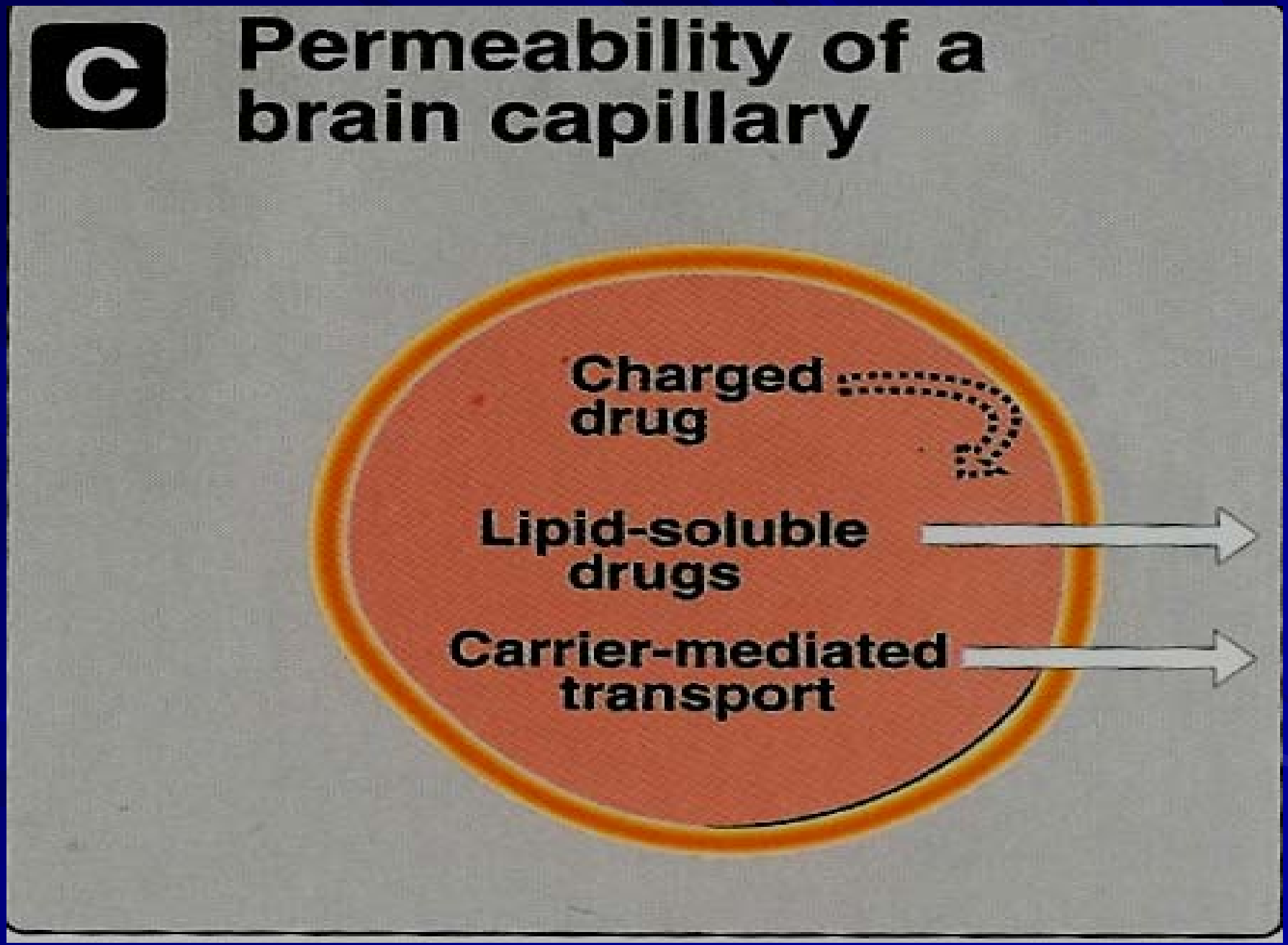
Brain has tight junction (Blood brain Barrier BBB)

Which drugs can penetrate CNS well?

- Only lipid soluble drugs or carrier-mediated transport
- Ionized (polar = hydrophilic drugs) can not penetrate CNS


A
Structure of endo-thelial cells in the liver
Large fenestrations allow drugs to exchange freely between blood and interstitium in the liver.
Drug
Slit junctions
Basement membrane


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

Barriers to drug distribution

Blood brain barrier (BBB):

Inflammation as in meningitis increase permeability to hydrophilic drugs.

e.g. penicillin & gentamycin

Placental barrier:

- Drugs that cross placental barrier reach fetal circulation
- Lipophilic drugs can cross this barrier.

Binding of Drugs

- Plasma proteins binding.
- Tissue proteins binding.

Characters of binding

Drugs exist in two forms free and bound forms in equilibrium.

Drug  unbound (free) + Bound

Unbound drug

1- Combine with receptors.

2- Pharmacologically active= produce action.

3- available for metabolism & excretion

4- has short duration of action.

Bound drug

1. Non diffusible form
2. Can not combine with receptors.
3. Pharmacologically inactive.
4. Not available for elimination (metabolism & excretion).
5. Provides long duration of action (t ½).

Plasma Protein Binding

Drugs can bind to plasma proteins as albumin or globulins

Prolongs duration of drug action (t1/2).

Tissues Binding

1. Bone

Tetracycline & heavy metals as lead (collagen).

2. Fat

Some drugs as thiopental.

3. Salivary Gland & Thyroid glands

Can accumulate iodides

4. Liver

Quinacrine (3000 times more in liver).
Chloroquine (nucleic acids).

5. Hair and skin : Arsenic (keratin).

Displacement

- Competition for the same binding site on the plasma proteins may occur between two drugs

Drug + Albumin-drug ⟶

Albumin-drug + free drug (more therapeutic/toxic effects)

- warfarin + Albumin-tolbutamide ⟶

  Albumin-warfarin + free tolbutamide ⟶ hypoglycemia.

- Aspirin + Albumin-warfarin ⟶

  Alumin-aspirin + free warfarin ⟶ bleeding

Redistribution

Redistribution of the drug from its site of action to other tissues e.g. thiopental

Termination

- Biotransformation.
- Excretion.
- Redistribution.