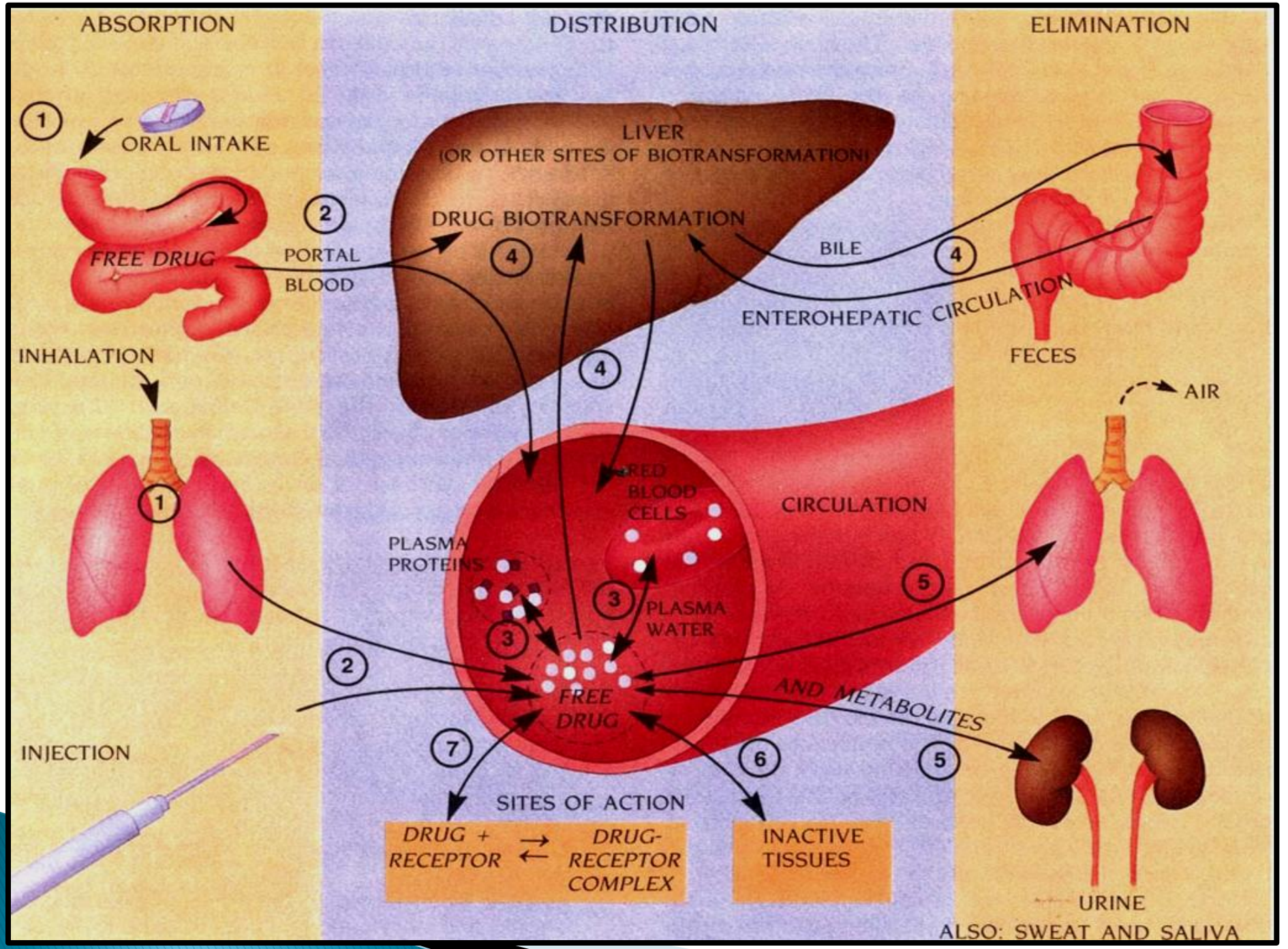
Distribution

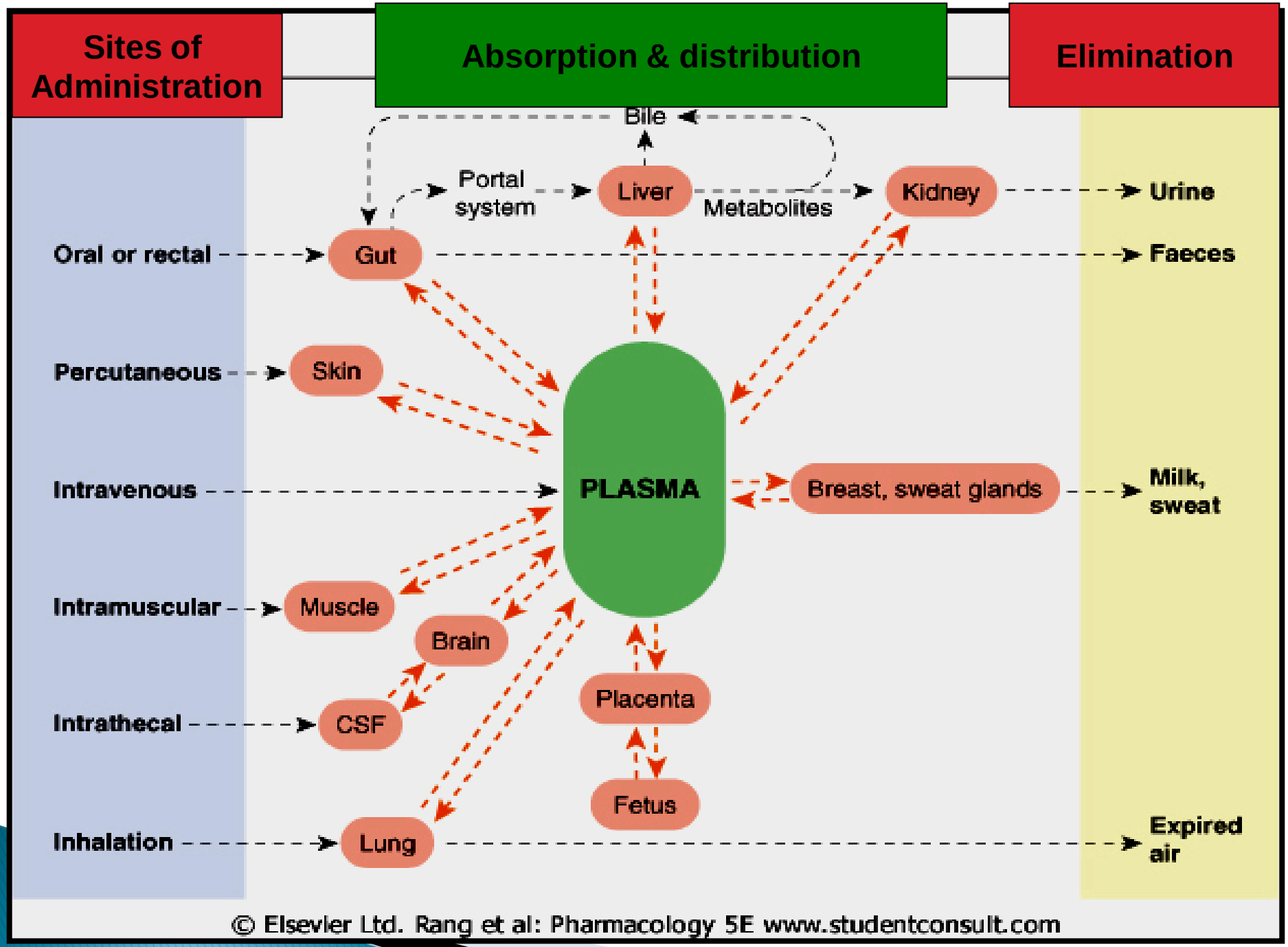
What student should know

- ***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.


ABSORPTION
DISTRIBUTION
ELIMINATION
1
ORAL INTAKE
LIVER
(OR OTHER SITES OF BIOTRANSFORMATION)
2
DRUG BIOTRANSFORMATION
FREE DRUG
PORTAL
BLOOD
4
BILE
4
ENTEROHEPATIC CIRCULATION
INHALATION
FECES
4
AIR
1
RED
BLOOD
CELLS
CIRCULATION
PLASMA
PROTEINS
3
PLASMA
WATER
5
3
2
FREE
DRUG
AND METABOLITES
INJECTION
7
6
5
SITES OF ACTION
DRUG +
RECEPTOR
DRUG-
RECEPTOR
COMPLEX
INACTIVE
TISSUES
URINE
ALSO: SWEAT AND SALIVA


Sites of Administration
Absorption & distribution
Elimination
Bile
Portal system
Liver
Kidney
Urine
Metabolites
Oral or rectal
Gut
Faeces
Percutaneous
Skin
Intravenous
PLASMA
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Placenta
Intrathecal
CSF
Fetus
Inhalation
Lung
Expired air
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The major body fluid are

1. **Extracellular fluids (22%)**
   - **Plasma (5 % of body weight = 4 L).**
   - **Interstitial fluid (16% = 10 L).**
   - **Lymph (1 %).**

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

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

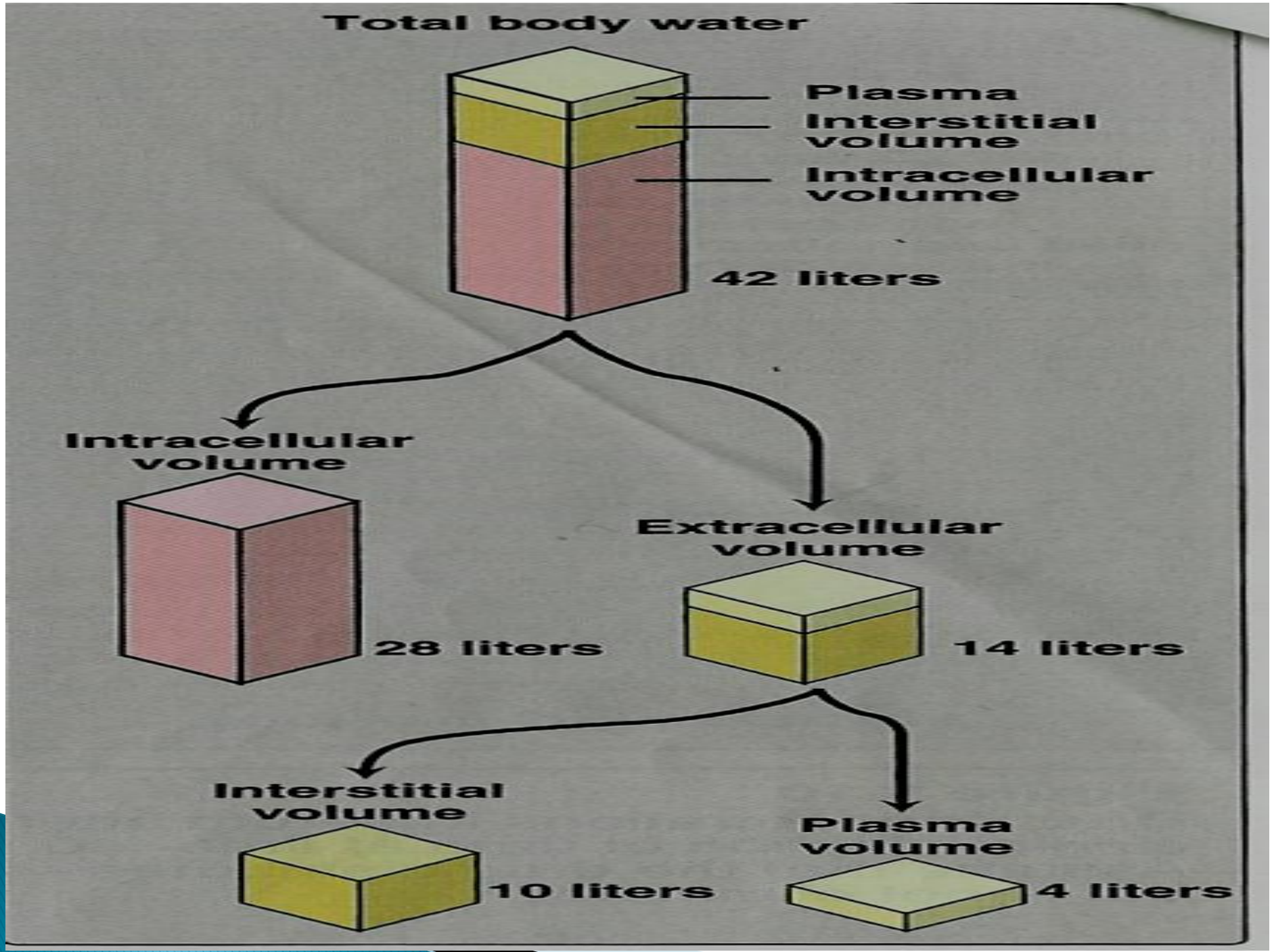
Total body fluids
(60% of body weight in 70-kg individual)

Total body Fluids (42 Liters)

→ **Plasma (4 L)**

→ **Interstitial fluids (10 L)**

→ **Intracellular volume (28 L)**


Total body water
Plasma
Interstitial volume
Intracellular volume
42 liters
Intracellular volume
28 liters
Extracellular volume
14 liters
Interstitial volume
10 liters
Plasma volume
4 liters

The major body fluid compartments are

- One compartment (Intravascular)
- Two compartments (Extravascular)
- Multi-compartments (Extravascular and Intravascular)

Drugs may distribute into

1. Plasma (vascular) compartment

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

2. Interstitial fluids (Two compartments):

- **Pass endothelium into interstitial fluids BUT can not cross cell membranes to intracellular fluids**
- **Distribute through extracellular fluids.**
- **Drug has low MW but hydrophilic**
- **Can not enter the cells**

e.g. aminoglycosides

3. Intracellular fluids (Multi-compartments):

- **Pass endothelium and cell membranes**
- **drugs have low MW and lipophilic**
- **Enter cells**
- **Distribute through plasma, interstitial fluids, and intracellular fluids**

  (Total body fluids= 42 L)

  e.g. Physostigmine

Apparent Volume of Distribution (Vd)

is the ratio of drug amount in the body to the concentration of drug in blood

$$Vd\ (L) = \frac{\text{total amount of drug in body (mg)}}{\text{concentration in blood (mg/L)}}$$

Large Vd = means long duration of action

Drugs with high Vd

- Relatively lipid soluble
- Distributed intracellularly
- Not efficiently removed by haemodialysis.
- e.g. phenytion, morphine, digoxin

Drugs with low Vd

- distributed in extracellular compartments.
- Polar comp e.g. Carbenicillin, gentamycin.
- High MW e.g. heparin – insulin
- High plasma protein binding e.g. warfarin.
- Do not cross BBB or placental barriers.

FACTORS AFFECTING DISTRIBUTION

1.Cardiac output and blood flow.

2. Physiochemical properties of the drug.

- **MW**
- **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.**

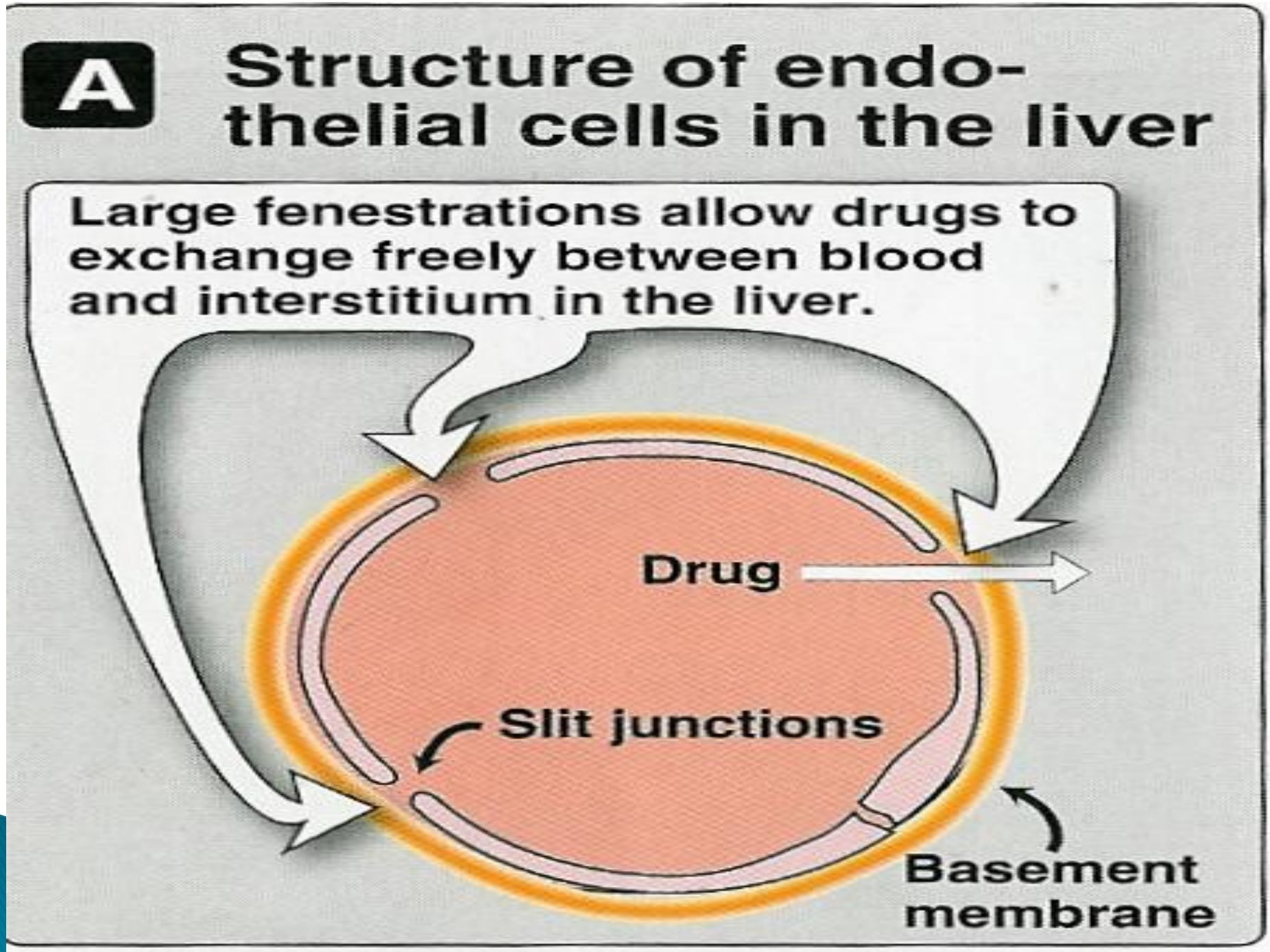
Physiochemical properties

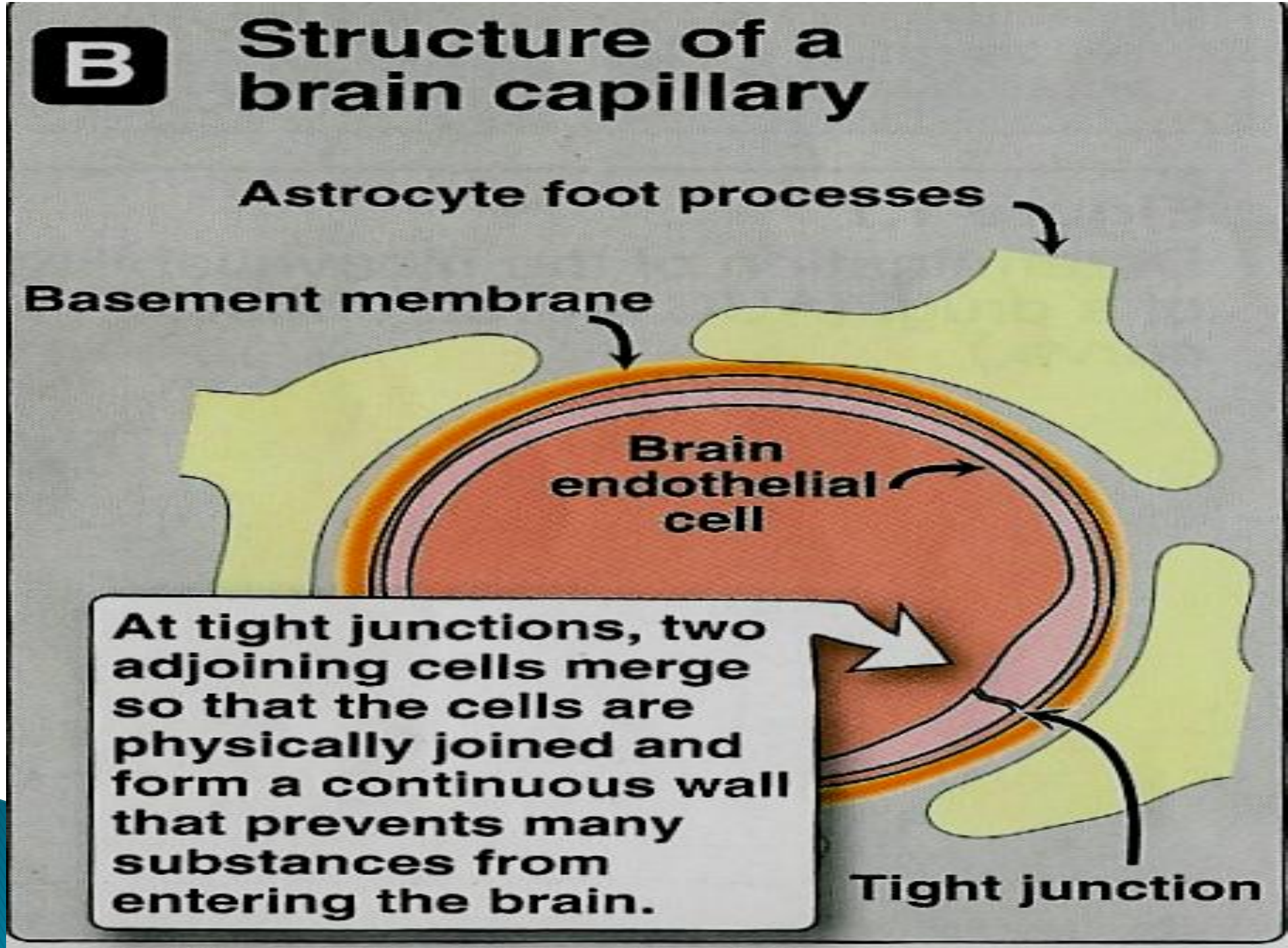
- **Most Lipid soluble drugs cross biological membranes**
- **Hydrophilic drugs do not readily cross membranes**

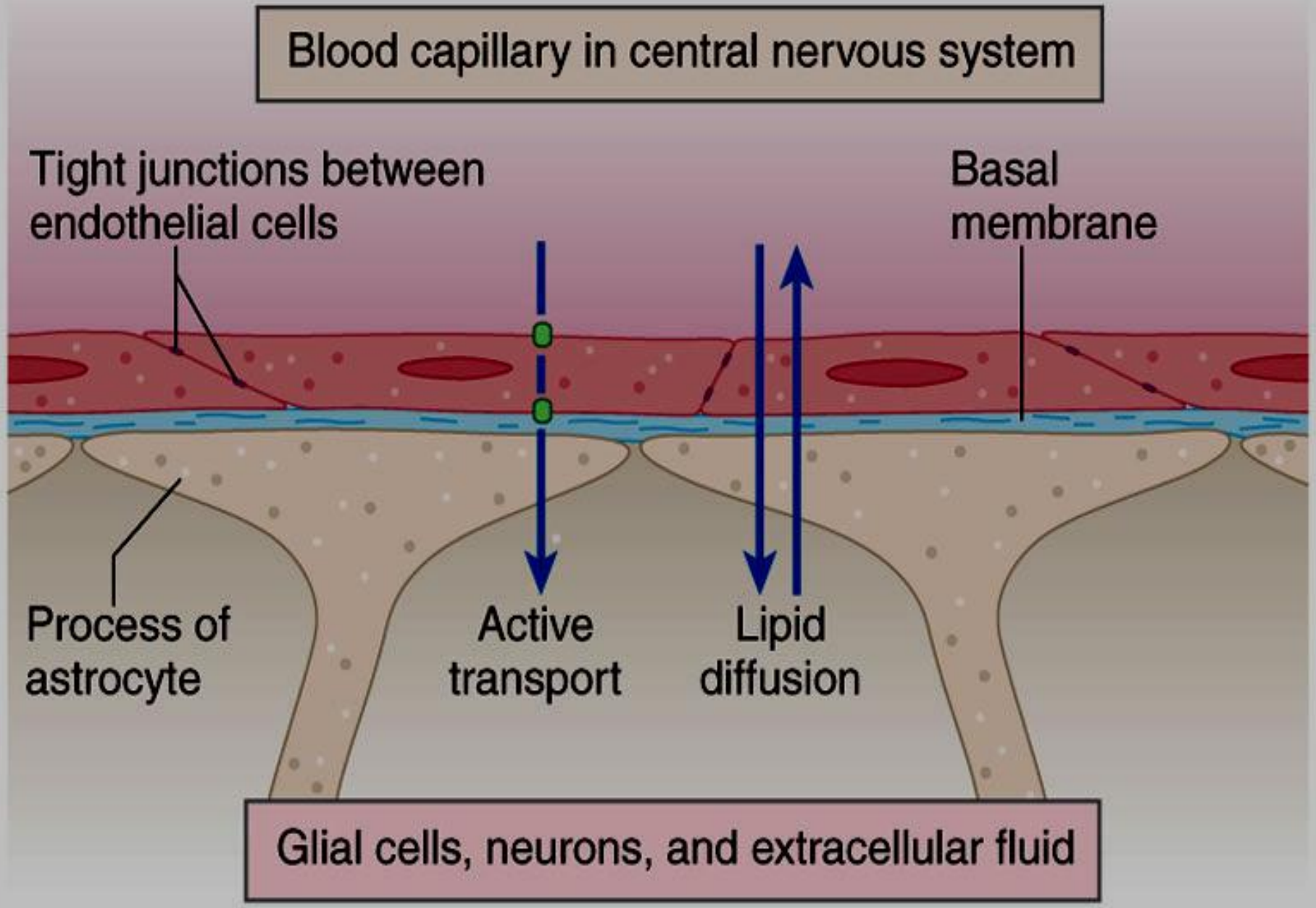
Capillary permeability

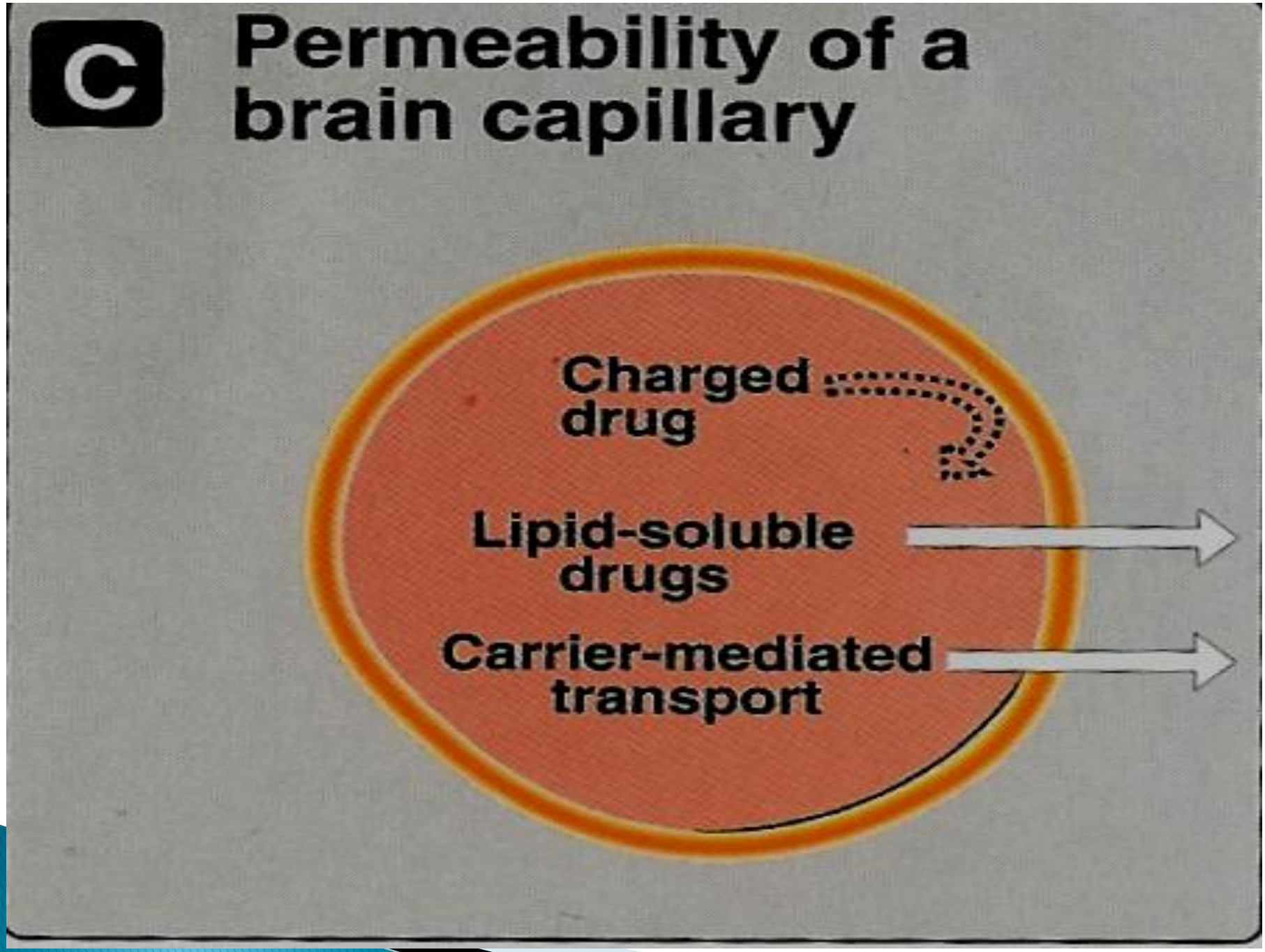
- **Endothelial cells of capillaries in tissues other than brain have wide slit junctions allowing easy movement & distribution.**

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


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

Physiological barriers to drug distribution

- **Cell membrane**
- **Blood brain barrier (BBB).**
- **Placental barrier.**

PLACENTAL BARRIER

- **Drugs cross placenta by simple diffusion.**
- **Lipid soluble drugs readily enter the fetal blood. What are the consequences?**
- **Warfarin ⟶ hemorrhage**

Blood brain barrier (BBB):

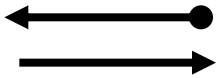
- Only lipid soluble drugs can cross BBB.
- Inflammation as in meningitis increase permeability to hydrophilic drugs
- e.g. penicillin & gentamycin

Binding of Drugs

- **Binding is either to**
  - **Plasma proteins binding.**
  - **Tissue proteins binding.**

Characters of binding

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

Drug  **unbound drug (free) + bound drug**

Unbound drug

1- Combine with receptors.

2- Pharmacologically active

3- available for metabolism & excretion

4- has short duration of action.

Bound drug

1. **Non diffusible form**
2. **Can not combine with receptors.**
3. **Not available for elimination (metabolism & excretion).**

4. Provides long duration of action (t ½).

Plasma Proteins

Albumin

Affinity for acidic drugs as warfarin, phenytoin, aspirin

Glycoprotein

basic drugs (cationic) as diazepam, quinidine.

Tissues Binding

Bone

Tetracycline & heavy metals as lead (collagen).

Fat some drugs as thiopental.

Salivary & Thyroid glands

Can accumulate iodides

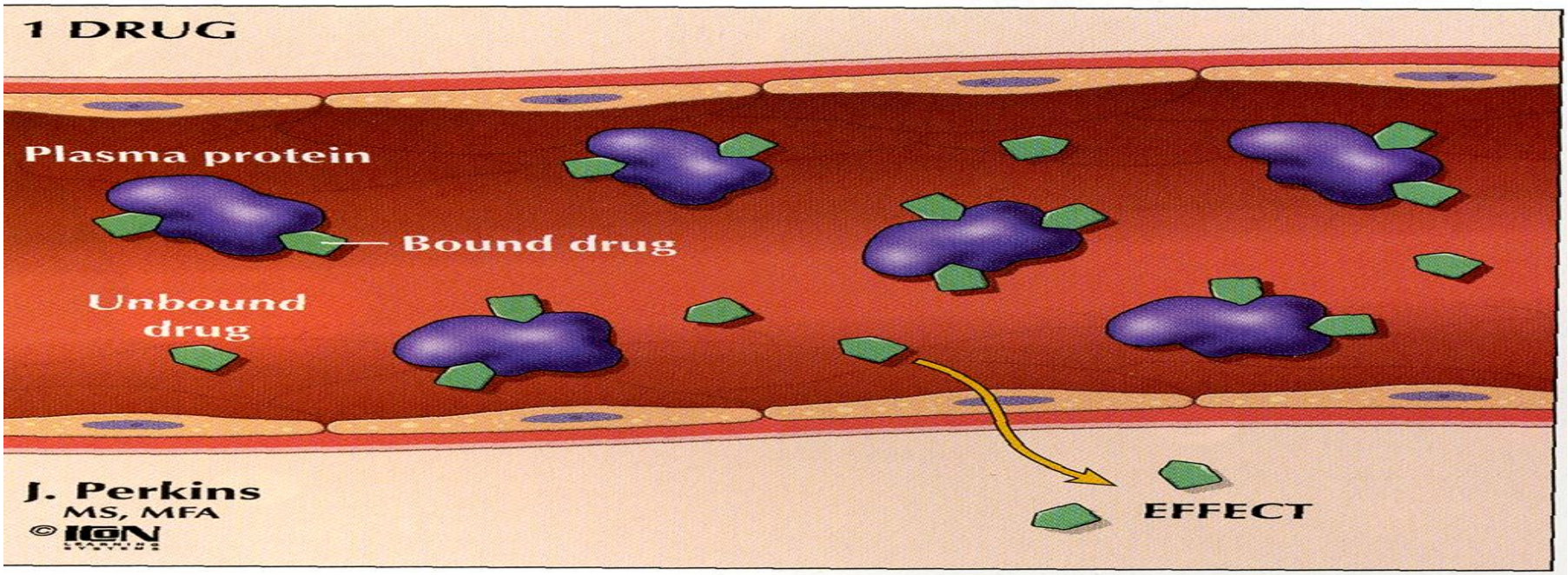
Liver chloroquine (nucleic acids).

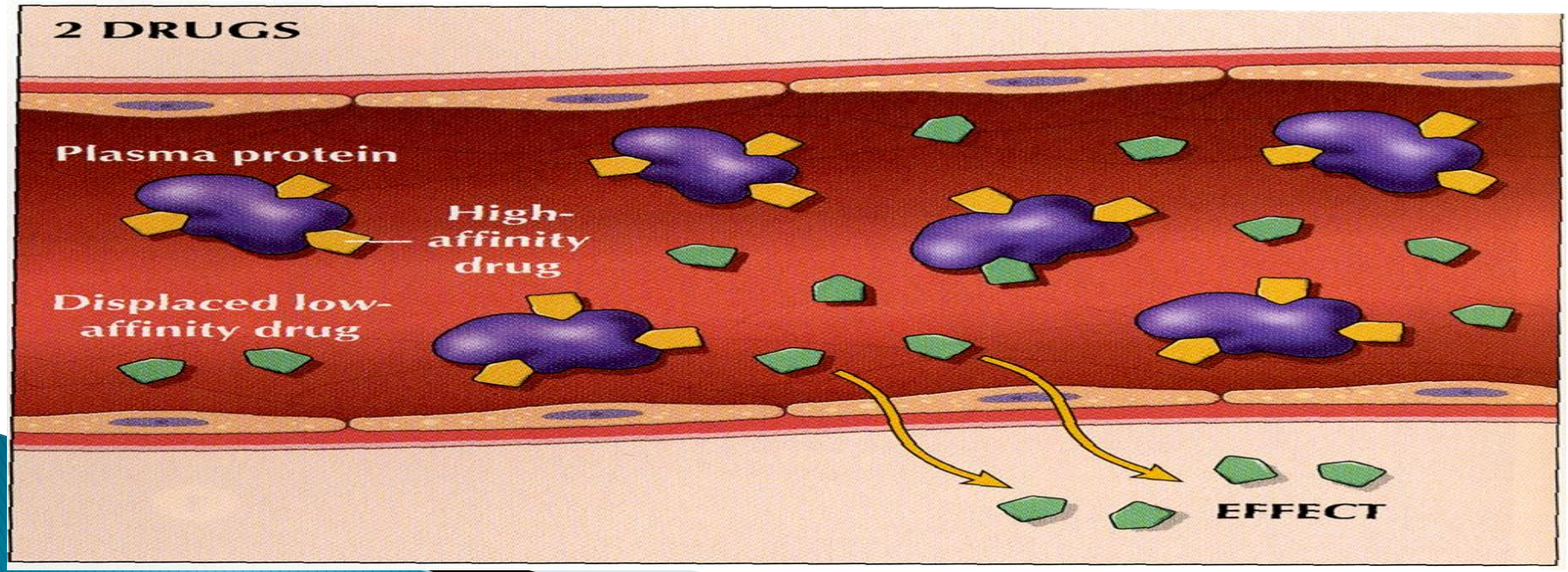
Hair and skin : Arsenic (keratin).

Displacement

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

- **Aspirin + Albumin-warfarin ⟶ Albumin-aspirin + free warfarin ⟶ bleeding.**


1 DRUG
Plasma protein
Bound drug
Unbound drug
EFFECT
J. Perkins
MS, MFA


2 DRUGS
Plasma protein
High-affinity drug
Displaced low-affinity drug
EFFECT

Characters & consequences of Binding

- **Usually reversible.**
- **determines volume of distribution (vd)**
- **Slows drug metabolism & elimination.**
- **Prolongs duration of drug action (t1/2).**
- **Clinically important drug interactions.**

Redistribution

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

Termination

- Biotransformation.
- Excretion.
- Redistribution.