Distribution

OUTLINE

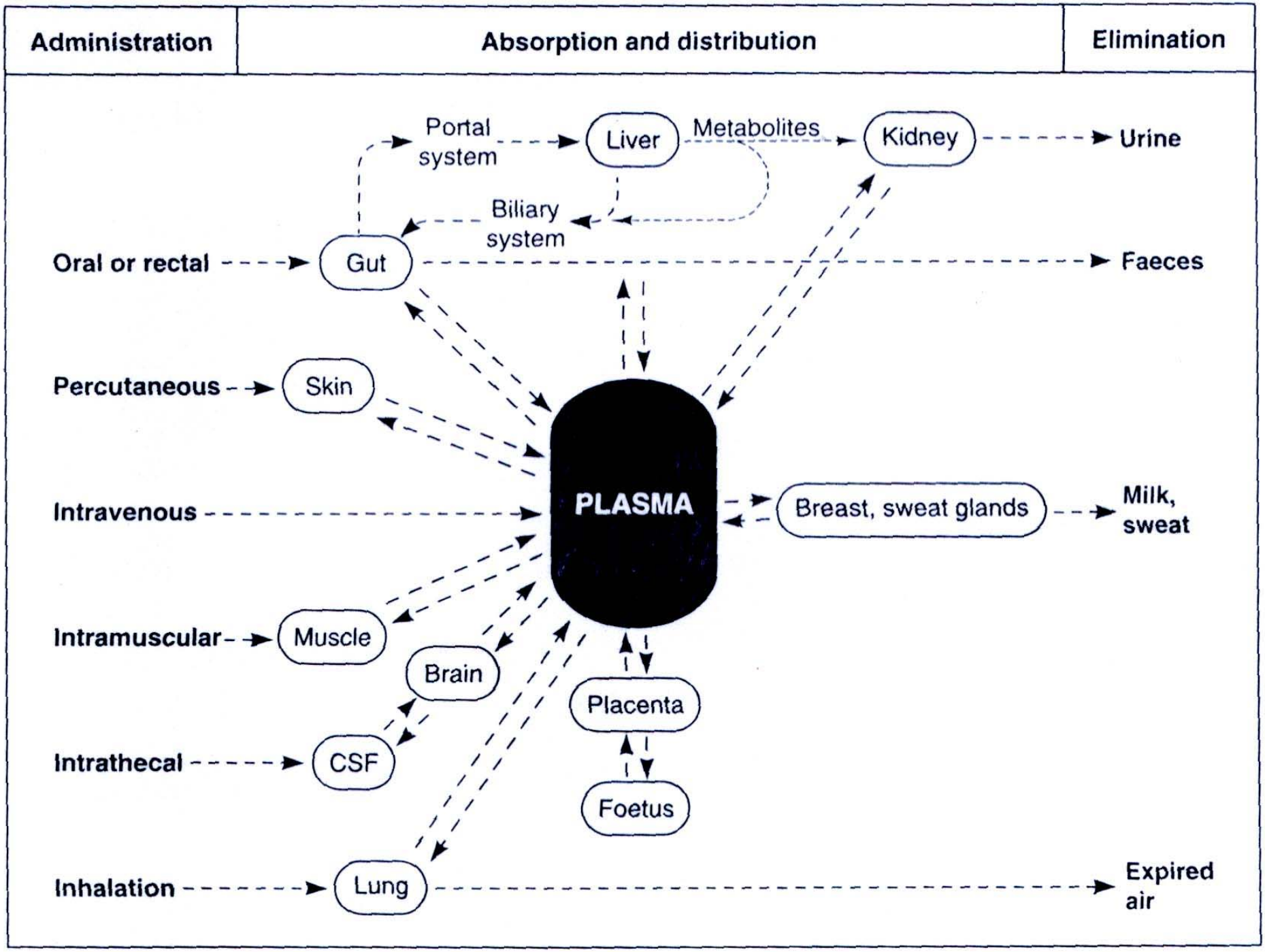
- Major body fluid compartments
- Concept of compartments.
- Apparent volume of distribution (vd).
- Plasma protein binding.
- Tissue binding.
- Redistribution

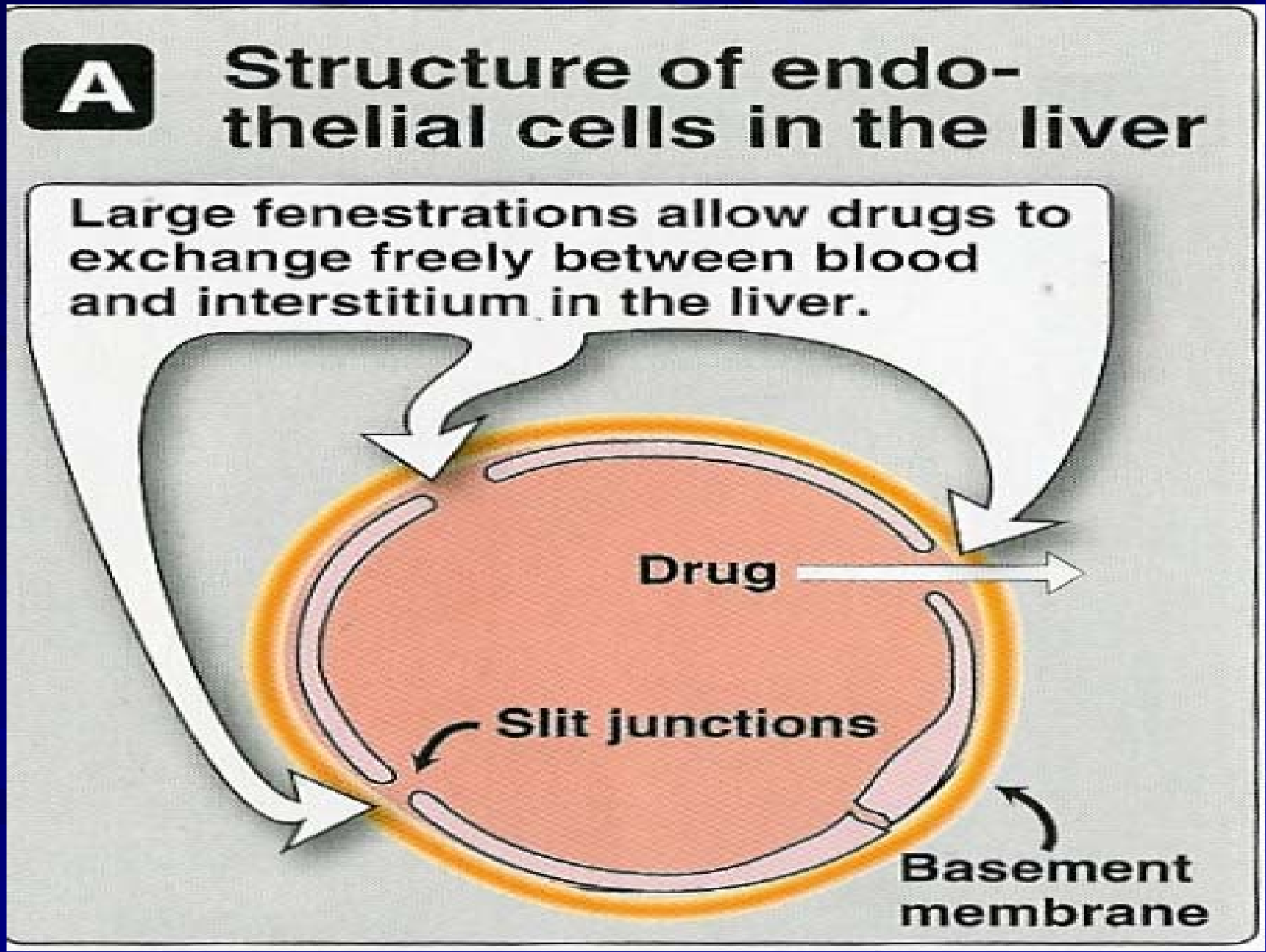
Distribution

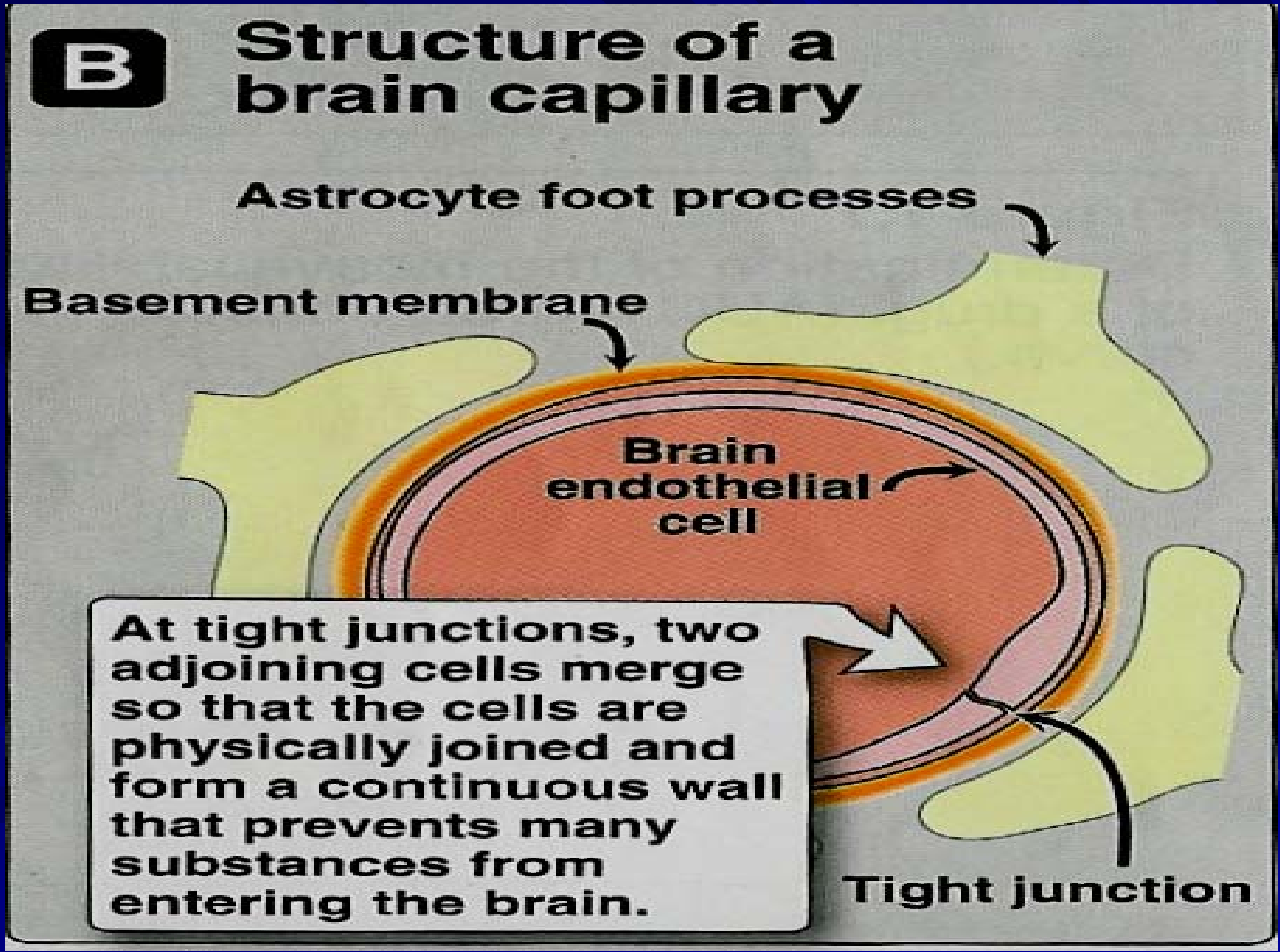
Is the process by which drugs leave blood and enters the interstitium and/or the cells of the tissues.

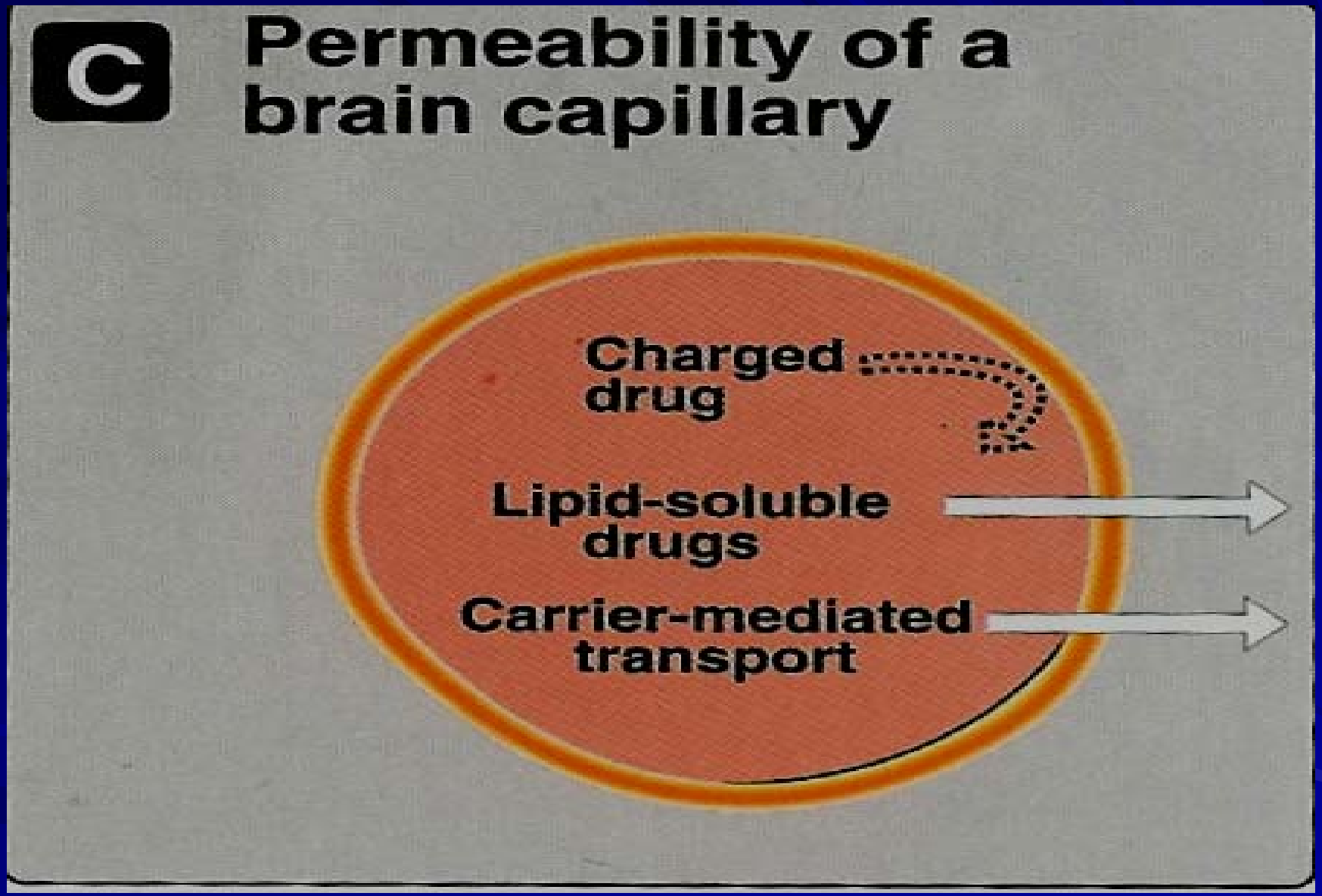
FACTORS AFFECTING DISTRIBUTION

1.Cardiac output and blood flow.
2. Physiochemical properties of the drug.
3. Capillary Permeability
4. Plasma protein binding
5. Tissue binding.
6. PH.
7. Pka.
8. Lipid solubility (Fat : Water partition).


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


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

The major body fluid compartments are

1. **Extracellular fluid (22%)**
   - Plasma (5 % of body weight = 4 L).
   - Interstitial fluid (16 %).
   - Lymph (1 %).
2. **Intracellular fluid (35 %)**

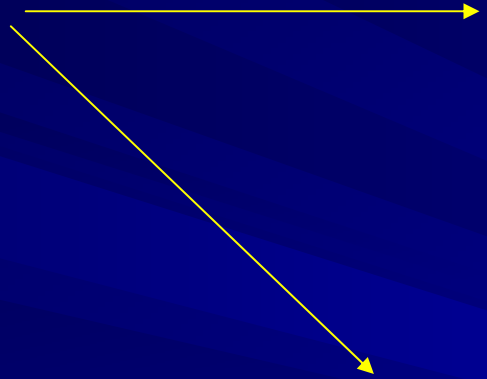
Sum of fluid contents of all cells in the body.

3. **Transcellular fluid (2%)**

cerebrospinal, intraocular, synovial, peritoneal, pleural & digestive secretions.

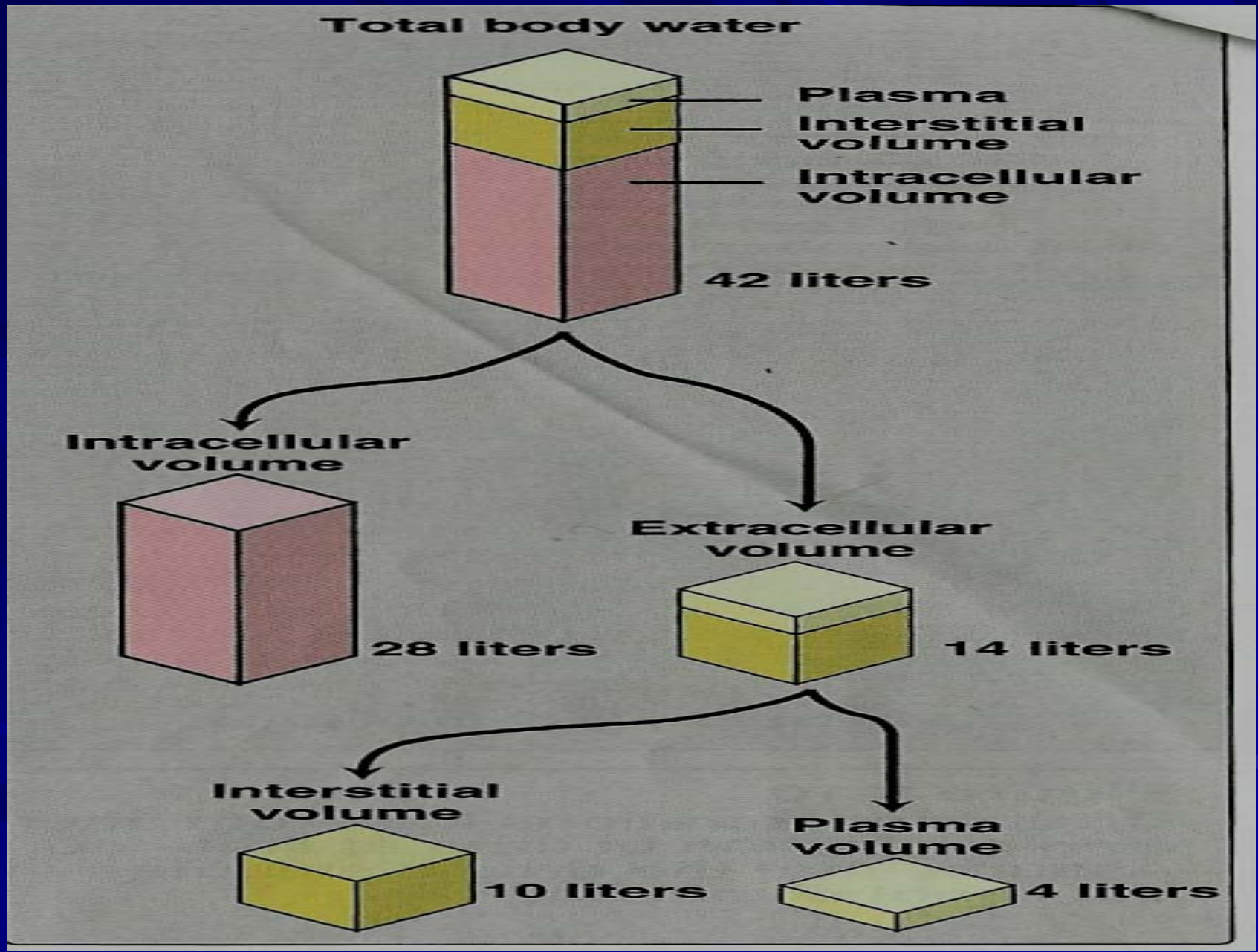
Total body fluids = 60% of body weight in 70-kg individual

42 L



Extracellular volume (14 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):**

The major body fluid compartments are

Intravascular (One compartment):

- **Trapped in blood**
- **Drug binds to plasma proteins or has high MW e.g.**

  heparin
- **can not move out of endothelial cells of capillaries**

Extravascular (two compartments):

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

BUT not cell membranes

- **Can not enter the cells**
- **Distribute through extracellular fluids.**

e.g. aminoglycosides

Extravascular and Intravascular (Multi-compartments):

- Has low MW and hydrophobic
- Pass endothelium and cell membranes
- Enter cells & Distribute through intra and extracellular fluids

e.g. Physostigmine

Apparent Volume of Distribution (Vd)

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

$$Vd\ (L) = \frac{\text{total amount of drug in body (mg)}}{\text{conc., in blood or plasma (mg/L)}}$$

Useful to calculate the amount of drug needed to achieve a desired plasma conc.

Volume of Distribution (Vd)

Drugs with high Vd

- higher concentrations in tissues than in plasma.
- Relatively lipid soluble .
- Distributed intracellularly
- Not efficiently removed by haemodialysis.
- e.g. phenytion, morphine, digoxin, tricyclic anti-depressants.

Volume of Distribution (Vd)

Drugs with low Vd

- confined to plasma & interstitial fluid.
- distributed in extracellular compartments.
- Polar comp or lipid insoluble drugs. e.g. Carbenicillin, vecuronium, gentamycin.
- High MW e.g. heparin – insulin-dextran.
- 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.
3. Capillary Permeability
4. Plasma protein binding
5. Tissue binding.
6. PH.
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8. Lipid solubility.

Physiological barriers to distribution

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

PLACENTAL TRANSFER

- Drugs cross placenta by simple diffusion.
- Lipid soluble drugs readily enter the fetal blood. **What are the consequences?**
- Morphine → respiratory depression
- Warfarin → hemorrhage
- Antithyroid drugs → Neonatal goiter

- Lipid soluble drugs.

  e.g. G. anesthetics, Thiopental
- Actively transported drugs (L-dopa)
- Ionized or polar drugs can not penetrate CNS
- Inflammation as in meningitis increase permeability.

  e.g. penicillin & gentamycin

Passage of Drugs Into CNS & CSF

Is controlled by blood brain barrier

- **Endothelial cells**
  - **Continuous**
  - **No slit junction**
- **Astrocytes**

Which drugs can penetrate CNS well?

Binding of Drugs

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

- Binding is interaction between drugs and charged groups (NH_3^-, COO^-).

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. Not available for elimination (metabolism & excretion).
4. Provides long duration of action (t ½).

Plasma Protein Binding

Plasma Proteins

Albumin

1. The major drug binding protein.
2. Affinity for acidic drugs (anionic) and hydrophobic drugs as warfarin, phenytoin, aspirin
3. Most hydrophilic and neutral drugs do not bind.
4. Binding to albumin is reversible.

Glycoprotein

basic drugs (cationic) as propranolol, diazepam, quinidine.

α-2 globulin: steroids, vit B12, thyroxine.

β-1 globulin: Iron.

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).

Characters & consequences of Binding

- Usually but not always reversible.
- determines volume of distribution (vd)
- Slows drug metabolism &elimination.
- Prolongs duration of drug action (t1/2).
- Clinically important drug interactions.

Displacement

- Competition for the same binding site on the plasma proteins may occur.

1. Between drugs and endogenous substrates, e.g. sulphonamides and bilirubin? (Jaundice and kernicterus).

Drug + Albumin-bilirubin ⟶

Albumin-drug + free bilirubin

2. Between two drugs ⟶ displacement of one drug & increasing its concentrations & effects.

- warfarin + Albumin-tolbutamide ⟶

  Albumin-warfarin + free tolbutamide ⟶ hypoglycemia.

- Aspirin + Albumin-warfarin ⟶

  Albumin-aspirin + free warfarin ⟶ bleeding.

Redistribution

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

Termination

- Biotransformation.
- Excretion.
- Redistribution.