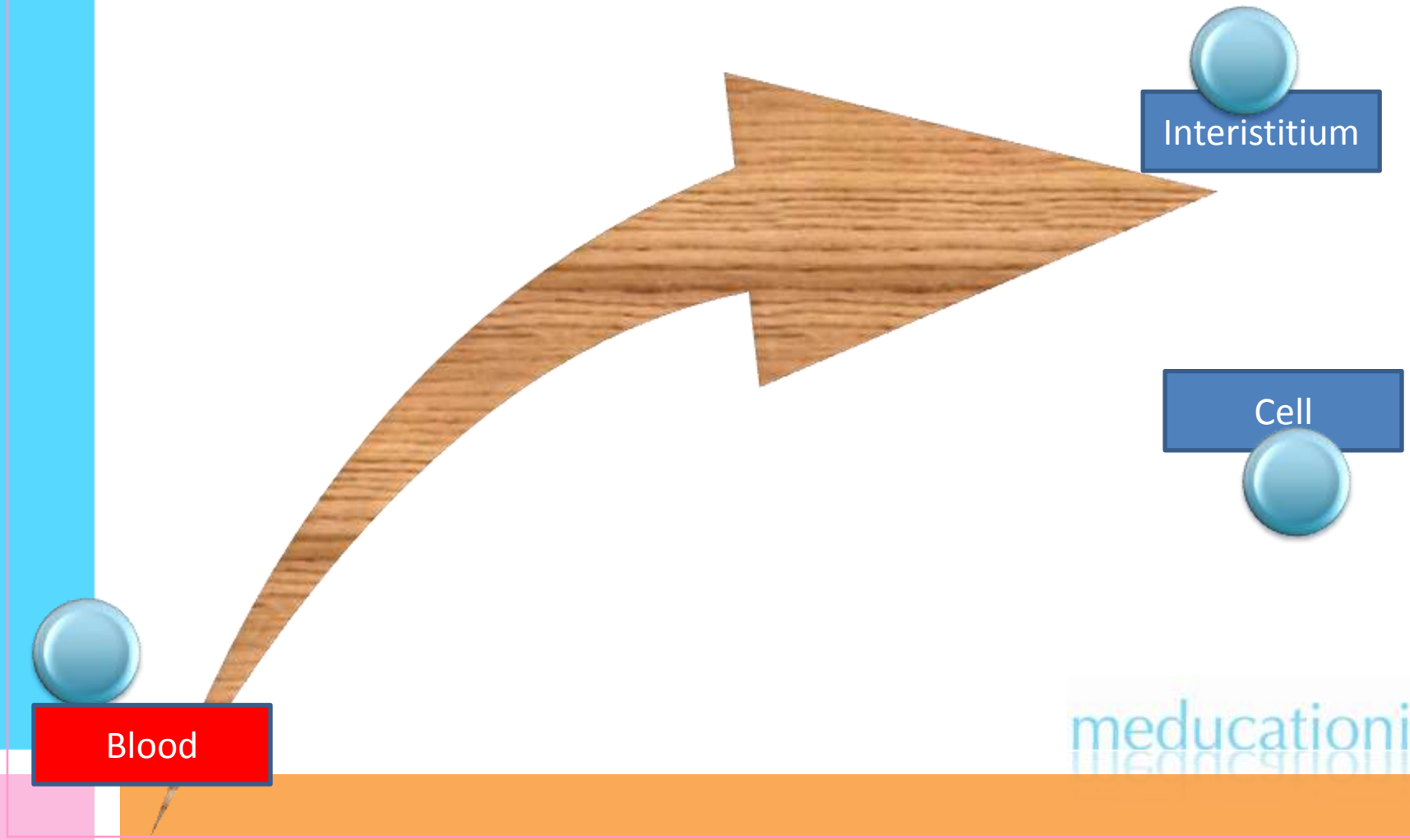
DRUG DISTRIBUTION

- Drug distribution: refers to the reversible transfer of a drug between the blood and the extra vascular fluids and tissues of the body (for example, fat, muscle, and brain tissue).

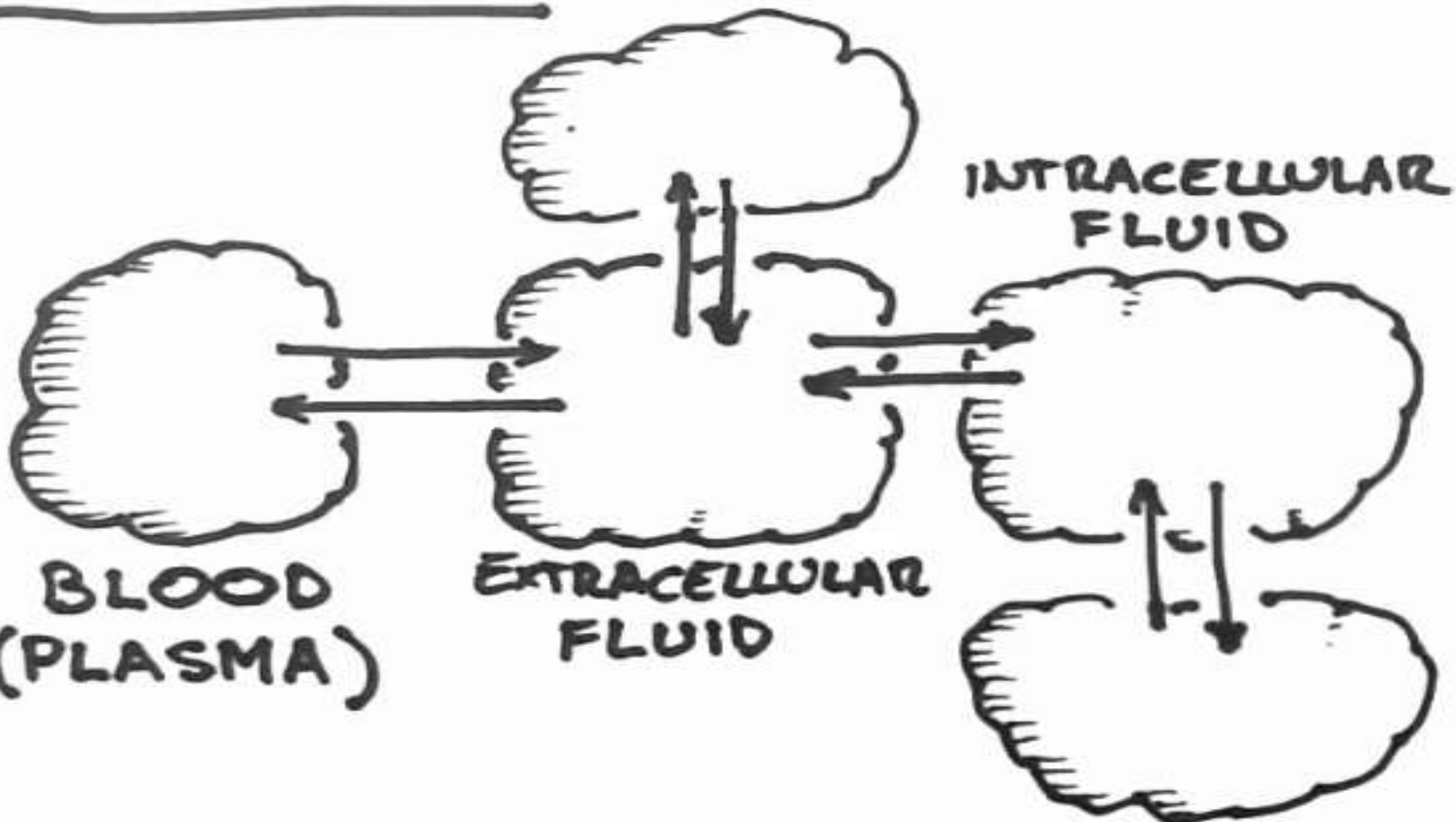
- Drugs come into the circulation after absorption
- From plasma, drugs have to cross the capillary membrane to come to interstitial space
- And then need cross the cell-membrane to enter into the intracellular fluid.

DRUG DISTRIBUTION



DRUG DISTRIBUTION

DISTRIBUTION FAT



OTHER
- CSF
- PERITONEUM
- SYNOVIAL FLUID
- FETUS

Factors Affecting Drug Distribution

- Distribution of drugs throughout the body fluid is not equal.

The reasons for unequal distribution are:

§ Drug factors
§ pH of the media
§ Regional blood flow
§ Drug binding…protein / tissue
§ Membranes

Drug factors

- Lipid solubility of the drugs
- Molecular weight of the drugs
- pKa of drug

Lipid solubility

- LS drugs (non-ionized) can cross easily the membranes & available everywhere
- WS drugs (ionized) can't cross the cell-membrane, and so remains in mostly ECF

Molecular weight

- Low molecular weight drugs can cross easily
- High molecular weight drugs (albumin) can't cross the capillary membrane & remains in plasma

pKa of drug & pH of media

- More dissociation….less crossing of membranes
- Blood is slightly alkaline (pH 7.4)
- Acidic low pKa drugs will be ionized more & less crossing of membranes
- Basic low pKa drugs will be ionized less & more crossing of membranes

Drug binding

Binding

- Plasma protein binding of the drugs
- Tissue binding property of the drugs

Plasma Protein Binding

- **Binding of Drugs to Plasma Proteins:**

- When the drugs appear in the circulation……

- A fraction of drug molecules bind with plasma protein (albumin)& another fraction remain free…….

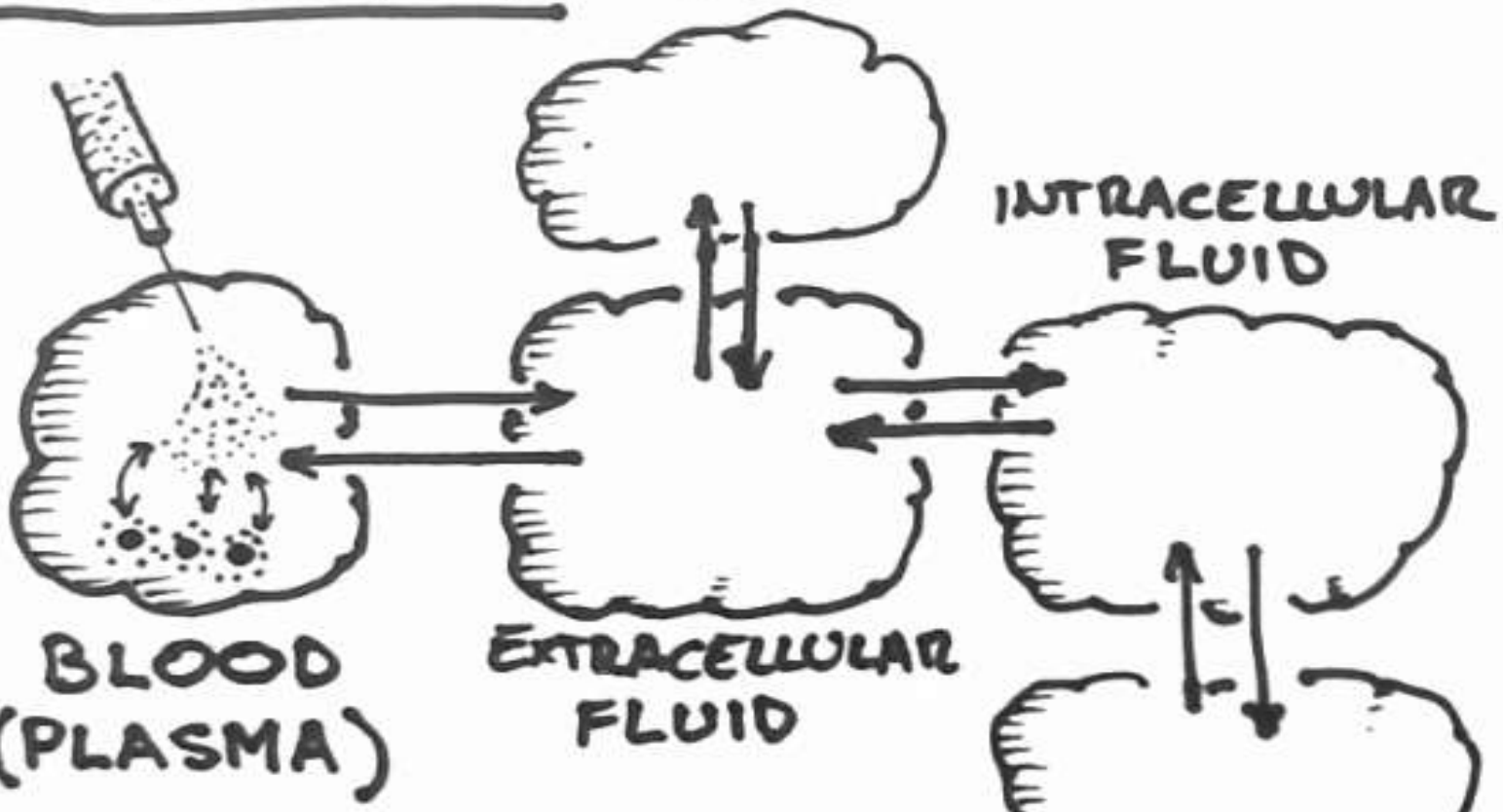
- There is always an equilibrium between bound & free drug concentration

- Drug with more plasma protein binding have less vd, > 95% bound Warfarin (99%),frusemide, thyroxine, clofibrate.

Binding with which plasma protein?

- Albumin
- alpha1-acid glycoprotein &
- Lipoprotein

DISTRIBUTION FAT



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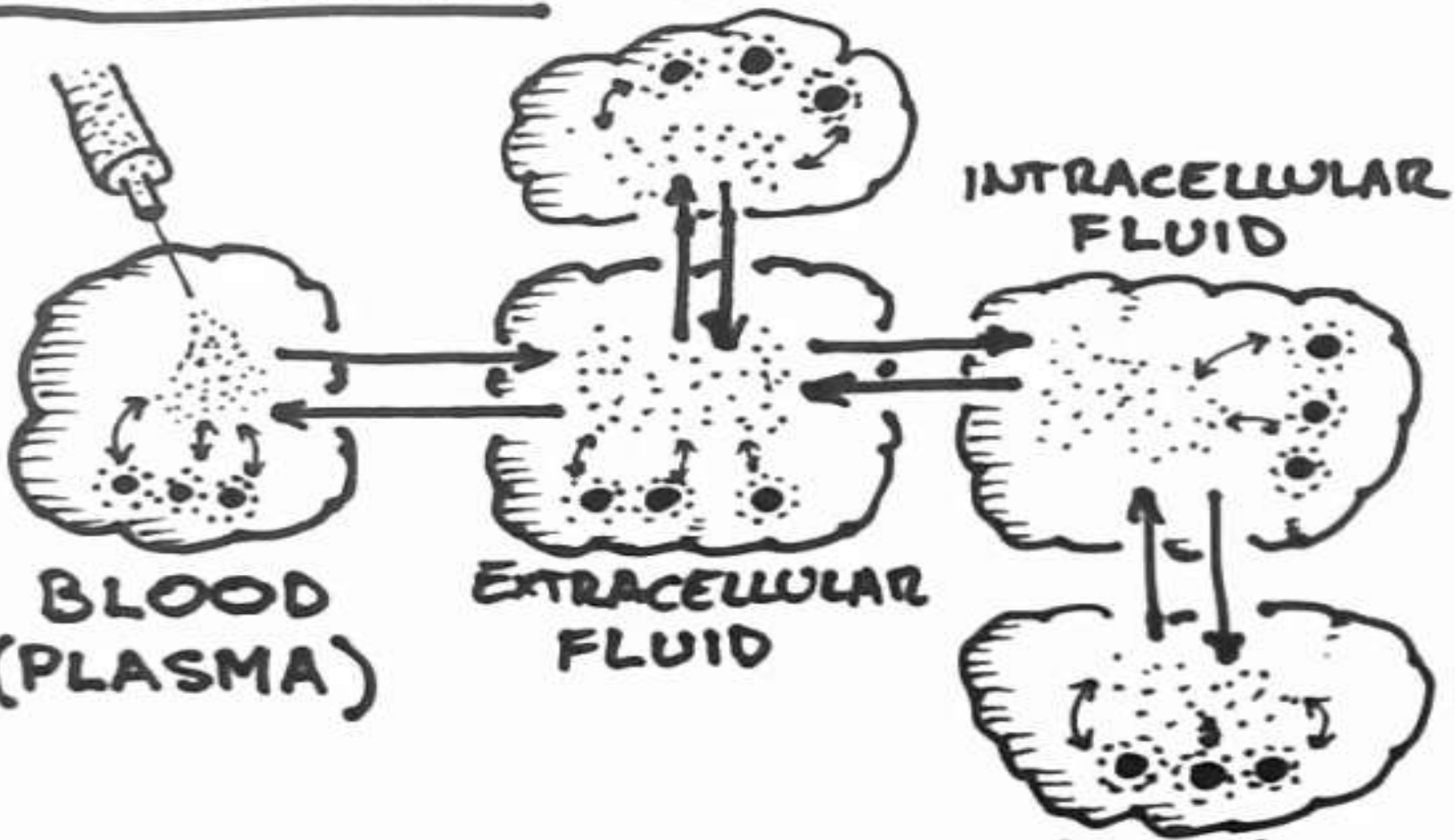
DISTRIBUTION FAT

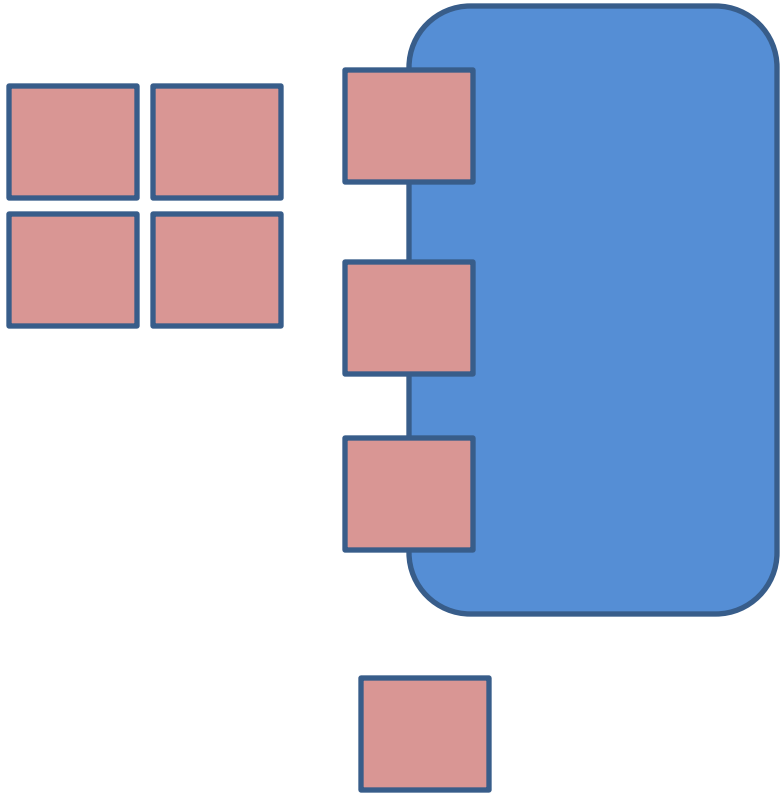


Plasma Protein Binding

Free drug ⇔ Bound drug

Always equilibrium

- This equilibrium will always be maintained whatever might be the amount of the drug in circulation at any time.

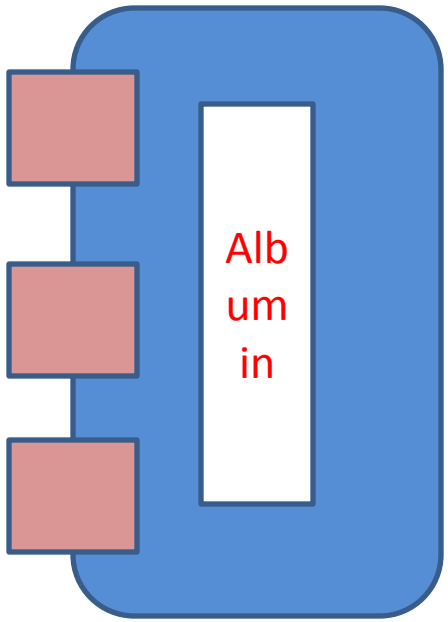


DRUG DISTRIBUTION

- Bound drugs remain as reservoir of drugs.

- When free drug concentration is decreased then bound drugs become free and maintains the equilibrium.

- **Only free drugs are active, metabolized & excreted.**



DRUG DISTRIBUTION

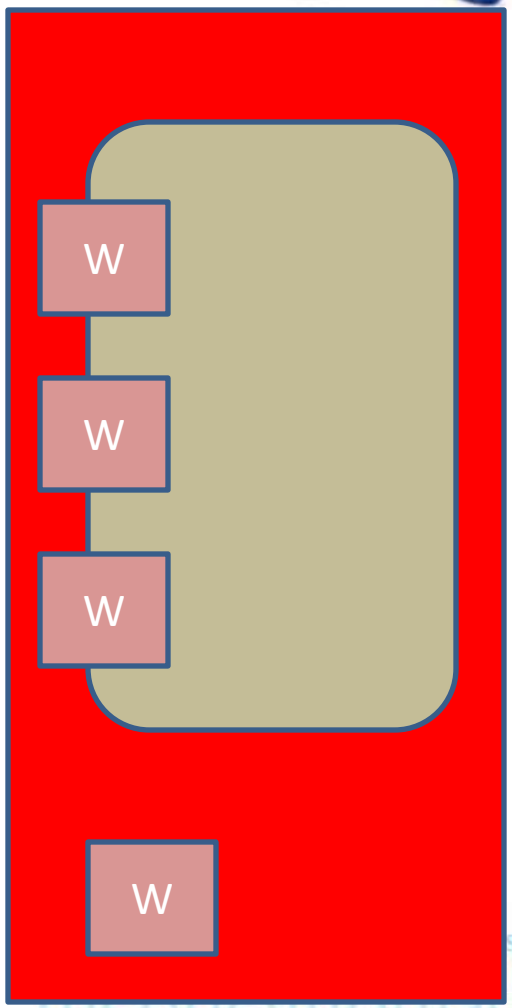
- Outcome of competition of 2 drugs for plasma protein binding ????????

- Drug interaction

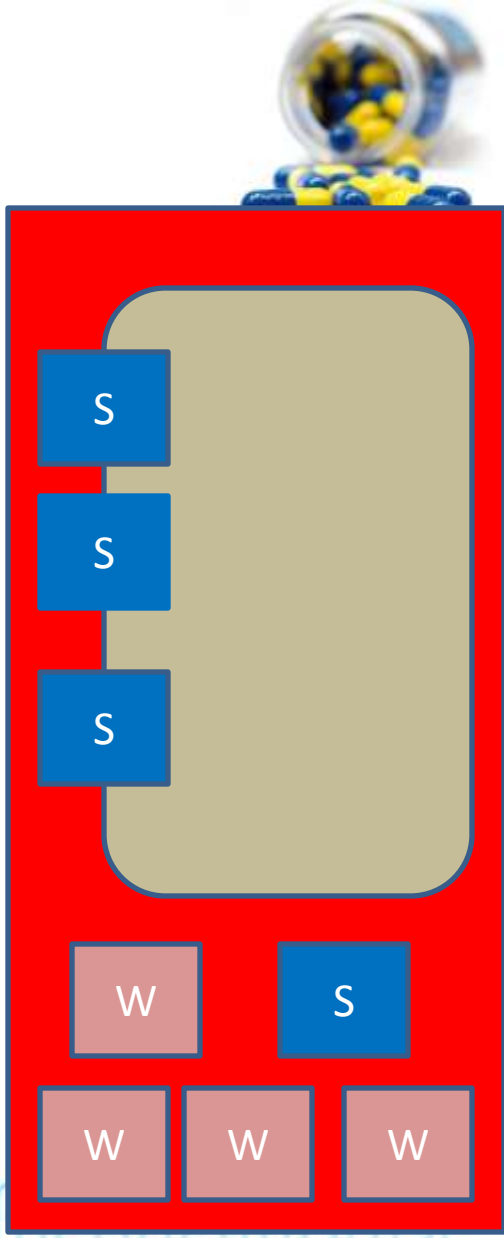
DRUG DISTRIBUTION

- Warfarin is highly bound to albumin, and only a small fraction is free.

- This means that most of the drug is sequestered on albumin and is inert.



DRUG DISTRIBUTION



- Warfarin+ sulfonamide if given together?

- If a sulfonamide is administered at same time, it will displaces warfarin from albumin.
- Leading to a rapid increase in the concentration of free warfarin in plasma.
- Because almost 100 percent is now free, compared with the initial small percentage

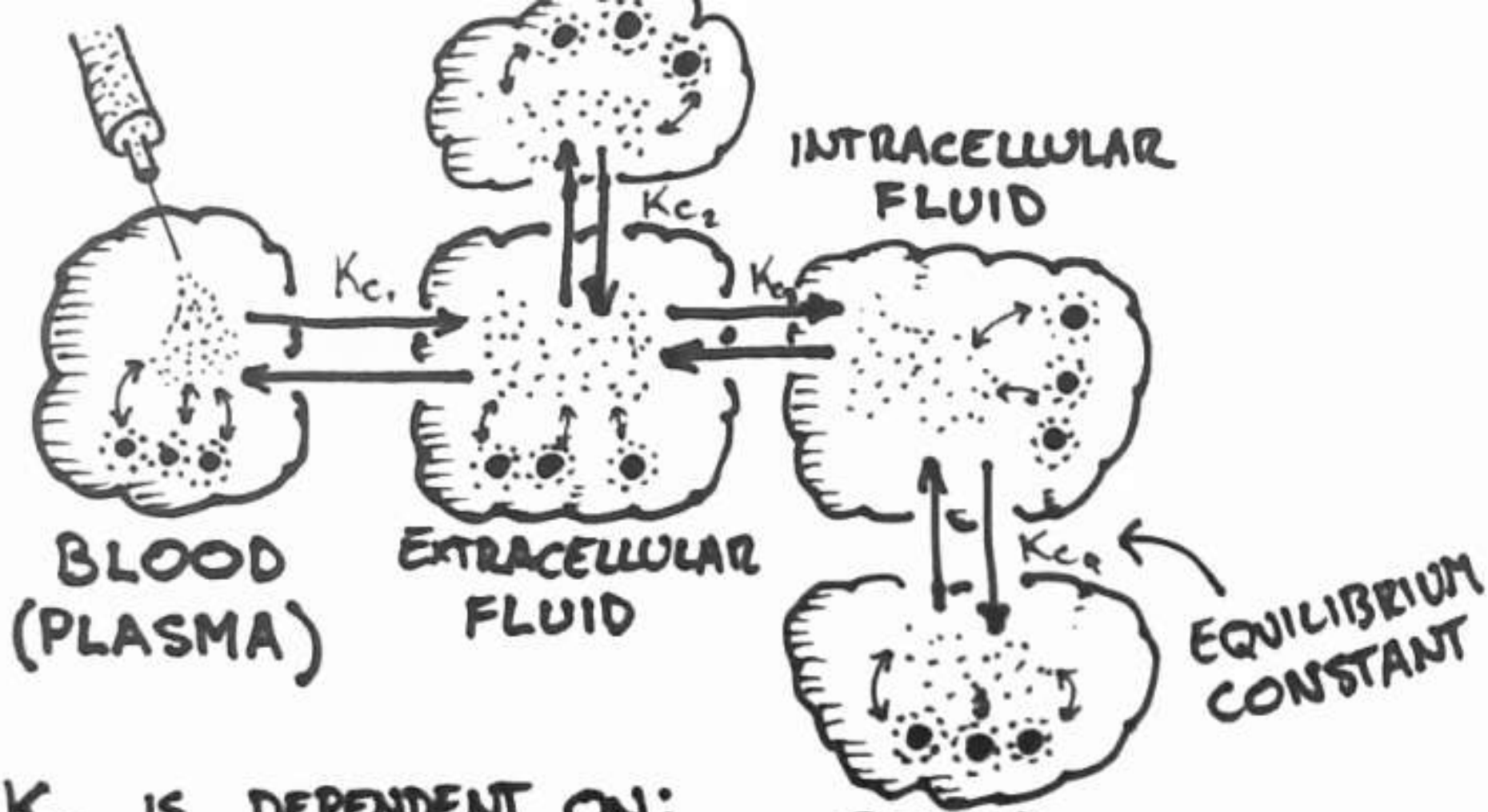
Redistribution of drug

- ✓ Highly lipid soluble drugs when given by i.v. or by inhalation initially get distributed to organs with high blood flow, e.g. brain, heart, kidney etc.
- ✓ If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of the drug action.
- ✓ Later, less vascular but more bulky tissues (muscles,fat) take up the drug and plasma concentration falls and drug is withdrawn from these sites.
- ✓ Greater the lipid solubility of the drug, faster is its redistribution. Eg. Thiopetal sodium.

Blood flow
(% from Cardiac Output)

- Liver 27.8%
- Kidney 23.3%
- Skeletal muscle 6- 15.6%
- Brain 13.9%
- Skin 4%
- Fat tissues 2%
- Placenta & Fetus 9%

- Drugs distributed quickly and completely in well perfused tissue (e.g Brain, heart, kidney).



K_c IS DEPENDENT ON:

- PERMIABILITY OF BARRIERS
- pH OF COMPARTMENTS
- BINDING CAPACITY

OTHER

- CSF
- PERITONEUM
- SYNOVIAL FLUID
- FETUS

Tissue binding

- Some drugs readily distribute in those specific tissues & remain accumulated there….

- Tetracycline to bone
- Phenobarbitone to brain
- Chlorpromazine to eye
- Chloroquine to kidneys etc…

Tissue Binding (Special affinity)

Selective distribution—this refers to the situation in which some drugs attain higher concentration in certain tissue compared to the other drugs depending upon—

a. the affinity of the drug for the tissue

b. selectivity of the drug binding

✓Eg. Chloroquine (anti-malarial drug) accumulates in the retina and causes retinopathy

✓Calcium accumulates in the bone

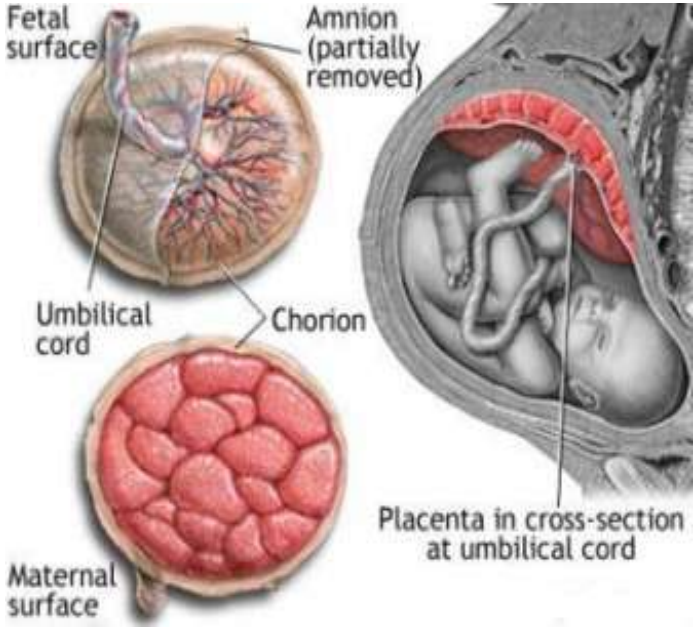
✓Iodine accumulates in the thyroid.

Blood Brain Barrier

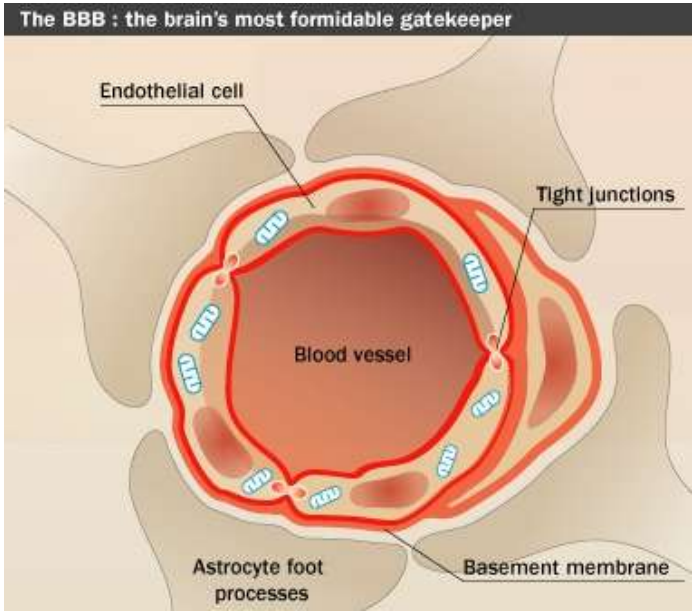
- This is a tight junction
- There is no fenestrations or slit in between the endothelial cells of capillaries
- Layer of astrocyte foot processes makes this more impermeable
- Only lipid soluble substances can cross the BBB

ANATOMICAL BARRIES

Placenta Barrier



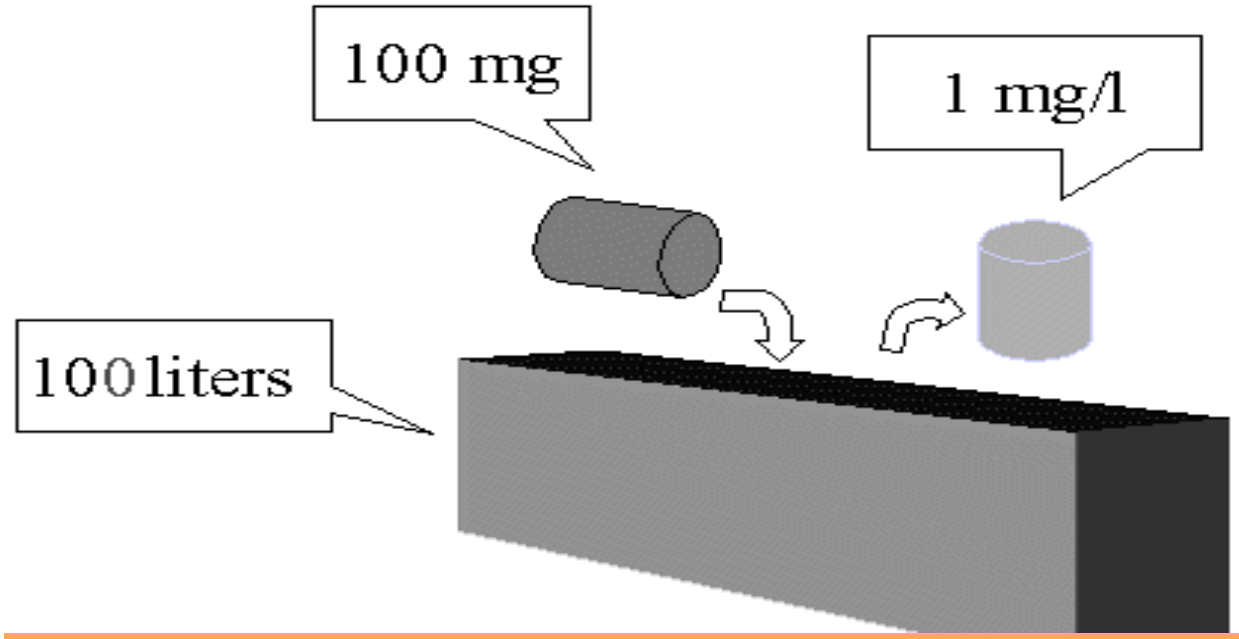
Blood brain barrier



Involves highly lipid soluble substance

Volume of distribution

- Volume of distribution (Vd) of drug:
- Vd means the amount of fluid in which the administered drug is distributed.



DRUG DISTRIBUTION

- The **Volume of distribution** (V_D), also known as **Apparent volume of distribution**, is used to quantify the distribution of a drug between plasma and the rest of the body after oral or parenteral dosing.

- It is called as Apparent Volume because all parts of the body equilibrated with the drug do not have equal concentration.

DRUG DISTRIBUTION

$$Vd = \frac{\text{Dose of the drug given (Q)}}{\text{Concentration of drug in plasma (Cp)}}$$

So, if Dose given: 100mg &

C_p : 1mg/L {*C_p is the plasma concentration* }

Then,

Vd = Dose/ C_p

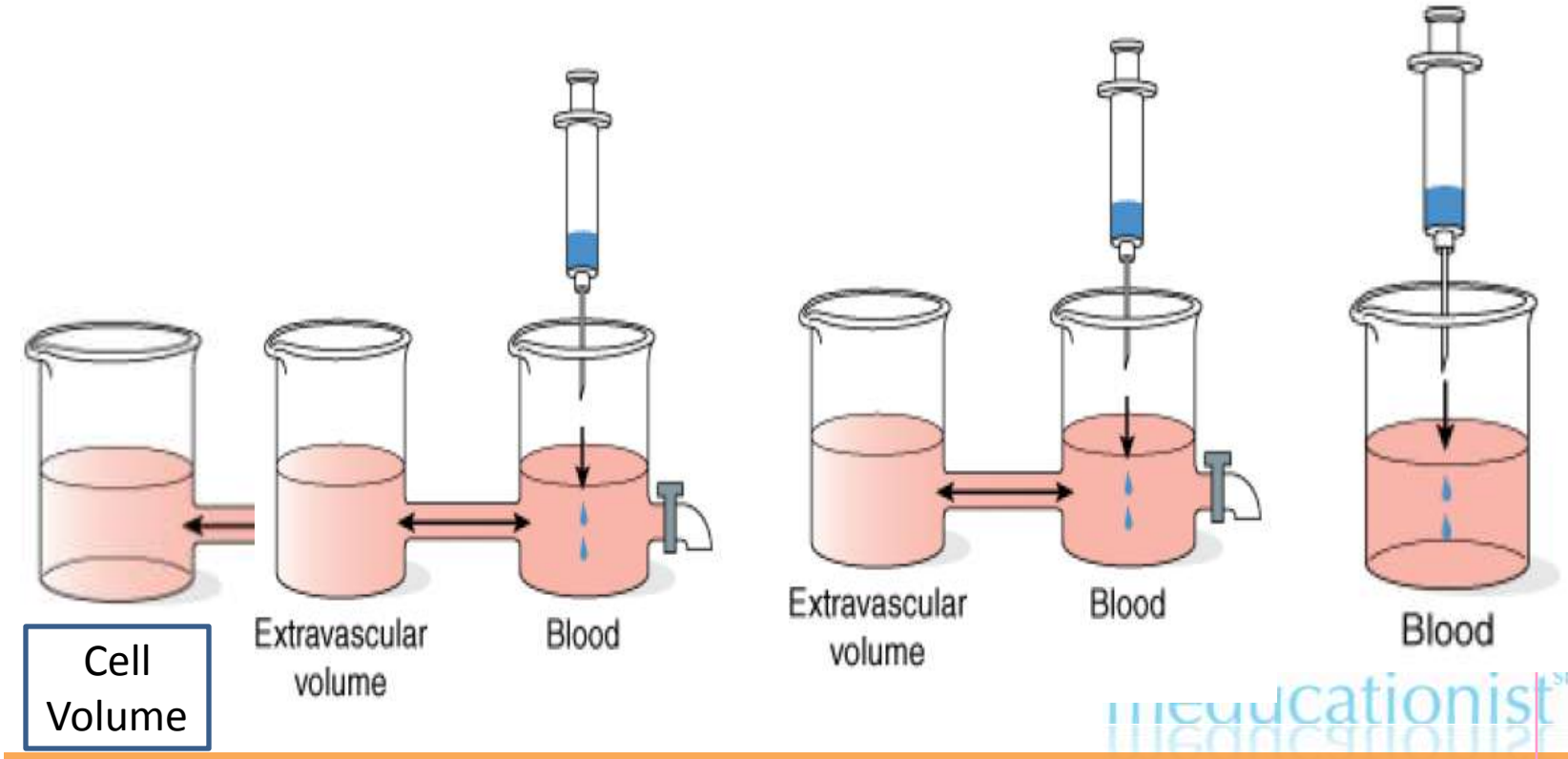
Vd = 100/1 = 100 L

DRUG DISTRIBUTION

- The size of fluid compartments of the body:
- Plasma 0.045 l/kg (4.5% of BW)
- Extracellular fluids 0.20 l/kg (20% of BW)
- Total body water 0.60 l/kg (60% of BW)

- Therefore, a drug which has an apparent volume of distribution of about 60% appears to be distributed in a compartment equivalent to the total body water

- Water compartments in the body:



DRUG DISTRIBUTION

- Volume distribution of heparin 4L means?

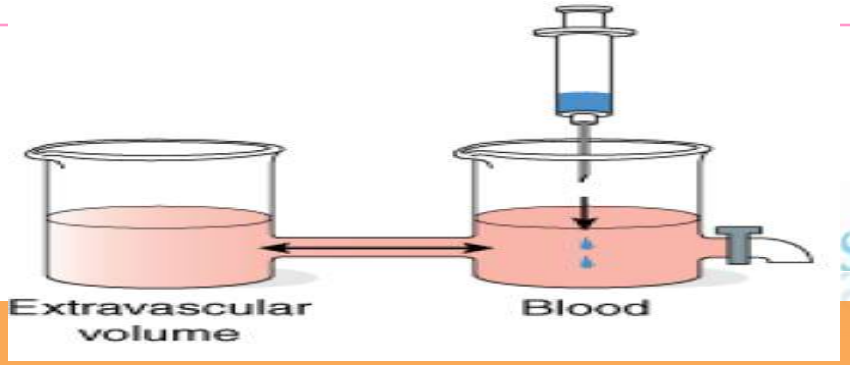
- It means heparin distributes about 4 liters of body fluid.
- So it remains in only 1 compartment, that is blood.

- Why so small volume of distribution?
- Because, Heparin has-
  - Very large molecular weight.
  - Extensive plasma protein binding.

DRUG DISTRIBUTION

- Volume distribution of Aminoglycosides is 14 liter means?

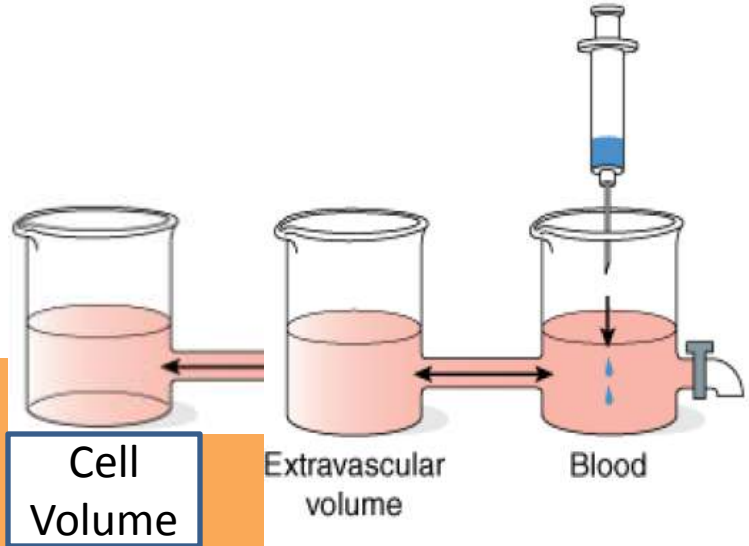
- This drug has a low molecular weight but is hydrophilic.
- So, it can move through the endothelial gap junctions of the capillaries into the interstitial fluid.
- It distribute into (plasma water + interstitial fluid) = extracellular fluid (14 liters)



DRUG DISTRIBUTION

- Why ethanol has high volume of distribution (60% total body water 42L)?

- Ethanol is a drug has a low molecular weight and is hydrophobic, so can it move into the Plasma+ Interistitium + cell.




Thank you!