Pharmacokinetics 2

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ILOS

- Define volume of distribution
- Recognize the clinical importance of factors affecting drug distribution
- Calculate volume of distribution
- Define Loading dose
- Rationalize importance of Loading dose

Pharmacokinetics [Distribution]

II) Distribution

• After absorption from whatever route of administration a drug will distribute according to the compartmental models.

These compartments are:

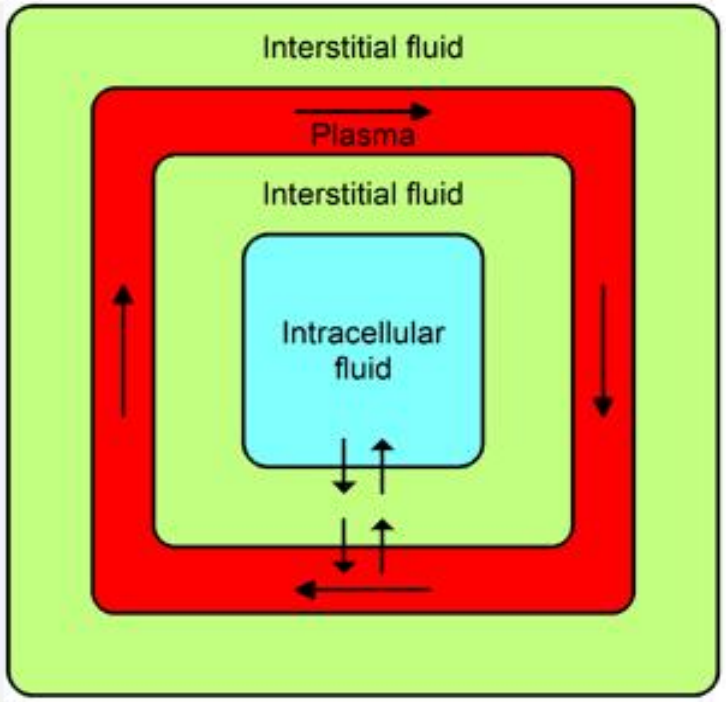
o **Intravascular:** Confined to the plasma = about **4** liters

o **Interstitial:** Confined to extracellular fluid = about **10** liters

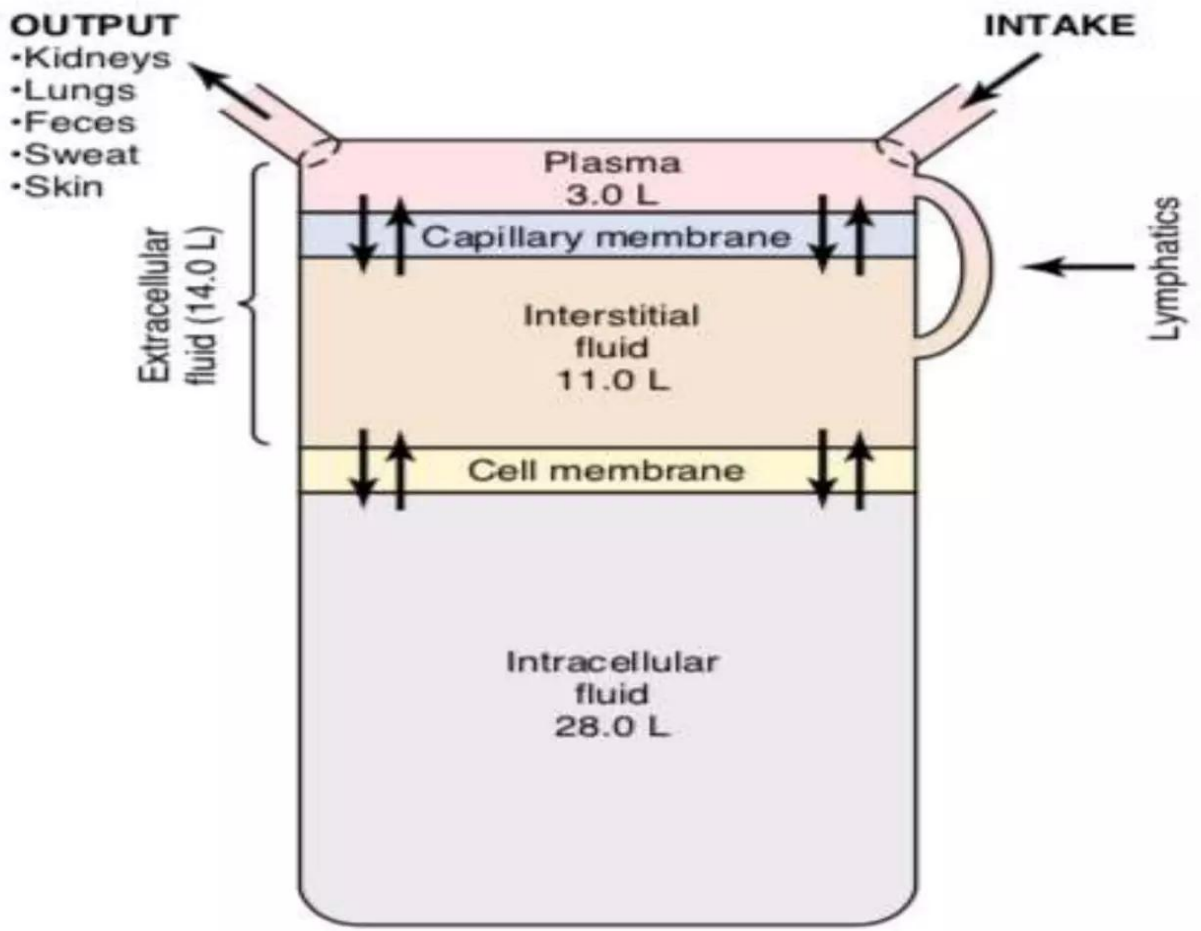
o **Intracellular** = about **28** liters

o **Extracellular fluid** = Intravascular + Interstitial= About **14** liters

o **All over the body** = Extracellular + Intracellular = about **42** liters.



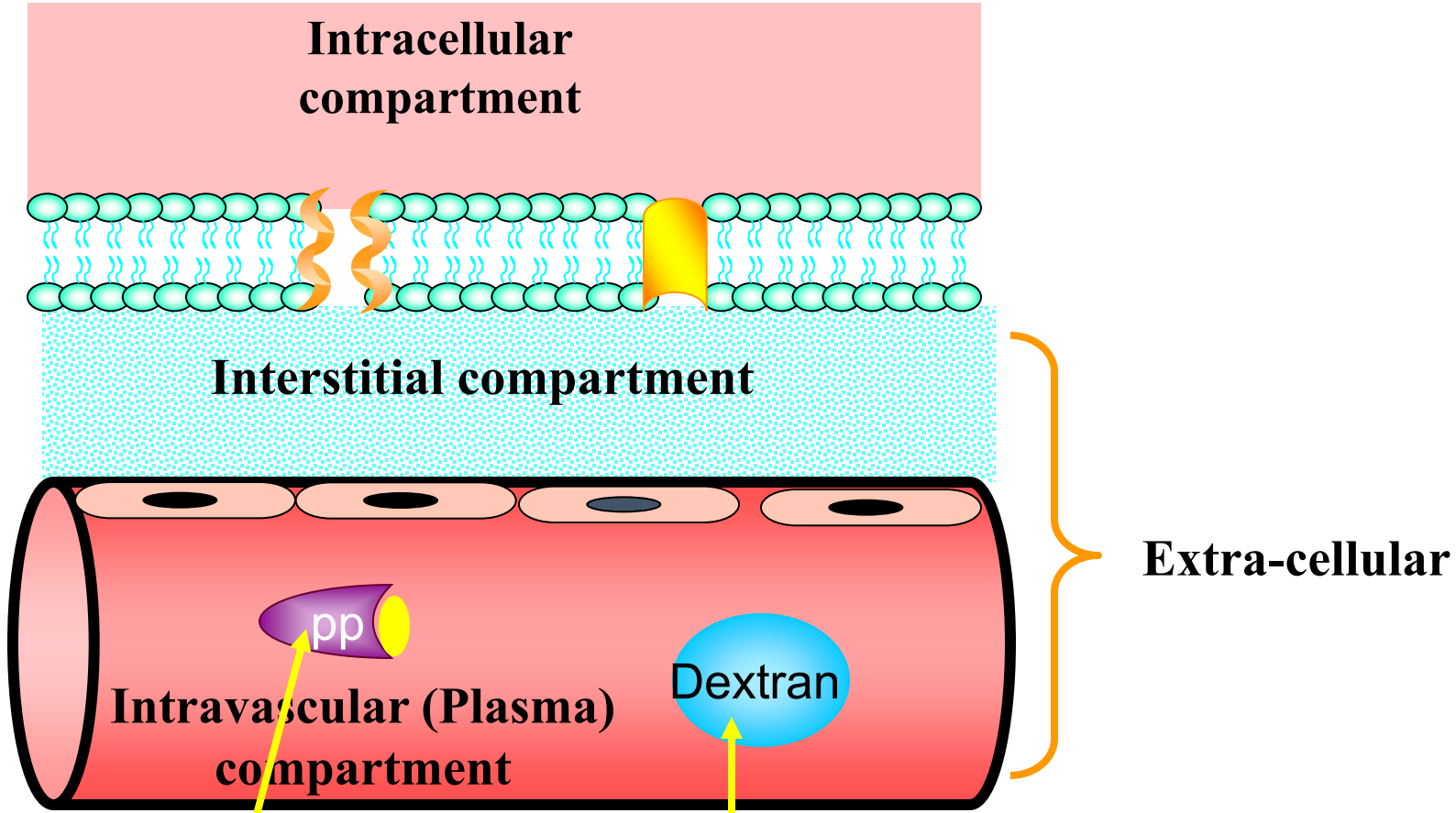
Pharmacokinetics [Distribution]



All over the body = Extracellular + Intracellular = **about 42 liters.**

Patterns of drug distribution??

One compartment model (intravascular)



2. highly bound to plasma proteins

1. High molecular weight

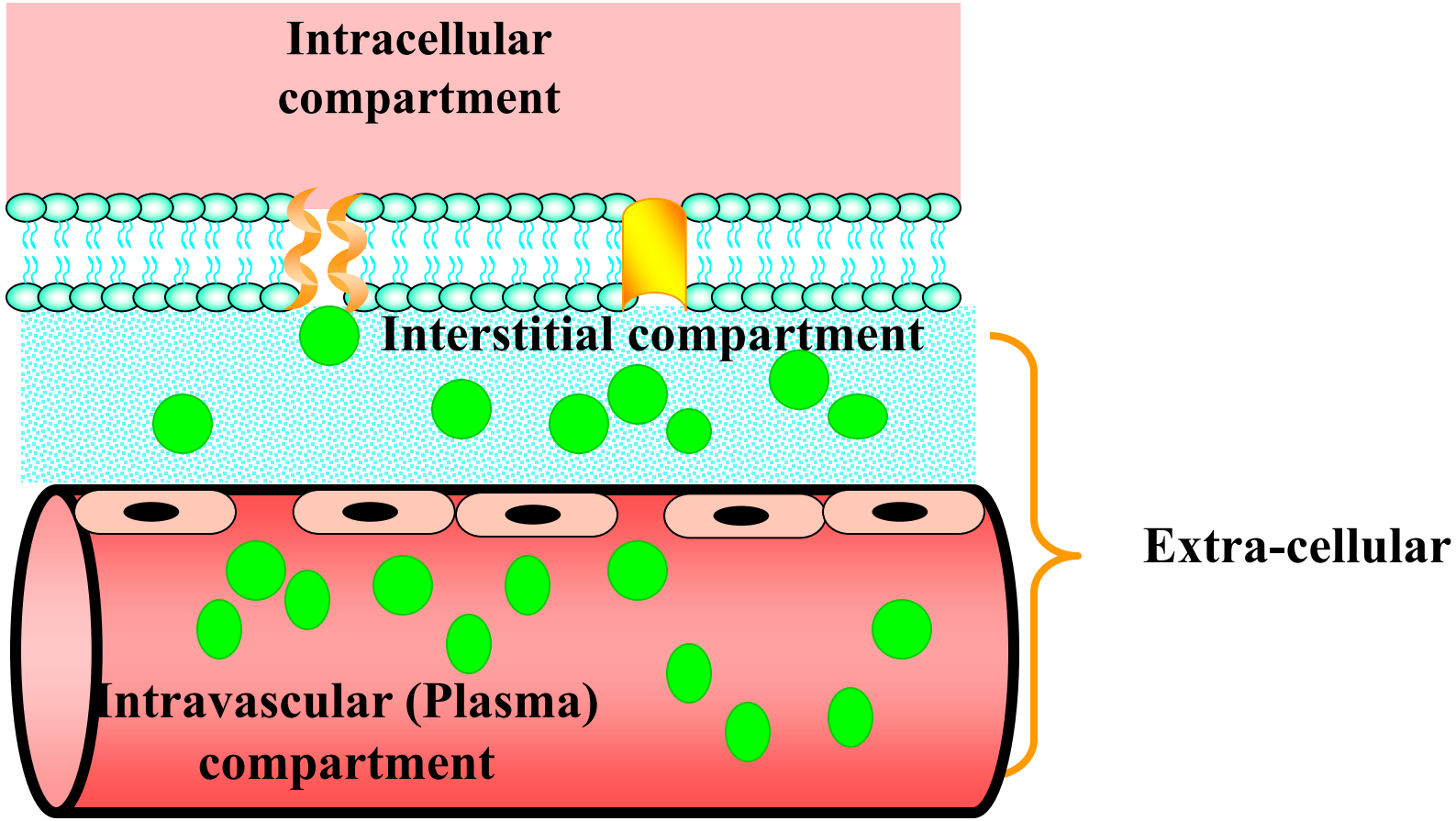
Pharmacokinetics [Distribution]

Patterns of distribution

1- One compartment model (intravascular):

- Drugs having **too large MW** to move out through endothelial slit junctions of the capillaries.
- **Are trapped intravascular** and distributed in a volume of plasma of **4 L** which is equal to 6% of a 70-kg body weight individual.
- E.g. **High MW Heparin** or drugs highly bound to plasma proteins as **warfarin**.

Two compartment model (extracellular distribution)



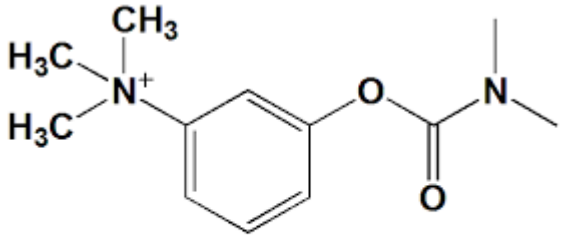
Quaternary ammonium compounds

Pharmacokinetics [Distribution]

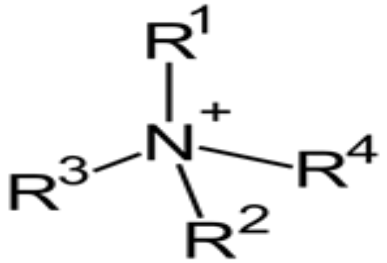
Patterns of distribution

2-Two compartments model (extracellular):

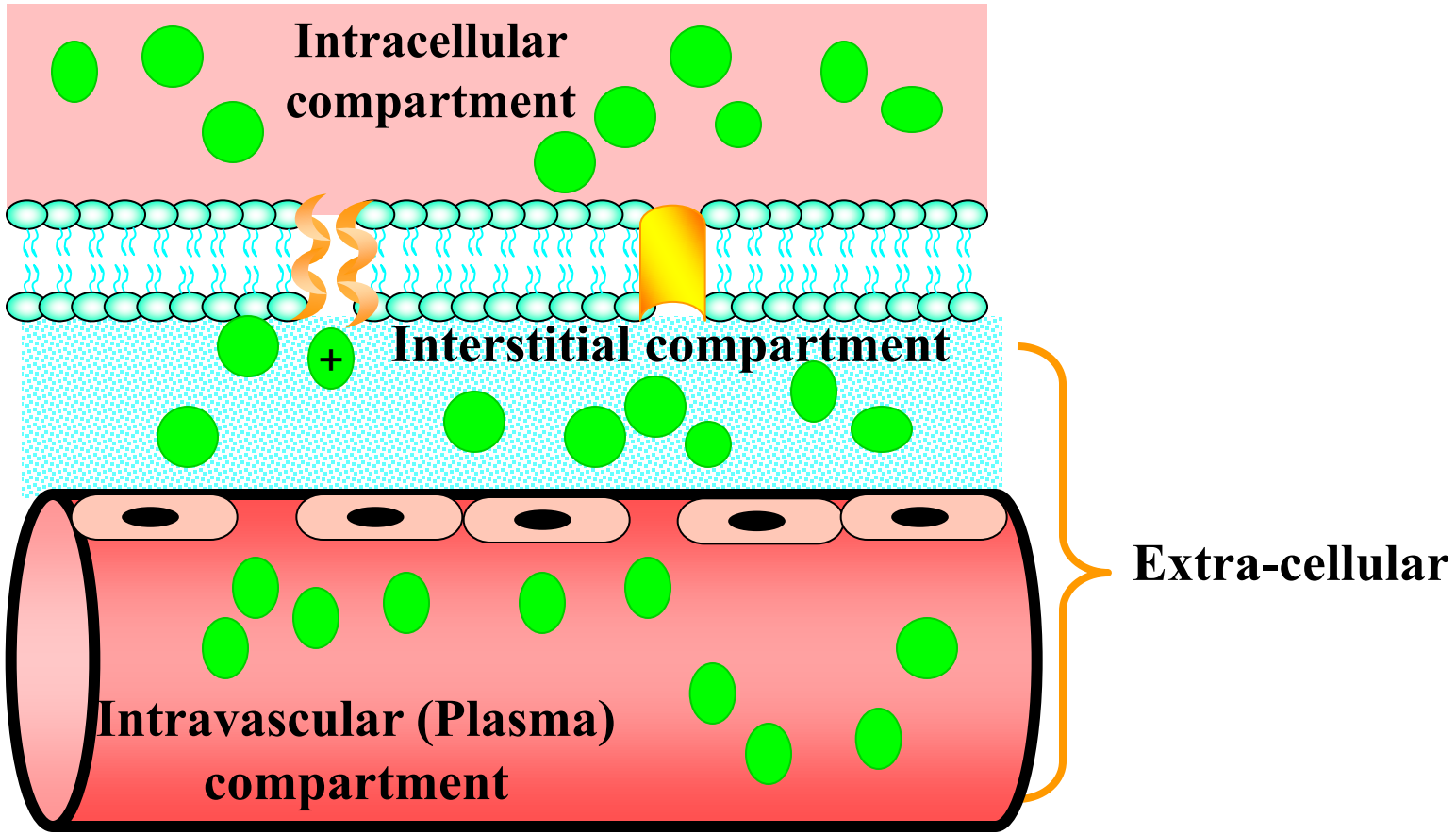
- These compartments are **intravascular and interstitial fluid**. Drugs having **low MW, but not lipid soluble**, are distributed to a volume of **14 L**= 20% of body weight e.g. **Quaternary ammonium compounds.**



Neostigmine



Multicompartmental model (extracellular and intracellular distribution)



Alcohol

Phenytoin

Pharmacokinetics [Distribution]

Patterns of distribution

3-Multicompartment model (Extra and intracellular):

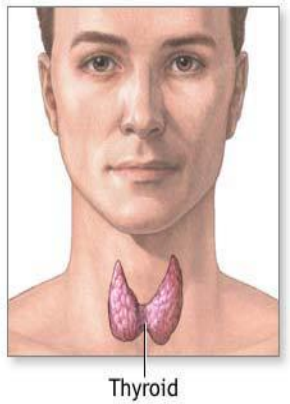
Drugs are distributed to total body fluids (42 L / 70 Kg). They are of low MW and are hydrophobic (Lipid soluble).

4. Other sites:

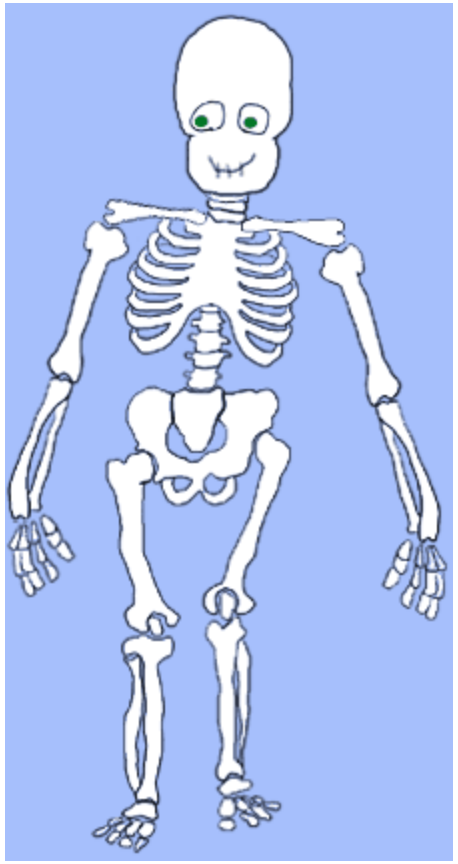
Some drugs have special affinity for certain tissue:

1. Iodine in thyroid.
2. Thiopentone in fat.
3. Tetracycline and calcium in bone and teeth.

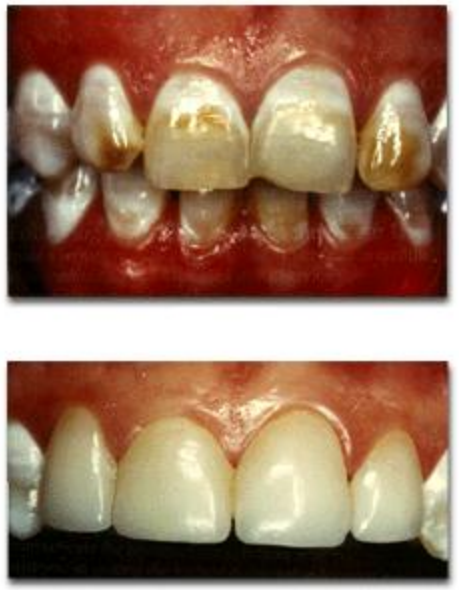
Selective distribution



Iodide in thyroid gland



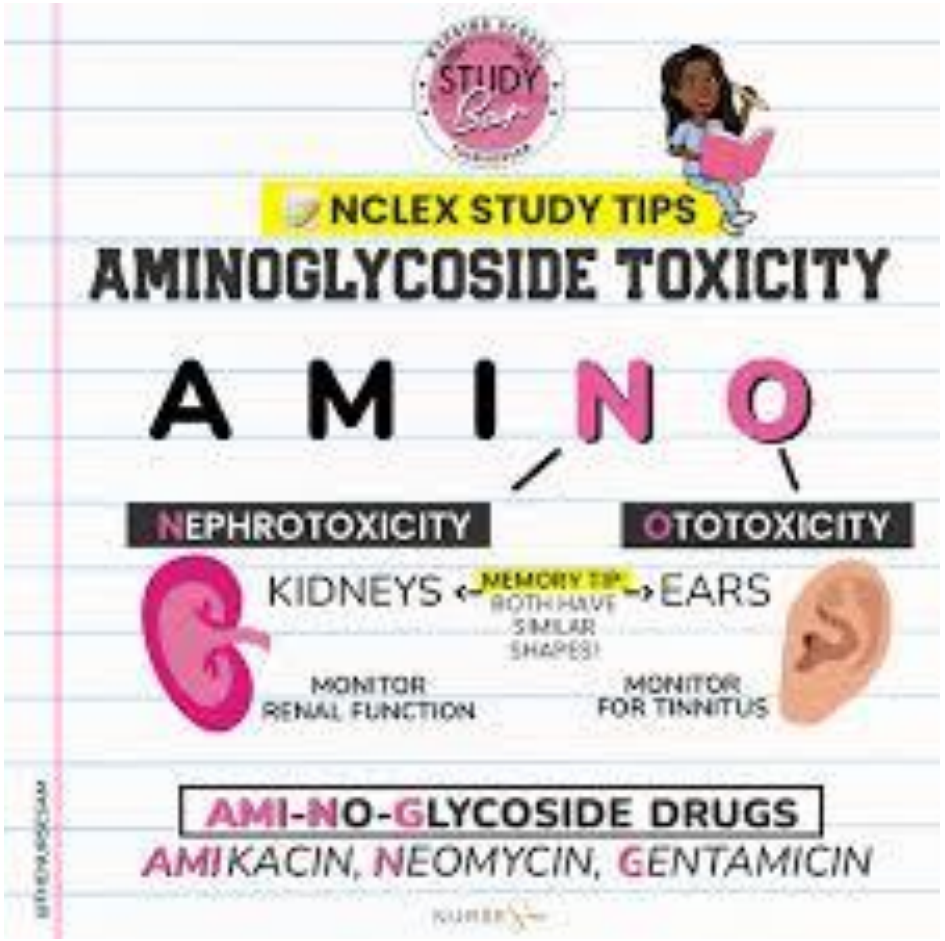
calcium in bones



Tetracycline in bone and teeth

Selective distribution

Aminoglycosides as streptomycin in Kidney and Vestibular system

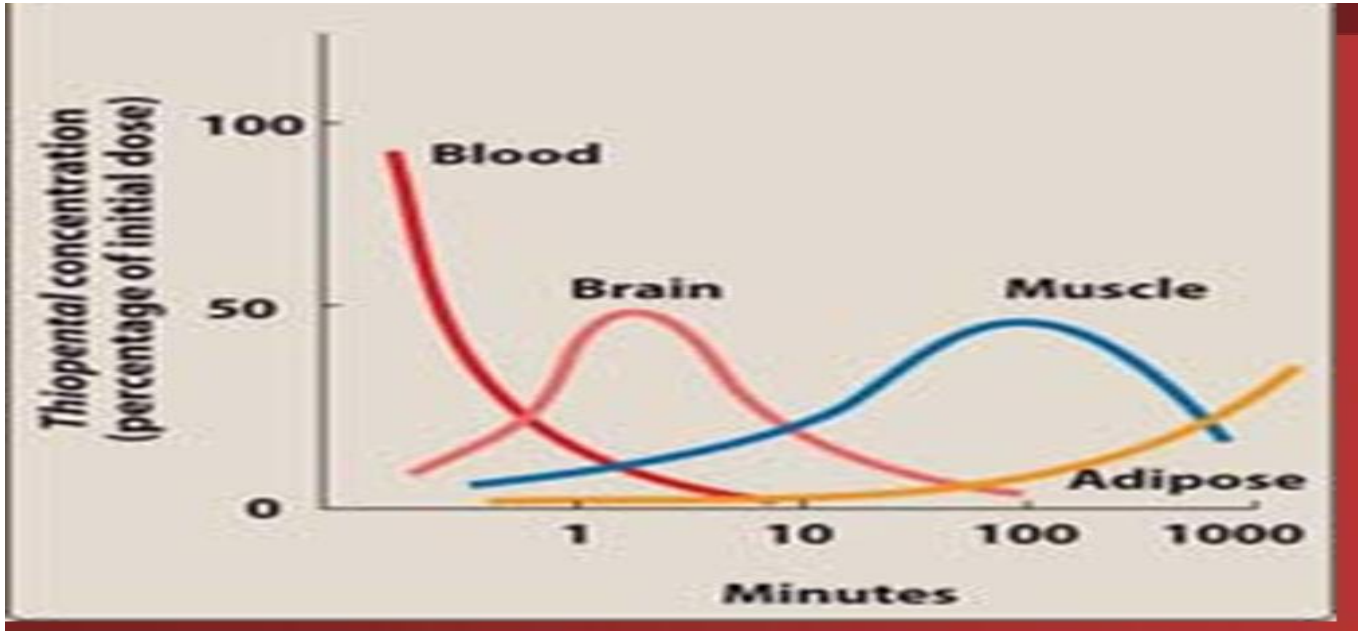


Thiopentone in fat

Pharmacokinetics [Distribution]

N.B: Redistribution:

- Can occur with **highly lipid soluble drugs as Thiopentone**. First this drug concentrates in **brain** due to high lipid content and blood flow, then it redistributes to less perfused tissues such as the **skeletal muscles** then lastly to the **fatty tissues.**
- **Importance of Redistribution:** duration of some drugs **as thiopentone depend on rate of redistribution not rate of metabolism or excretion.**



Pharmacokinetics [Distribution]

Factors affecting distribution of drugs:

1- Physicochemical properties of the drugs:

- Molecular weight (MW) – degree of ionization – lipid solubility.

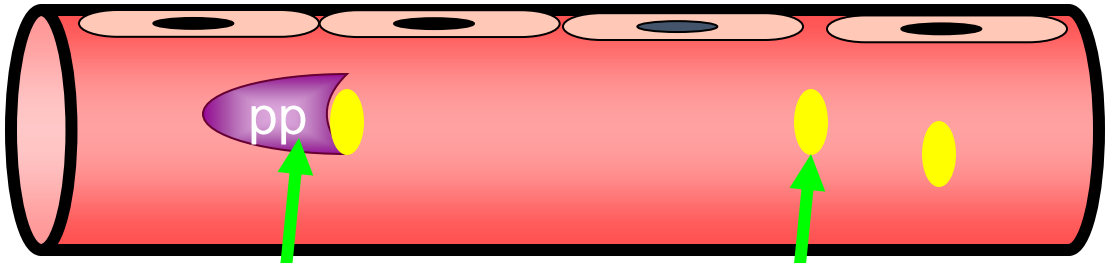
2- Binding to plasma proteins:

Upon entering the blood, drugs may be bound to plasma proteins (chiefly albumin). **Salicylates** are strongly bound to plasma proteins.

- So, **drugs are carried in blood** in 2 forms:

a) Free form: Pharmacologically **active** – diffusible – metabolized – excreted.

b) Bound form: inactive, non-diffusible, not metabolized and not excreted **(act as reservoir)**.



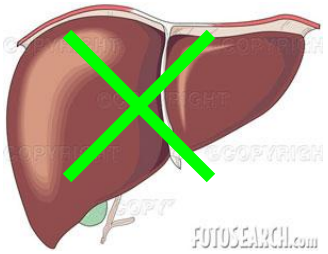
2-*Bound form*

inert,

non-diffusible,

not available for metabolism

&excretion.



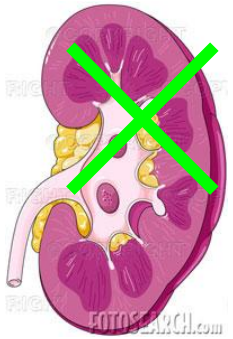
1-*Free form:*

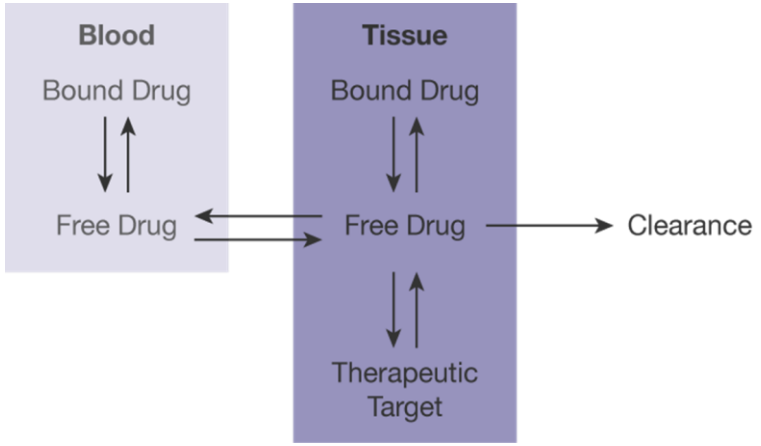
active,

diffusible,

available for biotransformation & excretion.

It acts as a **reservoir** for drug.





Pharmacokinetics [Distribution]

Factors affecting distribution of drugs:

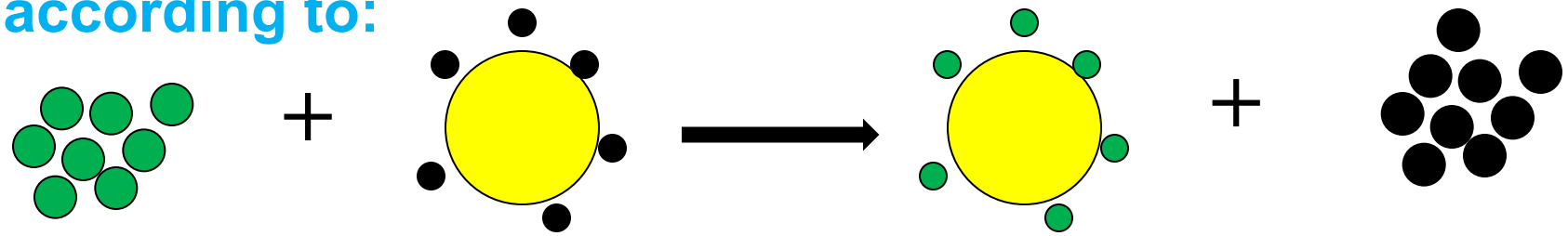
*****The amount of drug bound to plasma protein will change according to:**

- **Affinity for binding sites:** Competition between drugs for binding sites as a drug may displace another one from its binding site (cause drug interactions) e.g. **Salicylates can displace warfarin** → hemorrhage.

- **Hypoalbuminemia:** e.g. in starvation, malnutrition → ⇧ free drug → therapeutic dose changes to toxic dose e.g. **Phenytoin.**

- **The more the binding** the more the duration e.g. **Sulphonamides.**

The amount of drug bound to plasma protein will change according to:



Salicylates

Sulphonamide

Warfarin

Salicylates

Sulphonamide

Warfarin

Affinity for binding sites

Protein binding can prolong the plasma half life of the drug

e.g. sulphonamides.

Hypoproteinaemia may render the safe therapeutic dose of the drug into relative toxic dose e.g. Phenytoin.

Pharmacokinetics [Distribution]

Factors affecting distribution of drugs:

3- Passage across barriers:

a- Passage to central nervous system across blood brain barrier (BBB)

- **Non-ionized, lipid soluble drugs** can pass BBB **e.g.** Physostigmine can stimulate CNS, neostigmine cannot.

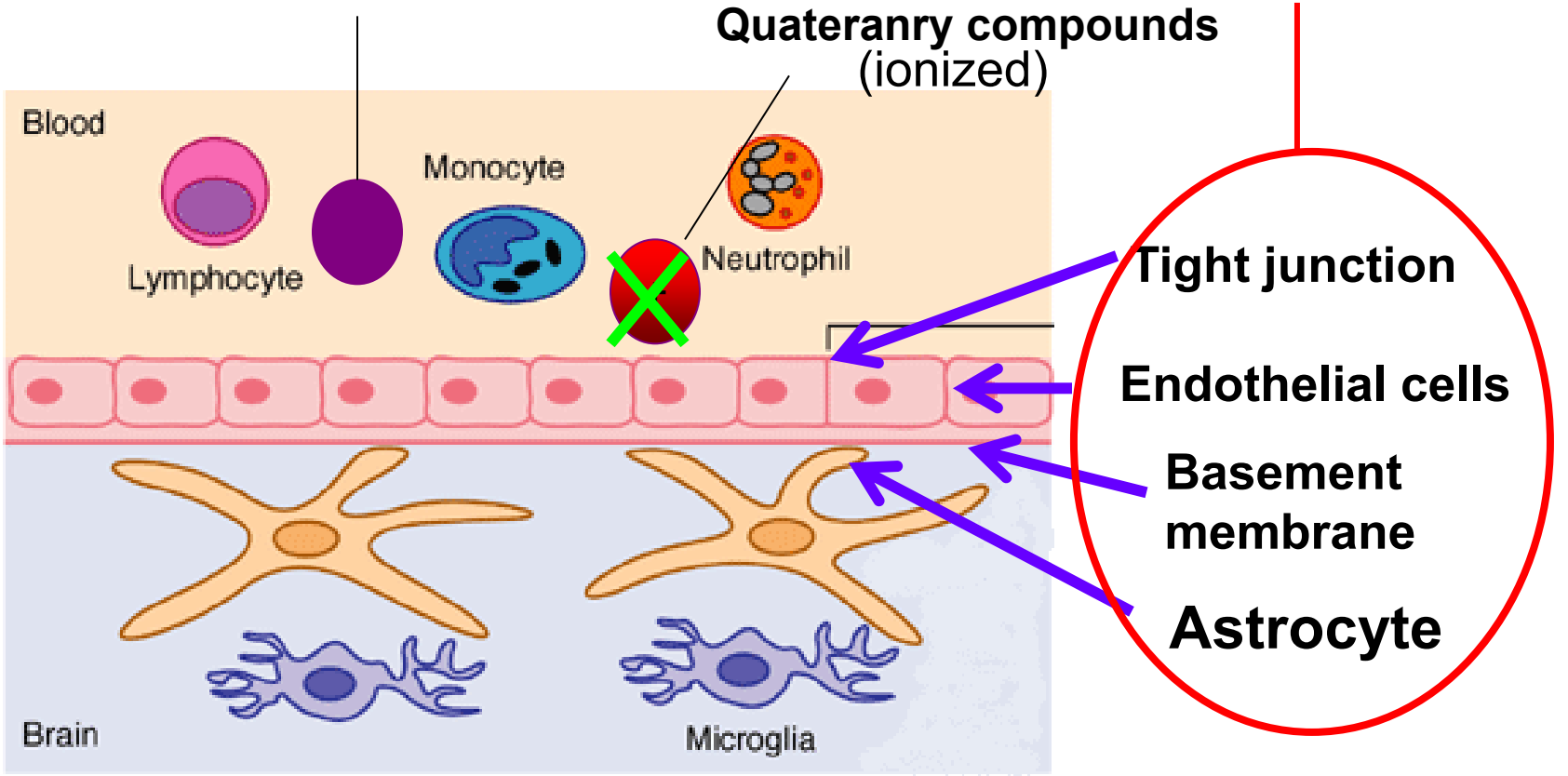
- **Inflammation (Meningitis) increases permeability of B.B.B. Penicillins** can pass inflammed meninges but NOT normal ones.

Passage of Drugs to CNS

Lipid soluble
non-ionized drugs

Blood brain barrier

Quaternary compounds
(ionized)



Pharmacokinetics [Distribution]

Factors affecting distribution of drugs:

b- Passage to fetus across placental barrier:

- The **placental barrier** acts like a **cell membrane**. So non-ionizable, lipid soluble drugs pass from mother to fetus more easily
- **Drugs that pass placental barrier may cause:**

*During pregnancy → **Teratogenicity** e.g. Tetracyclines

*During Labor → Neonatal asphyxia e.g. Morphine.

Passage of Drugs to the Fetus

The placental barrier acts like a cell membrane. **So non-ionized, lipid soluble drugs pass from the mother to the fetus more easily.

- **During pregnancy** → Teratogenicity e.g. **Tetracyclines**
- **During Labor** → Neonatal asphyxia e.g. **Morphine.**

Pharmacokinetics [Distribution]

Factors affecting distribution of drugs:

c- Passage of drugs through breast milk:

- Most drugs administered to lactating women are detectable in milk.
- pH of milk is more acidic (7.0) than that of plasma (7.4), so basic drugs ionize and accumulate in milk (ion trapping).
- Milk contains more fat than plasma which favors retention of lipid soluble drugs.

Pharmacokinetics [Distribution]

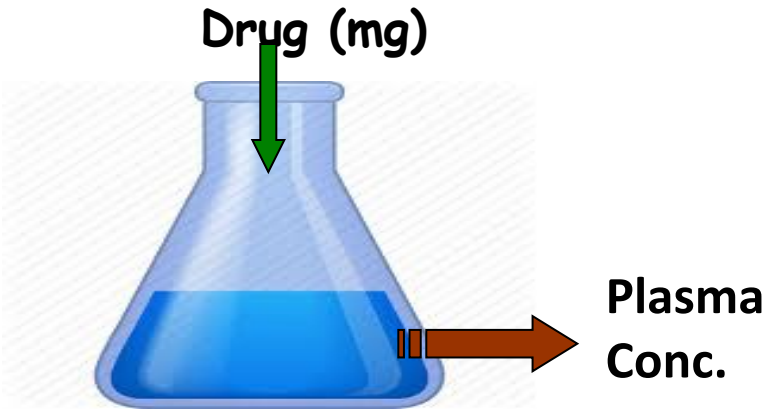
Apparent volume of distribution (Vd):

- If we assume that the body consists of **one big fluid compartment** and that the total amount of drug **(A)** would be uniformly distributed in that compartment such that it would have the same concentration as in plasma **(C).**

- Thus **the apparent volume of distribution (Vd) = A (mg) / C (mg/ml)**
- **A =total amount of drug in mg**
- **C = initial concentration of the drug in plasma in mg/ml.**

Volume of distribution

$$Vd = \frac{A}{C}$$



Assuming that the drug is distributed equally in one compartment

A =Total amount of the drug in mg

C =Plasma Concentration of the drug in mg/ml

Pharmacokinetics [Distribution]

Apparent volume of distribution (Vd) Significance:

1- Rough estimation of drug distribution:

- Drugs with **low Vd are retained in vascular compartment** due to high molecular weight or high binding to plasma proteins.
- Drugs with **high Vd occupy multicompartment or concentrated in tissues** (e.g. digoxin in heart).
- It is called apparent volume of distribution because Vd of some drugs as digoxin (500L/70kg) can extremely exceed any physical volume in the body.

Pharmacokinetics [Distribution]

Apparent volume of distribution (Vd) Significance:

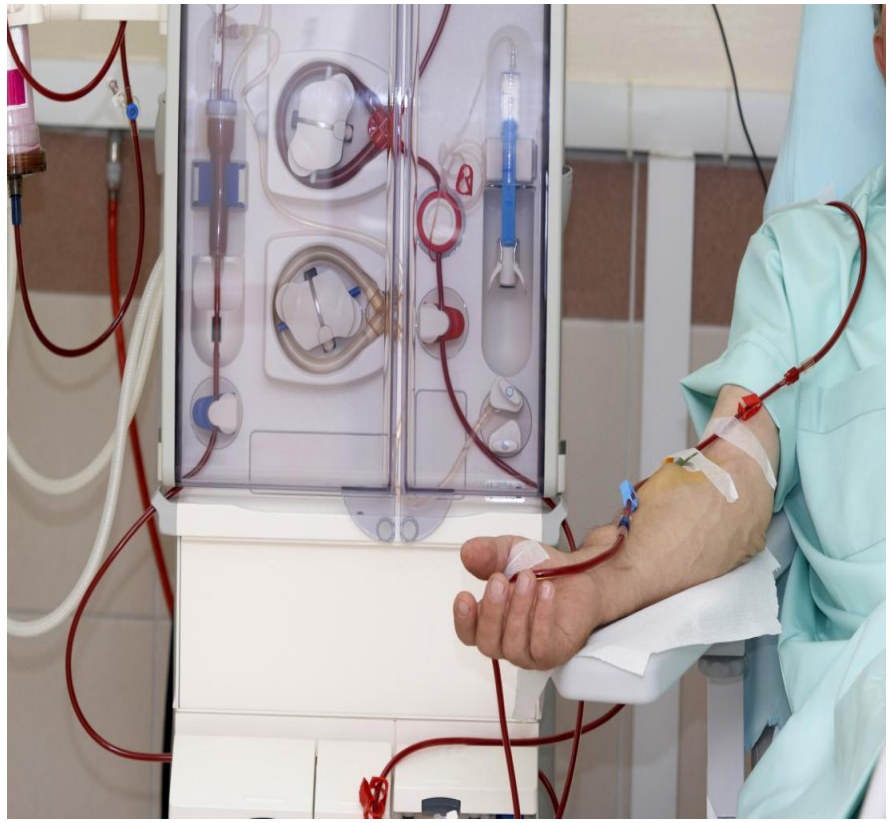
2- Determine the loading dose and the total amount of drug in the body:

** **A (mg) = Vd x C (mg/ml).**

** **Loading dose = Vd x Desired concentration (Css)**

3- In cases of drug toxicity

- **Dialysis can be done only with small Vd** which means most of drug is present in the circulation e.g. Aspirin.



Mcqs

1. **Which one of the following sentences is correct regarding the free form of drug? :**

a. Inactive biologically.
b. Pharmacologically active.
c. Not distributed.
d. Not metabolized and excreted.

2. **Which one of the following factors can increase passage of drugs in breast milk?:**

a. Lipid insolubility of drug
b. Alkaline nature of drug
c. High Acidity of drugs
d. High binding to plasma proteins

Thank You