Al- Anbar university - College of Medicine - Pharmacology department

Pharmacokinetics **Lec. 2,3,4**

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Pharmacology

1- **pharmacokinetics** :- what the body dose to drug.

2- **pharmacodynamics** what the drugs dose to body.

Pharmacokinetics

(Liberation, Absorption, Distribution, Metabolism and Excretion) (LADME)

- How the drugs come and goes?

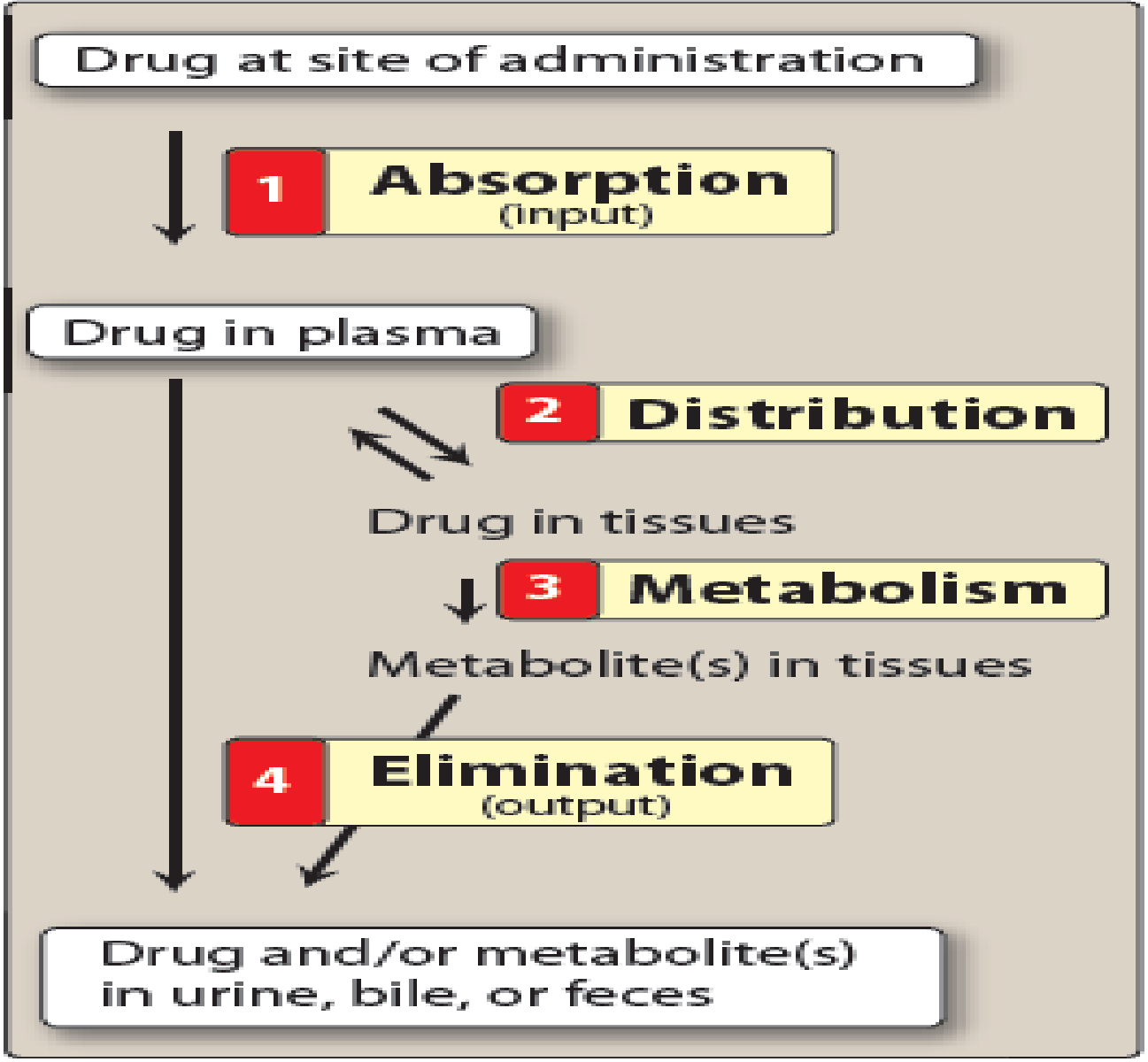


Figure 1.1
Schematic representation of drug absorption, distribution, metabolism, and elimination.

❖ **Absorption** is the movement of a drug from its site of administration to the blood stream.

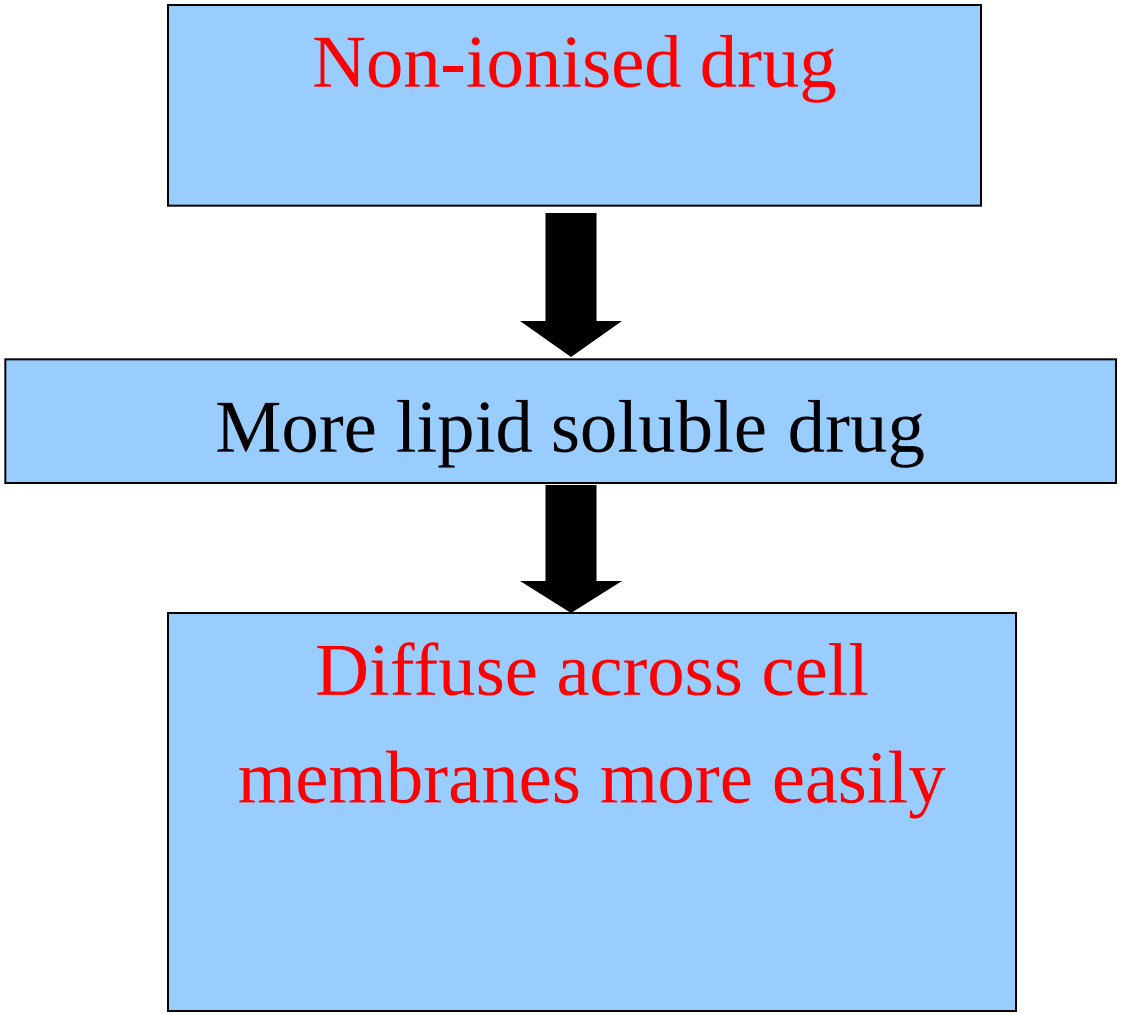
❖**When a drug is administered orally it has to pass through the gut wall which represents a complex biological barrier (complex lipid membrane) before entering the bloodstream.**

Characters：-

Most of drugs are absorbed by the way of passive transport.

- **Intravenous administration has no absorption.**
- **The absorptive speed affects the time of appearing effect.**

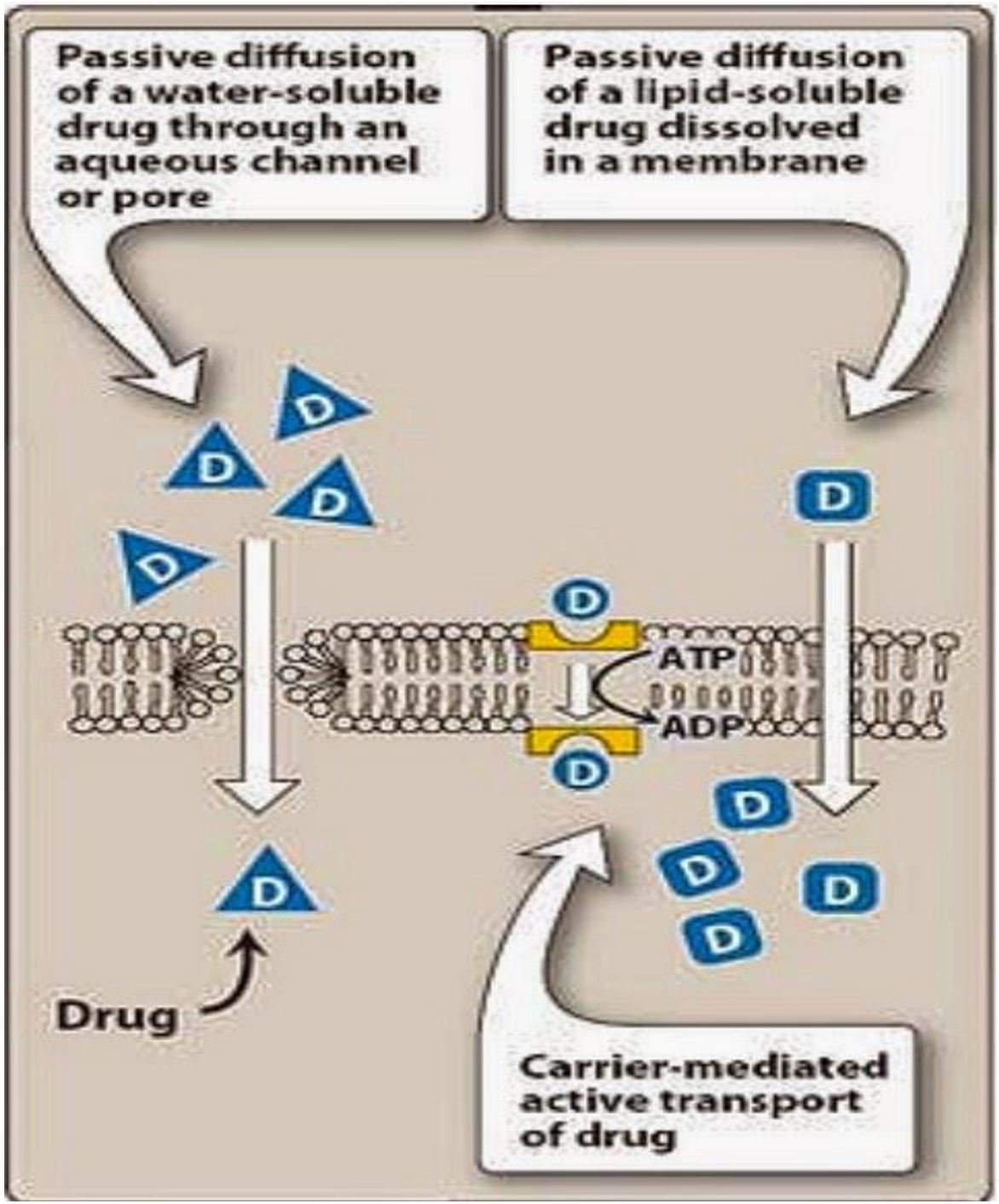
Absorption & Ionization



Factors affecting absorption:

- Nature of drug polypeptides e.g. insulin is broken down by intestinal enzymes, benzylpenicillin is destroyed by gastric acid
- Pharmaceutical formulation
- drug properties: - Lipid solubility, Molecular Weight, polarity, etc.
- Routes of Administration (important):
  - Enteral; parenteral
- Blood flow to the absorption site;
- Total surface area available for absorption

- Interaction with other medications - Iron absorption decrease if administrated with antacids.


Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
D
ATP
ADP
Drug
Carrier-mediated active transport of drug

Mechanisms of drug absorption:-

The passage of drug across cell membrane occur by one of the following processes:

a. Passive diffusion – concentration difference (from high to low) this is being the most important mechanism.
b. Active transport e.g. amino acids, or drugs e.g. ?-methyldopa that resembles endogenous substances.
c. Filtration through pores, limited to molecules of small size e.g. urea.
d. Pinocytosis by which small particles are engulfed by cells of the bowel.

Mechanisms of drug absorption:-

1- Passive diffusion: by

a. Simple	b. Filtration
-Main process of drug absorption. -Drug pass from area of high concentration. -No energy. -No carrier -Depend on: 1- Lipid Solubility of drug. High lipid increase absorption. depend on pH environment, pKa of drug **PKa = log (non-ionization/ionization)** 2- Degree of ionization. Weak acid more abs. in acidic environment so weak acid ionized in base media so leas absor. ↑↑Non ionization incr. Lipid solubility 3- Molecular size.	-Passage of substances (water & small sized molecules) through porous membranes by their hydrostatic pressure or osmotic pressure gradient.

2- Specialized transport:- (too large or poorly lipid soluble).

A-Active transport :

- The drug transferred across cell membrane by help of carrier system (enzymes) from outer surface of the membrane (low concentration) to inner surface (high concentration).
- It's active process (need energy).
-It's the usual mechanism for absorption of Na., K & other electrolytes.

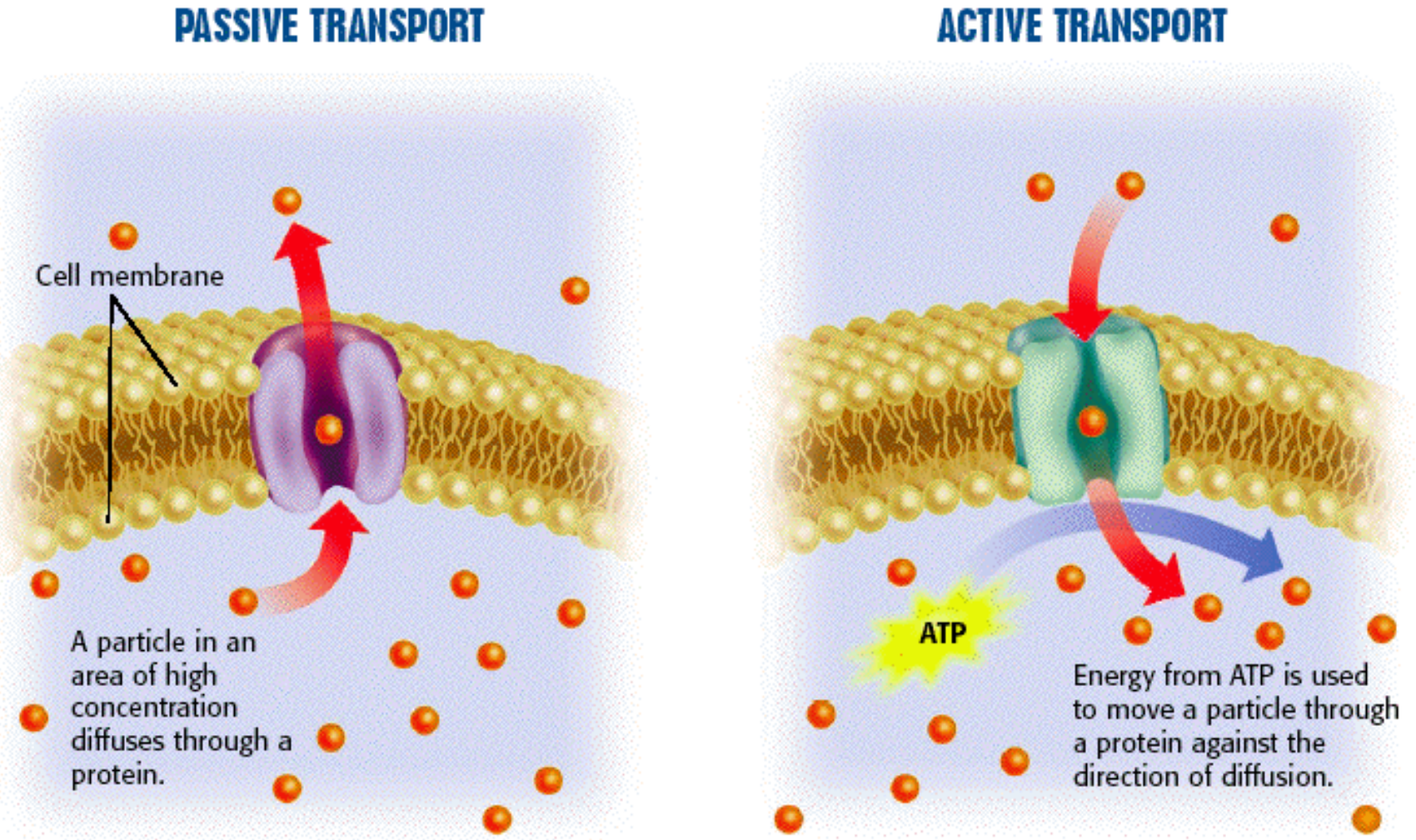
B- Facilitated diffusion:

- Non lipid soluble drugs diffuse through cell membrane by help carrier system (enzymes).
Differ from active process in that it's **not need energy.-**

C- Pinocytosis:

- Cells engulf drug molecules by invaginating their cell membrane to form vesicle that breaks off from cell membrane in the interior cell.
- It's the usual mechanism for absorption of drugs with large molecular weight engulfed inside cells.

Passive and Active Transport



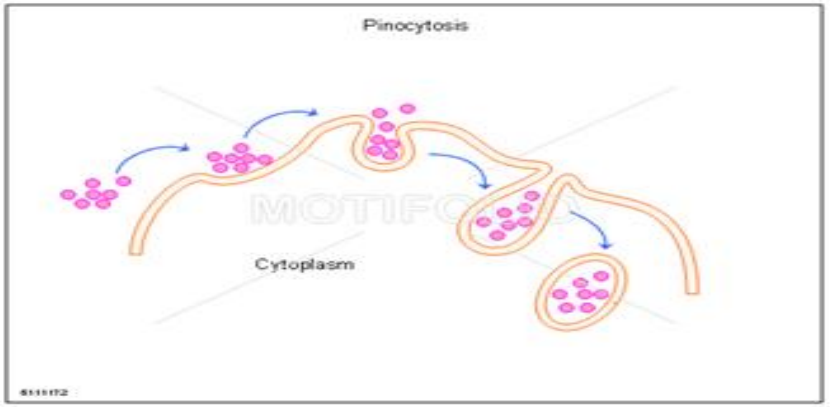
Endocytosis and Exocytosis

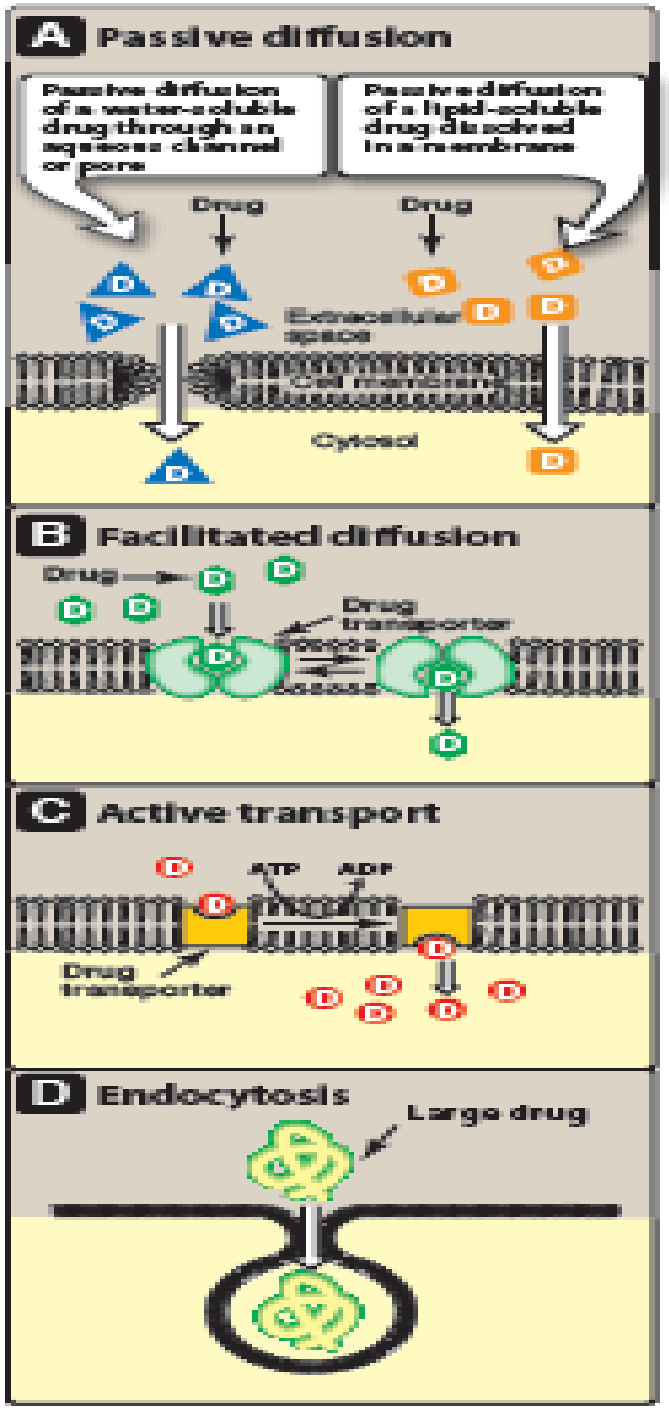
Endocytosis: uptake of membrane-bound particles.

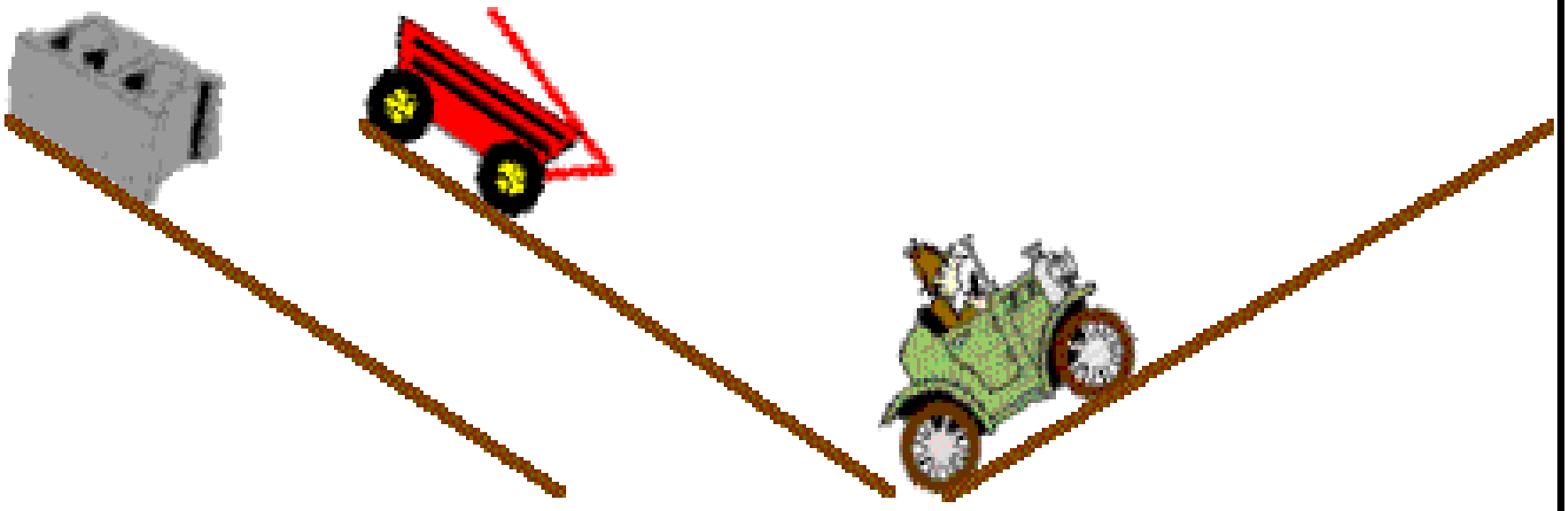
Exocytosis: expulsion of membrane-bound particles.

High molecular weight drugs or Highly lipid insoluble drugs

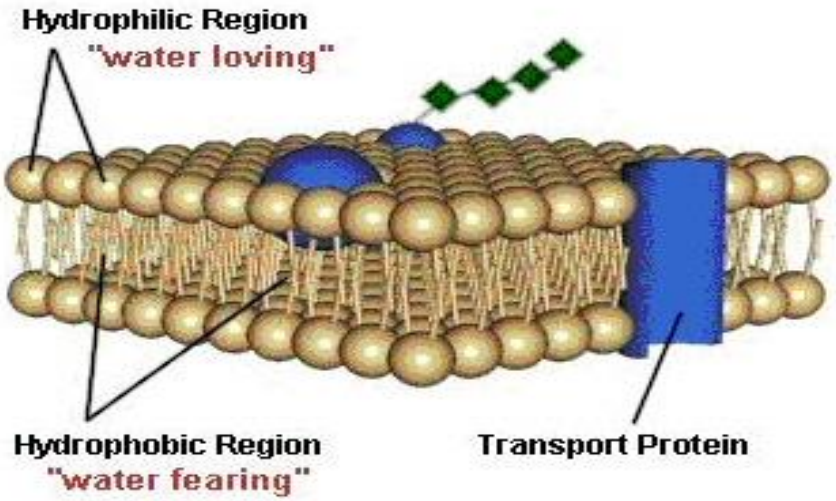
- PINOCYTOSIS
- The drugs which have MW over 900 can be transported by pinocytosis.
- It requires energy.
- The drug molecule holds on the cell membrane and then surrounded with plasma membrane and inserted into the cell within small vesicles.



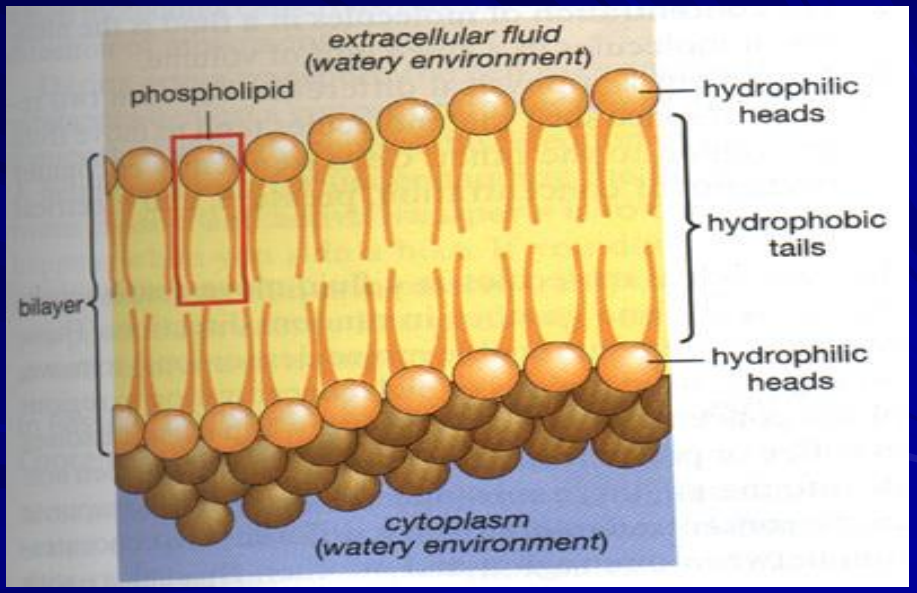

A Passive diffusion
Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
Drug
Drug
Extracellular space
Cell membrane
Cytosol
B Facilitated diffusion
Drug
Drug transporter
C Active transport
ATP
ADP
Drug transporter
D Endocytosis
Large drug

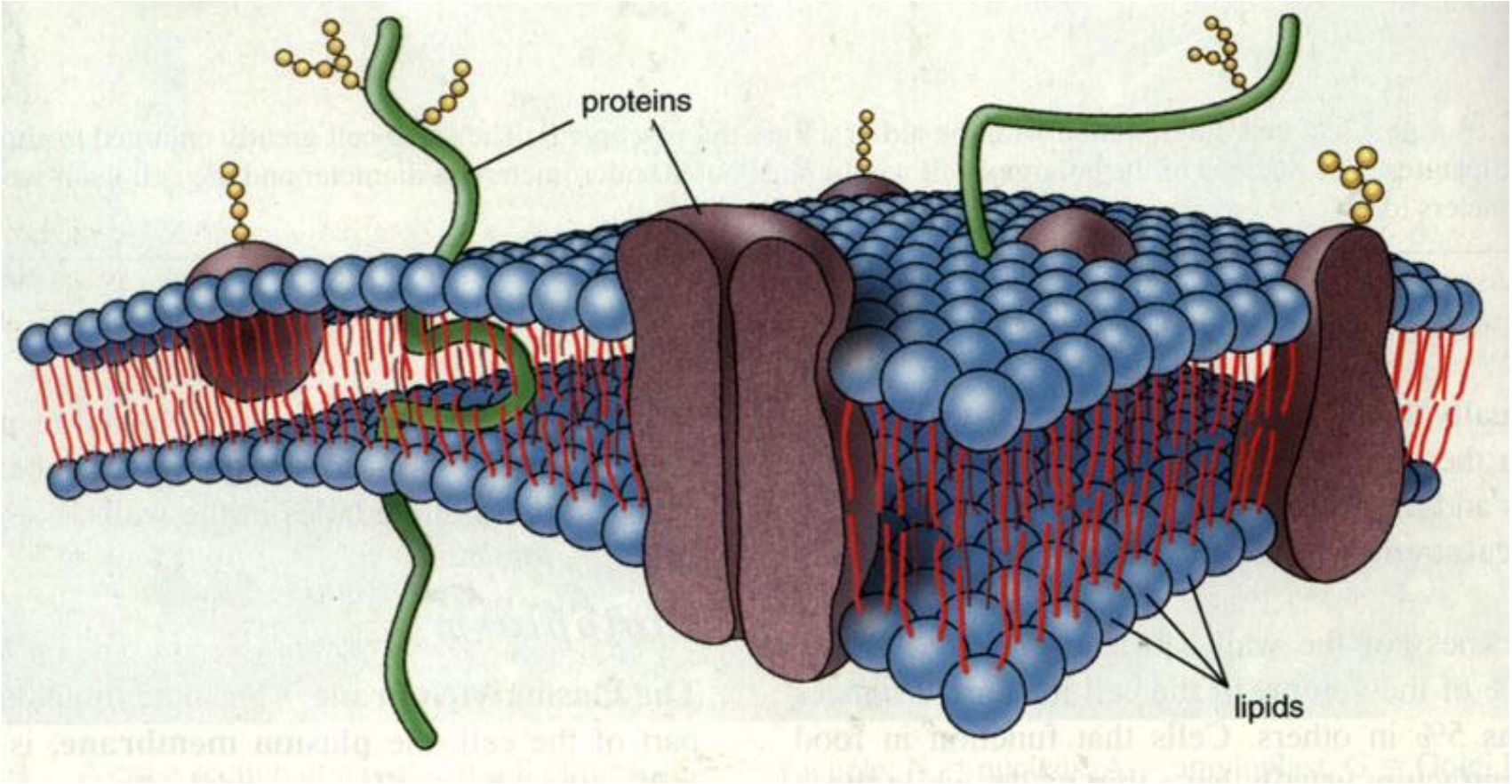

Passive
Facilitated
Active

Cell Membrane



Cell membrane





The structure of cell membrane？

How to transport it？

For acids pH= pKa + log. Ionised /non-ionised (aspirin

For base pH= pKa + log. non-ionised / Ionised (amphetamin)

Log ionization/non-ionization=pKa-pH (for a weak base) Amphetamine.

Weak base drugs increase ionized in Acidic medium ex. Amphetamine.

Weak acidic drugs increase ionized in Alkaline medium ex. Aspirin.

First pass Metabolism

Metabolism of drug in the gut wall reaching to portal circulation before reaching systemic circulation so the amount reaching system circulation is less than the amount absorbed.

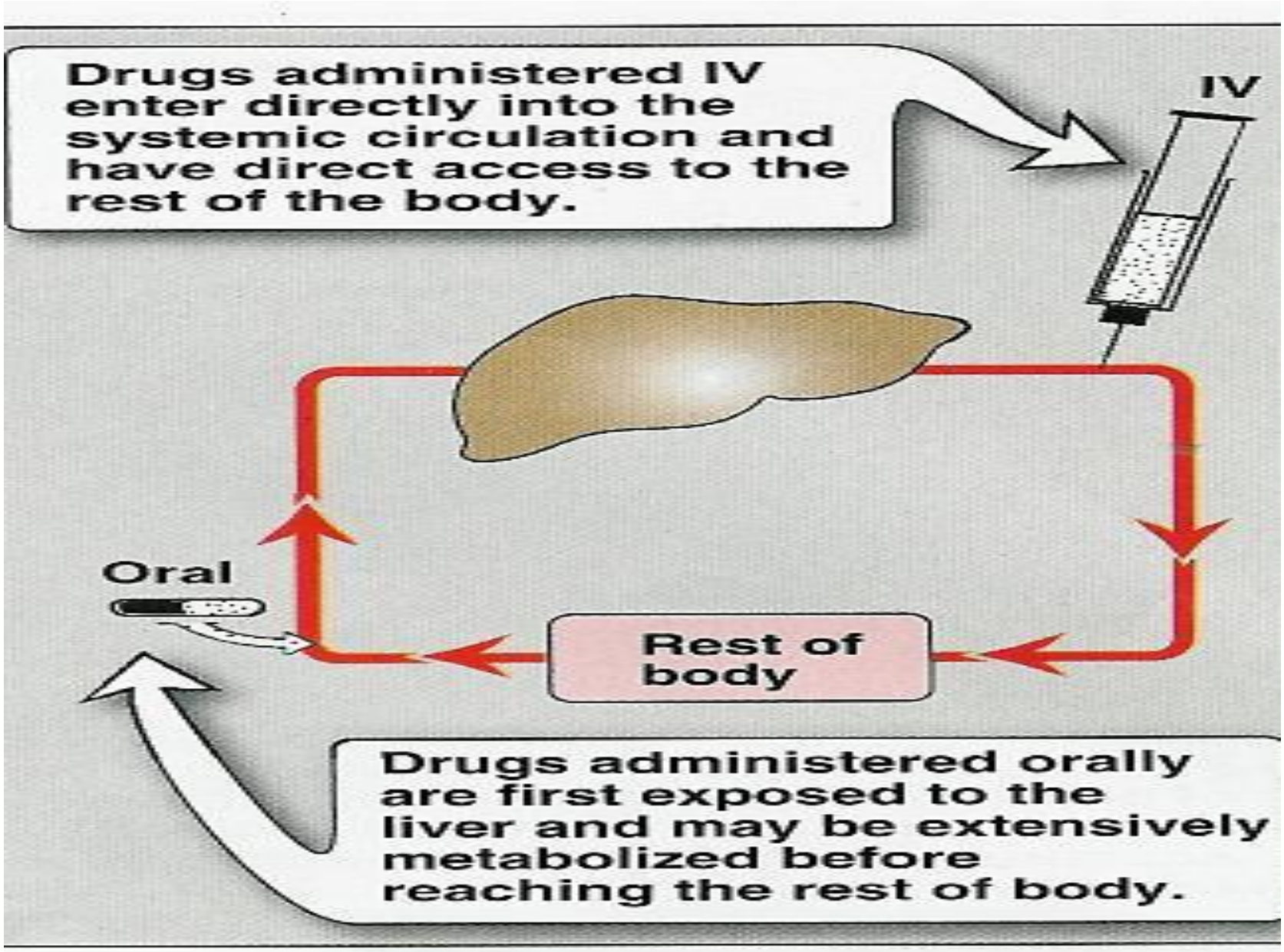
Where ?

- **Liver**
- **Gut wall**
- **Gut Lumen**

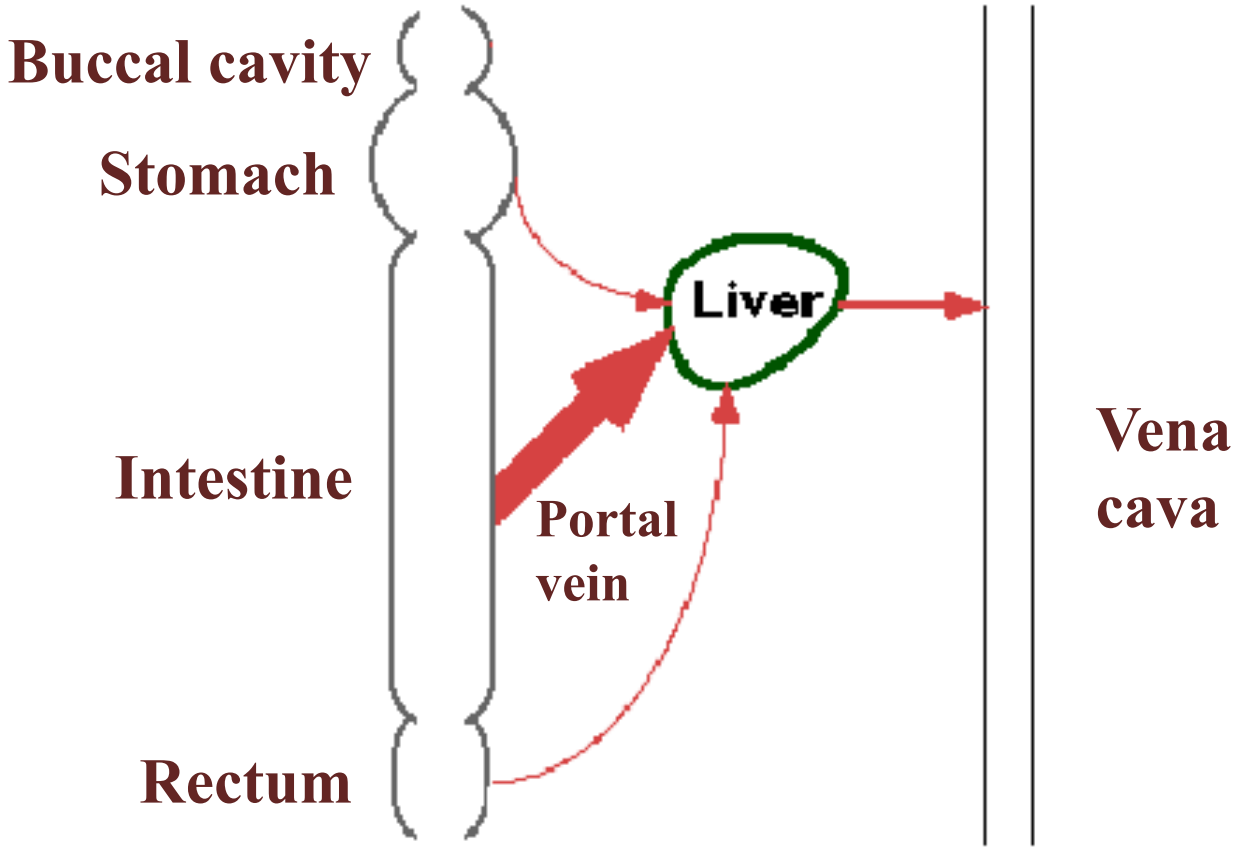
Result ?

- **Low bioavailability.**
- **Short duration of action (t ½).**

First pass effect



FIRST PASS ELIMINATION
Metabolism in the liver

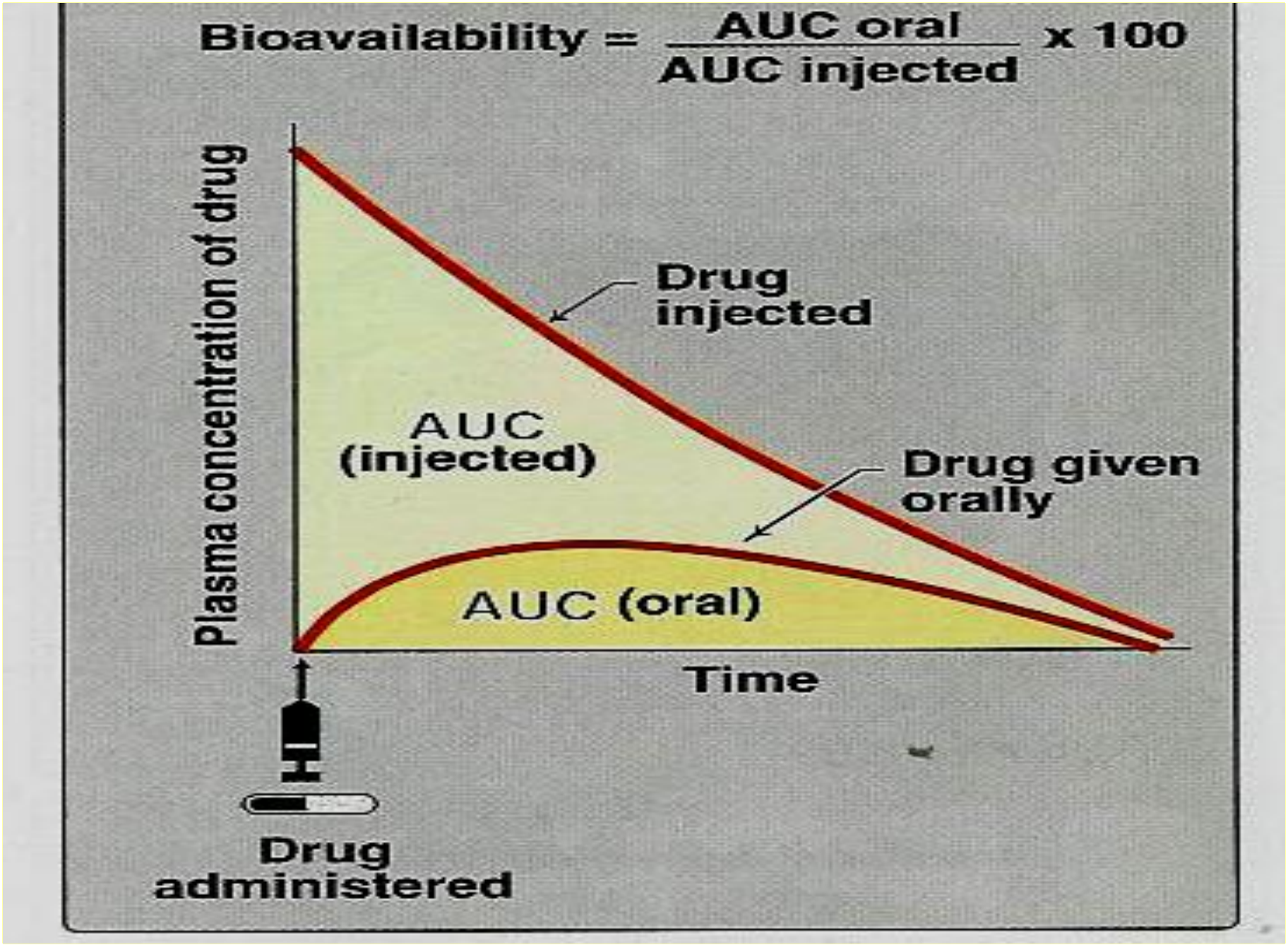


Bioavailability

Amount of unchanged drug that enters systemic circulation after administration and becomes available to produce action.

- **I.V. provides 100% bioavailability.**
- **Oral usually has less than I.V.**

- **Bio = AUC oral / AUC IV X 100**


Bioavailability = AUC oral / AUC injected x 100
Plasma concentration of drug
Drug injected
AUC (injected)
Drug given orally
AUC (oral)
Time
Drug administered

Factors Affecting Bioavailability:

- **Molecular weight of drug.**
- **Drug Formulation (ease of dissolution).**

(solution > suspension > capsule > tablet)

- **Solubility of the drug (lipophilic drugs good absorption and hydrophilic drugs poorly absorption)**
- **Chemical instability in gastric pH (Penicillin unstable in gastric PH & insulin destroyed in the GIT tract by derivative enzyme)**
- **First pass metabolism reduces bioavailability**

- **Blood flow to absorptive site**
  - **Greater blood flow increases bioavailability**
  - **Intestine has greater blood flow than stomach**
- **Surface area available for absorption.**
  - **Intestinal microvilli increases it**
- **Rate of gastric emptying**
  - **rapid gastric emptying fast transit to intestine.**

- **Intestinal motility (Transit Time)**
  - **Diarrhea reduce absorption**
- **Drug interactions**
- **Food**
  - **slow gastric emptying**
  - **generally slow absorption**
  - **Tetracycline, aspirin, penicillin V**

DISTRIBUTION

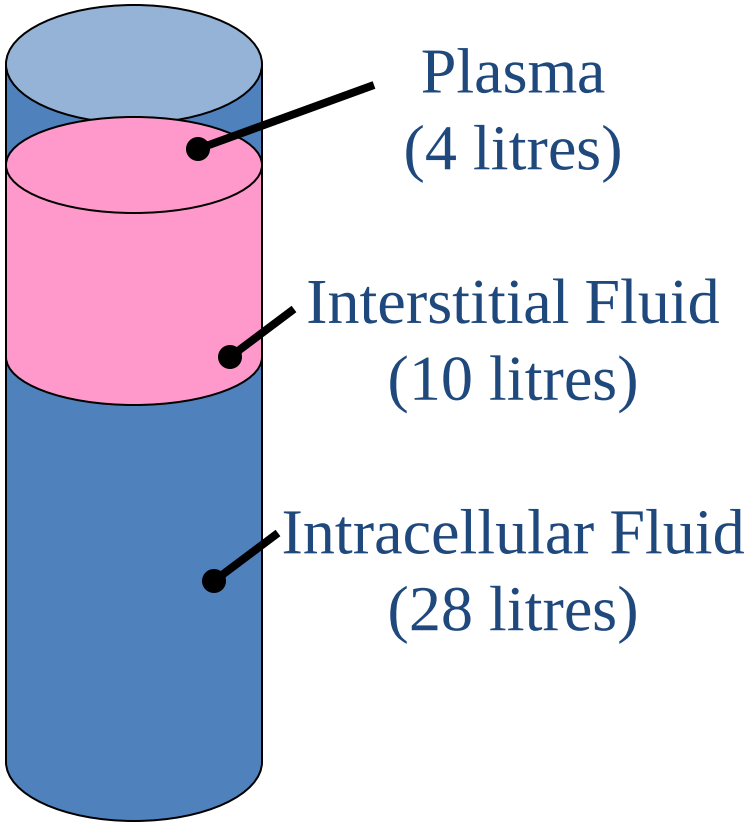
Distribution is passage of drug molecules to liquid compartments and tissues in the body via transportation across the capillary membrane.

Or

is the process by which a drug reversibly leaves the blood stream and enters the interstitial (extracellular fluid)and the tissue. For drug administrated IV absorption is not a factor.

Volume of Drug Distribution

- Drugs may distribute into any or all of the following compartments: (42 L)
  - **Plasma**
  - **Interstitial Fluid**
  - **Intracellular Fluid**



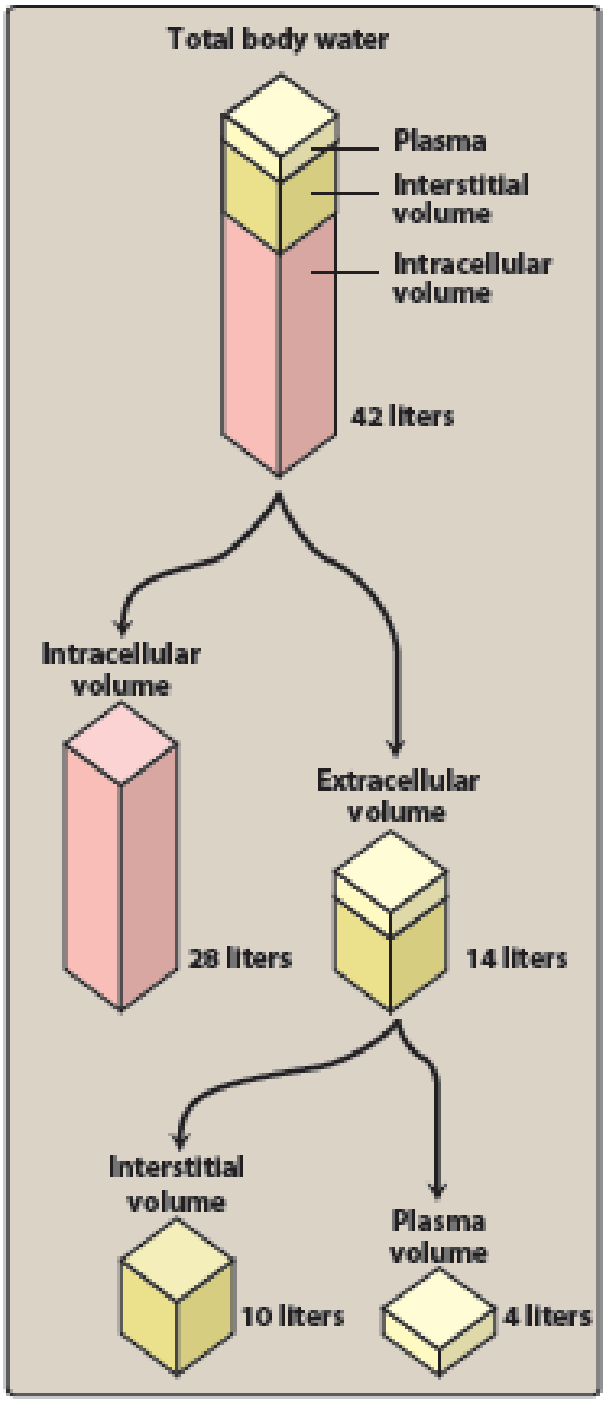
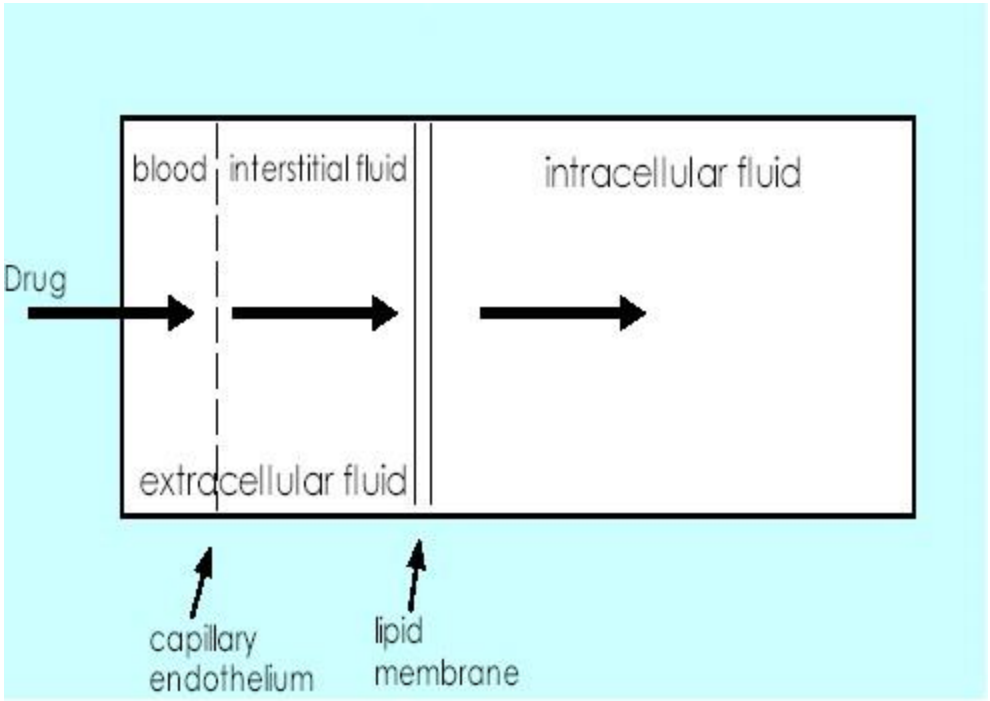


Figure.
Relative size of various distribution volumes within a 70-kg individual

Distribution

- The movement of drug from the blood to and from the tissues



DISTRIBUTION

- **The distribution of drugs can occur in 4 forms throughout the body:**
  - **Distribution only in plasma**: **drug retained in blood and can not filtrate through capillary endothelium e.g. protein bound drugs polysaccharides (as heparin).**
  - **Distribution to all body fluids homogenously:** Small and non-ionized few molecules like **alcohol**, **some sulfonamides**.
  - **Concentration in specific tissues**: **iodine** in thyroid; **chloroquine** in liver; **tetracyclines** in bones and teeth**; high lipophilic drugs** in fat tissue
  - **Non-homogenous (non-uniform) distribution form**: Most of the drugs are distributed in this form **according** to their **abilities to pass through the cell membranes** or affinities to the different tissues.

Notes

❑ Storage (Concentration-Sequestration) of the Drugs in Tissues

- Stored drug molecules in tissues serve as **drug reservoir**.
- The duration of the drug effect may get longer.
- May cause a late start in the therapeutic effect or a decrease in the amount of the drug effect.

Notes.

- Some drugs (especially general anesthetics) are very lipophilic, following the injection, firstly (initially) distributes to the well-perfused organs like central nervous system..
- Later, the distribution occurs to less perfused organs like muscles.
- At last, distribution of these drugs shifts to the very low-perfused tissues like adipose (fat) tissue.
- Redistribution results with the running away of the drugs from their target tissue and last their effect.

DISTRIBUTION

❑ Passage of the drugs to CNS:

- A **blood-brain barrier** exists (except some areas in the brain) which limits the passage of substances.
- **Non-ionized, highly lipophilic, small molecules** can pass into the CNS and show their effects.
- some antibiotics like penicillin can pass through the inflamed blood-brain barrier while it can't pass through the healthy one.

❑ Passage of the drugs to fetus:

- Some drugs can pass through b.b.b
- The factors that play role in simple passive diffusion, effect the passage of drug molecules to the fetus.
  - **Placental blood flow**
  - **Molecular size**
  - **Drug solubility in lipids**
  - **Fetal pH (ion trapping):** fetal plasma pH: 7.0 to 7.2; pH of maternal plasma: 7.4, so according to the ion trapping rules, **weak basic drugs** tend to accumulate in **fetal plasma** compared to maternal plasma.

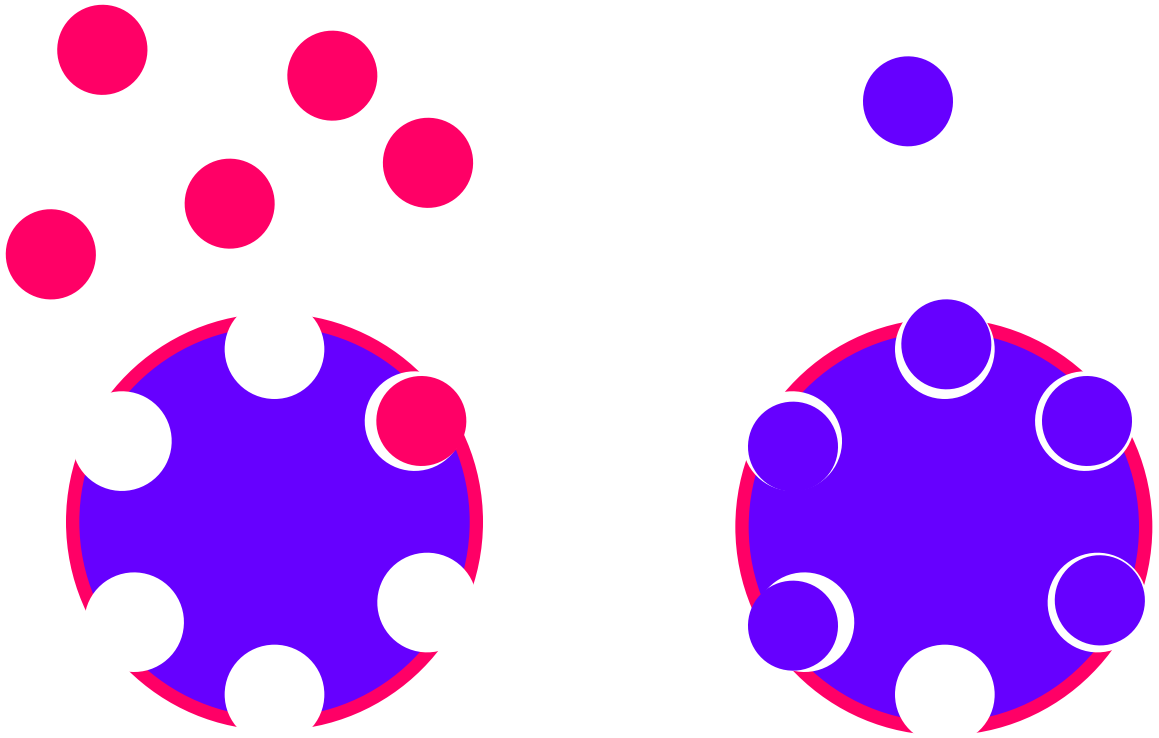
Thank you

Factors Affecting the Distribution of Drugs

- **Diffusion Rate**:
  - ✓ There is a positive correlation between the diffusion rate of the drug and the distribution rate
- **The Affinity of the Drug to the Tissue Components**:
  - ✓ Some drugs tend to be concentrated in particular tissues.
- **Blood Flow (Perfusion Rate):**
  - ✓ There is a positive correlation between the blood flow in the tissue and the distribution of the drugs.
  - ✓ Kidney, liver, brain and heart have a high perfusion rate (ml/100 g tissue/min) in which the drugs distribute higher;
  - ✓ Skin, resting skeletal muscle and bone have a low perfusion rate.
  - ✓ The total concentration of a drug increases faster in well-perfused organs.

- **Binding to Plasma Proteins**:
  - ✓The most important protein that binds the drugs in blood is **albumin** for most of the drugs.
  - ✓Especially, the **acidic drugs** (salicylates, vitamin C, sulfonamides, barbiturates, penicillin, tetracyclines, warfarin, probenesid etc.) are bound to albumin.
  - ✓**Basic drugs** (streptomycin, chloramphenicol, digitoxin, coumarin etc.) are bound to **alpha-1 and alpha-2 acid glycoproteins**, **globulins**, and alpha and beta lipoproteins

Protein binding



Effects of protein binding on kinetics of drug:

1- Facilitate drug absorption (by low concentration) of free molecules).

2- Facilitate drug distribution (act as carrier for insoluble drugs).

3- Prolongation of drug effect (by slow metabolism & excretion)

Volume of DISRIBUTION

Volume of Distribution = Amount of drug administered (dose) (mg) / concentration of drug in plasma (mg/ml).

- Most of the times, volume of distribution calculated in this way is not equal to the real total volume of physiological liquid compartments in which the drug is distributed.
- Lipid soluble drugs diffuse freely and have larger V.d. e.g. paracetamol.
- If the drug remains mostly in the plasma (bound) lead to small v.d.
- So it may be called as "**apparent volume of distribution (V_d)**".
- Drugs stored in the tissues lead to increase v.d.

Then the formula is:

Volume of Distribution (V_d) = d / C_0

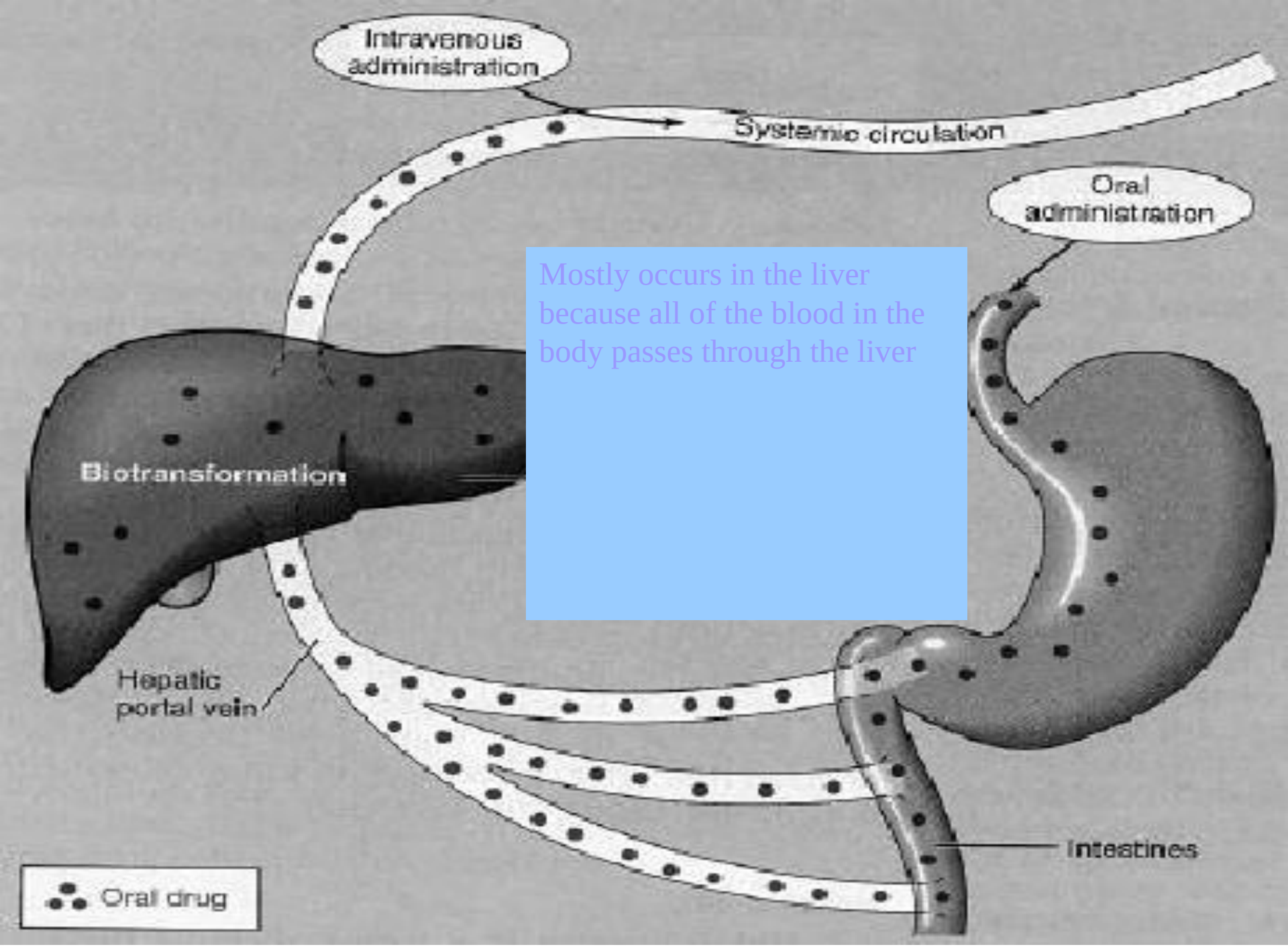
d= total amount of drug in the body (dose)

c= plasma concentration of the drug

e.g. dose = 25mg, plasma concentration= 1mg/L.

v.d.= 25 mg/1mg/l = 25L

Metabolism or BIOTRANSFORMATION


Intravenous administration
Systemic circulation
Oral administration
Mostly occurs in the liver because all of the blood in the body passes through the liver
Biotransformation
Hepatic portal vein
Intestines
Oral drug

- **The process of alterations in the drug structure by the enzymes in the body is called "biotransformation (drug metabolism)" and the products form after these reactions are called "drug metabolites".**

- **Some drugs which don't have any activity in vitro, may gain activity after their biotransformation in the body. These types of drugs are called "pro-drug" or "inactive drugs".**

- **Drug examples that gain activity after biotransformation (pro-drugs):**

PRO-DRUG	EFFECTIVE METABOLITE
Chloral hydrate	Trichloroethanol
Cortisone	Hydrocortisone
Enalapril	Enalaprilate
Lovastatin	Lovastatin acid
Clofibrate	Clofibric acid
L-DOPA	Dopamine

- **Drug examples that is transformed to more active compounds after biotransformation:**

DRUG	MORE ACTIVE METABOLITE
Imipramine	Desmethylimipramine
Codeine	Morphine
Nitroglycerin	Nitric oxide
Losartan	EXP 3174 (5-carboxylic acid metabolite)
Thioridazine	Mesoridazine

- **Drug examples that is transformed to less active compounds after biotransformation:**

DRUG	LESS ACTIVE METABOLITE
Aspirin	Salicylic acid
Meperidine	Normeperidine
Lidocaine	De-ethyl lidocaine (dealkylated)

- **Drug examples that is transformed to inactive metabolites after biotransformation**

DRUG	INACTIVE METABOLITE
Most of the drugs	Conjugated compounds
Ester drugs	Hydrolytic products
Barbiturates	Oxidation products

- The metabolites that are formed after biotransformation are generally *more polar*, more easily ionized compounds compared to the main (original) drug. So, these metabolites can be excreted from the body easily.

Organs that biotransformation occurs:

- **Liver**
- Kidney (tubular epithelium, sulphate conjugation)

ENZYMATIC REACTIONS

The enzymatic reactions which the drugs are exposed to:

1. Oxidation
2. Reduction
3. Hydrolysis

} PHASE I

4. Conjugation → PHASE II

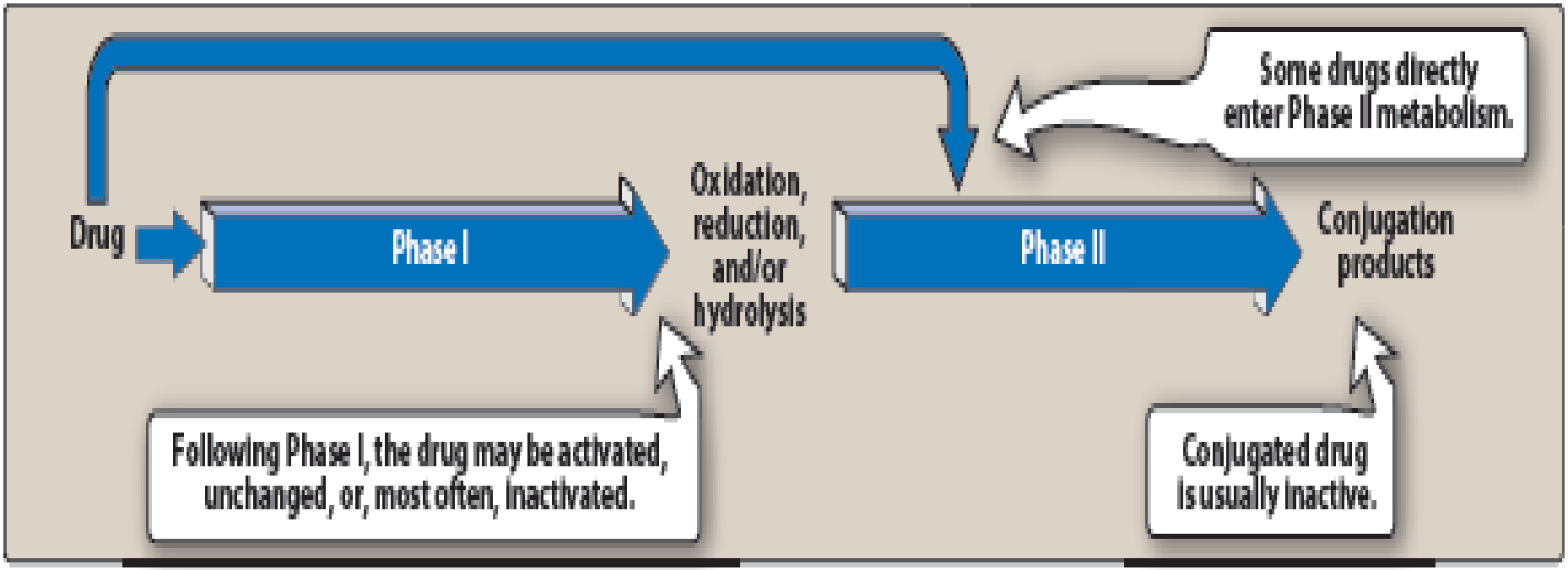


Figure 1.17
The biotransformation of drugs.

Thank you

Factors That Affect The Biotransformation of Drugs

1. Induction or inhibition of microsomal enzymes
2. Genetic differences
3. Age
4. Gender
5. Liver diseases

Induction or inhibition of microsomal enzymes

- Various drugs or environmental factors lead to increases in the activity of these enzymes by increasing the synthesis of microsomal enzymes.
- **The importance of the enzyme induction is the increasing metabolism rate of the drugs and the reduction in their activities.**
- On the other hand, some drugs stimulate the enzymes that inhibit them selves **(biochemical tolerance).**
- Unlike the enzyme induction, some drugs can inhibit the microsomal enzymes.

INDUCERS

ENZYME	DRUG or SUBSTANCE THAT INDUCES THE ENZYME
CYP1A2	Cigarette smoke, grilled meat (barbecue), aromatic polycyclic hydrocarbons, phenytoin
CYP2C9	**Barbiturates, phenytoin, carbamazepine, rifampin**
CYP2C19	NOT INDUCIBLE
CYP2D6	NOT INDUCIBLE
CYP3A4	**Barbiturates, phenytoin, rifampin, carbamazepine**, glucocorticoids, griseofulvin,

INHIBITORS

ENZYME	DRUG or SUBSTANCE THAT INHIBITS THE ENZYME
CYP1A2	Cimetidine, ethinyl estradiol, ciprofloxacin
CYP2C9	Amiodarone, isoniazid, co-trimoxazole, cimetidine, ketoconazole
CYP2C19	Fluoxetine, omeprazole
CYP2D6	Amiodarone, cimetidine, fluoxetine, paroxetine, haloperidol, diphenhydramine
CYP3A4	Ketoconazole, erythromycin, , isoniazid, Ca channel blockers, red wine, **grapefruit juice**

Genetic differences

- **Genetic polymorphism** in some of the enzymes that play role in biotransformation of drugs can cause changes in the activity of the drugs which are metabolized by these enzymes.

➢ **Hydrolysis of succinylcholine**: *Cholinesterase enzyme in plasma* play important role in the hydrolysis of succinylcholine which is generally used for its muscle relaxant activity.

- ✓ The metabolism of succinylcholine slows down in the individuals who have **atypical cholinesterase**
- ✓ the activity of succinylcholine can rise up to hours in individuals who have atypical cholinesterase enzyme **(long duration (prolonged) succinylcholine apnea).**

➢ **Acetylation of isoniazid**:

- ✓ Some individuals can metabolize this drug slowly (*slow acetylators*) and some faster (*rapid acetylators*).

➢ CYP2D6 polymorphism:

- CYP2D6 enzyme plays important role in the metabolism of many widely used drugs.

- The metabolism rate of some beta-blockers (metoprolol, timolol), some neuroleptics (thioridazine, perphenazine), and antitussives like dextromethorphan or codeine decrease significantly in the slow metabolizers.

Age & gender

- In newborns cytochrome P450 enzymes and glucuronosyl transferases are not sufficient.
- So, biotransformation of some drugs (diazepam, digoxin, acetaminophen, theophylline etc…) is very slow in newborns.
- Oxidation reactions performed by cytochrome P450 enzyme system are slower than normal metabolizing rates in elderly.
- The effect of aging on these enzymes can differ according to gender (reduction in enzyme activity is higher in old males) and between individuals.
- First-pass elimination shows a reduction with age as well.
- Metabolism rates of some drugs may change with gender. For example, succinylcholine and other choline esters and procaine are inactivated faster in men.

Liver Diseases

- **Especially**, the metabolism of drugs with a **"high hepatic clearance"** decreases in liver diseases.
- This leads to accumulation of drugs in the body which are metabolized in liver, and eventually causes an increase in the effect and adverse effects as well.
- **On the other hand, transformation of pro-drugs into their active forms occurs less in liver diseases.**

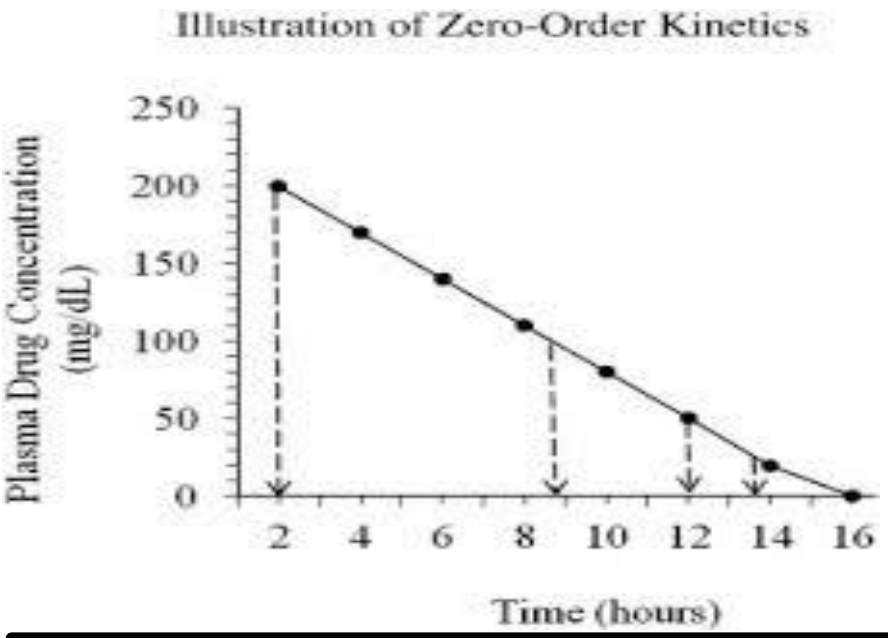
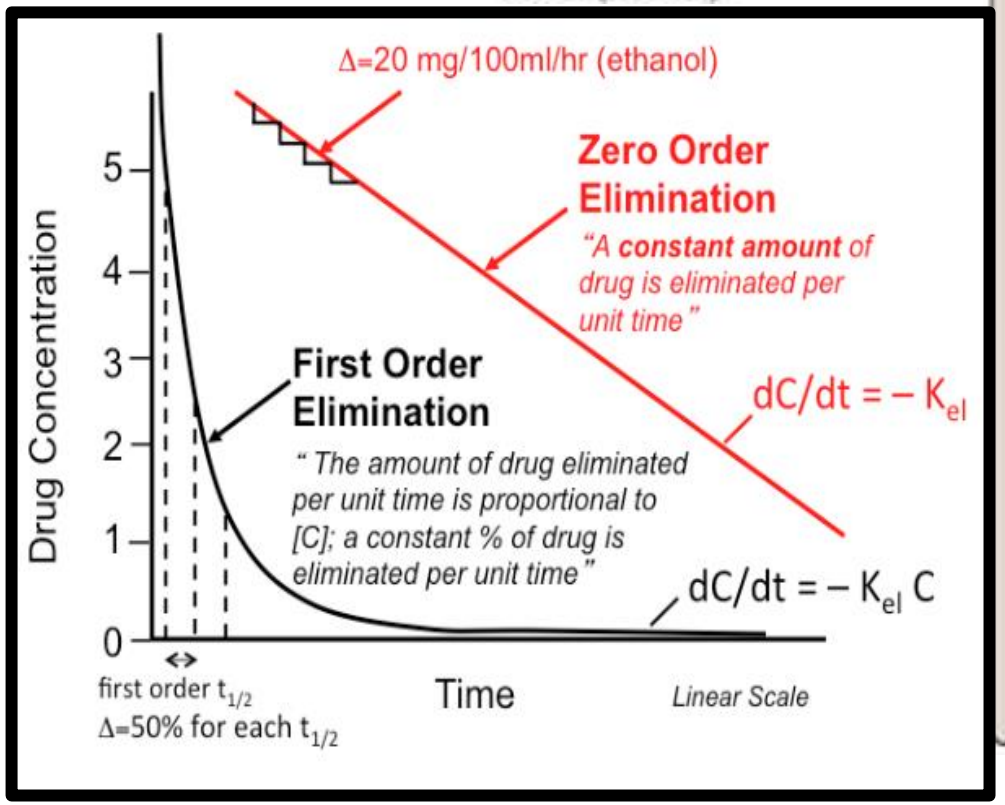
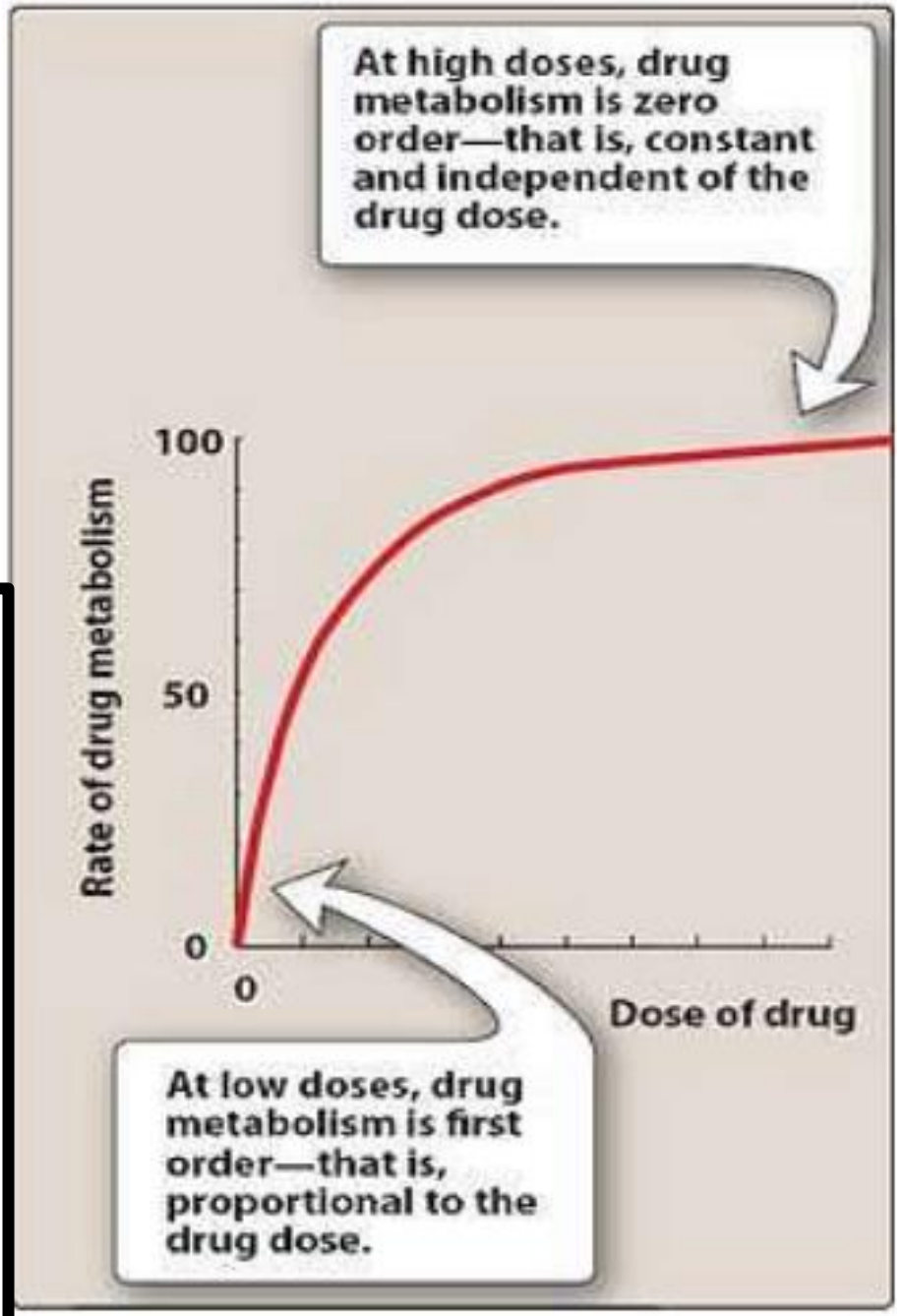


Illustration of Zero-Order Kinetics
Plasma Drug Concentration (mg/dL)
250
200
150
100
50
0
2
4
6
8
10
12
14
16
Time (hours)


Δ=20 mg/100ml/hr (ethanol)
Zero Order Elimination
"A constant amount of drug is eliminated per unit time"
dC/dt = – K_el
First Order Elimination
" The amount of drug eliminated per unit time is proportional to [C]; a constant % of drug is eliminated per unit time"
dC/dt = – K_el C
Drug Concentration
5
4
3
2
1
0
first order t1/2
Δ=50% for each t1/2
Time
Linear Scale


At high doses, drug metabolism is zero order—that is, constant and independent of the drug dose.
Rate of drug metabolism
100
50
0
0
Dose of drug
At low doses, drug metabolism is first order—that is, proportional to the drug dose.

First order kinetic: -The metabolic transformation of drugs is catalyzed by enzymes . The rate of drug metabolism is directly proportional to the concentration of free drug, and first order kinetics are observed.

- A constant % *fraction* of drug is eliminated per unit of time.

-Increase in plasma drug concentration lead to Increase rate of drug metabolism

-Half life is constant

Zero order kinetic: - With a few drugs, such as aspirin, ethanol, and phenytoin, the doses are very large. As the amount of drug rises in the plasma, certain processes that have limited capacity become saturated i.e the rate of the process reaches maximum at which it remains constant due to limited amount of enzymes even if dose increases, so it is not proportional to the dose this is also called rate limited

- Constant *amount* eliminated per unit of time.
- Rate of elimination is constant.
- Rate of elimination is independent of drug concentration.
- Example: Alcohol

Zero order kinetic

time	Plasma Co./unit	Rate of elimination
0	8	2 mg/l)/1h
1	6	2 mg/l)/1h
2	4	2 mg/l)/1h
3	2	2 mg/l)/1h
4	0	2 mg/l)/1h

Constant rate = (2mg/l)/1h

First order kinetic

time	Plasma Co./unit	Rate of elimination
0	8 mg/l	50%
1	4 mg/l	50%
2	2 mg/l	
3	1	
4	0.5	

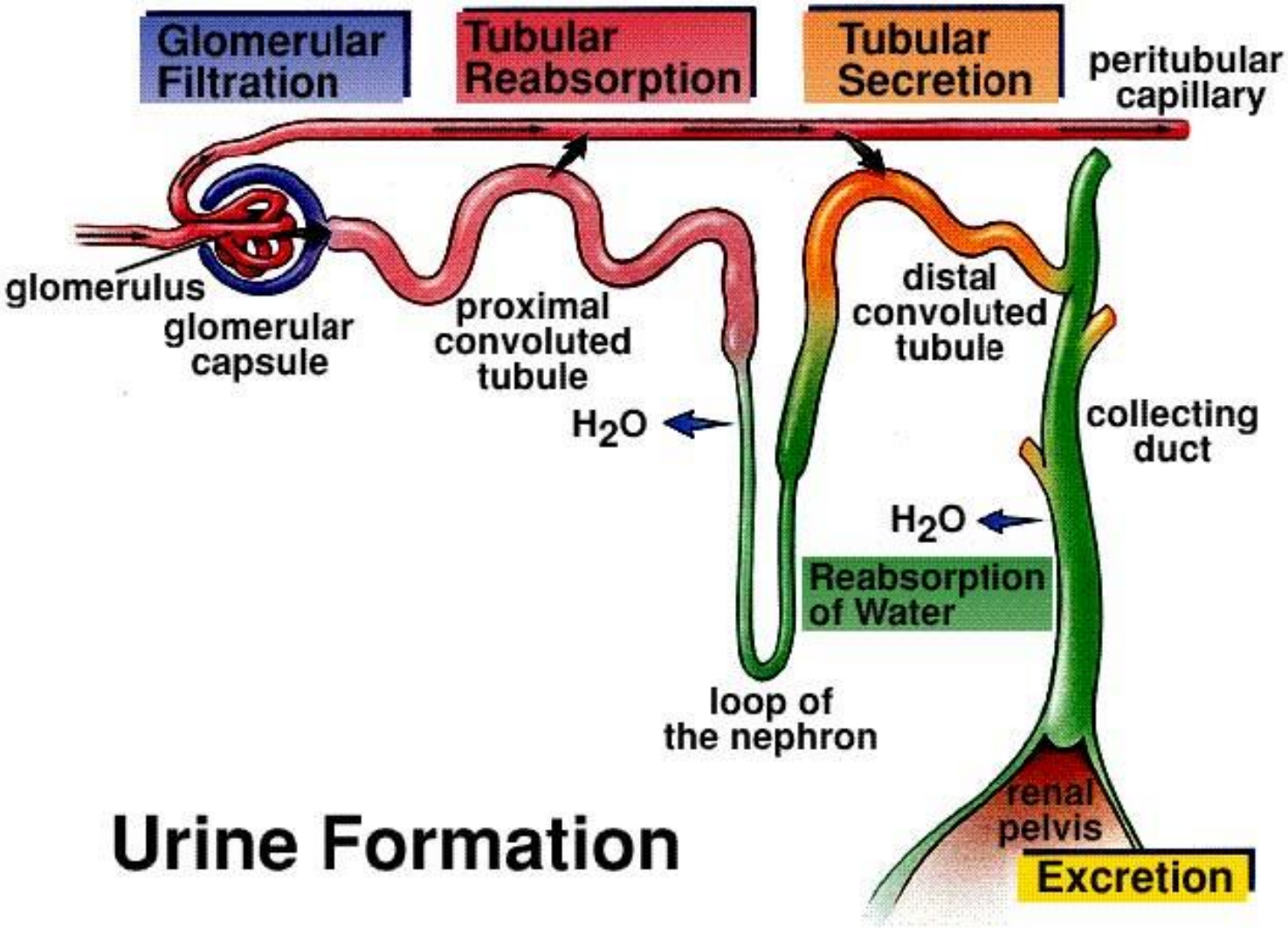
Constant proportion = (50% of drug)/1h

EXCRETION

OVERVIEW

- **RENAL EXCRETION**
- **BILIARY EXCRETION**
- **EXCRETION from the LUNGS**
- **EXCRETION into BREAST MILK**
- **FAECAL ELIMINATION**

RENAL EXCRETION



RENAL EXCRETION

- **Drugs and metabolites are excreted from the kidneys by a ways.**

  a) Glomerular filtration

  b) Tubular secretion

  c) Tubular Reabsorption

- **Filtration ……. Simple passive, free drug only, not protein bound**
- **Secretion ……. active, acids and bases**
- **Reabsorption…. passive, lipid soluble form only (pH)**

a) Glomerular filtration:

- ***Simple passive diffusion*** play role in glomerular filtration.
- The filtration rate is 110-130 ml/min.
- They are filtered from the glomerulus into proximal tubules **except the bound fraction of drug molecules to the plasma proteins.** Because albumin cannot be filtered from the glomerulus, the drugs cannot pass through into the proximal tubules.

b) Tubular secretion:

- **There are 3 important points about the tubular secretion mechanism of the drugs:**
  - ✓Tubular secretion occurs mainly in the **proximal tubules**.
  - ✓**Active transport** is the main mechanism for tubular secretion.
  - ✓Active secretion is Unaffected by change in pH and protein binding.
  - ✓The **efficiency (performance) of the excretion by tubular secretion is higher** than glomerular filtration route.
  - ✓ Clearance maximum in glomerular filtration is approximately 120 ml/min, whereas the clearance maximum of tubular secretion is about 600 ml/min.

- **Tubular reabsorption:**
  - ❖ This mechanism works in an opposite (counter) way by reducing the drug or metabolite excretion.
  - ❖ Tubular reabsorption occurs **mainly in distal tubules** and **partially in proximal tubules.**
  - ❖ It occurs by **simple passive diffusion** generally
  - ❖ **Most substances are reabsorbed across renal tubular cells if unionized and lipid soluble.**
  - ❖ **Changing the pH value of the urine** (making the urine acidic or basic) is going to change the ionization degree and the simple passive diffusion of the drug or the metabolite and lastly affect the excretion from the kidney.

- **if we make the urine acidic, the reabsorption of the weak acid drug from the renal tubules into the blood will increase, thus the excretion will decrease.**

- Basic drug is more rapidly excreted in acid urine. Conversely, acidic drugs are most rapidly excreted if the urine is alkaline.

Pharmacokinetic Principles:-

1- **Half-life** ($t_{1/2}$) is defined as the time required for the amount of drug in the body to decrease by half (50%).

t = 0.693 Vd/CL

CL = Clearance

4-5 half life to remove drug from body

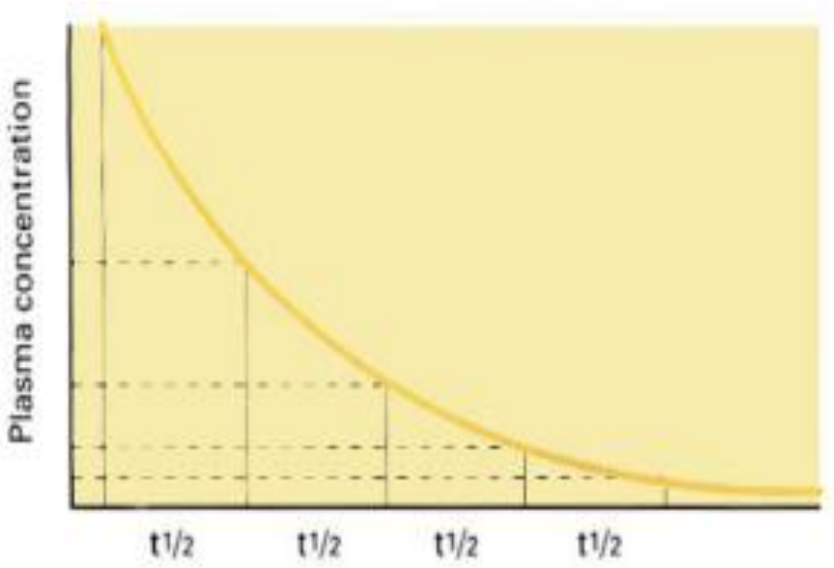
Factors affecting half-life

age

Renal excretion

liver metabolism

protein binding



HEPATIC CLEARANCE

- It can be described as "**the volume of plasma** that cleared from the drug **via metabolism in liver** per unit time (ml/min)"
- It is an indicator of the ***metabolism rate*** of the drugs.

2- **Clearance of a drug: -** is the rate of elimination by all routes relative to the concentration of drug in any biological fluid.

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Concentration}}$$

The *clearance* of a chemical is the volume of body fluid from which the chemical is, apparently, completely removed per unit time.

3- Loading dose: - Loading doses allow rapid achievement of therapeutic serum levels.

Thanks