Pharmacokinetics (PK)

- **Definition:** the way in which the body handles the drug

is a study of drug

- Absorption
- Distribution
- Metabolism
- Excretion

(ADME)

PK = Effect of the Body on the Drug

These factors coupled with dosage, determine the concentration of a drug at its sites of action and hence the intensity of its effects

Importance of PK

1 **Determination of serum Max drug concentration (Cmax) and the time to reach this concentration (Tmax) from drug concentration- time curve**

2 Adjustment of proper dosage regimen

The duration of activity of drug is often expressed as **half life ($t_{1/2}$)** i.e. **the time it takes for the concentration to fall by half**. Generally, the half life of a drug should determine the frequency of dosage.

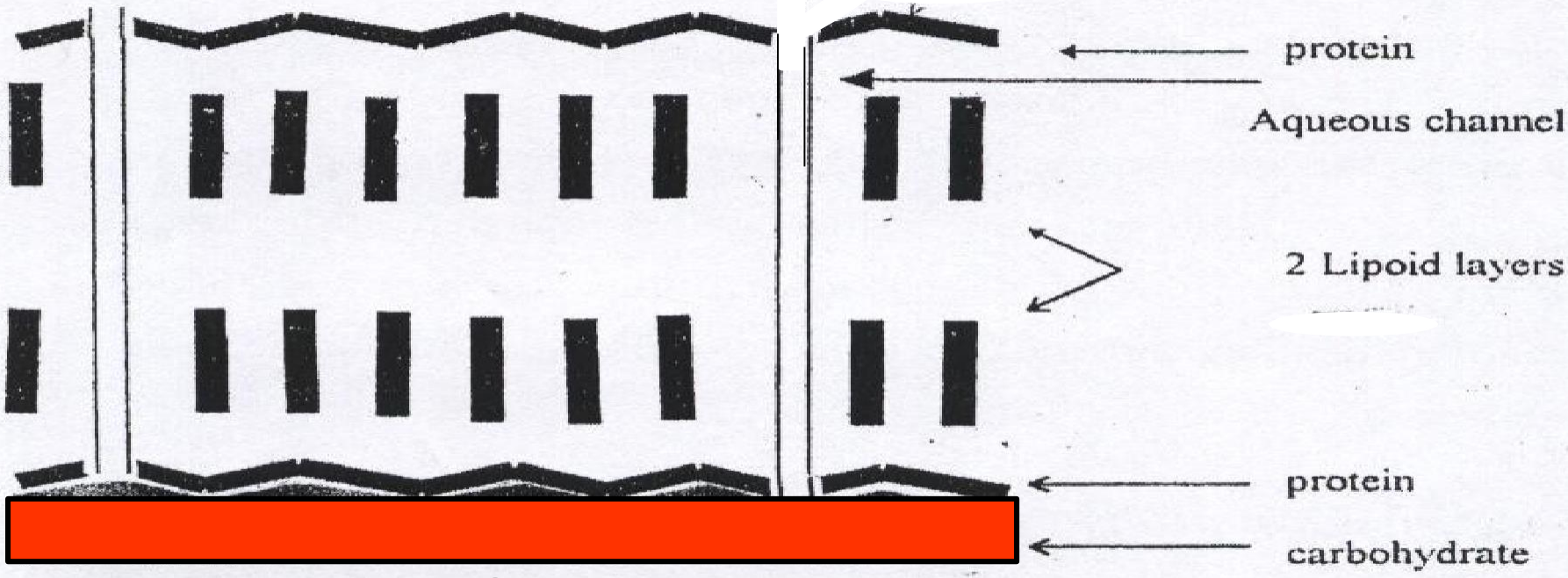
All the processes of pharmacokinetics are dependent upon its passage across **Cell Membrane**. Therefore it is essential to study the mechanism by which drugs cross the membranes

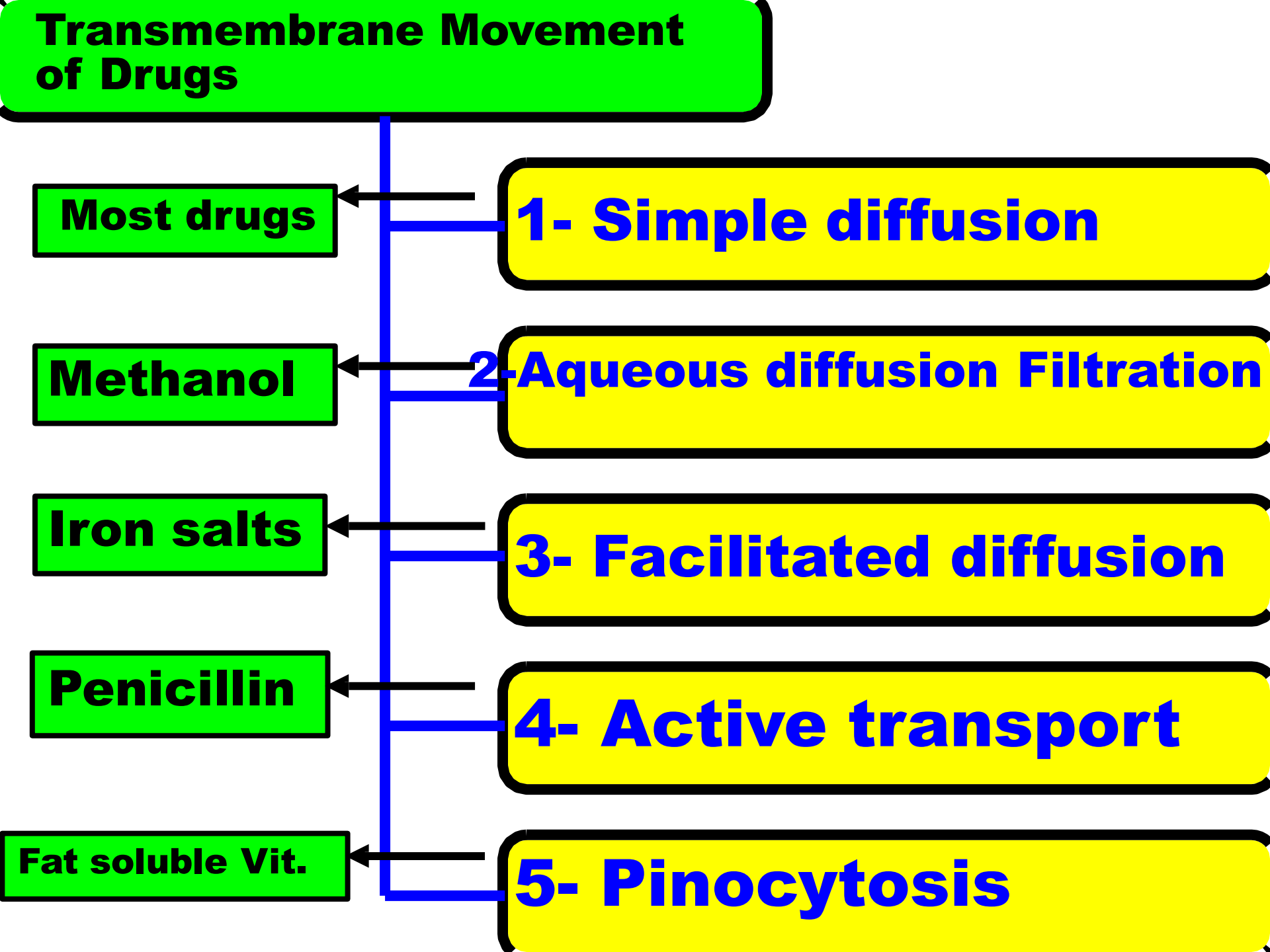
Drug transport: The movement of drug molecules in the body affects absorption, distribution and excretion. Drugs can cross cellular membranes by passive diffusion, carrier-mediated diffusion, active transport or endocytosis.

Cell Membrane

1. Inner bilipid layer
2. Two protein layers
3. An outer CHO layer

Along the membrane and at intervals there are aqueous channelsinside




Transmembrane Movement of Drugs
Most drugs
1- Simple diffusion
Methanol
2-Aqueous diffusion Filtration
Iron salts
3- Facilitated diffusion
Penicillin
4- Active transport
Fat soluble Vit.
5- Pinocytosis

Transmembrane Movement of Drugs

1 Simple diffusion:

Passage of lipid-soluble drugs by dissolution in the bilipid layer of cell membrane and the drug moves Along with concentration gradient.

- **The higher oil : water partion coefficient of a drug the faster is rate of its absorption e.g. Most drugs**

2- Filtration (Aqueous diffusion) :

Passage of drug molecules via the aqueous channels in cell Membrane Only limited to drugs of small M.Wt. (less than MW 100-150, e.g. Li^+, methanol)

the epithelial lining of the surface of the body, such as the cornea, gut and bladder.

Transmembrane Movement of Drugs

3 Facilitated (Carrier-mediated) diffusion:

Drug movement is facilitated by a carrier which combine with drug molecules to form a easily soluble complex

1. **No energy is required for drug movement**
2. **Movement depends upon drug chemical structure**
3. **It cannot move against a concentration gradient.**

Some amino acids (e.g. L-dopa) are absorbed into the brain in this way.

4- Active transport:

- **It is similar to facilitated diffusion in:**
  (1) Movement is mediated by a carrier
  (2) Depend upon drug chemical structure

- **But differ from facilitated diffusion in:**
  (1) Require metabolic energy which generated byNa K ATPase Enz.
  (2) Drug molecules move against concentration gradient

Example: iodine is transported into thyroid tissue, catecholamines and 5 - H.T. are transported into neuronal cells, and weak acids (e.g. penicillin) are actively transported into the renal tubules.

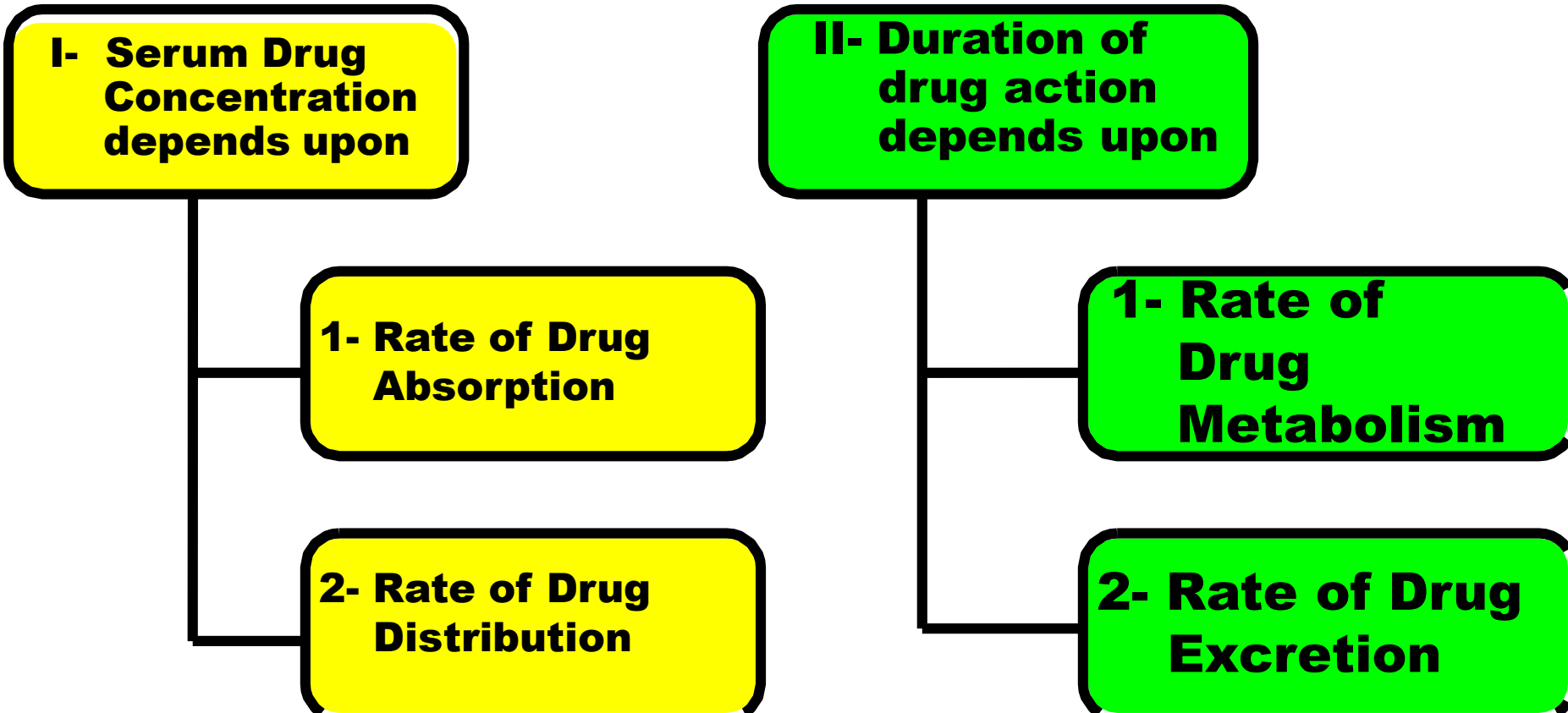
5- Pinocytosis (Phagocytosis): Drugs with high molecular weights (> 1000) are generally absorbed by this way engulfing extracellular drugs within membrane vesicles, they are then dissolved in the membranes and then released unchanged **inside the cell** **Example: Fat soluble vitamins (A,D,E,K) and polypeptides**

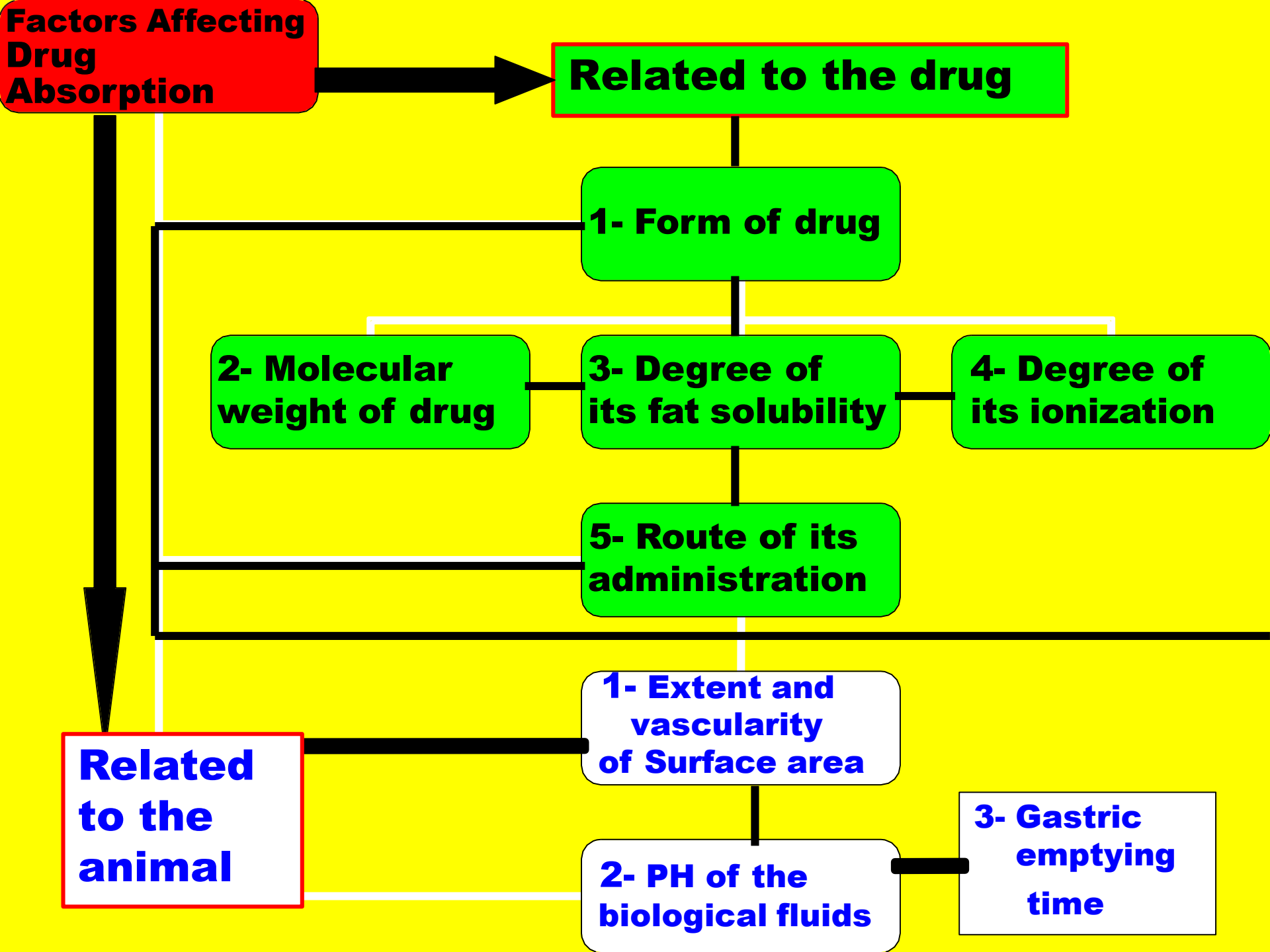
Differences between drug movements

Differences	S. diffusion	F. diffusion	A. transport
C. gradient	Along with	Along with	Against
Carrier	NO	Yes	Yes
Saturation	NO	Yes	Yes
Energy	NO	NO	Yes
Example	Lipid soluble Drugs	Glucose Iron	Penicillin

1-Absorption of Drugs

- Passage of drug molecules from the site of administration to the systemic circulation
- The drug begins its effect when it reaches to its target site by an effective concentration




Factors Affecting Drug Absorption
Related to the drug
1- Form of drug
2- Molecular weight of drug
3- Degree of its fat solubility
4- Degree of its ionization
5- Route of its administration
Related to the animal
1- Extent and vascularity of Surface area
2- PH of the biological fluids
3- Gastric emptying time

Factors Affecting Drug Absorption

1 Form of drug:

- **Liquid** drug forms (**Solutions, Mixtures and Syrups**) are **more** rapidly absorbed than **solid** forms (**Tabs and Caps**)

2 Molecular weight of drug:

- Drugs **of small M.Wt.** are **more rapidly** absorbed than drugs of **large M.Wt.**

3 Degree of drug solubility in lipid:

- The **greater the oil : water partion coefficient** of a drug the **faster** is the rate of its absorption.

4 Degree of drug ionization:

- **Non ionized** (**lipid soluble**) part of the drug is **more rapidly**
  absorbed than **ionized** (**water soluble**) part

5 Gastric emptying time:

- Drugs given on an empty stomach (Before meal) are more rapidly absorbed than drugs given on full stomach (After meal)

6 Extent and vascularity of absorbing Membrane:

- Drug absorption is proportional to surface area and vascularity of absorbing membrane

7 Presence of other dug (Adrenaline + Procaine)

- Adrenaline causes s/c vasoconstriction so it delays absorption of a local anesthetic procaine and prolong its anesthetic effect

8- Route of drug administration:

- After I/M or S/C, the drug is more rapidly absorbed than that which given orally

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- **After I/V administration:**

  The absorption time is Zero

  i.e. All administered dose (100%) is absorbed and distribution pattern is "Zero order kinetic"

- **Extravascular after (O, I/M, S/C):**

  The distribution pattern is "First order kinetic"

  i.e. Constant fraction of the administered dose is absorbed in a certain time which called absorption half-life "T½ ab"

Hepatic First - Pass Effect:

Following oral adm. the drugs are absorbed in the intestine and the portal circulation takes drugs first directly to the liver before they are distributed by the blood flow around the rest of the body. So some drugs are metabolized by the liver and excreted rapidly and so a very low bioavailability e.g. propranolol, morphine, verapmil and lidocaine. Other drug as nitroglycerin that is used for treatment of angina pectoris is given sublingually enters superior vena cava, whereupon it perfuses the coronary circulation but when taken orally it is rapidly inactivated in the liver. The first pass effect can be overcome by **raising the dose as in case of propranolol whoever this could be severe hypotension.**

PH and Degree of Drug Ionization

- Most drugs are either weak acids or weak bases
- In biological fluids, the drug is present in 2 forms: ionized and non ionized forms
- Non-ionized part is more lipid soluble and is able to diffuse rapidly across the cell membrane so rapidly absorbed
- For each drug there is an association constant → Ka and a dissociation constant → Kd

$$\text{Drug [AB]} \underset{kd}{\overset{ka}{\rightleftharpoons}} \text{[A] + [B]}$$

- PKa is the negative log of Ka
- PKa = PH at which 50% of the drug becomes ionized
- PH is the negative log of H+ ions concentration

Rapidly ionized drug → Slowly absorbed

Slowly ionized drug → Rapidly absorbed

The relationship between PH and Pka is determined using **Henderson - Hasselbalch** equations as follow:

- **For basic drugs:**

$$PKa = PH + \log \frac{\text{ionized base}}{\text{non ionized base}}$$

- **For acidic drugs:**

$$PKa = PH + \log \frac{\text{non ionized acid}}{\text{ionized acid}}$$

(NB : Log 1 = Zero)

- When PKa of a drug = PH of the biological fluid in which the drug is present, the ionization rate of this drug = 50%

Acidic drugs are rapidly absorbed from the stomach (Acidic)

Basic drugs are rapidly absorbed from the intestine (Alkaline)

Drug Bioavailability (F)

Relative rate and extent to which the given dose reach unchanged to the general circulation

OR Fraction of administered dose which reach the systemic circulation unchanged (intact)

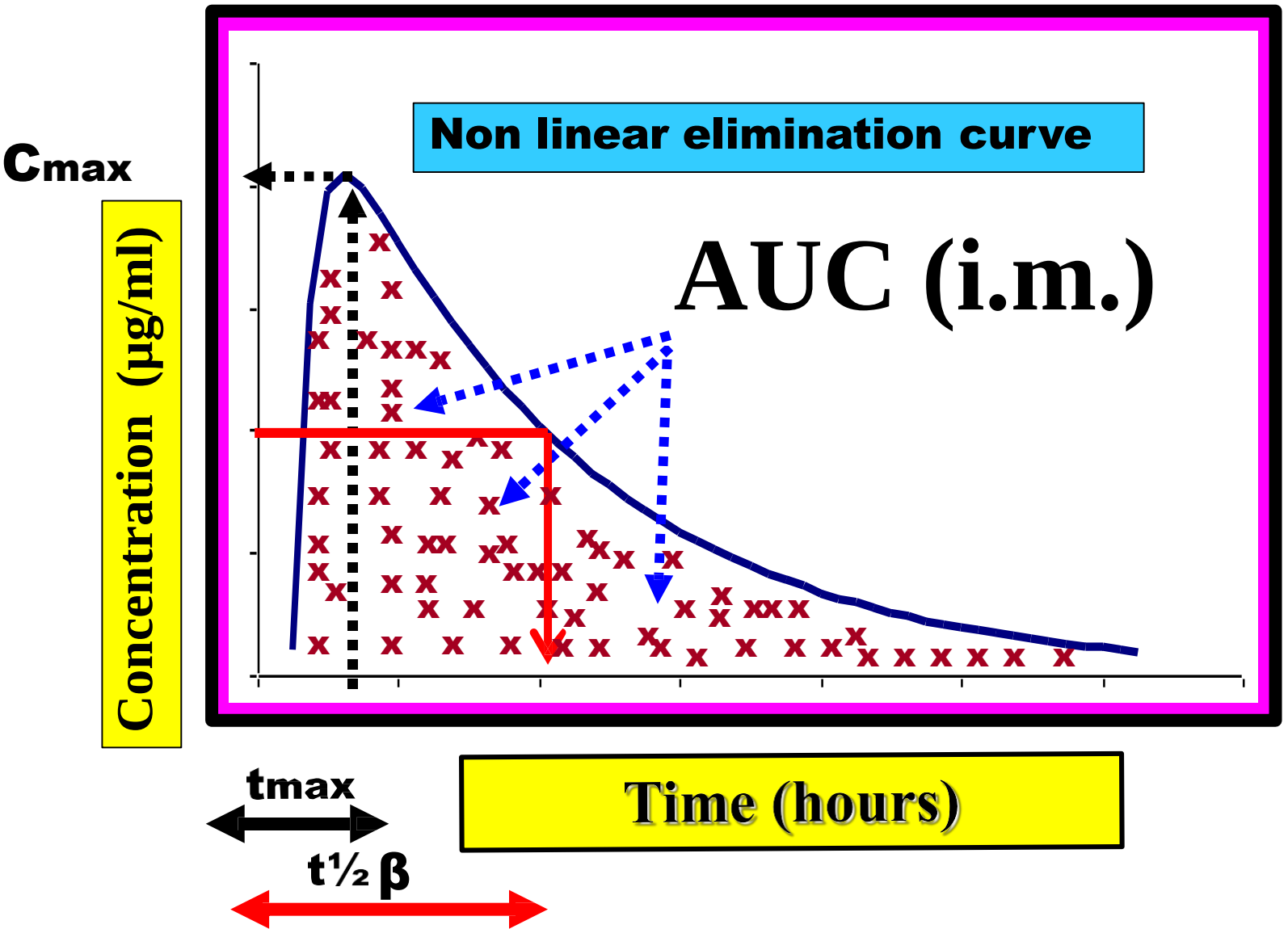
OR Fraction of the given dose which become available systemically unchanged

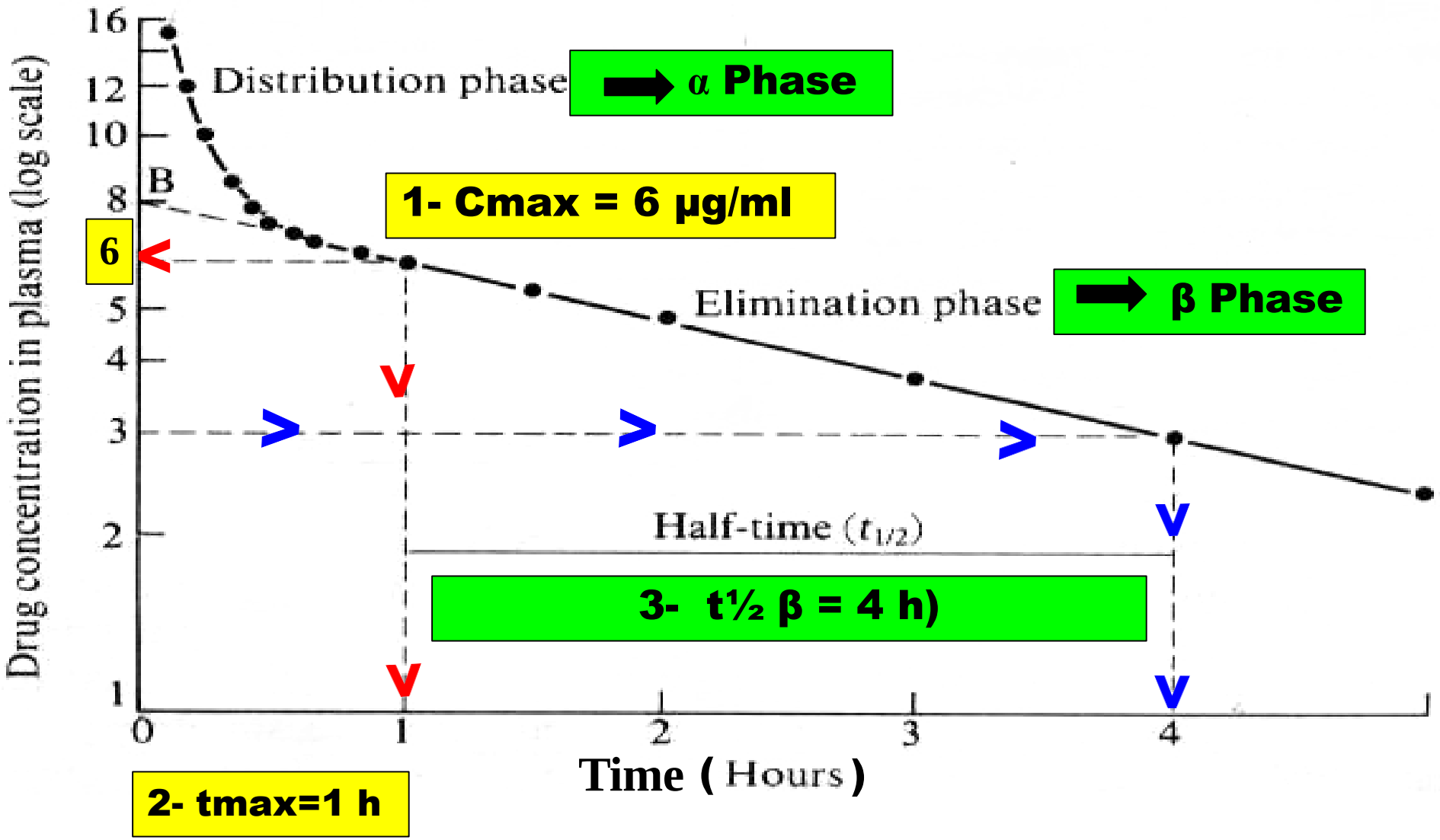
- **F is important for drugs which given orally or i.m.**

- **F% is obtained by comparing the area under serum concentration curve (AUC oral or i.m.) with that obtained when the same dose of the drug is given intravenously (AUC i.v.) using this formula:**

$$\text{Bioavailability (F\%)} = \frac{\text{AUC (oral) or (i.m.)}}{\text{AUC (i.v.)}} \times 100$$

Plasma drug concentration - time curve





Plasma drug concentration - time curve

2- Distribution of Drugs

After absorption, the drugs are distributed into different body compartments

- **Body compartments include:**
  - **1- Blood (plasma)**
  - **2- Total body water**
  - **3- Extracellular fluids**
  - **4- Interstitial fluids**
  - **5- Intracellular fluids**
  - **6- Fat and bones**
- **Compartment is a group of tissues or organs in which rate of drug uptake and drug loss are similar or equal.** **i.e. Drug uptake = drug loss**
- **Body compartments are divided into:**

1. **Central comp.** → **Plasma & highly perfusate organs**
2. **Peripheral comp.** → **Poorly perfusate tissues as fat and bones**

Patterns of drug distribution are:

1- One compartment model:

Drug remain only in the plasma and can not pass outside the vascular epithelium (B.Vs.)
e.g. Dextran sulphate (plasma expander)

2 Two compartment model:

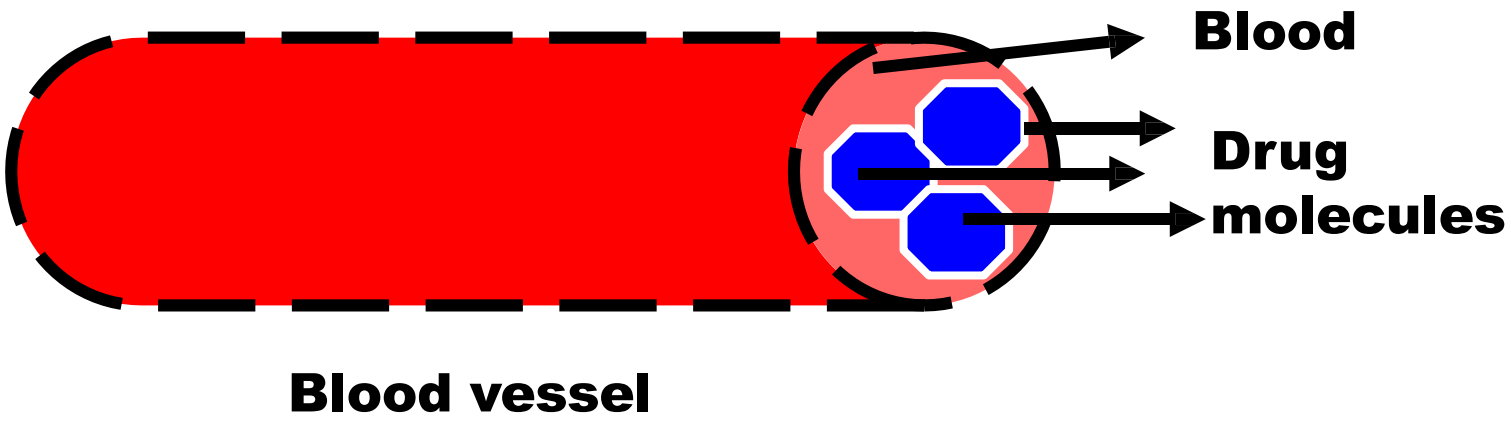
Drug pass the vascular wall and localized in exracellular fluids but can not pass across the cell membrane into cells e.g. most drugs, glucose and NaCl

3 Multicompartment model:

Drugs of low M.Wt. and high lipid solubility are distributed allover all the body compartments

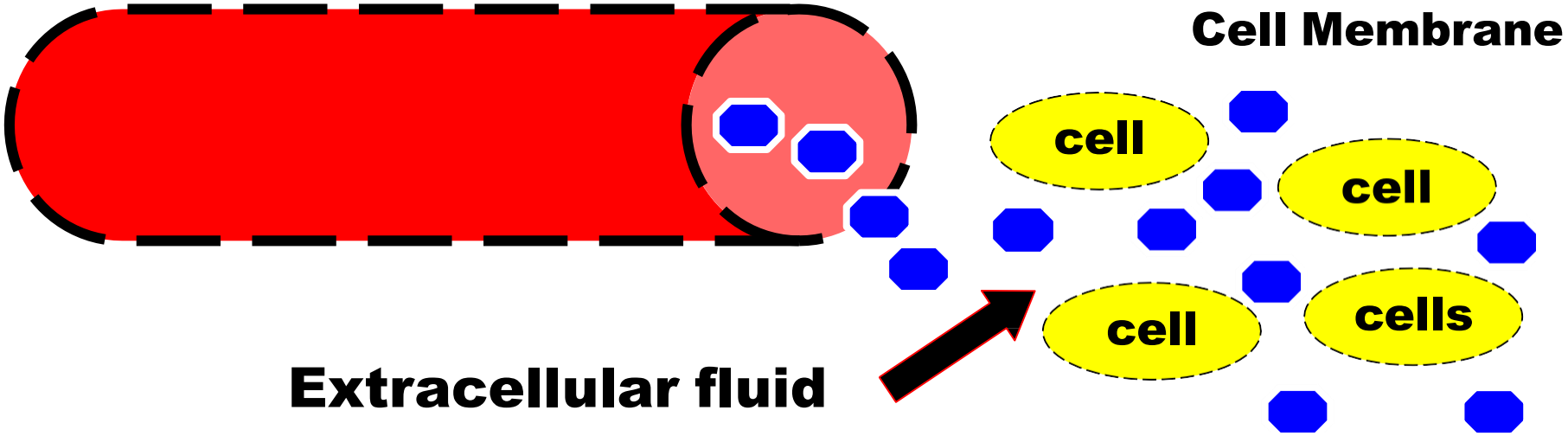
One compartment model

e.g. Dextran sulphate



Two compartment model

Most drugs



Volume of Distribution (Vd) and t½ of Drugs

Volume of distribution (Vd) is a hypothetical volume in which the drug is diluted to attain its serum concentration

$$\text{Volume of distribution (Vd)} = \frac{\text{Total amount of drug in the body}}{\text{Plasma drug concentration}}$$

- **A drug which is only restricted to the plasma will have a Vd of approximately 3 Liters in adult man (70 Kg B.WT.)**
- **High Vd of a drug indicates that the drug is more lipid soluble**

The duration of drug action is often expressed as half (time) life ($t_{1/2}$) → the time for plasma drug concentration to fall by the half

The half life of a drug is important to determine the frequency of drug administration (dosage regimen or schedule)

$t_{1/2ab}$ → **Absorption**

$t_{1/2\ \alpha}$ → **Distribution**

$t_{1/2\ \beta}$ → **Elimination**

Binding of Drugs to Plasma Protein

- **Drugs are carried in the blood in 2 forms:**

  1 Free form:

  - **Active pharmacologically**
  - **Diffusible**
  - **Available for metabolism and excretion**

  2 Bound form:

  - **Inactive pharmacologically &non diffusible**
  - **Not available for metabolism and excretion**
  - **Act as a reservoir of the drug**

- **Properties of drug binding to plasma proteins: 1- Reversible 2- Non selective**

- **Advantage or importance of binding of drugs:**
  1- Assist absorption of drugs from GIT
  2- Delay metabolism of drugs
  3 Delay excretion of drugs
  4 Prolong duration of drug action in the body
- **Disadvantage of binding of drugs:**
  1 Low free drug concentration is unable to treat deep infections as long acting sulphonamides is unable to treat meningitis
  2 Competition between 2 drugs for the same binding site may cause serious effect

  Example: competition between anticoagulant (phenindione) and aspirin when they are given together may cause serious hemorrhage

Drug Reservoirs in the Body

1 **Plasma proteins** (maily albumin):

the main storage place for most drugs

2 **Cells:**

Some drugs accumulate in cells e.g. antimalarial drug mepacrine is stored in the hepatic cells and iodine is stored in in the thyroid gland

3 **Fat:**

Many lipid-soluble drugs are stored in neutral fat e.g. 70% of hypnotic thiopental is stored fat and also fat soluble vitamins (A,D,E,K)

3- Metabolism of Drugs

- **Chemical reactions** which a drug undergoes in the body before its final elimination
- They occur mainly in the **liver** by **microsomal enzymes** which found in hepatocytes
- **Results (outcome) of drug metabolism:**
  - Active drug → Less active or inactive metabolites
  - Toxic drug → Less toxic or non toxic metabolites
  - Lipid soluble drug → Less lipid soluble, more polar and less bound metabolites which are easily eliminated.
- **Phases of drug metabolism:**
  - Phase I → Oxidation, Reduction and Hydrolysis
  - Phase II → Conjugation

Biotransformation Reactions

Examples of Oxidation Reactions:

1- Aromatic hydroxylation:

e.g. Actanilide → Hydroxyacetanilide

2- Side chain hydroxylation:

e.g. Pentobarbital → Hydroxy pentobarbital

3- N- dealkylation:

e.g. Meperidine → Demthylated meperidine

4- O- dealkylation:

e.g. Codeine → Morphine

5- Sulphoxidation:

e.g. Chlorpromazine → Chlorpromazine sulphoxide

Examples of Reduction Reactions:

1 Prontosil (dye) → Sulphanilamide (M)

2 Chloral hydrate → Trichloroethanol (NM)

3 Progesterone → Pregnandiol (NM)

Biotransformation Reactions

Examples of Hydrolysis Reactions:

1 Acetylcholine → Choline + Acetic acid

2 Atropine → Tropine + Tropic acid

Examples of Conjugation Reactions:

1 Sulphonamide + Glucoronic acid → Sulphon. Glucoronate

2 Benzoic acid + glycine → Hippuric acid

3 Paracetamol + sulphate → Paracetamol sulphate

4 Sulphanilamide + Acetyl CoA → Acetylsulphanilamide

Factors Affecting Drug Metabolism

1 Age of animal:

Drug metabolism is slow in young animals than in adults

2 Species of animals:

(A) Metabolism of sulpha drugs is poor in dogs why?
Because dogs lack acetylating enzymes

(B) Metabolism of suxamethonium is slow in ruminants why?
Because ruminants have a low amount of cholinesterase E.

(C) Metabolism of paracetamol is poor in cats why?
Because cats are deficient in glucuronyl transferase E.

3 Nutrition of animal:

Metabolism is slow in cases of malnutrition
Example: increased incidence of CCl4 toxicity in underfed sheep

4- Sex:

Males metabolize drugs more faster than females

5 Environment:

Cigarette smokers metabolize drugs more rapidly than non smokers

6 Presence of liver diseases:

In liver diseases as cirrhosis: Drug metabolism is slow

7 Enzyme inducers or inhibitors:

Enzyme inducers → enhance metabolism

e.g. Phenytoin, griseofulvin and some barbiturates

Enzyme inhibitors → delay metabolism

e.g. Phenylbutazone and dicoumarol

Induction of microsomal enzymes

The activity of microsomal enzymes can be increased by repeated administration of certain drugs. The dose of the drug, which was given with the inducer, should be increase to achieve its action in the body, as its metabolism will increase. Several hundred drugs are known to induce drug-metabolizing enzymes. The list includes long acting **barbiturates, volatile anaesthetics, CNS stimulants, antihistaminic and hypoglycemic**.

Examples of enzyme inducers:

Inducer	Drug whose metabolism is enhanced
Chlorcyclizine	Steroid hormones
Griseofulvin	Warfarin
Phenylbutazone	Aminopyrine, cortisol, digitoxin
Phenytoin	Cortisol, dexamethazone, digitoxin, theophylline
Barbiturates except secobarbital	Barbiturates, chloramphenicol, chlorpromazine, cortisol, coumarin, anticoagulants, digitoxin, phenylbutazone, phenytoin, testosterone.

Enzyme inhibition

Some drugs can inhibit the activity of the microsomal enzymes, so that the metabolism of other drugs given at the same time is also reduced and they begin to accumulate within the body and potentiation of toxicity is possible. For example, the duration of pentobarbitone-induced anaesthesia in cats and dogs is greatly prolonged following chloramphenicol therapy. The potentiating effect can still be seen 3 weeks after the cessation of chloramphenicol administration in dogs. The list of enzyme inhibiting drugs includes **SKF525A, Chloramphenicol, Ciprofloxacin, Cimetidine, Erythromycin, Isoniazid, Phenylbutazone and MAO inhibitors.**

Examples of enzyme inhibitors

Inhibitor	Drug whose metabolism is inhibited
- Allopurinol, - Chloramphenicol, - isoniazide	Antipyrine, dicoumarol, probencid, Tolbutamide
- Cimetidine	Chlordiazepoxide, diazepam, warfarin
- Dicoumarol	Phenytoin
- Oral contraceptives	Antipyrine
- Phenylbutazone	Phenytoin, tolbutamide

4- Excretion of Drugs

- **Routes of drug excretion:**

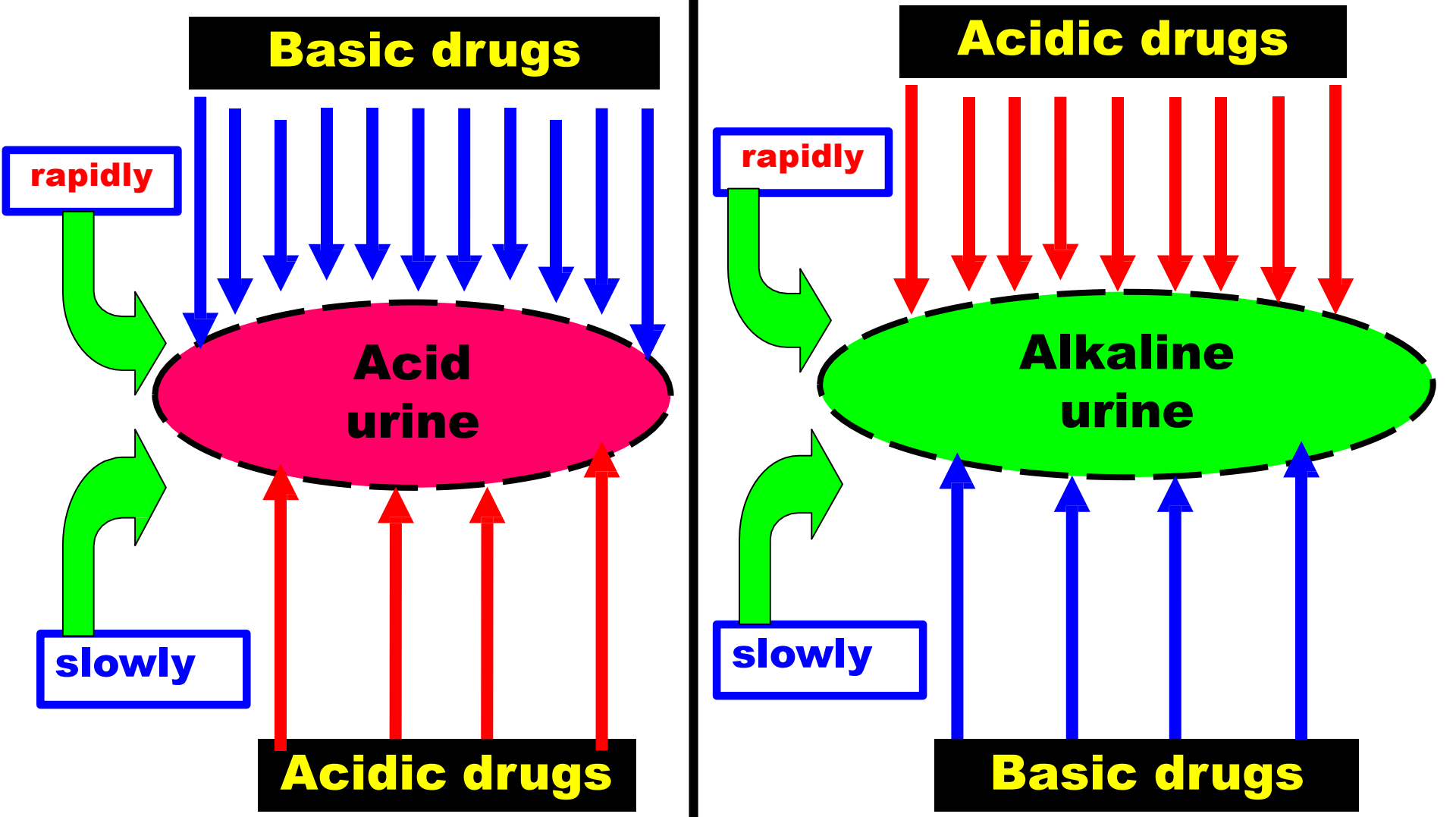
(I) Renal (II) Non renal

I- Renal route (Major site) by:

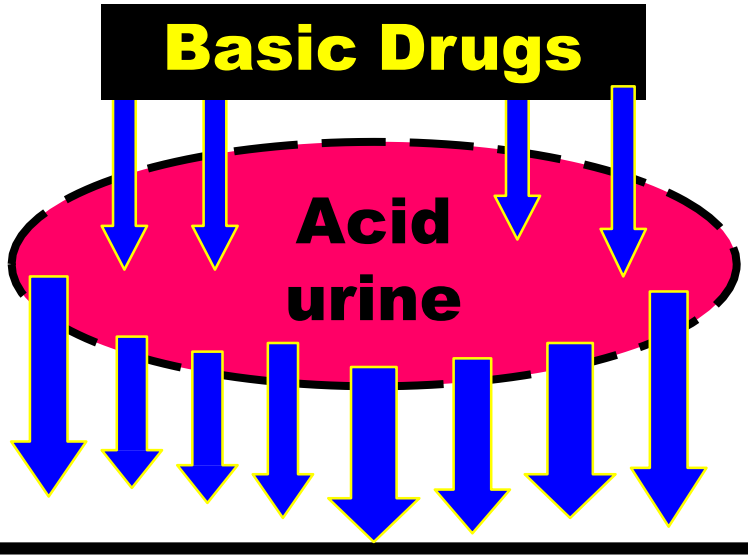
1 Glomerular filtration (GF): The drug passes along the hydrostatic pressure. GF Rate is measured by clearance of creatinine which is freely filtered and totally not reabsorbed into the blood

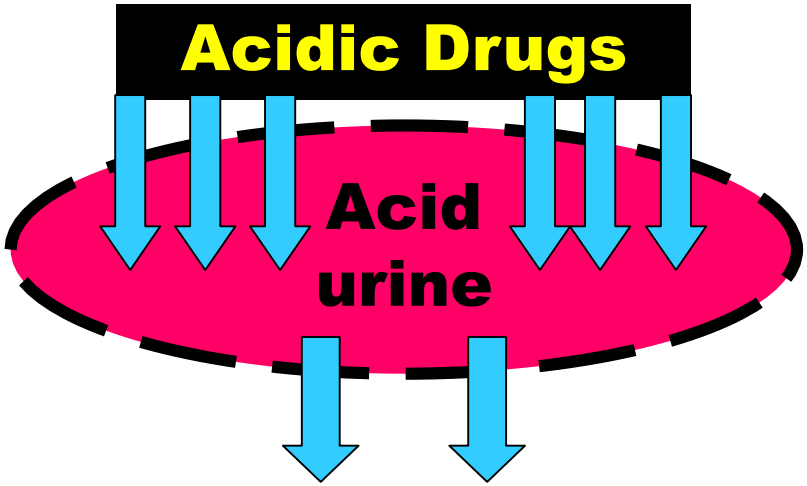
2 Active tubular secretion: responsible for excretion of some endogenous substances as uric acid and exogenous drugs as penicillin and probenecid

3 Passive tubular reabsorption and secretion: The drug should be non ionized (lipid soluble) and its excretion is influenced by PH of the urine


Basic drugs
rapidly
Acid urine
slowly
Acidic drugs
Acidic drugs
rapidly
Alkaline urine
slowly
Basic drugs

Renal Excretion of Drugs





Basic drug in acid urine → **Rapidly ionized**

↓

Slowly reabsorbed to blood

↓

More concentrated in urine

↓

More excreted in urine

Acid drug in acid urine → **Slowly ionized**

↓

Rapidly reabsorbed to blood

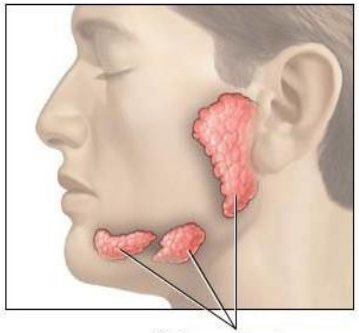
↓

Less concentrated in urine

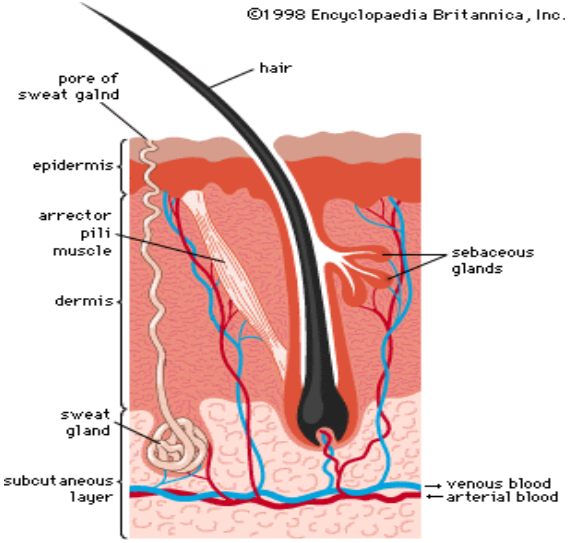
↓

Less excreted in urine

II- Non Renal Excretory organs of Drugs



1- Salivary Gl in saliva
e.g. Pot.iodide
Refampicin

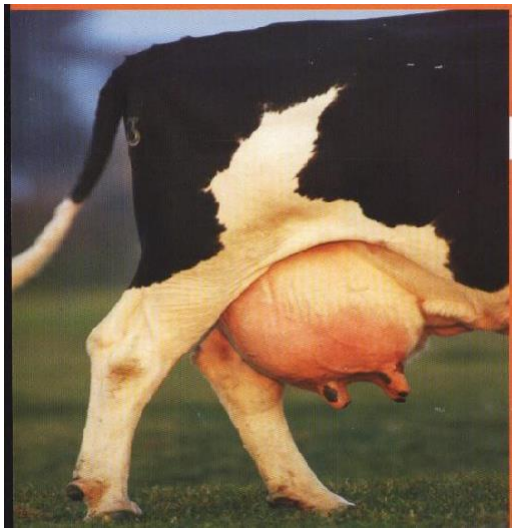


2- Sweat Gl in sweat
e.g. Refampicin

3- Lungs in expired air
e.g. Vol. anaesthesia

4- Liver in bile
e.g. Ampicillin
Phenolphthalein

5- Large intestine in stool
e.g. Streptomycin
Teracyclines



6- Mammary gland in milk
e.g. Penicillin
Choramphenicol

Methods of prolonging the duration of action of drugs

I-Delaying drug absorption:

Orally: by giving the drug on full stomach.

Parenterally:

1. Reduction in the solubility of the drug by giving drug in suspension form testosterone or combining drug with poor soluble compound e.g. procaine with penicillin.
2. Reduction in the vascularity of absorbing surface by adm. of vasoconstrictors as adrenaline with procaine.
3. Combination with oils e.g. adrenaline and penicillin in oil.
4. Combination with protein where the drug is slowly released from this combination e.g. insulin with protamine.
5. Combination with metal where the drug is slowly released from this combination e.g. penicillin with aluminium monostearate.
6. Estrification of certain drugs as sex hormones with weak organic acid as benzoic or propionic.
7. Implantation of drugs subcutaneously e.g. steroids.

Methods of prolonging the duration of action of drugs

II- Delaying drug metabolism in the liver by depressing the activity of microsomal enzymes by certain drugs as SKF525A.

III- Delaying renal excretion of drugs: by blocking tubular secretion of drugs e.g. tubular blocking agents as probenecid and PAHA.

IV-Increasing protein binding of drug in plasma e.g. long acting sulphonamides.