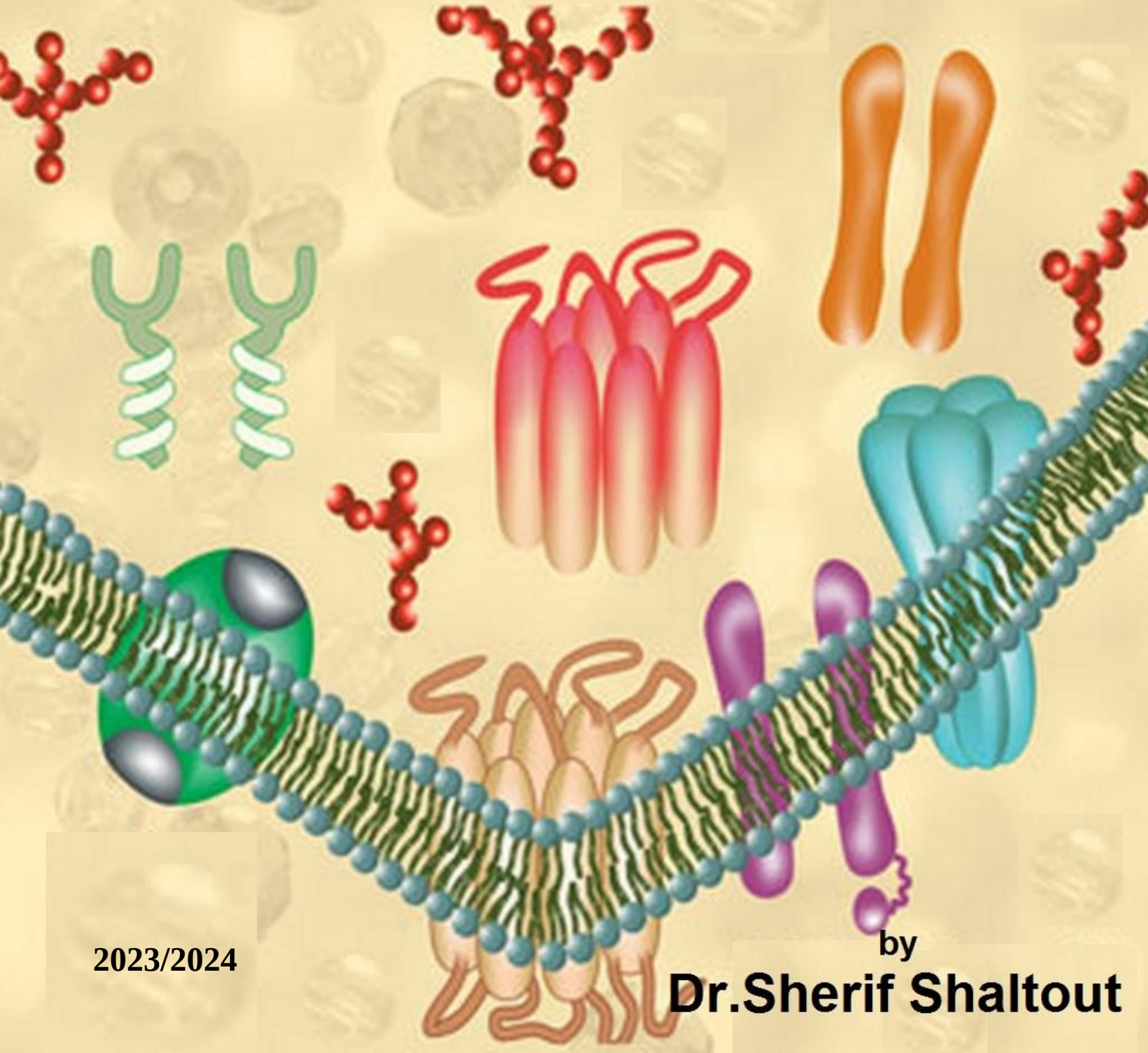
# General Pharmacolog



2023/2024

by
Dr.Sherif Shaltout

# GENERAL PHARMACOLOGY

This chapter provides basic knowledge necessary for subsequent study of individual drugs. Important terms & definitions are presented, together with the two basic areas of pharmacology; pharmacodynamics & pharmacokinetics.

## Pharmacology

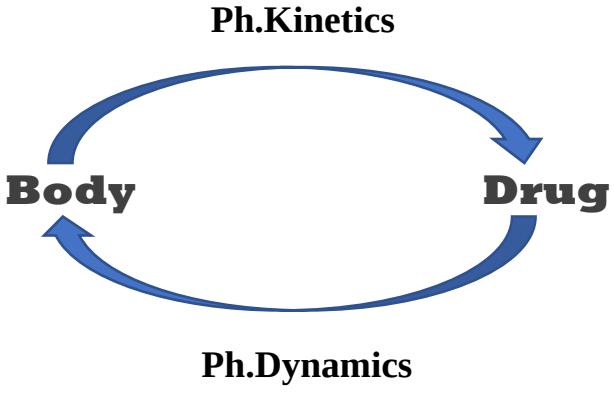
- It is the science that deals with drugs, their nature, pharmacodynamics, pharmacokinetics, therapeutic uses, adverse effects, preparations and administration.

## Drug

- It is a chemical substance that alters body functions and can be used for treatment, prevention or diagnosis of disease.

## Pharmacokinetics

- They are the studies of the **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion of drugs (**ADME**) and their mathematical relationship, i.e. **what body does to drugs.**




## Pharmacodynamics

- They are the studies of the biological and therapeutic effects of drugs and their mechanism of action, i.e. **what drugs do to the body.**

## Pharmacotherapeutics:

- Study the selection & use of the drugs for treatment, prevention or diagnosis of diseases

## Sources of drugs:

1. **Plant:** e.g. atropine from leaves of belladonna
2. **Animal:** insulin from the pancreas of pigs
3. **Mineral**: $MgSO_4$, iodine
4. **Microorganisms:** penicillin from the fungus penicillinum
5. **Synthetic:** in laboratory e.g. aspirin
6. **Biotechnology:** human insulin by genetic engineering

## Drug nomenclature:

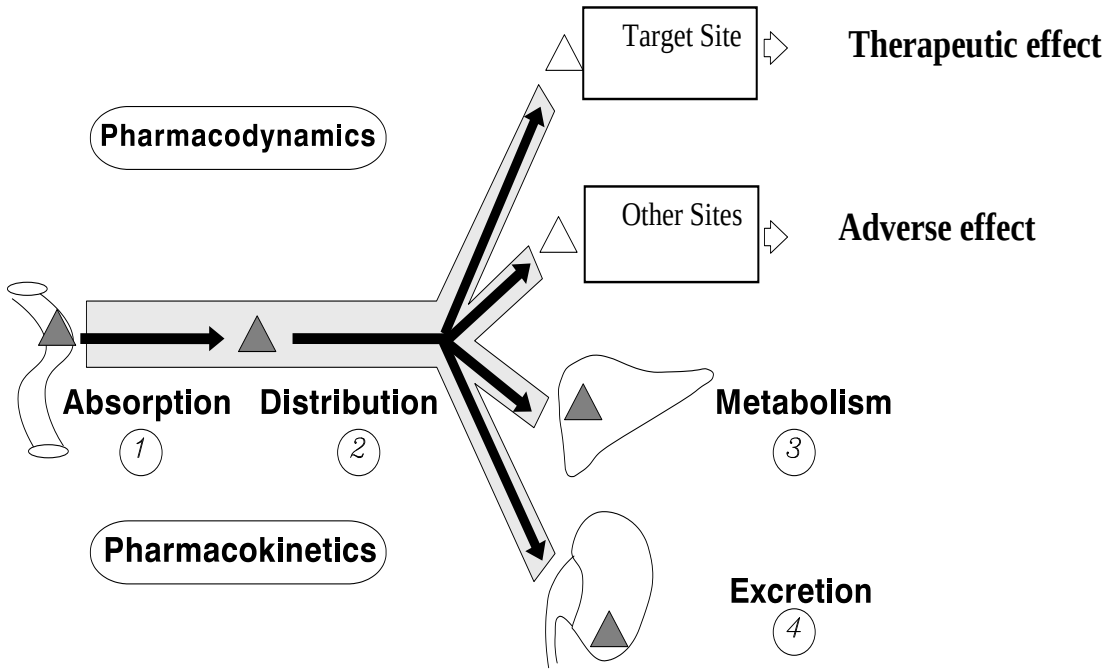
1. **Chemical name:** N-acetyl p-aminophen
2. **Generic name:** Acetaminophen (paracetamol)
3. **Trade name:** Panadol- Adol

| Routes of Administration | Advantages | Disadvantages | Dosage form |
|---|---|---|---|
| **Enteral** | | | |
| **1) Oral** | Most convenient, Safe, Economical , Easy | *Not suitable for: Unconscious, Uncooperative, excessive Vomiting or Diarrhea, Emergencies, Irritant drugs, drugs destroyed by (gastric acidity, enzymes , 1st pass effect) | *Solid: powder, effervescent granules, tablet (simple, sugar-coated, enteric coated, sustained release; SR), capsule (hard, soft, SR)<br><br>*Liquid: syrup, suspension, solution |
| **2) Rectal** | Escape 1st pass effect, useful if oral is unsuitable:…… | | *Solid: suppository<br><br>*Liquid: enema |
| **3) Sublingual** | *Escape 1st pass effect, acidity, enzymes<br>*Rapid absorption | | *Pellet, spray<br><br>*(buccal route for local effect: lozenge, wash, paint, gargle) |

| | | | |
|---|---|---|---|
| **Parenteral** | | | |
| **1) Intravenous (IV)** | Rapid onset, 100% bioavailab., suitable for emergency and large volume drugs | *Most dangerous<br>*transmission of diseases e.g. AIDS<br>*If allergy…> anaphylactic Shock<br>*Pyrogenic reaction<br>*Not suitable for oily preparation, irritant drugs | Ampule (single dose),<br>Vial (multiple doses),<br>bottle |
| **2) Intramuscular (IM)** | Suitable for mild irritant drugs, oily preparation | Unsuitable for large volume, | Ampule, vial |
| **3) Subcutaneous (SC)** | | | *Water solution or fine suspension<br>*SC implant: small rods |
| **Others** | | | |
| **Inhalation** | Excellent absorption due to rich blood supply and alveoli …>large surface area, porous, thin | | Gases, solution (nebulizer),<br>Fine powder(spinhaler),<br>vapours of volatile liquids |
| **Topical** | | | |
| **1) Local effect** | For skin,<br>nose,<br>eye | | Ointment, cream, lotion,<br>spray, drops<br>Drops, ointment |
| **2) Transdermal: TDS (Transdermal Delivery System)** | Prolonged effect and avoid 1st pass effect e.g. nitroglycerin, estrogen | | Patch, ointment, cream |

# P H A R M A C O K I N E T I C S

The term pharmacokinetics denotes the quantitative studying of drug **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion **(ADME)** and their mathematical relationship.




**Fate of the drug in the body**

## ABSORPTION OF DRUGS

❖ **Definition:** absorption is the passage of drug from the site of administration to the systemic circulation.

❖ **Methods of transport across cell membranes:**

**1- Passive transport:**

a. **Simple (lipid) diffusion:** the **lipid soluble** drugs can easily cross lipid membranes along concentration gradient with no energy.

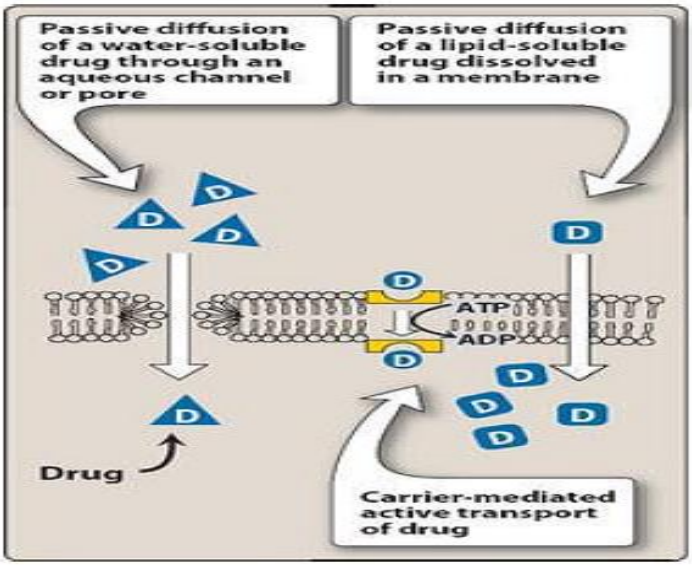
b. **Aqueous diffusion (filtration):** the **water soluble** drugs can pass only through water filled **pores or channels**.

2- **Carrier-mediated transport:** the drug passes across cell membrane by specialized carrier molecules (which are sites for saturation & competition):

   a. **Facilitated diffusion**: as simple diffusion but with aid of carrier. e.g. glucose uptake

   b. **Active transport**: the drug is carried against concentration gradient by energy. e.g. Na/K pump

3- **Endocytosis (pinocytosis):** it occurs in cases of large molecule by invagination of part of cell membrane and engulfing the drug molecule. Energy is needed. e.g. absorption of vit.B12 & intrinsic factor in terminal ileum.




## ❖ Factors affecting drug absorption:

## A. Factors related to drug:

**1. Molecular size:** small molecules are absorbed than large molecules

**2. Pharmaceutical preparations**

- **Dosage form:** - solutions are better absorbed than suspensions
  - sustained-release preparations are slow in absorption

- **Rates of disintegration & dissolution**:

  Rapid with paracetamol and slow with digoxin

**3. Lipid and water solubility:**

- Drug must be water soluble as well as lipid soluble

***- More lipid solubility → high lipid/water partition coefficient → better absorption***

**4. Ionization**: ***- Ionized (polar or charged) forms are poorly absorbed***

***- Unionized (non-polar or non-charged) forms are more absorbed***

e.g. - Quaternary ammonium compounds: always ionized → poor absorption

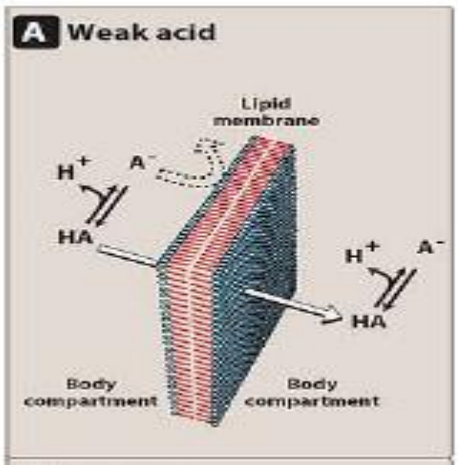
- Tertiary amines (physostigmine): always unionized → better absorption

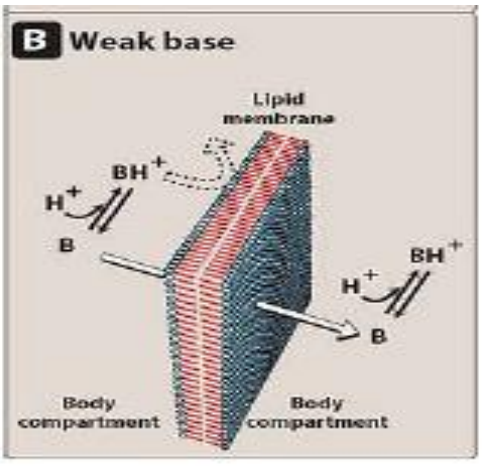
- ❖ Most drugs are either weak acids or weak bases.
- ❖ Acidic drugs (HA) release an H+ producing a charged anion (A-):

$$HA \rightleftarrows H^+ + A^-$$

- ❖ Weak bases (BH+) can also release an H+ producing the uncharged base (B):

$$BH^+ \rightleftarrows B + H^+$$




- ❖ Ionization depend on pH of the medium and pKa of the drug (pKa is a measure of the strength of the interaction of a compound with a proton).
- ❖ **The lower the pKa** of a drug, **the more acidic** is the drug. Conversely, **the higher the pKa**, **the more basic** is the drug.

❖ Relation between pH of the medium and pKa of the drug is presented by **(Henderson-Hasselbach equation):**

$$pka = pH + \log \frac{\text{concentration of protonated}}{\text{concentration of nonprotonated}}$$

® If the drug is weak **A**cid :

$$pka = pH + \log \frac{\text{concentration of } \mathbf{U}\text{nionized acid}}{\text{concentration of ionized acid}}$$

® lf the drug is weak base:

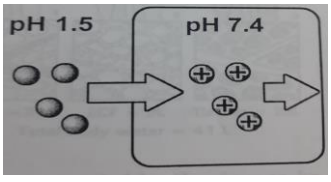
$$pKa = pH + \log \frac{\text{concentration of the ionizd base}}{\text{concentration of unionized base}}$$

- **pKa of a drug:** is the **pH** at which **50%** of the drug molecules exist in the **ionized** form and **50%** in the **unionized** form.

## Clinical Significance of $pK_a$

**1. GIT:** knowing site of drug absorption:

- Acidic drugs (e.g. Aspirin) become mostly unionized in acidic pH
- Basic drugs (e.g.Amphetamine) become mostly unionized in alkaline pH
- Streptomycin has a very high pKa→ always ionized→ very poor oral absorption
- **Ion trapping of aspirin**: Aspirin (pKa = 3.5) in the empty stomach (pH = 1.5) → more unionized → more absorbable into gastric cells, but once entered the cells (pH = 7.4) becomes more ionized → trapped inside these cells (aspirin trap) → death of the cells inducing "peptic ulceration".




**2. Kidney:** treatment of drug toxicity

- In drug poisoning, changing urinary pH → increases drug ionization and inhibits tubular reabsorption:
  - Alkalinization of urine is useful in acidic drug poisoning e.g. aspirin.
  - Acidification of urine is used in basic drug poisoning, e.g. amphetamine.

## B. Factors related to patient:

**1. Route of administration:** IV > Inhalation > IM > SC > Oral > Skin

**2. Absorbing surface:**

**a. Vascularity:** Alveoli > skeletal muscle > subcutaneous

**b. Surface area:** Intestine > Stomach

**c. State of health:** Diarrhea & malabsorption ↓↓ oral absorption

**3. Systemic circulation:** Shock & heart failure ↓↓ absorption

**4. Specific factors:** intrinsic factor for vit.$B_{12}$

**5. Presence of other drugs: -** vit.C ↑ absorption of iron

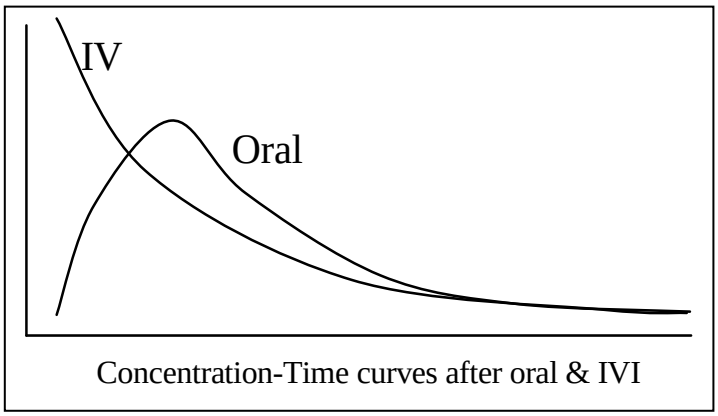
- Activated charcoal ↓↓ oral absorption of most of drugs
- Adrenaline SC → VC → ↓↓ absorption of local anesthetics → longer duration of action

### ❖ Bioavailability (Biological Availability)

-It is the percentage of unchanged drug reaching the systemic circulation after any route and becomes available for biological effect.

-It is calculated by: $\frac{\textbf{(AUC) after any route of administration}}{\textbf{(AUC) after IVI.}}$ **X 100**

**(AUC** = the **A**rea **U**nder the blood concentration-time **C**urve**)**



Concentration-Time curves after oral & IVI

## Factors Affecting Bioavailability

### I. Factors Affecting Drug Absorption from GIT (oral absorption)

**A. Factors related to drug:** …….

**B. Factors related to patient:** …….+

**4. Presence of food:**

- Empty stomach → ↑absorption (BUT it is bad if irritant drug e.g. Aspirin)
- Milk (calcium) ↓↓ oral absorption of tetracyclines

**5. pH:** - gastric acidity ↑ absorption of aspirin and barbiturates

- intestinal alkalinity ↑ absorption of amphetamine and ephedrine

**6. Gut motility:** marked alterations e.g. diarrhea ↓ absorption

**7. Gastric emptying:**

a. Metocloperamide → accelerates gastric emptying →

- ↑ absorption of paracetamol (rapid rate of disintegration & dissolution)

b. Atropine → slowdowns emptying →the REVERSE effects

## II. First-Pass Effect (First-Pass Metabolism; Presystemic Elimination)

- It is the metabolism of some drugs in a single passage through the liver, gut wall or the lungs before reaching the systemic circulation.

**A. Hepatic 1$^{ST}$ pass effect:** drugs absorbed from the GIT are carried first in the portal circulation to the liver. Some drugs are extensively metabolized in their first-pass e.g. nitroglycerin & propranolol.

**B. Gut 1$^{ST}$ pass effect:**

- Gastric acidity: benzyl penicillin
- Digestive enzymes: insulin & pituitary hormones
- Mucosal enzyme: L-dopa , alpha-methyldopa

**C. Pulmonary metabolism**: after aerosol inhalation (nicotine).

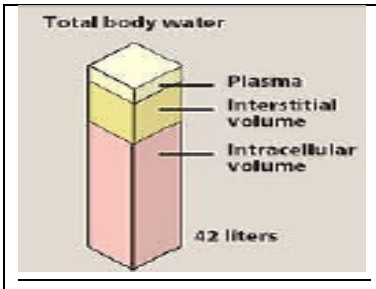
### How to overcome the First-pass Effect

1. **Increase oral dose**
2. **Other routes: Sublingual - Parenteral - Rectal (to some extent)**

# DISTRIBUTION OF DRUGS

❖ It is the passage of drug through body compartments which are separated by capillary walls and cell membranes.

❖ Body fluid compartments:




**1- intravascular volume = 4 L/70 Kg**

**2- interstitial volume = 10 L/70 Kg**

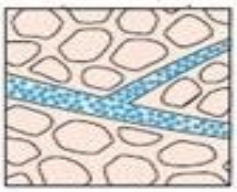
**(Extracellular volume)**

**3- intracellular volume = 28 L/70 Kg**

***Total body fluid = 42 L/70 Kg**

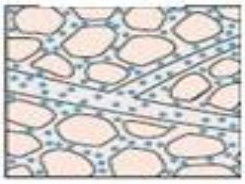
## Pattern of distribution:

**1. Plasma compartment (one compartmental model):**



- If a drug:
  - has a **high molecular weight** or
  - **binds strongly to plasma proteins**
- It is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment.
- e.g. Heparin , Dextran.

**2. Extracellular fluid (two compartmental models):**

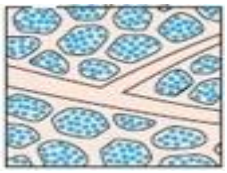


- If a drug has a **low molecular weight** and is **hydrophilic**
- It can move through the endothelial slit junctions of the capillaries into the interstitial fluid BUT cannot move across the lipid membranes of cells
- e.g. Aminoglycoside antibiotics, Mannitol.

**3. Extra & intracellular fluid (multi-compartmental model)**

- If a drug has a **low molecular weight** and is **lipophilic**
- It moves into the interstitium through the slit junctions and also moves through the cell membranes into the intracellular fluid.
- Some drugs uniformly distribute throughout whole body water e.g. Ethanol, sulphonamides.

- the majority of drugs distribute into several compartments, often binding cellular components for example, lipids (abundant in adipocytes and cell membranes), proteins (abundant in plasma and within cells), or nucleic acids (abundant in the nuclei of cells)



**4. Tissue reservoir:** Drugs concentrated in certain tissues

- **Iodine** in thyroid & salivary glands
- **Calcium & tetracyclines** in bone & teeth
- **Chloroquine** in liver
- **Thiopental** in fat (Redistribution ??)

## ❖ Volume of Distribution ($V_d$)

- Definition: the **apparent** volume of fluid required to accommodate the entire amount of the drug in the body in the same concentration as that present in plasma (i.e. when the drug is equally distributed between plasma and tissues).

$$V_d\ (L) = \frac{\text{Amount of drug in the body}}{\text{Plasma concentration}}$$

**($V_d$ = A/C or Q/C)**

- The apparent volume of distribution does not describe a real, physical volume, but rather, reflects the **ratio of drug in the extraplasmic spaces relative to the plasma space** as it assumes that the drug distributes uniformly, in a single compartment, e.g. the Vd for digoxin is 6 **L/Kg** (in adult 70 Kg) or 420 **L**.

- **Importance of $V_d$**

**1.** It is an estimate of the extent of **tissue uptake** of drugs:

- Small $V_d$ (e.g. frusemide) indicates that tissue uptake is limited.
- Large $V_d$ (e.g. digoxin) indicates extensive tissue distribution.

**2. In cases of drug toxicity**:

- Dialysis is **not useful** for **high $V_d$** drugs (most of drug is in the tissues).
- Dialysis is **useful** for **low $V_d$** drugs (most of drug is in the blood).

**3.** $V_d$ can be used to calculate the **loading dose (LD):**

**[LD = $V_d$ x $C_{ss}$** (Steady State plasma Concentration)]

**4.** $V_d$ can be used to calculate the **total amount of drug** in the body**:**

**[A = $V_d$ x $C_p$ ]**

## ❖ Factors Affecting Distribution of Drugs:

**1) Perfusion:** the amount of the drug which is delivered to a particular organ depends on the ***blood flow*** to that organ: ↑ blood flow → ↑ distribution.

**2) Diffusion:** the ability of the drug to diffuse across the cell membranes is governed by its ***lipophilicity***, ***ionization*** **&** ***molecular weight***: (as absorption)

**3) Binding to plasma proteins (PPs):**

- Most of drugs when introduced into the body are bound to plasma proteins (pp) e.g.

- **Albumin:** - the most important pp

  - Acidic & lipophilic drugs bind mainly with it

- **Other:** globulin, glycoprotein…etc

- Drug in blood exists in 2 forms: **free form** & **plasma protein bound form** which exist in equilibrium; when the free form is metabolized and/or excreted, another part is released from plasma proteins

| Free fraction | Bound fraction |
|---|---|
| • Active<br>• Diffusible<br>• Can be Metabolized<br>• Can be Excreted | • **In**active<br>• **Non**diffusible<br>• Can**not** be metabolized<br>• Can**not** be excreted<br>• Act as a reservoir for drug |

- **Significance of Binding to Plasma Proteins**

1. The binding of drug to plasma proteins **limits its tissue penetration & decreases its $V_d$.**
2. The bound drug cannot be eliminated → **prolongs the $t_{½}$** of the drug → **prolongs the effect** of drug.
3. **Hyboalbuminemia** e.g. starvation, malnutrition →**↑ free drug** → therapeutic dose changes to **toxic dose** e.g. phenytoin.
4. Competition for binding sites between drugs → **displacement of each other** → **clinically-significant drug interactions** e.g.

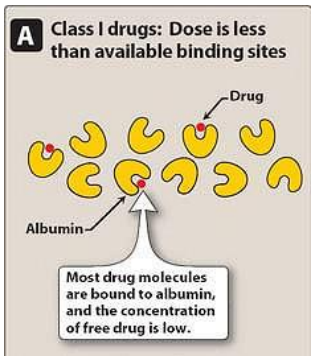
- Aspirin, sulphonamide displace warfarin → bleeding.
- Sulphonamide displaces bilirubin → kernicterus in premature neonates.

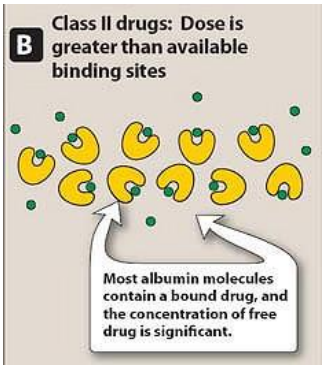
{When two drugs with high affinity for albumin are given, they compete for the available binding sites. The drugs with **high affinity** for albumin can be divided into two classes:

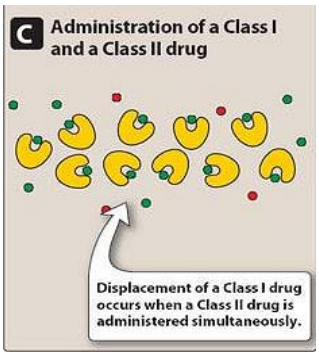
**1. Class I drugs:** If the dose of drug is less than the binding capacity of albumin i.e. **low dose/capacity ratio** → high bound fraction and **small free fraction**

**2. Class II drugs:** If the doses greatly exceed the number of albumin binding sites i.e. **high dose/capacity ratio → high free fraction**.

* When a patient taking a Class I drug, such as warfarin, is given a Class II drug, such as a sulfonamide antibiotic. Sulfonamide displaces warfarin from albumin, leading to a rapid increase in the concentration of free warfarin in plasma → ↑ therapeutic effects, as well as ↑ toxic effects → bleeding}



**4) Binding to cell and tissue constituents:**

- Drugs concentrated in certain tissues **(Tissue reservoir)**.

## ❖ Passage across barriers:

### Passage of Drugs to CNS

1. **Lipid-soluble** drugs pass freely through BBB, e.g. general anesthetics and other CNS depressants.
2. **3ry amines** can pass while 4ry $NH_4^+$ compounds (ionized) cannot.
3. **Some hydrophilic** antibiotics e.g. penicillin can pass **inflamed BBB** only

### Passage of Drugs to the Fetus

- Many drugs cross placental barrier by simple diffusion (depending on their lipid solubility & their degree of ionization) and can **harm the fetus:**
  - Drugs given in **3rd to 10th week** of pregnancy → **teratogenicity** e.g. thalidomide → phocomelia
  - Oral anticoagulants → fatal hemorrhage in the newborn.
  - Oral hypoglycemics (sulfonylureas) → prolonged neonatal hypoglycemia.
  - Aminoglycosides → 8th cranial nerve damage.
  - During labor, Morphine → respiratory depression (asphyxia neonatorum).

### Passage of drugs to breast milk

- Most of drugs administrated to lactating women are detectable in breast milk.
- pH of milk is more acidic (7.0) than that of plasma (7.4) → **basic drugs** accumulate in milk (ion trapping).
- Milk contains more fat than plasma → retention of **lipid soluble** drugs.

- **Drugs are contraindicated during lactation**:
  - Sedatives, hypnotics and narcotics → CNS depression in baby.
  - Oral penicillins and purgatives → diarrhea in baby.
  - Anticancer drugs → decrease growth of baby.
  - Bromocriptine & sex hormones → suppress lactation.

# BIOTRANSFORMATION

## (Metabolism)

❖ **These are**: the chemical changes that occur to drugs after absorption until excretion.

- Drug metabolism occurs **mainly in the liver**, also in other organs, e.g. intestinal lumen or wall, lung, plasma, skin and kidney.
- The aim of drug metabolism is **the conversion of the lipophilic drug to a more polar (hydrophilic, ionized)** metabolite which is easily excreted in urine.
- The hydrophilic drugs usually do not undergo metabolism and secreted unchanged in urine

### ❖ Types of Biotransformation Reactions

**Phase I (Non-Synthetic)**

- Phase I reactions include: **oxidation - reduction - hydrolysis**.
- **The most important reaction is oxidation by cytochrome P450 enzyme system.**
- Phase I reactions result in **unmasking of a polar group** (-OH, -SH, or -$NH_2$) → **an ionized metabolite** that can be easily excreted.

**Phase II (Synthetic)**

- An **endogenous substrate**, (e.g. glucuronic acid, glycine, glutathione, sulfate or acetic acid) is **conjugated with the functional group** of the drug or its metabolite → **nontoxic highly polar**, rapidly eliminated **conjugates.**
- **The most important is conjugated with glucuronic acid.**

## Phase I reactions

### A. Oxidation:

- **The most important is cytochrome P450 oxidases "CYP" (mixed function oxidases) which are hepatic microsomal enzymes**

*CYP is further classified by family, subfamily & gene into many isozymes. The name of each one is designated by the term CYP followed by 3 characters e.g. CYP 2C9:*

*1. The first Arabic numeral represents the family.*

*2. The alphabetic letter represents the subfamily.*

*3.The second Arabic numeral represents the individual gene within the subfamily.*

- Xanthine oxidase: converts xanthine → uric acid
- Monoamine oxidase (MAO): oxidizes catecholamines & serotonin

### B. Reduction:

- Nitroreductase → chloramphenicol
- Carbonyl reductase → naloxone

### C. Hydrolysis:

- It occurs mainly non-microsomal (in plasma and body fluids)
  - Cholinestrase → Ach.
  - Peptidase → insulin

**Consequences of phase I reactions:**

- The activity of the drug is modified in one of the following ways:

  1- Active drugs → inactive drugs (occurs with most drugs).

  2- Inactive drugs (prodrugs) → active drugs, e.g. cortisone to cortisol (hydrocortisone).

  3- Active drug → another active one, e.g. codeine to morphine.

  4- Active drug → a toxic metabolite e.g. methanol → formaldehyde → retinotoxic & paracetamol → toxic metabolite (NAPQI) → hepatotoxic in case of toxicity

## Phase II reactions

### A. Glucuronide conjugation:

- **It is the most common conjugation reaction**
- Glucuronide conjugates secreted in bile may be hydrolyzed by intestinal bacteria and free drug can be reabsorbed again i.e. enterohepatic circulation → prolong duration of drug action e.g. estrogen (so contraceptive pills are given once daily)

### B. Non-Glucuronide conjugation:

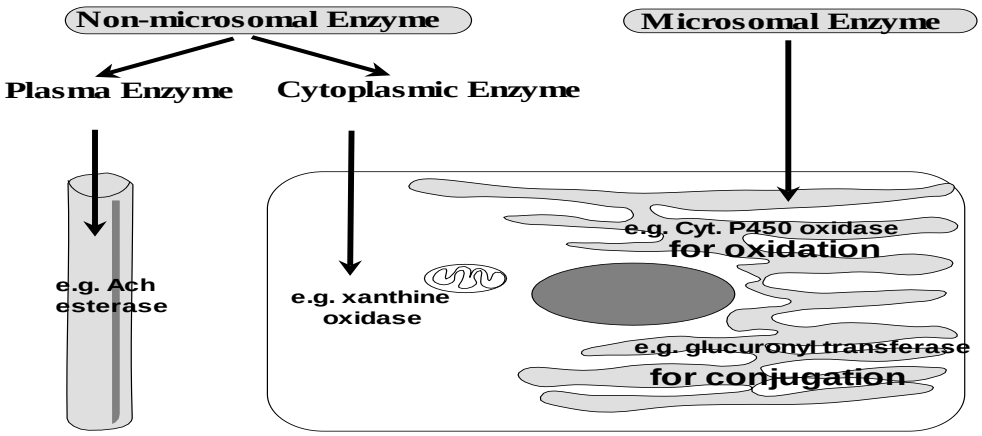
- Sulphate formation e.g. steroids
- Glycine conjugation e.g. salicylic acid
- Glutathione conjugation e.g. ethacrynic acid
- Acetyl conjugation (slow & rapid acetylation) e.g. isoniazid

**Consequences of phase II reactions:**

- Mostly result in drug inactivation
- Some exceptions can occur e.g. morphine is partially converted into morphine-6-glucuronide (active metabolite)

- **Most of drugs is metabolizes by phase-I followed by phase-II reactions**
  - Some drugs is metabolizes firstly by phase-II then by phase-I reactions e.g. isoniazid.
  - Some drugs undergo phase-I or phase-II only

- **Types of enzymes responsible for biotransformation reactions**



| Microsomal enzymes | Non-microsomal enzymes |
|---|---|
| **Site:** in the **liver,** in **microsomes of ER**. So, they are called hepatic microsomal enzymes | Present in **liver**, **GIT**, **lung**, **kidney**, **plasma**, **skin**: in **cytoplasm** and **mitochondria** |
| **Reactions:**<br>Phase-I: Oxidation<br>Reduction<br>Hydrolysis (few reactions)<br>Phase-II: Glucuronic a. conjugation Only | **Reactions:**<br>Phase-I: Oxidation<br>Reduction<br>Hydrolysis (mostly)<br>Phase-II: All Conjugations Except Glucuronic |
| **Substrate: lipophilic drugs** & bilirubin | **Lipophilic , hydrophilic drugs** (to terminate action as succinylcholine) & natural body constituents |
| **Affection by drugs: Inducible** | **Non-inducible** |

## ❖ Factors Affecting Biotransformation:

1. **Drugs: (Enzyme induction & enzyme inhibition**).

- Some drugs and environmental substances can **induce** or **inhibit** the microsomal enzyme activity and lead to undesirable drug interactions

***Clinical significance of Enzyme Induction:***

❖ Drugs stimulating the microsomal enzyme systems → ↑ activity →

- ↑ their own metabolism → **tolerance** e.g. **phenobaritone.**
- ↑ metabolism of other drugs metabolized by these enzymes and are given at same time→ drug interactions e.g.:
  - **Rifampicin** →↑ **oral contraceptive** metabolism → pregnancy
  - **Phenytoin** →↑ **cyclosporine** metabolism → transplant rejection
  - **Rifampicin** →↑ **warfarin** metabolism → therapeutic failure.
- ↑ metabolism of endogenous substrates e.g. **phenobarbitone** → ↑ elimination of **bilirubin** → used in treatment of neonatal jaundice)
- ↑ metabolism of vitamins e.g. phenytoin → ↑ of vit.D, vit.K, folic acid → osteomalacia, bleeding and megaloplastic anemia

- Enzyme induction is reversible. It occurs over a few days-months and passes off over 2-3 weeks after withdrawal of the inducer.

**Examples of Enzyme Inducers**

**Ph**enytoin & carbamazepine- **ph**enobarbitone – ri**f**ampicin - griseo**f**ulvin - ♂ androgen- nicotine- chronic alcohol ingestion.

***Clinical significance of Enzyme Inhibition:***

❖ Drugs inhibiting the microsomal enzyme systems → ↓ activity →

- ↓ their own metabolism →↑ drug level**.**
- ↓ metabolism of other drugs metabolized by these enzymes → drug interactions e.g.:
  - **Ciprofloxacin** →↓ **warfarin** metabolism → bleeding
  - **Cimetidine** →↓ **carbamazepine** metabolism → toxicity

- It occurs faster than enzyme induction.

**Examples of Enzyme Inhibitors**

**C**imetidine- **c**hloramphenicol - **c**iprofloxacin- erythromycin - ketocenazol - ♀ **(F)** estrogen, progesterone, contraceptive pills.

**2. Pathological factors which affect hepatic activity e.g.** liver failure starvation, cancer → ↓ activity of HME → need to adjust dose.

**3. Pharmacogenetic variations in metabolizing enzymes** e.g. slow & fast acetylators (see pharmacogenetics).

**4. Hepatic blood flow:** drugs ↓ hepatic blood flow → ↓drug matabolism

**5. Age:** ↓ enzymatic activity in extremities of age

- Premature babies have ↓ conjugate of chloramphenicol → fatal gray baby syndrome.

**6. Sex:** female sex hormones are HME inhibitors → receive lower doses than male.

7. **Drug properties:** lipophilicity → hepatic metabolism of drugs.

8. **Drug dosage:** toxic dose can deplete substances needed for drug detoxification e.g. paracetamol toxic dose → depletion of GSH→ accumulation of toxic metabolite NAPQI

## EXCRETION OF DRUGS

### 1- The kidney:

- **It is the most important route** of excretion. It occurs through:

**1. Glomerular filtration:**

- For hydrophilic free (non-bound) drugs with M.W. < 500 (i.e. < the glomerular pores). e.g. mannitol

**Factors affecting glomerular filtration**

- Glomerular filtration rate (GFR)
- Plasma protein binding (PPB) → prevents filtration

**2. Active tubular secretion**: through special transport system (carrier) → saturable & site for competition.

- Acid carrier e.g. for penicillins, probenecid, frusemide, uric acid
  - Probenecid →↓ tubular secretion of penicillin→↑ duration of action of penicillin
  - frusemide →↓ tubular secretion of uric acid →hyperuricemia as an adverse effect.
- basic carrier e.g. for digoxin, quinidine.

**3. Active tubular reabsorption**:

- Unionized form of drug (lipophilic) → tubular reabsorption

❖ **Changes in urinary pH:** affect excretion of drugs

- Alkalinization of urine (**Na** or **K** **A**cetate, **B**icarbonate, **C**itrate) → ↑ renal excretion of weak acid drugs e.g. Aspirin, Barbiturates
- Acidification of urine ($NH_4$**C**l or Ascorbic acid "vit.**C**") → ↑ renal excretion of weak base drugs e.g. amphetamine. ephedrine

**2- GIT:**

*** Saliva**: e.g. Morphine, Iodine, Metronidazole → metallic taste

*** Stomach:** e.g. Morphine→ gastric wash is done in aute morphine toxicity despite it is administrated by IV route.

*** Bile:** in active or conjugated form → intestine → EITHER

- Excreted in large intestine→ stool
- Reabsorbed → enterohepatic circulation e.g. Morphine, Rifampicin
- Some antibacterials are excreted in bile in an active form → useful in: - treatment of cholecystitis & typhoid fever e.g. Ampicillin
  - patients with renal impairment (No need for dose adjustment)

*** Stool:** conjugated metabolites & poorly absorbed orally

**3- Lungs:** e.g. volatile liquids (inhalant general anesthesia), gases ($CO_2$)

**4- Sweat:** e.g. Rifampicine → red discoloration of sweat

**5- Breast Milk: -** Many drugs are excreted in breast milk → can affect baby
**-** lipid soluble and basic drugs are trapped in breast milk

# PARAMETERS OF ELIMINATION

## 1. Systemic clearance (Cls)

### Definition

- It the volume of a fluid cleared from the drug per unit time.

$$\mathbf{Cls = K_{el} \ X \ V_d}$$

- **$K_{el}$ → Elimination rate constant = $\frac{0.693}{t_{1/2}}$**

[(0.693) is the natural logarithm of 2 (i.e. In 2) and gets into the equation because ($t_{1/2}$) involves a halving of concentration → $-Kel = \frac{In(C_2/C_1)}{t_{1/2}} = \frac{In\ (1/2)}{t_{1/2}}$ → $Kel = \frac{In(2)}{t_{1/2}}$]

- So, systemic clearance **Cl** = $\frac{0.693}{t_{1/2}}$ **X $V_d$**

- The systemic clearance is equal to the sum of individual organs clearances i.e. the clearnce by the liver, kidney, lung, ….etc.

***Cls = renal clearance (Clr) + non-renal clearance (Clnr)***

### Factors affecting drug clearance

1. Blood flow to the clearing organ (directly proportional).
2. Binding of the drug to plasma proteins (inversely proportional).
3. Activity of processes responsible for drug removal as hepatic enzymes, glomerular filtration rate and secretory processes (directly proportional).

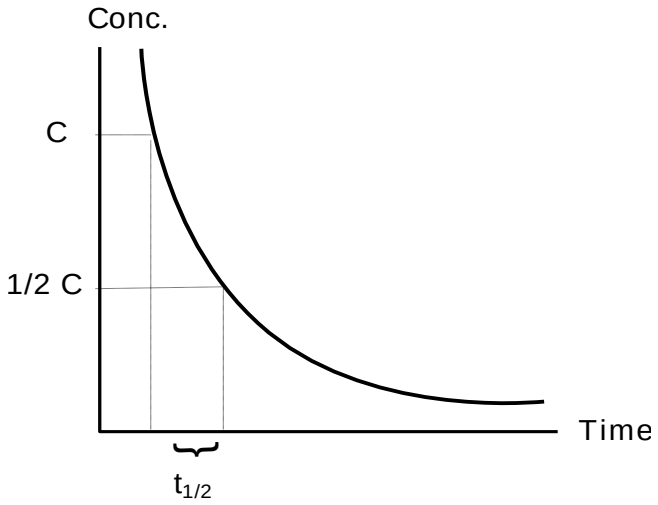
### Significance of clearance

1. Calculation of the maintenance dose **(MD**)
2. Adjustment of the **dosing regimen** for drugs eliminated by glomerular filtration e.g. dosing of gentamicin

## 2. Plasma (elimination) half life (t½)

### Definition

- It is the time required to eliminate 50% of drug from plasma.



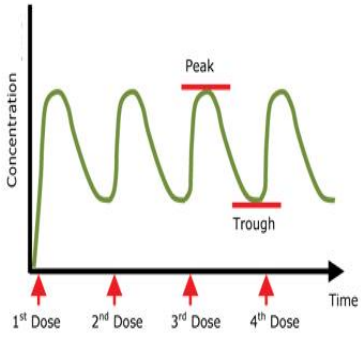

### Calculation:

- It depends on: Clearance & $V_d$
- The larger the $V_d$, the longer the t½ (it takes longer to remove drug from deep within tissue). The larger the Cl, the shorter the t½

$$t½ = \frac{0.693 \text{ X } Vd}{Cls}$$

### Value of elimination t½

1. It determines the **dosage interval (τ or $T_m$).**
   - If τ = t½ → this is an accepted choice to avoid wide fluctuations of the **peak** (highest pl.conc. of the drug) and **trough** (lowest pl.conc.).
   - If τ < t½ → more drug accumulation occurs.
   - If τ > t½ → decrease in drug concentration occurs between doses.




2. It indicates **$T_{ss}$ (time required to attain Css):** it is equal to 5 t½ (after 4 t½ ; > 95% of the Css is attained)
3. It indicates the **time** needed for **complete elimination**: occure after 5 t½
4. Drugs having long t½ are given once/day

## Factors affecting elimination t½

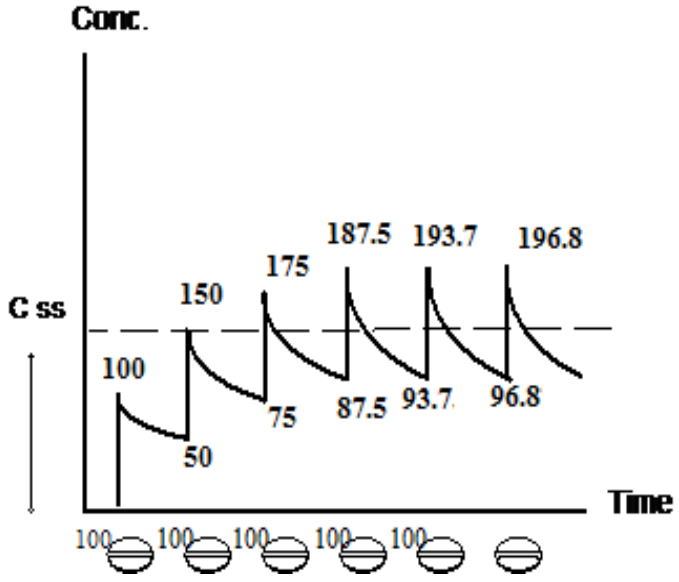
1. The state of the eliminating organs i.e. liver & kidney functions
2. The delivery of the drug to the eliminating organs e.g.:
   a. Plasma protein binding limits renal filtration and increase t½
   b. Drugs with very high $V_d$ may escape from elimination in the tissues and increase t½
   c. Blood flow (decrease renal bl.flow in HF may increase t½)

## 3. Steady state concentration (Css)

**Definition:** the steady level of drug in plasma achieved when the rate of administration equals the rate of elimination.

**The rule of (5):**

- The Cpss is reached after 5 t½
- If we change the dose, the new Cpss is reached after 5 t½
- If dosing stop, complete elimination of drug occurs after 5 t½



## 4. Loading dose (LD)

- **Loading dose (LD):** the dose given at the onset of therapy to achieve a rapid increase in plasma drug concentration to reach Cpss without toxicity.

$$\mathbf{LD_{IV} = V_d \ X \ Css \ (target \ C_P)}$$

$$\mathbf{LD_{Oral} = \frac{LD_{IV}}{F}} \text{ (fraction of oral bioavailability)}$$

  - Used for:
    1. drugs with **Long $t_{1/2}$** (e.g. amiodaron) or
    2. in an **Emergency**

## 5. Maintenance dose (MD)

- **Maintenance dose (MD):** the dose needed to keep the plasma drug concentration constant at Css (the dose needed to compensate the amount eliminated).
  - Dosing rate (rate of administration) = rate of elimination = Cl X Css
  - If drug taken by *continuous IV infusion:*

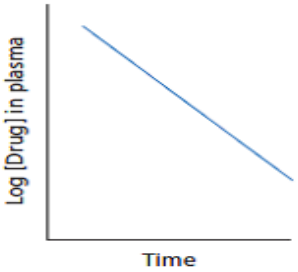
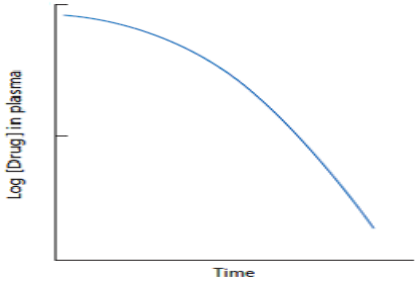
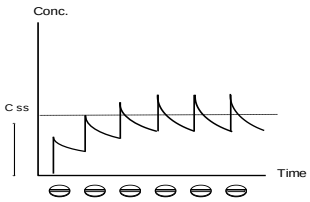
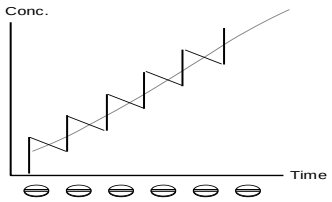
$$\mathbf{Infusion\ rate = CLs \ X \ Css}$$

  - If drug taken in *repetitive doses:*

$$\mathbf{MD_{IV} = CLs \ X \ Css \ X \ Tm} \text{ (dosing interval)}$$

$$\mathbf{MD_{Oral} = \frac{CLs \ X \ Css \ X \ Tm}{F}} \text{ (fraction of oral bioavailability)}$$

## 6. Kinetic orders

| A. First order kinetics | B. Zero order (saturation) Kinetics |
|---|---|
| • A constant **fraction** of drug is eliminated per unit time. | • A constant **amount** of drug is eliminated per unit time. |
| • Rate of elimination is **proportional** to the concentration of drug | • Rate of elimination is **constant** (limited capacity of kinetics due to saturation of involved enzymes and/or carriers |
| • It has a **linear** elimination kinetics i.e. plasma concentration can be expected at any time *(using log conc.-time disappearance curve)*   | • It has a **non-linear** elimination kinetics i.e. plasma concentration can NOT be expected at any time *(using log conc.-time disappearance curve)*   |
| • **Constant** t½. | • t½ is **not constant** |
| • A steady state concentration **(Css) is reached** on repeated dosing after 5 $t_{1/2}$.   | • **NO Css** is reached; repeated dosing → overshooting of drug concentration.   |
| • Modest changes in dose → are usually **tolerated** because when drug conc. ↑→ elimination ↑ by the same ratio. | • Modest changes in dose → **toxicity** due to drug cumulation |
| • Drug metabolites do **Not vary** with dose. | • Drug metabolites **may vary** with dose |
| • Examples: Most drugs. | Example: **Large dose of Aspirin, Alcohol, Phenytoin** (they follow 1st order kinetics at small doses) |

# PHARMACODYNAMICS

## Types of Drug Action:

- **Local or topical action**: drugs act on site of application e.g. ointment or eye drops.
- **Systemic or general action:** the drug acts after administration and distribution by circulation to various tissues. e.g. Aspirin
- **Reflex or remote action**: the drug acts locally at one site to produce reflex action elsewhere. e.g. Ammonia inhalation → irritation of nose → reflex stimulation of respiration

## Mechanism (Mode) of Action of Drugs

- Drugs can induce a tissue response, initially through:

**I**. **Body control systems (the regulatory proteins):** involving interactions with:

(1) Receptors (2) Ion channels

(3) Enzymes (4) Carrier molecules

**II**. **Other mechanisms**:

(5) Subcellular structures (6) Genetic apparatus

(7) Physical mechanisms (8) Chemical mechanisms

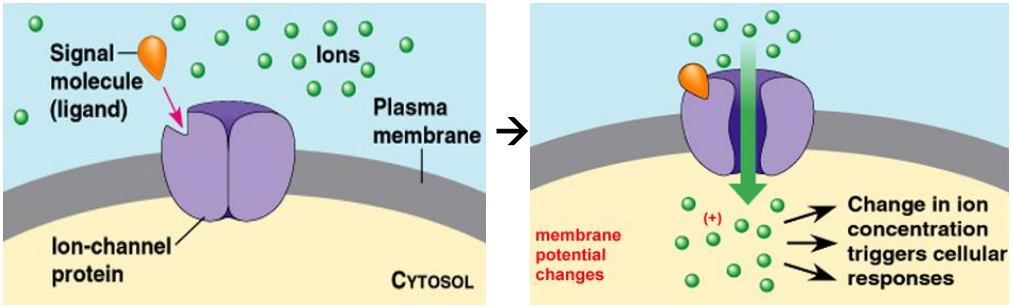
### 1) Receptor-Mediated Mechanisms

- **Receptors** are specific cellular macromolecules (usually proteins) that interact with a ligand (**binding**) to produce a response.
- **Ligand:** any molecule that can combine with the receptor. A ligand that activates receptor is called **agonist**. A ligand that blocks the receptor is called **antagonist**

## Types of receptors (signaling mechanisms or signal transduction):

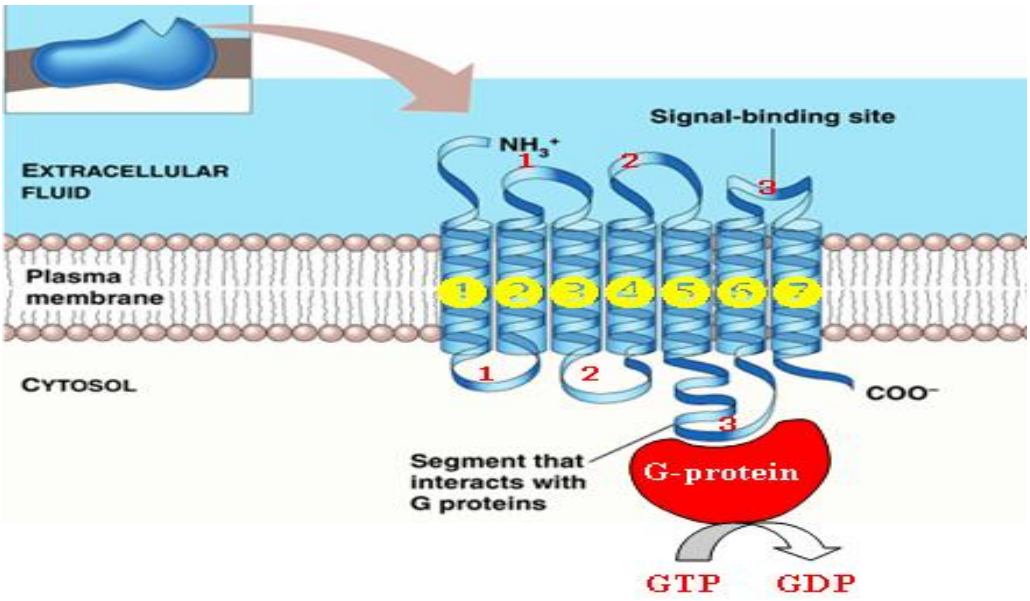
### 1. Ligand-gated ion channels: (for fast neurotransmitters)

- Receptors are ion-selective channels in the plasma membrane.
  - Binding of agonist to the extracellular part of receptor →opening of the channel → alteration in membrane potential or change in intracellular ion concentration → change in cell activity,
  - **e.g. $GABA_A$ receptors ($Cl^-$ channels).**




### 2. G protein-Coupled Receptors (for slow neurotransmitters)

- Receptor consists of 7 transmembrane subunits which are linked to G proteins.
- The G protein is a trimer (α, β and γ).
- Agonist binding → dissociation of α subunit which **regulates** activity of several effectors.



**Types of G Proteins**

a. $\mathbf{G_s}$ (stimulatory) → increased cAMP → activation of specific proteins.

b. $\mathbf{G_i}$ (inhibitory) → decreased cAMP → inhibition of specific proteins.

c. $\mathbf{G_q}$ (query) → increased DAG (diacylglycerol) and $IP_3$ (inositol triphosphate) → increased intracellular $Ca^{++}$ and activate PKC (protein kinase C)

- Examples: **β**-adrenergic receptors linked to $\mathbf{G_s}$ protein

**$\alpha_2$-** adrenergic receptors linked to $\mathbf{G_i}$ protein

**$\alpha_1$-** adrenergic receptors linked to $\mathbf{G_q}$ protein

## 3. Receptors *linked to* Tyrosine Kinase (RTKs)

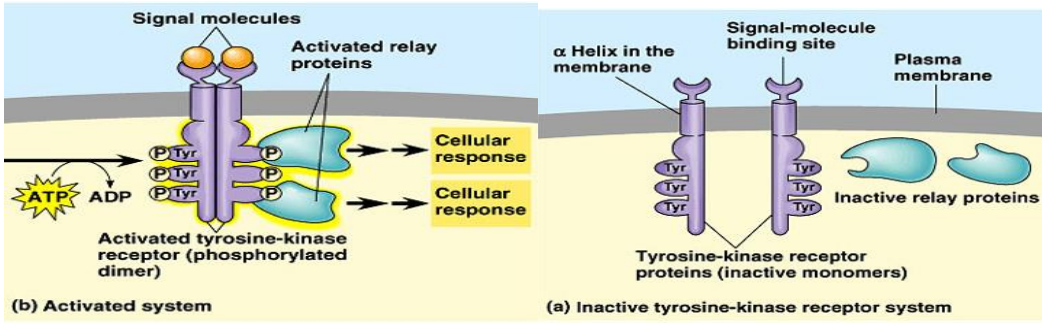
- The receptor is formed of two domains:

a. An extracellular domain, to which the agonist binds.

b. An intracellular domain, which is a tyrosine kinase enzyme (effector).

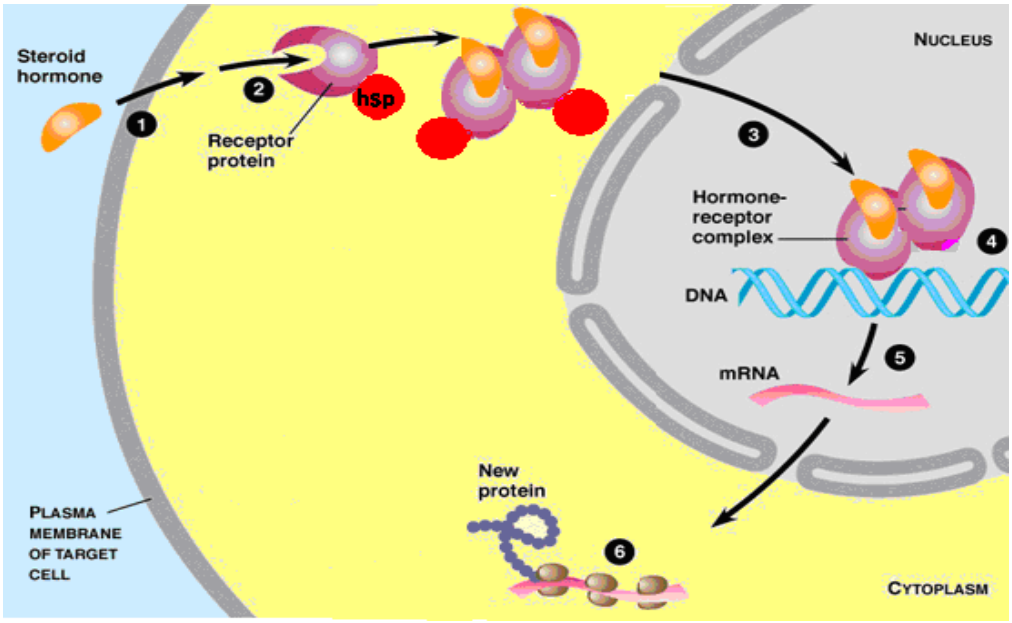
c. A transmembrane segment connecting two domains.

**- e.g. insulin receptors**




## 4. Intracellular (DNA-linked) receptors (very slow)

- The ligand enter the target cell and combine with intracellular receptor proteins → complex → acts on nuclear DNA → modify transcription of the nearby gene → modify protein production → changes in the structure or function of the target tissue.
- Examples: receptors for **corticosteroids, sex hormones, thyroid hormones and vitamin D**




### 5. Nitric Oxide (NO) Receptors:

- NO receptors are protein receptors inside the cell. Binding of NO receptors → formation of a "second messenger" within the cell.
- The most common: NO activates guanylyl cyclase enzyme → cyclic GMP (cGMP).
- NO receptors are activated by many drugs that increase NO level e.g. **nitroglycerine**.

## Biological response to drug-receptor binding:

$$\text{Drug (D)} + \text{Receptor (R)} \underset{\text{Kd}}{\overset{\text{Affinity } K_a}{\longleftrightarrow}} \text{D/R complex} \xrightarrow{\text{Efficacy}} \text{Response}$$

- **Affinity**: ability of drug to bind with the receptor to form D/R complex
- **Efficacy:** ability of D/R complex to evoke a response.
- $\mathbf{K_a}$ is the association constant
- $\mathbf{K_d}$ is the dissociation constant

- When a drug combines with a receptor, this may lead to:

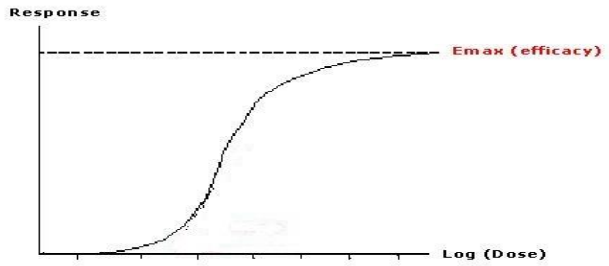
  1- Agonist effect or 2- Antagonist effect or 3- Partial agonist effect

## 1. Agonist effect:

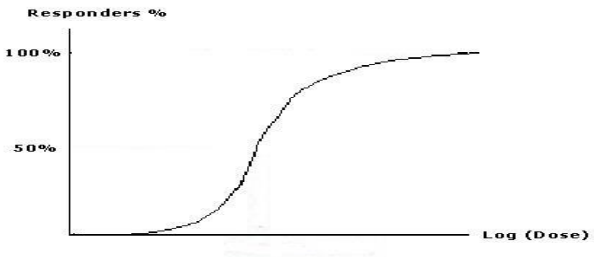
- Agonist has **1. Affinity 2. High Efficacy 3. Rapid rate** of ass. & diss.
- Theories for drug-receptor interaction:
  1. **Receptor occupation theory:** response (efficacy) depends on **number** of occupied receptors
     - When maximum effect is reached, still some receptors remain free **(spare receptors)**
  2. **Rate theory:** response (efficacy) depends on rate of association ($\mathbf{K_a}$) and rate of dissociation ($\mathbf{K_d}$)
- Response will never exceed a certain limit whatever the drug concentration. This is termed $\mathbf{E_{max}}$ i.e. the maximal response or effect
- e.g. **- acetylcholine (Ach) activates nicotinic receptors → skeletal muscle contraction**.

  **- adrenaline activates beta adrenoceptors → increased HR**
- They are 2 types of drug responses:

1. **Graded dose-response**: the response increases by increasing the agonist **e.g.** increases of heart rate against different doses of adrenaline.

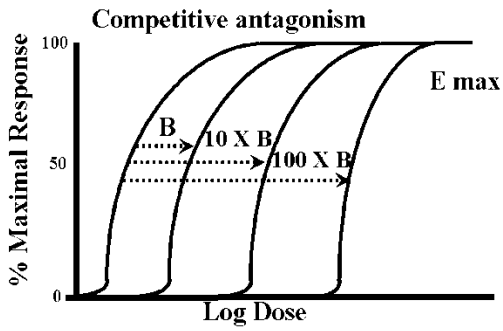
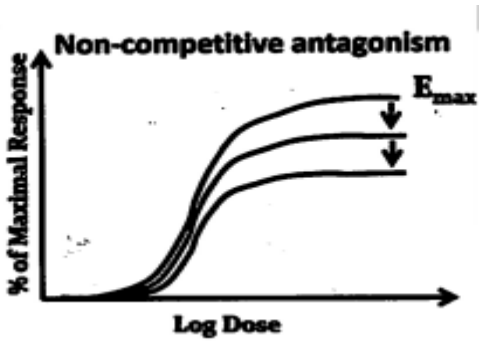



2. **Quantal dose-response** : the response is all or none **e.g.** the % of epileptic patients who are treated by different doses of an antiepileptic drug



## 2. Antagonist effect:

- Antagonist has: **1. Affinity** **2. No Efficacy** **3. Slow Rate** of ass. & diss.
  - Types of **receptor (pharmacological) antagonists:**

| 1- Competitive Antagonist | 2- Noncompetitive Antagonist |
|---|---|
| • Antagonist ***competes with the agonist*** for the ***same recognition site*** of the receptor. | • Antagonist ***binds irreversibly with recognition site*** of the receptor ***or to an allosteric site*** (a site away from recognition site) to prevent binding of agonist with receptor or prevent activation of receptor by agonist |
| • ***Duration*** of antagonism depends on the relative ***plasma concentrations of agonist and antagonist.*** | • ***Duration*** of antagonism depends on ***synthesis of new receptors*** |
| • Antagonist can be ***Displaced*** by excess agonist ***(surmountable)*** | • Antagonist can ***Not*** be Displaced by agonist ***(non-surmountable)*** |
| • Causes ***parallel shift to the right*** in the log dose-response curve i.e. ***No change in $E_{max}$ but ↓↓ in potency (↑↑ in $ED_{50}$)*** | • Causes ***downward shift*** in the log dose-response curve with ***↓↓ in $E_{max}$ , but No change in potency ($ED_{50}$)*** |
|  |  |
| • Examples: **Atropine** (muscarinic blocker) | • Example: **Phenoxybenzamine** (α – blocker) |

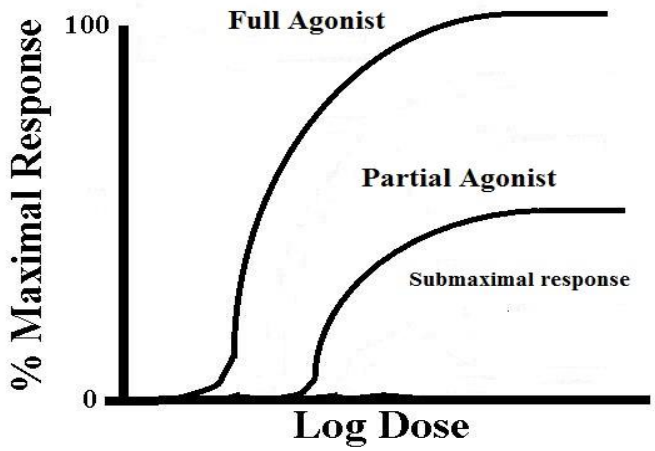
## 3. Partial Agonist (Agonist-Antagonist)

- In absence of the agonist: it has:

  **1. Affinity**

  **2. Moderate efficacy (submaximal effect)** whatever its concentration.

  **3. Moderate or slow rate** of association & dissociation.




- In the presence of the agonist, it acts as an antagonist i.e blocks effect of agonist.
- e.g. **Buprenorphine:** In the absence of a pure agonist e.g. morphine, it exhibits analgesic effects. In the presence of morphine it acts as an antagonist reducing its analgesic effect.

### Receptor Cycling or Turnover

- The number of receptors is not constant but the receptors are cycling (old receptors are internalized inside the cell and the new ones are externalized to the outside) and their number is continuously changing depending on the rate of recycling
- Binding of the **agonist** → ↓ number of receptors **[down regulation]**
- Binding of the **antagonist** → ↑ the number of receptors **[up regulation]**

**2) Drugs acting on ion channels:** drugs can modulate ion channels through:

- Voltage-gated ion channels: **Local anesthetics** ($Na^+$ channels).
- ATPase-sensitive ion channels: **Oral hypoglycemics** (ATPase-sensitive $K^+$ channels in pancreatic β cells)

- Ion channels modulated by G protein-linked receptors ($2^{ry}$ messenger)
- Ligand-gated ion channels (ion channel-linked receptors)

**3) Drugs Acting on Enzymes:** drugs can modulate enzyme through:

- Activation of enzyme systems.
- Inhibition of enzyme:
  - Neostigmine inhibit cholinesterase enzyme → increase Ach**.**
  - Aspirin inhibits cyclooxygenase enzyme → decreases PGs synthesis

**4) Drugs Acting on carrier systems**

- Drugs may affect carrier systems or transport processes in the plasmatic membrane. Examples:
  - **Digitalis** inhibit $Na^+/K^+$ ATPase pump in cardiac cell.
  - **Diuretics** affect ions transporters in renal tubules

**5) Drugs Acting on Subcellular Structures**

**Microtubules**: **Colchicine** disrupts microtubules inhibiting mitosis.

**6) Drugs Acting on the Genetic Apparatus**

- **Aminoglycosides** inhibit **bacterial protein** synthesis.
- **Anticancer** drugs affect **DNA** synthesis or function.

## 7) Drugs Acting Physically:

- **Demulcents** (soothing): **bismuth salts** coat intestinal mucosa.
- **Lubricants**: **liquid paraffin** is used in constipation.
- **Adsorbent**: **Kaolin** in treatment of diarrhea

  **Activated charcoal** in treatment of drug toxicity

## 8) Drugs Acting Chemically:

**a. Neutralization**: - **Antacids** neutralize HCL in peptic ulcer.

- Protamin sulfate (basic, +ve) for toxcicty of heparin (acidic, -ve)

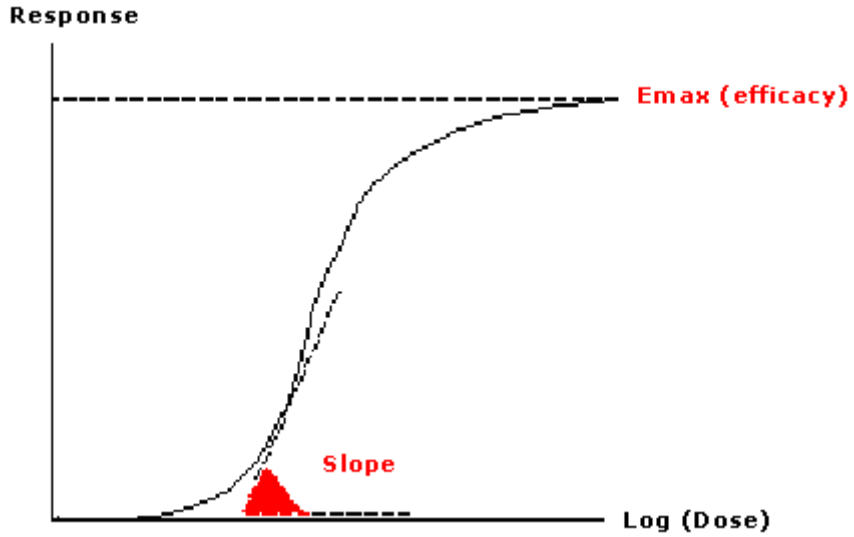
**b. Chelation;** is the capacity of organic compounds to form complexes with metals (chelates). The chelate may become more water-soluble and easily excreted. It is useful in treatment of heavy metal poisoning e.g. **EDTA** for lead & calcium) - **Deferrioxamine** for iron

# DOSE-RESPONSE RELATIONSHIP

## Dose-response curves

- The dose-response relationship can be represented graphically by 2 types of curves: the graded dose-response curve and the quantal (All/None) dose-response curve:

**I. Graded dose-response** curve is obtained if the degree of response is depicted against log the dose e.g. increases of heart rate against the dose.




**Parameters that can be obtained from the graded dose-response curve:**

1. **Maximal Efficacy ($E_{max}$)**: is the maximal **effect** produced by the drug *(= the maximum value of the dose-response curve)*

   - Value of knowing the ($E_{max}$):

   a) Knowing the maximal responding capacity of the organ

   b) Differentiation between full agonist and partial agonist

2. **Potency** of the drug is assessed from 2 parameters:

   a. **$ED_{50}$:** it is **dose** that produces 50% of the maximal response ($E_{50}$). The lower the $ED_{50}$ the more potent the drug is.

   - Value of knowing the ($ED_{50}$):

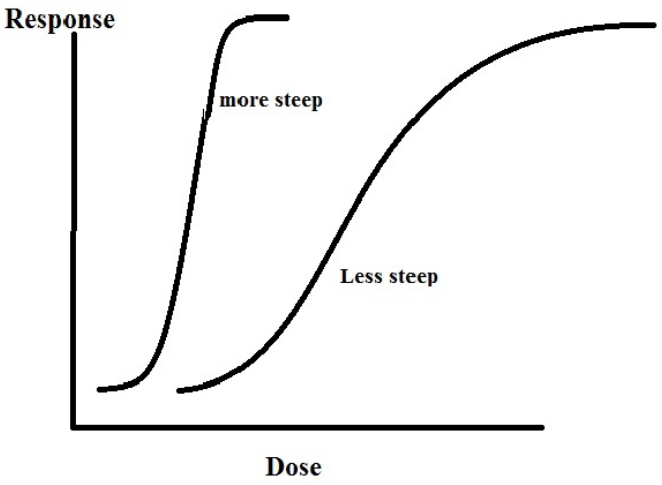
   a) Calculation of drug potency

   b) Comparing potencies of multiple drugs in one animal

**b. Steepness (Slope)** of the middle portion of the curve: meams sharpness of the response i.e. minimal change of the dose may lead to dramatic response

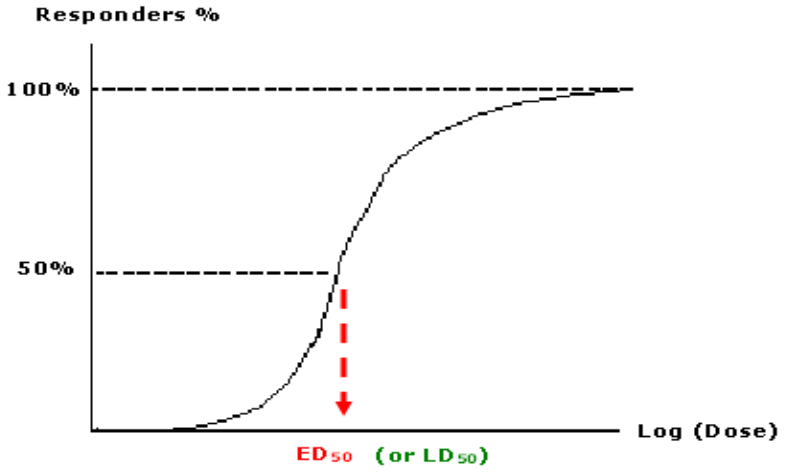
- Value of knowing the slope of the curve:

a) Comparing potencies of multiple drugs: the steeper the curve (the higher the slope) the more potent the drug is.




b) A drug having a steep curve may have multible actions e.g. effects on heart, brain, blood vessels; all decrease blood pressure

**II. Quantal (All/None) dose-response curve**: is obtained if the percentage of patients who respond to the drug is depicted against log the dose e.g. the % of epileptic patients who are treated by different doses of an antiepileptic drug



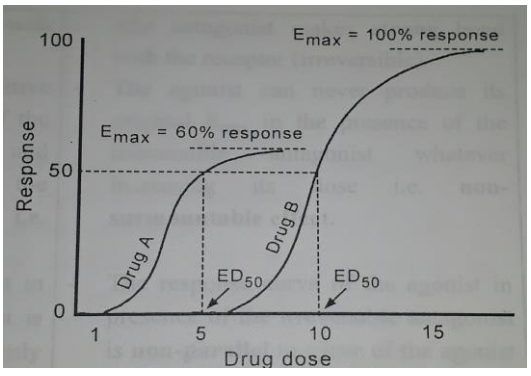
**Parameters that can be obtained from the All/None curve:**

1. **$ED_{50}$:** It is the **dose** that **cures 50%** of cases ($E_{50}$). It is used for comparison between drugs e.g. drug with a lower $ED_{50}$ → more potent than that with a higher $ED_{50}$.
2. **$LD_{50}$:** The **dose** that **kills 50%** of animals. lower $LD_{50}$ → more toxic. The dose used should not exceed 10% of the estimated $LD_{50}$.
3. **Therapeutic index (TI):**
   - It is the ratio between $LD_{50}$ & $ED_{50}$ → **TI = $LD_{50}/ED_{50}$.**
   - The **higher TI** ratio ( i.e. the $LD_{50}$ is much higher than the $ED_{50}$) → **the safer the drug**.
4. **Safety index (SI):**
   - It is the ratio between $LD_1$ & $ED_{99}$ → **SI = $LD_1/ED_{99}$.**
   - $LD_1$: the lowest toxic dose – $ED_{99}$: the highest therapeutic dose
   - The **higher SI** ratio → **the safer the drug** .

**Drugs with narrow therapeutic index**:

Aminoglycosides, anticoagulants, antiepileptics, lithium, quinidine, theophylline.

**Potency versus Efficacy**




- **Potency**: it is the effect of drug in relation to dose.
  - Potent drug means that the drug can give certain $E_{50}$ by a small dose, but this does not necessarily mean that it can give high $E_{max}$ by increasing its dose.
- **Efficacy**: it is the ability of the drug to give certain $E_{max}$
  - Efficacious drug means that the drug can give high $E_{max}$ by increasing its dose

**Clinically: Efficacy is more important than potency (why??)**

## Factors Modifying Dose-Response Relationship

### A. Factors related to drug:

**[1] Dose:** is the main factor modifying drug action.

**[2] Drug shape:**

- Most drugs have multible streoisomers e.g. D-glucose & L-glucose
- The receptor site is usually specific for one stereoisomer and not suitable for another like the hang and glove.
- Example: the S (+) isomer of methacholine is 250 times more potent than the R (-) isomer
- This phenomenon may explain how partial agonist is an agonist and antagonist in the same time because many drugs are used as "racemic mixtures" rather than pure isomers.

**[3] Drug size:**

- Most drugs have MW 100-1000 units.
- Drugs > MW 1000 cannot be absorbed or distributed.
- Drugs > MW 600 cannot cross placental barrier

**[4] Time of administration (chronopharmacology):**

- Many body functions (RBF, BP, HR….) have circadian rhythm and also many diseases (asthmatic attacks, anginal attacks…) are circadian phase dependent.
- ***Chronopharmacology:*** is the science dealing with tailoring drug medication according to the circadian rhythm of the body to get better response or to avoid possible adverse effects
- Examples:
    - Attacks of bronchial asthma are common at night (circadian variation of cortisol and inflammatory mediators) → better to give anti-asthmatic treatment in the evening

- Attacks of MI are common in early morning (circadian variation of sympathetic activity) → better to give anti-ischemic treatment before sleep.
- Irritant drugs should be given after meals to avoid gastric irritation e.g. iron
- C.N.S stimulant: should be given at day time.
- Drugs producing drowsiness as antihistamine drugs should be given at night

## [5] Route of administration

- Magnesium sulfate: orally act as a purgative, while IV it cause depression to cardiac, skeletal, smooth muscles and C.N.S.
- Doses of drugs given by injection route are less than that by oral route and have rapid onset of action

## [6] Drug combination (drug interaction):

- When two drugs are combined together, this may lead to:

**1- Antagonism**: one drug abolish the effect of the other (i.e. 1 + 1 = 0).

**2- Addition or summation:** the combined effects of two drugs are equal to the sum of their individual effects (i.e. 1 + 1 = 2) e.g. histamine and ACH on B.P.

**3- Synergism:** the combined effects of two drugs are greater than the sum of their individual effects (i.e. 1 + 1 = 3) e.g. sulphonamide and trimethoprim.

**4- Potentiation:** one drug lacks the specific effect but can potentiate the effect of another drug (i.e. 0 + 1 = 2) e.g. barbiturates has no analgesic effect but it can potentiate the analgesic effect of aspirin.

## [7] Cumulation:

- This occurs when the rate of administration of the drug exceeds the rate of its metabolism or excretion which leads to drug accumulation in the body and toxic effect e.g. digitalis.

## B. Factors related to patient:

### [1] Age:

- Children and elderly cannot tolerate the adult dose; accordingly the dose of the drug for them should be reduced.
- The child dose can be calculated by:
  - **a. Surface area method:**

    The child dose = Adult dose X Surface area of child ($m^2$)/ 1.73
  - **b. Age method:**

    The child dose = Adult dose X Age of child (years)/ age + 12
  - **c. Weight method:**

    The child dose = Adult dose X Weight of child (Kgs)/ 70
- Newborn infant especially premature infants are more susceptible to the effect of the drugs because:

  1-Lower total plasma protein levels.

  2-Immaturity of blood brain barriers (B.B.B).

  3-Underdevelopment of many hepatic microsomal enzymes.

  4-Reduced renal excretion of drugs ( low GFR & RBF)
- The elderly dose:

  60 - 80 years old =3/4 adult dose > 80 years old =1/2 adult dose

**[2] Weight:** all drug doses are calculated according to body weight (mg/kg)

### [3] Sex:

- Female patients need less doses than male patients because they have lower rate of drug metabolism due to:

  1- More fatty tissues which have low oxidation rate and are inert tissues.

  2- Estrogens which inhibit hepatic microsomal enzymes.
- In pregnant female: → some drugs are teratogenic e.g. antithyroid drugs.
- In lactating female: some drugs can pass to the fetus in milk e.g. phenobarbitone.

### [3] Pathological States:

- The effect of subcutaneous drugs is delayed in cases of shock or HF.
- Hepatic or renal diseases alter response to drugs
- Aspirin lower body temperature in case of fever

### [4] Tolerance (hyporeactivity):

- It is progressive reduced responsiveness to the drug on repeated administration so that higher doses are needed to produce the same original effect.

## A. Acquired tolerance:

**Pharmacokinetic tolerance:** *is tolerance due to decreased drug level e.g.*

- ↓ Absorption e.g. furosemide in heart failure (gut edema).
- ↑ Elimination e.g. ↑ metabolism with phenobarbitone

**Pharmacodynamic tolerance:** *is tolerance without decreased drug level e.g.*

- Desensitization of the receptors (conformational changes in receptor shape) e.g. opiates
- Down regulation of receptoes e.g. ß$_2$-agonists

**Special types of acquired tolerance:**

**a. Tachyphylaxis:** acute tolerance but the same original effect can not be obtained by ↑dose e.g. tolerance after few doses of ephedrine due to depletion of NE.

**b. Cross tolerance**: tolerance to related drugs e.g. cross tolerance between different members of opioids.

**c. Bacterial resistance**: to antimicrobials

## B. Congenital tolerance:

1. **Racial tolerance**: Negros are resistant to ephedrine
2. **Species tolerance**: rabbits tolerate large amount of atropine
3. **Individual tolerance**: due to genetic variation occurring to any individual in population

## [5] Drug intolerance (hyperreactivity or hypersusceptibility):

- It is exaggerated pharmacological response to the usual dose of the drug
- Mechanism:
  1. Increased sensitivity of receptors
  2. Up-regulation of receptors
- e.g. adrenaline in thyrotoxicosis.

## [6] Psychological (emotional) factors:

- Some patients may respond to a **placebo** (inert medication formed of sucrose or lactose) the same way they respond to the active drug.
- The placebo may be used for psychological therapy & in control studies to differentiate true drug effect from that 2ry to psychological factors

## [7] Drug dependence:

- **Habitation:** - psychic craving of the drug.
  - No physical disturbance
  - If sudden stoppage….> emotional distress.

  e.g. coffee and tea habits.
- **Addiction:** -psychological + physical dependence .
  - If sudden stoppage….> withdrawal symptoms

  e.g. morphine, barbiturates,smoking

## [8] Genetic a bnormalties (idiosyncrasy):

- It is abnormal response to drugs due to genetic abnormality in drug metabolism. These genetic abnormalities are revealed only by the effect of drugs.

### 1. Acetylation Polymorphism:

- People can be classified according their rate of acetylation reaction in liver into **Rapid** and **Slow** acetylators
- Examples, in slow acetylators:

  a. **Isoniazid** → peripheral neuropathy (due to interference with pyridoxine (vit B6) metabolism).

  b. **Hydralazine** → SLE-like (systemic lupus erythematosus-like).

- Examples in rapid acetylators:

  a. **Isoniazid** → hepatocellular necrosis (due to accumulation of toxic metabolites)

**2. Hemolytic Anemia due to G6PD Deficiency**

- Glucose-6-phosphate dehydrogenase (G6PD) is an important source of reduced glutathione which protects RBCs from hydrolysis by oxidizing drugs.
- Congenital (G6PD) deficiency → acute hemolysis in presence of some oxidant drugs as **antimalarials, sulfonamides and fava beans** (favism).

**3. Porphyrias**

- Normally, porphyrins precursors $\xrightarrow[\textbf{(ALA) synthase}]{\textbf{delta-aminolevulinic acid}}$ porphyrins $\xrightarrow[\textbf{enzyme}]{\textbf{second}}$ heme
  - Genetic deficiency of second enzyme → ↑ level of porphyrins with some drugs stimulating (ALA) synthase → cyanosis, severe CNS disturbances & may cause death.
  - **Barbiturates and sulfonamides** precipitate porphyria.

**4. Succinylcholine Apnea**

- Pseudocholine esterase enzyme is responsible for breakdown of neuromuscular blocker (succinylcholine). In genetic defect of the enzyme, **Succinylcholine** → respiratory muscle paralysis with apnea.

**5. Malignant Hyperthermia**

- Genetic disorder in which skeletal muscles fail to sequester $Ca^{++}$ in sarcoplasmic reticulum following administration of **succinylcholine and halothane** → marked muscle rigidity & sever hyperthermia.

## [9] Drug allergy:

- It is Abnormal response to drug mediated by immunogenic mechanisms.
- Drug allergy is dose-independent and occurs in minority of patients.
- Cross-allergy may occur within a group of chemically related drugs.

| Type | Mechanism | Examples |
|---|---|---|
| **Type I Reaction (immediate type; anaphylactic)** | **Antigen/IgE reaction on mast cell** → degranulation→ release of allergotoxins e.g. histamine → fever, rash, urtecaria, angioedema .... & even anaphylactic shock | **Penicillins** |
| **Type II Reaction (cytotoxic)** | **Antigen + IgG or IgM antibodies + complement** are fixed to a cell → cell lysis e.g. hemolytic anemia | **Methyldopa** |
| **Type III Reaction** | **Antigen + IgG antibodies + complement** are fixed to **endothelium** → vasculitis, glomerulonephritis | **Sulfonamides and Penicillin** |
| **Type IV Reactions (Delayed type; cell-mediated)** | **Antigen + sensitized T-cells** → release lymphokines→ inflammation e.g. allergic contact dermatitis | **topically applied drugs** |

**Diagnosis of Drug Allergy**

1. History and type of reaction.
2. Intradermal and conjunctival tests.

**Treatment of anaphylactic shock**

Epinephrine- hydrocortisone - antihistamines.