Pharmacology:

- "The science that deals with the study of drugs"
- It is divided into:
  1) **Pharmacokinetic:** What the body does to the drug or movement of the drug in the body
     It studies: ADME (Absorption, Distribution, Metabolism, and Excretion)
  2) **Pharmacodynamic:** What the drug does to the body or effect of the drug
  3) **Pharmacotherapeutics:** Deals with the use of the drug

Toxicology: It is a branch of pharmacology, which deals with the undesirable effects of chemicals & drugs on living system.

Drugs:

“Chemical agents that affect living processes (but do not create a new function in the cell & are used in diagnosis, treatment & prevention of disease or in prevention of pregnancy”

Drugs can be divided in two classes:

1- **Prescription only Medication (POM):** restricted for sale by prescription only.
2- **Over-the-counter (OTC) drugs:**
   - Used by the public without a prescription e.g.
   - OTC drugs can be allowed for short-term relief of symptoms where accurate diagnosis is unnecessary & for drugs that have a large margin of safety, *but* it is risky (may worsen preexisting conditions e.g. nasal decongestant drops may increase the blood pressure & may interact with prescribed medication)

Sources of drugs:

1) **Natural:**
   2. Animal ➔ Heparin – Insulin
   3. Microorganisms ➔ Antibiotics [Penicillin]
   4. Minerals ➔ Magnesium sulphate – Ferrous sulfate - Iodine

2) **Synthetic:**
   1. Chemically ➔ Sulphonamides
   2. Genetic engineering [r-DNA technology] ➔ Human insulin, tissue Plasminogen Activator (t-PA) & Erythropoietin

Drugs are identified by different names:

1- **Chemical name:** eg.: Acetylsalicylic acid
2- **Generic name (non-proprietary name):** it is given by the united states of adopted name council ➔ eg.: Aspirin
3- **Trade name (proprietary name):** eg.: Aspocid, Rivo
PHARMACOKINETIC [ADME]

It is the study of absorption, distribution, metabolism (biotransformation) & excretion

**DRUG PASSAGE ACROSS CELL MEMBRANE**

1- Simple diffusion (lipid diffusion)
2- Filtration (aquous diffusion) (Diffusion through aqueous channel)
3- Carrier mediated
4- Pinocytosis
5- Ion pair transport

---

1) **Simple diffusion (lipid diffusion):**
   1- Passively along concentration gradient
   2- No energy
   3- No carrier
   4- Depends on:
      - Lipid solubility & Lipid / water partition coefficient, the greater, the better, the absorption
      - Ionization which depend on: - pH of the medium
                                    - pk_a of the drug
**pk<sub>a</sub> [Ionization constant of the drug]:** “It is the pH at which 50% of the drug is ionized & 50% is unionized” e.g: Pk<sub>a</sub> of aspirin 3.5.

**pH of the medium:**
- Most drugs are weak acids or bases.
- Weak acids → less ionized in acidic environment.
- Weak bases → less ionized in alkaline environment.
- Vice versa
- Unionized drugs are lipid soluble.
- Ionized drugs are lipid insoluble.
- Degree of ionization is determined by [Handerson Hasselbalch equation]
  - For weak acid: \( pK_a = pH + \log \frac{\text{Conc. of Unionized}}{\text{Conc. of ionized}} \)
  - For weak base: \( pK_a = pH + \log \frac{\text{Conc. of ionized}}{\text{Conc. of Unionized}} \)

2) **Filtration (aquous diffusion):**
   1- Along hydrostatic or osmotic pressure gradient through large pores in endothelium & glomeruli.
   2- Water soluble
   3- Molecular weight (MW) not exceeding 100
   4- Free drugs only [not bound]

3) **Carrier mediated:**
   - **Active transport**
     - Against conc. gradient
     - Require energy
     - Require Carrier
     - e.g: secretion of penicillin by renal tubules
   - **Facilitated diffusion**
     - Along conc. gradient
     - No energy
     - Require Carrier
     - e.g: glucose uptake by cells

4) **Pinocytosis:**
   - It is the process of engulfing particles by the cells
   - It is Energy dependent
   - e.g: vit B<sub>12</sub> + intrinsic factor (IF).

5) **Ion pair transport:**
   For passage of strong electrolytes (e.g: quaternary ammonium compounds), where they pass through pairing with oppositely ions
Factors affecting absorption:

(1) Factors related to the Drug:

1. Physico-chemical properties:
   a. Water solubility: drugs must be water soluble
   b. Lipid solubility: drugs must be lipid soluble
   c. Lipid / Water partition coefficient: affects dissolution
      The higher \( \Rightarrow \) the more absorption
   d. Ionization: The greater \( \Rightarrow \) the lesser the absorption
   e. Valency: Ferrous (Fe\(^{++}\)) is better absorbed than ferric (Fe\(^{+++}\))
   f. Nature: Inorganic is better than organic

2. Pharmaceutical forms affects disintegration:
   eg.: Solutions are better absorbed than suspensions

(2) Factors related to the Patient:

1. Route of administration: I.V & pulmonary > I.M > S.C
2. Surface area & vascularity of absorbing surface
5. Specific factors eg: Intrinsic factor is needed for vit B\(_{12}\) absorption

Factors affecting oral absorption:

1) Factors related to the Drug: \( \Rightarrow \) see before

2) Factors related to the Patient
   \( \Rightarrow \) G.I.T factors:
   1. Surface area of the absorbing surface: eg.: small intestine (200 m\(^2\)) > stomach
      N.B.: drugs that may be absorbed from large intestine are \( \Rightarrow \) slowly release
      (SR) preparations – Sulfasalazine
   2. State of health of absorbing surface.: e.g. Malabsorption syndrome.
   3. Gut motility: Marked alteration as in diarrhea \( \Rightarrow \) \( \downarrow \) absorption.
   4. Gastric emptying:
      • Metoclopromide \( \Rightarrow \) \( \uparrow \) emptying \( \Rightarrow \) \( \uparrow \) absorption of rapidly disintegrated
        drugs { paracetamol & propranolol} \& \( \downarrow \) absorption of slowly disintegrated
        drugs { Digoxin}
      • Atropine & Stressful conditions \( \Rightarrow \) \( \downarrow \) emptying \( \Rightarrow \) the reverse effect.
   5. pH:
      • Gastric acidity\( \Rightarrow \)\( \uparrow \) absorption of weak acids {Aspirin - Barbiturates}
      • Intestinal alkanility \( \Rightarrow \) \( \uparrow \) absorption of weak bases { Amphetamine – Ephedrine}
   6. Specific factors: Intrinsic factor (IF) is essential for vit B\(_{12}\) absorption.
   7. Presence of food & other drugs:
      • Milk, Dairy products & Antacids \( \Rightarrow \) \( \downarrow \) Tetracycline & Quinolones absorption.
      • Tea, Phytate, Oxalates & Tetracycline \( \Rightarrow \) \( \downarrow \) Iron absorption.
      • Cholestyramine & Charcoal \( \Rightarrow \) \( \downarrow \) absorption of most drugs.
**First pass effect:**
- **Def.:** “Inactivation or elimination of part or whole of the drug before reaching the systemic circulation”
- **Sites:**
  1. Gut 1st pass effect:
     - Gastric acidity ➔ Benzyl penicillin
     - Digestive & mucosal enzymes ➔ Insulin, Tyramine & Isoprenaline
  2. Hepatic 1st pass effect
     - Complete ➔ Nitroglycerine – Lidocaine
     - Partial ➔ Propranolol

  • How to avoid & overcome hepatic 1st pass effect:
    - If partial ➔ ↑ the oral dose. e.g Propranolol
    - If complete ➔ Use other route of administration
      {Nitroglycerine ➔ Sublingually (SL) &Lidocaine ➔ Intravenously (IV) }

**DISTRIBUTION**

**Body fluid compartments:**
- Intracellular
- Extracellular ➔ Interstitial ➔ Plasma

- Total body water 42 liters/ 70 kg (0.6 liter/ kg).
- Intracellular volume = 28 L/70 kg.
- Extracellular volume = 14 L/ 70kg [10L/70kg intrestitial + 4 L/70kg plasma (0.05L/Kg)].

**Patterns of Distribution**

1. **Intra vascular {one compartmental model}**
   - High M. W ➔ Heparin & Dextran
   - Strongly bound to plasma protein ➔ Evans blue

2. **Extra cellular {2 compartmental model}**
   - Quaternary ammonium compounds: - N⁺ - (Neostigmine) & Mannitol

3. **Extra & intra cellular {Multicompartmental model}**
   - Ethanol
   - Tertiary amine : - N (Physostigmine)

4. **Drugs concentrated in certain tissues**
   - Iodine in thyroid
   - Chloroquine in liver
   - Calcium & Tetracycline in bone & teeth
   - Thiopental in fat
5- **Apparent volume of distribution** ($V_d$):

- **Definition:** “The volume of fluid required to contain the whole amount of drug in body in the same concentration as that present in the plasma”

\[
V_d = \frac{\text{Amount of drug administered (mg)}}{\text{Initial Conc. of drug in plasma (mg / ml)}} = \frac{A_p}{C_0}
\]

- **Importance:**
  1. Estimate the distribution of the drug in the body
     - Small ($V_d$) = Blood volume ➔ the drug is highly bound to plasma protein
     - Large ($V_d$) > Blood volume ➔ the drug is concentrated in tissues.
  2. In cases of toxicity:
     - Dialysis is useful in drugs with Small ($V_d$) but not with Large ($V_d$)
  3. Determine the loading dose (Loading dose = $V_d \times$ desired concentration)
  4. Estimate the total amount of the drug in body (= $V_d \times C_p$ mg/ml)

- **Effect of $V_d$ on the $t_{1/2}$ of a drug:**
  Delivery of drug to the organ of elimination depends on:
  1. Blood flow
  2. Fraction of the drug in the plasma
  - If the $V_d$ for a drug is large, most of the drug is in the extraplasmic space & is unavailable to the excretory organ.
  Therefore, any factor that ↑ the $V_d$ ➔ ↑ $t_{1/2}$ & duration of action

----

**Factors affecting distribution of drugs:**

1) **Physico-chemical properties of drugs:**
   Molecular weight–Ionization–Lipid solubility

2) **Binding to plasma proteins**
   1. A fraction of most drugs binds reversibly to plasma protein.
      - **Bound form** ➔ inactive – not filtered, not metabolized, not excreted, acts as a store
      - **Free form** ➔ active – filtered, metabolized - excreted
2. **Significance:**
   - Interactions:
     - *Phenylbutazone* displaces *Warfarin* ➔ Hemorrhage
     - *Sulfonamide* displaces Billirubin ➔ Kernicterus (Irreversible yellowish discoloration & damage of brain)
   - Hypoalbumenemia ➔ ↑ free fraction of some drugs as *Phenytoin*
   - Drugs that are extensively bound to plasma protein, as *Thiopentone*, their concentration of the free part when given IV will depend on the rate of injection, so *Thiopentone* is given at a relatively rapid rate

3) **Passage across barriers:**
   1. Passage of drugs to CNS:
      - Non-ionized lipid soluble drugs pass blood brain barrier (B.B.B) & affect the C.N.S. e.g *Physostigmine*.
      - Some hydrophilic antibiotics as *Penicillin* can pass inflamed BBB but can not pass the healthy one.
   2. Passage of drugs to fetus:
      - Non ionized lipid soluble drugs passes placental barrier & affect the fetus
      - Drugs may cause: - Teratogenicity
                       - Neonatal asphyxia
   3. Passage of Drugs through Breast Milk:
      - Most drugs administered to lactating women are detectable in breast milk.
      - pH of milk is more acidic (7.0) than that of plasma (7.4), so, basic drugs ionize & accumulate in milk
        (this is called ion trapping because they are effectively trapped).
      - Milk also contains more fat than plasma, which favors retention of lipid soluble drugs.
1-Aim:
“Conversion of lipophilic, non polar drugs into hydrophilic & polar to be easily excreted”

2-Classification:
A) Phase I “Non-synthetic”:
1- Oxidation:  - Phenacetin ➔ Acetaminophen
2- Reduction: - Chloralhydrate ➔ Trichloroethanol
3- Hydrolysis: - Acetylcholine ➔ Choline + acetic acid

* Results of phase I:
1- Convert Active ➔ Inactive       [- A.ch ➔ Choline + acetic acid]
2- Convert Active ➔ another active  [- Phenacetin ➔ Acetaminophen]
3- Convert Inactive ➔ Active       [- Cortisone ➔ Cortisol]
4- Convert drug into toxic metabolite [- Methanol ➔ Formaldehyde (retino-toxic)]

B) Phase II “Synthetic” or “Conjugation”:
1- Glucuroinc acid ➔ Chloramphenicol – Morphine
2- Glycine ➔ Aspirin
3- Methylation ➔ Noradrenaline
4- Acetic acid ➔ Sulfonamide – Isoniazid
5- Sulfate ➔ Phenols

* Results of Phase II--------- usually inactivation
{Except morphine, its conjugation ➔ activation}

N.B:
A: Most drugs pass through phase 1 then phase 2.
B: Some drugs pass directly into phase 2 without phase 1.
C: Some drugs as Isoniazid are firstly acetylated in phase 2 then hydrolyzed in phase 1 to isonicotinic acid.

3-Site of biotransformation:

<table>
<thead>
<tr>
<th>1) Microosomal</th>
<th>2) Non-microosomal:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- In microsomes of smooth endoplasmic reticulum of the liver</td>
<td></td>
</tr>
<tr>
<td>- Responsible for: Oxid. – Reduct. – Hydrolysis &amp; Glucuronide conjugation</td>
<td></td>
</tr>
<tr>
<td>- Cytochrome P-450 is the primary component of oxidative enzymatic system (Common cytochromes are shown in the figure)</td>
<td></td>
</tr>
<tr>
<td>- Responsible for: Oxidation – Reduction – Hydrolysis &amp; Conjugation other than glucuronic.</td>
<td></td>
</tr>
</tbody>
</table>
4-Factors affecting microsomal enzyme activity:

1) **Physiological:**
   - **Age:** Extremities of age → ↓ metabolism
   - **Sex:** Androgen → ↑ metabolism, while estrogen & progesterone → ↓ metabolism
   - **Starvation:** deplete glycine → ↓ glycine conjugation

2) **Pathological:**
   - **Liver disease:** → ↓ metabolism

3) **Pharmacological(Drugs):**
   - **Hepatic microsomal enzyme Inducers:**
     - They are the drugs that ↑ the activity of these enzymes → ↑ metabolism of other drugs & their own metabolism {Tolerance}
     - Examples:
       - Phenobarbitalone – Phenytion – Phenylbutazone
       - Smoking – Alcohol (chronic use) - Coffee - Tea
       - Rifampicin - Griseofulvin
       - Androgens
   - **Hepatic microsomal enzyme Inhibitors:**
     - They ↓ the activity of these enzyme → ↓ Rate of metabolism of other drugs → prolong their effect.
     - Example: (EG - DEVICES - KAO)
       - Estrogen & Progesterone - Grape fruit juice
       - Ketoconazole – Allopurinol – Omeprazole

4) **Pharmacogenetic variations:**
   - eg.: Slow & fast acetylators
EXCRETION

Drugs are eliminated from the body either unchanged or as metabolites.

**Routes of drug excretion:**

1. Renal
2. GIT:
   - Saliva e.g Iodides - Morphine
   - Stomach e.g Morphine
   - Bile ➔ Enterohepatic circulation ➔ Prolongation of action
   - Feces
3. Skin glands:
   - Sweat gland: eg: Rifampicin
   - Breast: eg: Nicotine – Morphine
   - Purgatives
4. Lung:
   - eg Gases {Nitrous oxide (N₂O)} & Vapors (Halothane)

**Renal excretion:**

*Renal excretion is the result of 3 processes:*

1. **Glomerular filtration:** For water soluble – Non bound drugs
2. **Active tubular secretion:** 2 transport systems (carriers):
   - One for organic acids (e.g Penicillin & probenecid)
   - One for organic bases (e.g Amphetamine)
3. **Passive tubular reabsorption:**
   - Unionized lipid soluble drugs are reabsorbed by passive diffusion.
   - Reabsorption may be affected by urinary pH:
     - Alkalization of urine {NaHCO₃ & Na citrate} ➔ ↑ excretion of acid drugs. e.g Aspirin
     - Acidification of urine {NH₄CL & Ascorbic acid} ➔ ↑ excretion of base drugs. e.g Ephedrine

*Factors affecting renal excretion:*

1. Glomerular filtration rate (GFR)
2. Plasma protein binding
3. pH of urine
4. pKₐ of the drug
NB.: How to prolong duration of action of a drug?

1- ↓ Absorption:
   • Coadministration of Vasoconstrictor with the drug
e.g: Adrenaline + Local anesthesia
   • Use of special preparations of the drug:
     - Sparingly soluble complexes:
       e.g Protamine zinc insulin - Procaine penicillin
     - Use of the drug in oil: e.g Vasopressin tannate in oil
     - Use of Slowly release (S.R) tablets
   • Use of special route of administration:
     eg: Subcutaneous (S.C) implantation

2- ↑ Protein binding: e.g: add Methoxy group to Sulfonamide

3- ↓ Metabolism: e.g: add Sulthiam (HME inhibitor) to Phenytoin

4- ↓ Excretion: e.g: Probenecid with Penicillin

PHARMACO-KINETIC PARAMETERS:

1) Bioavailability:
   • Def.: “The fraction [Proportion] of unchanged drug reaching the systemic
circulation after administration by any route”
   Or “The rate & extent to which the active drug is presented to the site of
action”
   • It is 100 % after I.V and variable after oral.
   • Oral Bioavailability = AUC_{oral} / AUC_{I.V} X 100
   • Factors affecting oral bioavailability:
     1- Factors affecting GIT absorption.
     2- First pass metabolism.

2) Clearance:
   - “It’s the volume of plasma cleared from the drug per unit time (ml / min)
   - CL_{total} = CL_{Hepatic} + CL_{Renal} + CL_{Pulmonary} + CL_{Others}
3) **Plasma half life** ($t_{1/2}$):
- “It’s the time needed for the plasma concentration to be reduced by 50%”
- It depends on: Clearance & $V_d$
- The drug reaches a plateau {Steady state concentration ($C_{SS}$)} after continuous administration for 4 - 5 $t_{1/2}$.

![Graph of Plasma half life](image)

4) **First order & Zero order kinetics:**

<table>
<thead>
<tr>
<th>First order kinetic</th>
<th>Zero order kinetic (saturation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) “Constant % (Fraction) of the drug is eliminated per unit time <strong>according</strong> to its plasma concentration”</td>
<td>(1) “Constant <strong>amount</strong> of the drug is eliminated per unit time <strong>regardless</strong> its plasma concentration”</td>
</tr>
<tr>
<td>(2) Rate of the elimination process is <strong>proportional</strong> to drug concentration</td>
<td>(2) Rate of the elimination process is <strong>not proportional</strong> to drug concentration</td>
</tr>
<tr>
<td>(3) Linear disappearance curve using log conc. time curve &amp; non linear using conc. time curve</td>
<td>(3) Non-linear disappearance curve using log conc. time curve &amp; linear using conc. time curve</td>
</tr>
<tr>
<td>(4) $t_{1/2}$ is <strong>constant</strong></td>
<td>(4) $t_{1/2}$ <strong>increases</strong> with concentration</td>
</tr>
<tr>
<td>(5) Repeated dosing $\Rightarrow C_{SS}$ is reached</td>
<td>(5) Repeated dosing $\Rightarrow C_{SS}$ is <strong>not</strong> reached</td>
</tr>
<tr>
<td>(6) Moderate changes in dose does not cause toxicity</td>
<td>(6) Moderate changes in dose can cause toxicity</td>
</tr>
<tr>
<td>(7) Example: most drugs</td>
<td>(7) Examples: Few drugs. e.g: Alcohol</td>
</tr>
</tbody>
</table>

![Graph of First order kinetic](image)

![Graph of Zero order kinetic](image)

** Few drugs (e.g: Aspirin & Phenytoin) the type of elimination is dose related. At low concentration $\Rightarrow$ first order & at high concentration $\Rightarrow$ Zero order.
Types of drug action:

1) Local or Topical action:
   - The drug acts at the site of application.
   - e.g: Skin ointment – Eye drops.

2) Systemic or General action:
   - The drug is absorbed & distributed by circulation to various tissues.
   - e.g: Aspirin

3) Reflex or Remote action:
   - The drug acts at a site locally to evoke a reflex response away {Remote} from its site of action.
   - e.g: Inhalation of ammonia \(\rightarrow\) irritation of nose \(\rightarrow\) reflex stimulation of respiration.
   - S.C camphor \(\rightarrow\) irritation \(\rightarrow\) reflex stimulation of respiration.

Mechanisms of drug action:

1) Physical:
   a- Adsorption \(\rightarrow\) Kaolin in diarrhea
   b- Osmosis \(\rightarrow\) Mannitol as osmotic diuretic & Mg So\(_4\) as purgative (laxative).

2) Chemical:
   a- Neutralization \(\rightarrow\) NaHCo\(_3\) (Antacid) + HCl (gastric acid) in treatment of Hyperacidity.
   b- Chelation \(\rightarrow\) Organic compound + Heavy metal \(\rightarrow\) non toxic easily excreted complex.
   e.g: - Dimercaprol {British Anti-Lewisite (BAL)}* for Mercury (Hg), Arsenic (As) & Antimony (Sb).
   - Desferrioxamine for ferric iron (Fe\(^{+++}\))

3) Actions on specific Targets:
   1- Interference with cell division:
      Anti-cancer drugs (Cytotoxic drugs). e.g: Nitrogen mustard.
   2- Interference with metabolic pathway:
      Sulfonamides stop growth of bacteria by competing with (PABA) \(\rightarrow\) \(\downarrow\) synthesis of folic acid.
   3- Action on enzyme:
      \(\downarrow\) Of enzymes e.g: - Aspirin \(\rightarrow\) \(\downarrow\) cyclooxygenase
      - Physostigmine \(\rightarrow\) \(\downarrow\) cholinesterase
      \(\uparrow\) Of enzymes e.g: \(\beta\) agonist \(\rightarrow\) \(\uparrow\) Adenylate cyclase \(\rightarrow\) \(\uparrow\) c. AMP
   4- Action on voltage gated ion channel: Local anesthesia \(\rightarrow\) block Na\(^+\) channels

---

*Dimercaprol: was developed during World War II by the British army as an antidote to lewisite, a vesicant arsenical war gas, hence its alternative name, British antilewisite (BAL)
5- Action on Receptors:
A Receptor is: “a chemosensitive macromolecule, present on the cell surface or within the cell, & reacts specifically with a ligand [Drug – Transmitter – Hormone] to produce a biological response”

Drug (D) + Receptor (R) $\xrightarrow{\text{Affinity}}$ $\frac{K_a}{K_d}$ D/R complex $\xrightarrow{\text{Efficacy}}$ Response

$K_a$ is the association constant
$K_d$ is the dissociation constant

*Affinity: Ability of the drug to bind with the receptor to form D/R complex.
*Efficacy or intrinsic activity: Ability of the D/R complex to evoke a response.

**Classification of drugs according to efficacy:**

Drugs or Ligands acting on receptors may be classified into:
Agonist, Antagonist, Partial agonist & Inverse agonist

<table>
<thead>
<tr>
<th>1) Agonist [Stimulant]:</th>
<th>2) Antagonist [Blocker]:</th>
<th>3) Partial agonist [Dualist]:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Has affinity &amp; efficacy</td>
<td>• Has affinity &amp; no efficacy</td>
<td>• Has affinity &amp; moderate efficacy (Submaximal effect)</td>
</tr>
<tr>
<td>• Rapid rate of association &amp; Dissociation</td>
<td>• Slow rate of association &amp; dissociation</td>
<td>• Moderate rate of association &amp; dissociation</td>
</tr>
<tr>
<td>• Block the action of agonist</td>
<td>• Block the action of agonist</td>
<td>• Block the effect of agonist</td>
</tr>
<tr>
<td>• e.g:</td>
<td>• e.g:</td>
<td>• e.g:</td>
</tr>
<tr>
<td>- Adrenaline</td>
<td>- β blockers (propranolol)</td>
<td>- Oxprenolol</td>
</tr>
<tr>
<td>- A.ch.</td>
<td>- Atropine</td>
<td>- Succinyllcholine</td>
</tr>
</tbody>
</table>

**NB.: Inverse agonist:** as agonist but produce the reverse effect of agonist
eg.: Benzdiazepine receptors:
- Benzodiazepines are agonists produce hypnosis & anticonvulsant effect
- β-carbolines are inverse agonists produce insomnia & convulsions

**NB.: Agonist has +ve efficacy – Inverse agonist has –ve efficacy – Antagonist has zero efficacy**

**Dose response curves:**
There are 2 curves to study the drug response:
1- Graded dose-response curve
2- Quantal dose-response curve
1- **Graded dose–response curve:**

- **Definition:** A plot of efficacy (some measured value, such as blood pressure) -versus- drug dose or concentration.
- **Shape:** it is hyperbolic but log-dose response curve is sigmoid [S-shaped]
- **Efficacy:** is the biologic response resulting from the binding of a drug to its receptor.
  - Measured by $E_{\text{max}}$ (maximal effect)
  - An efficacious drug has a higher $E_{\text{max}}$ value\(\Rightarrow\) (B > A>C)
- **Potency:** A potent drug induces the same response at a lower dose or concentration.
  - Measured by $ED_{50}$ (effective dose 50 = the dose which produce 50 % of the effect)
  - Or $EC_{50}$ (effective conc. 50 = the concentration which produce 50 % of the effect)
  - A potent drug has a lower ED 50 or EC50 value [The low $ED_{50}$, the more potent the drug\(\Rightarrow\) (A>B>C)

2- **Quantal dose–response curve:**

- **Definition:** A graph of discrete (yes-or-no) values, plotting the number of subjects attaining the condition (such as death, or cure from disease) -versus- drug dose or concentration.
- **Shape:** frequency distribution is bell shaped, while cumulative frequency distribution is S-shaped
- **$ED_{50}$:** The drug-dosage at which 50% of the population attains the desired response.
- **$LD_{50}$:** Lethal-Dose-50:The dose at which 50% of the population is killed from a drug.
- **Therapeutic index** = $LD_{50} / ED_{50}$
  - The ratio of median lethal dose to median effective dose.
  - The higher the therapeutic index, the better & safer the drug
- **Margin of safety** = $LD_{1} / ED_{99}$
  - The ratio of the dosage required to kill 1% of population, compared to the dosage that is effective in 99% of population.
  - The higher the margin of safety, the better & safer the drug
NB: Clinically, efficacy is more important than potency. If a drug fails to produce a desired response, shift to a drug with higher efficacy, not to a more potent drug.

**Receptors**

### Types of Receptors:

#### 1. Ligand-gated ion channels (ionotropic receptors)

- Membrane receptors coupled directly to ion channel
- **eg:** 1- Nicotinic receptors: composed of 5 subunits (2 α–β – γ– δ)
  - A.ch + N. receptor → opening of Na⁺ channel → Na⁺ influx → Depolarization
  - 2- GABAₐ receptors:
  - GABA + GABAₐ receptor → opening of Cl⁻ channel → Hyperpolarization

#### 2. G-protein-coupled receptors (metabotropic)

- Membrane receptors coupled to specific protein called G – protein on cytoplasmic surface of the membrane
- Binding of the drug with the receptor → stimulation of G-protein
  - Control opening of ion channel
  - Or regulate the activity of membrane enzyme → Change intracellular 2ⁿd messenger.
  - **eg:** β-adrenergic receptor:
    - Adrenaline + β-receptor → ↑Gs → ↑A.C → ↑c.AMP → ↑c.AMP dependent protein kinase leading to the effect.
  - Some types of G-protein: Gₛ (↑c.AMP) – Gᵢ (↓c.AMP) – Gₚ (↑intracellular Ca++)

(Rang & Dale 2003)
3) **Type 3: Tyrosine-Kinase – Linked receptors:**
- Membrane receptors which have cytoplasmic domain containing ”Tyrosine Kinase enzyme”
- eg: Insulin - Growth factor – Cytokine receptors

4) **Type 4: Intracellular receptors (receptors that regulate DNA transcription):**
- They are intracellular receptors present in cytoplasm or nucleus. They regulate DNA transcription in the nucleus (Drugs should be lipid soluble)
- e.g: Cortisone – Sex hormones – Vit .D - Thyroid hormone

**Regulation of Receptors:**
1- Continuous stimulation of Receptors with agonists \( \rightarrow \) ↓ Their number & sensitivity \( \rightarrow \) “Down -regulation”
2- Continuous blocking of Receptor with antagonists \( \rightarrow \) ↑ Their number & sensitivity \( \rightarrow \) “Up-regulation”

**Theories for Drug- Receptor interaction:**
1- Receptor occupation theory:
   - The amount of the action depends in *number* of receptor occupied

   ![Diagram](image)

   *N.B* when maximum effect is reached, still some receptors remain free (spare receptors)

2- Rate theory of Paton:
   - The amount of action depends on the *rate* of association \( (K_a) \) & dissociation \( (K_d) \)
   - Higher rates = Higher activity
ADVERSE EFFECTS OF DRUG
“DRUG TOXICITY”

1) Unpredictable
Type B (Bizzare)
- Not related to pharmacological actions of drug
- Not dose dependant
1- Allergy (Hypersensitivity)
2- Idiosyncrasy

2) Predictable
- Related to pharmacological actions of drug
Type A (Augmented): it is dose dependant
1- Side effects
2- Secondary effects
3- Over dose
4- Supersensitivity (In-tolerance)
5- Cytotoxicity
6- Iatrogenic disease
7- Drug-drug interactions
Type C (Continued): after continued use
1- Drug dependence & addiction
Type D (Delayed): adverse effects appear after cessation of the drug
1- Teratogenicity
2- Carcinogenicity
Type E (End dose): adverse effects occur on cessation of therapy after the last dose
Type F (Failure of therapy):
- Tolerance

1) Unpredictable
Type B (Bizzare)

1) Allergy (Hypersensitivity):
- **Definition:** Abnormal response to the drug due to overactive (exaggerated) immune response, where the drug acts as antigen or hapten

- **Mechanism:** It may be antibody mediated (types I, II, III) or cell mediated (type IV)

- **Criteria:**
  - May **not** occur on 1st exposure to drug (Type I occur on 2nd exposure)
  - Cross allergy between related drugs may occur e.g: Penicillins & Cephalosporins

- **Manifestations** of Allergy:
  **Type I:** Ag/Ab. reaction releases chemical mediators ⇒ Fever – urticaria – skin rash photosensitivity - angioneurotic oedema – bronchial asthma – anaphylactic shock
  **Type II** (Cytotoxic): activation of complement system ⇒ cytotoxicity eg.: hepatotoxicity by Chlorpromazine & bone marrow depression by dipyrone
  **Type III:** Immune complex are deposited on basement membrane of endothelium ⇒ destruction & vasculitis eg.: serum sickness & arthus reaction
  **Type IV** (Delayed): due to sensitized T lymphocyte eg.: contact dermatitis
2) Idiosyncrasy: (Pharmacogenetics):
- Abnormal response to the drug due to genetic abnormality
- Occur on 1st exposure to drug
- Examples:

<table>
<thead>
<tr>
<th>Genetic abnormality</th>
<th>Drug</th>
<th>Abnormal response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- (G-6–PD) deficiency</td>
<td><em>Primaquine</em> – <em>Aspirin</em> - <em>Phenacetin Sulfonamides</em> - <em>Chloramphenicol</em></td>
<td><em>Hemolytic anemia</em></td>
</tr>
<tr>
<td>2- Deficient Pseudo- choline esterase enzyme</td>
<td>Succinylcholine</td>
<td><em>Succinylcholine apnea</em></td>
</tr>
<tr>
<td>3- Mutation in the gene responsible for Ca** release from sarco- plasmic reticulum</td>
<td>- Succinylcholine - <em>Volatile anesthetics (eg.: Halothane)</em></td>
<td><em>Malignant Hyperthermia</em></td>
</tr>
<tr>
<td>3- Slow acetylators</td>
<td>Isoniazid</td>
<td><em>Peripheral neuritis</em></td>
</tr>
</tbody>
</table>

**Predictable**

**Type A (Augmented):**
1) **Side effects:** "Undesirable normal actions produced by therapeutic dose of the drug"
   - e.g. Dry mouth induced by atropine

2) **Secondary effects:** "Undesirable action secondary to normal action of the drug"
   - e.g. Broad spectrum antibiotics ➔ intestinal flora ➔ vit.K & B deficiency & superinfection

3) **Over-dose:** "Exaggerated normal response due to over-dose"

4) **Supersensitivity (Intolerance):** "Exaggerated normal response to the usual dose of the drug"
   - e.g. Adrenaline in thyrotoxic patient.

5) **Cytotoxicity:**
   - Cardiotoxicity: Halothane
   - Hepatotoxicity: Halothane
   - Nephrotoxicity: Gentamicin
   - Neurotoxicity: Streptomycin ➔ 8th nerve damage
   - Bone marrow inhibition: Chloramphenicol

6) **Iatrogenic disease (Drug-induced disease):**
   - e.g. Chlorpromazine ➔ Parkinsonism

7) **Drug-Drug interaction:** See latter (page 21)

**Type C (Continued):**

- **Drug Dependence:**
  - It is related to Tolerance
  - It is either: Habituation or Addiction
<table>
<thead>
<tr>
<th>Habituation</th>
<th>Addiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Psychic dependence</td>
<td>1- Psychic &amp; physical dependence</td>
</tr>
<tr>
<td>2- sudden stop ➔ Psychic craving</td>
<td>2- Sudden stop ➔ withdrawal symptoms (Abstinence syndrome)</td>
</tr>
<tr>
<td>3- e.g: Smoking – Coffee – Tea</td>
<td>3- e.g : Morphine – Barbiturates – Alcohol</td>
</tr>
</tbody>
</table>

---

**Type D (Delayed):**

1) **Teratogenicity:**
   - It is the ability of the drug to induce fetal malformation when given to pregnant mothers
   - FDA has classified drugs into 5 categories: A, B, C, D & X Where A is the safest category & X is highly teratogenic
   - e.g : * Aspirin ➔ cardiac septal defect
     * Thalidomide ➔ absent Limbs (Phocomelia)

---

2) **Carcinogenicity:**
   - e.g : Tobacco smoking ➔ bronchogenic carcinoma

---

**Type E (End dose):**

- Adverse effects occur on cessation of therapy after the last dose
- **Examples**
  - Withdrawal syndrome with morphine
  - Acute Addisonian crisis with chronic corticosteroid therapy cessation
  - Hypertension after clonidine withdrawal

---

**Type F (Failure of therapy):**

**Tolerance:**

* **Definition:** “Failure of responsiveness to the usual dose of a drug”

* **Types:**
  1- Congenital: - Species ➔ Rabbits tolerate belladonna
     Due to presence of atropinase enz.
  - Racial ➔ Ephedrine not mydriatic in Negroes
  - Individual ➔ Biological variation among persons
  2 –Acquired: This occur after repeated use of the drug
    - Cross tolerance: tolerance to one drug extends to related drugs e.g - Nicotine & Lobeline
    - Ethyl alcohol & Ether
    - Tachyphylaxis ➔ Acute acquired tolerance e. g repeated ephedrine on Bl.Pr.
    - Bacterial resistance to antibiotics

* **Mechanism of acquired Tolerance:**
  - ↓ Absorption - ↑ Metabolism - ↑ Excretion
  - Down regulation of receptors - Target cell adaptation
Drug- Interactions:

A) Pharmacokinetic Interactions:
1- Absorption: Motility - gastric emptying - pH - Contents ➔ See before
2- Distribution: Aspirin ➔ Displace oral anticoagulants ➔ Bleeding
3- Metabolism: HME inducers & inhibitors (see before)
4- Excretion: - Probenecid ➔ ↓ active tubular secretion of Penicillin
   - Effect of pH (see before)

B) Pharmacodynamic Interactions:
May be: addition, synergism, potentiation, antagonism, or reversal

1- Addition (summation):
   - Active drug + Active drug ➔ Algebric sum of activity (1+1= 2)
   - e.g : A. ch + Histamine on intestinal contractility

2- Synergism:
   - Active drug + Active drug ➔ more than algebric sum of activity (1+1 = > 2)
   - e.g : - Ethanol + Barbiturate ➔ severe ↓ CNS
     - Curare + Ether ➔ severe muscle paralysis

3- Potentiation:
   - In active drug ➔ ↑ activity of active drug (0 + 1 = >1)
   - e.g : - Physostigmine + A.ch
     - Barbiturate + Aspirin

4- Antagonism:
Drug antagonism may be classified generally into:

I- Chemical:
   - Neutralization ➔ Heparin + Protamine sulfate
   - Chelation ➔ BAL + Hg or As

II- Physiological (Functional):
   - 2 drug + 2 receptors ➔ 2 opposing actions
   - e.g Adrenaline & Histamine on Bronchi
     - Adrenaline ➔ B₂ ➔ Bronchodilatation
     - Histamine ➔ H₁ ➔ Bronchoconstriction

III – Pharmacological:
   a) Pharmacokinetic antagonism:
      as Phenobarbitone (Which is HME inducer) with Warfarin
   b) Pharmacodynamic antagonism:
      - 2 Drugs acting on one receptor
      - Types: Competitive & Non- competitive
Non-competitive antagonism:
1- Excess agonist can **not** displace antagonist
2- *Non* competitive antagonist causes *non* parallel shift of Log D/R curve to Rt
   (same potency $\rightarrow$ same $ED_{50}$
   & $\downarrow$ efficacy $\rightarrow E_{max}$ $\downarrow$)
3- May be reversible or Irreversible
   - Reversible antagonist (bind reversibly)
     as *Snccinyl-choline*
   - Irreversible antagonist (bind covalently
     & irreversibly to the receptor)
     as *Organo-phosphorus compounds & phenoxybenzamine*

Competitive antagonism:
1- Excess agonist can displace antagonist
2- Competitive antagonist causes parallel shift to the Rt of log D/R curve
   (potency $\rightarrow$ $ED_{50}$ $\uparrow$
   & same efficacy $\rightarrow E_{max}$)
3- e.g *Atropine & A.ch*

5- Reversal:
   e.g *Adrenaline + Phentolamine* on blood pressure
DOSAGE OF DRUGS (POSOLOGY)

1- **Therapeutic dose**: average dose for an adult required to produce a therapeutic effect
2- **Initial dose**: Initial Large dose to start treatment
3- **Maintenance dose**: Daily dose required to maintain the therapeutic effect attained by initial dose
4- **Maximal tolerated dose**: Largest dose with out toxic effect
5- **Lethal dose**: Dose that produces death (Therapeutic index see before)
6- **TD<sub>50** (median toxic dose)**: dose that would produce particular toxic effect in 50% of animals.
7- **LC<sub>50** (median lethal concentration)**: in situations where the agent is not administered directly to the animals, toxicant potency is presented as the median lethal concentration to which the animals are exposed in the environment that will result in 50% mortality of the population of animals.

Factors modifying the dosage of Drugs

1- Age, weight, surface area  
2- Sex  
3- Route of administration  
4- Time of administration  
5- Pathological state  
6- Emotional state  
7- Supersensitivity  
8- Hypersensitivity  
9- Idiosyncrasy  
10- Tolerance  
11- Cumulation  
12- Drug – Drug interaction

1) **Age, weight & Body surface area:**
   - **Age:**
     Decrease the dose in Extremities of age
     1- Elderly: due to 1- ↓ Renal excretion  
       2- ↓ Hepatic metabolism
     2- Children: due to 1- Immature kidney, liver & BBB  
       2- ↓ Plasma protein
   
   * Calculate the dose by:
     - **Clark’s formula (< 1 year)**  
       infant dose = adult dose x \[
       \frac{\text{Weight in pounds}}{150}
       \]  
       or  
       \[
       \frac{\text{Weight in Kg}}{70}
       \]
     - **Young’s formula (> 1 year)**  
       child dose = adult dose x \[
       \frac{\text{Age in years}}{\text{Age + 12}}
       \]
   
   - **Weight:**
     1. More accurate than age especially in children  
     2. ↑ Body weight (BW) due to fat is not taken in consideration (except with anesthesia) as fat is an inert tissue
   
   - **Surface area:** is a better guide to appropriate drug dosage than bodyweight.
     The dose for a child can be approximated as:
     \[
     \text{Adult dose} \times \frac{\text{surface area of child (in m}^2)}{1.8}
     \]
     where 1.8 is the average body surface area of a 70 kg adult.
2) Sex:
   1- Females require Smaller doses than males due to:
      - Bigger % of Fat
      - Estrogen is HME inhibitor
   2- Females should avoid drugs during some periods:
      - Menstruation → Aspirin & Catheterics → Bleeding
      - Pregnancy → Teratogens – Catheterics – Uterine stimulants
      - Labor → Morphine →↓ R.C in newborn
      - Lactation → Purgatives – Penicillin – Tetracycline – Chloramphenicol

3) Route of administration:
   1- I.V dose < IM < S.C < Oral
   2- Route of administration may modify the action of the drug e.g Mg SO₄
      a- Orally on an empty stomach → Purgation
      b- I.V →↓ CNS - ↓ smooth m. - ↓ sk. m - ↓ Heart
      c- Rectally →↓ CSF Pressure (as retention enema)

4) Time of administration:
   1- If the drug is irritant → after meals & if non irritant → before meals
   2- If the drug ↑ CNS (Ephedrine) → not given at bed time

5- Pathological state:
   1- Some drugs acts only in presence of disease e.g Aspirin → Antipyretic only in presence of fever
   2- Supersensitivity: e.g adrenaline in thyrotoxicosis
   3- Affect drug kinetics (ADME): e.g cummulation of drugs in renal failure

6) Emotional state:
   - some patients improve by psychological rather than pharmacological effect of the drug (placebo effect)
   - Placebo is inert material (Sucrose or Lactose)

7) Hypersensitivity
8) Supersensitivity
9) Tolerance
10) Idiosyncrasy

11- Cummulation:
   - This occurs when rate of intake > rate of elimination → the drug accumulate in body & produce toxic effect. e.g Digitalis – Thyroxin – Heavy metals

12- Drug–drug interaction: → see before
**Routes of Drug administration**

1) **Enteral**
   - Oral
   - S.L
   - Rectal

2) **Parenteral**
   - Injection
   - S.C implants

3) **Inhalation**

4) **Topical**
   - For Local effect
   - For Systemic effect [TDS]

**(1) Oral administration:**
- **Advantages:** Easy – Economic – safe – Convenient
- **Disadvantage:** Not suitable for
  1- Unconscious
  2- Uncooperative
  3- Excessive vomiting
  4- Excessive Diarrhea
  5- Emergencies
  6- Drugs not absorbed from G.I.T if systemic action is intended (e.g: Streptomycin for TB)
  7- Drugs that are irritant
  8- Drugs destroyed by gastric acidity (e.g: Benzyl penicillin)
  9- Drugs destroyed by digestive enzymes (e.g: Insulin)
  10- Drugs with extensive 1st pass effect (e.g: Lidocain)

**(2) S.L administration**
- **Advantages**
  1. Escape 1st pass metabolism
  2. Escape G.I.T enzymes & acidity
  3. Rapid absorption
  4. The action can be terminated by spitting out the tablet

**(3) Rectal administration**
- **Advantages**
  3. Suitable for unconscious
  4. Suitable for uncooperative
  5. Suitable for patient with vomiting
  6. Suitable for irritant drugs
  7. Suitable for large volume drugs

**NB.:** Rectal route may be: 1. *Suppository* or 2. *Enema*

<table>
<thead>
<tr>
<th>Retention enema</th>
<th>Evacuant enema</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Small volume</td>
<td>• Large volume</td>
</tr>
<tr>
<td>• Given slowly at low head pr.</td>
<td>• Given rapidly at high head pr.</td>
</tr>
<tr>
<td>• e.g: Mg sulfate - Prednisolon</td>
<td>• e.g: soap</td>
</tr>
</tbody>
</table>

25
4) Parenteral route

1- I.V. :

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 100% Bioavailability</td>
<td>1. Most dangerous</td>
</tr>
<tr>
<td>2. Rapid onset</td>
<td>2. Transmission of disease, e.g: AIDS &amp; Hepatitis</td>
</tr>
<tr>
<td>3. Suitable for Emergency</td>
<td>3. If allergy → Anaphylactic shock</td>
</tr>
<tr>
<td>4. Suitable for irritant &amp; large volume drugs</td>
<td>4. If very irritant → phlebitis &amp; thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td>5. If Extravasation → Necrosis</td>
</tr>
<tr>
<td></td>
<td>6. Pyrogenic reaction</td>
</tr>
<tr>
<td></td>
<td>7. Nitroid reaction → flush, e.g.: atropine</td>
</tr>
<tr>
<td></td>
<td>8. Velocity reaction → e.g.: Aminophylline</td>
</tr>
<tr>
<td></td>
<td>9. Once injected, No return</td>
</tr>
<tr>
<td></td>
<td>10. Not suitable for oily preparation</td>
</tr>
</tbody>
</table>

2- I.M: Suitable for mild irritant drugs

3- S.C: Drugs should be Non-irritant

<table>
<thead>
<tr>
<th>↑ S.C absorption by:</th>
<th>↓ S.C absorption by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Massage</td>
<td>1. Application of cold</td>
</tr>
<tr>
<td>2. Application of heat</td>
<td>2. Addition of V.C, e.g: adrenaline</td>
</tr>
<tr>
<td>3. Addition of hyaluronidase anz.</td>
<td>3. In cases of shock</td>
</tr>
</tbody>
</table>

4. Intra dermal → sensitivity tests

5. Intra arterial → for - Diagnosis [Arteriography] - Treatment [Dissolution of Thrombosis]

6. Intra cardiac → adrenaline in arrest

7. Intra peritoneal → peritoneal dialysis

8. Intra articular → cortisone in arthritis

9. Intra bone marrow

10. Intra thecal → in subarachnoid space, e.g: [spinal anesthesia]

N.B: I.V > I.M > S. C

2) Subcutaneous pellet implantation

   e.g: [Levonorgestrel (Norplant) provides effective contraception for 5 year]

5) Inhalation

   - Advantages: Excellent absorption due to
     1. Rich Blood supply
     2. Alveoli → Large surface area--Porous-- Thin

6) Topical

   1) For Local effect
   2) For systemic effect [Transdermal Delivery System (TDS)]
      - Advantage of T.D.S: 1- Prolonged effect
        2- Avoidance of 1st pass effect
      - Example of T.D.S → Nitroglycerin - Clonidine - Scopolamine - Estrogen
GERIATRIC PHARMACOLOGY

Pharmacokinetic changes:

a- Absorption:
Age may alter the rate of absorption (but not the extent) due to:
1- ↓ Gastric emptying
2- ↑ Gastric pH
3- ↓ Splanchnic blood flow
4- Impaired intestinal motility

b- Distribution:
Distribution is changed due to:
1- ↓ Lean body mass
2- ↓ Body water ⇒ ↓ V_d of water soluble drugs (eg.: Paracetamol)
3- ↑ Body fat % ⇒ ↑ V_d of fat soluble drugs (eg.: Diazepam)
4- ↓ Serum albumin ⇒ ↑ free form of some drugs (eg.: Warfarine)
5- ↑ α-acid glycoprotein

c- Metabolism:
- The metabolism of some drugs is ↓ due to:
  1- ↓ Hepatic blood flow
  2- ↓ HME activity
- Phase I is affected more than Phase II

d- Excretion:
Excretion is ↓ leading to:
- Prolongation of t_{1/2} of most of drugs
- ↑ Adverse drug reaction (eg.: Digoxin – Aminoglycoside – H_2 blockers)

Pharmacodynamic changes:

1- Sensitivity may ↑ to many drugs (eg.: Analgesics – Benzodiazepines – Warfarin) due to:
   - Pharmacokinetic changes & ↓ Haemostatic response
2- Sensitivity may ↓ to some drugs (eg.: β-receptors) due to:
   ↓ number or sensitivity of receptors
3- Sensitivity of Baroreceptors may ↓ ⇒ ↑ risk of postural hypotension
4- The incidence of adverse drug reaction is ↑ due to:
   a- Multiple disease & Polypharmacy
   b- Patient errors due to: ↓ compliance - ↓ memory - ↓ vision
   c- Kinetic changes: ↓ drug elimination
   d- Dynamic changes: ↑ drug sensitivity

Generally start with small doses then ↑ gradually, Use minimal numbers of drugs & observe for S.E.
PEDIATRIC PHARMACOLOGY

Both the pharmacokinetics and pharmacodynamics to drugs may differ between neonates (<1 ms), infants (1-12 ms) & children compared with adults, because many metabolic & physiological processes are immature at birth & develop rapidly in the first months of life.

Pharmacokinetics:

A) Absorption:
- The rate of absorption (but not the extent) may be reduced in neonates due to: slow rates of gastric emptying and intestinal transit
- But total absorption of poorly absorbed drugs may be increased, because of longer contact with the intestinal mucosa.

B) Distribution.
Distribution is changed due to:
1. ↑ Body water ⇧ \( V_d \) of water soluble drugs
2. ↓ Body fat % ⇧ \( V_d \) of fat soluble drugs
3. ↓ Serum albumin ⇧ free form of some drugs
4. ↑ plasma concentrations of free fatty acids and bilirubin compete with drugs for plasma protein binding sites and vice versa.
NB.: Drugs that are strongly bound to albumin should not be used during neonatal jaundice because they may displace bilirubin from protein binding sites ⇧ the risk of kernicterus.

C) Metabolism:
- In neonates: The metabolism of some drugs is ↓ due to immature enzymes, especially for substrates of CYP1A2 and glucuronidation.
- In children: enzyme systems mature & become more extensive than in adults, because the relative liver mass and hepatic blood flow are higher.

D) Renal elimination:
- In neonates: Renal function is much less developed than in children or adults. (The GFR is 40% of the adult level & tubular secretory processes are poorly developed). Elimination of drugs such as digoxin, gentamicin & penicillin will therefore be delayed.

Pharmacodynamics:
- In neonates: Sensitivity of many drugs may be ↑ due to pharmacokinetic changes ⇧ dose in neonates
- In children: Sensitivity of many drugs may be ↓ due to larger \( V_d \) & faster hepatic elimination ⇧ dose in young children
PHARMACOECONOMICS

Definition:
Pharmacoeconomics is application of economic evaluation methods to identify, measure & compare costs & outcomes (consequences) of relevant medical interventions (e.g. drugs, services and diagnostic tests).

Costs of therapeutic intervention:
These are either direct costs, indirect costs or intangible costs

A- DIRECT COSTS:
- Direct medical costs:
  - Prescription drug costs
  - Outpatient physician’s follow up visits (single or repeated)
  - Costs of diagnostic procedures (laboratory investigations, new medical devices, procedures and diagnostic tests).
  - Costs of negative consequences of treatment as the medications needed to treat adverse effects or drug interactions.
  - The use of corrective medications if wrong approaches are conducted.
- Direct non-medical costs:
  - e.g. Transportation costs to hospital

B- INDIRECT COSTS:
- Costs of illness to patient or his society as loss of income due to illness and being away from work.

C- INTANGIBLE COSTS:
- Cost of pain or suffering.

Pharmacoeconomic assessment methods:
1- Cost minimization analysis.
2- Cost benefit analysis.
3- Cost effectiveness analysis.
4- Cost utility analysis.

1- Cost minimization analysis:
- It compares the cost of two or more alternative therapies that have identical (equivalent) outcomes.
- The least costly of the alternatives is selected. Cost is the only distinguishing feature

2- Cost benefit analysis:
- The outcomes of alternatives studied are not considered equal. They are measured in monetary terms.
- A benefit /cost ratio is then calculated to determine which alternative provides the greatest benefit relative to the costs.
3- **Cost effectiveness analysis:**
- The outcomes of alternatives are not measured in monetary units, but in *physical units* e.g. in terms of years of life saved.
- Although, Cost effectiveness analysis does not assume equal outcomes, it should compare alternatives with similar objectives. A cost /effectiveness ratio for each alternative is established.
- In this type of analysis, the least costly alternative is not necessarily the selected one. The most expensive alternative may be considered the cost effective if it has an additional benefit worth the extra cost.

4- **Cost utility analysis:**
It is very similar to cost effectiveness but the analysis is measured *in terms of utility*. The outcome is measured as *quality adjusted life years*. e.g in cancer, two medications may extend a patient life by 10 years but one causes undesirable effects as nausea & depression. On the other hand the second drug does not cause these effects. Therefore, the quantity and quality of life are both important consideration.

---

**Advantages of pharmacoeconomics:**

1- **Choosing** treatments & other health care strategies, **balancing** the potential benefits of these strategies against their costs & **comparing** to other costs.
2- Has a role in **evaluation of new medications** (formulary decision making).
3- It can help **assign priorities for better health** and longer life.
4- It is **a framework for decision makers** to guide them in:
   - Reducing costs.
   - Improving outcomes.
   - Error reduction.
   - Prevention of adverse effects and the consequences of these effects such as unnecessary hospitalization.
   - Using health care resources efficiently to produce as much benefit as they can.

---

**Doing more and better pharmacoeconomic evaluation is not enough. It requires a change in personal attitude. Every one should realize that our resources are limited and must be spent wisely. Health professionals are concerned not only about the individual patients but should be concerned by the health of the population and manage cases accordingly.**