❖ Pharmacokinetic terms: -

Pharmacokinetics involves drug movement through the body (ie, "what the body does to the drug") to reach sites of action, metabolism, and excretion. Pharmacokinetics is made up of **four phases**:

1. **Absorption**
2. **Distribution**
3. **Metabolism**
4. **Excretion.**

All these processes largely determine serum drug levels, onset, peak and duration of drug actions, drug half-life, therapeutic and adverse drug effects, and other important aspects of drug therapy.

1. **Absorption:** is the movement of the drug from the site of administration into the bloodstream.
   - Routes of administration other than intravenous may result in partial absorption and lower **bioavailability.**

   - **Bioavailability:** is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. **Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration.**

   - There are three ways in which drug particles are absorbed. These are: 1. Passive diffusion. 2. Active transport. 3. Pinocytosis.

☺☺ Numerous factors affect the rate and extent of drug absorption:

1. **Rout of administration.**
2. **Effect of pH on drug absorption**
3. **Blood flow to the absorption site:** The intestines receive much more blood flow than the stomach, so absorption from the intestine is favored over the stomach.
4. **Total surface area available for absorption:** With surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.
5. **Lipid and water solubility:** Drugs that are more lipid soluble usually are absorbed more rapidly than others because they can cross the lipid cell membranes easily.
6. **Physiologic condition** of the patient affects drug absorption.

2. Distribution

It is the process by which a drug reversibly leaves the bloodstream and enters the (extracellular fluid) and the tissues.

** The distribution of a drug into these different tissues depends on many factors: -

1) Blood flow
2) Lipid and water solubility.
3) Plasma Protein binding.
4) Blood supply to the target tissue.
5) Capillary permeability.

3. Drug metabolism

is the method by which drugs are inactivated or bio-transformed by the body. Metabolism of drugs occurs primarily in the liver. Some metabolism also occurs in other tissues, most notably the small intestine mucosa, lungs, kidney, brain, olfactory mucosa, and skin.

** Most often, an active drug is changed into one or more inactive metabolites, which are then excreted. Other drugs (called prodrugs) are initially inactive and exert no pharmacologic effects until they are metabolized.

** In some cases, metabolism can result in molecule more active than the original. For example, the narcotic analgesic **codeine** undergoes biotransformation to **morphine**, which has significantly greater ability to relieve pain.

** Most drugs are metabolized by enzymes in the liver **(called the cytochrome P450 [CYP] or the microsomal enzyme system);** red blood cells, plasma, kidneys, lungs, and GI mucosa also contain drug-metabolizing enzymes.

** There are two general types of metabolic reactions, which are known as ***Phase 1*** **and** ***Phase 2 reactions*****.**

❖ **Factors affecting metabolism of drugs: -**

1) The health condition of liver and kidneys.
2) Age.
3) Chemical properties of the drug.
4) Drug-drug interactions.
5) Enzyme induction and enzyme inhibition.

4. Excretion

It occurs mainly through the kidneys, although some drugs are also excreted in bile, feces, lungs, sweat, and breast milk.

- Diseases and pathophysiologic changes in the kidney, such as renal failure, decrease the effectiveness of the kidney in drug excretion.

❖ Pharmacodynamics: -

It refers to how a medicine changes the body. A more complete definition explains pharmacodynamics **as the branch of pharmacology concerned with the mechanisms of drug action and the relationships between drug concentration and responses in the body.**

There are two theory of drug actions: -

1. Receptor theory of drug action.
2. Non receptor drug action.

❁ Receptor: - Receptors are macromolecules mainly proteins located on the surfaces of cell membranes or within cells (cytoplasm or in nucleus).

Drug (D) + Receptor ®……> Drug receptor complex…….> Response

Non-receptor drugs	Receptor drugs
1. Act at higher concentrations.	1. Act at low concentrations.
2. Do not react with specific receptors.	2. React with specific receptors.
3. Do not show structure activity relationships.	3. Show structure activity relationships.
4. Do not have specific antagonists.	4. Can be antagonized with specific antagonists.
5. Examples: osmotic diuretics (mannitol),	5. Examples: Acetylcholine, adrenaline, nor-adrenaline, histamine .
6. Act by: I. Altering pH, e.g.: gastric antacid neutralize HCl secreted by partial cells of the stomach. II. Altering membrane Osmosis. e.g.: diuretics.	6. Act by: I. activating receptors, called (**agonists**), e.g.: epinephrine-like drugs act on the heart to increase the heart rate, II. inactivating receptors, called (**antagonists**), e.g. atropine antagonize acetylcholine. III. Interacting with (**inhibiting**) enzymes, e.g.: allopurinol is reversible inhibitor of xanthine oxidase.

***** Drug safety: - two indexes represent the safety of the drug**

1. **Therapeutic index:** it is a value representing the margin of safety of a drug**. The higher the therapeutic index, the safer the drug.**

$$\text{TI} = \frac{LD_{50}}{ED_{50}}$$

2. **The margin of safety (MOS)** is another index of a drug's effectiveness and safety. In general, the higher the MOS value, the safer the medication.

❖ **Drug-drug and Drug-food interactions: -**

Drug interactions occur when two or more substances (drugs) taken together. The substance causing the interaction may be another drug, a dietary supplement, an herbal product, or a food.

** Drug interactions occur by different mechanisms which lead to either: -

1. Inhibition of drug action
   Ex: tetracycline + milk >>>>>> inhibit therapeutic action of tetracycline.
2. Enhanced of drug action
   Ex: lopinavir+Ritonavir >>>> Greater reduction in (HIV) level than occur when either drug is used alone.
3. Totally new and different response
   Ex: when used alone disulfiram (Antabuse) has no pharmacological effects. Disulfiram+ alcohol >>>> (new action) >>>> severe headache, flushing, dyspnea, palpitations, and blurred vision.

Drug interactions occur at two levels:

1. **Pharmacokinetic interaction:** include changes in the absorption, distribution, metabolism, or excretion of medications.
   - **a.** Ex: tetracyclines + antacid (containing Al^{+3}, Mg^{+2}, Ca^{+2}), milk>>> **(reduce antibacterial absorption).**
   - **b.** Ex: Diazepam (Valium)+ Phenytoin (Dilantin)>>> increase adverse effects of phenytoin (displacement from blood protein) >>> **(distribution interaction).**
   - **c.** Ex: phenobarbital + nifedipine (Adalat)>>>> less blood pressure reduction **(metabolism interaction).**
   - **d. Ex:** NSAIDS+ Methotrexate>>>> NSAIDs will block the secretion of methotrexate **(excretion interaction)**

❖ Adverse drug reaction (ADR):

It is an undesirable and potentially harmful action caused by the administration of normal doses of medication.

Classification of (ADR):

- Type A (Augmented): dose dependent, e.g: anticoagulant → bleeding.
- Type B (Bizarre) (not dose dependent, e.g: penicillin → anaphylaxis
- Type C (Chemical) can be predicted from the chemical structure of the drug/metabolite, e.g: paracetamol → hepatotoxicity
- Type D (Delayed) Can be due to accumulation, e.g. analgesic → nephropahy.
- Type E (Exit/End of treatment) e.g. Phenytoin withdrawal → Seizures,
- Type F (Familial): failure of reaction.
- Type G (Genotoxicity): genetic reaction (e.g: favasim).
- Type H (Hypersensitivity).
- Type U (Unclassified).