Unit V – Problem 2 – Pharmacology

- **Biotransformation (metabolism):**
  - **Definition**: the chemical modification made by an organism on a chemical compound.
  - **Sites for drug biotransformation:**
    - ✓ Liver is the major organ.
    - ✓ Brain: levodopa (used to treat Parkinson's disease).
    - ✓ Kidney: insulin & vitamin D.
    - ✓ Lung: Nicotine.
    - ✓ Gut: in the gut lumen or gut wall.
    - ✓ Plasma.
- **Phase I reaction:**
  - **Definition**: it the biotransformation (chemical alteration) of a parent drug in the body by: oxidation (CP450), reduction, hydrolysis or combination of these processes.
  - Producing a metabolite of the drug that will gain center for conjugation thus it can be used in phase II reaction.
- **Phase II reaction (conjugation):**
  - **Definition**: for the process of conjugation, there must be:
  - A parent drug with center for conjugation or a phase I metabolite that gained a center for conjugation. **These centers are:**
    - ✓ Carboxyl (-COOH).
    - ✓ Hydroxyl (-OH).
    - ✓ Amino (-NH2).
    - ✓ Sulfydryl (-SH).
  - Conjugating agent.
  - Transferase enzyme.
  - Energy.

Conjugating agents	Transferase enzymes
Glucouronic acid	Glucouronyltranferase
Sulfate	Sulfotransferase
Acetic acid	Acetyltransferase
Glycine	Glycotransferase
Methylation	Methyltransferase

- **Purpose for conjugation**: it makes the product inactive, more polar & readily excreted than the parent drug.

Biotransformed drugs can become:	
Equally potent with parent drug	Acetylsalicylic acid ---> salicylic acid
More potent that parent drug	Diazepam ---> Nordiazepam
Less potent than parent drug	-
More toxic than parent drug	Methanol ---> formic acid

- **Note: biotransformation converts pro-drug to active product.**
- A drug might go through phase I & phase II reaction before being eliminated, or it might directly go through phase II reaction and the eliminated, or it might be eliminated without going through these phases.

- **First-pass effect (liver is the major site):**
  - **Definition**: it is the extent of biotransformation that occurs to an orally administered drug (in the gut lumen/wall and/or liver) before it enters the systemic circulation.
  - **Bioavailability**: the amount of drug in the systemic circulation which was not altered by biotransformation.
  - Drugs given **sublingual** or **rectal** undergo less first-pass effect and have higher bioavailability.
  - Drugs which undergo first-pass effect are highly affected by severe cirrhosis.
  - Oral dose of a drug that undergoes first-pass effect should be greater than IV dose.
- **Microsomal (MFO) system:**
  - Located in the SER of hepatocytes.
  - Catalysis oxidation of phase I reaction.
  - High lipid-soluble drugs are good substrates.
  - **It involves:**
    - ✓ Oxygen
    - ✓ NADPH
    - ✓ Cytochrome P450
    - ✓ Cytochrome P450 reductase.