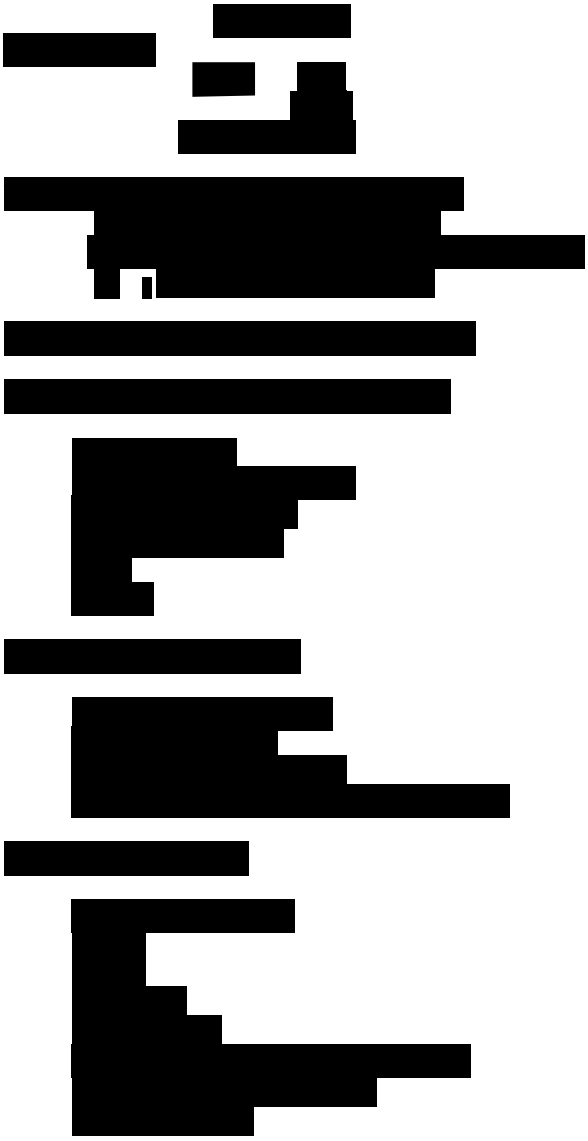

3.8 Biotransformation (Metabolism)

(Biological - All living organism, Transfer- shifting, Formation- process).

Biotransformation means the chemical processes in living things that change food or other substances into energy and materials for growth and other effect. It is a chemical alteration or change of the drug in the body from one phase to another phase. It is needed to render nonpolar (lipid soluble) compounds polar (lipid insoluble) so that they are not reabsorbed in the renal tubules and are excreted. The primary site for drug metabolism is liver, other are- lungs, kidney, intestine, skin and plasma.

Biotransformation of drugs may lead to the following.

Inactivation:-

Most drugs and their active metabolites are rendered inactive or less active, e. g. ibuprofen, paracetamol, lidocaine, chloramphenicol, propranolol and its active metabolite 4-hydroxypropranolol.

Active metabolite from an active drug:-

Many drugs have been found to be partially converted to one or more active metabolite; the effects observed are the sum total of that due to the parent drug and its active metabolite.

Activation of inactive drug:-

Few drugs are inactive as such and required conversion in the body to one or more active metabolites. Such a drug is called a prodrug. The prodrug may offer advantages over the active form in being more stable, having better bioavailability or other desirable pharmacokinetic properties or less side effects and toxicity. Some prodrugs are activated selectively at the site of action.

The biotransformation of drugs depends on the two enzymes:-

1. **Microsomal**
2. **Non-microsomal**

1. Microsomal enzymes:- These are located on smooth endoplasmic reticulum, attached with inside the cell and present in liver, kidney, intestine, mucosa and lungs. They catalyse most of the oxidation, reduction, hydrolysis and Glucuronide conjugation.

2. Non-microsomal enzymes:- These are present in the cytoplasm and mitochondria of hepatic (liver) cell as well as in other tissues including plasma. The flavor-protein oxidases, esterases, amidases and conjugases are non-microsomal.

Biotransformation reactions can be classified or categorized into:
According to R. T. Williams:-

1. **Phase I/Non-synthetic/Functionalization reaction**
2. **Phase II/ Synthetic/Conjugation reaction**

Based on latest researcher:-

3. **Phase III/Specially for Glutathione conjugation, excreted via Bile in the Gut**

1. Phase I /Non-synthetic/ Functionalization reaction:-

A functional group is generated or exposed; metabolite may be active or inactive.

Oxidation:-

This reaction involves addition of oxygen (negatively charged radical) or removal of hydrogen (positively charged radical). Oxidations are the most important drug metabolizing reactions. Oxidative reactions are mostly carried out by a group of aromatic, olefins, allylic, aliphatic and alicylic compounds.

Reduction:-

This reaction is the converse of oxidation and involves cytochrome P-450 enzymes working in the opposite direction. Alcohols, carbonyl, aldehydes, quinones are reduced drugs

Hydrolysis:-

This is cleavage of drug molecule by taking up a molecule of water. Hydrolysis occurs in liver, intestines, plasma and other tissues. Examples of hydrolysed drugs are choline esters, amides, procaine, lidocaine, procainamide, aspirin, carbamazepine-epoxide, pethidine, oxytocin.

$$\text{Ester} + H_2O \rightarrow \text{Acid} + \text{Alcohol}$$

Cyclization:-

This is formation of ring structure from a straight chain compound, e.g. proguanil.

Decyclization:-

This is opening up of ring structure of the cyclic drug molecule, e.g. barbiturates, phenytoin.

2. Phase II/ Synthetic/Conjugation reaction:-

An endogenous radical is conjugated to the drug, metabolite is mostly inactive; except few drugs, e. g. glucuronide conjugate of morphine and sulfate conjugate of minoxidil are active.

These involve conjugation of the drug or its phase-I metabolite with an endogenous substrate, usually derived from carbohydrate or amino acid, to form a polar highly ionized organic acid, which is easily excreted in urine or bile. Conjugation reactions have high energy requirement.

Glucuronide acid conjugation:-

This is the most important synthetic reaction carried out by a group of UDP-glucuronosyl transferases (UGTs). Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose. Examples are- chloramphenicol, aspirin, paracetamol, diazepam, lorazepam, morphine and metronidazole.

Acetylation:-

Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A, e.g. sulfonamides, isoniazid, PAS, dapsone, hydralazine, clonazepam, procainamide. Multiple genes control the N-acetyl transferases (NATs), and rate of acetylation shows genetic polymorphism (slow and fast acetylators).

Methylation:-

The amines and phenols can be methylated by methyl transferases (MT); methionine and cysteine acting as methyl donors, e.g. adrenaline, histamine, nicotinic acid, methyldopa, captopril, mercaptopurine.

Sulfate conjugation:-

The phenolic compounds and steroids are sulfated by sulfotransferases (SULTs), e.g. chloramphenicol, methyldopa, adrenal and sex steroids.

Glycine conjugation:-

Salicylates, nicotinic acid and other drugs having carboxylic acid group are conjugated with glycine, but this is not a major pathway of metabolism.

α- Amino acid conjugation:-

Compounds having organic and inorganic residues are conjugated with the help of α- Amino acid; these are not a major pathway of metabolism.

Ribonucleoside/nucleotide:-

This pathway is important for the activation of many purine and pyrimidine antimetabolites used in cancer chemotherapy. A variety of metabolites (some more, some less) of a drug may be produced.

Stereoisomers of a drug may be metabolized differently and at different rates, e.g. S-warfarin rapidly undergoes ring oxidation, while R-warfarin is slowly degraded by side chain reduction.

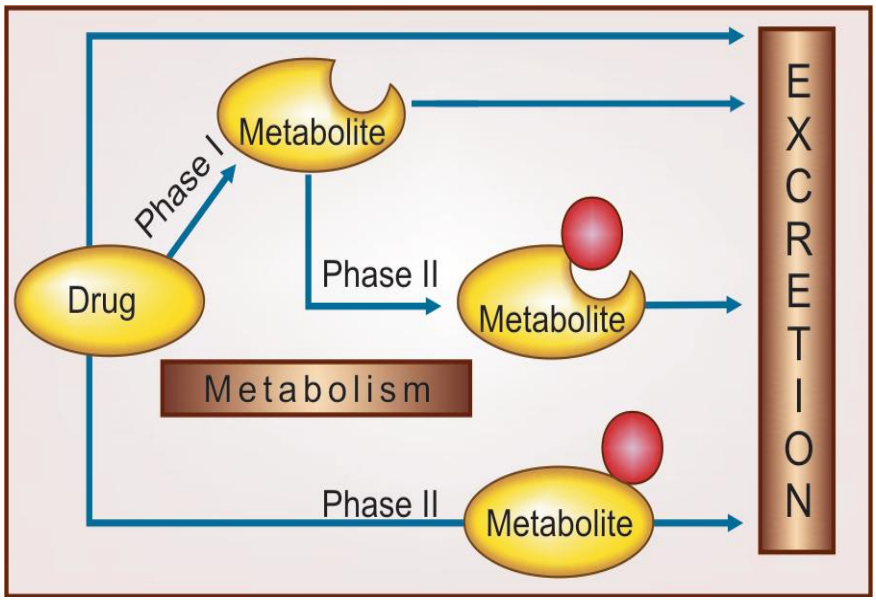

Fig. 5. Simultaneous and/or sequential metabolism of a drug by phase I and phase II reactions

On the basis of latest research:-

3. Phase III/Glutathione conjugation:-

This is carried out by glutathione-S-transferase (GST) forming a mercapturate. It is normally a minor pathway. However, it serves to inactivate highly reactive quinone or epoxide intermediates formed during metabolism of certain drugs, e.g. paracetamol. When large amount of such intermediates are formed (in poisoning or after enzyme induction), glutathione supply falls short—toxic adducts are formed with tissue constituents → tissue damage.

3.9 Factor Affecting Metabolism

Factor affecting drugs metabolism are:-

1. Physiochemical properties of drugs

a) Induction & inhibition of drug metabolizing enzymes
b) Environmental chemicals

2. Biological factors

a) Species differences
b) Strain differences
c) Sex differences
d) Age
e) Diet
f) Pregnancy
g) Hormonal imbalance
h) Disease states