1. ABSORPTION AND BIOAVAILABILITY OF A DRUG

The process whereby a drug initially enters body fluids is referred to as absorption.

Before a drug can act within the body, it must be absorbed into the **blood stream** which carries it to its site of action.

The rate of absorption is determined by the rate of transfer of the drug across barriers between the sites of administration and action.

The route of administration largely determines the latent period between administration and onset of action .

Drug metabolism has two important effects ;

I. The drug is made more hydrophilic

II. The metabolites are usually less active than the parent drug. However, this is not always so, and sometimes the metabolites are as active or more active than the original drug.

For example, diazepam is metabolised to nordiazepam and oxazepam, both of which are active

Some drugs are administered as **'prodrugs'**, in an inactive or less active form to promote absorption, by-pass potential destruction by stomach enzymes or to reduce exposure to other moieties. Such prodrugs remain inactive until they are metabolised in the body to the active form

For example, levodopa is metabolised to active dopamine, while methyldopa is metabolised to more active α-methylnoradrenaline

Oxidation: Oxidative reactions involve mixed-function oxidases (cytochrome P-450s) found in microsomes. **Microsomal oxidation** involves the introduction of hydroxyl group into the drug molecule or an alkyl or amino group may be removed e.g. conversion of phenacetin to active compound to p-acetaminophenol (dealkylation) or of amphetamine to benzyl-methyl-ketone (deamination)

Oxidation can also be catalysed by **non-microsomal** oxidative enzymes e.g. alcohol dehydrogenase oxidize alcohol to aldehyde, aldehyde dehydrogenase converts aldehyde to carboxylic acid, Xanthine containing drugs like caffeine, theophylline and theobromine are oxidized by xanthine oxidase to uric acid

A mitochondrial enzyme monoamine oxidase (MAO) causes oxidative deamination of substances like adrenaline, 5-HT and tyramine while diamine oxidases endogenously metabolise histamine

Reduction: Many halogenated compounds and nitrated aromatic compounds are reduced by the microsomal enzymes e.g. halothane and chloramphenicol

Drugs like chloral hydrate and disulfiram are reduced by non-microsomal enzymes

Hydrolysis: This is usually carried out by enzymes 'esterases' that hydrolyse (split with addition of water) the esters. These enzymes are microsomal, non-microsomal and microfloral in origin. Drugs like Ach, procaine, atropine and neostigmine e.t.c. are metabolised by esterases

Hexamine is hydrolysed in the urinary tract at an acidic pH, to formaldehyde and ammonia; formaldehyde exerts an antibacterial action in the urinary tract

Glutathione Conjugation: Some drugs combine with glutathione to form non-toxic conjugates. e.g.

Acetylation: Acetylation reaction are common for aromatic amines and sulfonamides and requires acetyl-COA and N-acetyl transferase. Drugs such as PASA, INH, and procainamide are transformed by this mechanism. There is a bimodal distribution of acetylating ability of individuals. Patients can be classified into slow and fast acetylators. In the case of INH, slow acetylators come down with serious reactions such as peripheral neuropathy

Methylation: Mainly involves endogenous compounds metabolism and catalysed by methyltransferases which include phenylethanolamine-N-transferase (noradrenaline), imidazole-N-methyl transferase (histamine), catechol-O-methyltransferase (catechols) and S-methyltransferase (thiols)

Epinephrine and norepinephrine are metabolised to metanephrine and normetanephrine respectively.