BIOTRANSFORMATION (METABOLISM)

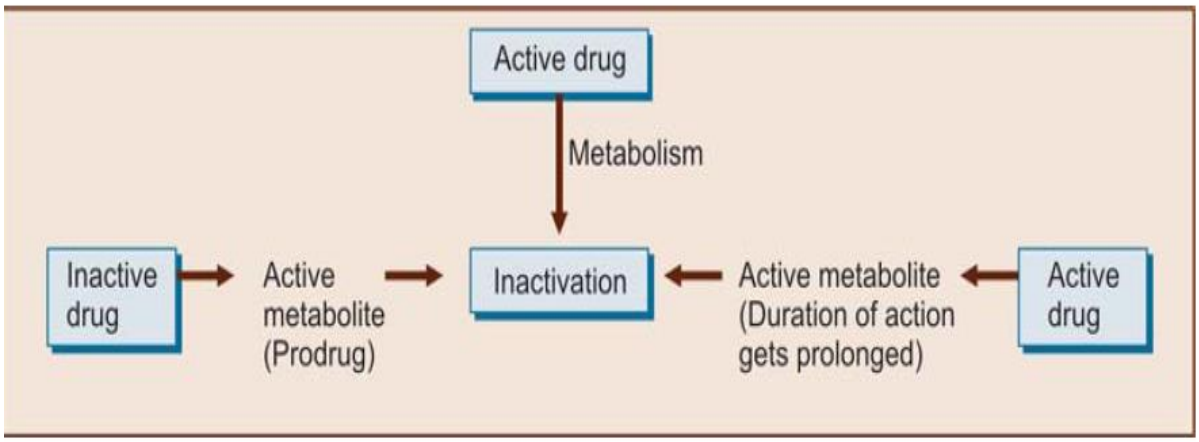
Biotransformation is the process of biochemical alteration of the drug in the body. Body treats most drugs as foreign substances and tries to inactivate and eliminate them by various biochemical reactions. These processes convert the drugs into more polar, water-soluble compounds so that they are easily excreted through the kidneys. Some drugs may be excreted largely unchanged in the urine, e.g. frusemide, atenolol.

Site The most important organ of biotransformation is the liver. But drugs are also metabolised by the kidney, gut, mucosa, lungs, blood and skin.

Table 3.2: Consequences of biotransformation

Active drug to inactive metabolite	*Active drug to active metabolite*	*Inactive drug to active metabolite (prodrug)*
e.g. Morphine Chloramphenicol	e.g. Primidone ▸ Phenobarbitone Digitoxin ▸ Digoxin Diazepam ▸ Oxazepam	e.g. Levodopa ▸ Dopamine Prednisone ▸ Prednisolone Enalapril ▸ Enalaprilat

Table 3.3: Biotransformation



Enzymes in biotransformation The biotransformation reactions are catalysed by specific
enzymes located either in the liver microsomes (microsomal enzymes) or in the cytoplasm and mitochondria of the liver cells and also in the plasma and other tissues (nonmicrosomal enzymes).
The chemical reactions of biotransformation
can take place in two phases .
1. Phase I (Non-synthetic reactions)
2. Phase II (Synthetic reactions

Phase I reactions convert the drug to a more polar metabolite by oxidation, reduction or hydrolysis. Oxidation reactions are the most important metabolising reactions, mostly catalysed by mono-oxygenases present in the

liver (Table 3.4). If the metabolite is not sufficiently polar to be excreted, it undergoes phase II reactions.

Phase II reactions In phase II reactions, endogenous water-soluble substances like glucuronic acid, sulfuric acid, glutathione or an amino acid combine with the drug or its phase I metabolite to form a highly polar conjugate which is inactive and gets readily excreted by the kidneys. Large molecules are excreted through the bile

Table 3.4: Important drug biotransformation reactions

Reactions	*Examples of drugs*
Oxidation	Phenytoin, Diazepam, Ibuprofen, Amphetamine, Chlorpromazine, Dapsone
Reduction	Chloramphenicol, Halothane
Hydrolysis	Pethidine, Procaine
Conjugation reactions	
Glucuronide conjugation	Chloramphenicol, Morphine
Acetylation	Sulfonamides, Isoniazid
Methylation	Adrenaline, Histamine
Glutathione conjugation	Paracetamol

Metabolism (or) Biotransformation (A.D.M.E)

Note:- Drug (lipid soluble) $\xrightarrow[(LS \rightarrow WS)]{\text{Biotransformation}}$ polar (water soluble) → kidney → Elimi

site:- Liver, kidney, gut mucosa, lungs, skin

Metabolism may result—

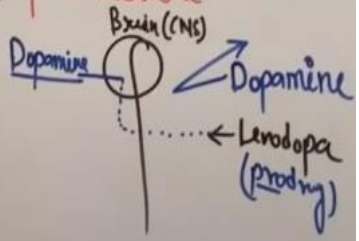
① Inactivation:- Paracetamol, Lidocaine, propranolol,

② Active metabolite from Active drug- Allopurinol → Alloxanthine (Active Drug)

Digitoxin → Digoxin, codeine → Morphine,

③ Activation of Inactive drug - (prodrug)* more active, stable, more B.A*

Levodopa → Dopamine, Enalapril → Enalaprilat, prednisone → prednisolone.



* Enzyme in Biotransformation-

① Microsomal Enzyme- present in liver microsome

Points:- ① They need NADPH and Oxygen.

Exa:- (1) NADPH- cytochrome P-450 reductase (74 types)

(2) Hemoprotein- cytochrome P-450 (CYP/P-450)

② Non microsomal- present in cytoplasm and mitochondria of liver cells.