• Biotransformation of drugs is defined as the chemical conversion of one form to another. The term is used synonymously with metabolism.

I) Inhibition:

A decrease in the metabolizing ability of an enzyme is called as enzyme inhibition.

The process of inhibition may be two types:

1. Direct inhibition
2. Indirect inhibition

1. Direct inhibition:

May result from interaction at the enzymic site, the net outcome being a change in enzyme activity. Direct inhibition can occur by one of the three mechanisms.

a. Competitive inhibition:

. Results when structurally similar compounds compete for the same site of an enzyme, such an inhibition due to substrate competition is reversible and can be overcome by high concentration of one of substrate.

Eg: Methacholine inhibits metabolism of acetyl choline by competing with it for cholinesterase.

b. Noncompetitive inhibition:

Arises when structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs. Since the interaction is not structure specific, metals like lead, mercury and arsenic and organophosphorus insecticides inhibit the enzymes noncompetitively.

Eg: Isoniazid inhibits the metabolism of phenytoin by the same enzymes.

c. Product inhibition:

Results when the metabolic product competes with the substrate for the same enzyme. Certain specific inhibitors such as Xanthine oxidase inhibitors (eg: allopurinol) and (MAO inhibitors (eg: phenelzine) also inhibit the enzyme activity directly.

Direct enzyme inhibition is usually rapid (a single dose of inhibitor may be sufficient) and therefore more important than enzyme induction.

2. Indirect inhibition:

Is brought about one of the two mechanisms:

a. Repression is defined as the decrease in enzyme content. It may be due to a fall in the rate of enzyme synthesis as affected by ethionine, puromycine and actinomycin D or because of rise in the rate of enzyme degradation such as by carbon

tetrachloride, carbon sulfide, disulfiram etc.

b. Altered physiology: due to nutritional deficiency or hormonal imbalance.

Enzyme inhibition is more important clinically than enzyme induction, especially for drugs with narrow therapeutic index.

Eg: Anticoagulants, antiepileptics, hypoglycemics, Since it results in prolonged pharmacological action with increased possibility of precipitation of toxic effects.

Inhibitors	Drugs with Decreased Metabolism
MAO inhibitors	Barbutyrates, tyramine
Coumarins	Phenytoin
Allopurinol	6-Mercaptopurine
PAS	phenytoin, hexobarbital

II. Induction:

The phenomenon of increased drug metabolizing ability of the enzymes (especially of microsomal monooxygenase system) by several drugs and chemicals is called as enzyme induction and the agents which bring about such an effect are known as inducers.

- Most enzymes inducers have following properties:

1. They are lipophyllic compounds
2. They are substrate for the induced enzyme system
3. They have long elimination half lives.

- Mechanisms involved in enzyme induction are:

1. Increased in both liver size and liver blood flow
2. Increase in both total and microsomal protein content
3. Increased stability of enzyme.

4. Increased synthesis of cytochrome P-450
5. Proliferation of smooth endoplasmic reticulum

• Two categories of inducers have been defined.

1. Phenobarbital type inducers include several drugs and pesticides which increase the rate of metabolism of a large number of drugs. It can increase enzyme activity up to 4 times.

2. Polycyclic hydrocarbon type inducers include 3-methyl cholanthrene and cigarette smoke.

3. Some drugs such as carbamazepine, meprobamate cyclophosphamide, rifampin, etc. stimulate their own metabolism, the phenomenon being called as auto-induction or self-induction.

Consequences of enzyme induction include:

1. Decrease in pharmacological activity of drugs
2. Increased activity where the metabolites are active
3. And altered physiological status due to enhanced metabolism of endogenous compounds such as sex hormones.

Inducers	Drugs with enhanced metabolism
Barbiturates	phenytoin, oral contraceptives
phenytoin	oral contraceptives
Alcohol	phenytoin, Phenobarbital

- [redacted]

Biliary excretion: Irreversible transfer of drug or drug metabolites from the plasma to the bile through the hepatocytes.