BIOTRANSFORMATION OF DRUGS

Q: What is biotransformation?

A: It is the chemical modification(s) on a chemical compound made by an organism.

→ Mineralization = a process where an organism produces an inorganic substance e.g. CO_2, NH_4^+ or H_2O.

∴ Catabolism is a form of biotransformation.

* Chemical alteration of nutrients, amino acids, toxins etc.

DRUGS

– transformation of drugs to render them polar or more polar.
i.e. Nonpolar ⟶ polar

– A drug is a XENOBIOTIC = A foreign chemical substance found within an organism that is not normally naturally produced by or expected to be present within that organism.

– Specifically, drugs e.g. antibiotics are xenobiotics in humans. They are "pollutants" in a human body.

– Removal of xenobiotics in the body is through "Xenobiotic metabolism."
= Deactivation + Excretion ← Urine, Feces, Breath, Sweat
⇓ mainly liver

Xenobiotic metabolism = Drug metabolism

Q. What is drug metabolism?

A. It is the biochemical modification of pharmaceutical substances (xenobiotics) with a concomitant conversion of lipophilic compounds to hydrophilic products.

"The rate of metabolism determines the duration and intensity of a drug's pharmacological action".

However; Although drug metabolism is meant to detoxify a drug, there are cases where its metabolites <u>can</u> themselves be the cause of toxicity e.g. Ethanol → Acetaldehyde.

* DRUG METABOLISM is divided into 3 phases;
  - I = Modification.
  - II = Conjugation.
  - III = Further modification and excretion.

PHASE I

- Includes oxidative, reductive and hydrolytic reactions. Also cyclization and decyclization.
- In these type of reactions, a <u>polar group</u> is either introduced or unmasked so the drug molecule becomes more soluble and can be excreted. (water)

(i) Oxidative

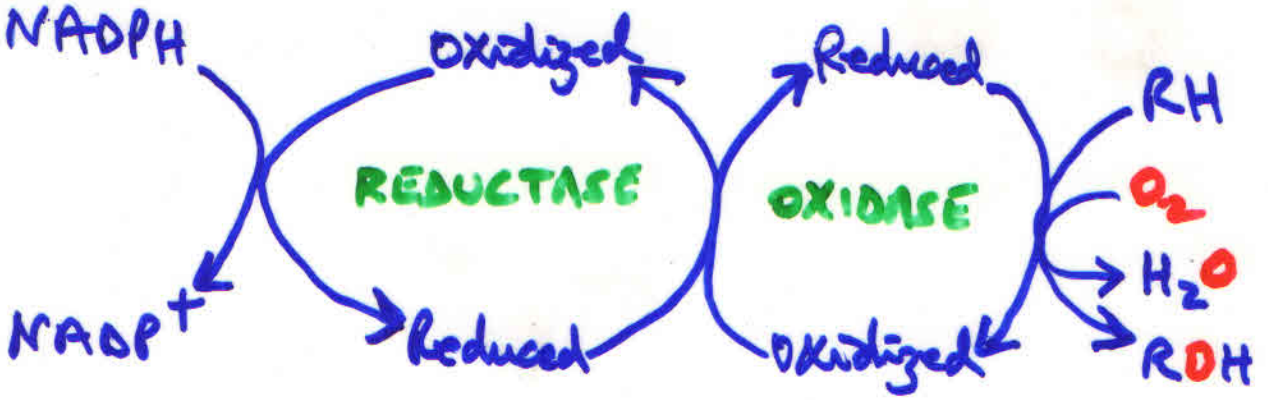
- Catalysed by a large and diverse group of enzymes = Cytochrome P450 system.
- The enzymes carry out mixed-function oxidations where one atom of O_2 is inserted into a drug (organic) substrate while the other oxygen atom is reduced to water = Hydroxylation reactions $RH \rightarrow ROH$.

$$RH + O_2 + NADPH + H^+ \longrightarrow ROH + H_2O + NADP^+$$

- In humans, over 57 genes have been identified that code for various CYP enzymes = isoenzymes.
- Drugs may increase (induction) or decrease (inhibition) the activity of various CYPs.
  * Drug interactions
- Human CYPs are primarily membrane-associated proteins located in the ER or in the IMM. They metabolize many endogenous and exogenous chemicals. Some are monosubstrates others are bisubstrates or multisubstrates.

* CYPs are monooxygenases or Hydroxylases
  ||
  Mixed-function Oxygenases = carry out monooxygenase reaction = Multicomponent reactions.

Reaction Mechanism of CYPs = Eucaryotic



CYPs = a complex of cytochrome P450 reductase (FAD and FMN binding) and cytochrome P450 oxidase (Fe^{2+}/Fe^{3+} binding).

NADPH ⟶ FAD ⟶ FMN ⟶ P450 oxidase ⟶ O_2

(FAD ⟶ FMN = P450 reductase)

Drugs: Phenothiazines, paracetamol, steroids.

(ii) Reductive

Occurs concomitantly with oxidative.
i.e. $O_2 \rightarrow H_2O$.

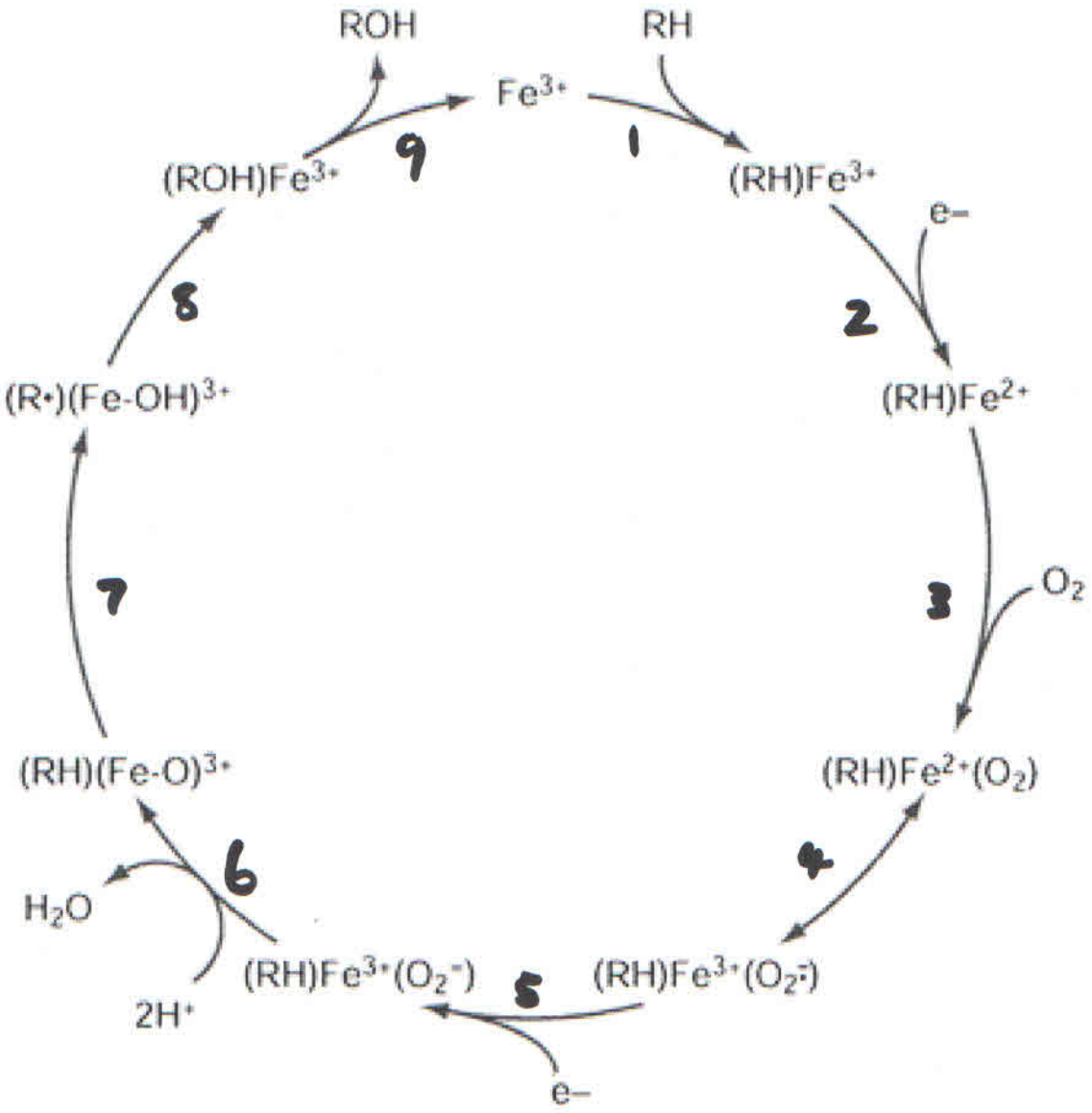
(iii) Hydrolysis

e.g. Esterases = Hydrolases ⇒ They split esters into an acid and an alcohol using water = Hydrolytic cleavage.

Acetylcholine $+H_2O$ ⟶ Acetate + choline

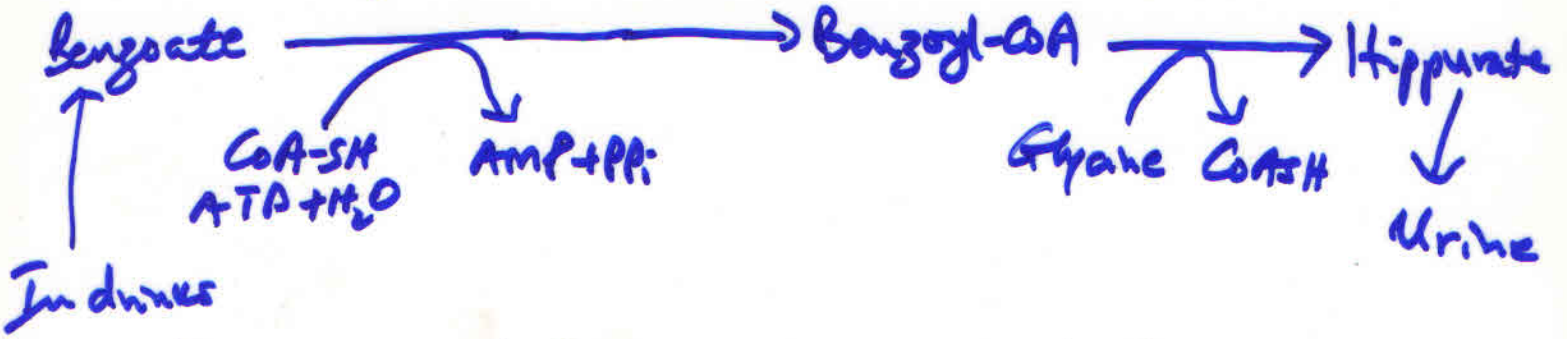
Acetylcholinesterase
"
Acetylhydrolase

REACTION MECHANISM OF CYTOCHROME P450 SYSTEM



e.g. Amidases - hydrolyze amides = Amidohydrolases

Benzoate degradation



e.g. Epoxide hydrolase = Epoxide hydratase
Converts epoxides to trans-dihydrodiols.

↑ degradation of aromatic compounds e.g. Anti-epileptic drug Phenytoin

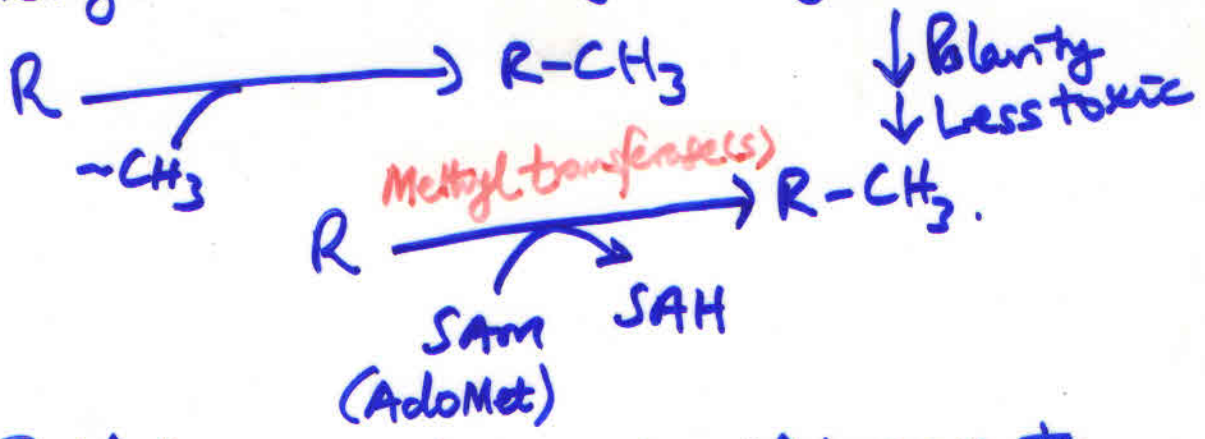
PHASE II

The metabolites are conjugated with charged groups (compounds) e.g. GSH, Sulfate, Glycine or glucuronate.

- Sites of conjugation include carboxyl, hydroxyl, amino and sulfhydryl groups.

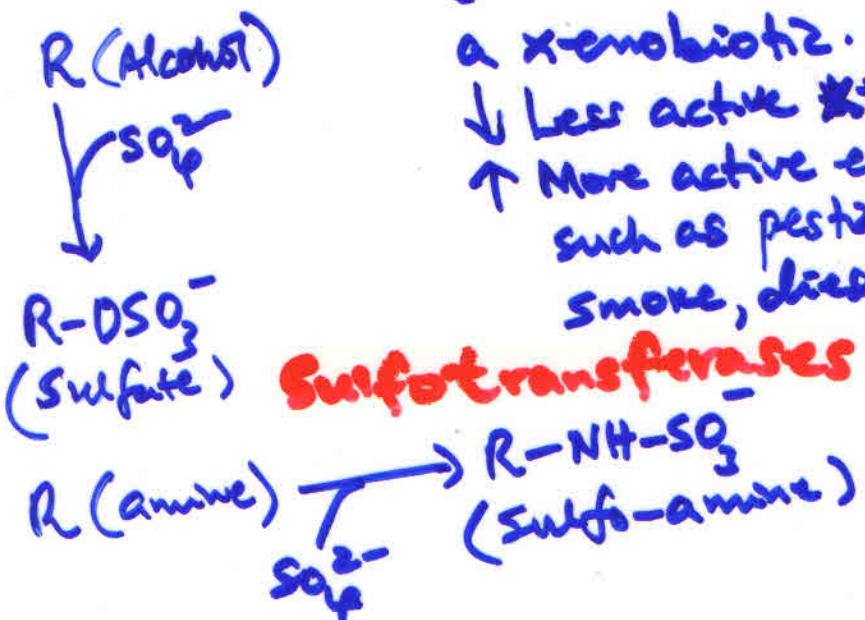
* Conversion of an active metabolite to an inactive metabolite (products) ↑ Mwt. ↑ Polar ⟹ more polar groups which are "easily" transported.
* Active metabolite = is an active form of a drug after it has been processed by the body i.e. has undergone biotransformation.
* An active metabolite may be a prodrug.

e.g. 1: Methylation = addition of a methyl group.



e.g. 2: Sulfation = addition of sulfate group to another molecule.

Coenzyme = 3'-phosphoadenosine-5'-phosphosulfate (PAPS). It transfers a sulfate to a xenobiotic.



↓ Less active xenobiotic
↑ More active e.g. Aromatic amines such as pesticides, hair dyes, smoke, diesel engine exhaust.

e.g. 3: Acetylation = addition of acetyl group.

$CH_3-C(=O)-$ N-Acyltransferases

Choloyl CoA + Glycine ⇌ CoA + Glycocholate

e.g. 4: Glucuronidation = attaching a chemical unit glucuronic acid = addition of glucuronic acid to a substrate.

Drugs, pollutants, bilirubin.

e.g. 5: Glutathione conjugation

$R + GSH \xrightarrow{GSTs} R\text{-}GSH$ ↑ Polarity

(Drug) = Electrophilic

e.g. 6: Glycine conjugation

Benzoate ⟶ Hippurate

PHASE III – Further modification + Excretion

Some xenobiotic conjugates may undergo further modification before excretion.

e.g. Glutathione conjugates ⟶ R-Cystine

Glut. Glycine

↓

Acetylated R

Tissues involved:

liver, GI tract, lungs, kidneys, skin, epithelial cells.

Q. What are the factors that affect drug metabolism?

1. ~~Duration~~
2. Intensity } ↓ pharmacological action

* Depends on the rate they are metabolized to inactive products.

↑ Enzyme induction = ↑ Duration ↑ Intensity

* Cytochrome P450 monooxygenase system is the most important pathway.

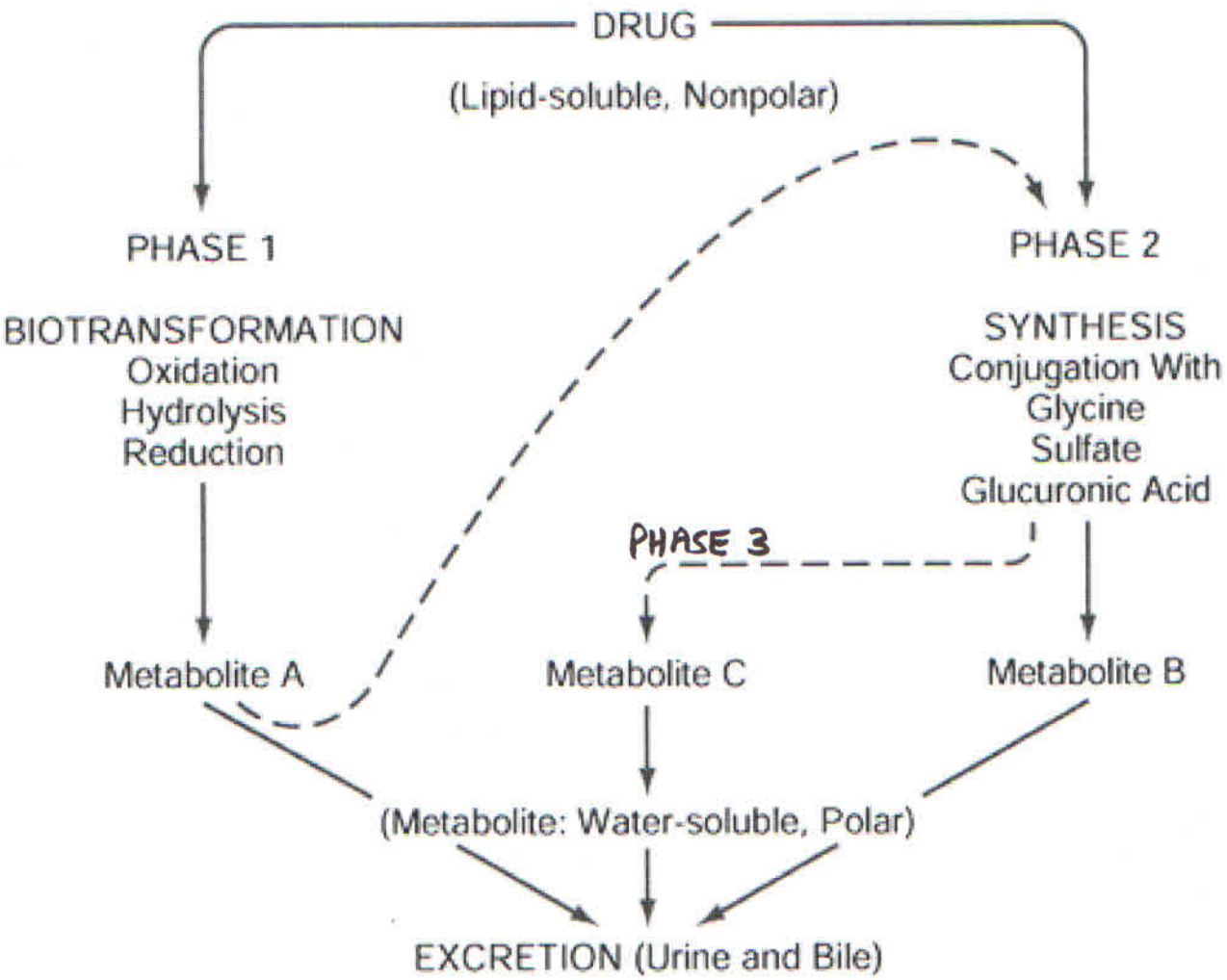
Also.

1. Age.
2. Individual variation.
3. Gender.
4. Nutrition.
5. Liver.
6. CYP 1–30% deficiency (Ethnic differences).
7. Pathological factors.

PHASE II REACTIONS

Mechanism	Involved enzyme[8]	Co-factor	Location
methylation	methyltransferase	S-adenosyl-L-methionine	liver, kidney, lung, CNS
sulphation	sulfotransferases	3'-phosphoadenosine-5'-phosphosulfate	liver, kidney, intestine
acetylation	• N-acetyltransferases • bile acid-CoA:amino acid N-acyltransferases	acetyl coenzyme A	liver, lung, spleen, gastric mucosa, RBCs, lymphocytes
glucuronidation	UDP-glucuronosyltransferases	UDP-glucuronic acid	liver, kidney, intestine, lung, skin, prostate, brain
glutathione conjugation	glutathione S-transferases	glutathione	liver, kidney
glycine conjugation	acetyl Co-enzyme As	glycine	liver, kidney

SCHEME : GENERAL BIOTRANSFORMATION OF DRUGS



Q. What are the general characteristics of xenobiotics?

- Lipophilic.
- Penetrate membranes by diffusion.
- Transported in blood by lipoproteins.

Q. How do humans generally eliminate xenobiotics?

- Make them water soluble !!!!!
- Excrete them.

PHASE I – Polar groups introduced = modify.

II – Covalent conjugation to endogenous compounds.

III – Increase their molecular weight, make them more polar for ease of excretion.

→ Sugars, amino acids, inorganic ions.

NB

1. Xenobiotic metabolism may either decrease or increase toxicity;
   a) Parent compound toxic / Metabolites non-toxic.
   b) Parent compound non-toxic / Metabolites toxic.

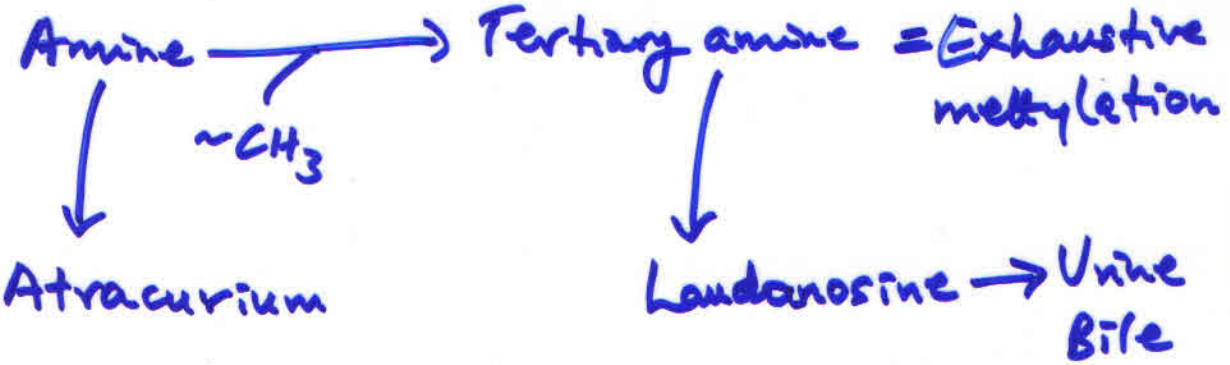
2 outcomes / Possibilities

1. Compound is more toxic than original.
   = ACTIVATION
2. Compound is less toxic than original.
   = DETOXIFICATION

Further:

1. The pattern of drug metabolism is common to all animal species.
2. It is biphasic < Stepwise biotransformation.
   Synthetic reactions.
   Phase I – Biotransformation < Oxidation (hydroxylation)
   Hydrolysis
   Reduction
   Phase II – Synthesis = conjugation of a drug or its metabolite with an endogenous compound e.g. Glycine, sulfate, glucuronic acid.
3. Biotransformation is a result of drug interaction with <u>enzymes</u> present in plasma, cytoplasm, mitochondria and the ER.
   Phase I = mainly in the ER
   " <u>II</u> = mainly in cytoplasm = an aqueous environment.
4. Substrates of Phase I reactions are seldom substrates of Phase <u>II</u> reactions – <u>but</u> products of Phase I metabolism are <u>often</u> substrates of Phase <u>II</u> metabolism.
5. Genetic factors contribute greatly to both qualitative and quantitative differences in drug metabolism among species/individuals. e.g. Some ethnic groups show intolerance to e.g. Alcohol.

6. A few drugs are metabolized by non-enzymatic means = non-enzymatic metabolism e.g. Atracurium, a neuromuscular drug is inactivated in plasma by <u>Hoffman elimination</u> at physiological pH and temperature.



7. Drug metabolizing enzymes are microsomal or non-microsomal (cytoplasmic). Cytoplasmic ~~drugs~~ enzymes are <u>not</u> inducible.

8. High Mwt. conjugates → Bile
   low M.Wt. conjugates → Urine
   *Unconjugated drug/metabolite → ↑ Toxicity
   *Glucuronidation – most common and important.

<u>READ FURTHER</u>.

1. Google "Xenobiotic metabolism"
   ↓
   On 1st page, click (ranked no. 7); "Drug metabolism – SlideShare"
   Read thru' pages 1–69. = A good summary of biotransformation of drugs – with specific drugs!