DETOXIFICATION (Short note)

BIOTRANSFORMATION OF XENOBIOTICS (short answer)

- Detoxification – series of biochemical reactions occurring in the body to convert foreign (toxic) compounds to non toxic or less toxic & more easily excretable forms.

Biotransformation

→ It removes unessential nutrients (food, oxygen etc) in to substances required for normal body functions.

eg: phenoxybenzamine.

- Xenobiotics are compounds which may be
  - → accidentally ingested
  - → taken as drugs
  - → compounds produced in the body by bacterial metabolism

→ Human body has a well developed capacity to biotransform most xenobiotics as well as body waste.

eg. bilirubin

→ Liver plays the most important role in biotransformation

→ The compounds that are detoxified include:

a) compounds accidentally ingested like preservatives, food additives and adulterants

b) Drugs which are taken for therapeutic purposes.

c) compounds produced in the body which are to be eliminated.

eg: bilirubin, steroids

d) Compounds produced by bacterial metabolism

eg: amines produced by decarboxylation of amino acids

Enzyme systems.

→ cytochrome P450 enzyme family is involved in biotransformation.

→ These are heme containing membrane proteins, localised in smooth endoplasmic reticulum of liver.

→ Also called mixed function oxidases.

$$R-H + O_2 + NADPH \longrightarrow R-OH + H_2O + NADP^+$$

R-H : Represent xenobiotics

Requires:
- P450 flavoprotein – NADPH.
- P450 reductase
- Molecular O_2

Metabolise ~ 50% of drugs, carcinogens & pollutants. Important.

Phases of Detoxification process

→ Three phases may occur together or separately

- Phase One Reactions: Alteration of the toxic substance.
- phase Two reactions: Involves conjugation of the altered toxic substance.
- Phase Three reactions: Products of phase II further metabolised.

→ Generally detoxification of compound involves phase I and phase II reactions.

Phase One: modify / alter foreign molecule by adding a functional group

→ Results in formation of compounds with decreased toxicity (detoxification) and sometimes increased toxicity (entoxification)

eg: methanol → formic acid.

Phase one reactions include: Hydroxylation, oxidation, reduction, hydrolysis, dealkylation etc.

Phase I Reactions (Question).

1. Oxidation reactions:-

→ Aliphatic or aromatic hydroxylation

eg: Toluene → benzyl alcohol
mixed Function oxidase

→ Oxidation and detoxification of alcohol

Alcohol → aldehyde
alcohol dehydrogenase

Aldehyde → acid
aldehyde dehydrogenase

2. Reductive Reactions

Nitro compounds.

Nitro benzene → amine.

3. Hydrolysis:

Esters, amines, hydrazine, amides etc.

Aspirin → salicylic acid + acetic acid.

Phase II Reactions.

Conjugation:

A foreign compound combine with a conjugating agent and get converted into soluble non toxic derivatives which are easily excreted.

→ Occurs mainly in liver.

→ Conjugation reaction occurs with a xenobiotic or its metabolite after phase I reaction.

→ May occur either directly or after phase I reaction (oxidation, reduction etc)

→ The effect of conjugation is to make the compound more water soluble (polar)

and therefore, more easily excreted in the urine or bile.

Conjugating Agent	Active form.
Sulphate	PAPS.
Acetic Acid.	Acetyl CoA.
Methyl group.	SAM.
Glucuronic acid.	UDP Glu. Acid.
Cysteine	Glutathione.
Glycine.	

→ Most common phase two reactions.

Glucuronic acid.

Enzyme: UDP glucuronyl transferase

UDP Glucuronic acid + R-OH
⟶ R-Glucuronide + UDP.

Sulphate:

• Enzyme: sulfokanesferase.

→ Phenol + PAPS ⟶ Phenyl sulfate + PAP.

→ PAPS - 3'phospho adenose - 5 phospho sulfate.

Glycine.

→ Benzoic acid + glycine → Hippuric acid.

Methylation

→ SAM is the methyl donor and enzyme is methyl transferase.

→ Epinephrine ⟶ metanephrine

Glutamine

phenyl acetic acid + Glutamine → phenyl acetyl glutamine

Acetylation

→ Conjugation with acetic acid

eg: Detoxification of drugs like sulfanilamide, isoniazide etc.

In some cases phase II reactions may further be metabolised by phase III reactions.

Phase III

→ Not very common.

→ further conjugation with glutathione in certain cases.

Environmental toxins (1 mark)

these are cancer - causing chemicals and endocrine disruptors.

→ Both naturally occuring and human made.

1 mark • Naturally occurring environmental toxins are: lead, mercury, radon, formaldehyde, benzene and cadmium.

1 mark • Human made chemicals: BPA phthalates and pesticides.

In toxic doses, all of these compounds can negatively affect human health

→ Cancer : radon, formaldehyde, benzene

→ Endocrine disruptors : BPA, pesticides, phthalates

→ Organ failure or developmental problems:
lead, mercury, cadmium.