Detoxification is the process by which toxic compounds are converted to less toxic, and eventually non-toxic, substances. These are then eliminated from the body through urine and bile.
Detoxification occurs in liver

- Toxic endogenous catabolites
  - ammonia
  - bilirubin

- Toxic exogenous xenobiotics
Xenobiotics are strange compounds those enter the body. They can come as
1. food additives,
2. Preservatives
3. Drugs
Toxins due to infection & contaminated food items
In the large intestine the following unwanted compounds are produced.
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- Indole ➔ tryptophan
- Cadaverine ➔ lysine
- Tyramine ➔ tyrosine
- Phenol ➔ phenylalanine
TYPES OF REACTIONS IN DETOXIFICATION

1. HYDROLYSIS
2. OXIDATION
3. REDUCTION
4. CONJUCATION
MECHANISM OF DETOXIFICATION

❖ Metabolism of xenobiotics
  – Phase I- oxidation, reduction & hydrolysis
  – PHASE II- conjugation involving
    1. Glucaronic acid
    2. Amino acid
    3. Glutathione
    4. Sulphate
    5. Acetate
    6. CH3(methyl) group
OXIDATION

- **ALCOHOLS, ALDEHYDES, AMINES, AROMATIC HYDROCARBONS & SULPHUR**

- **ALCOHOL** :- aliphatic & aromatic alcohols undergo oxidation to acids.

  $$\text{CH}_3\text{OH} \rightarrow \text{HCOOH}$$

  methanol $\rightarrow$ formic acid
C₂H₅OH → CH₃COOH
ethanol → acetic acid

C₆H₅CH₂OH → C₆H₅COOH
benzyl alcohol → benzoic acid
**ALDEHYDES:** oxidised acids

C₆H₅CHO → C₆H₅COOH

Benzaldehyde → Benzoic acid

C₃Cl₃CHO → CCl₃COOH

Chloral → Trichloroacetic acid
AMINES & THEIR DERIVATIVES

RCH2NH2 → RCOOH + H2N-CO-NH2
ALIPHATIC AMINE  aliphatic acid + urea

Aromatic aminoacids → phenols
C6H5NH2 → HO-C6H4-NH2
Aniline  p- amino phenol
AROMATIC HYDROCARBONS :-

- Benzene oxidized to mono, di- and trihydroxy phenols.

  benzene → phenol + quinol, catechol + hydroxyquinol
SULFUR COMPOUNDS: -
- Organic sulfur oxidized sulfuric acid

DRUGS: -
- Meprobamate oxidized HO-meprobamate

excrete urine
ROLE OF CYTOCHROME P<sub>450</sub>

- OXIDATION reactions of detoxification catalyzed by monooxygenase or cyt. P<sub>450</sub> (mixed function oxidase)- in microsomes.
- P450 refers absorption peak (at 450nm) exhibited by the enzyme when exposed to carbon monoxide.
- Reactions of cyt. P450 involves the addition of OH group to aliphatic or aromatic compounds.

RH + O$_2$ + NADPH $\rightarrow$ ROH + H$_2$O + NADP
**SALIENT FEATURES OF CYT. P450**

1. Multiple forms exist 20-200, 6 species worked in detail
2. Hemoproteins, heme as prosthetic group
3. Highest concentration in microsomes of liver, in adrenal gland & mitochondria.
4. NADPH dependent action
5. Phospholipid- phosphatidyl choline is a constituent of cyt. P450. which is necessary for the action of enzyme.
6. Inducible enzyme- its synthesis increases by the administration of drugs such as phenobarbital.

REDUCTION

C₆H₂OH(NO₂)₃ → C₆H₂OH(NO)NH₂
Picric acid → picraminic acid

CCl₃.CH(OH)₂ → CCl₃CH₂OH
Chloral → trichloroethanol

C₆H₅NO₂ → C₆H₅NH₂
Nitrobenzene → aminobenzene
HYDROLYSIS

- Hydrolysis of ester, glycoside, & amide imp. In the metabolism of xenobiotics.

Aspirin $\xrightarrow{\text{H}_2\text{O}}$ salicylic acid + acetic acid

Acetanilide $\xrightarrow{\text{H}_2\text{O}}$ aniline + acetic acid

$(\text{C}_3\text{H}_7\text{O})_2\text{POF} \xrightarrow{\text{H}_2\text{O}} (\text{C}_3\text{H}_7\text{O})_2\text{PO(OH)} + \text{HF}$

DIISOPROPYL FLUORO DIALKYL PHOSPHATE

DIALKYL PHOSPHATE
ATROPINE → tropic acid + tropine

Procaine → p-aminobezoic acid + diethylaminoethanol
CONJUGATION

- Xenobiotics + conjugates

  less toxic/ easily excretable compounds

Xenobiotics + substances produced in body.

- Conjugation may occur directly or after phase I reaction.
8 different conjugating agents identified in the body

1. Glucuronic acid
2. glycine
3. Cysteine (of glutathione)
4. Glutamine
5. Methyl group
6. Sulphate
7. Acetic acid
8. thiosuphate
X-OH + UDP-glucuronic acid

\[ \text{UDP-glucuronyl transferase} \]

XO- glucuronide + UDP

- Certain drugs induce the glucuronyl transferase & This increase glucuronyl formation
Conjugation may occur with compounds containing hydroxyl, carbonyl, suhydril or amino group.

Eg;

Phenol + UDP-glucuronic acid

\[ \text{Phenyl glucurononide} + \text{UDP} \]
Bezoic acid + UDP-glucuronic acid

Bezyl glucuronide + UDP

Bilirubin + UDP-glucuronic acid

Bilirubin di-glucuronide
GLYCINE:

Benzoyl Co A + Glycine → Hippuric acid + CoA SH

Phenyl acetic acid + Glycine → Phenylaceturic acid

Cholic acid + Glycine → Glycocholic acid
CYSTEINE:

R-X + Glutathione

HX

GSH Transferase

R-SG

Gamma glutamyl transpeptidase

glutamate

Cysteinylglycine

Cysteinylglycinase

glycine

R-Cysteine

N-acetyltransferase

Acetyl CoA

Mercapturic acid

CoA
GLUTAMINE:

Phenyl acetic acid + Glutamine → Phenylacetylglutamine

METHYL GROUP OF S-ADENOSYL METHIONINE:

SAM + X-OH → S-Adenosylhomocysteine + XO-CH3

SULFATE:

Sulfotransferase

Phenol + PAPS → Phenyl sulfate + Phosphoadenosylphosphate
ACETIC ACID:
Sulfanilamide + Acetyl CoA → Acetyl sulfanilamide + CoASH

THIOSULFATE:
Cyanide + Sodium thiosulfate → Thiocyanate + Sodium sulfate