Metabolism of Xenobiotics
(Detoxification)

Xenobiotic is a compound that is foreign to the body. It may include drugs, chemical carcinogens, polychlorinated biphenyls (PCBs) and insecticides

the process of detoxification with examples.

Detoxification: It is a process by which toxic compounds are converted into less toxic and easily extractable forms.

Sites of Xenobiotic Metabolism

i. **Liver:** It is a major site for detoxification.

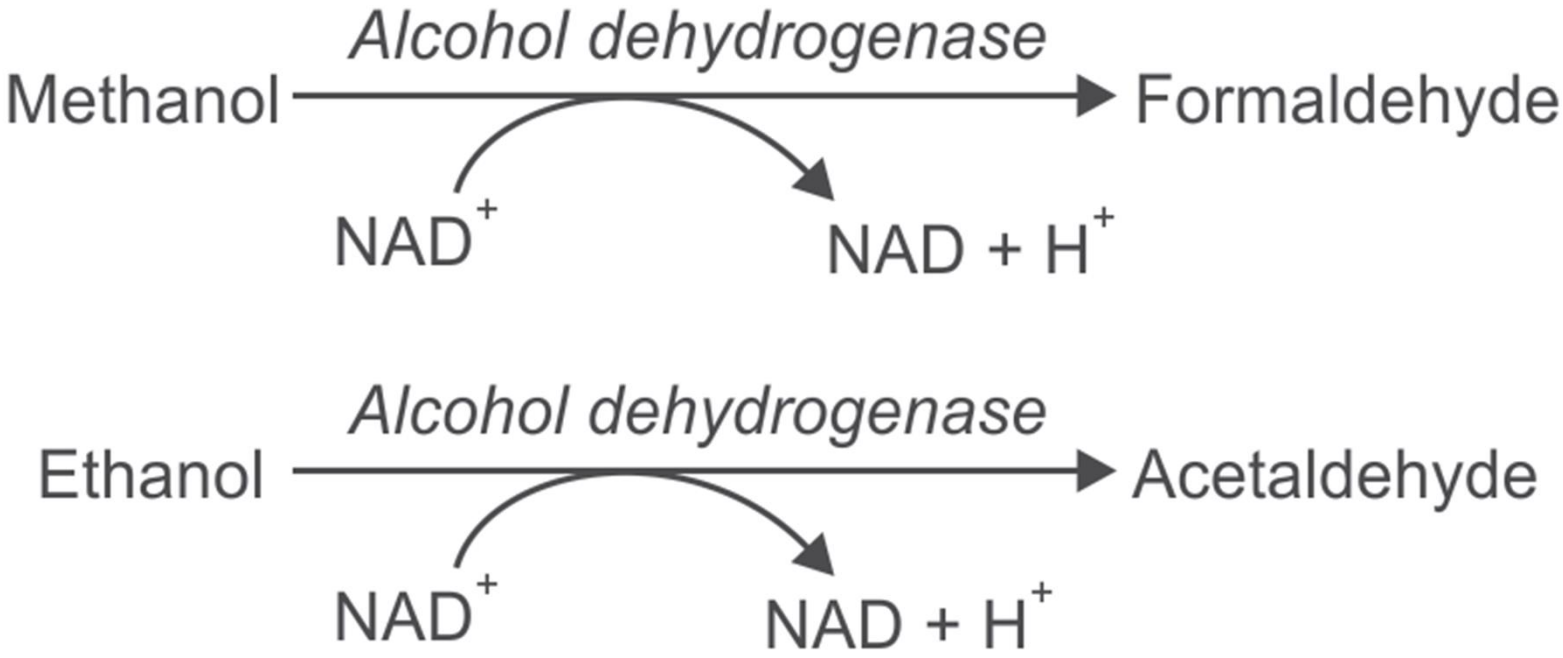
ii. **Non-hepatic sites:** Intestinal mucosa, kidney, lung, gastrointestinal (GI) tract and placenta

Xenobiotic are Detoxified in Two Phases

Phase 1

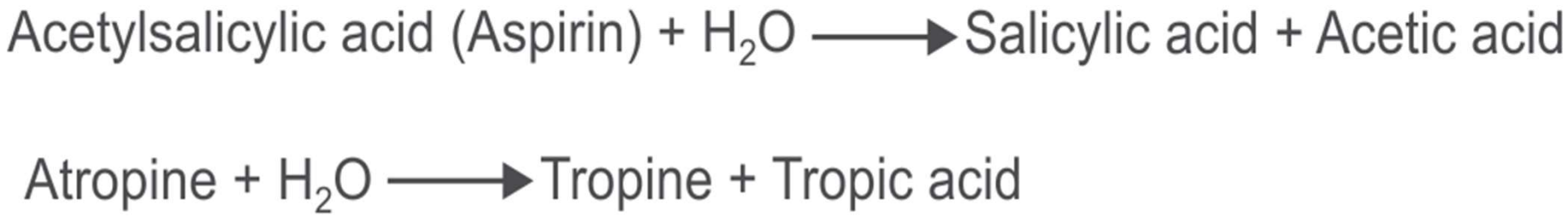
Attachment of new functional groups or transformation of existing functional groups by hydrolysis, oxidation, reduction, etc.

i. **Oxidation:** It is the removal of hydrogen or addition of oxygen. Oxidation is carried out by CYP450 system, alcohol dehydrogenase, aldehyde dehydrogenase and monoamine oxidase**.** For example,



ii. **Reduction:** It is the removal of oxygen and addition of hydrogen or electrons.
For example,

iii. **Hydrolysis:** It is the breakdown of compounds by addition of water.
For example,



Phase 2

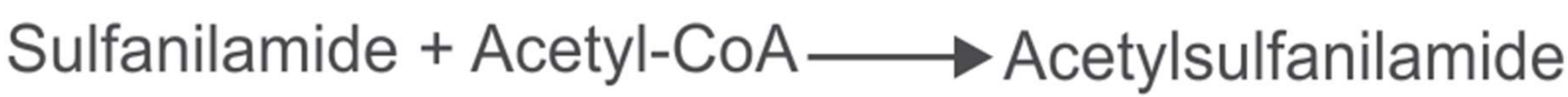
Conjugation: The existing functional group of a compound is conjugated by glucuronidation, acetylation, methylation, attachment of an amino acid or other mechanisms. Most of the conjugated compounds are water soluble and can be easily excreted.

i. **Glucuronidation:** The compound is conjugated with glucuronic acid.
For example,

ii. **Conjugation with glycine.**
For example

iii. **Acetylation.**

For example



iv. **Methylation.**

For example

v. **Sulfation.**

For example

compounds detoxified

i. Indole.
ii. Aspirin.
iii. Paracetamol.
iv. Cyanide.
v. Phenobarbital.
vi. Isoniazid.

i. **Indole:** Undergoes deamination and decarboxylation to produce indolepyruvate and finally indoleacetate.

ii. **Aspirin:** It is detoxified by hydrolysis.

iii. **Paracetamol (acetaminophen):** It is detoxified by both glucuronidation and sulfation. Paracetamol can also be detoxified by CYP2E1 to produce N-acetyl-p-benzoquinoneimine (NAPQI), which conjugates with glutathione (GSH) to form inactive compound.

iv. **Cyanide:** Conjugates with thiosulfate to form less toxic thiocyanate.

v. **Phenobarbital:** Detoxified by hydroxylation by CYP450 group of monooxygenases in the liver followed by glucuronidation.

vi. **Isoniazid (antitubercular drug):** Undergoes acetylation. Genetic variations in the enzymes (acetyl transferases) lead to slow and fast acetylators.

the role of glutathione in detoxification mechanism.

i. Glutathione (γ-glutamyl-cysteinylglycine) is a tripeptide consisting of glutamic acid, cysteine and glycine.

ii. Carcinogens (R) are conjugated with GSH, a reaction catalyzed by glutathione S-transferase to form glutathione conjugate, which is further metabolized and excreted as mercapturic acid (Fig. 20.1).