Detoxification

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- Increasingly, humans are subjected to exposure to various foreign chemicals **(xenobiotics)**—drugs, food additives, pollutants, etc.

- Knowledge of the metabolism of xenobiotics is basic to a rational understanding of pharmacology and therapeutics, pharmacy, toxicology, management of cancer and drug addiction.

Humans Encounter Thousands of Xenobiotics That Must Be Metabolized before Being Excreted

- A **xenobiotic** is a compound that is foreign to the body. The principal classes of xenobiotics of medical relevance are drugs, chemical carcinogens, and various compounds that have found their way into our environment by one route or another, such as certain insecticides.

- More than 200,000 manufactured environmental chemicals exist. Most of these compounds are subject to metabolism (chemical alteration) in the human body, with the liver being the main organ involved; occasionally, a xenobiotic may be excreted unchanged. At least 30 different enzymes catalyze reactions involved in xenobiotic metabolism.

- It is convenient to consider the metabolism of xenobiotics in two phases. In **phase 1,** the major reaction involved is **hydroxylation,** catalyzed by members of a class of enzymes referred to as **monooxygenases** or **cytochrome P450s.** Hydroxylation may terminate the action of a drug, though this is not always the case.

- In **phase 2,** the hydroxylated or other compounds produced in phase 1 are converted by specific enzymes to various polar metabolites by **conjugation** with glucuronic acid, sulfate, acetate, glutathione, or certain amino acids, or by **methylation.**

- The overall purpose of the two phases of metabolism of xenobiotics is to increase their **water solubility (polarity)** and thus **excretion** from the body. Very hydrophobic xenobiotics would persist in adipose tissue almost indefinitely if they were not converted to more polar forms. In certain cases, phase 1 metabolic reactions convert xenobiotics from **inactive** to **biologically active** compounds.

- In other cases, additional phase 1 reactions (eg, further hydroxylation reactions) convert the active compounds to less active or inactive forms prior to conjugation. In yet other cases, it is the conjugation reactions themselves that convert the active products of phase 1 reactions to less active or inactive species, which are subsequently excreted in the urine or bile. In a very few cases, conjugation may actually increase the biologic activity of a xenobiotic.

- The term "**detoxification**" is sometimes used for many of the reactions involved in the metabolism of xenobiotics. However, the term is not always appropriate because, as mentioned above, in some cases the reactions to which xenobiotics are subject actually increase their biologic activity and toxicity.

Conjugation Reactions Prepare Xenobiotics for Excretion in Phase 2 of Their Metabolism

- In phase 1 reactions, xenobiotics are generally converted to more polar, hydroxylated derivatives. In phase 2 reactions, these derivatives are conjugated with molecules such as glucuronic acid, sulfate, or glutathione. This renders them even more water-soluble, and they are eventually excreted in the urine or bile.

Five Types of Phase 2 Reactions

- Glucuronidation.
- Sulfation.
- Conjugation with Glutathione.
- Acetylation.
- Methylation.

The Activities of Xenobiotic-Metabolizing Enzymes Are Affected by:

- Age.
- Sex.
- Other Factors:
- The activities of these enzymes may differ substantially among species.
- genetic factors.

Responses to Xenobiotics Include Pharmacologic, Toxic, Immunologic, & Carcinogenic Effects:

- The first is **cell injury** (cytotoxicity), which can be severe enough to result in cell death.
- Second, the reactive species of a xenobiotic may bind to a protein, altering its **antigenicity.**
- Third, reactions of activated species of chemical carcinogens with **DNA** are thought to be of great importance in **chemical carcinogenesis.**

- Certain xenobiotics are very toxic even at low levels (eg, cyanide). On the other hand, there are few xenobiotics, including drugs, that do not exert some toxic effects if sufficient amounts are administered.