

# Biotransformation

- **Metabolism:** the sum of all chemical reactions that occur within a living cell. The purpose of cellular metabolism is to maintain the **homeostasis** of the cell within a **population** of other cells.
- **Homeostasis** a state of balance among all the body systems needed for the body to survive and function correctly.
- **Homeostasis** is any self-regulating process by which an organism tends to maintain stability while adjusting to conditions that are best for its survival. If homeostasis is successful, life continues; if it's unsuccessful, it results in a disaster or death of the organism
- **Metabolism** is usually divided into two categories: Anabolism and Catabolism
- **Anabolism** is the **synthesis of larger** molecules **from smaller one**, e.g., The synthesis of a **protein from its amino acid building blocks**. Require: input of energy
- **Catabolism** refers to the **degradation of larger molecules to smaller ones**, e.g., the breakdown of starch to glucose. Produce: energy

# Metabolic Pathways

**Anabolic:** Small molecules are assembled into large ones. *Energy is required.*



**Catabolic:** Large molecules are broken down into small ones. *Energy is released.*

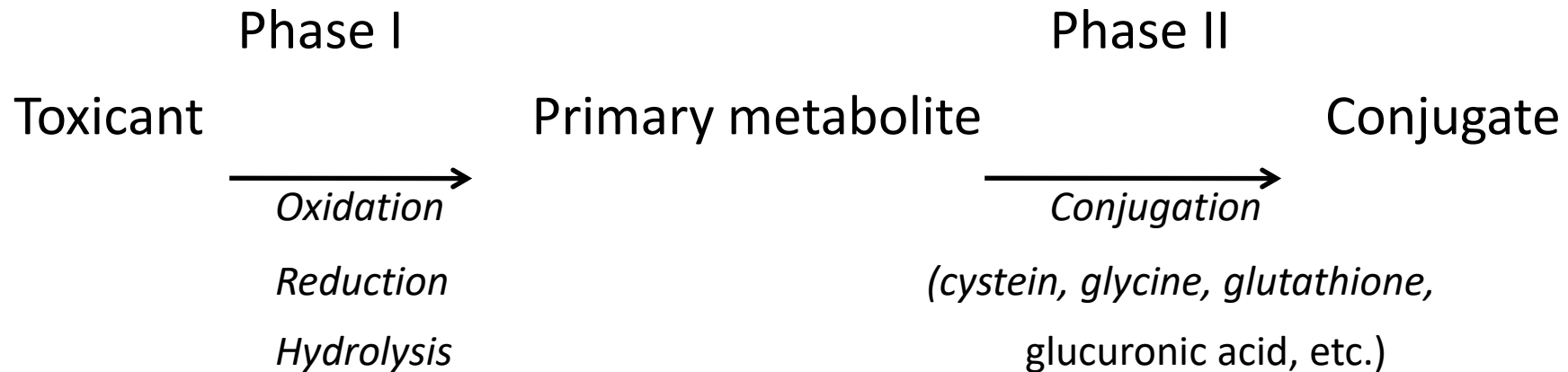


# Biotransformation

- Following their absorption into a mammal, Environmental toxicants (xenobiotics) are subjected to metabolic conversion in the body, resulting in structural changes. This metabolic process is called ***biotransformation***
- It may occur in any of several body tissues and organs, including skin, lung, intestine, liver, and kidney.
- The **liver** carries out the majority of the chemical reactions because it contains a large number of **nonspecific enzymes** capable of biotransformation of xenobiotics.
- The enzymes involved in the biotransformation are named ***mixed-function oxidase (MFO)***, commonly known as **cytochrome P450 or CYP450**.
- Biotransformation in the liver is thus a critical process in the body's defense against the toxic effects of a wide variety of xenobiotics.
- Without this capability, toxicants would eventually **accumulate** and produce **death**

# Types of Biotransformation

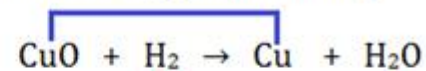
- The process of xenobiotic biotransformation consists of two phases: Phase I and Phase II
- Phase I: oxidation, reduction, and hydrolysis
- Phase II: composed of conjugation reactions



# Types of Biotransformation

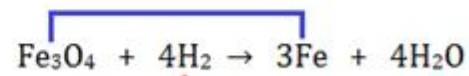
- **Oxidation** describes the **loss** of electrons / hydrogen or **gain** of oxygen / **increase** in oxidation state by a molecule, atom or ion
- **Reduction** describes the **gain** of electrons / hydrogen or a **loss** of oxygen / **decrease** in oxidation state by a molecule, atom or ion
- **Hydrolysis** is a chemical reaction during which one or more water molecules are split into hydrogen and hydroxide ions which may go on to participate in further reactions.

Removal of oxygen [Reduction]



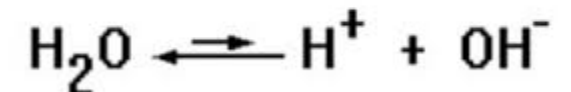
Addition of oxygen [Oxidation]

Removal of oxygen [Reduction]



Addition of oxygen [Oxidation]

Hydrolysis



- Polar ---hydrophilic---water loving---lipid insoluble



and philic means loving.. so polar means water soluble...and non lipid soluble... i always



# Phase I Reaction

- Phase I is a catabolic reactions that break down the toxicant into various components
- In most cases these reactions make the chemical less toxic, more water soluble, and easier to excrete
- In phase II, the final product is usually water soluble and, therefore, easier to excrete from the body.
- It is important to understand that these Phase I and II reactions may occur simultaneously or sequentially.

# Mechanism of Biotransformation: Phase I

- A **lipophilic foreign chemical** is first oxidized in a *Phase I* reaction so that a functional group, such as  $\text{-OH}$ ,  $\text{-NH}_2$ ,  $\text{-COOH}$ , or  $\text{-SH}$ , is introduced into the molecule, forming a product called a **primary metabolite**
- A **slightly increase in hydrophilicity usually occurs as result of the reaction**



# Mechanism of Biotransformation: Phase II

- Phase II reactions, are synthetic or conjugation processes
- A primary metabolite from Phase I biotransformation, or a parent xenobiotic, reacts with an **endogenous substance** (glycine, cysteine, GSH, glucuronic acid, sulfates) and **form a conjugate**
- Most Phase II biotransformation results in substantial increase in xenobiotic **hydrophilicity**, thus promoting the **excretion of xenobiotics**

# Types of Biotransformation

- A chemically ***conjugated system*** is a system of atoms covalently bonded with alternating single and multiple (e.g. double) bonds (e.g.,  $\text{C}=\text{C}-\text{C}=\text{C}-\text{C}$ ) in a molecule of an organic compound.
- This system results in a general delocalization of the electrons across all of the adjacent parallel aligned p-orbitals of the atoms, which increases stability and thereby lowers the overall energy of the molecule.

# Characteristics of Biotransformation

- The NADPH-cytochrome P450 system, commonly known as the ***mixed-function oxygenase system (MFO system)***, is the most important enzyme system involved in Phase I biotransformation
- Phase I enzymes localized in the smooth endoplasmic reticulum of cells of most mammalian tissues, is particularly **abundant in the liver**
- Most Phase II enzymes are located in the **cytoplasmic matrix**
- Required cofactors: NADH, NADPH, O<sub>2</sub>, glucose 1-phosphate, glucuronate, ATP, cysteine, and GSH

# Characteristics of Biotransformation

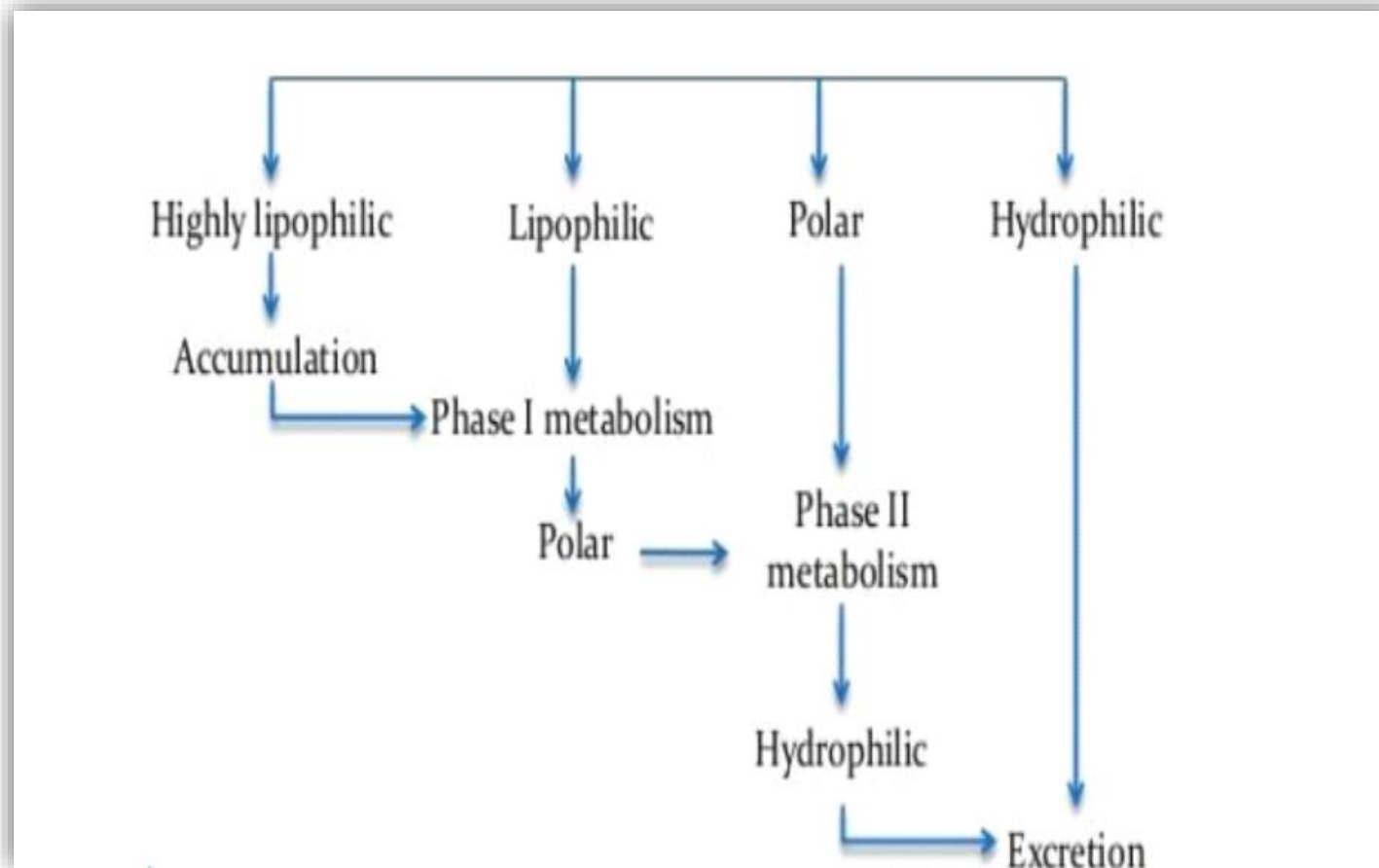
- **Adenosine-5'-triphosphate (ATP)** is a multifunctional nucleotide, and is most important in cell biology as a coenzyme that is the "molecular unit of currency" of intracellular energy transfer. In this role, ATP transports chemical energy within cells for metabolism.
- **Cysteine** is an  $\alpha$ -amino acid with the chemical formula  $\text{HO}_2\text{CCH}(\text{NH}_2)\text{CH}_2\text{SH}$ . It is a non-essential amino acid, which means that humans can synthesize it.
- **Glutathione (GSH)** is a tripeptide. It contains an unusual peptide linkage between the amine group of cysteine and the carboxyl group of the glutamate side chain. Glutathione, an antioxidant, protects cells from toxins such as free radicals.

# Consequence of Biotransformation

- Removal of xenobiotics from a biological system is carried out primarily by biotransformation and excretion mechanisms
- Some xenobiotics, especially the **lipophilic ones**, are readily reabsorbed by the kidney cells
- Unless the chemicals are converted to more polar metabolites, they will remain in the body, mostly in the fatty tissues, for a long period
- The resultant products from biotransformation are more **hydrophilic** or polar than parent compound, and thus more readily excreted

# Biotransformation

## Pathways of Metabolism



- Mid-Term examination: 10/03/2023
- Assignment submission last date: 07/04/2023