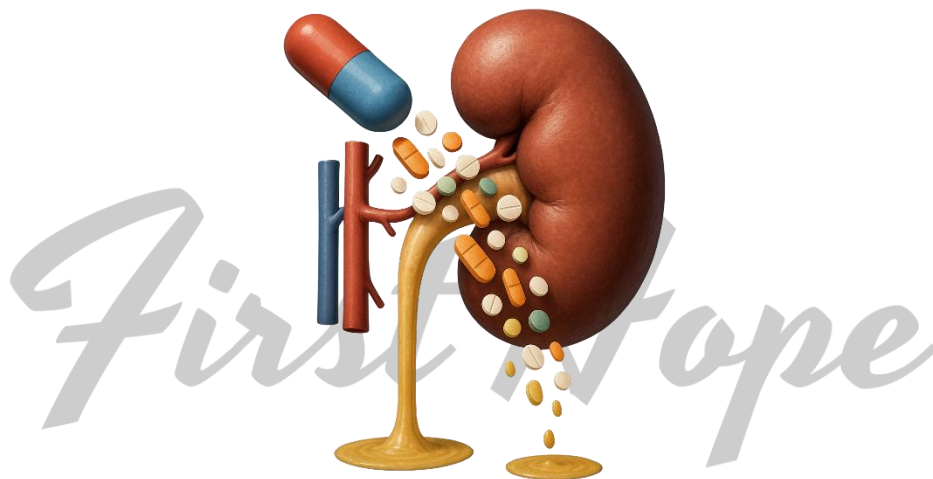


Elimination

Drug Elimination

- **Drug elimination** is the process by which an active drug or its metabolites are removed from the body.
- It is a fundamental component of pharmacokinetics — the study of how drugs move through the body — and plays a crucial role in determining both the duration of a drug's action and its half-life.
- Elimination is essential for:
 - Terminating the drug's pharmacological effects.
 - Preventing toxic accumulation.
 - Maintaining therapeutic efficacy.



Definition

- In pharmacokinetics, **elimination** refers to the **irreversible removal** of a drug from the body. This is the final step following:
 - **Absorption**
 - **Distribution**
 - **Metabolism**
- Elimination ensures that drugs do not persist in the body longer than necessary, reducing the risk of adverse effects.

Major Processes Involved in Elimination

Drug elimination involves two major and interrelated processes:

A. Metabolism (Biotransformation)

- **Primary Site:** Liver
- Drugs are chemically modified (usually into more water-soluble compounds) to facilitate their excretion.

- Metabolism may activate, inactivate, or convert drugs into toxic or non-toxic metabolites.

B. Excretion (Removal from the Body)

- **Primary Route:** Renal (via kidneys)
- **Other Routes:** Bile, sweat, saliva, feces, lungs (for volatile substances), and breast milk.
- Excretion removes the parent drug or its metabolites.

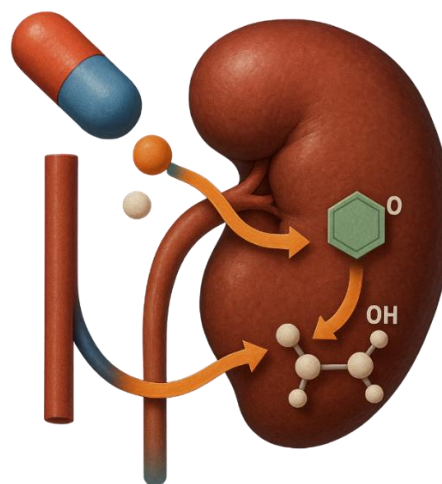
Clinical Significance of Elimination

- **Slow Elimination:** Can lead to drug accumulation and toxicity.
- **Rapid Elimination:** May reduce drug efficacy due to insufficient plasma levels.

Drug Metabolism (Biotransformation)

What is Drug Metabolism?

- Drug metabolism (also known as biotransformation) is the enzymatic conversion of a drug from its original chemical structure (parent compound) to metabolites, which are often more water-soluble and easier for the body to excrete.
- This transformation mainly occurs in the liver, though other tissues like the lungs, kidneys, intestines, and skin may also play roles.
- The goal of metabolism is to:
 - **Inactivate the drug**
 - **Increase water solubility** (to facilitate excretion)
 - **Sometimes activate a prodrug** into its active form



Sites of Drug Metabolism

- **Liver** (primary organ, rich in metabolic enzymes)
- Intestinal wall

- Plasma
- Lungs
- Kidneys

Phases of Drug Metabolism

Phase I (Functionalization Reactions)

- These reactions introduce or expose a functional group (-OH, -NH₂, -SH, -COOH) in the drug, making it more polar.
- These reactions mainly involve oxidation, reduction, and hydrolysis.
- The most important enzyme system in this phase is the Cytochrome P450 (CYP) enzyme system in the liver.

Examples:

- **Oxidation** (CYP450) – Diazepam → Oxazepam
- **Reduction** – Warfarin → Reduced Warfarin
- **Hydrolysis** – Aspirin → Salicylic Acid
- May activate, inactivate, or form active metabolites (e.g., **Codeine → Morphine**).

Phase II (Conjugation Reactions)

- These reactions attach a large, polar molecule (e.g., glucuronic acid, sulfate, glycine) to the drug or Phase I metabolite, making it highly water-soluble for excretion.
- Phase II reactions mostly occur in the liver.

Examples:

- **Glucuronidation** – Morphine → Morphine-6-glucuronide
- **Sulfation** – Acetaminophen metabolism
- **Acetylation** – Isoniazid metabolism
- Some drugs bypass Phase I and undergo direct Phase II metabolism (e.g., Morphine, Paracetamol).

Factors Affecting Drug Metabolism

- **Age** – Newborns & elderly have reduced metabolism.
- **Genetics** – Polymorphisms affect enzyme activity (e.g., slow/fast acetylators in isoniazid metabolism).

Enzyme Induction/Inhibition:

- Inducers (increase metabolism, ↓ drug effect) – Rifampin, Phenytoin, Carbamazepine.
- Inhibitors (decrease metabolism, ↑ drug effect) – Ketoconazole, Erythromycin, Grapefruit juice.
- **Liver Disease** – Reduces metabolism (e.g., Cirrhosis slows drug clearance).



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