Biotransformation of Drugs (Drug Metabolism)

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◈ Definition

Biotransformation (also called drug metabolism) refers to the chemical modification of a drug within the body to facilitate its inactivation, activation, or excretion.

◈ Importance (Pharmacokinetic relevance)

Biotransformation determines:

- Duration of drug action
- Rate of elimination
- Toxicity or safety profile

◈ Outcomes of Biotransformation

→ Inactivation → Drug converted to inactive form → Excreted

→ Activation → Conversion of *prodrug* to active form

→ Formation of toxic metabolites → Adverse effects

Sites of Biotransformation

Site	Major Drugs Metabolized
Liver	Paracetamol, Prazosin, Morphine, Nitroglycerine, Propranolol
GIT	Catecholamines, Chlorpromazine, Salbutamol
Lungs	Prostaglandins
Plasma	Suxamethonium
Skin / Kidneys / Adrenals	Minor sites for metabolism

Types of Biotransformation

1. Non-Enzymatic (Spontaneous)
    - Occurs without enzymes.
    - Due to molecular rearrangement in body fluids.
    - Example: Hofmann elimination → *Atracurium, Mustine HCl*

2. Enzymatic

- Involves specific enzyme systems:
    - Non-microsomal enzymes → Esterases, Amidases, Oxidases, Conjugases
      Examples:
        - Monoamine Oxidase → *Catecholamines*
        - Alcohol Dehydrogenase → *Ethanol*
    - Microsomal enzymes → Found in smooth endoplasmic reticulum

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 Microsomal Biotransformation

Occurs in the Endoplasmic Reticulum, forming microsomes during tissue homogenization.

Enzyme System:

Microsomal Mixed Function Oxidase System (Monooxygenase System)

Also known as Cytochrome P450 system.

⚙️ Components:

- Cytochrome P450 – Hemeprotein (main enzyme)
- NADPH–Cytochrome P450 Oxidoreductase – Flavoprotein
- NADPH – Reducing agent
- Oxygen molecule (O_2) – Required for oxidation

🔄 Flowchart: Microsomal Biotransformation Mechanism

Drug + Cytochrome P450 (Fe^{3+})

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Complex formation → Drug–P450 (Fe^{3+}) complex

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Electron transfer from NADPH via flavoprotein (FAD/FMN)

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$Fe^{3+} \rightarrow Fe^{2+}$ (reduction)

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Drug + Cytochrome P450 (Fe^{2+})

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Oxygen binds to Fe^{2+}–Drug complex → forms activated oxygen complex

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Second electron transfer → Oxygen activation

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One O-atom → incorporated into drug → oxidized metabolite formed
Other O-atom → combined with hydrogen → H_2O formed
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Cytochrome P450 regenerated (enzyme reused) 🔁

🔬 Cytochrome P450 (CYP450)

- Hemeprotein enzyme family involved in oxidation of drugs.

- Naming system: e.g. CYP3A4
    - Root: CYP
    - Family: 3
    - Subfamily: A
    - Isoform: 4

◈ Genetic Polymorphism:

Some individuals have variable CYP activity → affects drug metabolism (e.g. poor vs extensive metabolizers).

🍖 Reactions of Biotransformation

Biotransformation occurs in two phases:

🌀 Phase I Reactions (Non-synthetic / Catabolic)

Purpose: Introduce or unmask functional groups (–OH, –COOH, –SH, $–NH_2$) → makes drug more polar & water-soluble.

Location: Endoplasmic reticulum.

◈ Possible Outcomes

- Inactive metabolite → excreted
- Active metabolite → may undergo phase II or produce pharmacological action
- Toxic metabolite → may cause adverse effects
- Prodrug → activated by phase I

⚛ Types of Phase I Reactions

Reaction Type	Subtype / Example
Oxidation	– Aromatic hydroxylation → *Phenobarbitone* – Aliphatic hydroxylation → *Meprobamate* – Dealkylation → *Theophylline* – N-oxidation → *Aniline* – S-oxidation → *Chlorpromazine* – Deamination → *Amphetamine* – Desulfuration → *Parathion*
Reduction	– Azo reduction → *Prontosil* – Nitro reduction → *Chloramphenicol* – Carbonyl reduction → *Methadone*

Hydrolysis	– Ester hydrolysis → *Procaine* – Amide hydrolysis → *Lignocaine*

💥 Phase II Reactions (Synthetic / Conjugation)

Purpose: Conjugation of drug (or phase I metabolite) with an endogenous compound, forming polar, inactive, and easily excretable conjugates.

🔶 Outcomes

→ Drug (Phase I) → Phase II → Excreted

→ Some drugs directly undergo Phase II (e.g. Isoniazid)

→ Occasionally form active or toxic metabolites

📜 Types of Phase II Reactions

Type of Conjugation	Endogenous Reactant	Enzyme (Transferase)	Example
Glucuronidation	UDP-Glucuronic acid	UDP-Glucuronyl transferase	Morphine

Acetylation	Acetyl-CoA	N-Acetyl transferase	Isoniazid
Glutathione conjugation	Glutathione (GSH)	GSH-S-transferase	Acetaminophen
Glycine conjugation	Glycine	Acyl-CoA glycine transferase	Salicylic acid
Sulfate conjugation	PAPS (3'-phosphoadenosine-5'-phosphosulfate)	Sulfotransferase	Methyldopa
Methylation	S-Adenosyl methionine (SAM)	Methyltransferase	Epinephrine

🔄 Flowchart: Overall Drug Biotransformation

Drug (lipid soluble) → *Phase I (Oxidation / Reduction / Hydrolysis)* → Polar metabolite → *Phase II (Conjugation)* → Highly polar metabolite → Excreted via kidneys / bile 🚽

💡 Clinical Significance

- Explains drug interactions (e.g. enzyme induction or inhibition)
- Helps understand dose adjustment in hepatic diseases
- Predicts toxicity of metabolites (e.g. acetaminophen

toxicity via NAPQI)

⚖️ Factors Affecting Biotransformation of Drugs

🔹 1. Enzyme Induction

Definition:

↑ *Drug-metabolizing enzyme activity* due to prolonged drug exposure → increased rate of metabolism.

🔹 Mechanism

Prolonged drug administration → ↑ Enzyme synthesis or ↓ degradation → Enhanced metabolism → Reduced plasma concentration of drugs

🔹 Common Enzyme Inducers

Phenytoin → CYP450 inducer

Phenobarbital → CYP2B, CYP3A

Rifampicin → Broad CYP inducer

Smoking → Induces CYP1A2

Charcoal-broiled foods / Plasticizers → Induce microsomal enzymes

◈ Clinical Significance

→ Slow onset (requires days)

→ Parent drug → Metabolite (↑ rate)

Consequences:

- ⚠ Therapeutic failure: Oral contraceptives + Rifampicin → reduced efficacy
- ☣ Toxicity: Acetaminophen in chronic alcoholics → ↑ NAPQI (hepatotoxic)
- 🔁 Auto-induction: Carbamazepine induces its own metabolism
- 🌿 Beneficial effect: Phenobarbital → induces glucuronyl transferase → treats neonatal jaundice

- 💊 Dose adjustment required for drugs with *low therapeutic index* (e.g. warfarin, theophylline)

🔁 Flowchart: Enzyme Induction

Prolonged drug administration → ↑ Enzyme synthesis → ↑ Drug metabolism → ↓ Drug concentration → Therapeutic failure / altered efficacy

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🔷 2. Enzyme Inhibition

Definition:

↓ *Drug-metabolizing enzyme activity* → slower biotransformation → ↑ plasma levels.

🔷 Mechanism

Competitive or non-competitive binding to CYP enzymes → prevents metabolism of other drugs.

🔷 Common Enzyme Inhibitors

Cimetidine

Ketoconazole

Macrolides (e.g. Erythromycin)

Grapefruit juice

◈ Clinical Significance

→ Rapid onset

→ Parent drug → metabolite (↓ rate)

Consequences:

- ⚠ ↑ Toxicity risk (due to accumulation)
- Competition between drugs for same enzyme
- Suicide inhibitors: e.g. *Chloramphenicol* binds irreversibly to enzymes
- Dose adjustment required for *narrow therapeutic index* drugs (e.g. phenytoin, warfarin)

Flowchart: Enzyme Inhibition

Drug A (inhibitor) + Drug B (substrate) → ↓ Enzyme activity → ↓ Drug B metabolism → ↑ Plasma concentration of Drug B → Potential toxicity

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🧬 3. Genetic Variations

Definition:

Differences in enzyme expression due to genetic polymorphisms → alter metabolism rate between individuals.

◈ Examples

Enzyme / Gene	Variation	Effect / Drug Example
Pseudocholinesterase	Genetic deficiency	Prolonged action of *succinylcholine*
CYP2C9 (*1 / *2 / *3)	Polymorphism	Alters *warfarin* metabolism
CYP2D6 (PM / UM types)	Polymorphism	Affects *tamoxifen, amitriptyline*
N-acetyltransferase (NAT2)	Fast / slow acetylators	*Isoniazid* metabolism

🧠 Key Concept:

- Fast metabolizers → ↓ plasma levels → ↓ toxicity risk
- Poor metabolizers → ↑ plasma levels → ↑ toxicity risk

➡️ Foundation of pharmacogenetics / personalized medicine

👶👴 4. Age

Extreme age groups show altered biotransformation:

Age Group	Reason	Example / Effect
Neonates / Infants	Immature enzyme systems	*Chloramphenicol* → gray baby syndrome
Elderly	↓ hepatic blood flow, polypharmacy	↑ sensitivity to *diazepam*, *propranolol*

➡️ Dose calculation must consider age (mg/kg basis).

5. Gender

- Influenced by basal metabolic rate (BMR) and hormonal levels
- Drugs: *Salicylates, Benzodiazepines, Propranolol* show variation
- Pregnancy: Hormonal changes alter metabolism

6. Pathological Conditions

Diseases can reduce enzyme activity:

Condition	Effect
Hepatic disease	↓ enzyme synthesis
Cardiovascular disease	↓ hepatic blood flow
Pulmonary disease	↓ oxidation reactions
Thyroid disorders	Alter metabolism rate

7. Diet & Nutritional Status

Dietary Factor	Effect
High protein / vitamin / mineral diet	↑ enzyme activity
Malnutrition	↓ metabolism
Charcoal-broiled foods / Cruciferous vegetables	Enzyme induction
Grapefruit juice	Enzyme inhibition
Chronic alcoholism	Enzyme induction (CYP2E1)

8. Environmental Factors

- Smoking → induces CYP1A2
- Pesticides / Pollutants → alter hepatic enzyme function

9. Racial Differences

Different ethnic groups may show variation in enzyme activity.

E.g. Caucasians, Africans, and Asians differ in CYP2D6 and NAT2 polymorphisms.

10. Drug Interactions

- Competition: Two drugs for same enzyme → inhibition
- Induction / Inhibition: One drug alters metabolism of the other → therapeutic failure or toxicity

11. Chemical Structure of Drug

- The structure determines its metabolic pathway.

- Minor structural differences → major differences in metabolism.

💉 12. Drug Dose / Concentration

- High doses may saturate enzyme systems → alternate toxic pathways used.

- Example:

  Acetaminophen

  - 95% → Glucuronidation / Sulfation (safe)
  - ~5% undergoes oxidation via CYP2E1 → forms toxic intermediate → N-acetyl-p-benzoquinone imine (NAPQI) → NAPQI is neutralized by conjugation with Glutathione (GSH) → harmless
  - In overdose → GSH depleted → unconjugated NAPQI binds to hepatocellular proteins → cell necrosis → acute liver damage / hepatic failure ⚠

💧 13. Route of Administration

First-Pass Metabolism (Pre-Systemic Metabolism)

🧠 Definition:

The metabolism of a drug *before it enters the systemic circulation* — mainly when given orally.

📍 Sites:

- Liver
- Gastrointestinal (GIT) wall

📉 Effect:

Reduces the bioavailability of the drug.

💊 Example:

Nitroglycerine → undergoes extensive first-pass metabolism

➡️ therefore administered sublingually to bypass the

liver and reach systemic circulation directly ♡

🔄 Flowchart: Summary of Factors Affecting Biotransformation

Drug metabolism rate

← Influenced by →

→ Enzyme induction / inhibition
→ Genetics
→ Age / Gender
→ Disease states
→ Diet & Environment
→ Drug interactions / Dose / Route

↓

Alters → Drug plasma level → Therapeutic efficacy / Toxicity ⚖️