



Metabolism

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METABOLISM

By the end of this lecture, students should:


- ▶ *Recognize the importance of biotransformation*
- ▶ *Know the different sites for drug metabolism*
- ▶ *Define the major phase I and phase II metabolic reactions.*
- ▶ *Describe the modulation of liver microsomal enzymes by inducers and inhibitors*
- ▶ *Mention two drugs that are known as enzyme inducers and inhibitors.*
- ▶ *Know the impact of first pass metabolism on drug bioavailability.*

Drug Metabolism (Biotransformation)

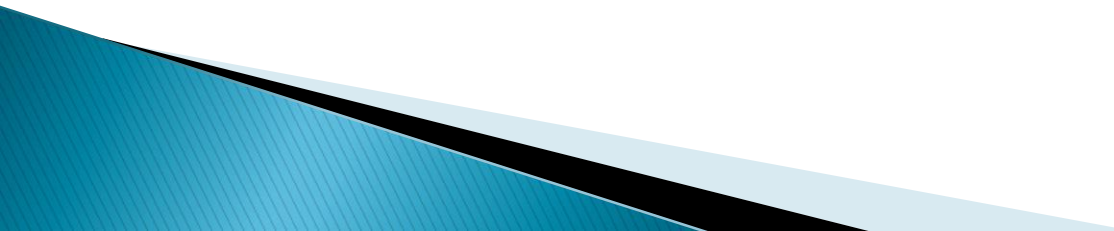
Definition

- ▶ Chemical reactions which occur in the body to change drugs from nonpolar lipid soluble forms to polar water soluble forms that are easily excreted by the kidney.

Importance of metabolism

- ▶ **Inactivation or termination** of drug action (most drugs).
 - ▶ **Detoxification** Biotransformation is required for protection of body from toxic metabolites
 - ▶ **Activation of prodrug (convert inactive form of drug to active form)** e.g. levodopa – carbidopa, prednisone – prednisolone
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Organ sites of drug metabolism

- Liver (the major site).
 - Intestinal Mucosa and Lumen
 - Plasma
 - Kidney
 - Skin
 - Lung
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Intestinal Mucosa and Lumen

Gut Mucosa

- Mono-Amine Oxidase (MAO) .

Gut lumen (bacterial flora)

- Glucouronidase.

Plasma

Enzymes

substrate

**Catechol O-Methyl
Transferase (COMT)**

**catecholamines
(e.g. adrenaline)**

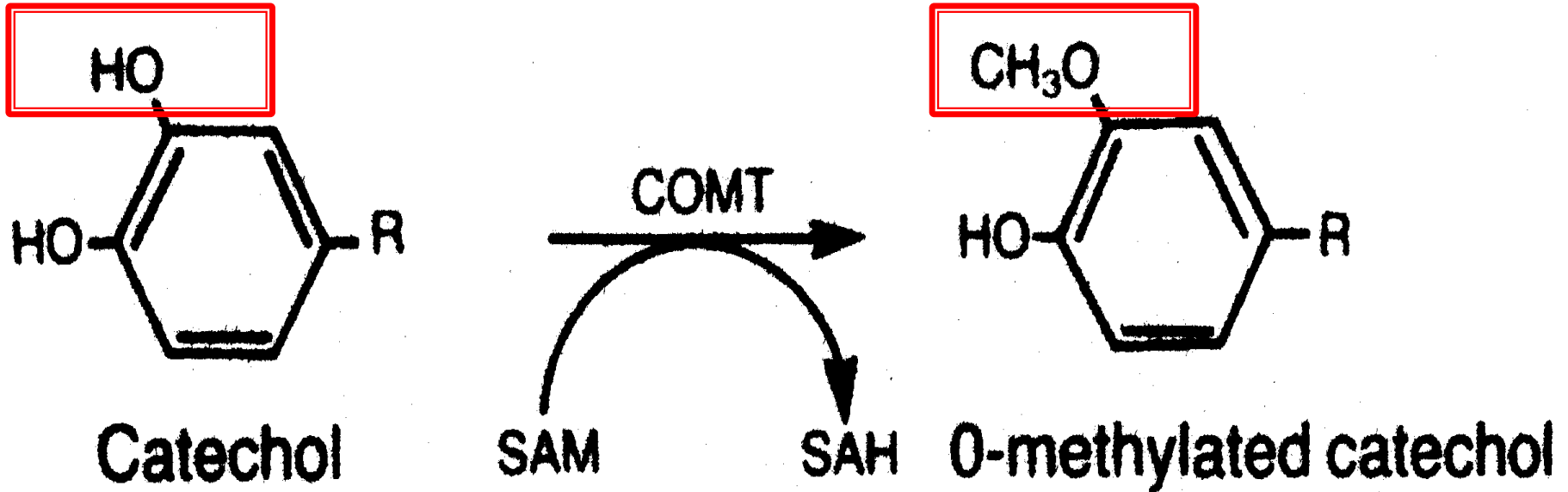
Esterases

**Esters
Act on drugs as Local
anesthetics**

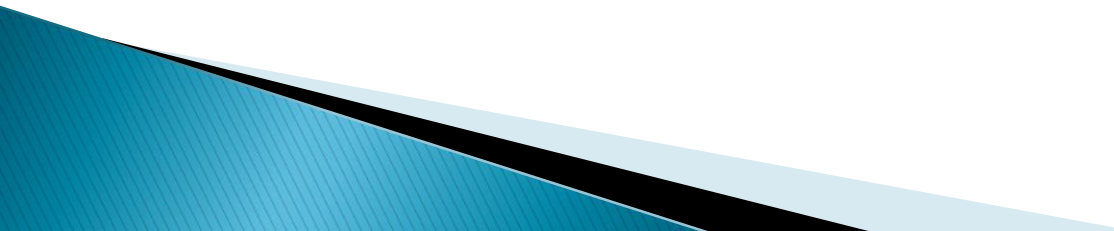
Amidases

**amides
Act on drugs as local
anesthetics**

Catechol o-methyl transferase



Cellular sites of drug metabolism

- **Cytoplasm**
 - **Mitochondria**
 - **Lysosomes**
 - **Microsomes**
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Mitochondria

➤ N-acetyl transferase:

Introduction of acetyl group (CH_3COO^-)

➤ Monoamine oxidase enzyme (MAO):

oxidation of catecholamines as adrenaline

Cytoplasm

e.g. Alcohol dehydrogenase: oxidation of alcohol

Alcohol \longrightarrow Aldehyde \longrightarrow Acid

Ethanol \longrightarrow acetaldehyde \longrightarrow acetic acid.



Microsomes

Microsomal enzyme system = Cytochrome P-450.

There are more than 20 families CYP1, CYP2, CYP3

Sub-families are identified as A, B, and C etc.

In human: only 3 isoenzyme families are important

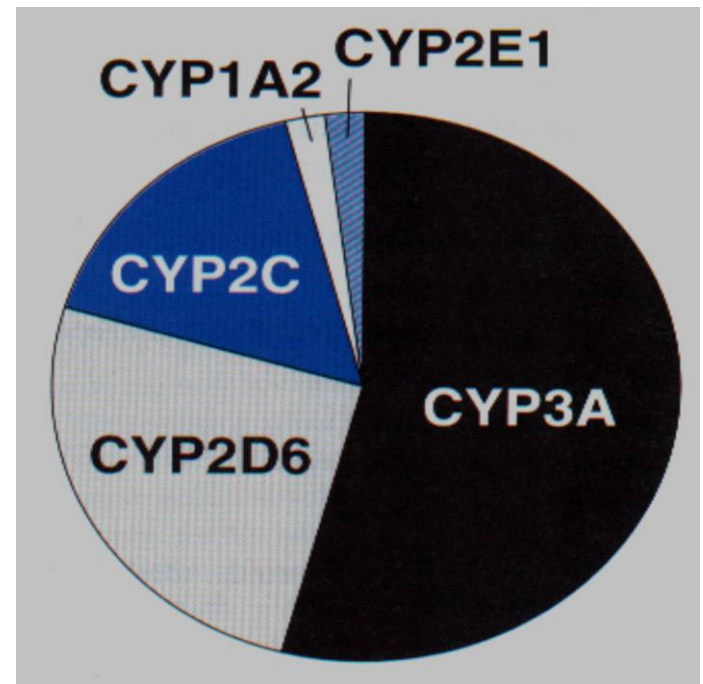
CYP1, CYP2 and CYP3



Oxidation - Cytochrome P-450

CYP 3A4/5 carry out biotransformation of the largest number (30–50%) of drugs.

Expressed in liver and intestine (responsible for first pass metabolism at this site).



Types of hepatic metabolic reactions

Two phases of hepatic metabolic reactions:

Phase I metabolic reactions include:

- ▶ **Oxidation.**
- ▶ **Reduction.**
- ▶ **Hydrolysis.**

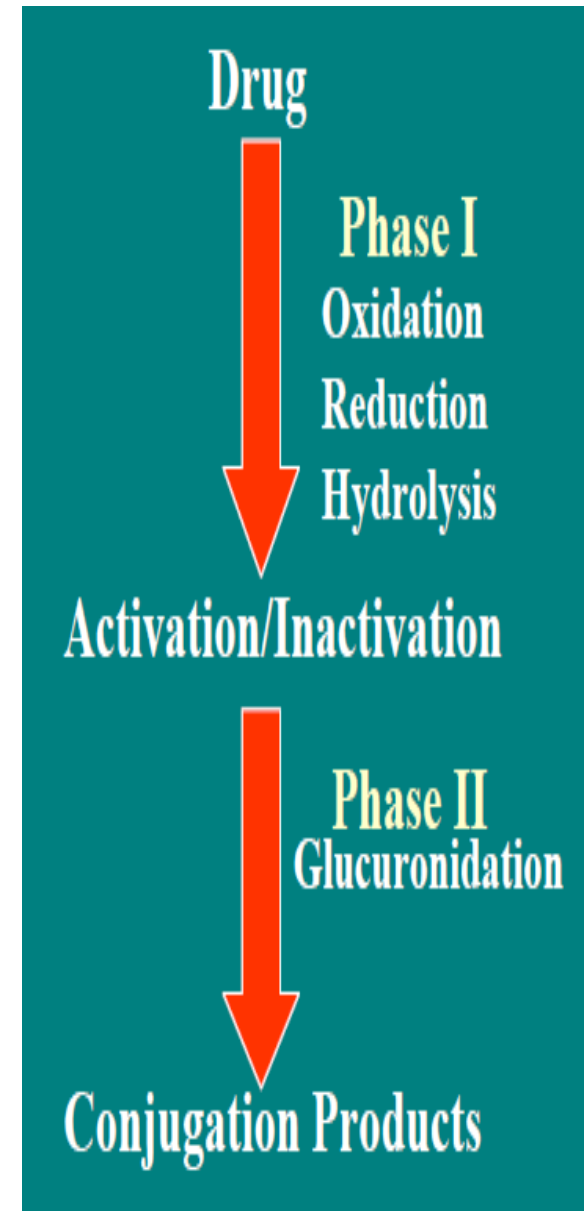
Phase II metabolic reactions include

- ▶ **Conjugation reactions**

Types of hepatic metabolic reactions

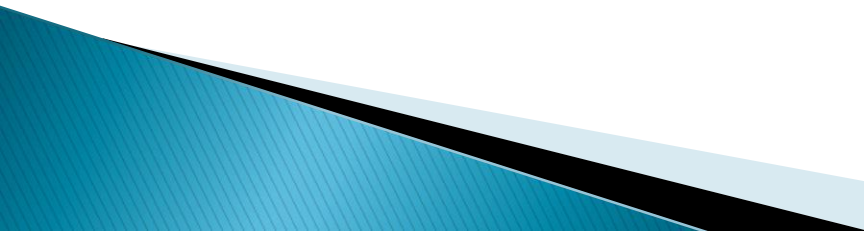
Phase I:
metabolites may be active
or inactive.

Phase II:
metabolites are usually
inactive.



Oxidation Reactions

Oxidation

- Is addition of oxygen or removal of hydrogen.
 - Is the most important drug metabolizing reaction.
 - May be **microsomal** or **non-microsomal**.
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Oxidation Reactions

Microsomal oxidation

- ▶ occurs in microsomes
- ▶ e.g. cytochrome P450 enzymes, NADPH and oxygen

Non microsomal oxidation

- ▶ occurs in cytosol or mitochondria

These enzymes include **oxidases & dehydrogenases**

Non-microsomal Oxidation

Dehydrogenases

Are required for oxidation of alcohols

e.g. Alcohol dehydrogenase (convert alcohol to aldehyde).

e.g. Aldehyde dehydrogenase (convert aldehyde to acid).

Non-microsomal Oxidation

Oxidases

1) Monoamine oxidase (MAO):

- ▶ Is responsible for the metabolism of catecholamines as adrenaline and serotonin.
- ▶ e.g. **Moclobemide**
 - Is a monoamine oxidase inhibitor.
 - It increases serotonin in the brain.
 - Used as antidepressant drug.

Non-microsomal Oxidation

2) Xanthine oxidase:

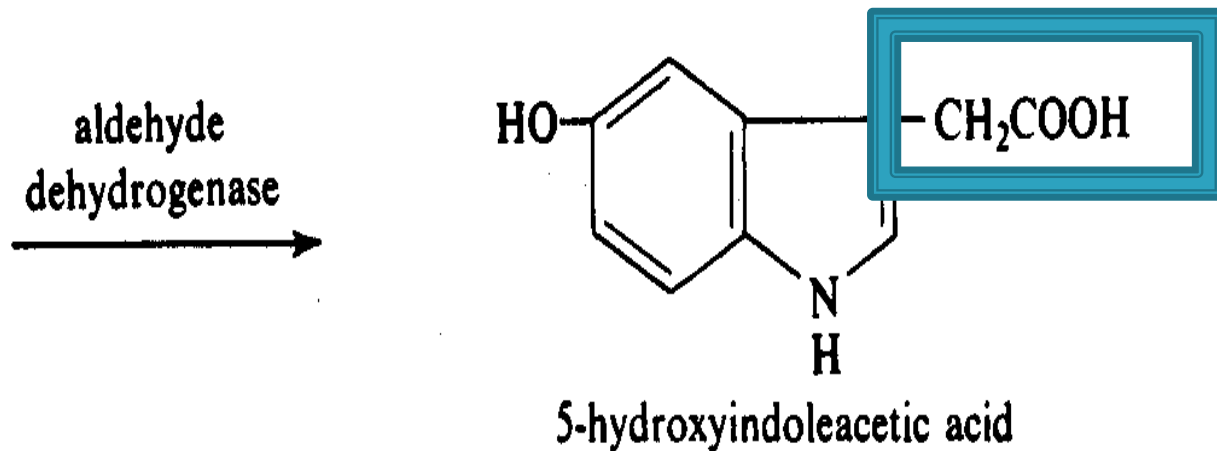
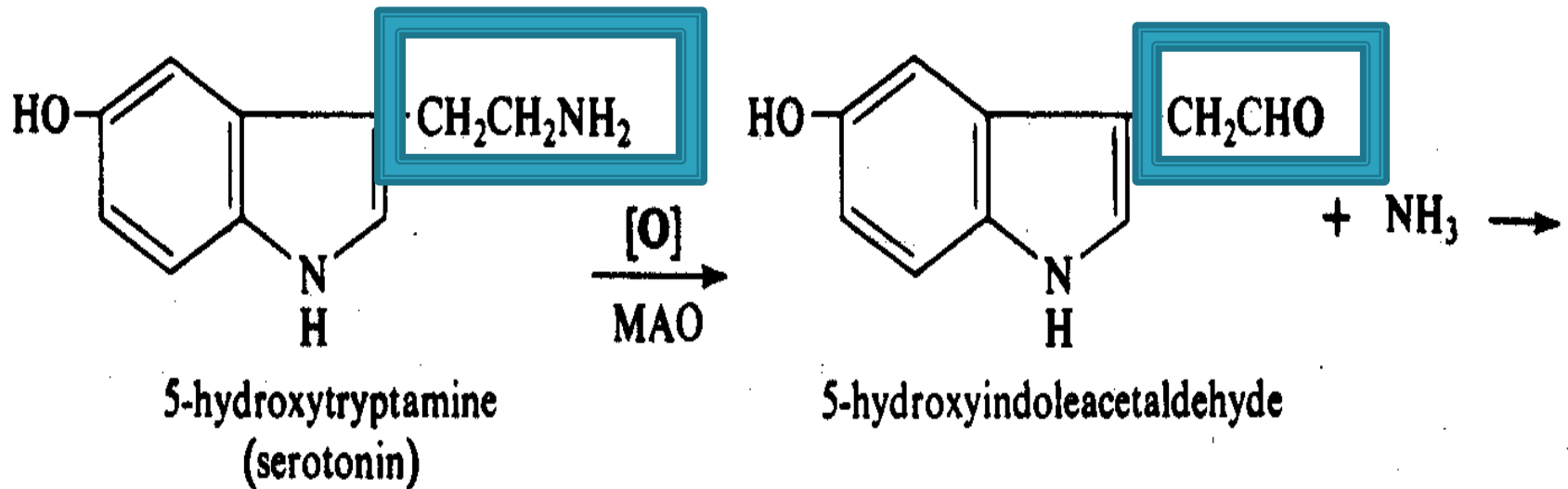
Is required for the oxidation of xanthine

oxidase

oxidase

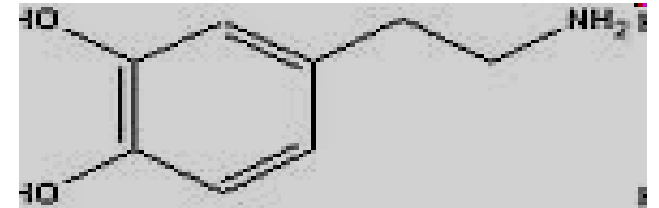
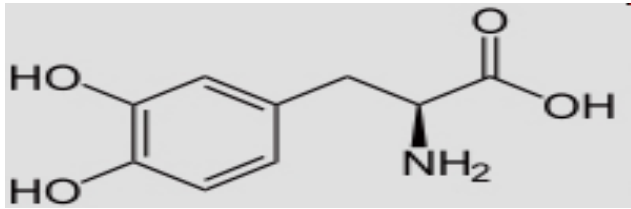
- Hypoxanthine \longrightarrow xanthine \longrightarrow uric acid
- uric acid accumulation \longrightarrow **GOUT**
- **Allopurinol**
- is an inhibitor of xanthine oxidase
- used in the treatment of gout.

Monoamine oxidase (MAO)



Reduction reactions

- **Removal of oxygen or addition of hydrogen.**
- **may be microsomal or non microsomal.**
- **Examples: levodopa**

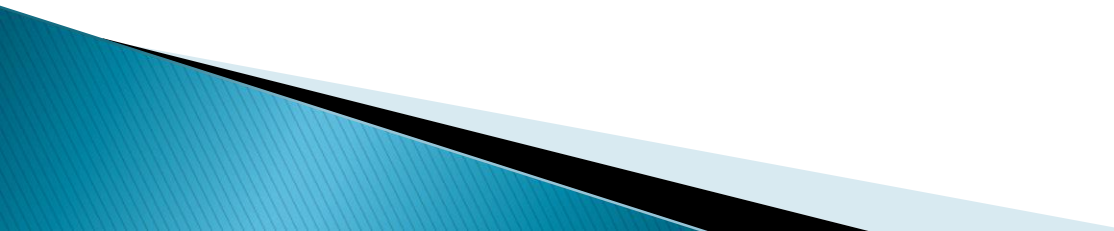


DOPA- decarboxylase

Levodopa (DOPA)

Dopamine

Hydrolysis

- All are *non microsomal*
 - occurs by addition of water molecules in presence of enzymes as (**esterases & amidases**)
 - **Esterases:** hydrolyze drugs that are **esters**
 - **Amidases:** hydrolyze drugs that are **amides**
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Hydrolysis

- Esters as **acetylcholine** (neurotransmitter).

Ester + H₂O



Acid + Alcohol

esterase

Acetylcholine —————→ **acetate + choline.**

- Amides as **lidocaine** (used as local anesthetic)

Amide + H₂O



Acid + amine

Phase I reactions can result in

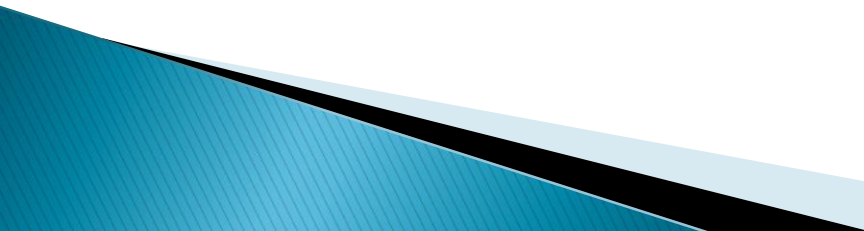
- **Activation of pro-drug**
e.g. levodopa to dopamine
- **Inactivation of drug (termination of action)**
- **Conversion of active drug to active metabolite**
- **Conversion of nontoxic drug to toxic metabolite**

Paracetamol → hepatotoxic metabolite (hepatic necrosis)

- **Product might undergo phase II**

Phase II Conjugation Reactions

Conjugation of metabolite coming from (phase I) with endogenous substance as methyl group, acetyl group, sulphate, amino acid or glucouronic acid to produce conjugate that is **water soluble** and **easily excreted in urine or bile**.



Types of conjugation reactions

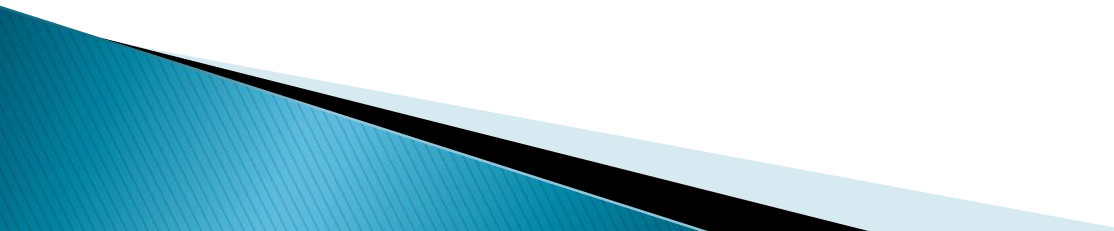
Conjugation reaction	Enzyme required
glucouronide conjugation	<u>Glucouronyl transferase</u>
Acetylation ($\text{CH}_3 \text{COO}^-$)	<u>N-acetyl transferase</u>
Sulphation (SO_4^{--})	<u>Sulfo transferase</u>
Methylation (CH_3)	<u>methyl transferase</u>
Amino acids conjugation	Glycine conjugation

Phase II metabolic reactions:

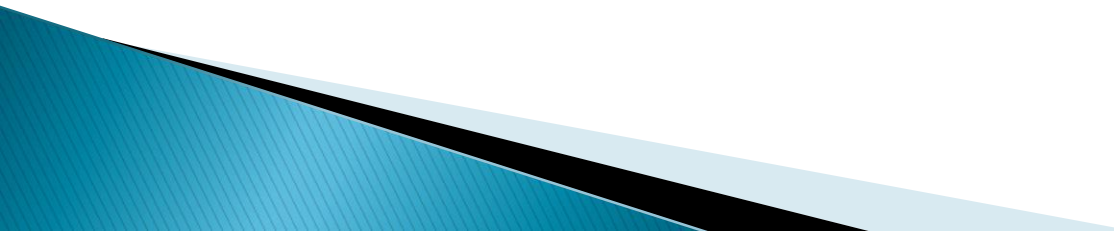
- ▶ All are non microsomal **except** glucouronidation
- ▶ Glucouronide conjugation is a microsomal process (**the most common of phase II reactions**).
- ▶ Deficiency of **glucouronyl transferase** enzyme in neonates may result into toxicity with chloramphenicol (**Gray baby syndrome**).

Characteristics of Phase II metabolites

Phase II metabolites are:

- ▶ **Usually pharmacologically inactive.**
 - ▶ **Polar**
 - ▶ **more water soluble.**
 - ▶ **Easily excreted in urine.**
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Factors affecting metabolism

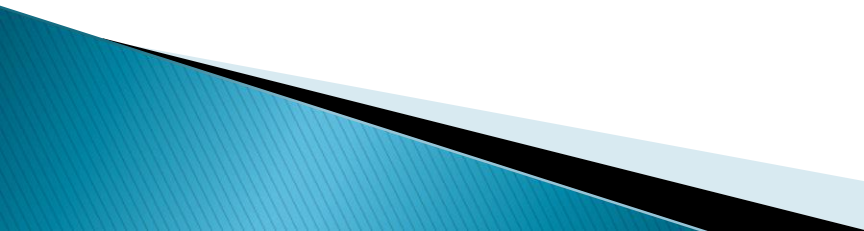
- ▶ **Age:** ↓ rate of metabolism in neonates & elderly
 - ▶ **Diseases:** ↓ rate of metabolism in liver diseases
 - ▶ **Degree of Protein Binding:** ↓ rate of metabolism
 - ▶ **Concurrent use of drugs:** Induction & inhibition
 - ▶ **Nutrition:** malnutrition ↓ rate of metabolism
 - ▶ **Genetic polymorphism**
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Factors affecting metabolism

Genetic polymorphism

- ▶ Metabolism may vary from population to another due to the existence of different forms of the metabolic enzymes.
- ▶ E.g. metabolism of **isoniazid** (Anti-TB), etc.
- ▶ **Slow acetylator phenotype** → results in decrease in isoniazid metabolism & accumulation of isoniazid with risk of **peripheral neuropathy**
- ▶ **Rapid acetylator phenotype** → results into excess metabolites produced with risk of **hepatitis**.

Enzyme Induction & inhibition

- **Liver microsomal enzymes inducers:** drugs that increase activities of liver microsomal enzymes & increase the metabolism of drug itself and other drugs taken with the inducer at the same time.
 - **Liver microsomal enzymes inhibitors:** drugs that decrease activities of liver microsomal enzymes & decrease the metabolism of the drug itself and other drugs taken concurrently.
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Enzyme inducers

Alcohol

Cigarette smoking

Phenobarbitone **hypnotic**

Phenytoin **(antiepileptic)**

Rifampicin **(Anti TB)**

Enzyme inhibitors

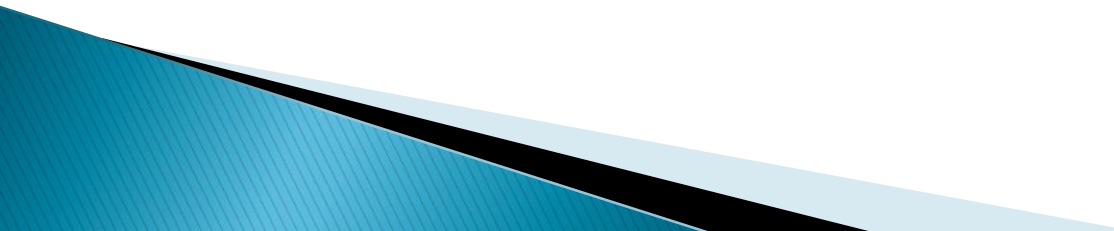
Grape fruits

Cimetidine

Erythromycin **(antibiotic)**

Ketoconazole **(antifungal)**

Enzyme induction may result in:

- ▶ ↑ the metabolism and excretion of the inducer drug itself and co-administered drugs.
 - ▶ ↓ the action of the inducer drug itself & co-administered drugs.
 - ▶ **Tolerance may occur:** decrease in the pharmacological action of the drug by continuous or repeated administration .
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Enzyme induction may result in:

- **Drug interactions may occur:** decrease in action of one drug by administration of another drug
e.g. oral contraceptives & phenytoin (inducer).
- Failure of oral contraceptive may lead to pregnancy if combined with phenytoin.

Enzyme inhibition may

- ▶ **↓ Delay the metabolism and excretion of the inhibitor drug and co-administered drugs.**
- ▶ **↑ Prolong the action of the inhibitor drug & co-administered drugs.**
- ▶ **e.g. warfarin & erythromycin (inhibitor).**
- ▶ **Inhibition of warfarin metabolism may lead to increase its anticoagulant effect (risk of bleeding).**