# METABOLISM

## OUTLINE

- Definition
- Sites of metabolism.
- Types of metabolic reactions.
- Modulation of liver microsomal enzymes.
- First pass metabolism.

# Drug Metabolism (Biotransformation)

## Definition

- Chemical reactions which lead to modification of drugs.

- **Sites**
  - **Liver (the major site).**
  - **Extra hepatic.**

## I. Liver (Hepatic sites)

- Cytoplasm.
- Microsomes.
- Mitochondria

## Microsomes

- Microsomal enzyme system = mixed function oxidase = mono-oxygenase.
- Components
  - Cytochrome P-450.
  - Flavoprotein NADPH.
  - Molecular oxygen, $Mg^{++}$.
  - In all cells, mostly in liver and intestinal mucosa

## Mitochondria

- Monoamine oxidase enzyme (MAO).
- Acetylation.

## Cytoplasm

- Alcohol dehydrogenase

# II. EXTRAHEPATIC SITES

- Plasma
  - COMT (Catechol o-methyl transferase).
  - Esterases.
  - Amidases.
- Kidney
- Skin
- Lung

## Intestinal Mucosa and Lumen

- **Gut Flora**
- Glucouronidase.
- Azoreductase.

- **Gut Mucosa**
- Monoamine Oxidase.
- Sulphatase.

# TYPES OF METABOLIC REACTIONS

- Phase I Reactions (Nonsynthetic).
- Phase II Reactions (synthetic)

# Phase I Reactions (Nonsynthetic)•

- Oxidation.
- Reduction.
- Hydrolysis.

# I. Oxidation Reactions

- Introduce or unmask functional groups (OH)
- Microsomal (CYT-P450).
- Non-microsomal.

# Microsomal Oxidations

Drug + O2 + NADPH + $H^+$ $\longrightarrow$ changed drug + H2O + $NADP^+$.

## 1. Aliphatic hydroxylation.

Phenobarbital $\rightarrow$Hydroxy phenobarbital.

## 2. Aromatic hydroxylation

Phenacetin $\rightarrow$ 2-hydroxy phenacetin (Paracetamol)

# Microsomal Oxidations

## 3. Amine Oxidation

Aniline to nitrobenzene.

$NH_2 \rightarrow NO_2$

## 4. Sulphoxidation

Parathione to Paroxon.

# •Non-microsomal Oxidation

- Oxidation by soluble enzymes in cytosol or mitochondria of cells.

- Dehydrogenases and oxidases.

Ethanol ⟶ acetaldehyde ⟶ acetic acid.

$CH_3CH2OH \rightarrow CH_3CHO \rightarrow CH3COOH.$

Methanol ⟶ formaldehyde ⟶ formic acid

$CH_3OH \rightarrow HCHO \rightarrow HCOOH.$

- **Monoamine oxidase ( MAO )**

  **Catecholamines (noradrenaline)**

- **Xanthine oxidase**

  **Hypoxanthine → xanthine → uric acid.**

# II. Reductions•

- **Microsomal**
  - Nitrobenzene → Aniline.

    $NO_2 \rightarrow NH_2$

- **Non microsomal**
  - Chloral hydrate → Trichloroethanol (active).

    $CCl_3 - CHO \rightarrow CCl_3 - CH_2OH$

# III. Hydrolysis•

- All are NON microsomal
- Esters-C-O- and amides –C-N-

Acetylcholine →choline + acetate.

$$R1\text{-}COOR2 \longrightarrow R1COOH + R2OH.$$

Procainamide ( lidocaine, local anaesthetic).

$$R1 - CONH - R2 \longrightarrow R1 - COOH + R2NH2.$$

# Characteristics of Phase I products•

**1. Inactivation (Abolish the activity)**

- **Oxidation of Phenobarbital and alcohol.**
- **Hydrolysis of acetylcholine.**

**2. Conversion of active drug to another active one.**

| | |
|---|---|
| **Diazepam.** | **Oxazepam.** |
| **Phenylbutazone** | **Oxyphenbutazone.** |
| **Codeine, Heroin** | **Morphine.** |
| **Propranolol** | **4–hydroxy propranolol.** |

## 3. Conversion of drugs to toxic metabolites.

- Paracetamol → acetaminophen hepatotoxicity
- Halothane → metabolite hepatotoxicity
- Cyclophosphamide → acrolein, bladder toxicity
- Phenacetin → aniline derivatives methemoglobinemia

## 4. Activation of prodrug

- chloral hydrate → trichloroethanol.
- Enalapril → Enalaprilat
- Cortisone → Hydrocortisone

## 5. Product might undergo phase II.

# Phase II Conjugation Reactions (Synthetic Reactions)

Conjugation of drug or metabolite (phase I) with endogenous substance as methyl group, acetyl group, sulphate, amino acid or glucouronic acid.

## Phase II Reactions, Synthetic Reactions• (conjugation ):

- Glucouronide conjugation.
- Amino acids e.g. glycine.
- Acetylation reactions: $CH_3$-CO
- Sulphate conjugations. SO4
- Methylation reactions e.g.$CH_3$

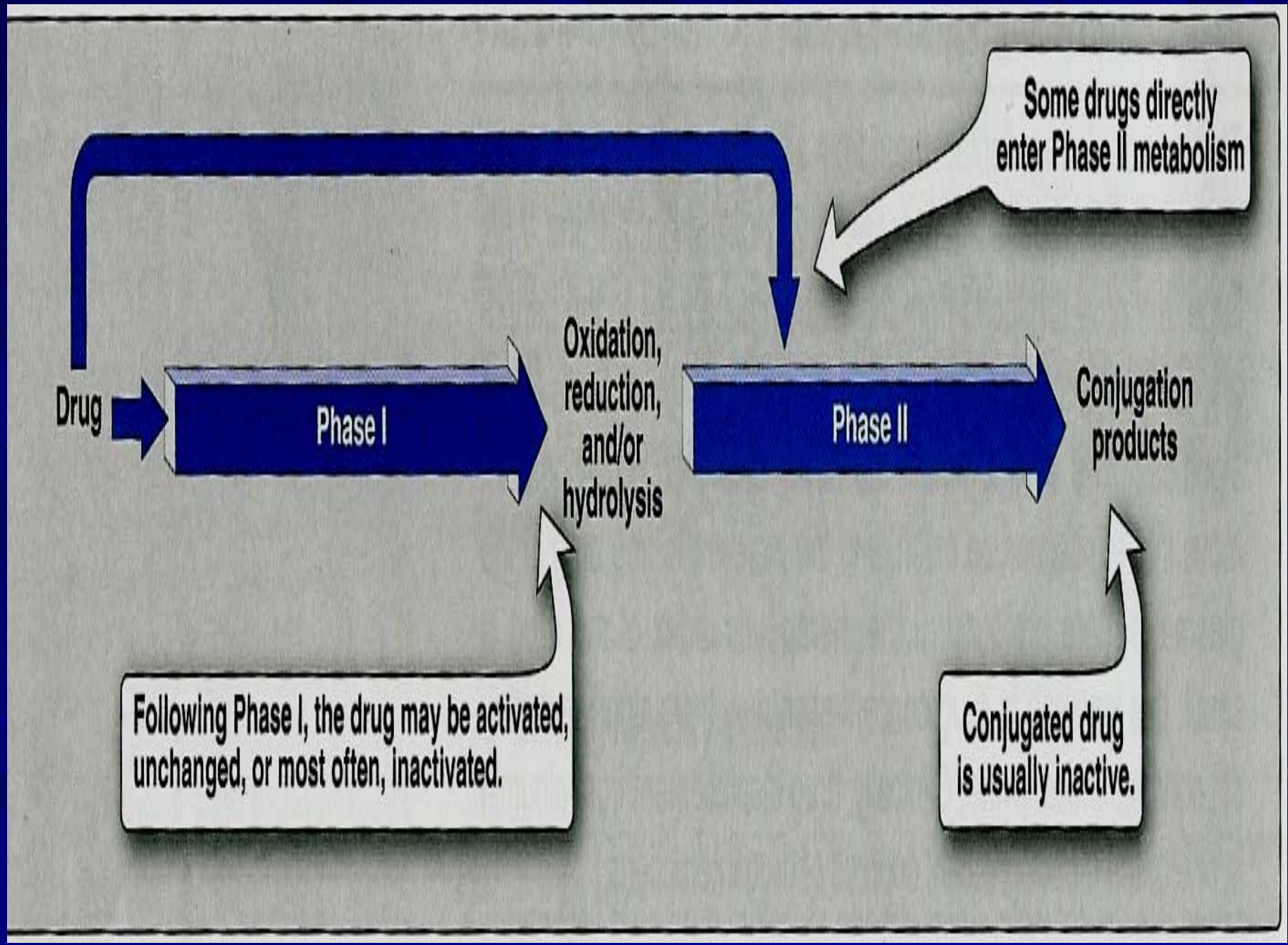
  Noradrenaline $\rightarrow$ Adrenaline.

# Phase II Reactions, Synthetic Reactions• (conjugation ):

- All non microsomal **EXCEPT** Glucouronidation (Catalyzed by glucouronyl transferase).
- Glucouronidation is
  - The most common reaction
  - The most important reaction.
  - Deficient in neonates chloramphenicol (**Gray baby syndrome**).

# Characteristics of Phase II Products

- Product = Conjugate
- Usually Pharmacologically inactive.
- Polar
- more water soluble.
- more readily excreted in urine.


Some drugs directly enter Phase II metabolism
Drug
Phase I
Oxidation, reduction, and/or hydrolysis
Phase II
Conjugation products
Following Phase I, the drug may be activated, unchanged, or most often, inactivated.
Conjugated drug is usually inactive.

# Factors affecting metabolism

## (Modulation of liver microsomal enzymes)

- Induction
- Inhibition

# Liver Microsomal Inducers

- Alcohol
- Cigarette smoking
- Barbiturates (Phenobarbitone, hypnotic)
- Phenytoin (antiepileptic)
- Rifampicin (Anti TB)
- Grisofulvin (antifungal).

## Enzyme induction may result in:

- Increase metabolism of the inducer.
- Decrease its pharmacological action.

  ( TOLERANCE ).
- Increase the metabolism of co-administered drugs (drug interactions)

  Barbiturates & Warfarin.

  Phenytoin & Oral contraceptives.

  Rifampicin & Hydrocortisone

- Increase tissue toxicity by metabolite paracetamol, phenacetin.

- As Therapy (phenobarbitone & Hyperbilirubinemia).

# Liver Microsomal Inhibitors

- Cimetidine (anti-peptic ulcer)
- Erythromycin (antibiotic)
- Ketoconazole (antifungal)
- Grape fruits
- Isoniazid
- Disulfuram
- Chloramphenicol
- Primaquine
- Probenicid

## Enzyme inhibition may

- retard the metabolism and excretion of the inhibitor and co-administered drugs.
- prolong the action of the inhibitor & co-administered drugs.

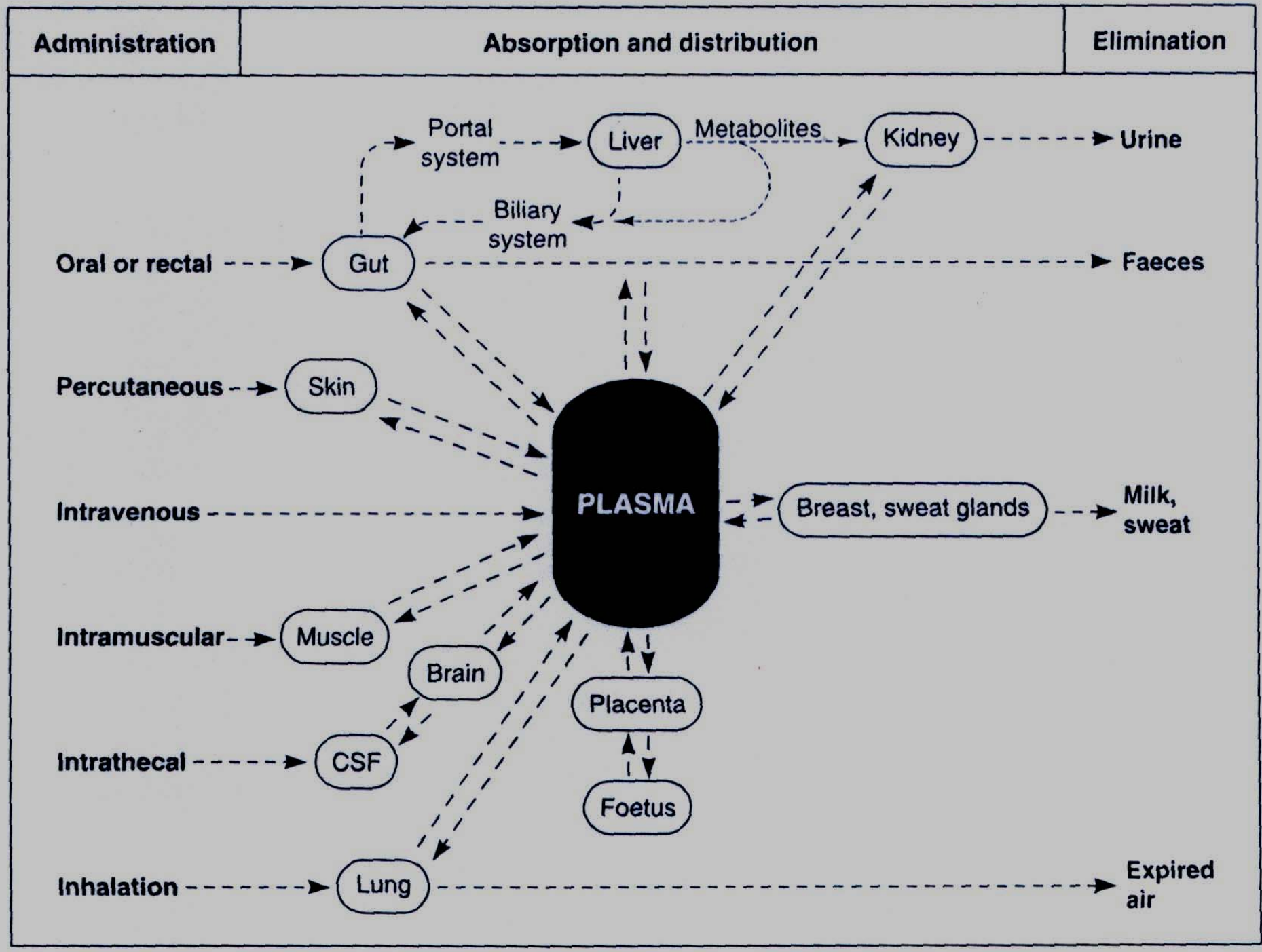
# First pass Metabolism

- Following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entry into systemic circulation.
- Drug can be metabolized before reaching the systemic circulation.
- so the amount reaching system circulation is less than the amount absorbed

# First pass Metabolism

**Where ?**

- **Liver**
- **Gut wall**
- **Gut Lumen**
- **Portal blood**


Administration
Absorption and distribution
Elimination
Portal system
Liver
Metabolites
Kidney
Urine
Biliary system
Oral or rectal
Gut
Faeces
Percutaneous
Skin
PLASMA
Intravenous
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Placenta
Intrathecal
CSF
Foetus
Inhalation
Lung
Expired air

# First pass Metabolism

**Result ?**

**Low bioavailability.**

**Short duration of action (t ½).**

# First pass Metabolism

- How it is given ?
- Examples
  - Aspirin
  - Morphine
  - Propranolol
  - Verapamil
  - Salbutamol
  - Glyceryl trinitrate.