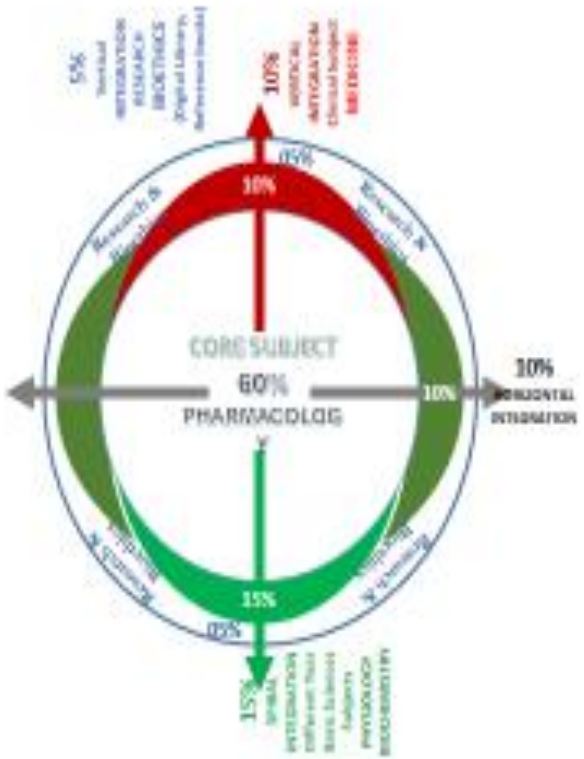
# BIOTRANSFORMATION OF DRUGS

**Sources:**

**Bertram G. katzung Basic & Clinical Pharmacology 15th Edition**

**Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th edition.**

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures




| 3rd Year Pharmacology LGIS | |
|---|---|
| Core Subject – 60% | |
| **Pharmacology** | |
| Horizontal Integration – 10% | |
| **Same Year Subjects** | • Pathology (10%) |
| Vertical Integration – 10% | |
| **Clinical Subjects** | • Medicine (10%) |
| Spiral Integration – 15% | |
| **Different Year Basic Sciences Subjects** | • Physiology (10%)<br>• Biochemistry (5%) |
| Vertical Integration – 05% | |
| **Research & Bioethics** | |

# LAY OUT/SOPs

- Definition
- Site of metabolism
- Outcomes and aim of biotransformation
- Hoffman elimination
- Classification of biotransformation
- Drug metabolizing enzymes
- Cytochrome P450 enzyme
- Phase I reaction
- Phase II reaction
- Factors affecting biotransformation

# LEARNING OBJECTIVES

- At the end of this session, students will be able to

- Define biotransformation
- Classify biotransformation
- Describe phase I and phase II reactions with examples and factors
- Discuss microsomal and non microsomal enzyme

# CORE SUBJECT

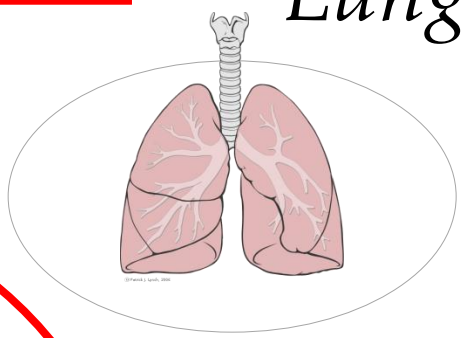

# DEFINITION

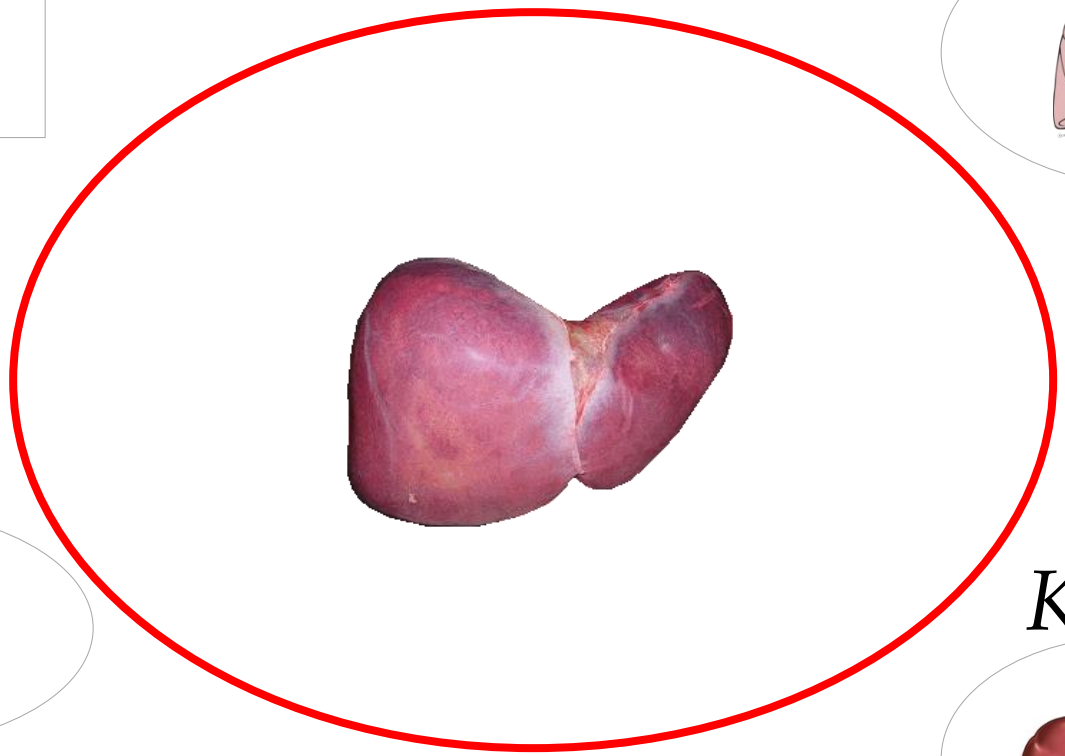
- Chemical alteration of the drug in the body is called “Biotransformation or drug metabolism”.

# SITES OF METABOLISM

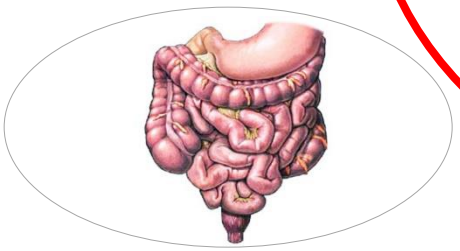
*Every tissue*

*Lungs*

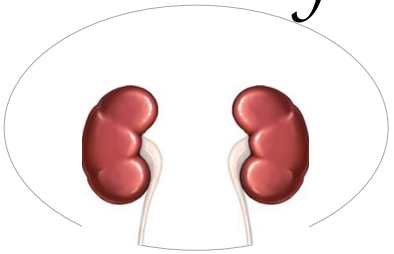




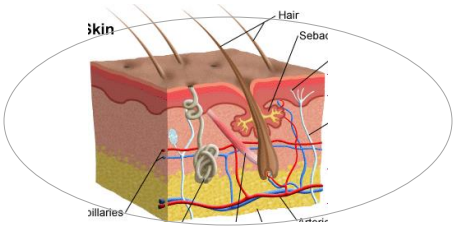
*G I T*



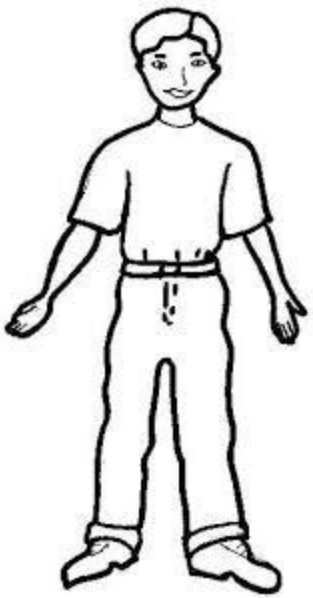
*Kidneys*



*Skin*



# AIM OF BIOTRANSFORMATION

LIPID SOLUBLE  WATER SOLUBLE

*Biotransformation*

# OUTCOMES OF BIOTRANSFORMATION

- **ACTIVE DRUGS** are converted into

✓Inactive metabolites

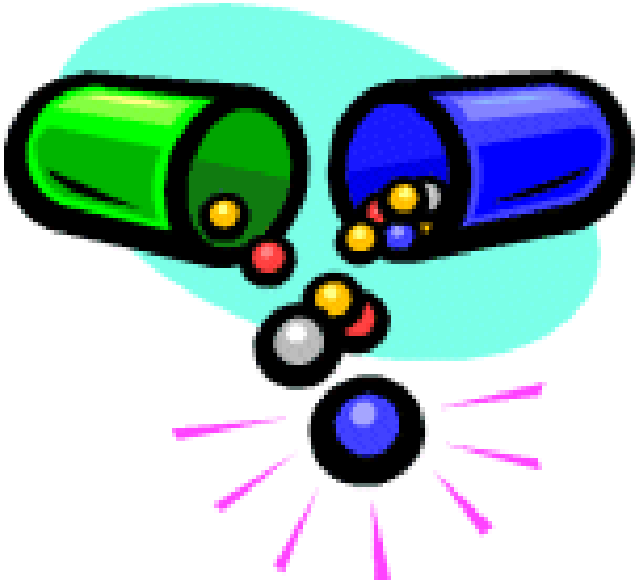
✓ Active metabolites

✓Toxic Metabolites

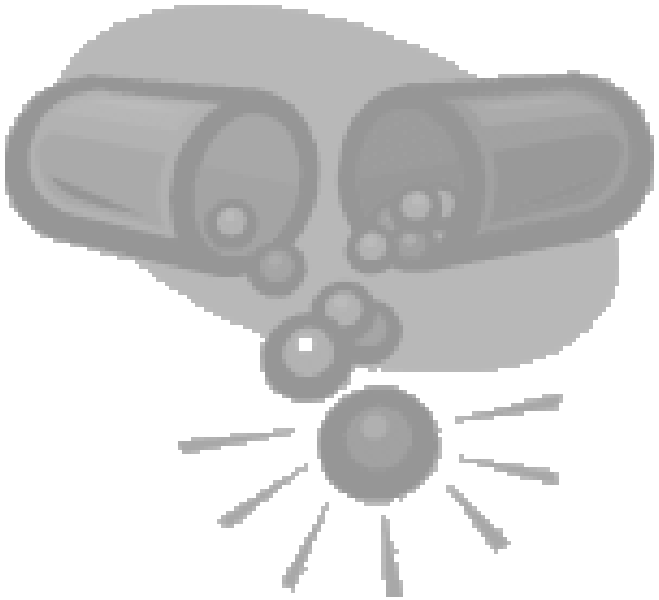
✓More Active than parent

1

*ACTIVE DRUG*



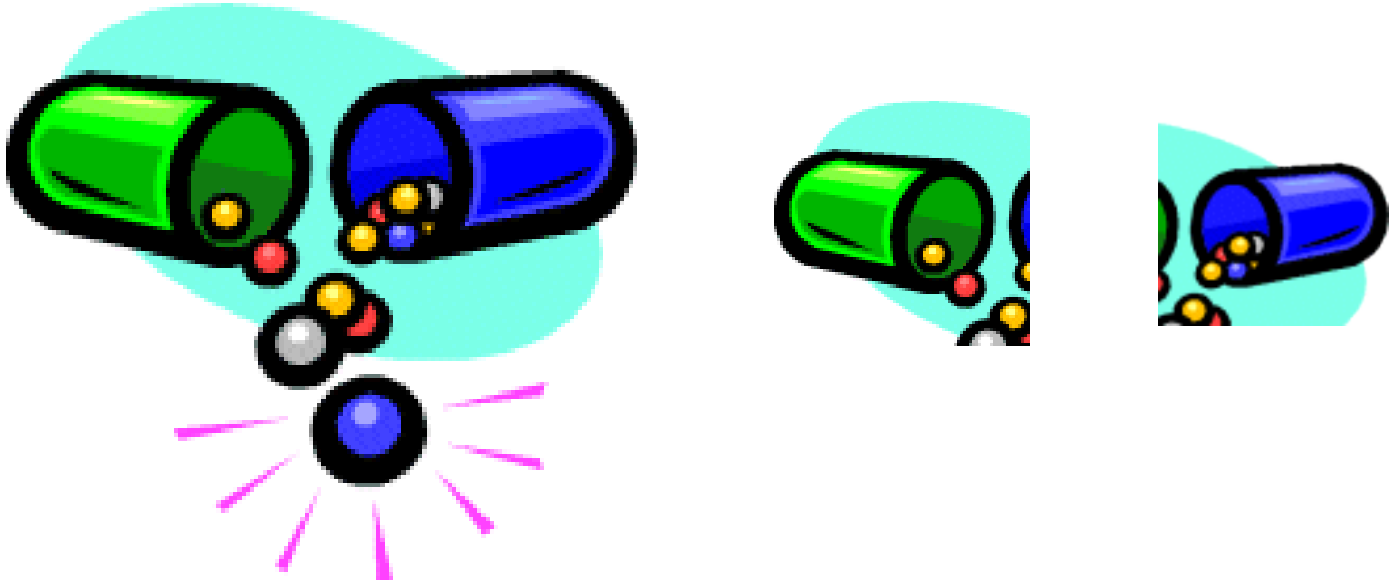
*INACTIVE DRUG*



Chloramphenicol
Propranolol
Phenobarbitone

2

*ACTIVE DRUG* *ACTIVE METABOLITE*



Codeine → Morphine

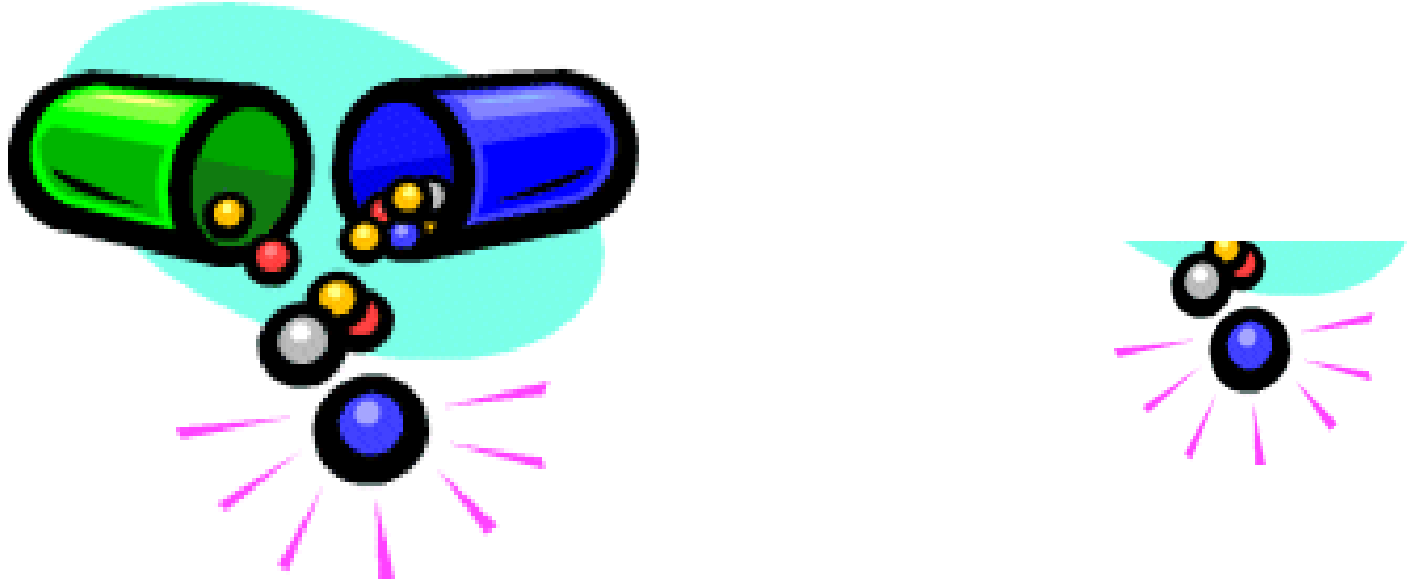
Digitoxin → Digoxin

Imipramine → Desipramine

3

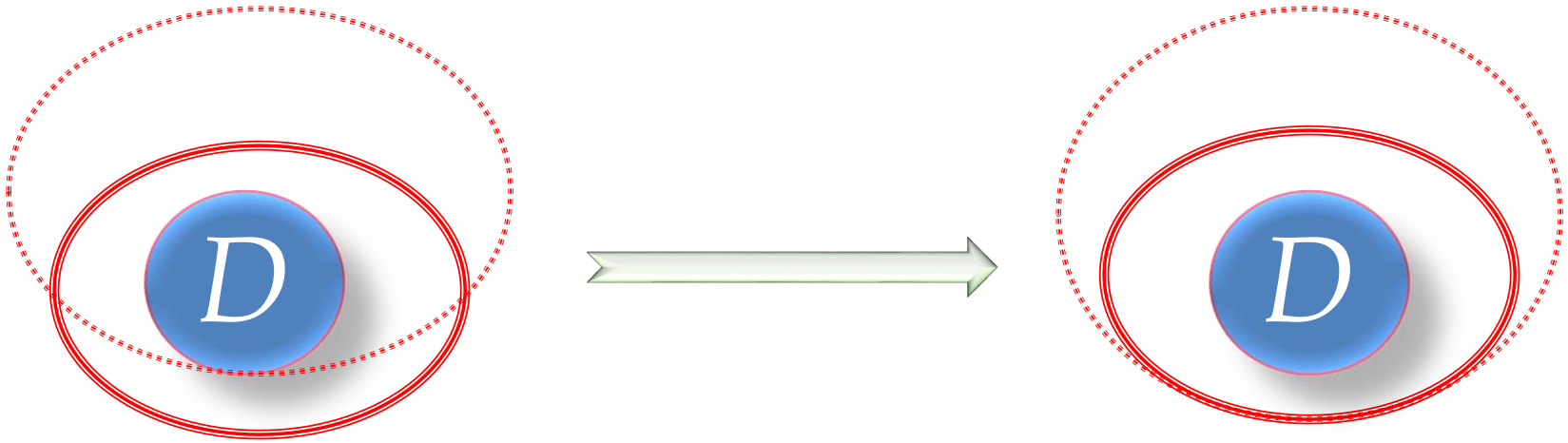
*ACTIVE DRUG*

*TOXIC METABOLITE*



Paracetamol

4




*INACTIVE*
*PRO DRUG*

*ACTIVE*
*D R U G*

Levodopa → Dopamine
Prednisone → Prednisolone
Bacampicillin → Ampicillin

# HOFFMAN ELIMINATION

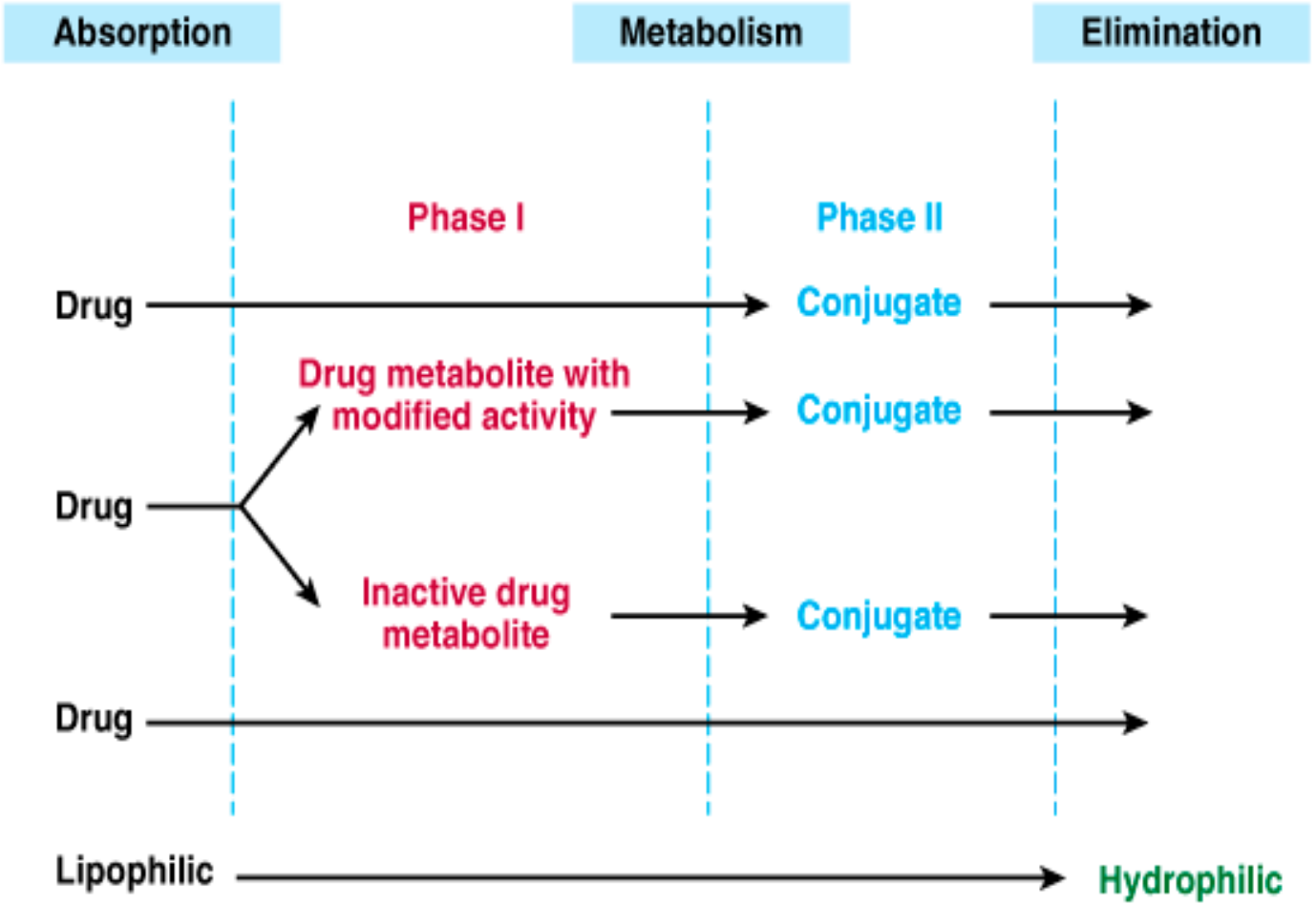
- “This refers to inactivation of the drug in the body fluids by spontaneous molecular rearrangement without the agency of any enzyme.”

- E.g Atracurium
- Hexamine
- Mistine HCL

# DRUS EXCRETED UNCHANGED

- Hydrophilic drugs (polar) are not metabolized and are excreted unchanged.
- Streptomycin and Neostigmine

Figure 4–1




Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com



Phase I and phase II reactions, and direct elimination, in drug biodisposition. Phase II reactions may also precede phase I reactions.

# SPIRAL INTEGERATION WITH BIOCHEMISTRY

# CLASSIFICATION

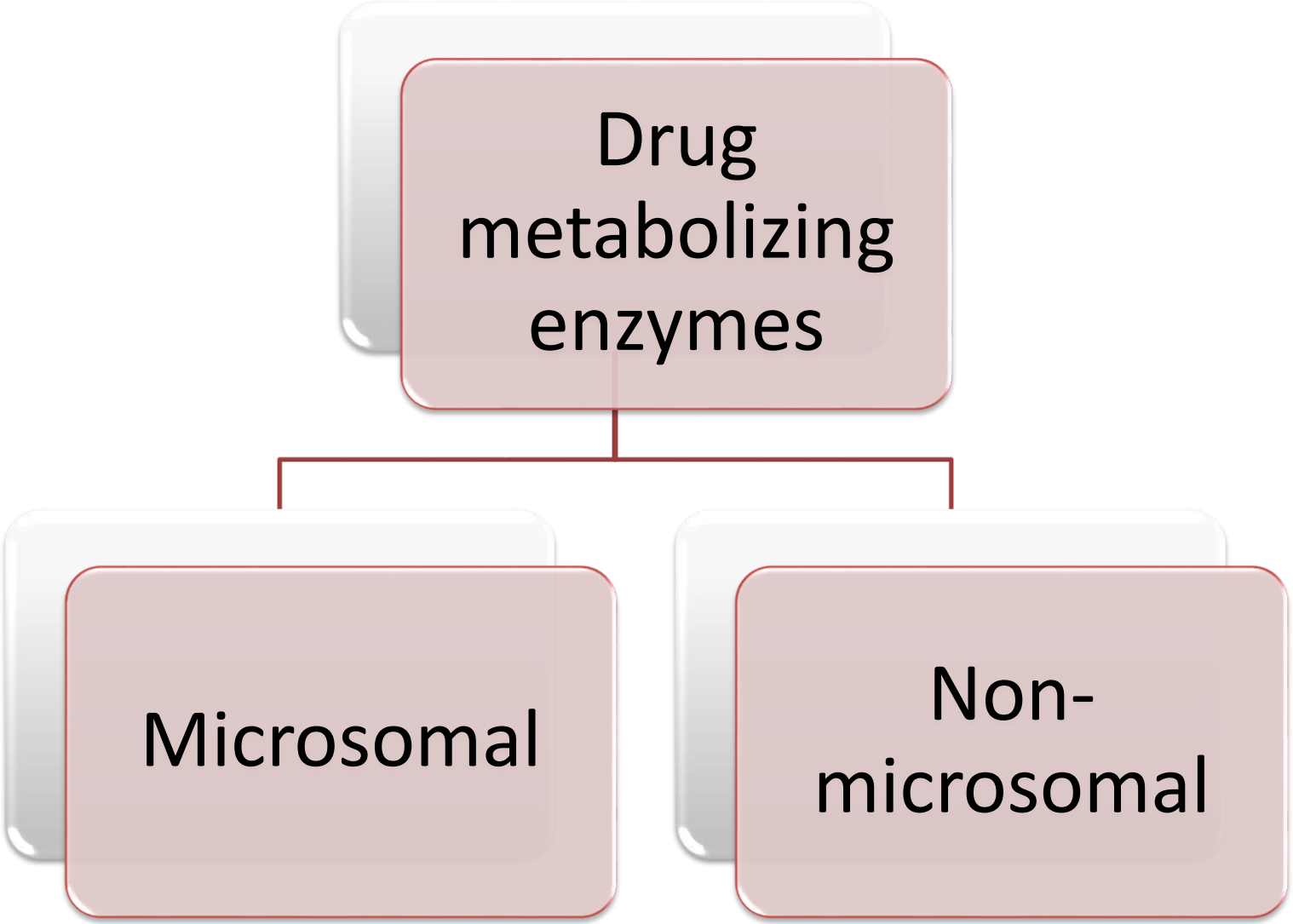
## ❖*Phase I reaction*

- ✓Oxidation
- ✓Reduction
- ✓Hydrolysis
- ✓Cyclization
- ✓Decyclization

## ❖*Phase II reaction*

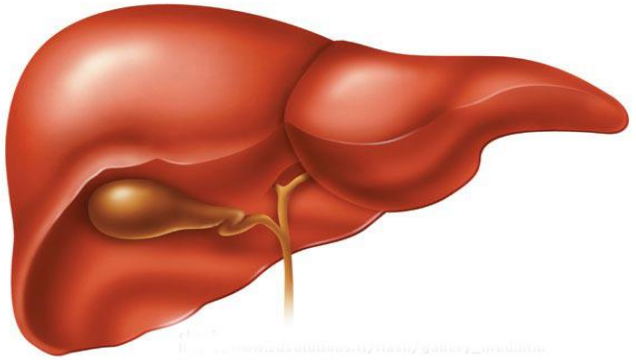
- ✓ Conjugation
- ✓ Acetylation
- ✓ Methylation

# CORE SUBJECT AND SPIRAL INTEGRATION WITH BIOCHEMISTRY

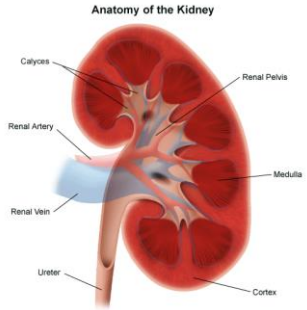

Drug metabolizing enzymes
Microsomal
Non-microsomal

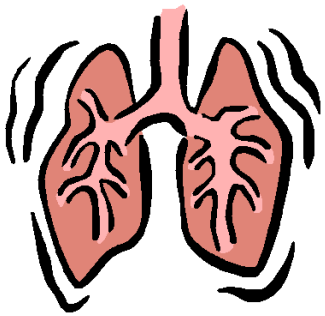
# MICROSOMAL ENZYMES

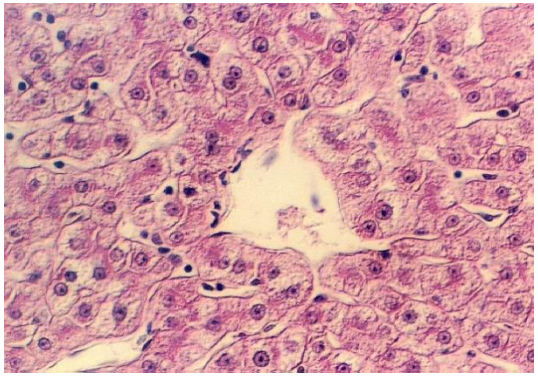
- Found predominately in the smooth Endoplasmic Reticulum of liver



- Other areas:





# NON-MICROSOMAL ENZYMES

- Found in the cytoplasm and mitochondria of hepatic cells
- Other tissues including plasma

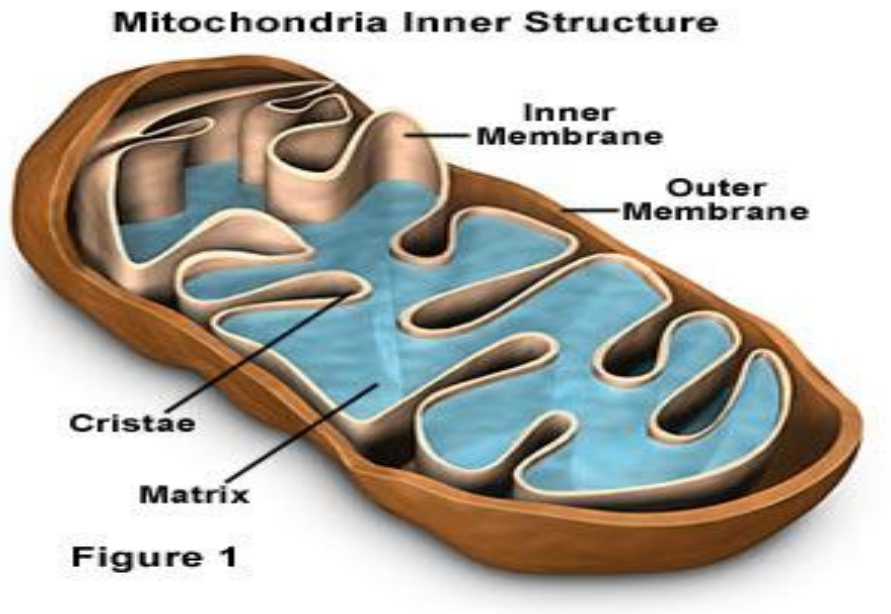


Figure 1

# Microsomal Enzymes

- ***Inducible***
  - **Drugs, diet, etc**

# Non-microsomal enzymes

- ***Not inducible***

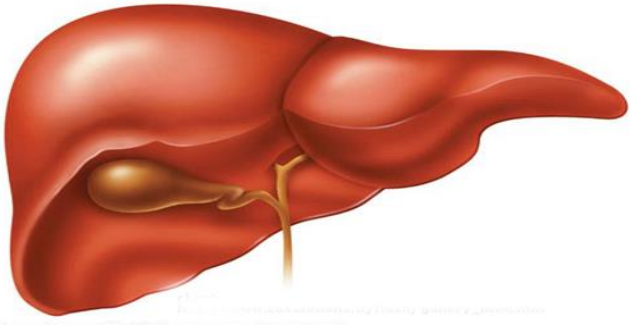
# CYTOCHROME P-450 ENZYMES

## a. General features

- A large number of families (at least 18 in mammals) of cytochrome P-450 (abbreviated “CYP”) enzymes exists

- This enzyme system is the one most frequently involved in phase I reactions.

## b. Localization



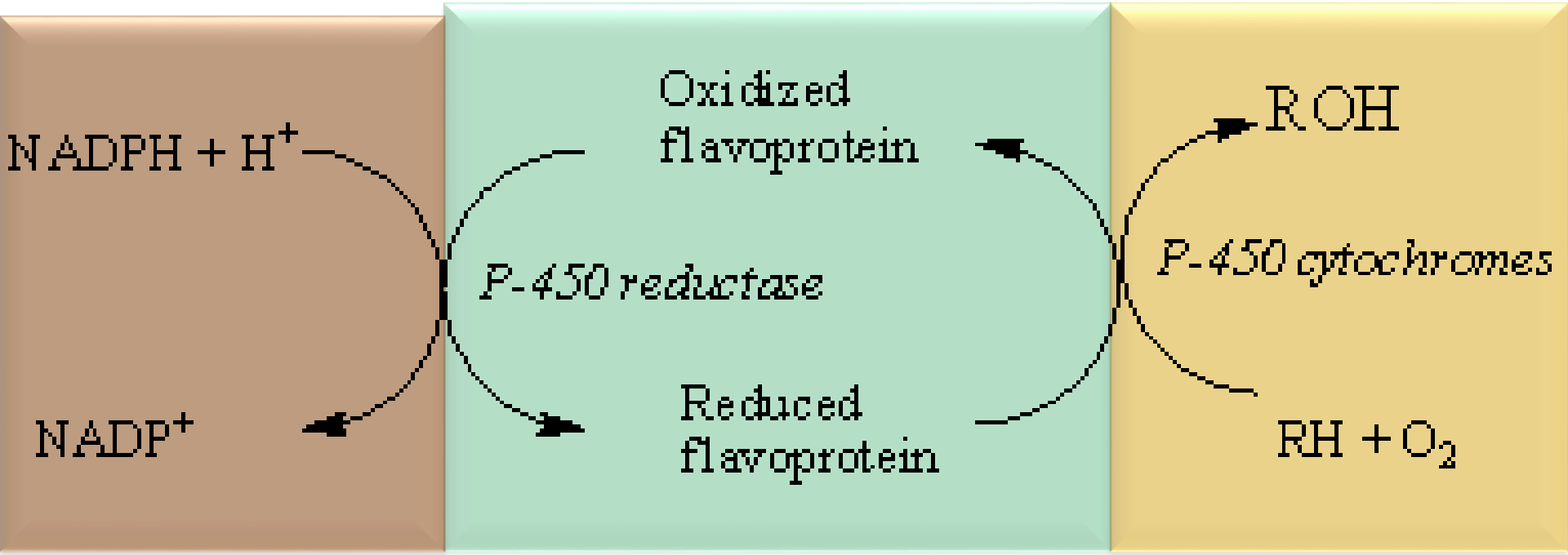
- The **primary location** of cytochrome P-450 is the **liver**,

- Other tissues, including:
  - the adrenals
  - ovaries and testis
  - tissues involved in steroidogenesis and steroid metabolism.

- The enzyme's subcellular location is the **endoplasmic reticulum.**

c. coupled to **cytochrome P-450 reductase.**

**d. Mechanism of reaction**




RH = drug, ROH = oxidized drug

# PHASE I REACTION

- A polar functional group is either introduced or unmasked
- ✓ ***E.g***. **–OH, -COOH, -NH2 and –SH**

- *Functionalization reactions*.

- Non-synthetic in nature.

# ENZYMES CATALYZING PHASE I

- Cytochrome P-450
- Aldehyde and alcohol dehydrogenase
- Deaminases
- Esterases
- Amidases
- Epoxide hydratases

# PATHWAYS OF METABOLISM

- CYTOCHROME 450-DEPENDENT OXIDATION

- Hydroxylation
- Dealkylation
- Sulfoxidation
- Deamination
- Desulfuration

# Continued…

## CYTOCHROME 450- INDEPENDENT OXIDATION

- Monoamine Oxidase - MAO
- Alcohol Dehydrogenase
- Xanthine oxidase

# OTHER PHASE I REACTIONS

- Reduction- Halothane, Chloramphenicol
- Hydrolysis-Procaine, Lidocaine
- Cyclization-Proguanil
- Decyclization-Barbiturates, Phenytoin

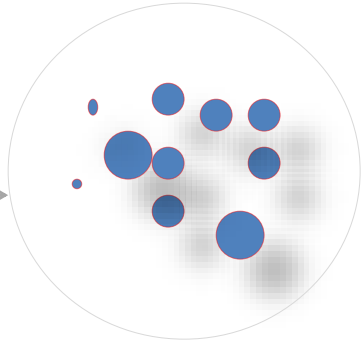
# PHASE II REACTION

- These reactions usually involves covalent attachments of small polar endogenous molecules.
- Products usually very hydrophilic
- They are also called conjugation, synthetic or anabolic reactions.

# ENZYMES CATALYZING PHASE II

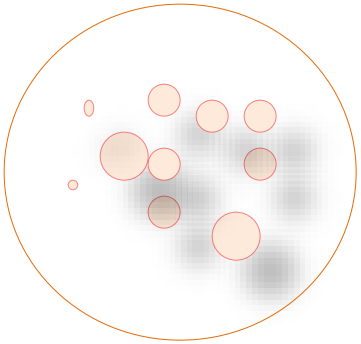
- Glucuronosyl Transferases
- Sulfotransferases (ST)
- Acetyltransferase
- Methylases

*Oxidation Reaction*

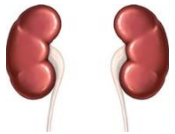


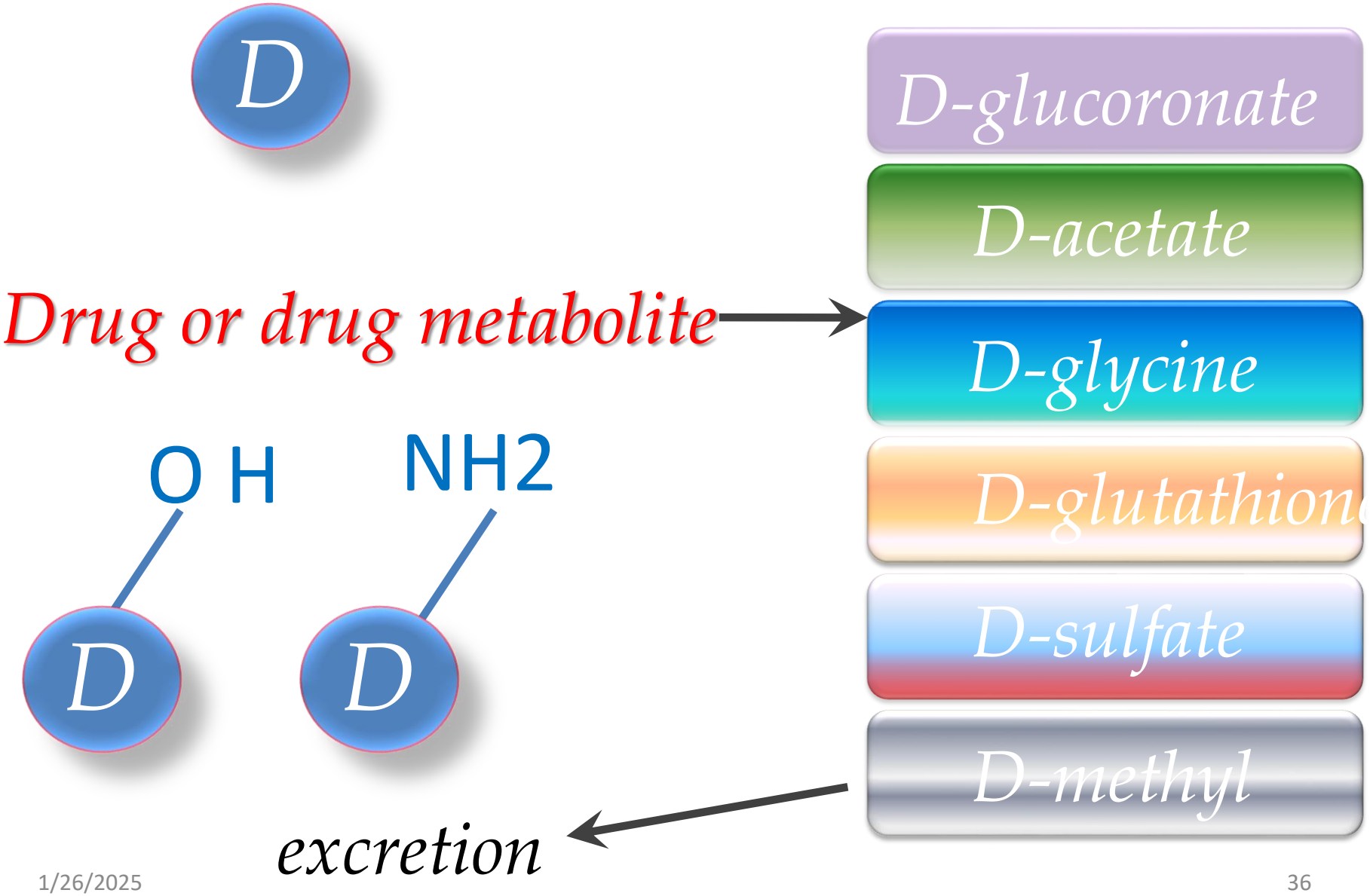
D

*Conjugation*



*Reaction*




D
Drug or drug metabolite
O H
NH2
D
D
D-glucoronate
D-acetate
D-glycine
D-glutathion
D-sulfate
D-methyl
excretion

# EXAMPLES

- Glucuronide Conjugation

✓ Chloramphenicol, Aspirin, Phenacetin, Bilirubin, Steriods

- Acetylation

✓ Sulphonamides, isoniazid,Hydralazine

- Methylation

✓ Adrenaline, Histamine

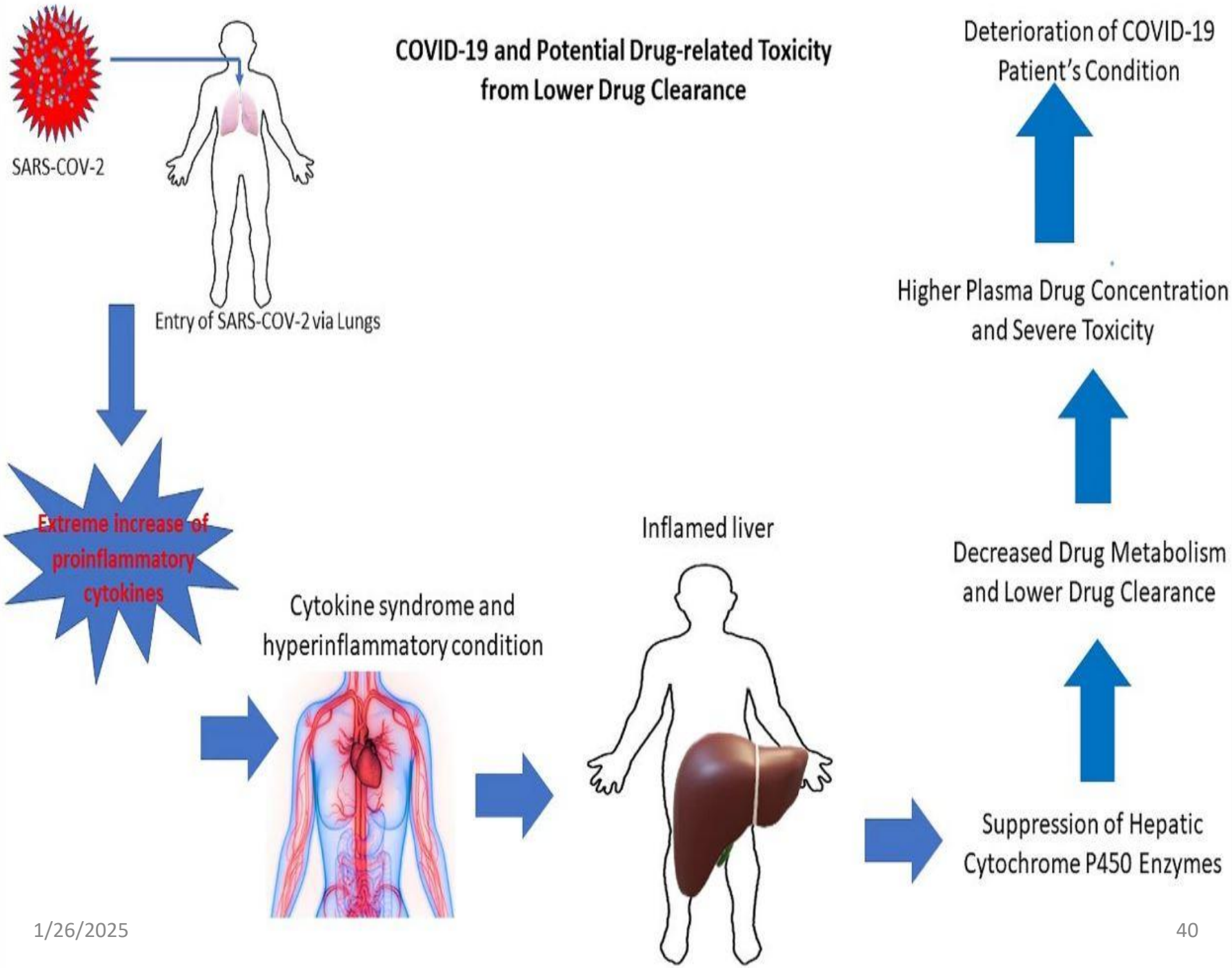
- Glutathione conjugation

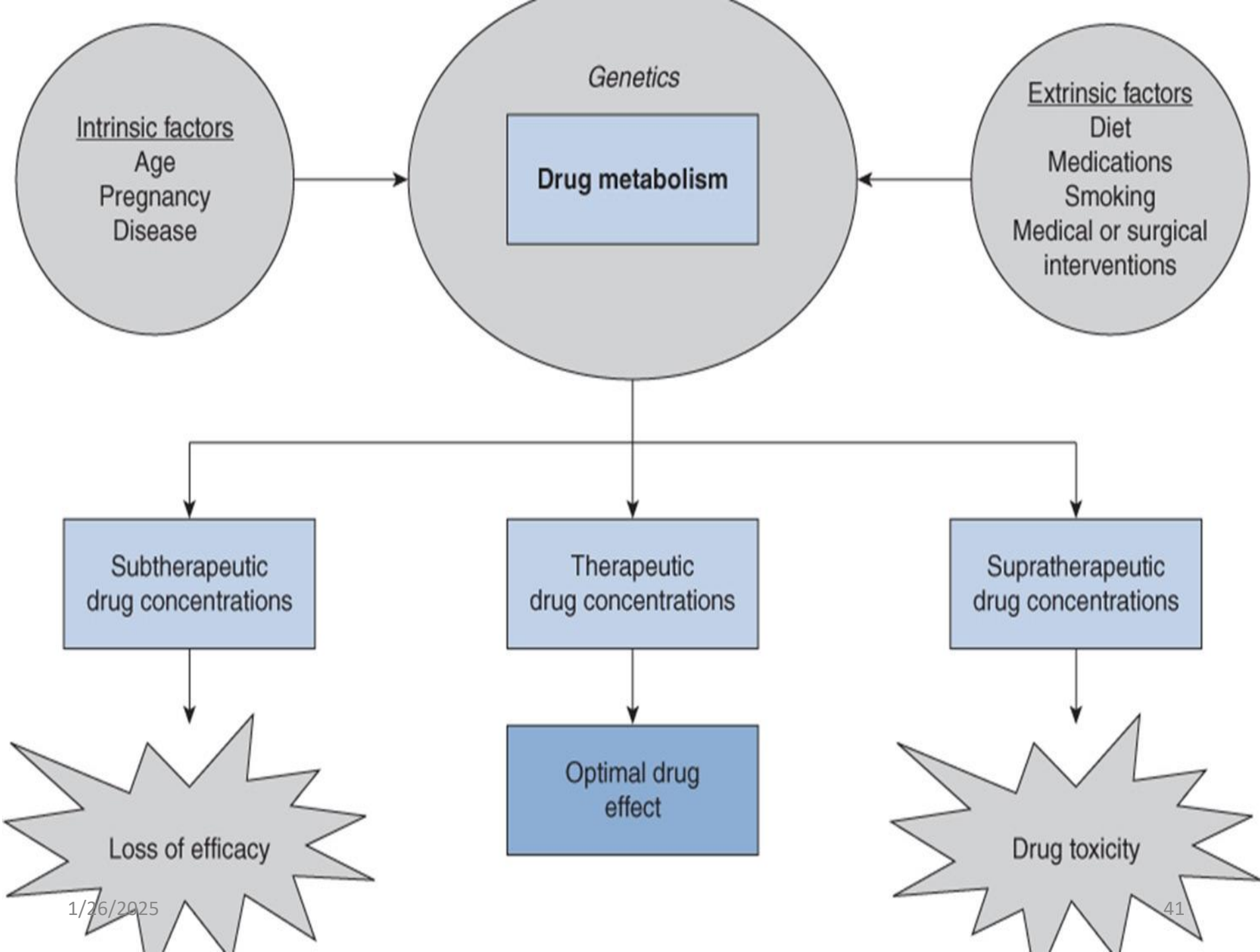
✓ Paracetamol

# HORIZONTAL INTEGRATION WITH PATHOLOGY AND VERTICAL INTEGRATION WITH MEDICINE

# FACTOR AFFECTING BIOTRANSFORMATION OF DRUG

- Age
- Gender
- Diet
- Individual differences
- Routes of administration
- Pathology of liver
- Pharmacogenetics
- Enzyme induction and enzyme inhibition


COVID-19 and Potential Drug-related Toxicity from Lower Drug Clearance
SARS-COV-2
Entry of SARS-COV-2 via Lungs
Extreme increase of proinflammatory cytokines
Cytokine syndrome and hyperinflammatory condition
Inflamed liver
Suppression of Hepatic Cytochrome P450 Enzymes
Decreased Drug Metabolism and Lower Drug Clearance
Higher Plasma Drug Concentration and Severe Toxicity
Deterioration of COVID-19 Patient's Condition


Intrinsic factors
Age
Pregnancy
Disease
Genetics
Drug metabolism
Extrinsic factors
Diet
Medications
Smoking
Medical or surgical interventions
Subtherapeutic drug concentrations
Therapeutic drug concentrations
Supratherapeutic drug concentrations
Loss of efficacy
Optimal drug effect
Drug toxicity

# BIOETHICS AND RESEARCH


- Zhong O, Wang J, Tan Y, Lei X, Tang Z. Effects of NAD+ precursor supplementation on glucose and lipid metabolism in humans: a meta-analysis. Nutrition & Metabolism. 2023 Mar 18;19(1):20.

- Yuan X, Wang J, Yang S, Gao M, Cao L, Li X, Hong D, Tian S, Sun C. Effect of the ketogenic diet on glycemic control, insulin resistance, and lipid metabolism in patients with T2DM: a systematic review and meta-analysis. Nutrition & diabetes. 2023 Nov 30;10(1):38.

# ARTIFICIAL INTELLIGENCE

- Dudas B, Miteva MA. Computational and artificial intelligence-based approaches for drug metabolism and transport prediction. Trends in Pharmacological Sciences. 2023 Dec 9.

# EOLA

- What is the mechanism by which the body terminates the action of some drugs and also serves to activate prodrugs?
- A. Bioavailability
- B. Biotransformation
- C. Enzyme induction
- D. Enzyme inhibition

# EOLA

What drug's metabolism has phase 2 preceding phase 1?

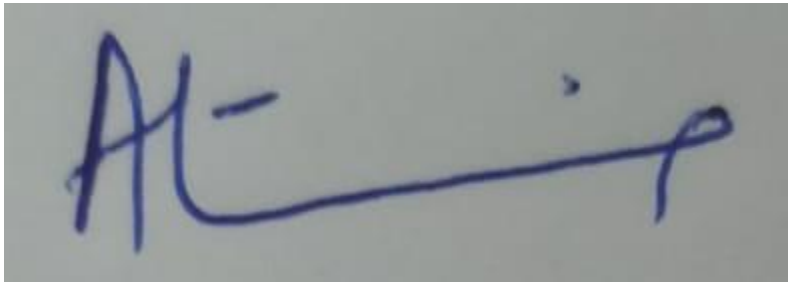
- A. Mitomycin C
- B. Ketoconazole
- C. Isoniazid
- D. Tamoxifen
- E. Morphine

# EOLA

- Which enzyme is responsible for conjugating bilirubin in the liver and facilitating its excretion?
- A. UDP-glucuronosyl transferase
- B. N-acetyltransferase
- C. Pseudocholinesterase
- D. Vitamin K epoxide reductase
- E. Alcohol dehydrogenase

# TAKE HOME MESSAGE

- Important concept in selecting the dose and dosage form for a particular indication.
- Pharmacogenetic studies focus on biotransformation of drugs



*Thank You*