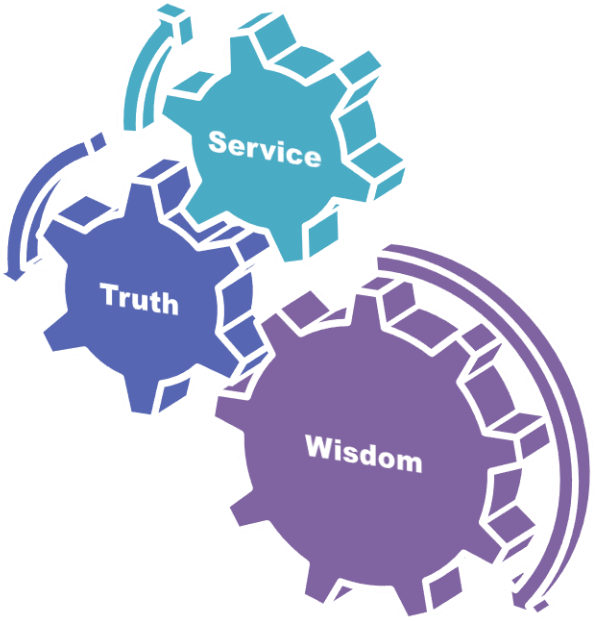
BIOTRANSFORMATION OF DRUGS

Sources:

Bertram G. katzung Basic & Clinical Pharmacology 15th Edition

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

University Moto, Vision & Values

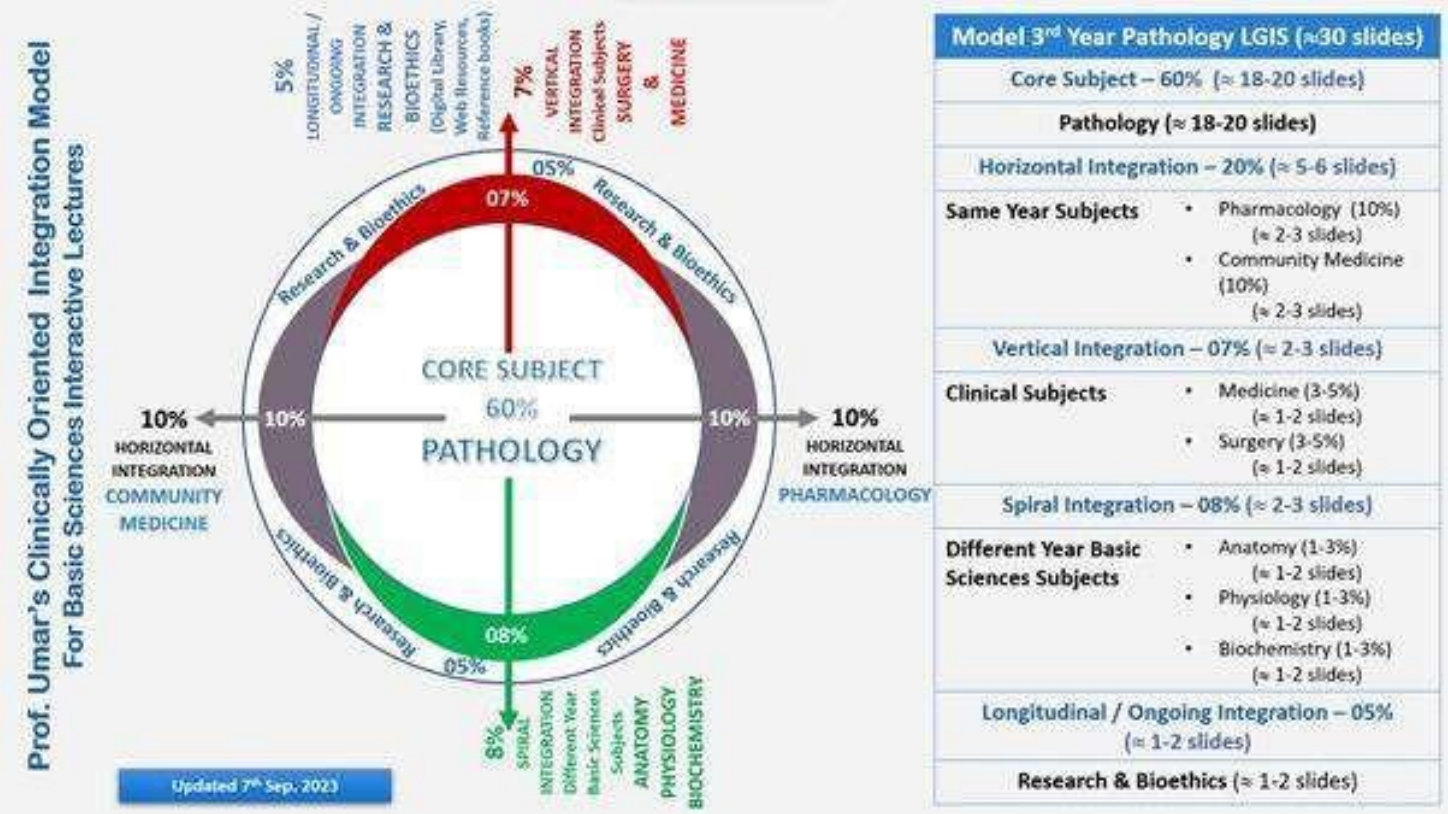


Vision and Values

Highly recognized and accredited center of excellence in Medical Education, using evidence-based training techniques for development of highly competent health professionals, who are critical thinkers, experiential self-directed life long learners and are socially accountable

Mission Statement

To impart evidence-based research-oriented health professional education in order to provide best possible patient care and inculcate the values of mutual respect, ethical practice of healthcare and social accountability.



Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

Pre Lecture Assessment

- 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

Pre Lecture Assessment

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

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

Pre Lecture Assessment

- 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

Pre Lecture Assessment

- An antibiotic (rifampin) and an anticoagulant (warfarin) were administered daily together to a hospitalized patient for a week following a heart valve replacement. During this time the warfarin dosage was adjusted to get an INR of 2-3 and an increase in prothrombin time. On day 8, the rifampin was discontinued, and the patient was discharged. The same dosage of warfarin was continued for the next two weeks after discharge. What change would be expected at the end of the two weeks post-discharge?

A. Prothrombin time would be decreased
B. warfarin plasma levels would remain unchanged
C. warfarin plasma levels would be increased
D. the patients INR would be below normal (<1.0)
E. the patients INR would be normal (1-1.3)

Pre Lecture Assessment

Which of the following drugs has self -induction to stimulate their own metabolism?

A. Pentobarbital
B. Meprobamate
C. Contraceptives
D. Cortisol
E. Rifampicin

Which of the following is not a characteristic of the moieties that are transferred to the substrate in phase II reactions?

A. Large molecular sized groups are attached
B. Strong polar groups are attached
C. Strong nonpolar groups are attached
D. Simple endogenous molecules are transferred
E. Strong functional groups are exposed

Pre Lecture Assessment

A drug undergoes biotransformation to form a metabolite that is pharmacologically active. Which of the following terms best describes this scenario?

A. Prodrug
B. Active metabolite
C. Inactive metabolite
D. Parent drug
E. Toxic metabolite

Which of the following factors can lead to a decrease in drug metabolism in the elderly population?

A. Increased liver blood flow
B. Enhanced Phase I liver enzyme activity
C. Decreased liver size and function with aging
D. Increased renal excretion of metabolites
E. Increased conjugating moieties

Pre Lecture Assessment

- A 45-year-old male patient is prescribed a drug that undergoes extensive metabolism by the liver, primarily through cytochrome P450 enzymes. The patient has a history of chronic alcohol use. How might the patient's chronic alcohol use affect the biotransformation of this drug?

  A) Alcohol will inhibit the cytochrome P450 enzymes, leading to slower drug metabolism.

  B) Alcohol will induce the cytochrome P450 enzymes, leading to faster drug metabolism.

  C) Alcohol will have no effect on the metabolism of the drug.

  D) Alcohol will decrease liver enzyme activity, resulting in reduced drug metabolism.

  E) Alcohol will increase the formation of inactive metabolites, reducing drug effectiveness.

Pre Lecture Assessment

- A patient with a reduced function genetic variation in the CYP2D6 enzyme may experience altered drug metabolism. What effect would this genetic variation most likely have on drug metabolism?

A) The patient would metabolize drugs faster, potentially requiring higher drug doses.
B) The patient would metabolize drugs more slowly, potentially leading to drug toxicity.
C) The patient's drug metabolism would remain unaffected.
D) The patient would experience no change in the metabolism of drugs metabolized by other enzymes
E) The patient would metabolize drugs more quickly, leading to reduced therapeutic effects.

LEARNING OBJECTIVES

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

- Define biotransformation
- Recognize the clinical consequences of biotransformation
- Describe phase I and phase II reactions
- Discuss microsomal and non microsomal enzyme
- Discuss factors affecting biotransformation of drugs

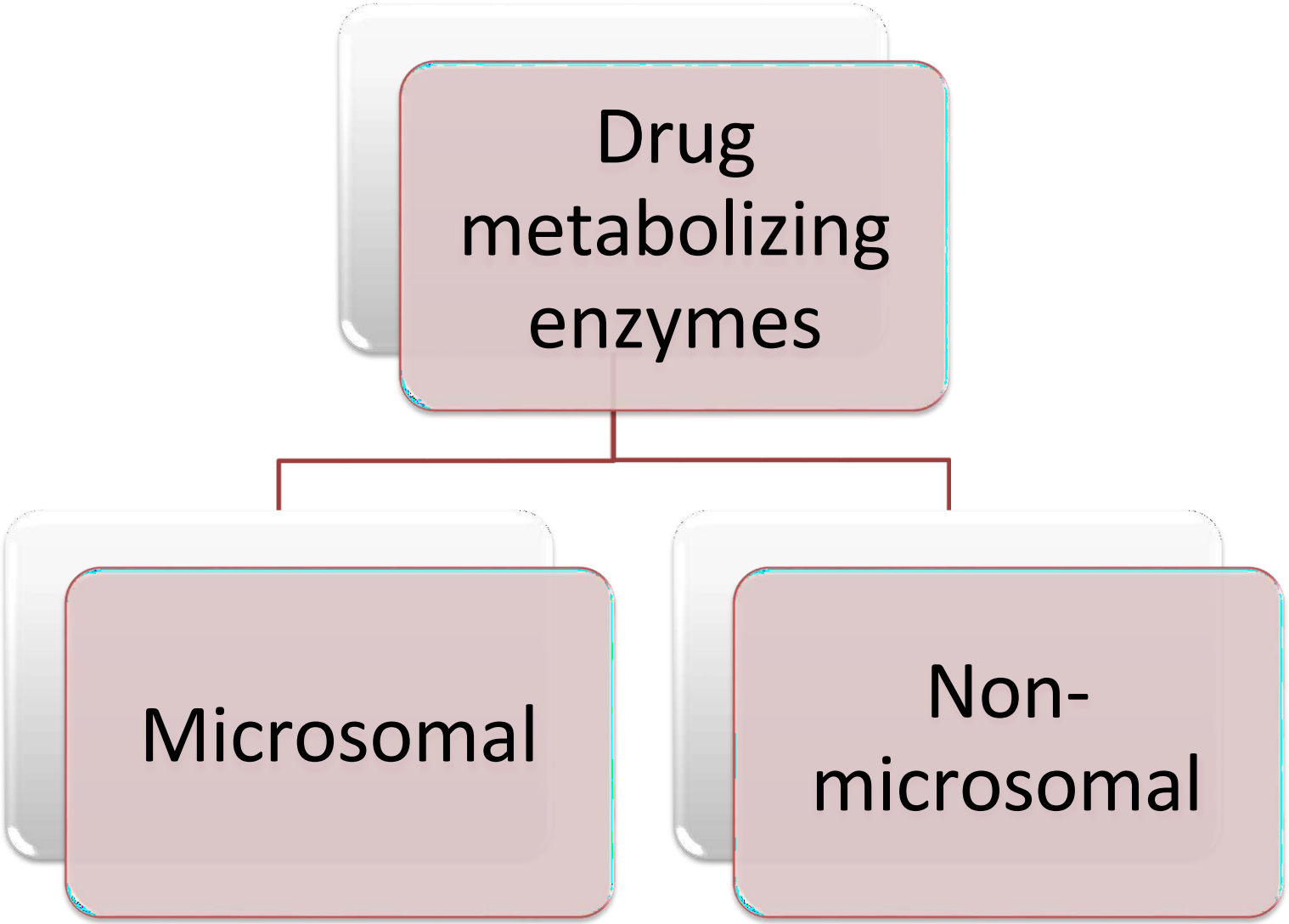
CLASSIFICATION

❖*Phase I reaction*

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

❖*Phase II reaction*

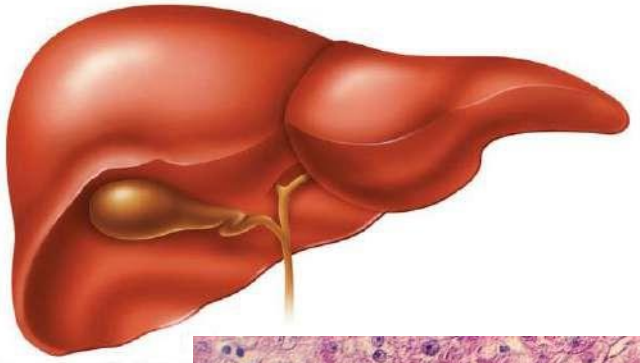
- ✓ Conjugation
- ✓ Acetylation
- ✓ Methylation



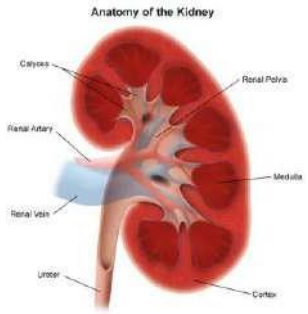
SPIRAL INTEGERATION WITH BIOCHEMISTRY

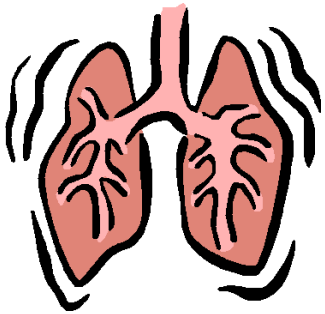
MICROSOMAL ENZYMES

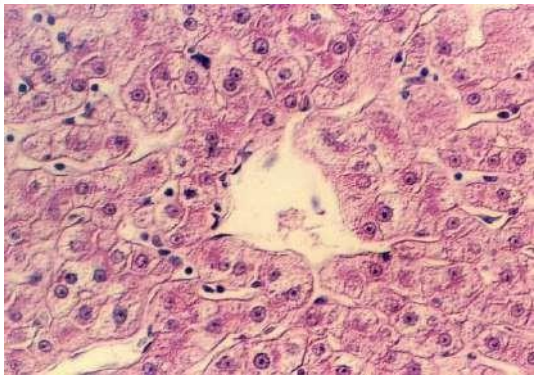
- Found predominately in the smooth Endoplasmic Reticulum of liver



- Other areas:

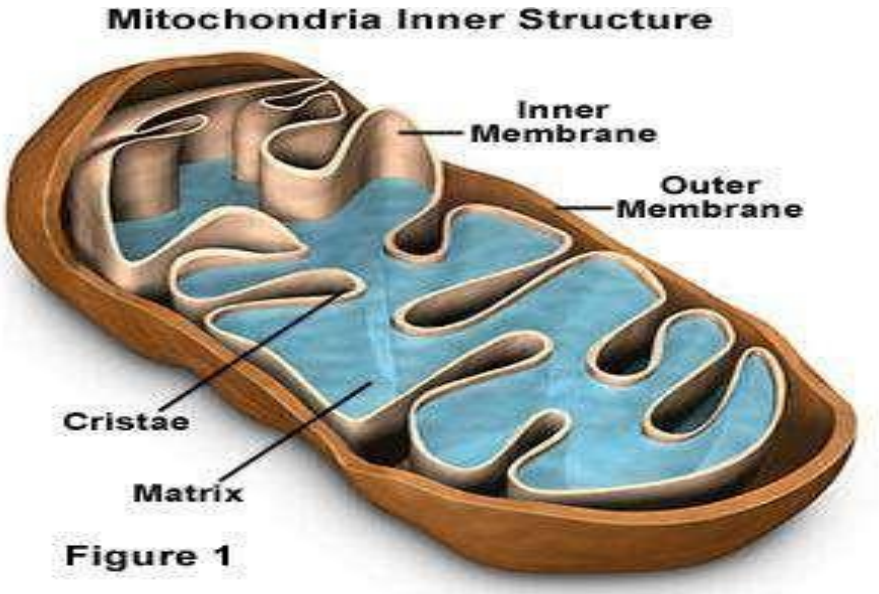






NON-MICROSOMAL ENZYMES

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



Microsomal Enzymes

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

Non-microsomal enzymes

- ***Not inducible***

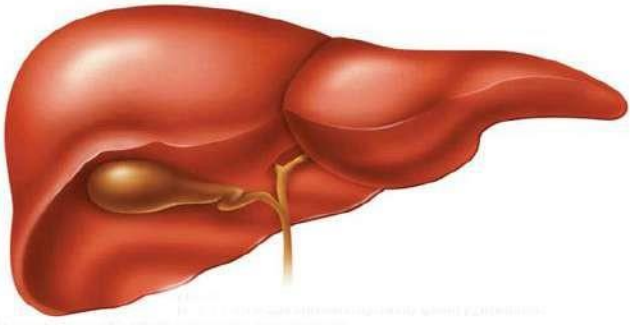
CYTOCHROME P-450 ENZYMES

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



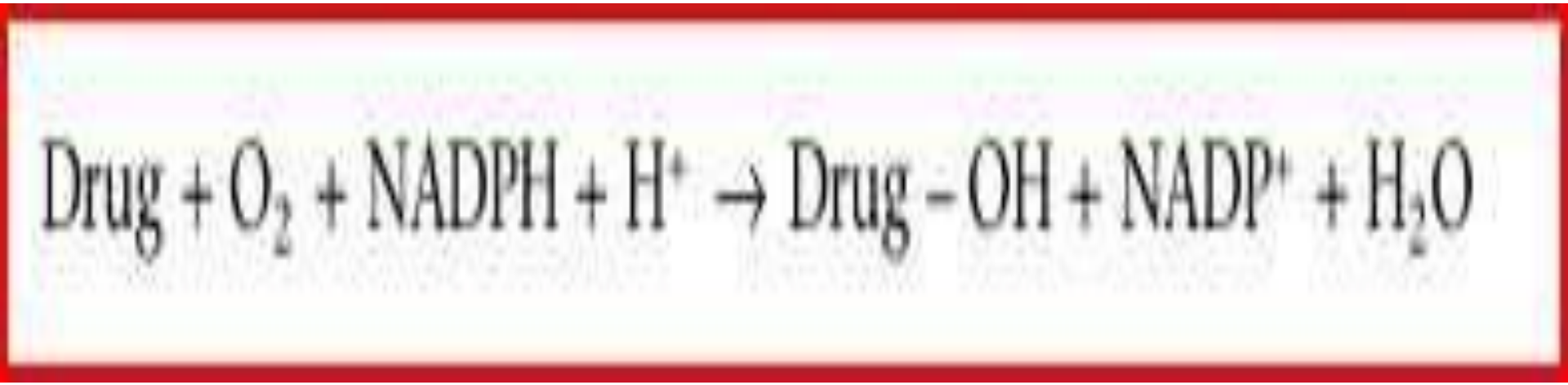
- The **primary location** of cytochrome P-450 is the **liver**,

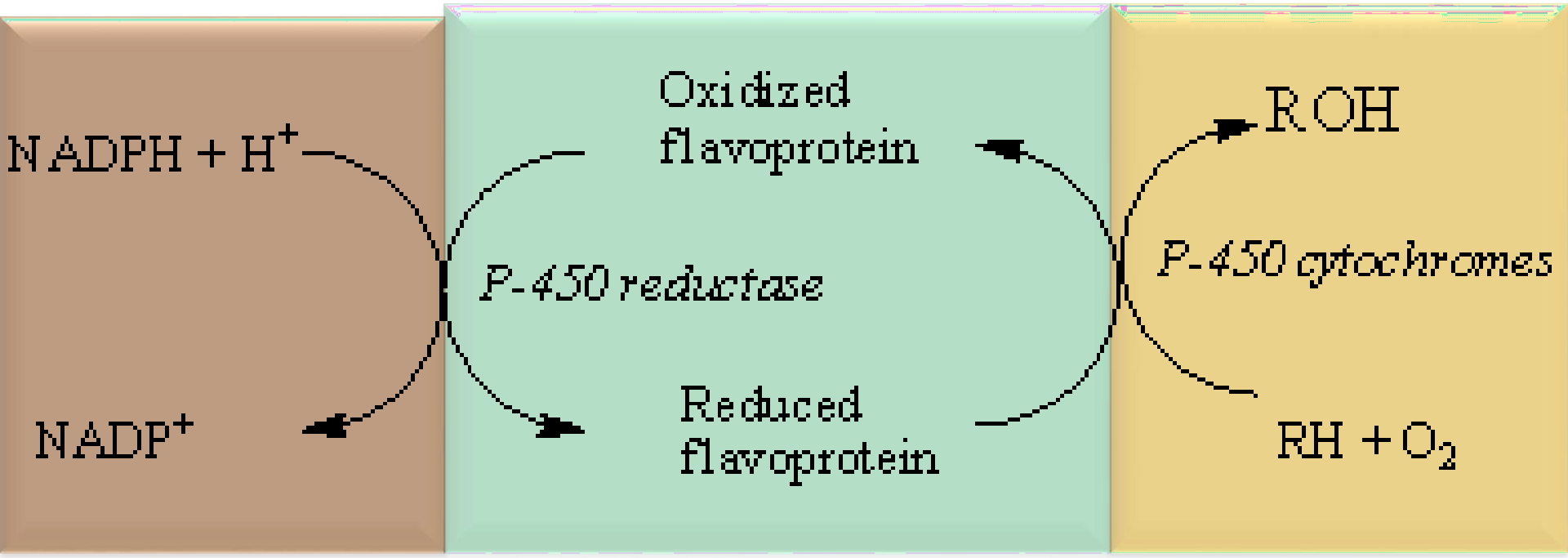
- Other tissues, including:
  - the adrenals
  - ovaries and testis
  - tissues involved in steroidogenesis and steroid metabolism.

- 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

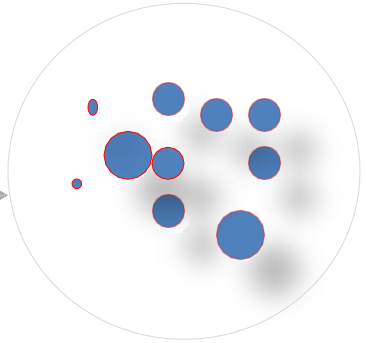
PHASE II REACTION

- 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

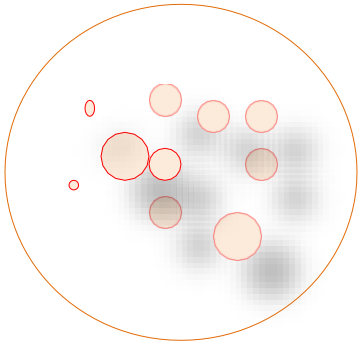
- Glucuronosyl Transferases
- Sulfotransferases (ST)
- Acetyltransferase
- Methylases

Oxidation Reaction

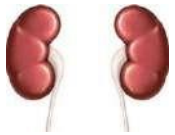


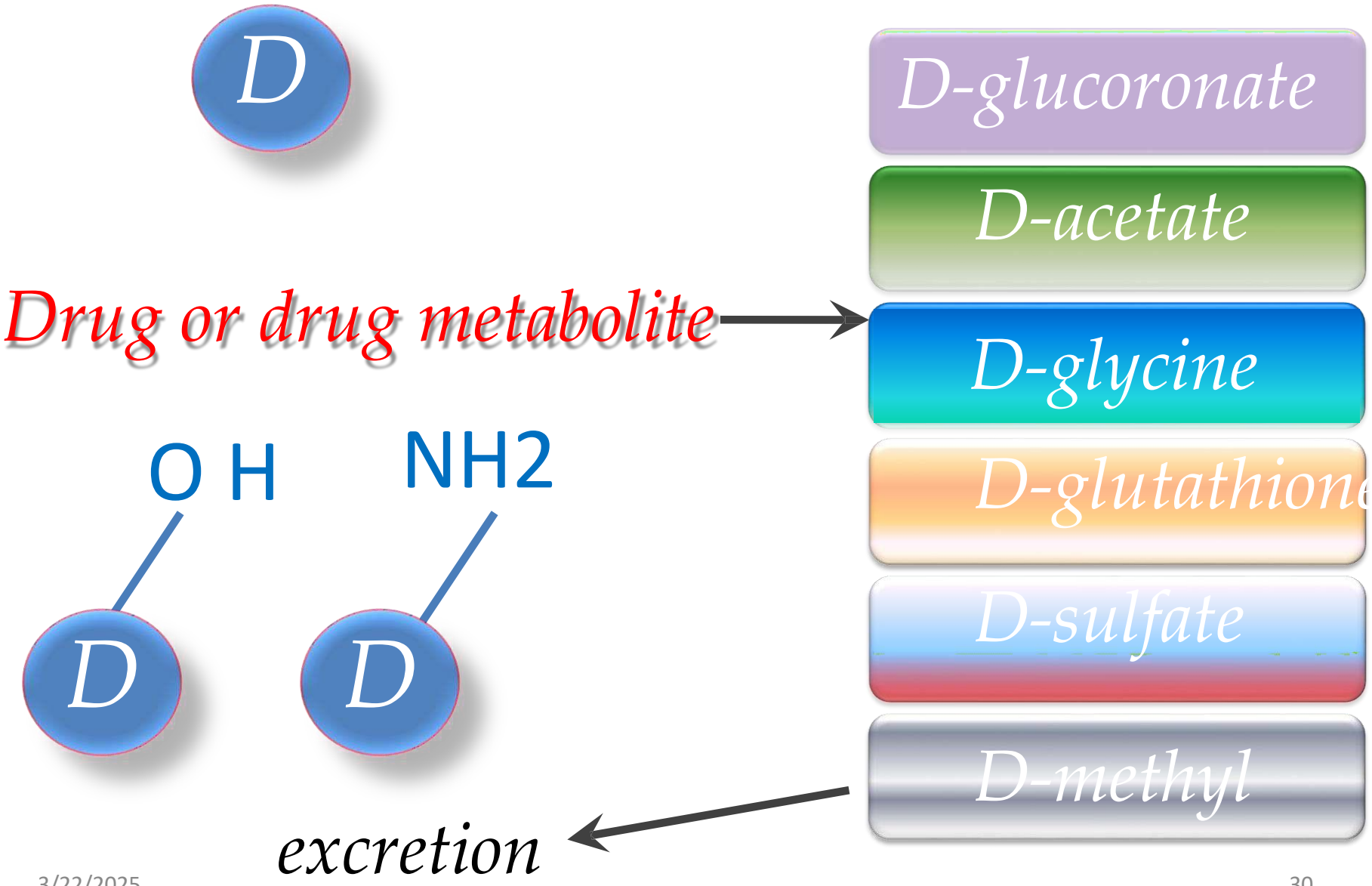
D

Conjugation



Reaction




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

EXAMPLES

- Glucuronide Conjugation

✓ Chloramphenicol, Aspirin, Phenacetin, Bilirubin, Steriods

- Acetylation

✓ Sulphonamides, isoniazid,Hydralazine

- Methylation

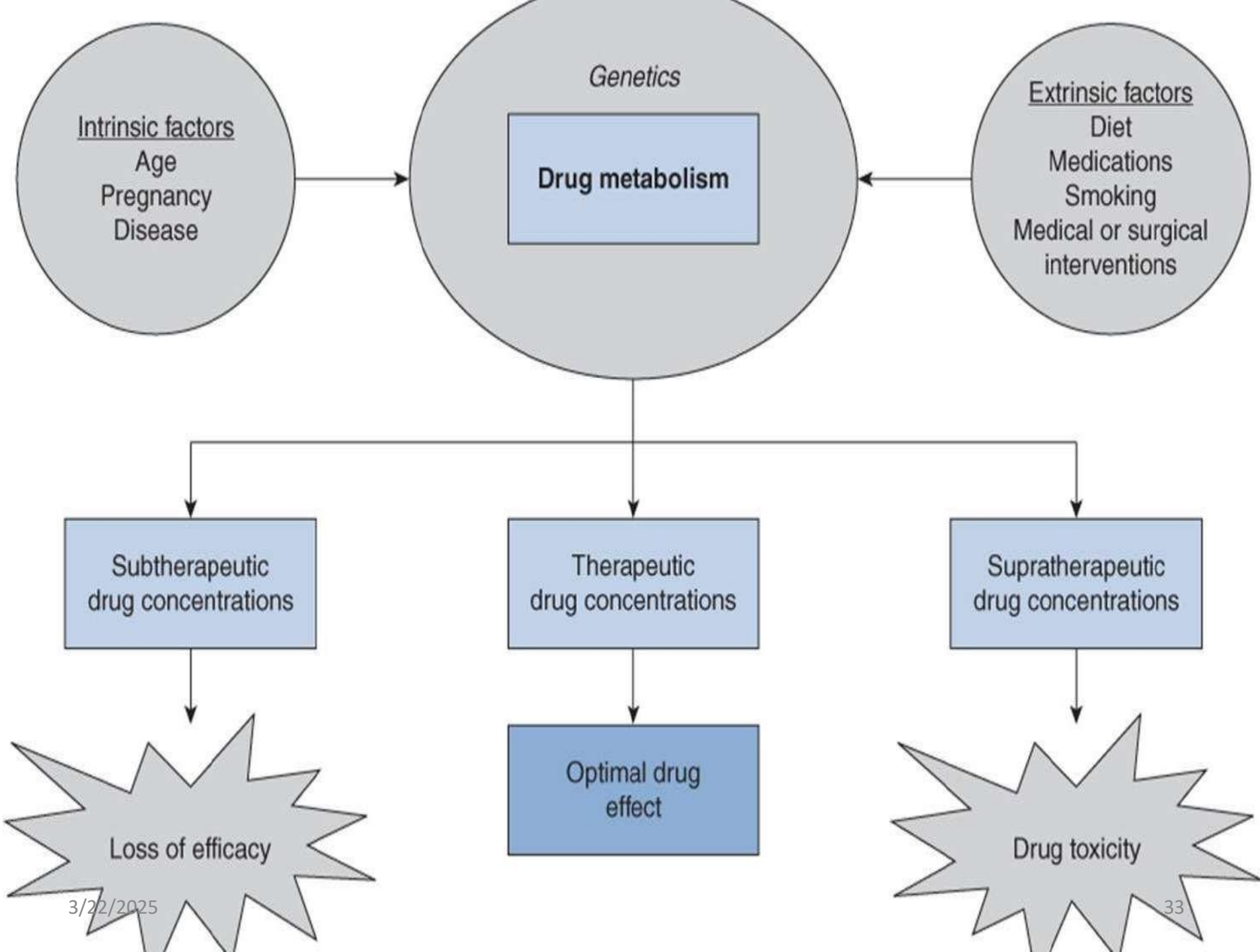
✓ Adrenaline, Histamine

- Glutathione conjugation

✓ Paracetamol

FACTOR AFFECTING BIOTRANSFORMATION OF DRUG

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


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.

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