Metabolism of Xenobiotics

Introduction of xenobiotics
Biotransformation
Cytochrome P450
phase I and Phase II reactions
Biomedical importance of xenobiotics

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Xenobiotics/Detoxification/Biotransformation

- (Gk ***Xenos*** means **"stranger"**

(any foreign substance which the body does not recognize)

- biotics = metabolism

- **Xenobiotics** means **metabolism of foreign molecules/compounds.**

- Also called- **Detoxification**

(conversion of toxic substances to less toxic molecules).

- Also called- **Biotransformation**

(because not every time toxic molecules converted to the less toxic it may be converted to the less toxic molecules to more toxic molecules.

Types of Xenobiotics

- **Exogenous-**

The foreign molecules which gain entry through dietary food stuffs, or in the form of certain medicines/ drugs used for a therapeutic cause or are inhaled through environment .

Examples*: Drugs, food additives, pollutants, insecticides, etc.*

- **Endogenous-**

These are synthesized in the body or are produced as metabolites of various processes in the body.

Examples*: Bilirubin, Bile acids, Steroids, Eicosanoids and certain fatty acids.*

Purpose of Biotransformation

1. **facilitates excretion:** Converts lipophilic to hydrophilic compounds

2. **Detoxification/inactivation**: converts chemicals to less toxic forms

3. **Metabolic activation**: converts inactive drug to its active form

Metabolism of Xenobiotics

- **Detoxification Reactions**

All the biochemical reactions, involved in the conversion of foreign, toxic and water insoluble molecules to non toxic, water soluble and excretable forms are called ***Detoxification / Biotransformation reactions.***

- **Metabolism of xenobiotics occurs in two phases-**

Phase I & Phase II

- The overall purpose of the two phases (phase I & phase II) of metabolism of xenobiotics is to increase their **water solubility (polarity)** and thus **excretion** from the body.

Phase I : Phase 1 reactions converts xenobiotics from **inactive to biologically active and/or more toxic to less toxic** compounds.

- The major reactions involved are **oxidation, reduction and hydroxylation.** In addition to these, a wide range of reactions also take place during phase I-

- **Deamination**
- **Dehalogenation**
- **Desulfuration**
- **Epoxidation**
- **Peroxygenation**

Phase 2 (Conjugation reactions): Phase 2/conjugation reactions converts active products of phase 1 reactions to **less active or inactive species and/or converts molecules to water soluble & polar in nature,** which are subsequently easily excreted in the urine or bile.

- The compounds produced in phase 1 are converted by specific enzymes to various polar metabolites by **conjugation** with- (4G M SAT)
- **Glucuronic acid**
- **Glycine**
- **Glutamine**
- **Glutathione**
- **Methylation**
- **Sulfation**
- **Acetylation**
- **Thiosulfation**

Sites of detoxification/biotransformation

- Liver
  - Primary site! Rich in enzymes
  - Hepatocytes contain wide variety of enzymes to process xenobiotics
  - Acts on endogenous and exogenous compounds

- Extra-hepatic metabolism sites
  - Intestinal wall
    - Sulfate conjugation
    - Esterase and lipases - important in pro-drug metabolism
  - Lungs, kidney, placenta, brain, skin, adrenal glands

Xenobiotic-Metabolizing Enzymes (XME)

Phase I enzymes:

- Cytochrome P_{450}
- Flavin Containing Monooxygenase
- Epoxide Hydrolase
- Alcohol /Aldehyde Dehydrogenases
- Monoamine Oxidases
- Xanthine oxidase

Phase II enzymes: "Transferases"

Sulfotransferases (ST)

UDP-glucuronosyltransferases (UGT)

Glutathione S-transferases (GST)

Cytochrome P_{450}

- Most of the oxidation reaction of detoxification are catalysed by monoxygenese or cytochrome P_{450}. *The P_{450} refers to the absorption peak of this enzyme at 450 nm, when it is exposed to the Carbon monoxide (CO).*
- Multiple forms of Cyt. P_{450} are available ranging from 20 to 200.
- They are all hemoproteins, containing heme as the prosthetic group.
- It is found in the highest concentration in the microsomes of liver. The mechanism of action of Cyt. P_{450} is complex and is dependent on NADPH.

PHASE I REACTIONS

1. Oxidation

- A large number of foreign compounds are detoxified by oxidation.

- Example of compounds: **Alcohols, Aldehydes, Amines, Aromatic hydrocarbons and sulfur compounds** etc.

Ethanol → **Acetic acid**

Benzaldehyde → **Benzoic acid**

Aniline → **p- Amino phenol**

Benzene → **Phenol**

Organic sulfur → **Sulfuric acid**

2. Reduction

- The following are the reactions of detoxification by reduction.
- Example of compounds: **Picric acid, Chloral, Nitrobenzene etc.**

Picric acid → **Picramic acid**

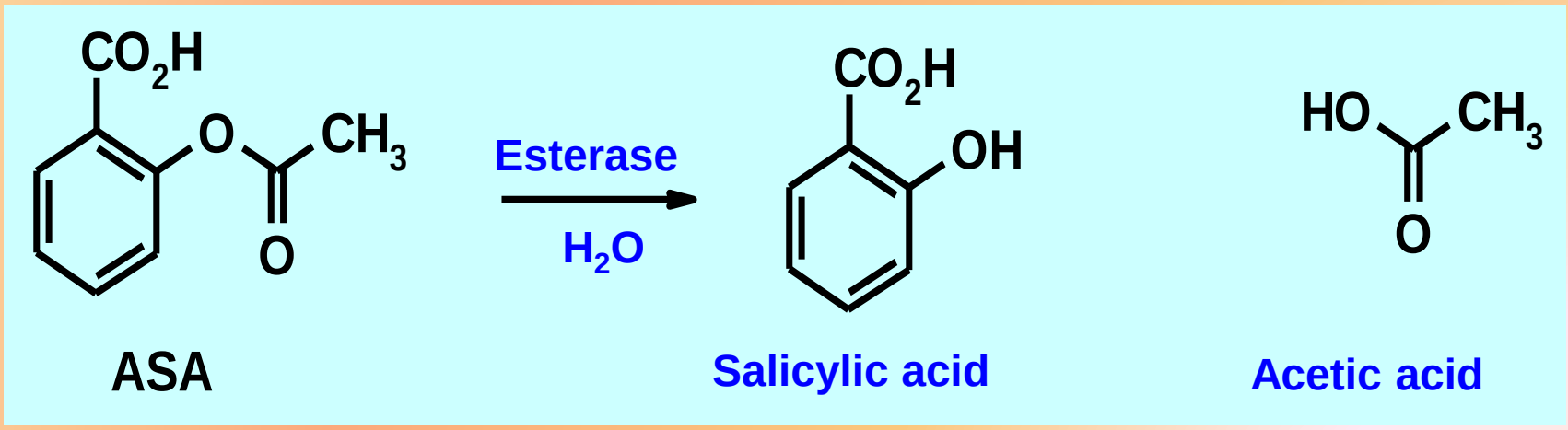
Chloral → **Trichloroethanol**

Nitrobenzene → **Aminobenzene**

3. Hydrolytic Reactions

- The hydrolysis of the bonds such as **ester, glycoside and amide** is important in the metabolism of xenobiotics.

- Example of compounds: **Aspirin, Acetanilide, Atropine** etc.



Acetylsalicylic Acid
(Aspirin)

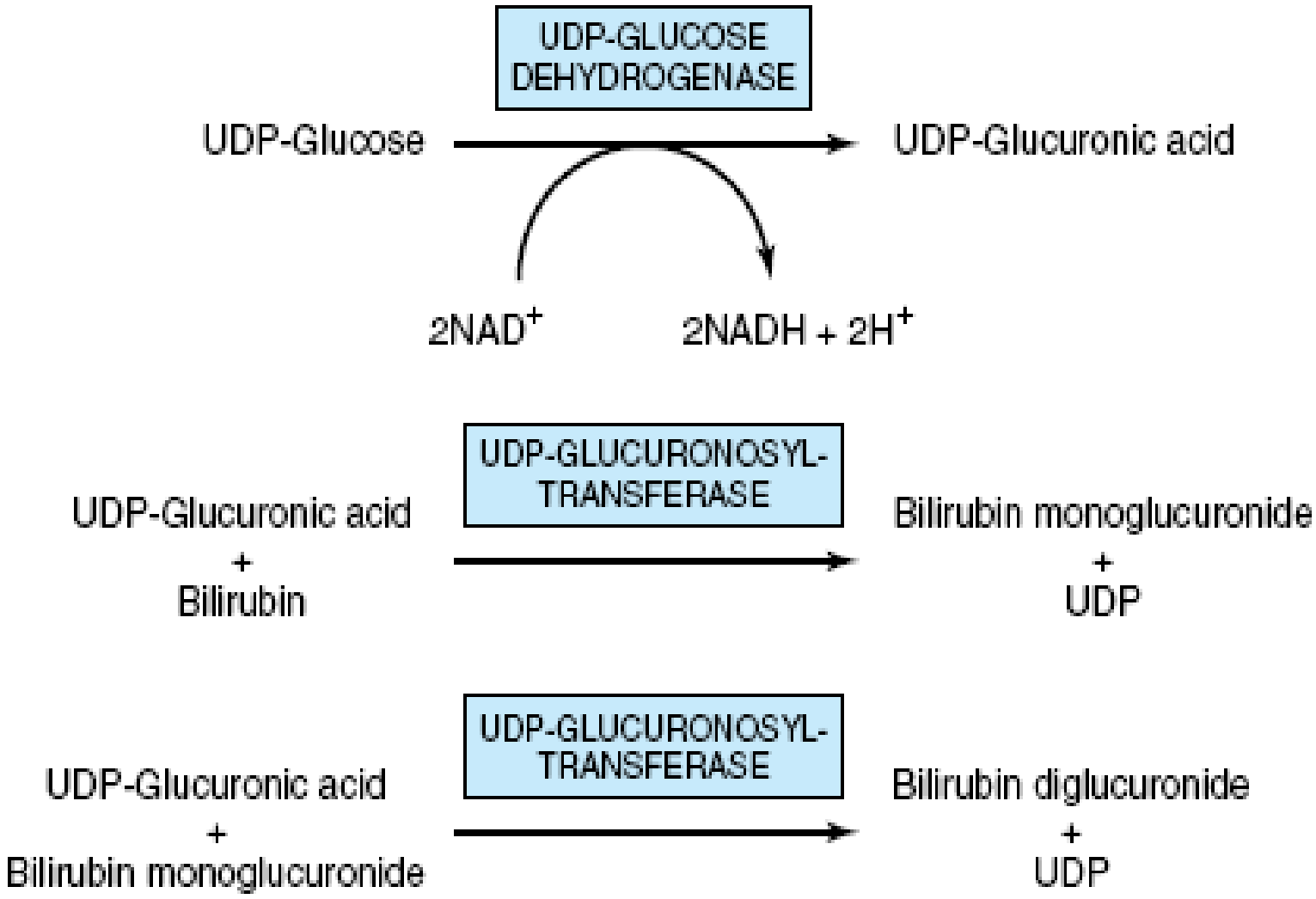
PHASE II REACTIONS

(CONJUGATION REACTIONS)

1. Glucuronidation

- Conjugation with **glucuronic acid** is most frequent conjugation reaction.
- UDP-glucuronic acid (UDPGA) is the glucuronyl donor and active form.
- UDP-glucuronyl transferases (UGT), present in both the endoplasmic reticulum(ER) and cytosol, are the catalysts.
- Compounds such as *2-acetylaminofluorene (a carcinogen), aniline, benzoic acid, meprobamate (a tranquilizer), phenol, bilirubin and many steroids* are excreted as glucuronides.

Glucuronidation of bilirubin



2. Conjugation with Glycine

- Example: Glycine conjugated with **Cholic acid, Benzoyl CoA** and form **Glycocholic acid** and **hippuric acid.**

Cholic acid + Glycine → **Glycocholic acid**

Benzoyl CoA + **Glycine** → **Hippuric acid**

3. Conjugation with Glutamine

- Example: Glutamine conjugated with **Phenyl acetic acid** and form **Phenylacetylglutamine .**

Phenyl acetic acid + Glutamine → **Phenylacetylglutamine**

- Phenylacetylglutamine is excreted in phenylketonuria (PKU) patients urine.

4. Conjugation with Glutathione

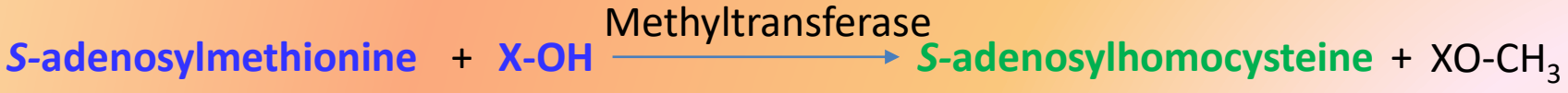
- Glutathione (**γ-glutamyl-cysteinylglycine**) is a **tripeptide** consisting of **glutamic acid, cysteine, and glycine (G-C-G)**.

  - **Cysteine** part of the glutathione is very important in the detoxification process.

R-cysteine + aromatic compound $\xrightarrow{\text{N-acetyl transferase}}$ Mercapturic acid

5. Methylation

- **Enzyme: methyltransferases**
- ***S*-adenosylmethionine (SAM) is methyl donor for methylation of certain xenobiotics.**



6. Sulfation

- Compounds such as **alcohols, arylamines, and phenols** are sulfated. Other biologic sulfation reactions are sulfation of steroids, glycosaminoglycans, glycolipids, and glycoproteins.

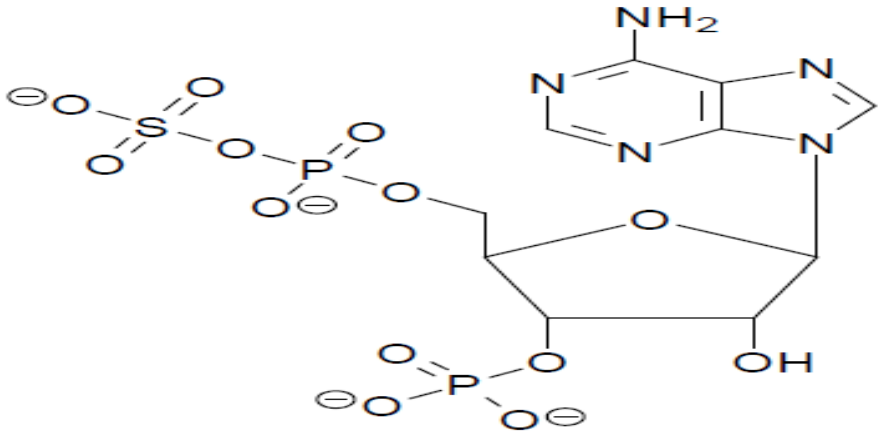
- The **sulfate donor** is "**adenosine 3-phosphate-5-phosphosulfate" (PAPS)- Active form of sulfate.**

PAPS phosphoadenosyl phosphosulfate

Physiological sulfations:

Glycosaminoglycanes
heparine, dermatane sulfate,
keratane sulfate,
chondroitine sulfate etc.

Sulfoglycosphingolipids
(acidic glycolipids, sulfatides)



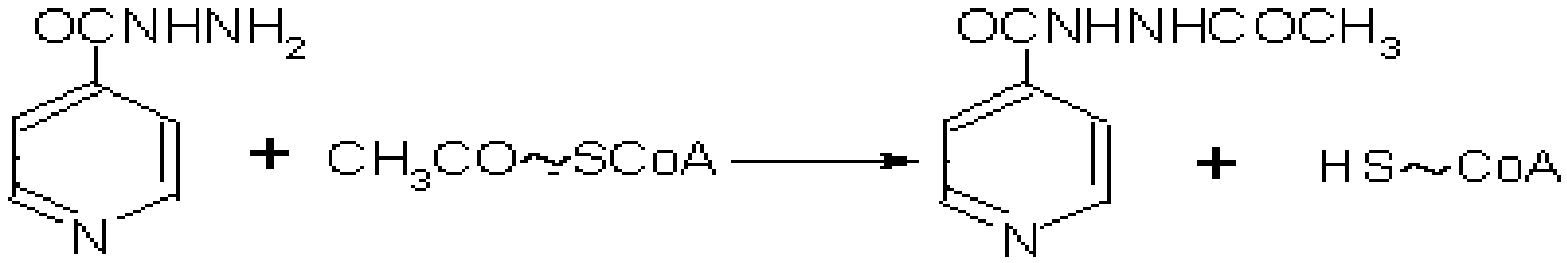
Phenol + PAPS —(Sulfotransferase)→ **Phenyl Sulfate + Phospho-adenosyl-phosphate (PAP)**

7. Acetylation

- Acetyl CoA (Active acetate) is the active form of acetic acid. That takes part in conjugation.
- The drug **isoniazid and sulfanilamide** are converted to acetyl derivatives.

$$X + \text{Acetyl-CoA} \longrightarrow \text{Acetyl-X} + \text{CoA}$$

Sulfanilamide + Acetyl CoA ⟶ Acetyl Sulfanilamide + CoASH



isoniazid **Acetyl isoniazid**

8. Thiosulfation

- ***Conversion of cyanide to thiocyanate.***

Cyanide + Thiosulfate ⟶ Thiocyanate + Sodium sulfate

Biomedical importance

Humans are subjected to exposure to various foreign chemicals; xenobiotics. Knowledge of the metabolism of these xenobiotics is helpful in understanding of-

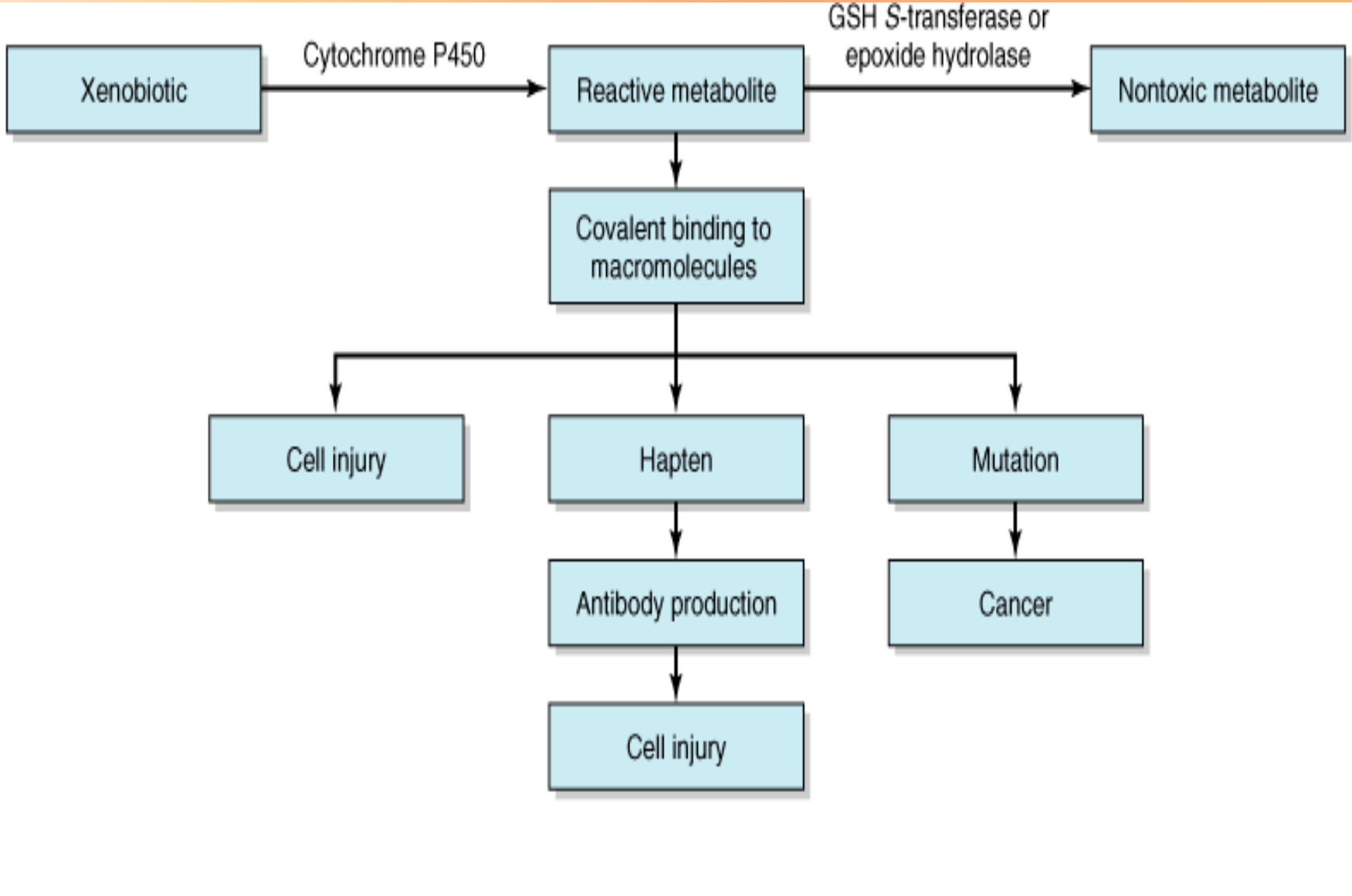
- *Pharmacology and therapeutics of drugs*
- *Toxicological studies of compounds*
- *Management of various diseases*

THANK YOU

Factors affecting biotransformation of drugs

- Prior administration of the drug or Co-administration of other drugs
- Diet
- Hormonal status
- Genetics
- Age
- Functional status of Liver and Kidney

Effects of Xenobiotics



- Main organ involved in detoxification – Liver.
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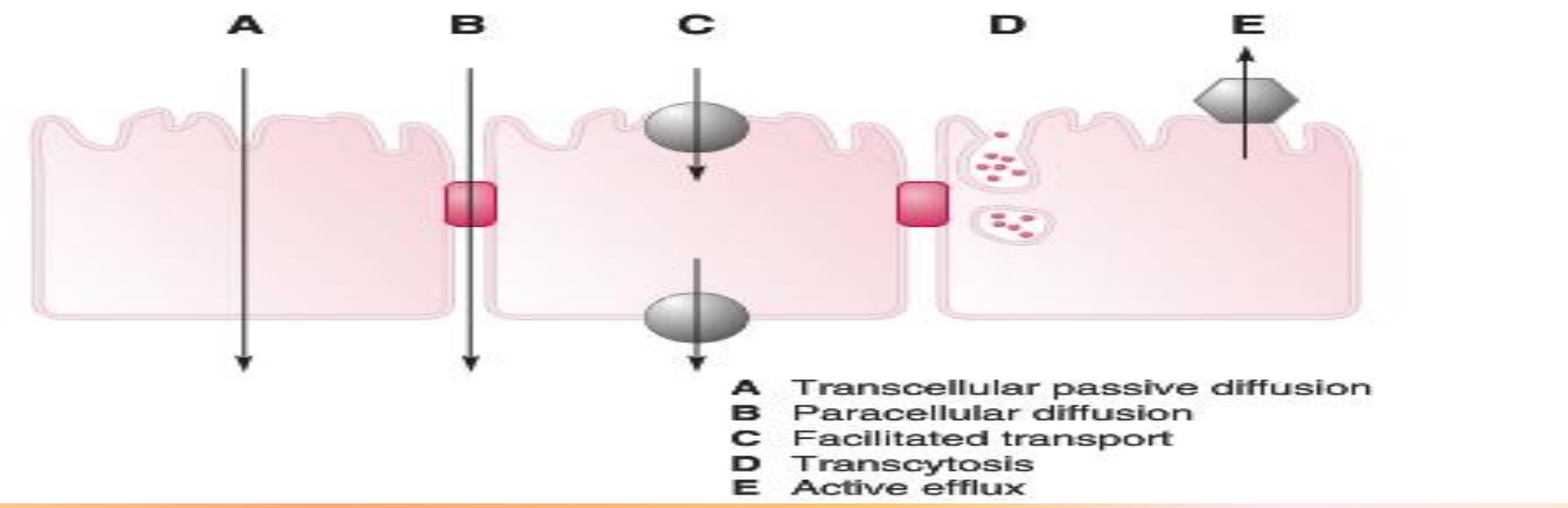
Entry of xenobiotic into cells

- Xenobiotics structurally similar with physiological substrates can utilize all available transport systems.
- **Simple diffusion** – lipophilic substances, dépends on concentration gradient (liver – freely permeable, big pores in cell membrane, most affected in poisoning)
- **Facilitated diffusion – transporters**
- **Active transport – primary and secondary**
- **Endocytosis**



Excretion of xenobiotics from body

- chemically modified (more polar) xenobiotics are excreted by urine, bile, stool, or sweat.
- volatile substance by lungs.
- Through enterohepatic circulation.

Conjugation reactions and reagents

Reaction	Reagent	Group in substrate
Glucuronidation	UDP-glucuronate	-OH, -COOH, $-NH_2$
Sulfation	PAPS	-OH, $-NH_2$, -SH
Methylation	SAM	-OH, $-NH_2$
Acetylation	acetyl-CoA	-OH, $-NH_2$
Sulfide formation	glutathione	Ar-halogen, Ar-epoxide
Amide formation	glycine, taurine	-COOH

Excretion of xenobiotics from cell

- primary active transport – needs energy: ATP hydrolysis
- special ATP-ases called **ABC (ATP binding cassettes)** localized in cell membranes, export xenobiotics from cells into ECF
- **MRP (multidrug resistance proteins)** – in increased expression, they cause the resistance towards medicines