Metabolism of xenobiotics

INTRODUCTION

- Human beings are continuously

exposed to several foreign compounds such as drugs, pollutants, food additives, cosmetics, pesticides, etc., certain unwanted compounds are produced in the large intestine by the bacteria which enter the circulation. They are called as Xenobiotics.

Xenos means stranger- it is a Greek word.

INTRODUCTION

- Whether they are ingested accidently or in some other way, they may be absorbed from the GI track, and enters into the organs and tissues of the body. Hence these compounds should be removed from the body quickly.

DEFINITION

- 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 as Detoxification or Biotransformation reactions.
- The purpose of which is to increase their water solubility (polarity) and thus excretion from the body.
- In some cases, these reactions may instead increase the toxicity of a foreign compound, then these reactions are called as Entoxification reactions.

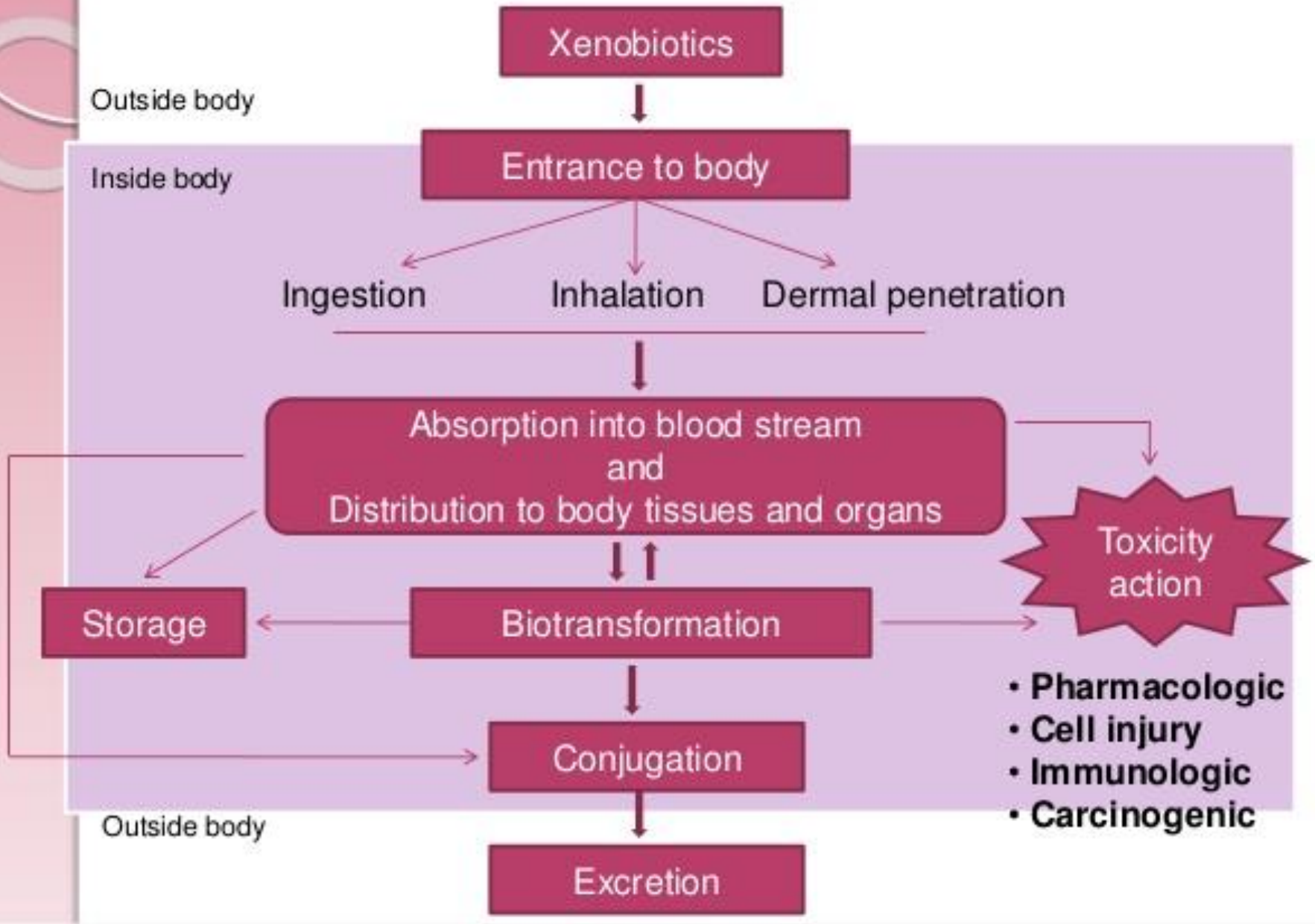
Medical Importance

- Detoxification is a process by which we reduce the level of toxins in our body.
- It protects the body and its organs from deleterious effects of toxins.
- Reducing the levels of toxins in our body, reduces the strain on the immune system.
- It removes most of the drugs consumed from the body.

Medical Importance

- Occasionally, detoxification may generate toxic substance, from a relatively non-toxic substance
- It can cause changes to our cells and DNA.
- Toxins can be a major causative factor for the incidence of cancer.

FATE OF XENOBIOTICS



TYPES OF XENOBIOTICS

Xenobiotics can be

Endogenous

Bilirubin, bile acids, steroids, eicosanoids, and certain fatty acids.

Exogenous

Drugs, food additives,pollutants, insecticides, chemical carcinogens. etc.

METABOLISM OF XENOBIOTICS

- It occurs in to two phases.
- which may occur together or separately

Phase I

Oxidation, Reduction, and Hydrolysis

Oxidation is followed by

Phase II

conjugation reactions

Compounds involved in conjugations

Glucuronic acid,
Amino acids (glycine)
Glutathione,
Sulphate, acetate, and methyl group.

Purpose and consequences

- Purpose

- converts lipophilic to hydrophilic.
- Facilitates excretion.

consequence

- Changes in solubility characteristics
- Detoxification
- Metabolic activation.

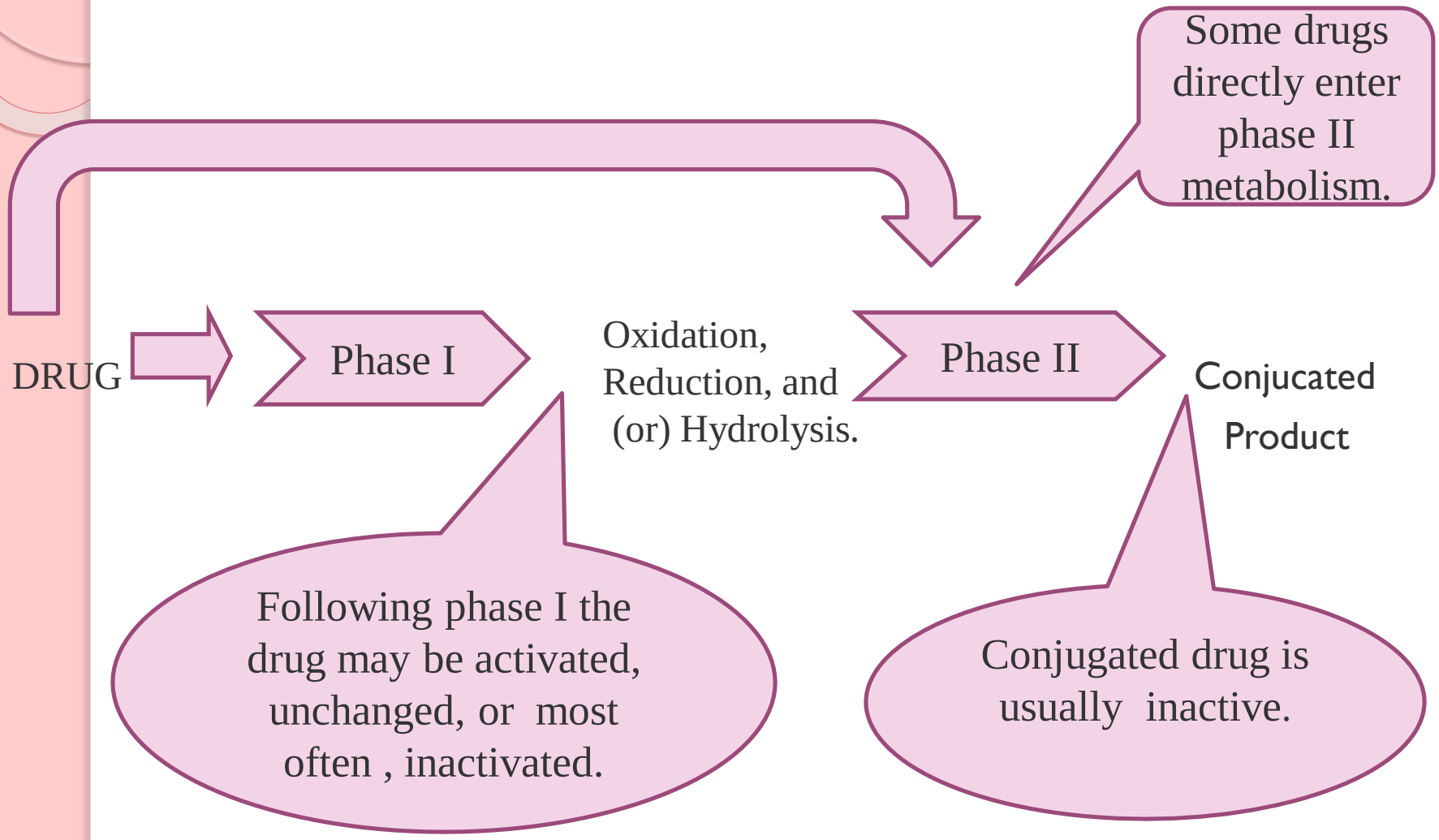
Overview of biotransformation reactions

- Phase I reactions can also convert xenobiotics from inactive to biologically active compounds.(Metabolic Activation).
- In these cases the original xenobiotics can be called as prodrugs or procarcinogens.

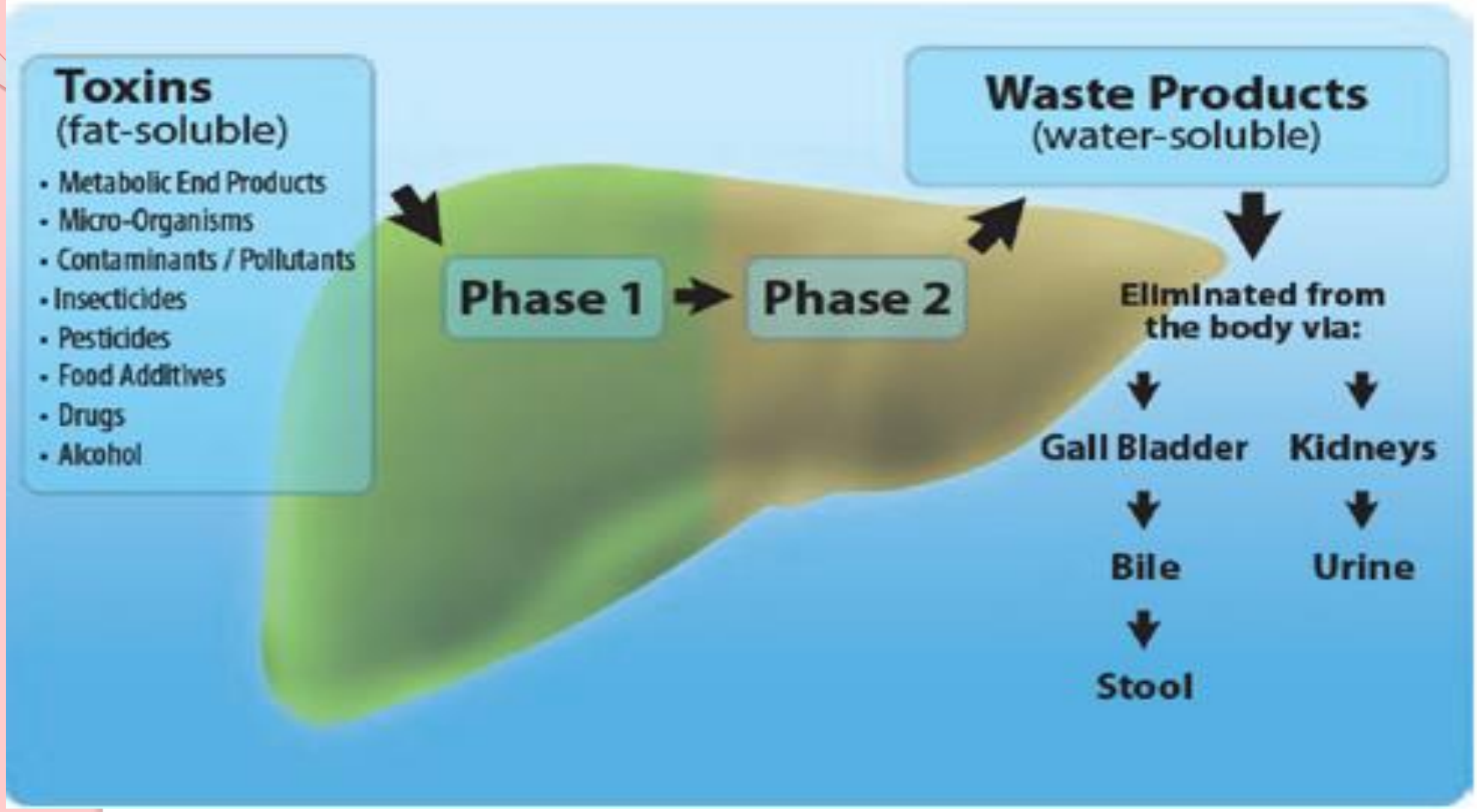
Overview of biotransformation reactions

- Phase II-conjugation reactions can convert the active products of Phase I reactions to active or inactive species. Which are then excreted in urine or bile.
- In few cases, the conjugation may actually increase the biological activity of xenobiotic (Metabolic action)

Overview of detoxification reactions



Role of liver



BIOTRANSFORMATION

Potentially toxic xenobiotic

Detoxification

Inactive metabolite

Relatively harmless

Metabolic Activation

Reactive intermediate

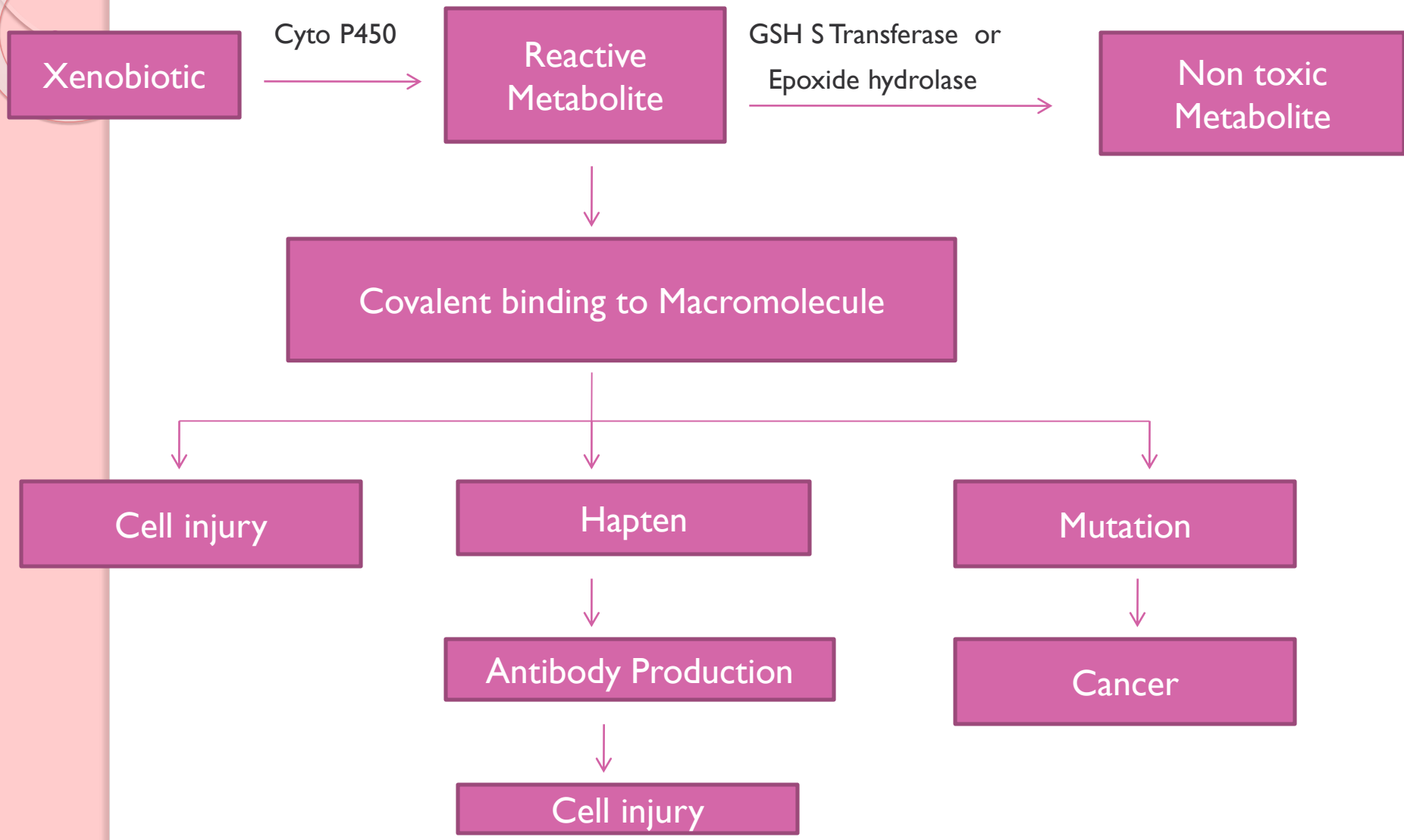
Comparing Phase I and Phase II

Particulars	Phase I	Phase II
Types of reactions.	Oxidation. Reduction. Hydrolysis.	Conjugations.
Increase in hydrophillicity.	Small .	Large.
General mechanisms.	Exposes functional groups.	Polar compounds added to functional group.
Consequences.	May result in metabolic activation.	Facilitates excretion.

Factors affecting detoxification of drugs

- Prior administration of drugs or co-administration of other drugs.
- Diet.
- Hormonal status.
- Genetics.
- Diseases (decrease in cardiac and pulmonary disease)
- Age and developmental status.
- Functional status of liver and kidney.

EFFECT OF XENOBIOTICS



Phase I reactions

- Phase I reactions are :
- Oxidation.
- Reduction.
- Hydrolysis reactions.
- They are also known as hydroxylation reactions. Since they introduce or expose a functional group that serves as the active center for sequential conjugation in phase II reactions.

Enzymes of phase I reactions

- Mainly catalyzed by members of the enzymes known as monooxygenases, mixed function oxidases, (or)cytochrome P_{450}s.
- Other important enzymes are
- Aldehyde and alcohol dehydrogenase
- Deaminases.
- Esterases.
- Amidases.
- Epoxide hydrolases.

Oxidation

- Most of the foreign substances are detoxified by oxidation.
- These includes alcohols, aldehydes, amines, aromatic hydrocarbons and sulphur compounds.
- Aliphatic compounds are more easily oxidized than aromatic ones.

Oxidation

- Indole and Skatole are produced from tryptophan, by the action of microbes.
- They are responsible for the dis agreeable odour of the feces.
- They undergo oxidation.
- Indole → Indoxyl.
- Skatole → Skatoxyl.

OXIDATION OF ALCOHOLS

- Both aromatic and aliphatic alcohols undergo oxidation to form their corresponding acids.
- Ex:

Methanol → formaldehyde → formic acid.

Ethanol → Acetaldehyde → acetic acid

Benzyl alcohol →Benz aldehyde → benzoic acid.

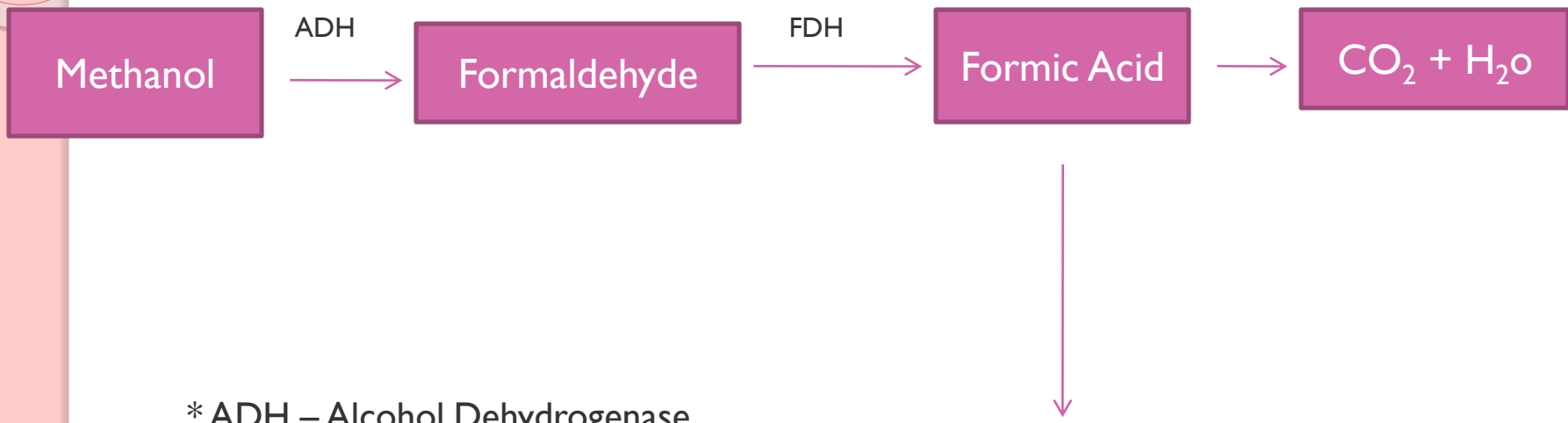
Methanol toxicity

- It has relatively low toxicity.
- It is metabolized in the liver.
- In the first step of degradation, methanol is transformed to formaldehyde via enzyme ADH
- Transformation of formaldehyde to formic acid via aldehyde dehydrogenase is faster.

Methanol toxicity

- The metabolism of formic acid is very slow.
- Thus it often accumulates in the body ,which results in metabolic acidosis.
- The major damage occurs to the optic nerve.
- Ethanol is given as an antidote, since it is the substrate of ADH, methanol is spared.

Methanol Toxicity



* ADH – Alcohol Dehydrogenase
* FDH – Formaldehyde Dehydrogenase

Oxidation of aldehydes

- Aldehydes are oxidised to corresponding acids.
- Acid thus formed is further conjugated in phase II
- Ex: Benz aldehyde → benzoic acid.

  Benzoic acid is conjugated with glycine to form Hippuric acid.

  This reaction is exclusively takes place in the liver.

  Hippuric acid excretion test is used to determine the detoxification functions of liver.

  Normal level of excretion - 0.5 – 1.0 g/day.

Oxidation of aromatic hydrocarbons

- Aromatic hydrocarbons are oxidized to phenolic compounds.
- Which can further conjugated with glucuronic acid (or)sulphuric acid in phase II reactions, so as to be excreted through urine.

Benzene ⟶ Mono, Di, Tri hydroxy phenol

Oxidation of amines

- Many primary aliphatic amines undergo oxidation to form the corresponding acids and nitrogen is converted to urea.

- EX: Benzyl amine → Benzoic acid + urea.

- While aromatic amines are oxidised to phenols.

  Aniline → P- Amino phenol.

Oxidation of anilids and sulphur containing compounds

- Anilids are oxidized to corresponding phenols.
- Acetanilide is oxidized in the body to form P-acetyl amino phenol.
- Acetanilide is a constituent of analgesic drug.
- Sulfur compounds:
- Organic sulfur is oxidized to sulfuric acid.

Oxidation (entoxification)

- Oxidation of certain compounds may also result in the production of more toxic compounds(entoxification).
- Hence their formation is prevented.
- EX: Methanol---------->Formic Acid.

  Halagenated Alcohol------> Halogenated Acid.
- Ethylene glycol ----------> oxalic Acid.

Cytochrome $P_{450.}$

- Most of the oxidation reactions of detoxification are catalysed by monooxygenase(or)cytochrome $P_{450.}$ This enzyme is also known as mixed function oxidases, which is associated with the microsomes of the liver.
- Most of the reactions of cytochrome P_{450} involve the addition of a hydroxl group to aliphatic or aromatic compounds which may be represented as
- RH+ O_2+NADPH+H^+---------- >OH+H2O+NADP
- RH represents a wide variety of xenobiotics which may include drugs, carcinogens, pesticides pollutants etc.,

Properties of human cytochrome P_{450}.

- They are all hemoproteins.
- Exhibit broad substrate specificity.(act on many compounds).
- Versatile catalysts(since it catalyse 60 types of reactions).
- Larger amount is found in microsomes of liver. But found in other tissues such as intestine, lung, brain etc.

Properties of human cytochrome $P_{450.}$

- It is located in smooth ER.
- They are NADPH dependent enzymes.
- In some cases, their products are mutagenic (or) carcinogenic.
- They are inducible enzymes. Its synthesis is increased by administration of drugs such as phenobarbitol.
- A phospholipid– phosphotidyl choline is a constituent of cytochrome P_{450} system and is necessary for the action of this system.

Reduction

- Reduction is less common and less important than oxidation in human beings.
- Picric acid ----------> Picramic acid
- Reduction of aldehydes:
- EX: chloral hydrate----------> Trichloroethanol.
- Chloral hydrate is a sedative.

Reduction

- It is excreted after conjugation with D-glucuronic acid as corresponding glucuronide.

- Reduction of Nitro compounds:

- P- nitrobenzene---------> P- aminobenzene.
- P- nitrophenol----------> P- aminophenol.

Hydroxylation

- Detoxification of a number of drugs and steroids occur by hydroxylation.
- These reactions are catalyzed by cytochrome $P_{450.}$ dependent monooxygenases.
- Pentobarbital $\xrightarrow{cytP_{450}}$ Hydroxy phenobarbital.
- phenobarbital an anticonvulsant drug.

Hydroxylation

- Meprobamate undergo hydroxylation
- Meprobamate → P-OH meprobamate.
- Meprobamate is a tranquilizer.

Chloral used as a Hypnotic.

Hydrolysis

- Certain therapeutic compounds undergo hydrolysis.
- Hydrolysis of the bond such as ester,glycoside, and amide is important in the metabolism of xenobiotics.
- EX: Aspirin $\xrightarrow{H20}$ Acetic acid + salicylic acid.
- (Acetyl salicylic acid).(hydrolysis in the ester bond)
- Atropine $\xrightarrow{\text{Hydrolised}}$ Tropic acid +Tropine.
- Atropine is a psychoactive drug.
- Acetanilide $\xrightarrow{H2O}$ Aniline + Acetic acid.
- Procaine ----- > P-aminobenzoic acid + diethyl amino ethanol.

Phase II Reactions of xenobiotics.
Conjugation

- Conjugation is a process by which the foreign molecules and their metabolites are coupled with a conjugating agent and are converted to soluble, non-toxic derivatives which are easily excreted in urine.
- Conjugation reactions can occur either independently (or) can follow phase I (hydroxylation) reactions.
- Conjugation takes place in liver. But it can also occur in kidney.
- After conjugation the products are generally rendered non-toxic but in certain condition they are left unchanged (or) become more toxic.

Conjugation

- Types of phase II reactions:
- Glucuronidation.
- sulfation.
- Acetylation.
- Methylation.
- Conjugation with amino acids.
- Conjugation withG-SH.

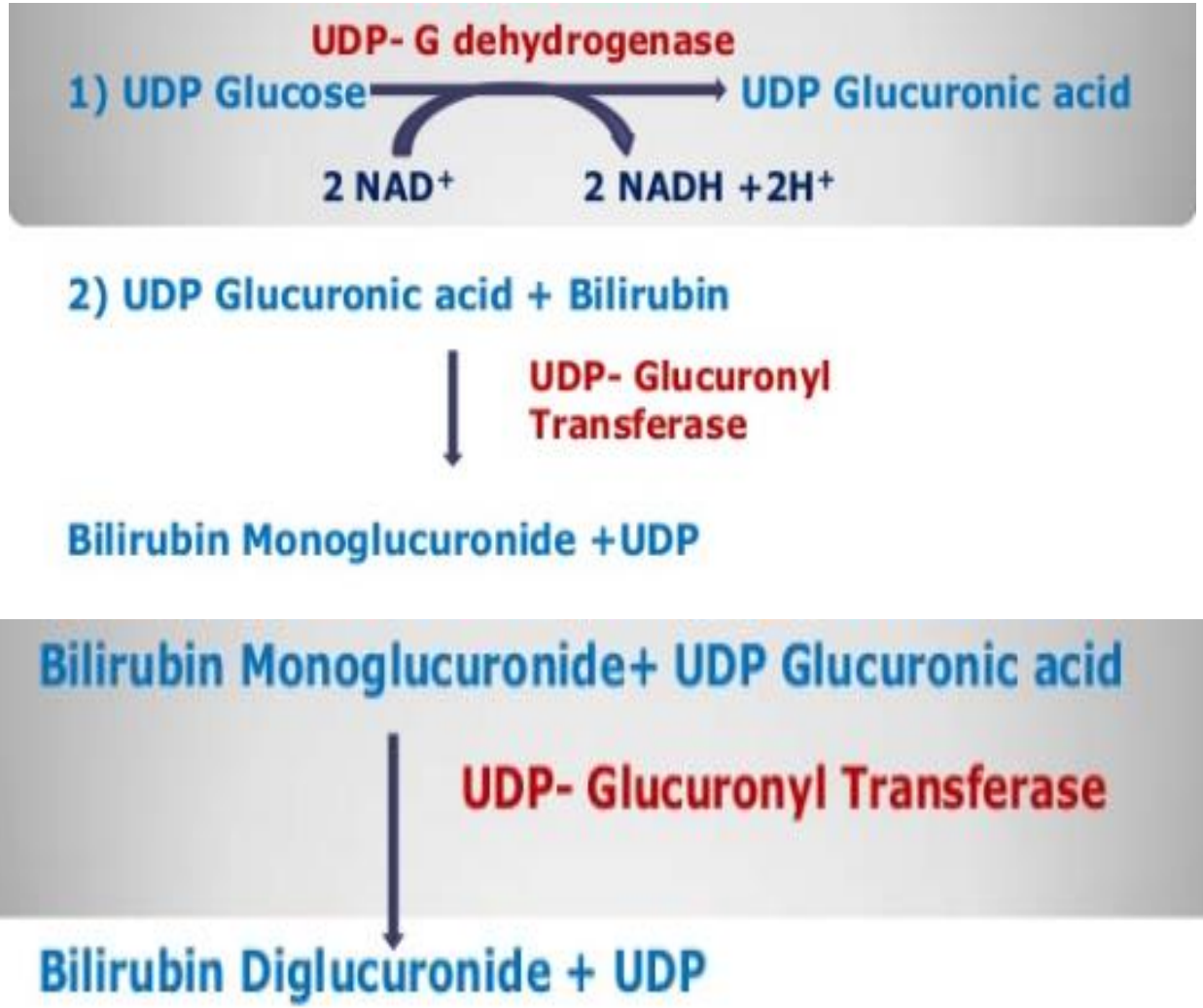
Glucuronidation.

- It is the most common Conjugation reaction.
- UDP-glucuronic acid, is the glucuronyl donor, which is formed in the uronic acid pathway of glucose metabolism.
- Glucuronyl transferase, present in both the ER and cytosol are the catalysts.
- The glucuronide may be attached to oxygen, Nitrogen, (or) sulphur groups of the substrates.

Glucuronidation.

- Compounds conjugated with glucuronic acid are :
- Bilirubin.
- Aromatic acid---Benzoic acid.
- Phenols, secondary, tertiary aliphatic alcohols.
- Antibiotics like chloramphenicol.
- Hormones--- Thyroid hormone, derivatives of corticosteroids and sex hormones metabolites.
- 2-acetaminofluorene (a carcinogen).
- Aniline.
- Meprobamate (a tranquilizer).

Conjugation with bilirubin



Conjugation with bilirubin

- Most of the bilirubin excreted in the bile is in the form of bilirubin diglucuronide.
- Bilirubin-UGT activity can be induced by certain drugs.
- Which includes phenobarbital when these drugs are administered, it increase the formation of glucuronide.

Sulfation

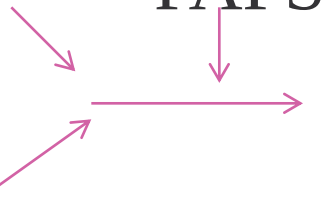
- Compounds which are conjugated with sulphate are phenols, cresols, indole, steriods,oestrogen and androgen etc.,
- The active form of sulfate is 3’phosphoadenosine 5-phosphosulfate (PAPS) involve in conjugation reactions and the enzyme sulfotransferase catalyze the process.
- PAPS donate the sulphate group.

Sulfation

- Phenol+PAPS $\xrightarrow{\text{sulphotransferase}}$ phenyl sulphate + PAP

- Skatoxyl
- Indoxyl

PAPS



Ethereal sulphate+PAP

Acetylation

- Compounds which are conjugated with acetic acid are sulphanilamide, PABA, Isoniazid.
- Acetyl coA is the active form of acetic acid.
- These reactions are catalyzed by Acetyl transferase.
- Which are present in the cytosol of various tissues particularly liver.
- Sulfanilamide +Acetyl coA $\xrightarrow{\text{Acetyl transferase}}$ +acetyl sulfanilamide + coASH.
- PABA $\xrightarrow{\text{Acetyl coA}}$ Acetylated PABA.

Methylation

- Methylation is limited in the body.
- Compounds conjugated with methyl group are Nicotinamide, p-methyl amino azobenzene, P-dimethyl amino benzene, estrogen, Catecholamine, etc.,
- S-adenosyl methionine -----methyl donor.(active form)

Methylation

- Reactions ------ >transmethylation

- Enzyme involved----->Methyl transferase.
- Nicotinamide $\xrightarrow{CH_3}$ N-Methyl Nicotinamide
- p-Methyl amino azobenzene $\xrightarrow{CH_3}$ P- Dimethyl amino azobenzene (hepatic Carcinogen)

Conjugation with amino acids

- Compounds which are conjugated with glycine
- are benzoic acid, phenyl acetic acid, cholic acid, and deoxy cholic acid.

Ex: Benzyl coA + Glycine----- > Hippuric acid.

Phenyl acetic acid + Glycine---- > Phenyl aceturic acid.

Cholic acid + Glycine---- > Glycocholic acid.

Deoxycholic acid + Glycine---Glycodeoxycholic acid.

Conjugation with glutathione

- Glutathione -- > a tripeptide consist of Glutamic acid, cysteine, and glycine(active conjugating agent).
- Organic compounds such as alkyl or aryl halides, alkenes, nitro compounds and epoxides get conjugated with cysteine of glutathione.
- The glutamate and glycine of glutathione are removed and an acetyl group is added to the cysteine residue.
- Results in formation of mercapturic acid.

Detoxification by drugs

- Some of the drugs are administered to detoxify foreign substances .
- The toxic effects of certain heavy metals such as arsenic, mercury, and cadmium could be overcome by administering **BAL**(British Anti Lewisite). 2,3 Mercapto propanol.
- This drug was developed during II world War and was used as a detoxifying agent for certain war poisons.

Detoxification by drugs

- **BAL** readily combines with metals and gets easily excreted into urine.
- Metals binds with – SH group of enzymes, there by inactivating them.
- BAL acts as an antidote by virtue of pulling away the SH groups from the heavy metals.
- Such a liberation helps in the detoxifying mecahnism.

SUMMARY

- Xenobiotics are the chemical compounds foreign to the body, such as drugs, food additives, and environmental pollutants.
- Xenobiotics are metabolised in two phases.
- The major reactions of phase I is hydroxylation catalyzed by a variety of monooxygenases, also known as cytochrome P_{450}.
- In phase II the hydroxylated species are conjugated with a variety of hydrophilic compounds such as glucoronic acid, sulfate

SUMMARY

Glutathione,etc.

- The combined operation of these two phases renders lipophilic compounds into water soluble compounds that can be eliminated from the body.
- Xenobiotic can produce a variety of biologic effects, including pharmacologic responses, toxicity, immunologic reactions and cancer.