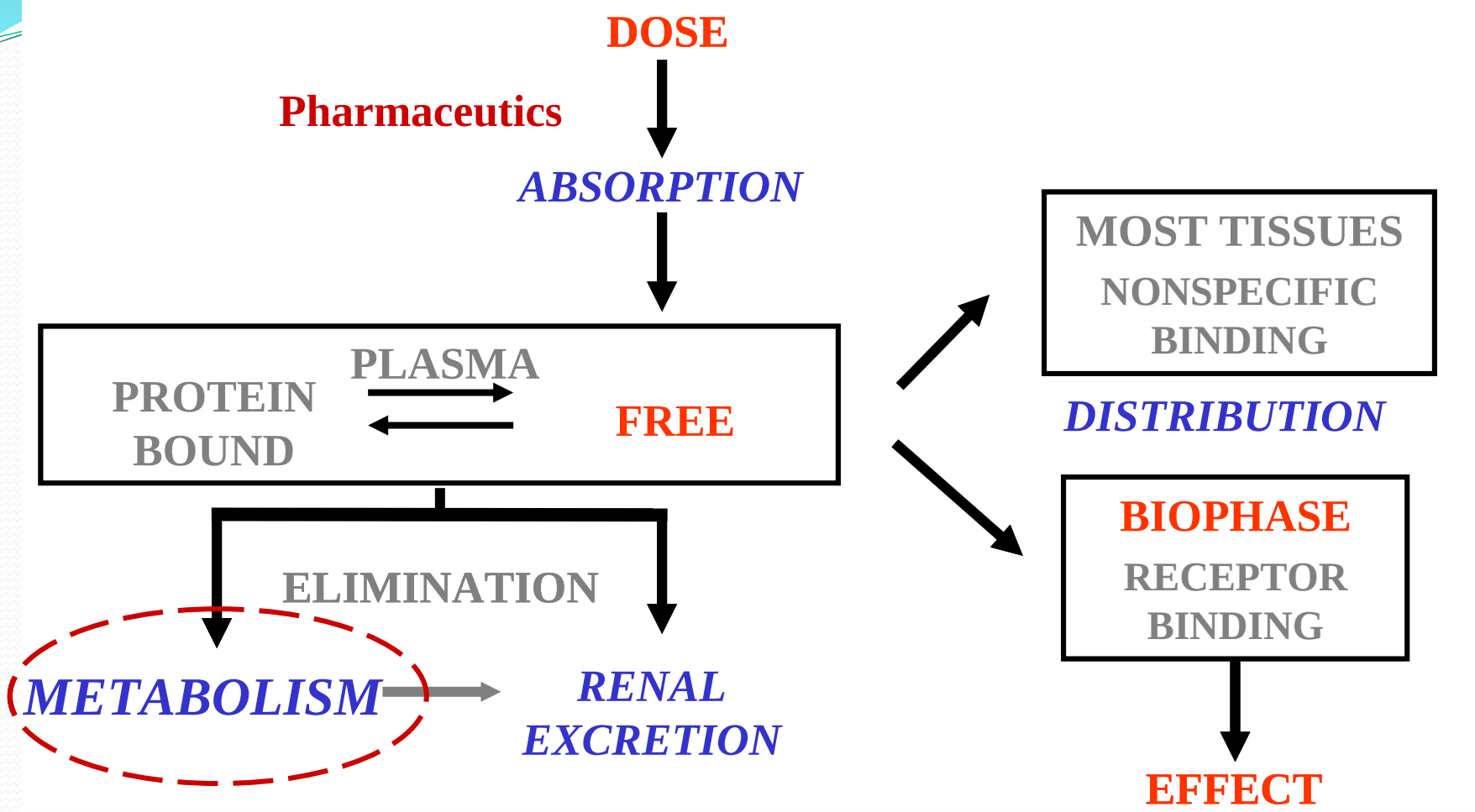
DRUG METABOLISM

By Dr shahid

Objectives

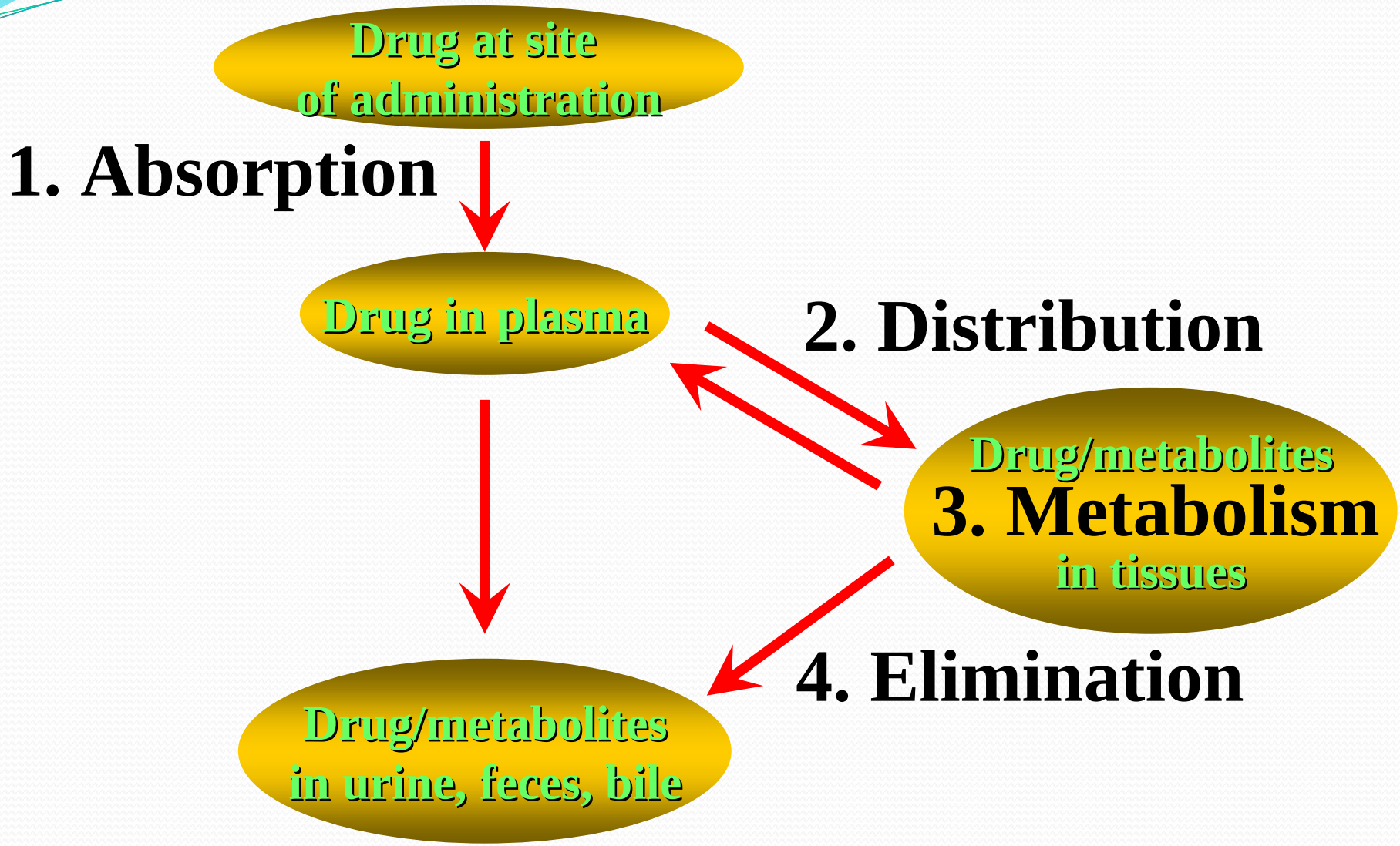
- At the end of presentation you should be able
- To define drug metabolism
- Fate of metabolim
- Implication
- Types/phases of metabolism
- Hepatotoxic drugs

The Fate of a Drug



Pharmacokinetics

Pharmacodynamics


Drug at site of administration
1. Absorption
Drug in plasma
2. Distribution
Drug/metabolites
3. Metabolism
in tissues
4. Elimination
Drug/metabolites in urine, feces, bile

BIOTRANSFORMATION

- Chemical modification of drugs or foreign compounds (xenobiotics) in the body.

- The apparent function of drug or xenobiotics metabolism is their transformation into water-soluble derivative which can be easily eliminated via renal route.

Implications For Drug Metabolism

1. Termination of drug action(inactivation
2. Activation of prodrug
3. Active metabolites from active drug

- Objective of studying drug metabolism

- - medicinal chemists aware of the chemical processes involved in the biotransformation of drugs
- - so design of new more safe drugs.

BIOTRANSFORMATION CAN LEAD TO THE FOLLOWING

- **Inactivation**

Eg: drugs like paracetomol, ibubrufen, chloromphenical etc and their metabolites are rendered inactive or less active.

- **Active metabolite from active drug**

ACTIVE DRUG	ACTIVE METABOLITE
allopurinol	alloxanthine
Digitoxin	Digoxin
Morphine	Morphine 6 glucoronide
Cholrol hydrate	trichloroethanol

- **Activation of inactive drug**
- Certain drugs are inactive and need activation in the body.
- Prodrug gives more bioavailability and less toxic effects.

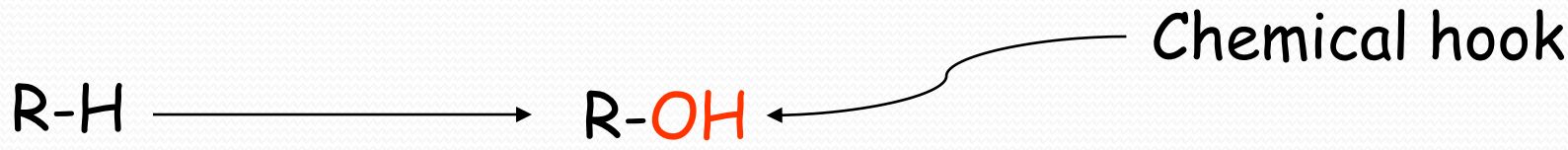
Prodrug	Active metabolite
Levodopa	Dopamine
Sulindac	Sulfide metabolite
Predinosone	Prednisolone

Effect of drug metabolism

Active drug → Inactive Drug

Inactive prodrug —Metabolic activation→ Active drug → Inactive metabolite

- Lipid Solubility



Major Sites of Metabolism

- Drug metabolism can occur in every tissue (e.g. gut, lung, kidney)..

- **The LIVER is the chief organ for drug metabolism because:**

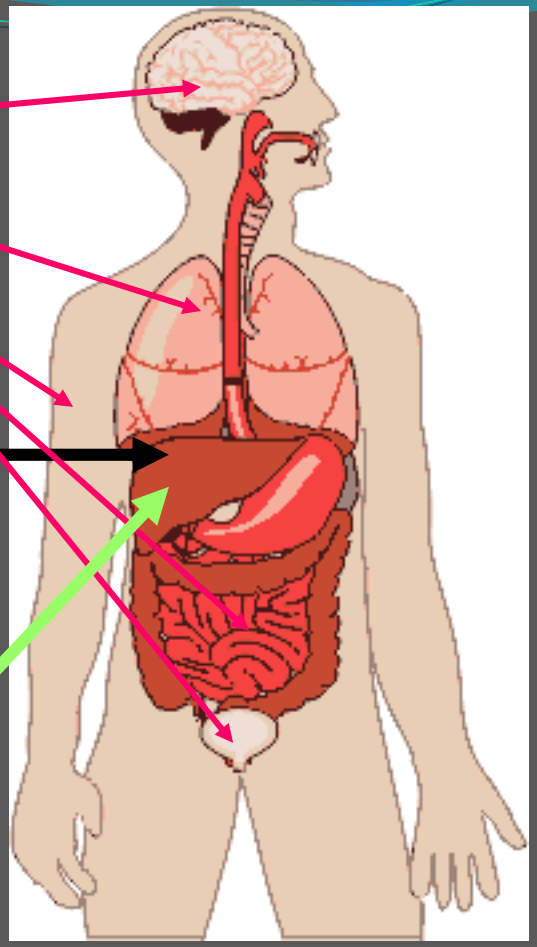
- **The blood flow through the liver is high**
- **Hepatocytes contain numerous metabolic enzymes**

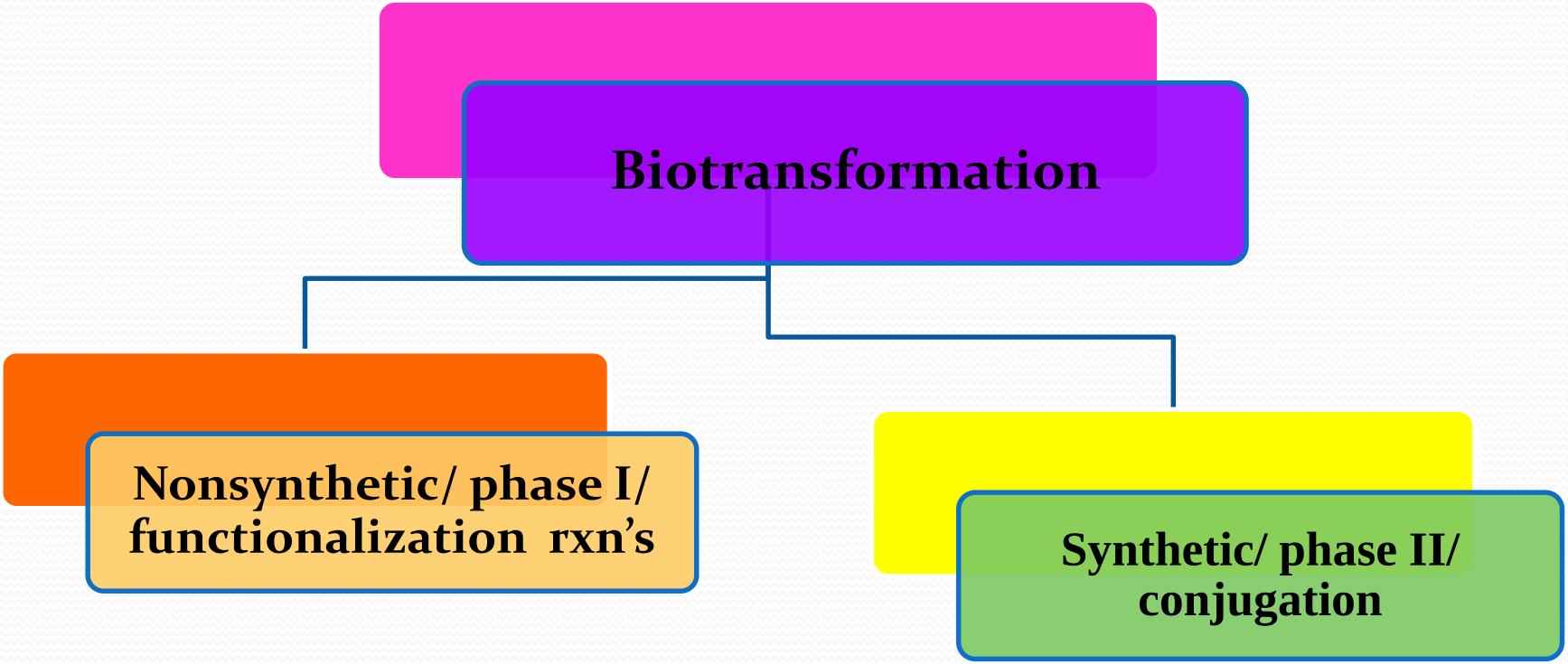
High	liver
Medium	lung, kidney, intestine
Low	skin, testes, placenta, adrenals
Very low	nervous system

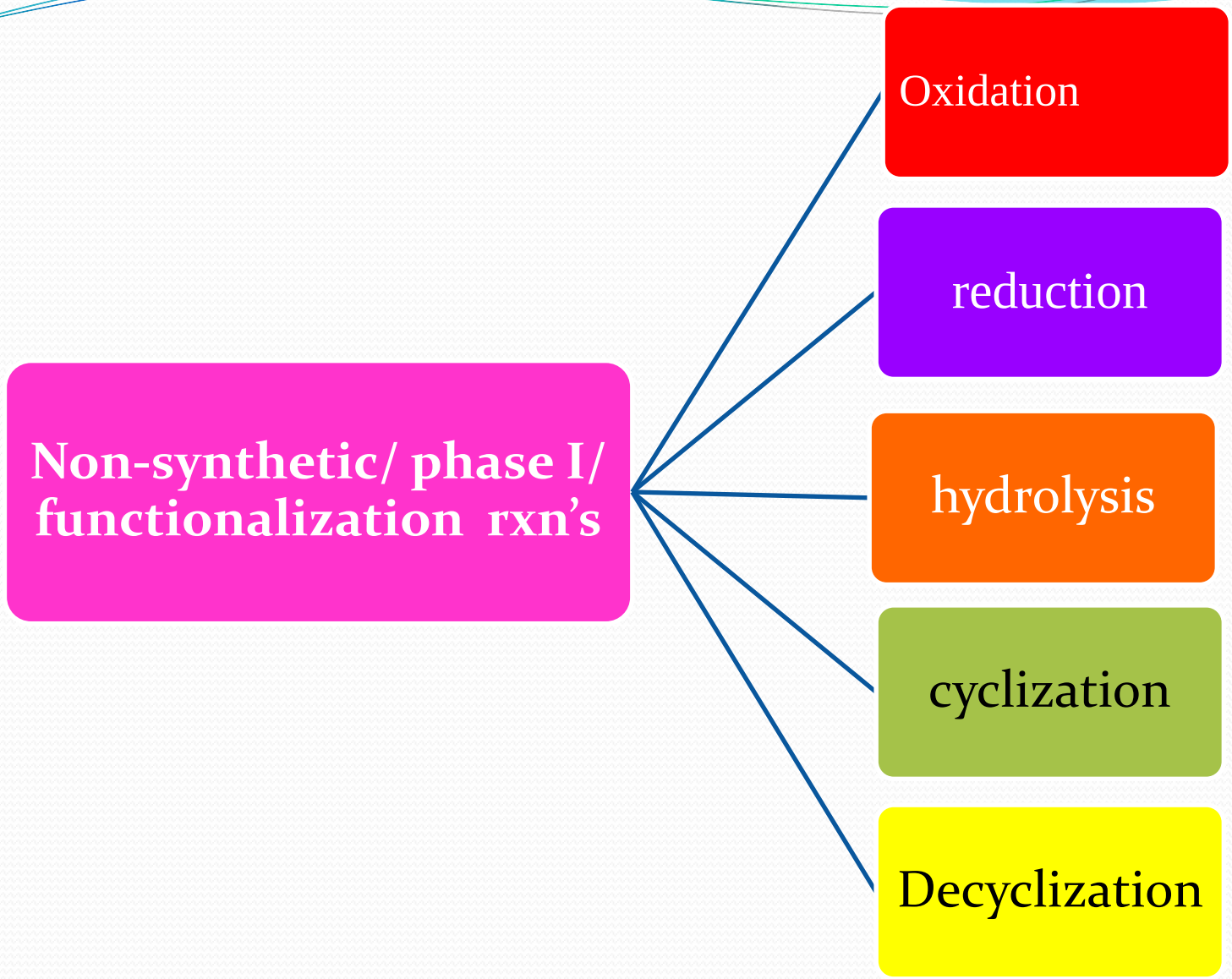
Extrahepatic microsomal enzymes
(oxidation, conjugation)

Hepatic microsomal enzymes
(oxidation, conjugation)

Hepatic non-microsomal enzymes (acetylation, sulfation,GSH, alcohol/aldehyde dehydrogenase, hydrolysis, ox/red)




Biotransformation
Nonsynthetic/ phase I/ functionalization rxn's
Synthetic/ phase II/ conjugation


Non-synthetic/ phase I/ functionalization rxn's
Oxidation
reduction
hydrolysis
cyclization
Decyclization

Oxidation

- hydroxylations
  - aromatic, aliphatic, nitrogen
- dealkylations(N-, S-, P)
- deaminations
- N-, S-, P- oxidations
- S-replacements
- epoxidations
- others

oxidoreductases

oxidases

- *monoamine oxidases*
- *mixed function oxidases*

Reduction

- azo reduction
- nitro reduction
- disulfide reduction
- others

oxidoreductases

reductases

Hydrolysis

- esters
- amides

esterases

amidases

peptidases

lipases

PHASE I

Oxidation

- Involves addition of oxygen or removal of hydrogen.
- Reactions mostly occur in liver by a group of enzymea
  - mono-oxygenases,
  - cyt P450 reductase.
- Various oxidation reactions are
  - Hydroxylation _phenytoin to hydroxy phenytoin
  - Dealkylation _codeine to morphine
  - Oxidative deamination
  - Oxidation at C,N or S atoms
- Eg: barbiturates, phenothiazines, steroids, paracetomol.
- **60% of drugs are metabolized primarily by CYPs.**

1. Oxidation reactions

The great majority of these oxidations are carried out by the haemoprotein cytochrome P-450 which is embedded within the phospholipid environment of the microsomes derived from the endoplasmic reticulum of living cells.

Cytochrome P_{450} (CYPs)

- Cytochrome P_{450} is a family of enzymes located in the endoplasmic reticulum of liver.
- When liver is homogenized and biochemically fractionated these enzymes are found in the microsomal fraction (small closed ER membrane fragments). Thus these enzymes are called microsomal enzymes.

- **Cytochrome P_{450}** enzymes perform many of the most important biotransformation reactions.
- These enzymes oxidize a wide variety of compounds foreign to the body.
- There are at least 18 different forms of **cytochrome P_{450}** identified in humans, produced by different genes.
- **60% of drugs are metabolized primarily by CYPs.**

2. Reduction reactions

Reduction

- Involves removal of oxygen or addition of hydrogen.
- Reactions mostly occur in liver by a group of
  - cyt P450 reductase
- Eg: Alcohols, Warfarin, Chloramphenicol etc.

- It is a major route of metabolism for aromatic nitro,keto and azo compound as well as for a wide variety of aliphatic and aromatic N-oxides which are reduced to tertiary amines.
- Chloramphenicol to aryl amine metabolite(nitro reduction
- Cortisone to hydrocortisone(keto reduction)

Hydrolysis

- Cleavage of drug by addition of water.

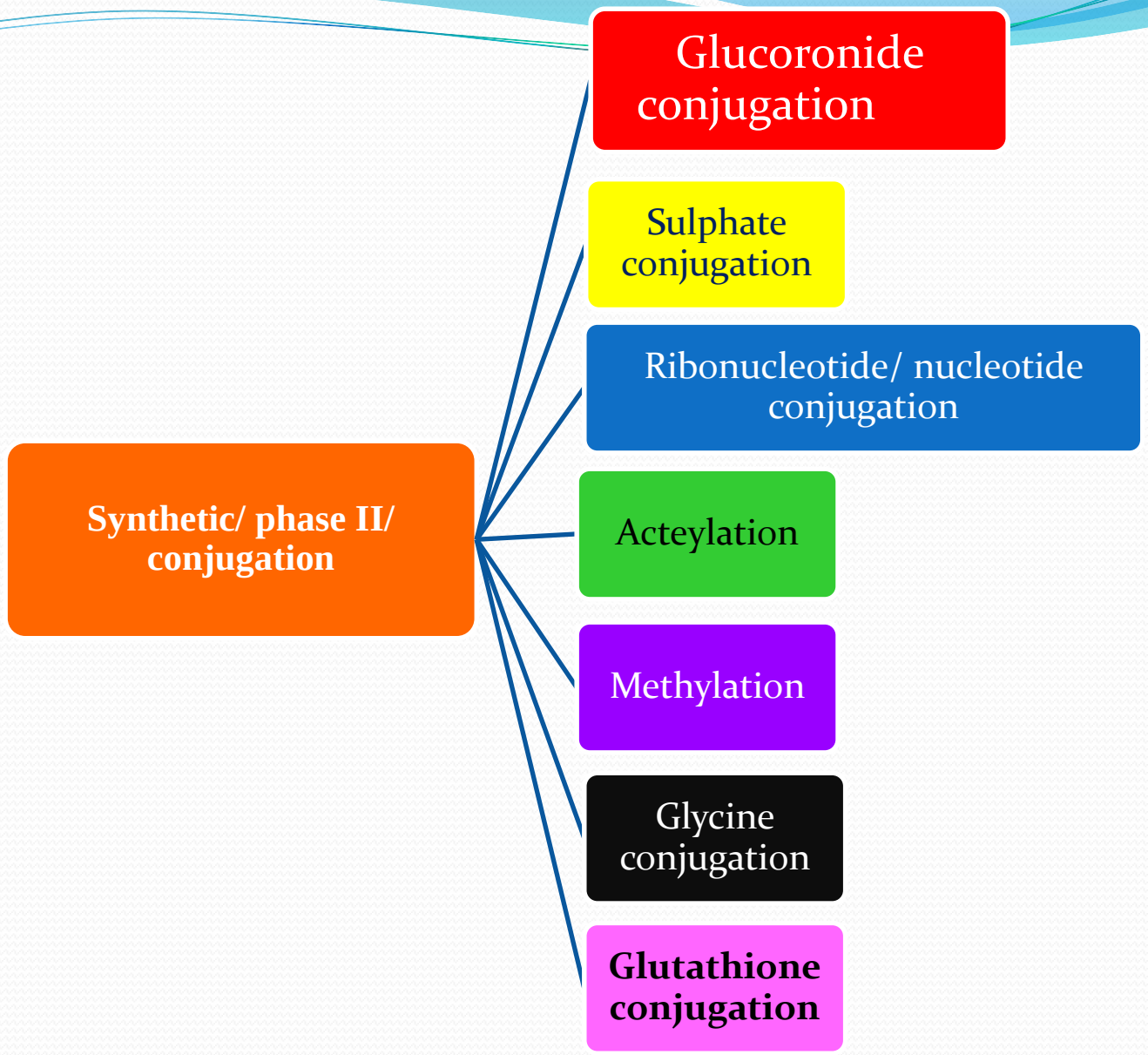
  Ester + water ⟶ acid + alcohol in presence of enz esterase.
- Occurs in liver, intestine , plasma.
- Amides and polypeptides are hydrolysed by amidases and peptidase enz.
- Eg: Aspirin, procaine, oxytocin etc.

Cyclization

- Involves formation of ring structure from straight compound.
- Eg: Proguanil

De- Cyclization

- Involves formation of open structure from ring compound.
- Eg: barbiturates, phenytoin etc.
- Is a minor pathway.


Synthetic/ phase II/ conjugation
Glucoronide conjugation
Sulphate conjugation
Ribonucleotide/ nucleotide conjugation
Acteylation
Methylation
Glycine conjugation
Glutathione conjugation

Phase II or Conjugation Reactions

-in Conjugation reactions phase 1 metabolites combine with endogenous substances dericed from crabohydrate/ptoteins

-Covalent bond formation between functional group of drug and endogenous substrate

- They are catalyzed by enzymes known as transeferases.

- They involve a cofactor which binds to the enzyme in the close proximity of the substrate and carries the endogenous molecule or moiety to be transferred.

- Forms highly ionized organic acid which is excreted in urine or bile.
- Generally conjugation reactions have high energy requirements.

Glucoronide conjugation

- Most important reaction carried out by UDP glucoronsyl transferases (UGT).
- Drugs with hydroxyl and carboxylic acid are easily conjugated with glucoronic acid.
- Glucoronidation increases the mol. Wt of the drug and thus favors excretion in bile.
- Drug excreted in gut by bile is hydrolyzed bacteria and is reabsorped back and undergo same process, so this enterohepatic circulation prolongs the action of drugs.
- Eg: Aspirin , paracetamol, morphine etc.

- Beside xenobiotics, a number of endogenous substrates, notably bilirubin and steroids are eliminated as glucuronide conjugates.

- In neonates and children, glucuronidation processes often are not fully developed. In such subjects, drugs and endogenous compounds (e.g. bilirubin) that are normally metabolized by glucuronidation may accumulate and cause serious toxicity.
- For example, neonatal hyperbilirubinemia and gray baby syndrome, result from accumulation of toxic levels of the free chloramphenicol.

Acetylation

- Drugs having amino or hydrazine are conjugated by acetyl co-enzyme.
- Multiple genes control the N-Acetyl transferases and rate of acetylation shows genetic polymorphism
- Eg: Sulphonamides, hydralazine, clonazepam etc.

Methylation

- Methionine and cysteine are methyl donors.
- Amines and phenols are methylated by methyl transferase.
- Eg: Adrenaline, histamine, nicotinic acid etc.

Suphate conjugation

- Phenolic compounds and steroids are sulphated by sulfotransferases.
- Eg: Cholramphenicol, Adrenal, Methyldopa etc.

Glycine Conjugation

- Salicylates and other drugs with carboxylic acid are conjugated with glycine.

Ribonucleoside / nucleotide synthesis

- is a important pathway for activation of drugs in chemotherapy.
- Mainly purine and pyramidine drugs are used.

ENZYME INDUCTION

Drugs induce the synthesis of microsomal enzyme proteins

- Phenytoin
- Rifampicin
- Smoking
- Carbamazepine
- Phenobarbitone

ENZYME INHIBITION

One drug can inhibit the metabolism of another drug

- ↑ in circulating levels of slowly metabolised drug
- Prolongation or potentiation of its effects Valproate
- Ketoconazole
- Cimetidine
- Ciprofloxacin

Hepatotoxic Drugs

Introduction

- Liver plays a key role in detoxifying harmful substances .
- Toxic hepatitis is liver inflammation due to toxic chemicals, drugs or certain poisonous mushrooms.
- Among patients with acute liver failure, drug-induced liver injury is the most common cause.

Hepatotoxic Drugs

Drugs causing Hepatotoxicity

1. ANTIBIOTICS

- -Amoxicillin / clavulanate
- -Trimethoprim / sulfamethoxazole
- -Fluoroquinolones
- -Macrolides
- -Nitrofurantoin
- -Minocycline

2. ANTIEPILEPTICS

- -Phenytoin
- -Carbamazepine
- -Lamotrigine
- -Valproate

Hepatotoxic Drugs

Drugs causing Hepatotoxicity

3.ANTI-TUBERCULAR:

-Rifampicin

-Isoniazid.

4.NSAID:

-Acetaminophen

-Nimesulide

-Diclofenac

5.HYPOLIPIDEMIC DRUGS

-STATINS

-Niacin

-Fibrates

Hepatotoxic Drugs

Drugs causing Hepatotoxicity

6. ANAESTHETIC AGENTS

- -Halothane
- -Chloroform
- -Isoflurane, Enflurane & Desflurane
- -Nitrous oxide.

7. ANTIRHEUMATIC DRUGS

- -Sulphasalazine
- -Gold salt
- -Azathioprine
- -Methotrexate

Hepatotoxic Drugs

Drugs causing Hepatotoxicity

8.ANTIRETROVIRAL DRUGS

- Protease inhibitors
  - Ritonavir
  - Indinavir
  - Nelfinavir
- NRTI
  - Lamivudin
  - Tenofovir
  - Zidovudine
  - Didanosine
- NNRTI
  - Nevirapine
  - Efavirenz

THANK YOU