Drug Metabolism

Biotransformation: Chemical alteration of the drug in body that converts nonpolar or lipid soluble compounds to polar or lipid insoluble compounds

https://www.ncbi.nlm.nih.gov/books/NBK442023/

https://www.news-medical.net/health/Drug-Metabolism.aspx#:~:text=Drug%20metabolism%20is%20the%20term,the%20reactions%20are%20concentrated%20there.

Consequences of biotransformation

- Active drug → Inactive metabolite : Pentobarbitone, Morphine, Chloramphenicol
- Active drug → Active metabolite: Phenacetin
- Inactive drug → active metabolite: Levodopa

Enzymes involved in metabolism

Microsomal enzymes

Cytochrome P-450 monooxygenase
Flavin monooxygenases
NADPH cytochrome c reductase
UDP-Glucoronosyl transferases
Glutathione-S-transferases
Epoxide hydrolases, etc

Non-microsomal enzymes

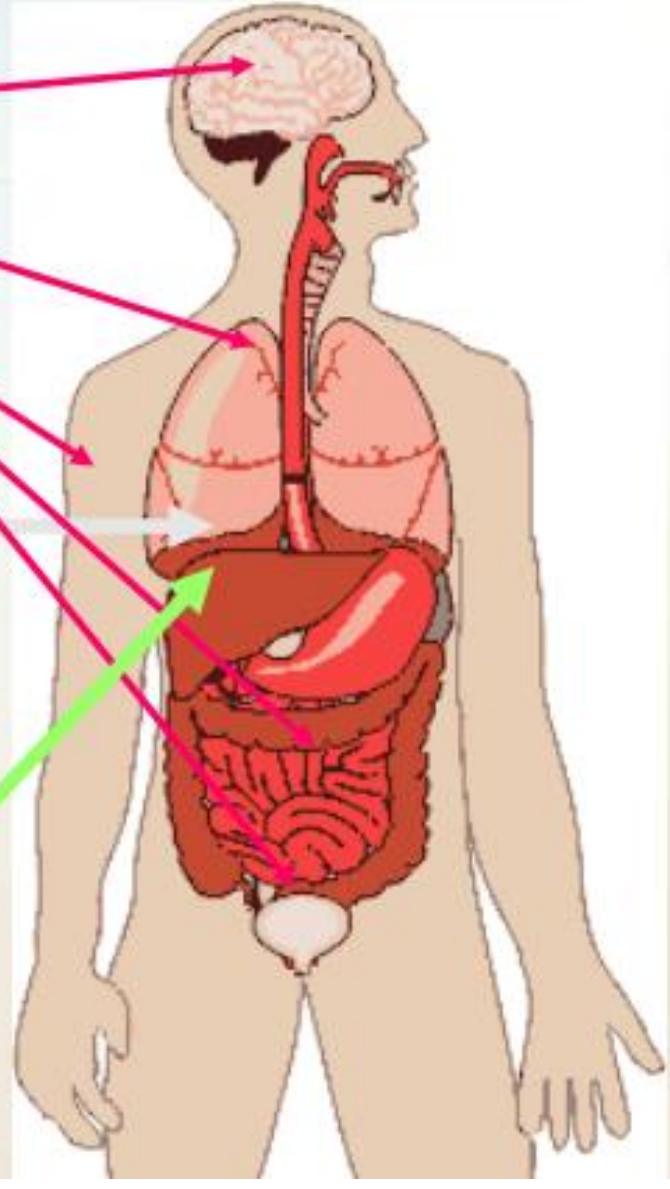
Alcohol dehydrogenase
Aldehyde dehydrogenase
Aldehyde reductase
Epoxide hydrolase
Esterase
Sulfotransferase
Glutathione S- transferase
N-acetyltransferase, etc

Sites of Drug Metabolism

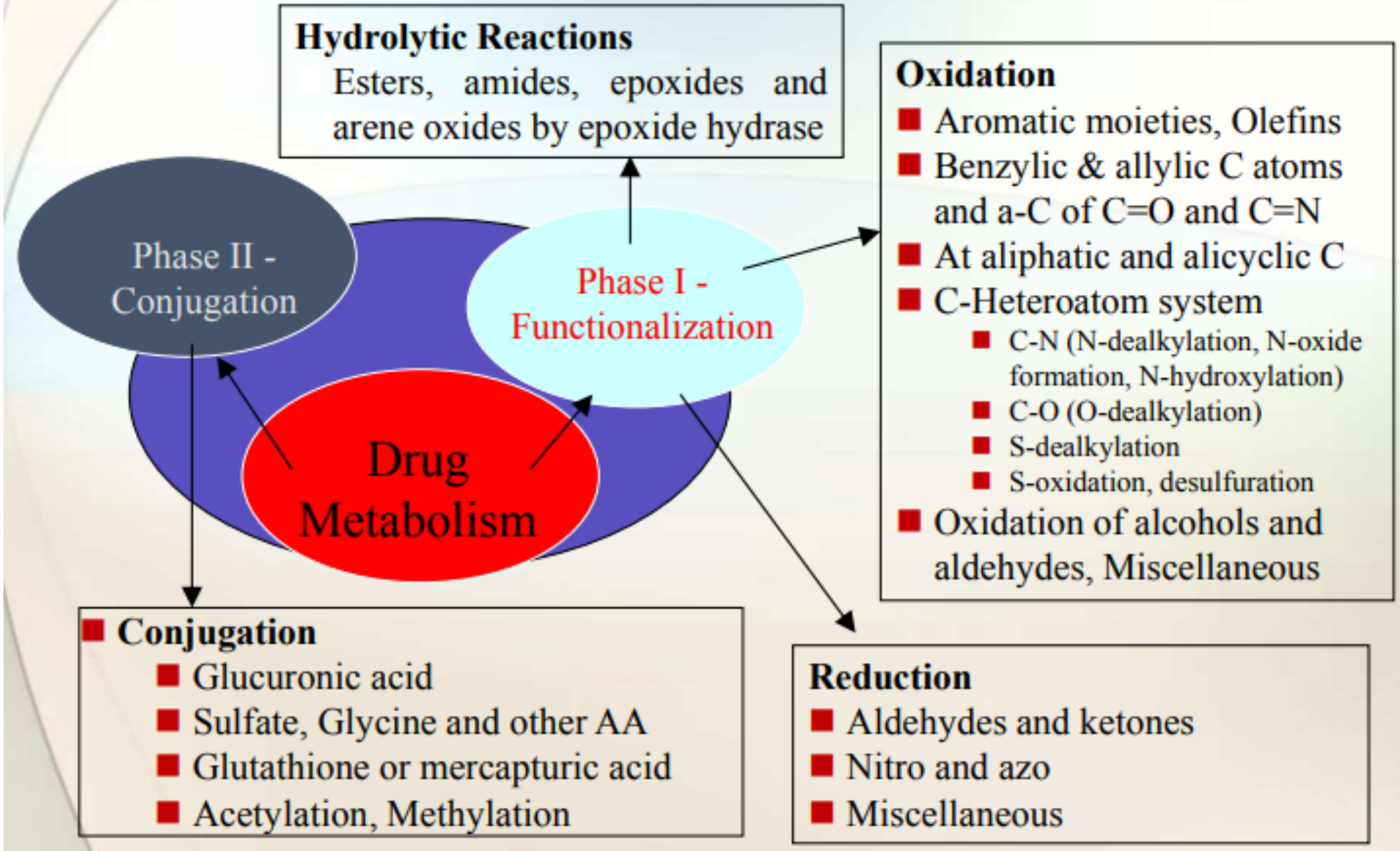
Extrahepatic microsomal enzymes (oxidation, conjugation)

Hepatic microsomal enzymes (oxidation, conjugation)

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



Phases of Metabolism



Phase-I /Functionalization / Non synthetic reactions:

- Attechment of functional groups (OH, COOH, NH_2 etc)
- Metabolite- active or Inactivate
- Convert to more hydrophilic in nature

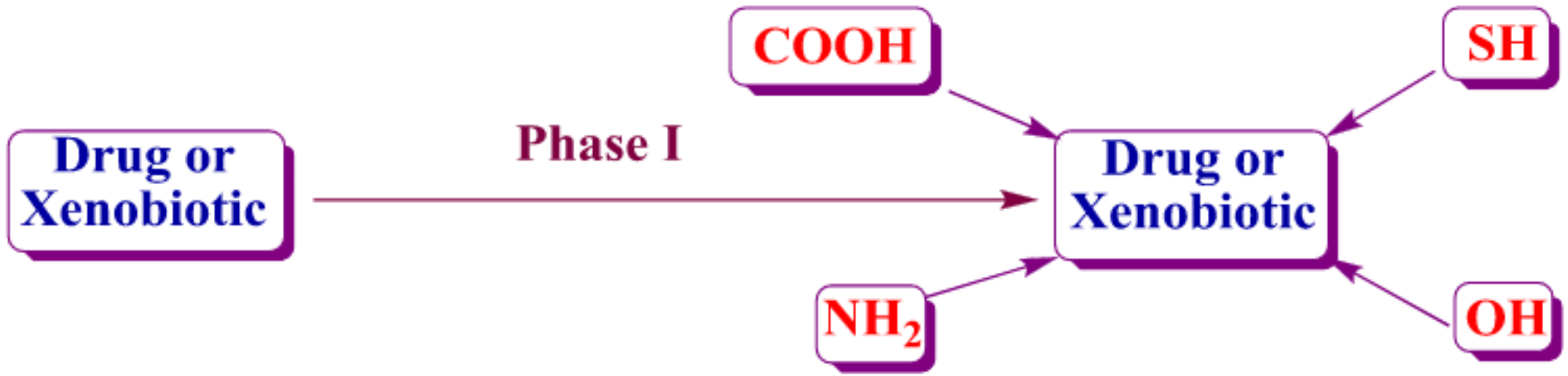
- Examples:
- Oxidation-phenytoin, barbiturates

- Hydrolysis-aspirin

- Reduction- benzodiazepines

Phase I Reactions

- The purpose of this phase is to introduce a polar functional group into the xenobiotic or drug molecule to increase its water solubility so that it can be easily excreted and /or conjugated and excreted.



This can be achieved by:

1- Direct introduction of the functional group (e.g., aromatic and aliphatic hydroxylation).

2- Modifying or "unmasking" existing functionality (e.g., hydrolysis of ester to yield a free COOH group).

Phase II

- Conjugation reactions
- Subsequent reaction in which a covalent linkage is formed between a functional group on the parent compound or Phase I metabolite and an endogenous substrate such as glucuronic acid, sulfate, acetate, or an amino acid

to further increase aqueous solubility

Phase-II reactions

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