



BIOTRANSFORMATION

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CLEARANCE OF DRUGS

- Definition
- Why needed?
- Either
 - Unchanged
 - **Metabolites**
- Polarity of compounds



BIOTRANSFORMATION

- Definition

- Sites

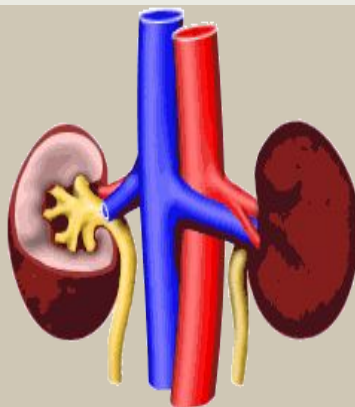
- Liver
- GIT



- Others

- Lungs
- Skin

- Kidneys

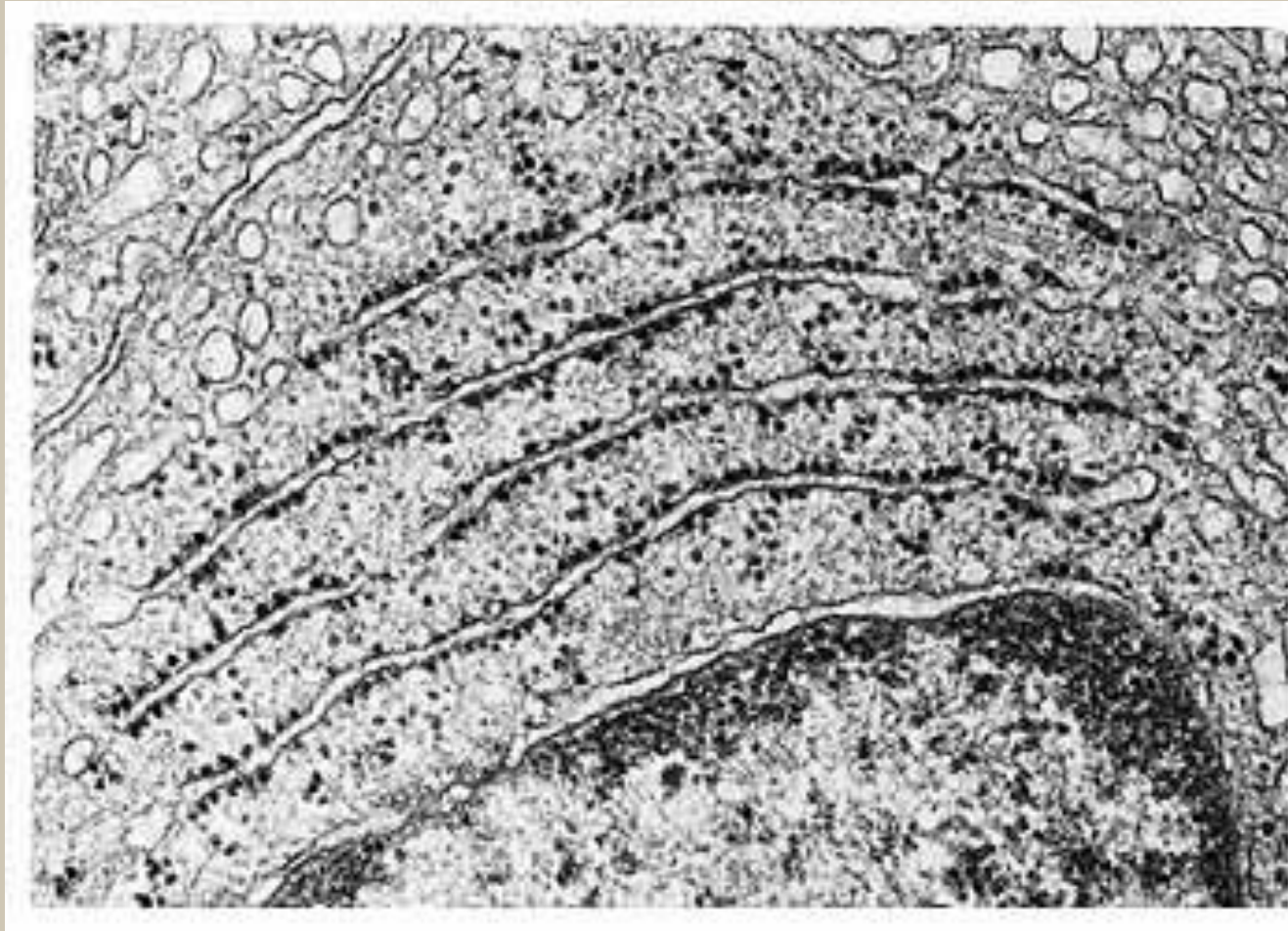


Phases

- Phase I - Nonsynthetic
 - make polar by unmasking a functional group like -OH, -NH₂, -SH.
 - oxidation-add O, remove H
 - reduction-remove O, add H
 - hydrolysis - add H₂O
- Phase II - Synthetic
 - make very polar
- Generally act in tandem



Nonsynthetic or Phase I Reactions: Site



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Nonsynthetic or Phase I Reactions:

oxidation

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

Reduction

- azo reduction
- nitro reduction
- disulfide reduction
- others

oxidoreductases

reductases

hydrolysis

Hydrolysis

- esters
- amides

esterases

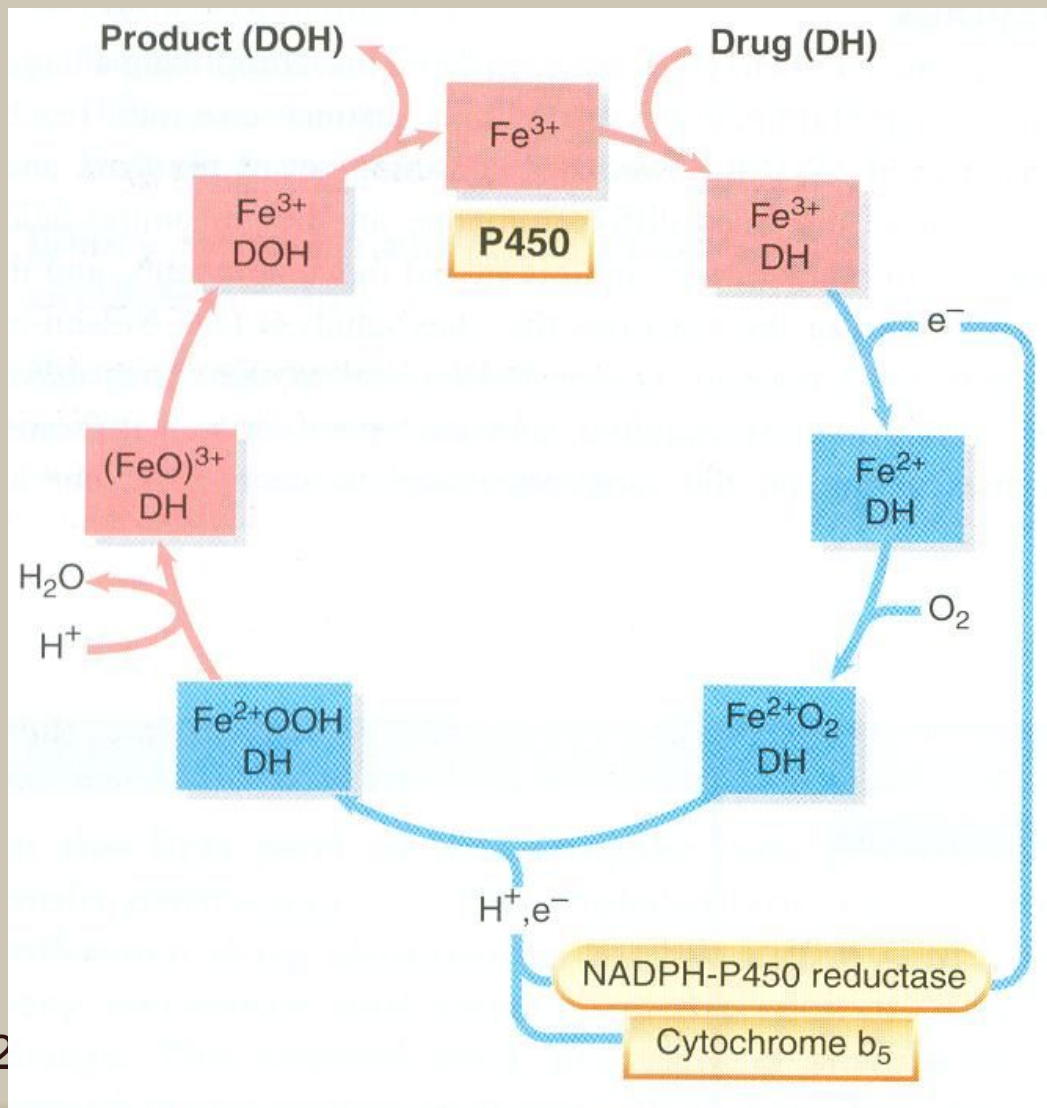
amidases

peptidases

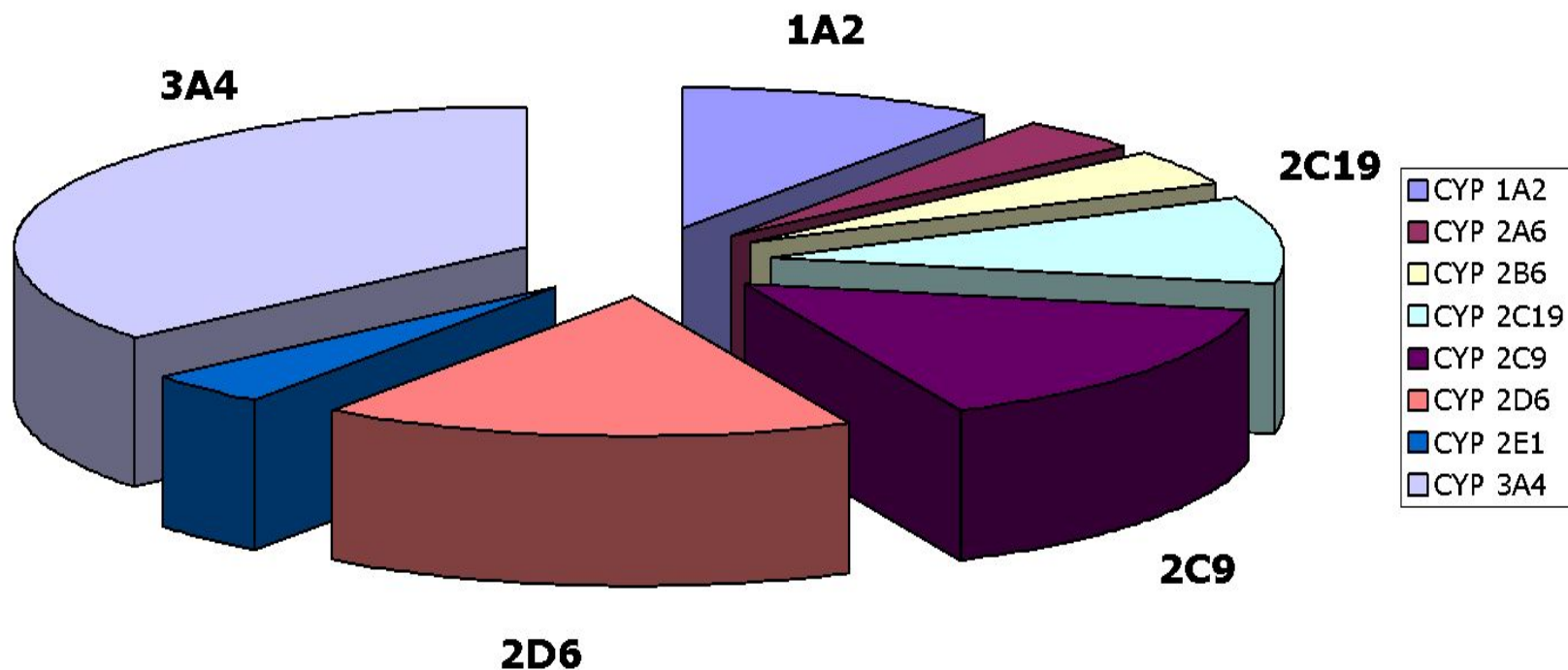
lipases



Nonsynthetic or Phase I Reactions: Cyt P450



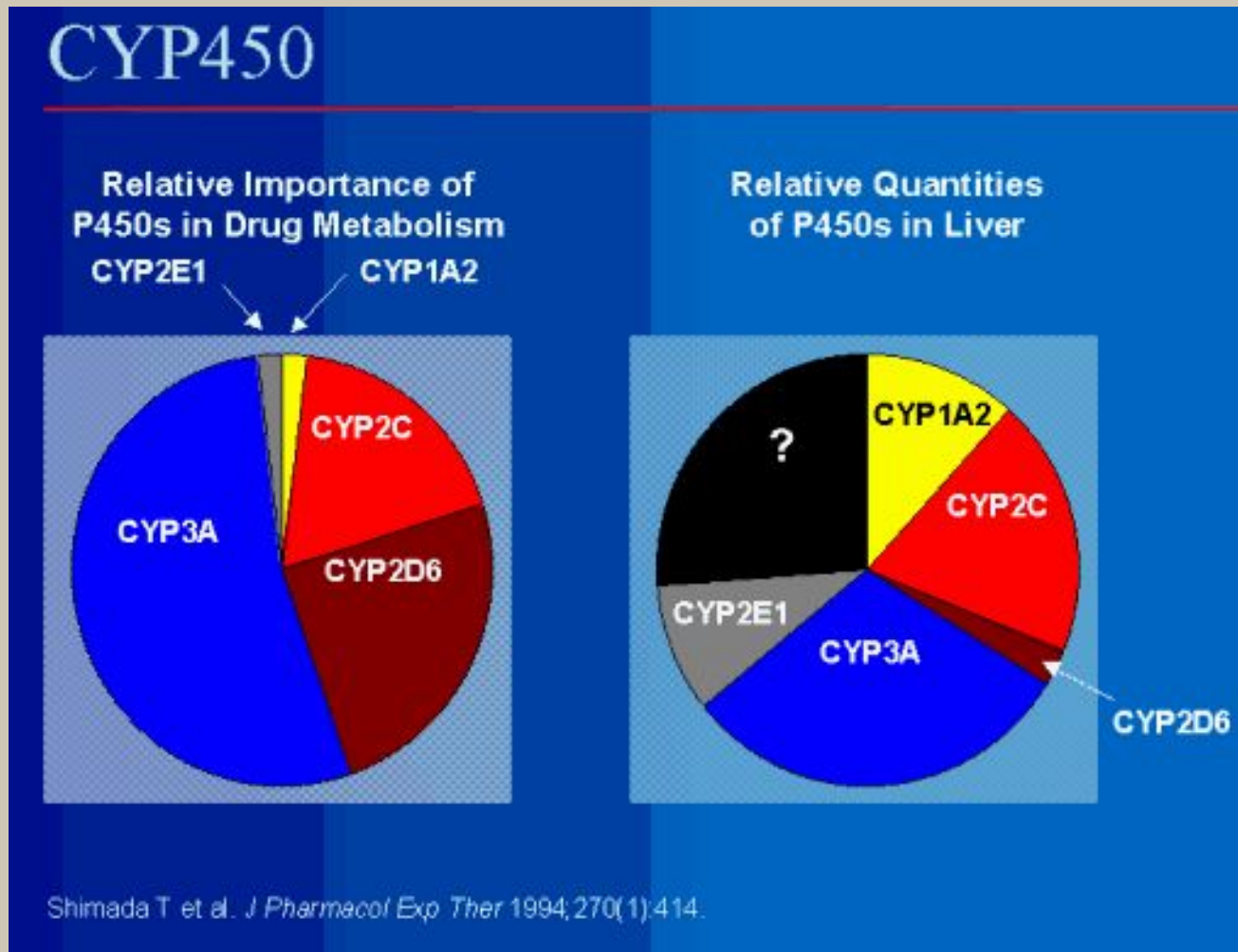
Nonsynthetic or Phase I Reactions: Cyt P450



Cytochrome P450 Nomenclature,
e.g. for CYP2D6

- CYP = cytochrome P450
- 2 = genetic family
- D = genetic sub-family
- 6 = specific gene

Nonsynthetic or Phase I Reactions: Cyt P450



Enzyme Induction

- Enhance synthesis:
 - Phenobarbital, Steroids
- Reduce rate of degradation:
 - ‘Substrate Stabilization’
 - Clotrimazole, Ethanol



Enzyme Inhibition

- Binding/Inactivation of heme iron:
 - Imidazoles, Macrolides
- Inactivation of the enzyme protein:
suicide inhibitors:
 - Chloramphenicol
- combination of above:
 - Secobarbital

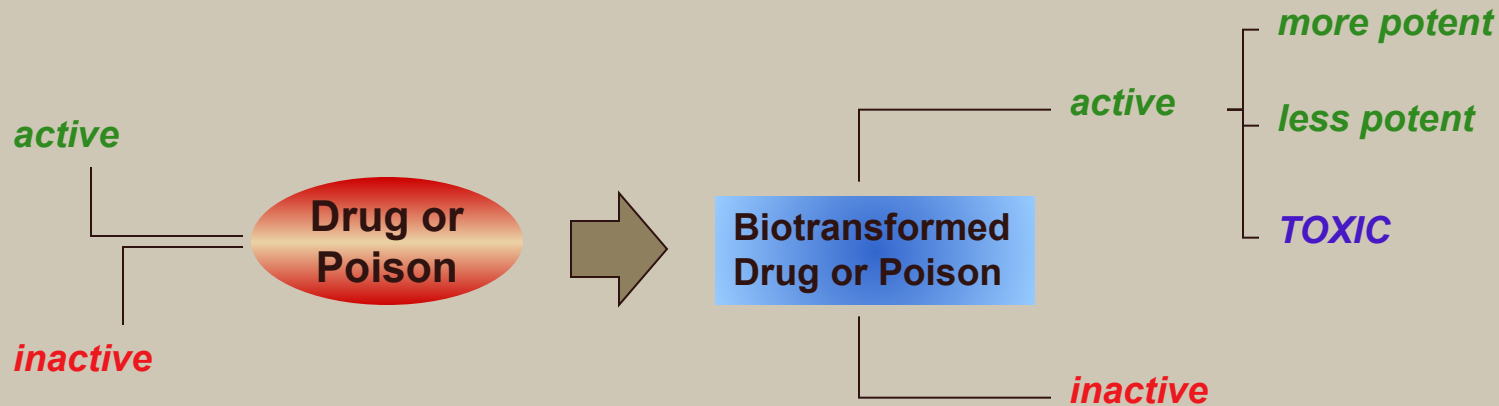


Synthetic or Phase II Reactions:

- Involves high energy intermediates
- Glucuronidation, Acetylation, Methylation, Glutathione/ Glycine/ Sulfate/ Water Conjugation.
- Transferases in microsomes or cytosol
- Role of nutrition in regulation of drug conjugation



Results of Biotransformation



In general -

- nonsynthetic reactions
 - precede synthetic reactions
 - can produce active metabolites
- synthetic reactions
 - produce inactive metabolites

Clinical Relevance

- Individual Differences
- Age & Sex
- Genetic Factors
- Diet & Environmental factors
- Drug interactions
- Diseases



THANK YOU

REFERENCES

- Goodman & Gilman's Pharmacological Basis of Therapeutics. Ed. 10
- Pharmacology: by Range, Dale & Ritter. Ed. 4
- Katzung's Basic and Clinical Pharmacology. Ed. 8.

