



# **BIOTRANSFORMATION**

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# CLEARANCE OF DRUGS

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



# BIOTRANSFORMATION

- Definition

- Sites

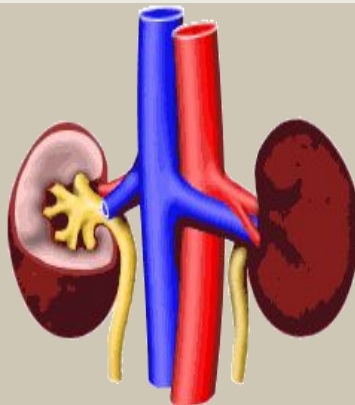
- Liver
- GIT



- Others

- Lungs
- Skin

- Kidneys

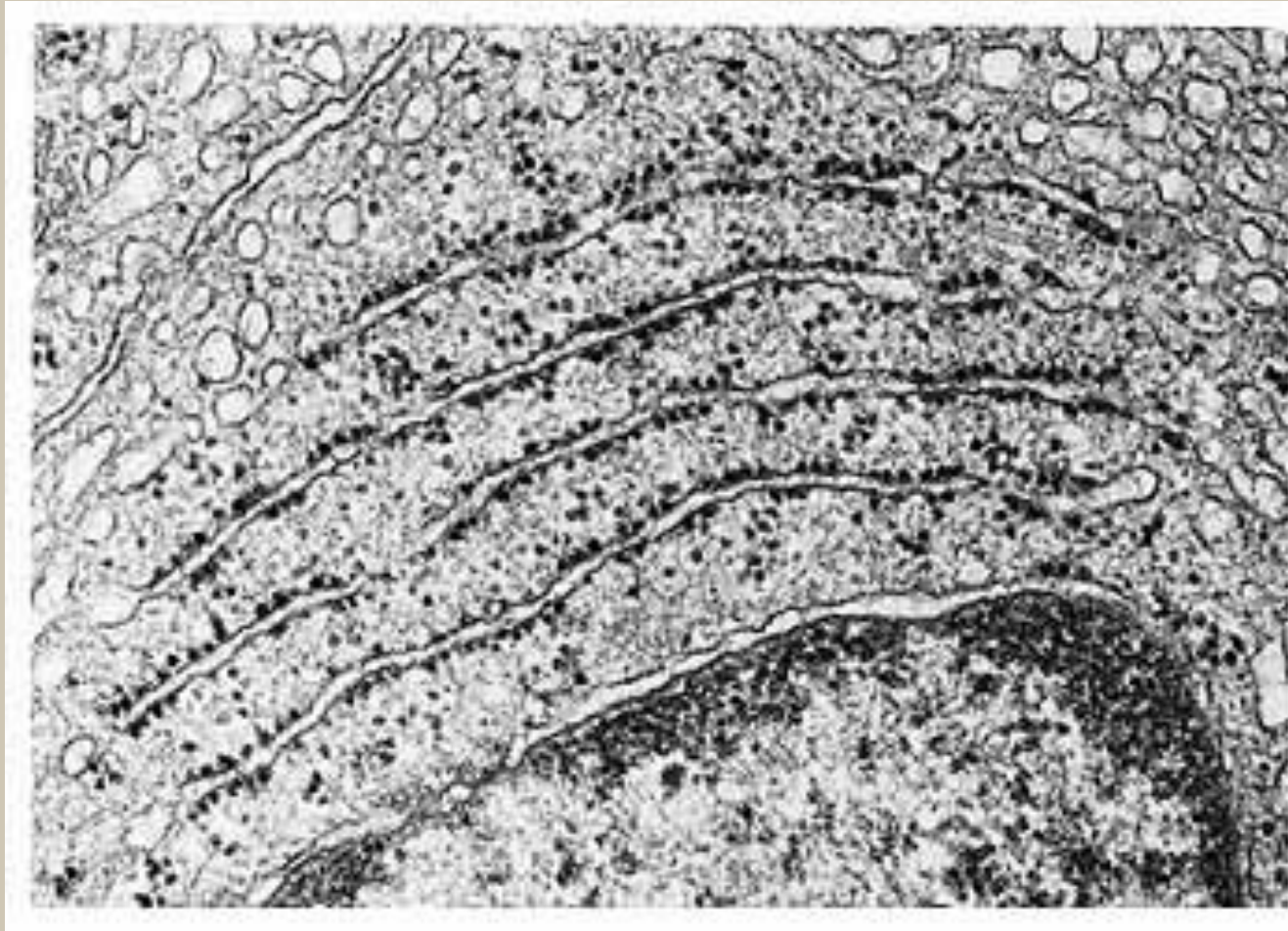


# Phases

- Phase I - Nonsynthetic
  - make polar by unmasking a functional group like -OH, -NH<sub>2</sub>, -SH.
  - oxidation-add O, remove H
  - reduction-remove O, add H
  - hydrolysis - add H<sub>2</sub>O
- Phase II - Synthetic
  - make very polar
- Generally act in tandem



# Nonsynthetic or Phase I Reactions: Site



12/22/2021

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# Nonsynthetic or Phase I Reactions:

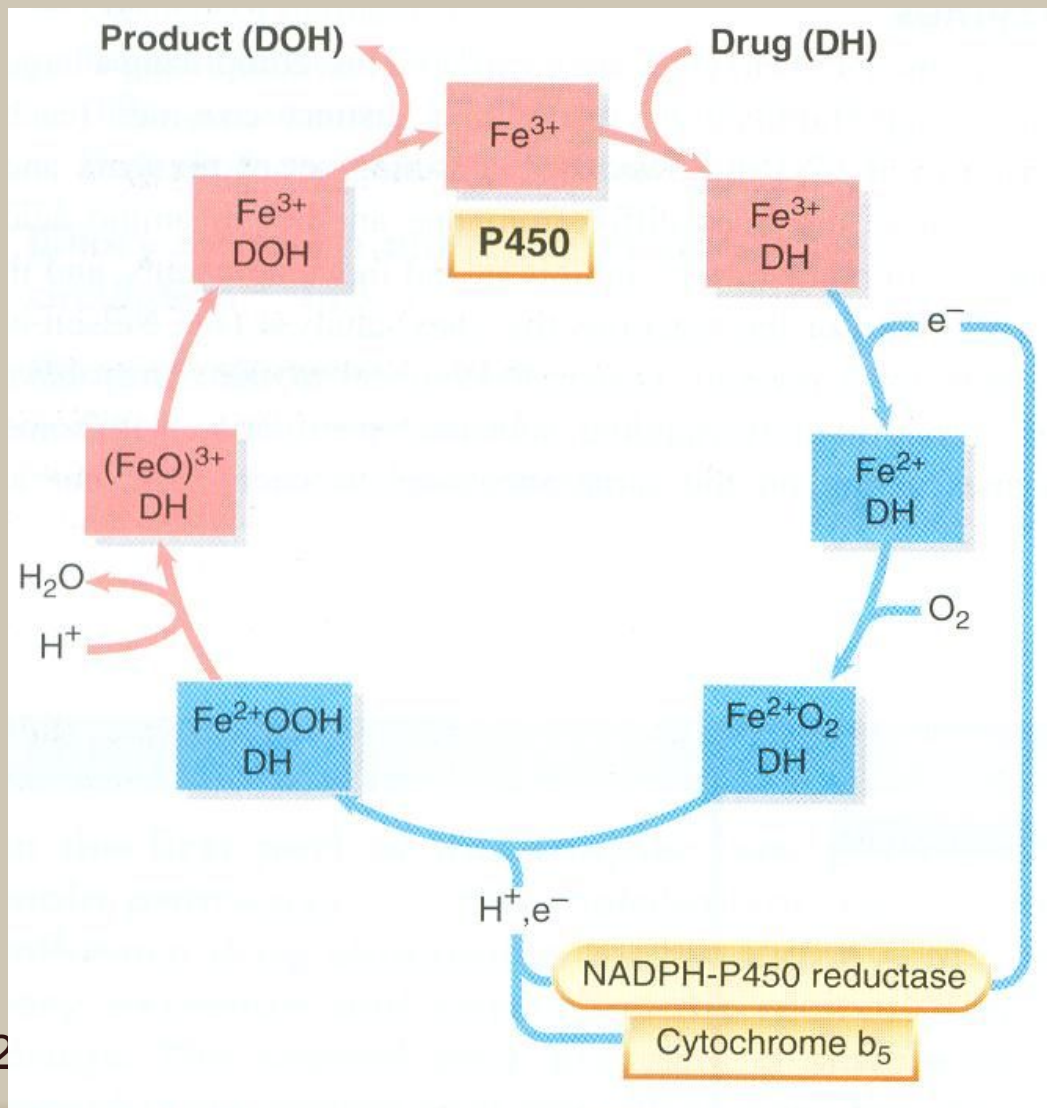
n Oxidatio	<ul style="list-style-type: none"><li>•hydroxylations aromatic, aliphatic, nitrogen</li><li>•dealkylations(N-, S-, P)</li><li>•deaminations</li><li>•N-, S-, P- oxidations</li><li>•S-replacements</li><li>•epoxidations</li><li>•others</li></ul>	<i>oxidoreductases</i> <i>oxidases</i> <i>monoamine oxidases</i> <i>mixed function oxidases</i>
on Reducti	<ul style="list-style-type: none"><li>•azo reduction</li><li>•nitro reduction</li><li>•disulfide reduction</li><li>•others</li></ul>	<i>oxidoreductases</i> <i>reductases</i>
sis Hydroly	<ul style="list-style-type: none"><li>•esters</li><li>•amides</li></ul>	<i>esterases</i> <i>amidases</i> <i>peptidases</i> <i>lipases</i>

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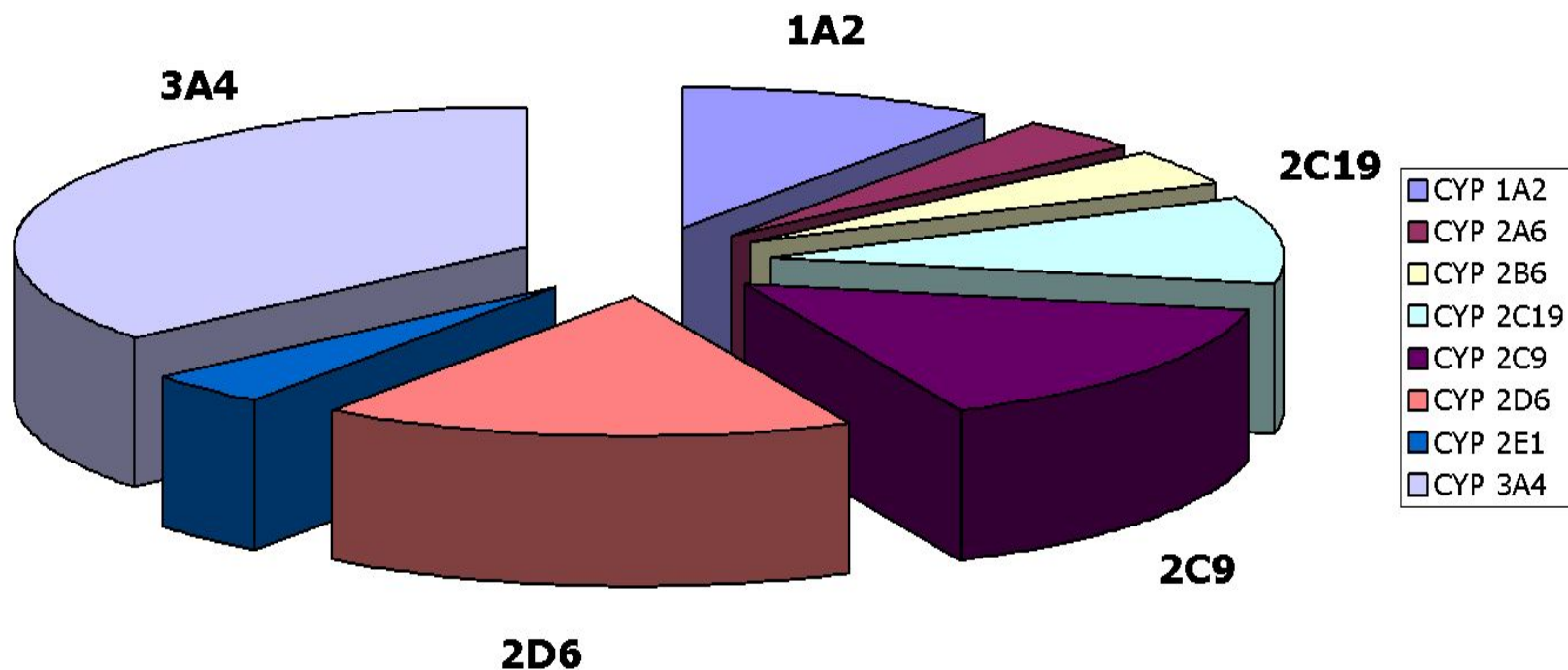




# Nonsynthetic or Phase I Reactions: Cyt P450



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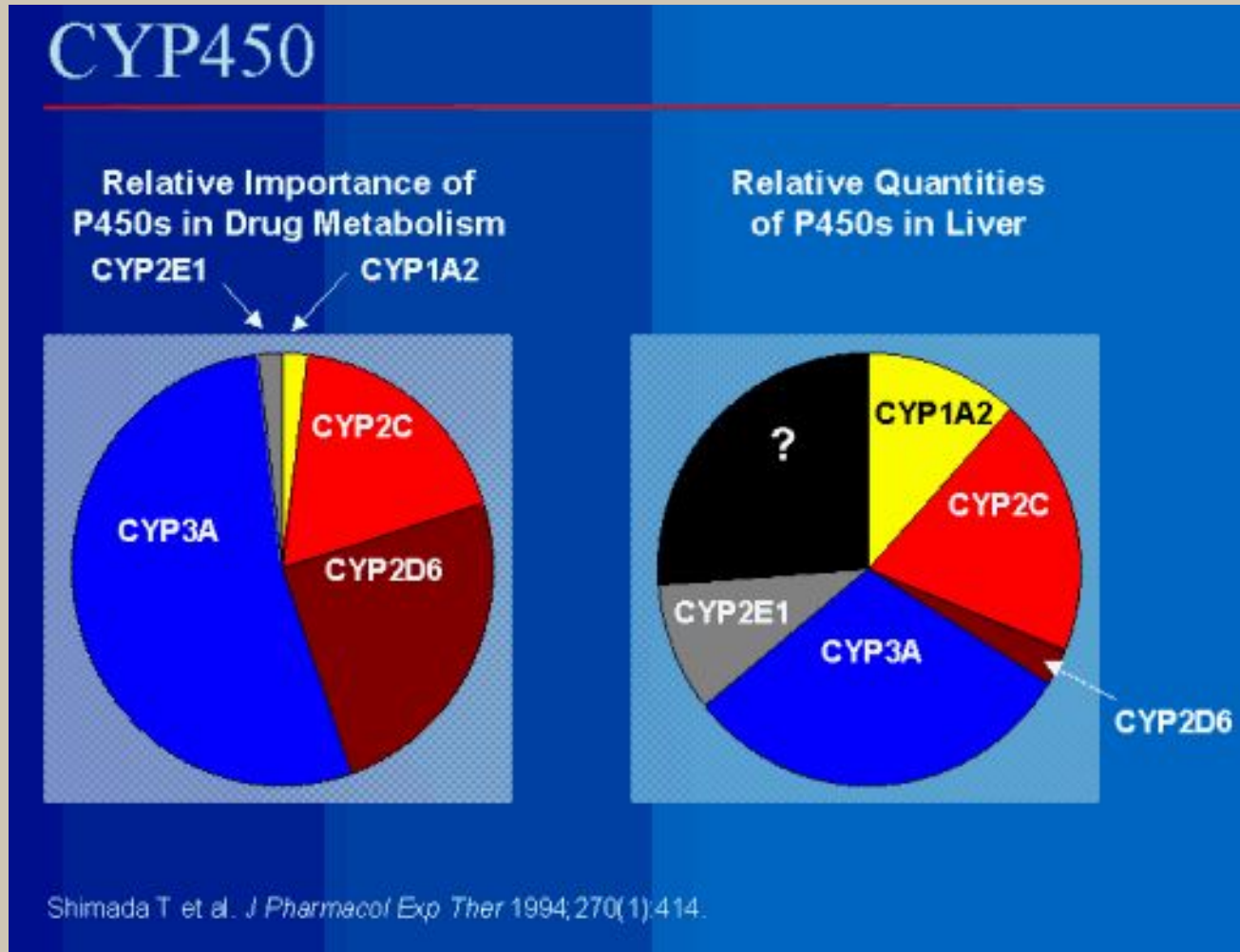


Cytochrome P450 Nomenclature,  
e.g. for CYP2D6

- 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

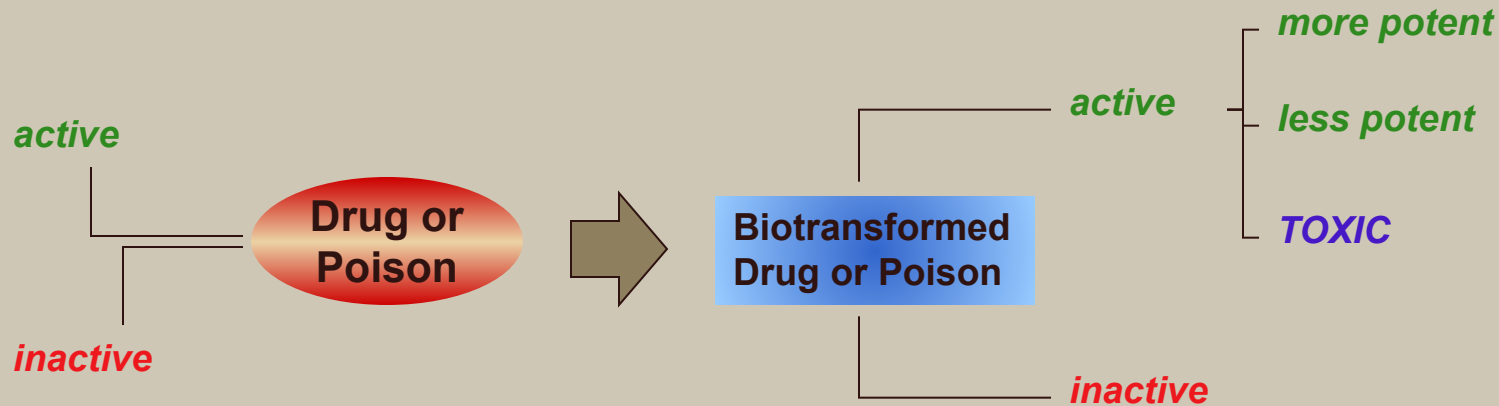


# Synthetic or Phase II Reactions:

- 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.

