BIOTRANSFORMATION

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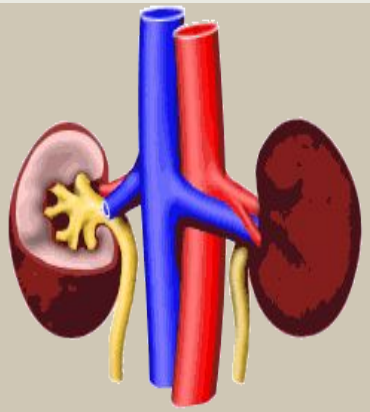
CLEARANCE OF DRUGS

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

BIOTRANSFORMATION

- Definition
- Sites
  - Liver
  - GIT

- Kidneys

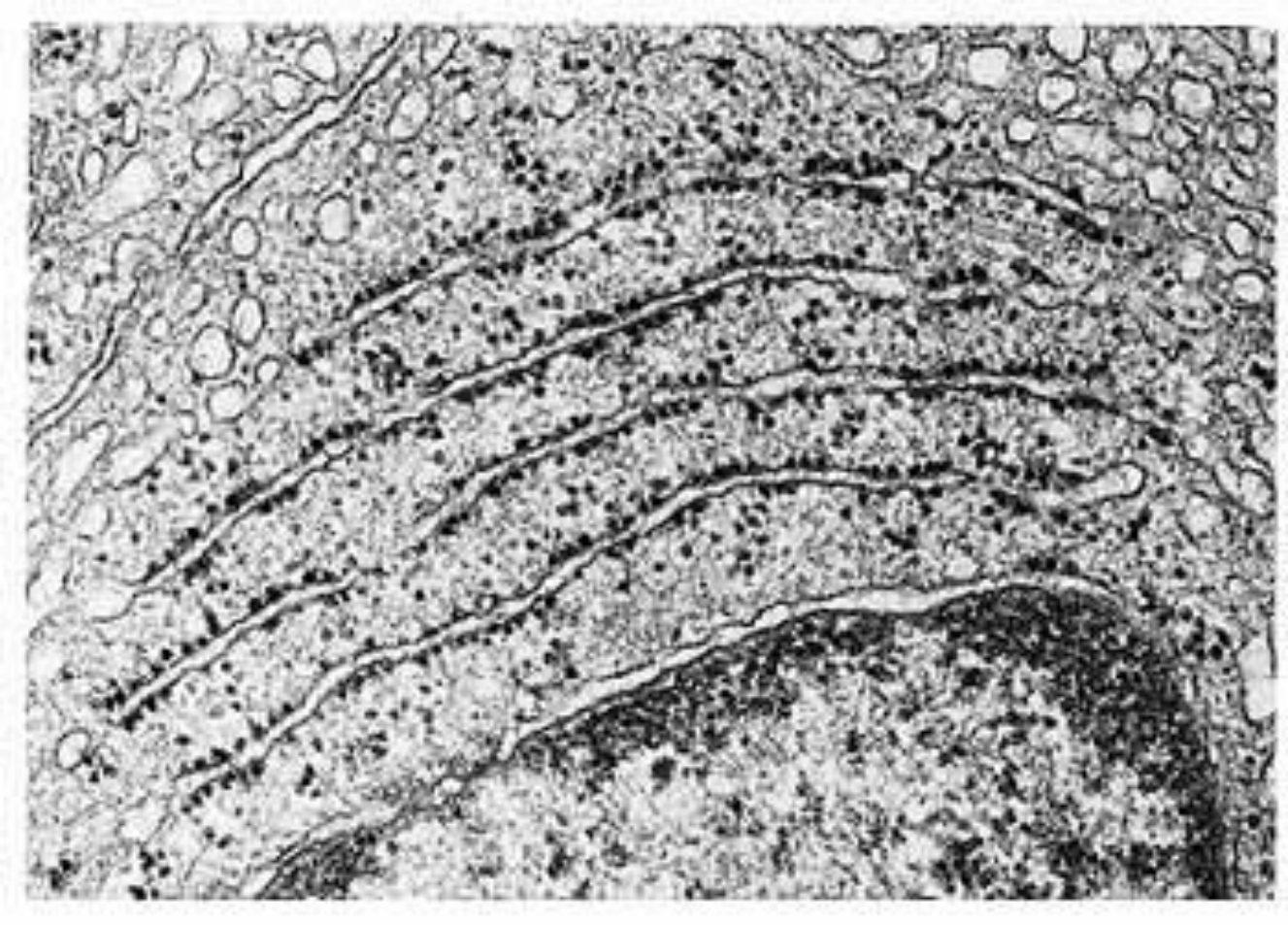


- Others
  - **Lungs**
  - **Skin**

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 H_2O
- Phase II - Synthetic
  - make very polar
- Generally act in tandem

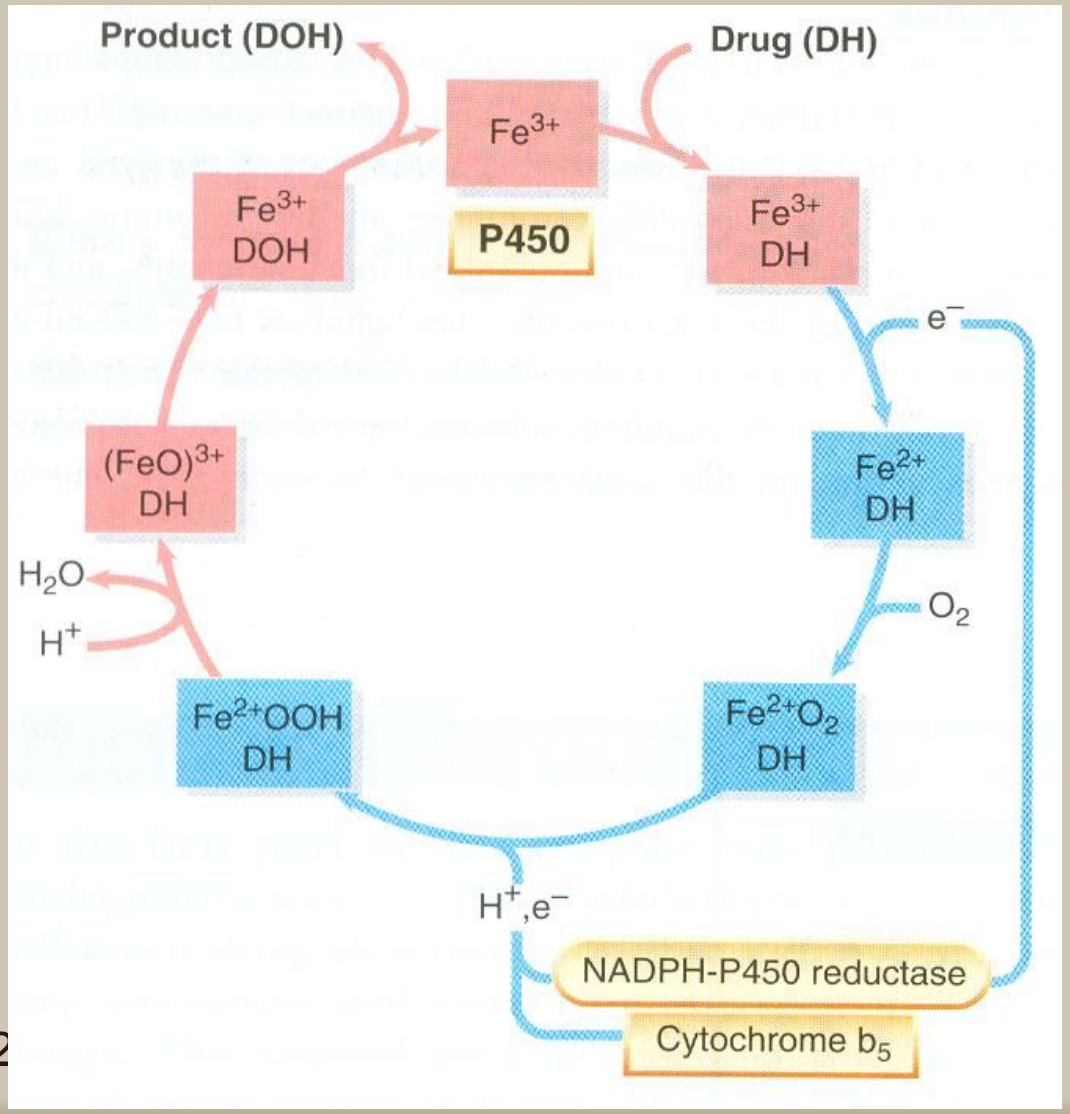
Nonsynthetic or Phase I Reactions: Site



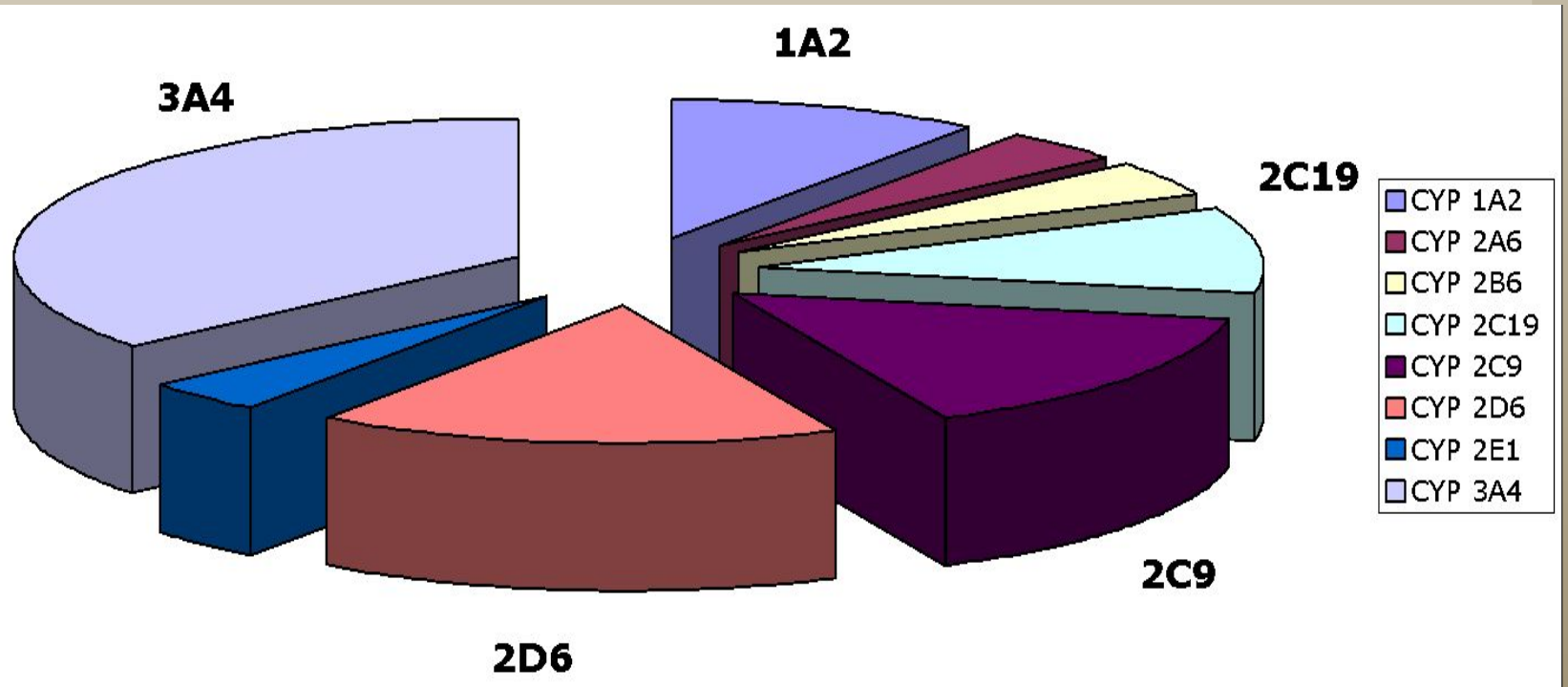
Nonsynthetic or Phase I Reactions:

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	Reducti	•azo reduction •nitro reduction •disulfide reduction •others	*oxidoreductases* *reductases*
Hydrolysis	Hydroly	•esters •amides	*esterases* *amidases* *peptidases* *lipases*

Nonsynthetic or Phase I Reactions: Cyt P450



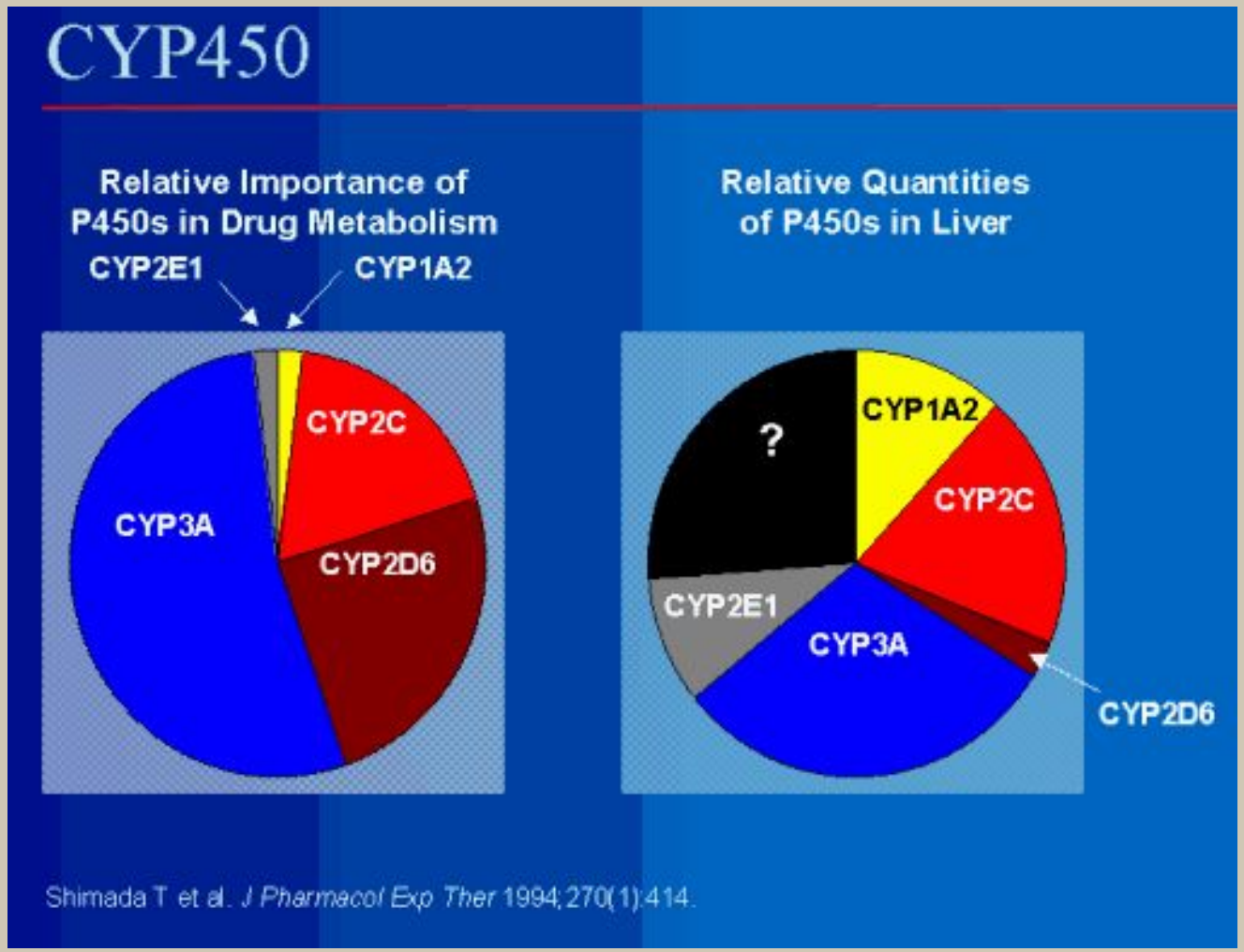
Nonsynthetic or Phase I Reactions: Cyt P450



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

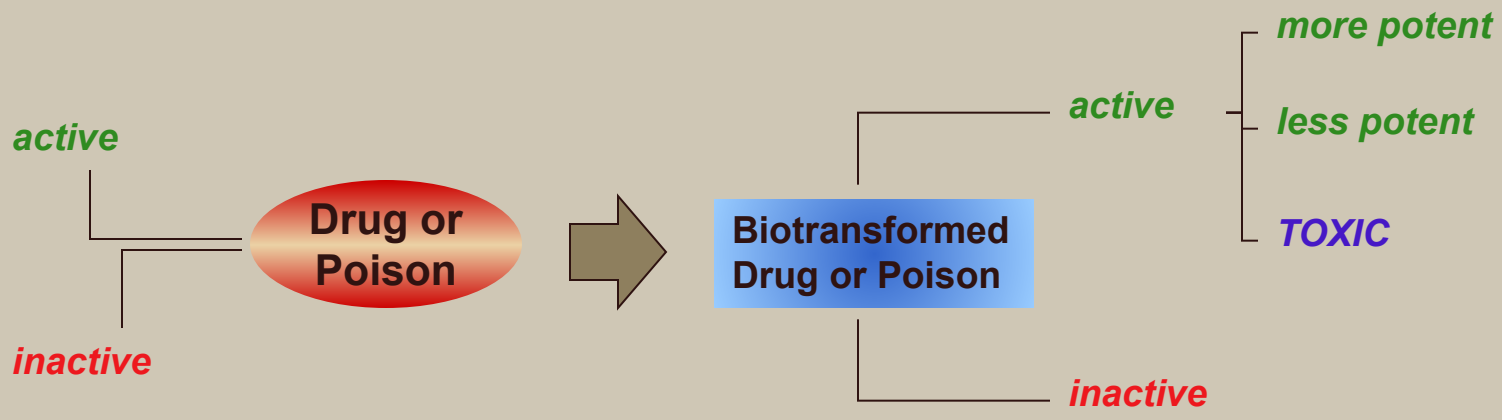
Enzyme Inhibition

- 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.