Xenobiotics Metabolism

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Terminology

- **Biotransformation**
  - Process where by a substance is changed from one chemical to another by a chemical reaction within the body
- **Xenobiotics**
  - Compounds which may be accidentally ingested or taken as drugs or compounds produced in the body by bacterial metabolism
- **Detoxification**
  - Process to decrease toxic nature of substance

- Biotransformation may produce
  - Less harmful substance
  - More harmful substance
    - Bioactivation
    - e.g. Vinyl chloride----------> vinyl chloride epoxide----------> liver cancer
- Xenobiotics
  - = foreign chemicals
  - e.g.
    - Drugs
    - Food additives, Pollutants
    - Some plants xenobiotics act as antioxidant
  - How xenobiotics are handled at cellular level?

Xenobiotics metabolism

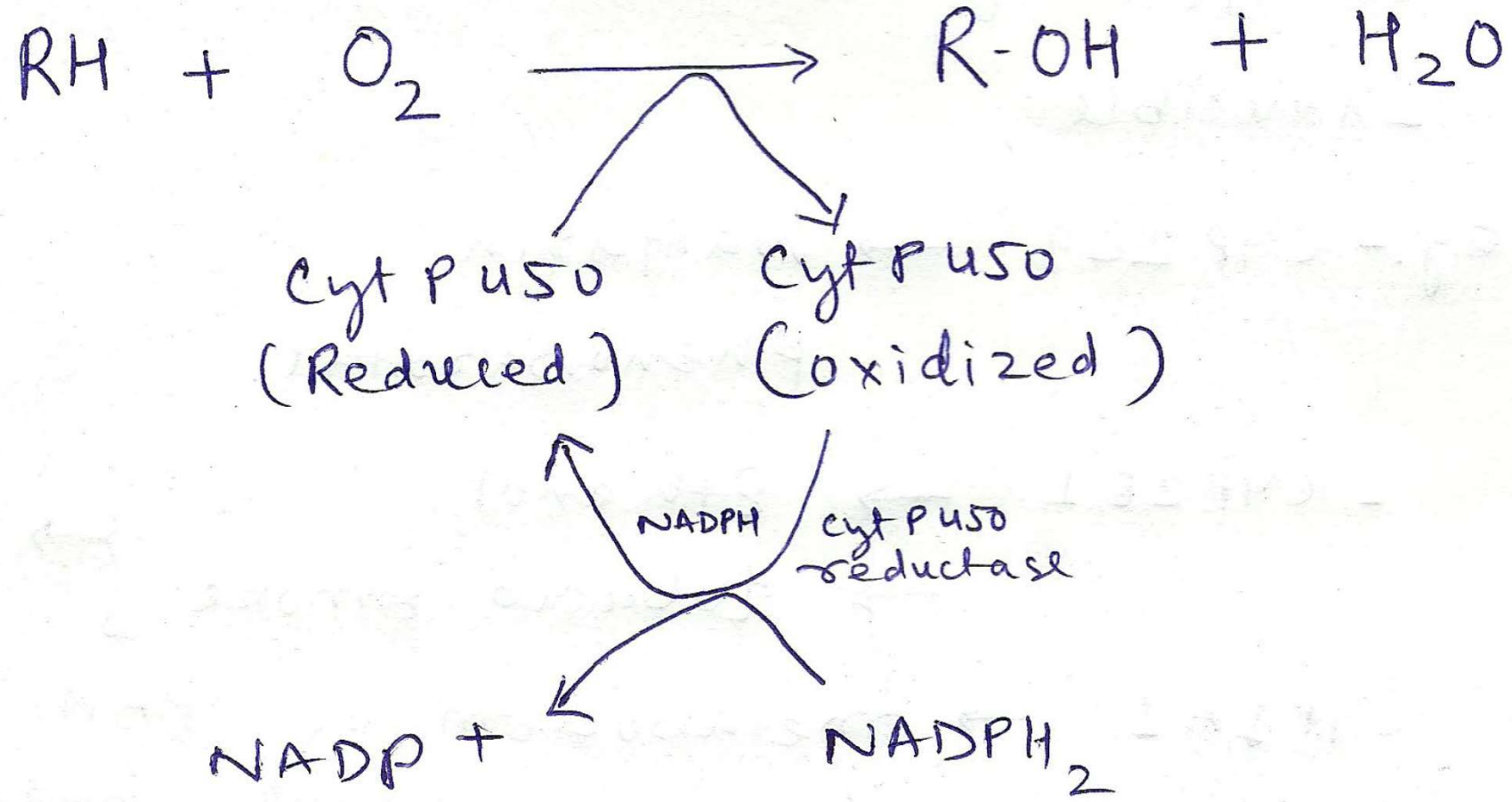
- Organ mostly commonly involved is Liver
- At least 30 different enzymes for xenobiotics metabolism
- It occurs mainly in two phases
  - It increase polarity (water solubility) so excreted by kidney
- Prodrugs/procarcinogens
  - Inactive form ----------> Active form

Phases of xenobiotics metabolism

- **Phase-I**
  - Hydroxylation
    - Most common
    - Monooxygenase/CytP450
  - Deamination
  - Dehalogenation
  - Desulfuration
  - Epoxidation
  - Peroxygenation
  - Reduction

- **Phase-II**
  - Conjugation
    - Glucuronic acid
    - Sulfate
    - Acetate
    - Glutathione
    - Amino acids
    - Methylation

- **Hydroxylation by cytochrome P450**
  - It is monooxygenases (mixed function oxidases, hydroxylase)
  - $AH + O_2 + ZH_2$ ------→ $AOH + Z + H_2O$
  - Incorporate one oxygen
  - One oxygenase reduced to H_2O
  - 57 CytP450 genes
  - 150 different enzymes
  - It contain Heme
  - Located in ER (Liver, intestine), mitochondria (adrenal gland)
  - Convert lipophilic substance into hydrophilic

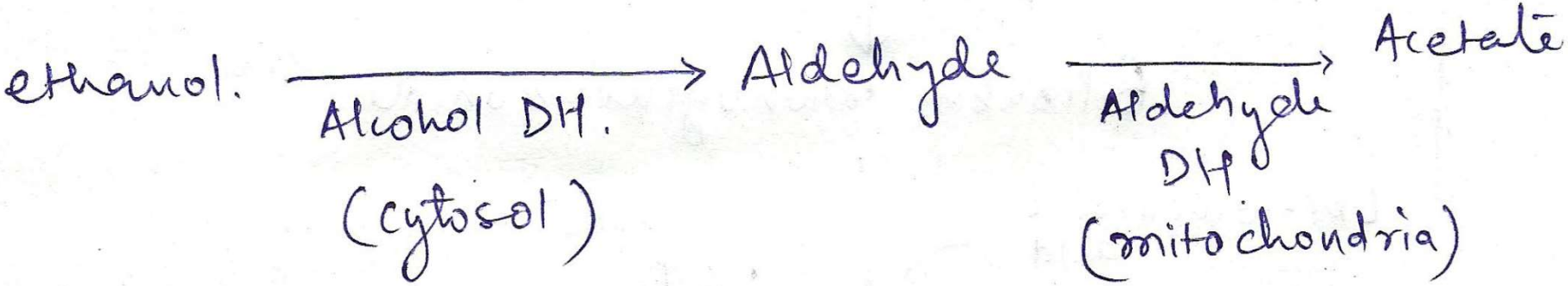

RH + O2
R-OH + H2O
Cyt P450 (Reduced)
Cyt P450 (oxidized)
NADPH
Cyt P450 reductase
NADP+
NADPH2

- When chemically reduced and exposed to CO spectrophotometric absorption is maximum at 450nm
- Almost 50% drugs are metabolized by CytP450
- Large no of isoforms
- *CYP1A2 (gene)* ----- → CYP1A2 (enzyme)
  - CYP- Cytochrome P450 gene
  - 1- Family
  - A- Subfamily
  - 2- Individual member of subfamily
- Wide substrate specificity (metabolized thousands chemical)

- NADPH is required not NADH
- Phosphatidyl choline is component
- Inducible
  - CYP2C9
    - Warfarin
    - Phenobarbital
  - CYP2E1
    - Ethanol
    - Tobacco
- CYP1A1
  - Metabolism of PAH (polycyclic aromatic hydrocarbons)

- Polymorphic forms
  - Variation in drug response
  - CYP2A6
    - Metabolism of nicotine---------→ conitine----------→ cancer, dependency
    - Three polymorphic forms
      - Two null type- no effect
      - One wild type- dependency
- Also for
    - Vit D activation
    - Steroid hormone synthesis

- **Oxidation**
  - e.g. Alcohol



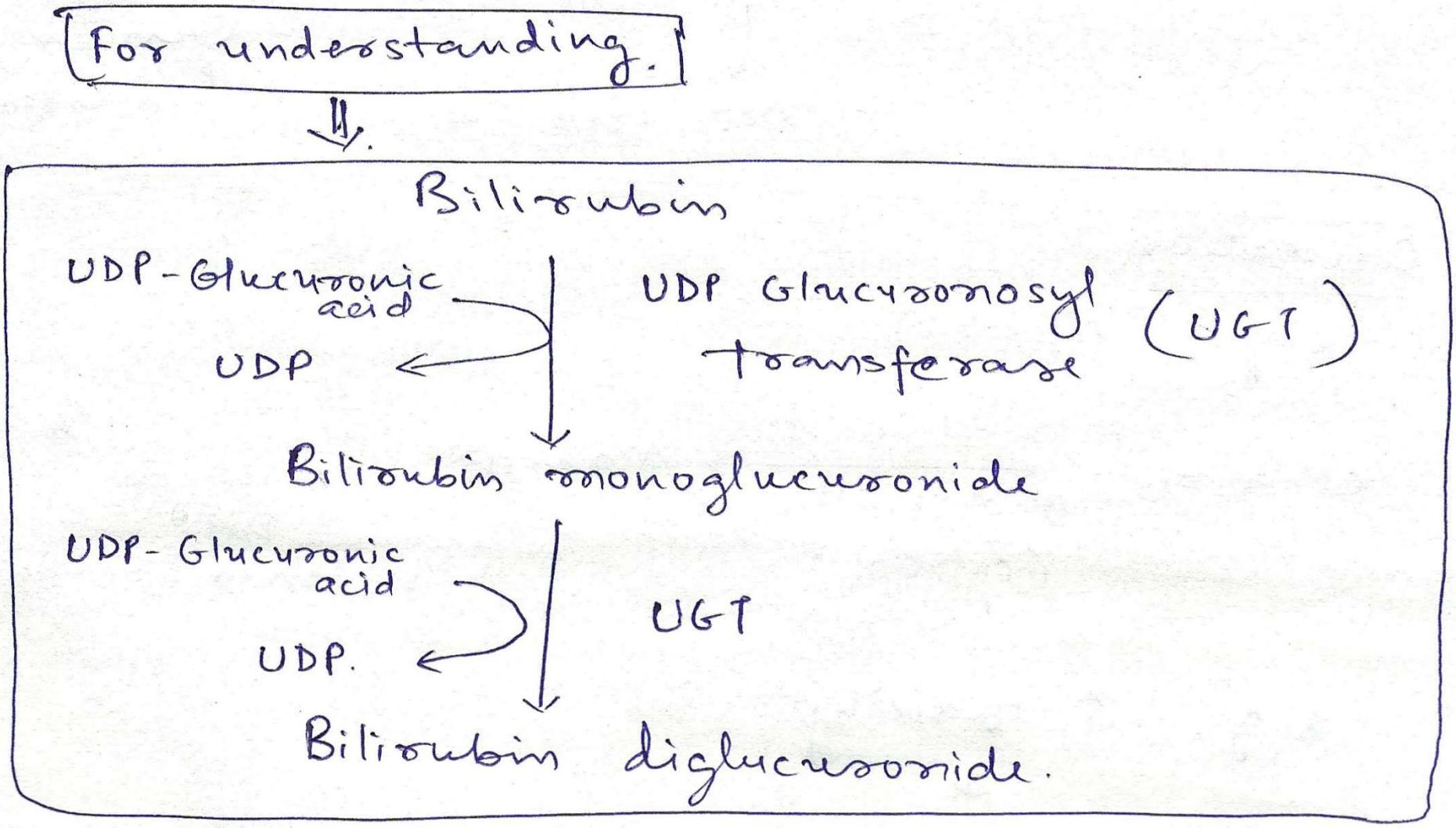
  - It may increase toxicity
    - Methanol----------→ formic acid

- **Reduction**
  - Nitro compounds
- **Hydrolysis**
  - Aspirin
  - Procaine
  - xylocaine

- **Phase-II (Conjugation)**
  - Molecules normally present in the body added to the reaction site
  - Non toxic + easily excretable

  1. Glucuronidation
     - Most common conjugation
     - e.g. aniline, benzoic acid, phenol, steroids

For understanding.



- **Sulphate conjugation**
  - Phenolic
  - Alcoholic compounds
  - Enzyme- sulfo-transferase
  - Group transferred- PAPS (Phospho adenosine phosphor sulphate)
- **Glutathione**
  - Enzyme- Glutathione-S-transferase
  - Group- Cysteine
  - E.g.- Alkyl or aryl halides, epoxides

- **Acetylation**
  - Enzyme- acetyl transferase
  - Group- acetate
  - e.g.- Sulfanilamide, INH, PAS
- **Glycine**
  - Benzoic acid + Glycine ----------→ Hippuric acid
- **Glutamine**
  - Phenyl acetate

- **Methylation**
  - Enzyme- methy transferase
  - Group- SAM (S- adenosyl methionine)
  - It decrease water solubility
    - E.g.- mercury ------→ Lipophilic ----------→ Neurotoxic
- **Phase- III**
  - Further conjugation with glutathione
- Factors affecting xenobiotics metabolism
  - Genetic factors
  - Age
  - Gender

Thank You