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DRUG METABOLISM

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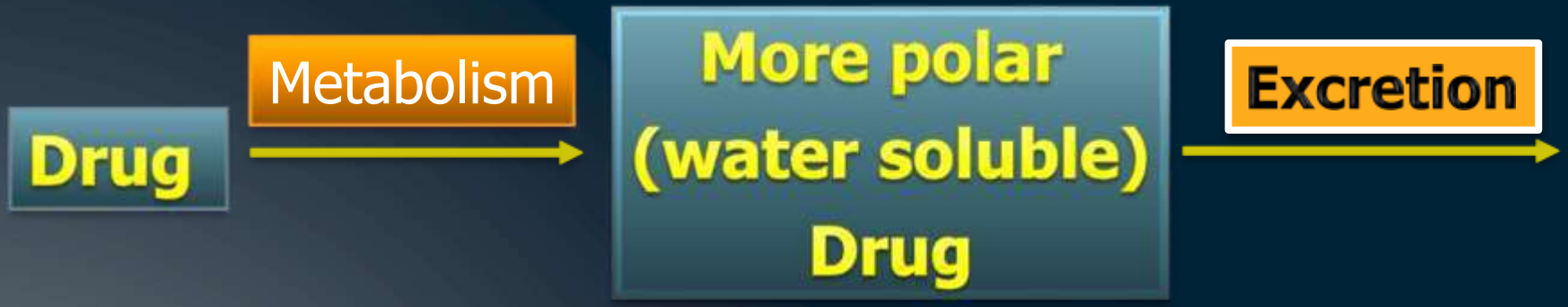
Drug Metabolism

Drug Metabolism / Biotransformation

- The chemical modification of drugs with the overall goal of getting rid of the drug
- Enzymes are typically involved in metabolism.

Biotransformation is the enzyme catalysed chemical alteration of the drug in the body.

Drug Metabolism

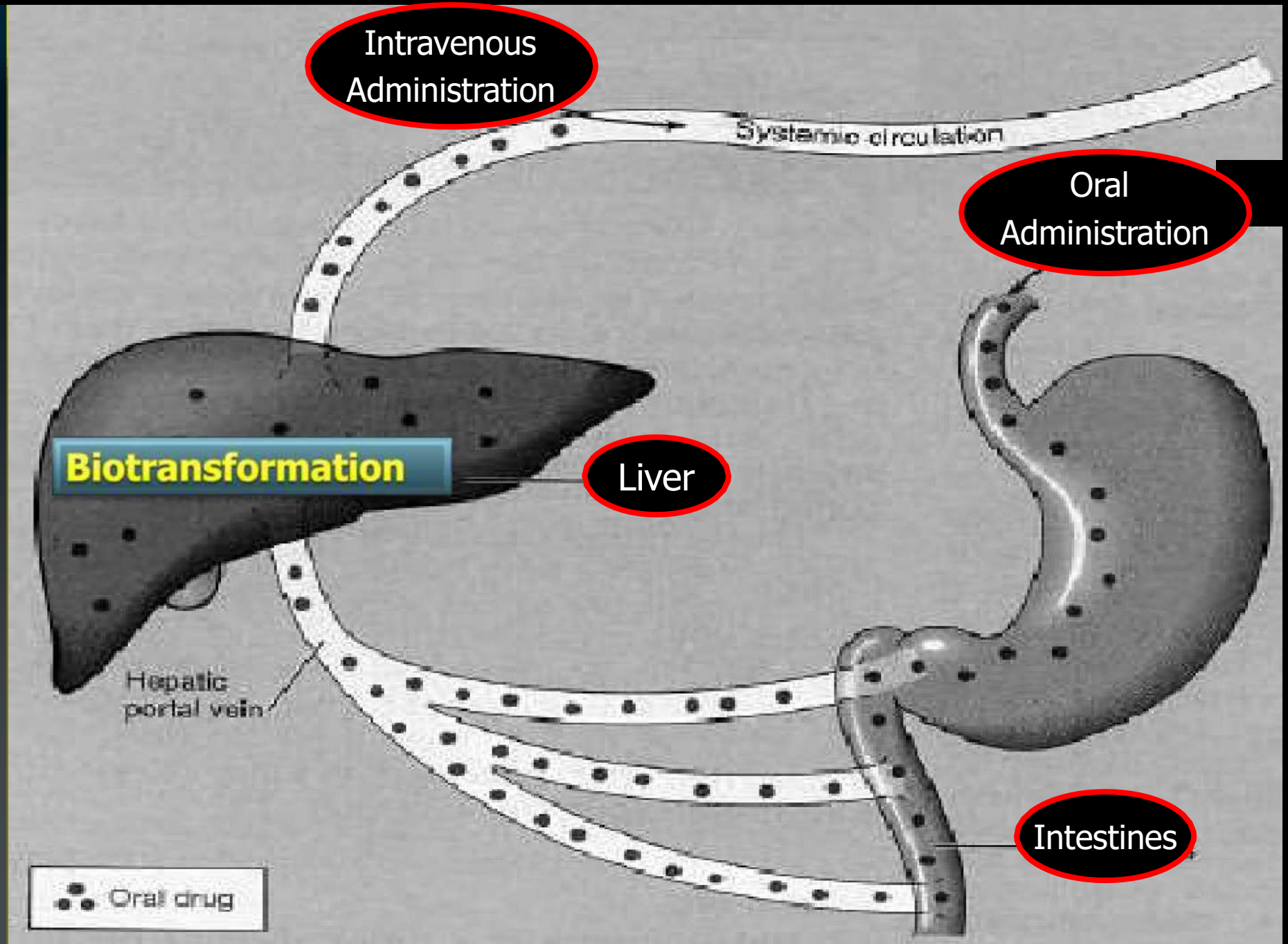


Sites of Drug Metabolism

- Metabolism occurs in many tissues
- E.g. brain, kidney, lung, plasma, intestine.

But mostly in the liver because …

all of the blood in the body passes through the liver.


Intravenous Administration
Systemic circulation
Oral Administration
Biotransformation
Liver
Hepatic portal vein
Intestines
Oral drug

Consequences Of Metabolism

Drug metabolism != Drug inactivation

- The metabolite may have…
  - **No or reduced activity (inactivation)**

    Most drugs and their active metabolite are rendered inactive.

    Examples- Phenobarbitone, Chloramphenicol, Morphine, Propranolol.

Phenobarbitone → **Hydroxyphenobarbitone (inactive)**

Consequences Of Metabolism

The metabolite may have…

- **Equal activity to the drug**

  Many drugs have been found to be partially converted to active metabolite.

  Examples-

Consequences Of Metabolism

The metabolite may have…

- **Increased activity (Prodrug)**

Prodrugs refers to precursor drug that in itself has little or no biological activity and is metabolised to pharmacologically active metabolite.

Features:

- Toxic properties not seen with the parent drug
- Stable drug
- Better PK profile and bioavailability.

First Pass Effect

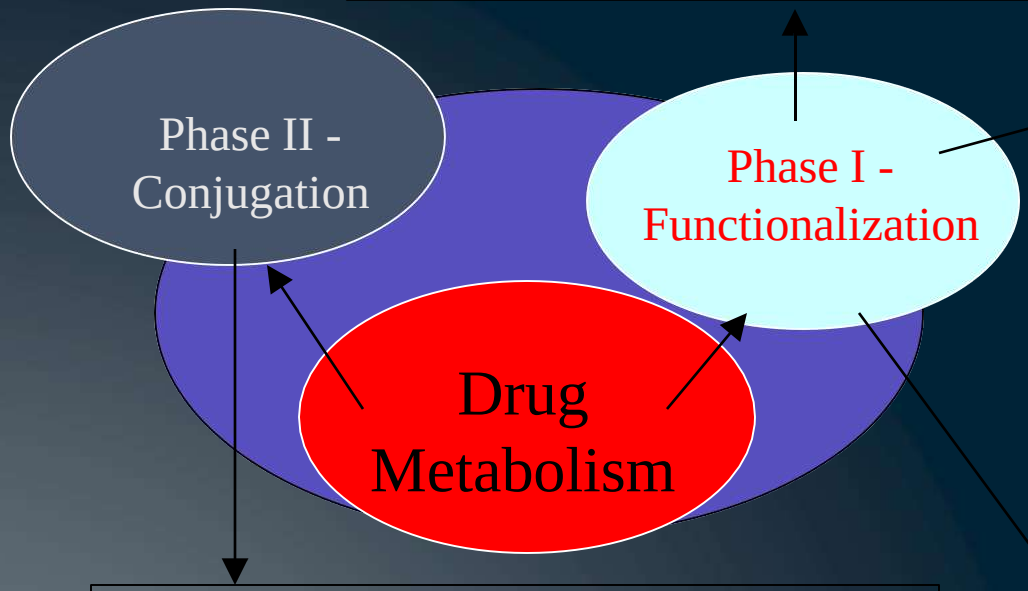
- Biotransformation of drug by liver or gut enzymes before compound reaches systemic circulation
- Results in lower systemic bioavailbility of parent compound, diminished therapeutic response.
- First pass effect may be bypassed if the drug is administered IV or Sublingually.

Examples: Propafenone, Isoniazid, Propanolol

Drug Metabolising enzymes

- Microsomal
- Non-microsomal
- Non –enzymatic biotransformation

Phases of Metabolism



Hydrolytic Reactions

- Esters, amides, epoxides and arene oxides by epoxide hydrase

Oxidation

- Aromatic moieties, Olefins
- Benzylic & allylic C atoms and a-C of C=O and C=N
- At aliphatic and alicyclic C
- C-Heteroatom system
  - C-N (N-dealkylation, N-oxide formation, N-hydroxylation)
  - C-O (O-dealkylation)
  - S-dealkylation
  - S-oxidation, desulfuration
- Oxidation of alcohols and aldehydes, Miscellaneous

Conjugation

- Glucuronic acid
- Sulfate, Glycine and other AA
- Glutathione or mercapturic acid
- Acetylation, Methylation

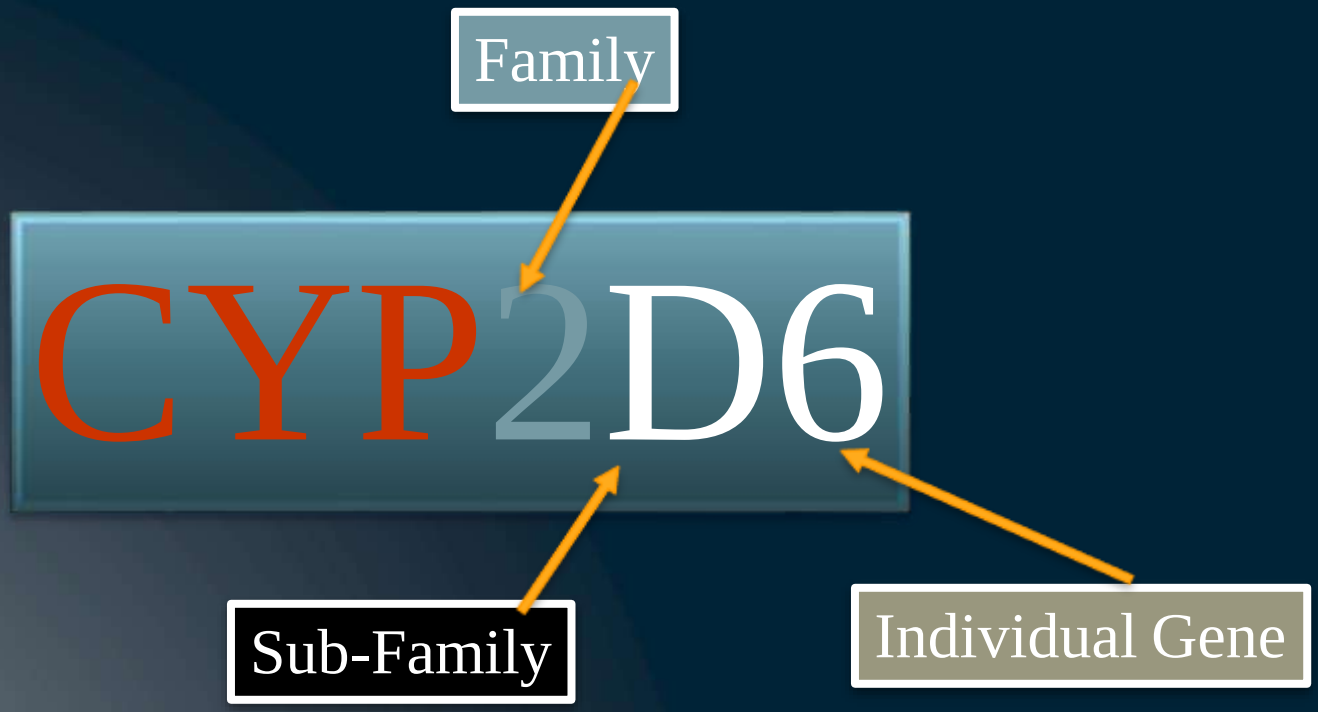
Reduction

- Aldehydes and ketones
- Nitro and azo
- Miscellaneous

Microsomal Enzymes

- Microsomal cytochrome P450, monooxygenase family of enzymes, which oxidize drugs.
- Location-smooth endoplasmic reticulum in Liver, Kidney, intestinal mucosa, and lungs.
- They catalyze:
  - Oxidation, reduction, hydrolysis (phase I reactions)
  - Glucuronide conjugation (phase II reactions)

CYP450 Nomenclature



Enzyme characteristics

% of drugs metabolised by enzyme

- 3A4 60%
- 2D6 25%
- 1A2 15%
- 2C9 Small no. but significant interactions
- 2C19 Small no. but significant interactions
- 2E1 ?

Non-microsomal Enzymes

- Location :
  - Cytoplasm, mitochondria of hepatic cells.
- Examples :
  - Monoamine oxidases (MAO), Esterases, Amidases, Transferases, Conjugages
- Reaction catalysed are all Phase II reactions except glucuronidation.
- These are non-inducible
- May show genetic variations.

BIOTRANSFORMATION REACTIONS

Nonsynthetic / Phase I:
Metabolite may be active or inactive.

Synthetic / Phase II:
Metabolite is mostly inactive (conjugation)

Comparing Phase I & Phase II

Enzyme	Phase I	Phase II
Types of reactions	Oxidation Reduction Hydrolysis	Conjugations
Increase in hydrophilicity	Small	Large
General mechanism	Exposes functional group	Polar compound added to functional group
Consquences	May result in metabolic activation	Facilitates excretion

Phase I reactions: Oxidation

Addition of oxygen (-ve charged radical) or removal hydrogen (+ve).

Reactions

Microsomal oxidation	Non Microsomal oxidation
• Hydroxylation (Phenobarbitone to hydroxyphenobarbitone) • Oxygenation • Deamination • Dealkylation	• Mitochondrial oxidation (Epinephrine by MAO) • Cytoplasmic oxidation (alcohol by alcohol dehydrogenase) • Oxidative deamination (Histamine)

Reduction

- Converse of oxidation
- Drugs primarily reduced are chloralhydrate, chloramphenicol, halothane.

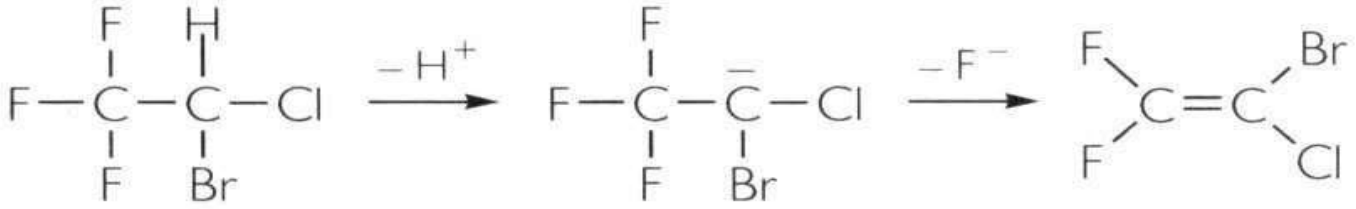


Figure 1.25 Reductive defluorination of halothane.

Phase I: Reductions

- Azo reduction (Microsomal)

  eg: prontosil to sulfanilamide

- Carbonyl reduction (Non microsomal)

  Alcohol dehydrogenase (ADH)

  - Chloral hydrate is reduced to trichlorothanol

Phase I: Hydrolysis

- Carboxyesterases (Non microsomal)
  - Hydrolysis of esters : procaine to PABA by plasma cholineesterases

Hydrolysis

- Cleavage of drug molecule by taking up a molecule of water.

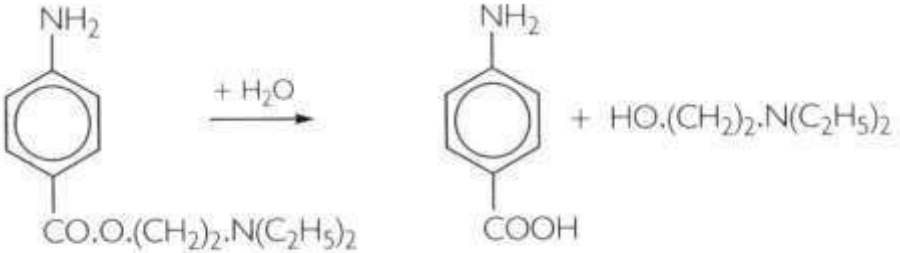


Figure 1.26 Hydrolysis of procaine.

- Sites: Liver, intestines, plasma and other tissues
- Examples: Choline esters, Procaine, Isoniazid, pethidine, oxytocin.

Phase II: Conjugations

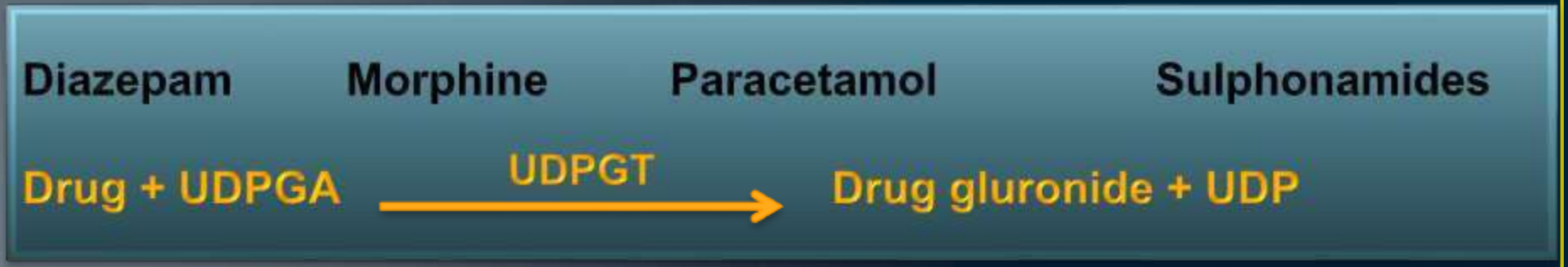
- MICROSOMAL
  - ✓ Glucuronide conjugation
- NON-MICROSOMAL
  - ✓N acetyl conjugation
  - ✓Sulfate conjugation
  - ✓Methyl conjugation
  - ✓Glutathione conjugation
  - ✓Glycine conjugation
  - ✓Glutathione conjugation
  - ✓Ribonucleoside conjugation

Phase II: Glucuronide Conjugations

- Parent drug or their phase I metabolite that contain phenolic, alcoholic, carboxylic group undergoes conjugation with uridine diphospate glucuronic acid (UDPGA).
- Catalytic enzyme : UDP –glucuronyl transferase
- yield drug- glucuronide conjugates that are polar.

Examples :

Diazepam Morphine Paracetamol Sulphonamides



Phase II : NON-MICROSOMAL CONJUGATION

Conjugation Reaction	Enzyme	Examples
N acetyl conjugation	N-acetyltransferase	Dapsone, Sulphonamides, Histamine
Sulfate conjugation	Sulfotransferase	Paracetamol, Corticosteroids
Methyl conjugation (minor Pathway)	Transmethylase	Catecholamines

ENZYME INDUCTION

Enzyme Induction

- Several drugs (inducers) induce the growth of smooth endoplasmic reticulum leading to enhanced microsomal enzyme activity.
  - ✓Accelerates metabolism
  - ✓Decrease pharmacological response of not only the inducer itself but also of the coadministerd drug (substrate).
- Occurs gradually over 1-2 weeks

Enzyme Induction

Enzyme inducers	Enzymes induced	substrates
Phenobarbitone Phenytoin carbamazepine	CYP3A4	Midazolam Macrolides Calcium channel blockers
Rifampicin Phenobarbitone	CYP3A4 & CYP2C9	Oral contraceptives Warrfarin

Clinical importance

- Increased drug metabolism :
  - Decreased plasma levels and therapeutic effects of the substrate (co administered drug)
  - Increase drug activity if the metabolite is active
  - Examples : OC pills , Warfarin (therapeutic failure)
- Therapeutic use of enzyme induction

Treatment of neonatal Jaundice ; Phenobarbitone induces foetal gluronyl transferase which catalyses conjugation of bilirubin

Enzyme Inhibition

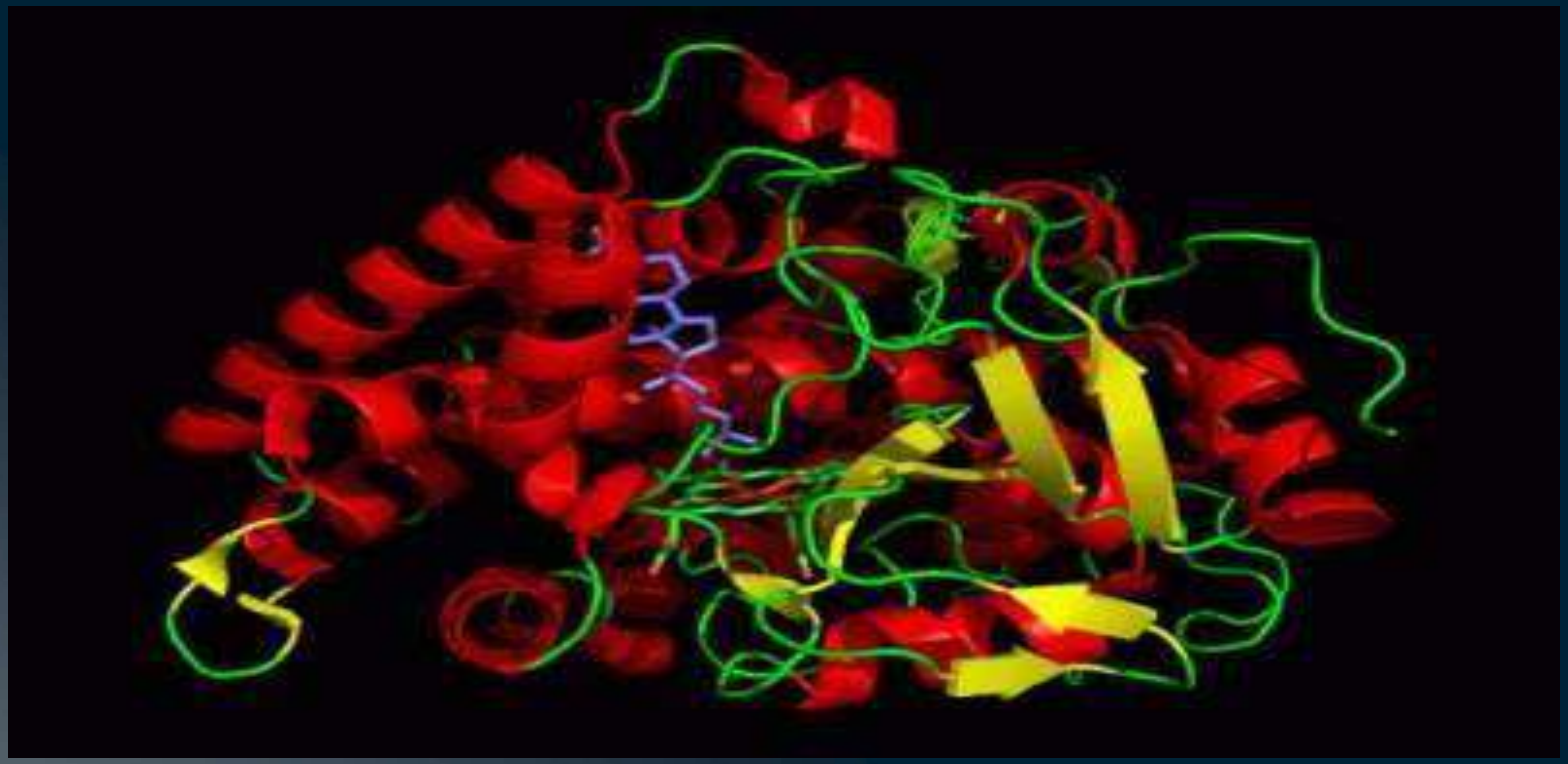
- Often rapid, reversible and relatively short acting.
- E.g. erythromycin and Terfanadine
  - Erythromycin causes a rapid increase in plasma Terfenadine concentration if given concurrently.
- Note: Erythromycin is a substrate and an inhibitor of CYP 3A4

Some Enzyme Inhibitors

- Cimetidine
- Fluoxetine
- Erythromycin
- Chloramphenicol

Non –enzymatic bio-transformation

- Hoffman's Elimination
- Example: some drugs like atracurium (skeletal muscle relaxant) are metabolized in plasma through molecular rearrangement without involvement of enzyme action.



Thank You