General Pharmacology

- Pharmacokinetics
- Pharmacodynamics
- Drug-drug interactions

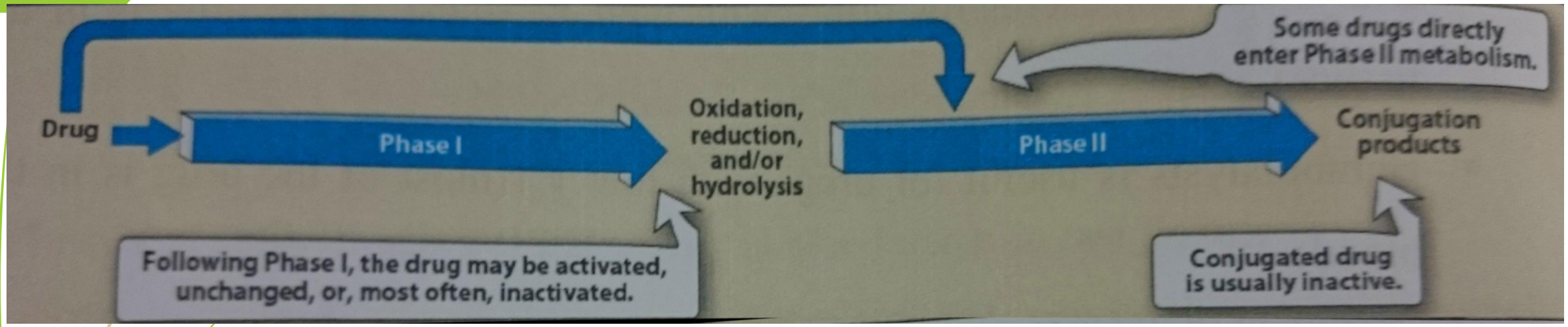
BIOTRANSFORMATION (METABOLISM)

- These are changes that occur to drugs after absorption until excretion.
- Drug metabolism occurs mainly in the *liver*.
- The aim of drug metabolism is the conversion of ionized drugs to non-ionized, water-soluble metabolite which is *easily excreted*

Consequences of drug metabolism:

1. Convert ***active*** drug to ***inactive*** metabolite (most drug).
2. Convert ***inactive prodrug*** into ***active drug*** e.g. enalapril enalaprilat (active) & prednisone prednisolone (active).
3. Convert ***active*** drug to ***inactive*** metabolite e.g. codeine morphine.
4. Convert drug to **toxic** metabolites e.g. halothane & paracetamol toxic epoxides which are conjugated with glutathione. Glutathione deficiency may precipitate paracetamol or halothane hepatotoxicity.

Types of biotransformation reactions:



Phase I (functionalization) reactions:

- Phase I reaction include: oxidation, reduction and hydrolysis.
- **The** most important reaction is oxidation by cytochrome p_{450} (CYP) oxidases.
- **Phase** I reaction result in conversion of active drug to inactive metabolite (some times convert the prodrug to active drug). If the metabolite is water-soluble it is excereted, if not, it enters phase II.

- **Phase II (biosynthetic "conjugation") reactions:**

An endogenous substrate (e.g. glucronic acid, sulfate, glutathione, amino acids, or acetate.) is conjugated with the parent drug or its phase I metabolite.

- This result in formation of non-toxic, highly polar (ionized), water-soluble and rapidly eliminated conjugates.

Metabolizing enzymes:

A. Microsomal enzymes e.g.
   - Cytochrome P_{450} oxidases and their family 1 & subfamily 2 (CYP 2 1 C9 2).
   - Glucuronyl transferases for conjugation.

B. Non-microsomal enzymes e.g. dehydrogenase, esterases (plasma) & xanthine oxidases (cytoplasm).

Factors affecting biotransformation:

1. Physiological changes (age & sex).
2. Pathological factors (liver cell failure).
3. Pharmacogenetic variation in metabolizing enzymes e.g. slow and fast acetylators.
4. Enzyme induction & enzyme inhibition.

Enzyme induction:

- Many drugs are able to include (increase activity) of microsomal enzymes resulting in **increased rate of metabolism of** the inducing drug as well as other drugs metabolized by microsomal enzymes.
- **Some inducing drugs:**

- Phenobarbitone
- Phenytoin
- Carbamazepine
- Rifampicin
- Nicotine

Consequences of enzyme induction:

1. **failure of drug action:** Rifampicin (enzyme inducer) may enhance metabolism of progesterone and warfarin.

2. Increase metabolism of the inducing drugs. This leads to tolerance e.g. phenobarbitone.

3. Increase metabolism of endogenous substrate e.g. phenobarbitone may be used to enhance eliminiation of bilirubin in physiological jaundice.

4. **Drug interactions:**

- Rifampicin enhances metabolism of warfarin, and may lead to failure of contraception (enhance metabolism of progesterone).
- Antiepileptics increase the metabolism of each others and the combination may lose its efficacy gradually.
- Prolonged use of enzyme iducers may produce rickets or osteomalacia due to increased metabolism of vitamin D.

- Enzyme induction is reversible. It occurs over few days and passes off over 2 – 3 weeks after withdrawal of inducer.

Enzyme inhibition:

- Many drugs inhabit activity of microsomal enzymes resulting in decreased rate of metabolism of other drugs i.g. potentiate their pharmacological actions.
- Some enzyme inhibitor drugs:

- Erythromycin	- Climetidine	- Ciprofloxacin
- Contraceptive pills	- Allopurinol	- Na^+ valproate

- **Consequences of enzyme inhibition on metabolized drugs:**

1. Exaggerated pharmacological action.
2. Exaggerated adverse effects.
3. Increased duration of action and half life of some drugs.
4. Drug-drug interactions.

EXCRETION OF DRUGS

Kidney is the most important organ for excretion. Excretion occurs through:

1. Glomerular filtration:
   All free drug molecules whose size is less than the glomerular pores are filtered into bowman's capsule.
2. Proximal convoluted tubules (PCT):

- Secretion of drugs occurs primarily in the PCT by energy-dependent active transport systems.
- Active secretion occurs either through acid carrier e.g. for penicillin, probenicid & salicylic acid or basic carrier for amphetamine &quinine.

3. Distal convoluted tubules:

- Lipophilic drugs may be reabsorbed back to systemic circulation.
- Alkalinization of urine (by $NaHCO_3$) keeps acidic drugs ionized and increases their excretion.
- Acidification of urine (by ascorbic acid "Vit.C" or ammonium chloride) leads to ionization of weak bases and enhancement of their excretion.

Other sites of excretion:

1. **Bile: with enterohepatic recycling** e.g. rifampicin, doxycycline, ciprofloxacin & azithromycin, or without enterohepatic recycling e.g. ceftriaxone and cefoperazone.
   - Biliary excretion of these drugs increased their efficacy in treatment of enteric and biliary diseases.
2. Lungs e.g. volatile anesthetics.
3. Saliva e.g. iodides.
4. Sweat e.g. rifampicin.
5. **Milk:** this is important in lactaaing mothers.