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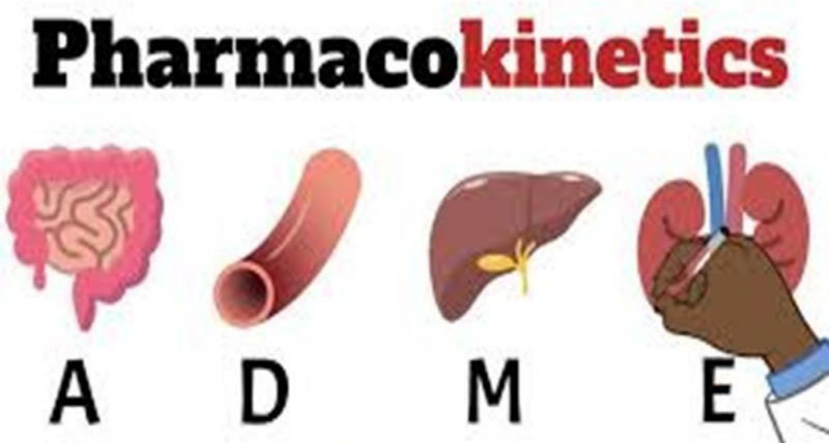
Pharmacology
Med – Lecture 5

Pharmacokinetics III

With Dr. Hamzeh Al-Shar`e , MD

Original Slides for Dr. Heba Hassan

Pharmacokinetics



What the body does to the drug?

- Absorption
- Distribution
- **Metabolism**
- Excretion

Drug Distribution (Metabolism)

➢The importance of biotransformation is the conversion of unionized drugs to ionized, water-soluble metabolite which is easily excreted.

➢The liver is the main organ of metabolism but can occur in other organs like the lungs, kidneys and intestine

➢ The duration and intensity of drug action are both determined by the rate of drug metabolism (Extra)

➢ When drugs are extensively metabolized during the initial pass through the liver, it is called first pass effect (Extra)

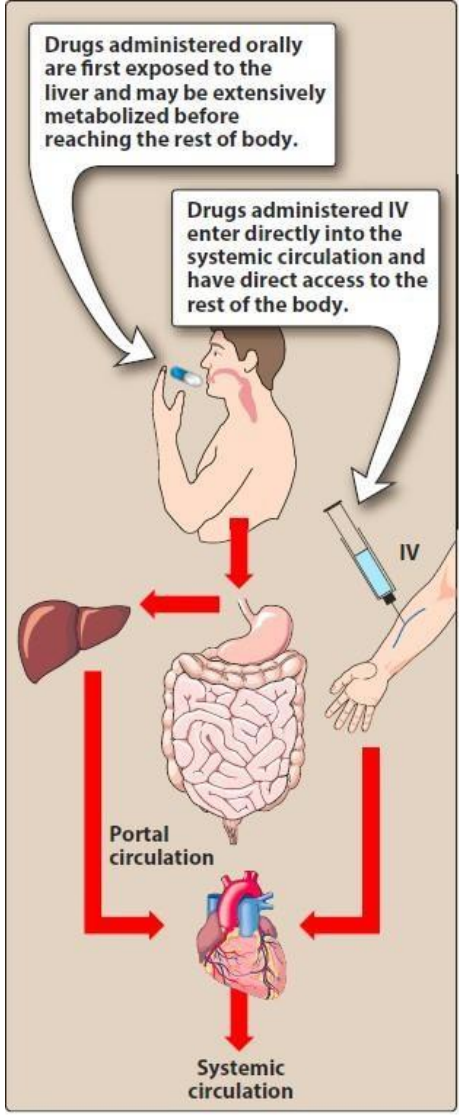


Figure 1.11
First-pass metabolism can occur with orally administered drugs. IV = intravenous.

Consequences of Drug Distribution

1. Convert **active** drug to **inactive** metabolite (most drugs)
2. Convert **inactive** prodrug into **active** drug

   e.g. enalapril → enalaprilat (active)
3. Convert **active** drug to **active** metabolite

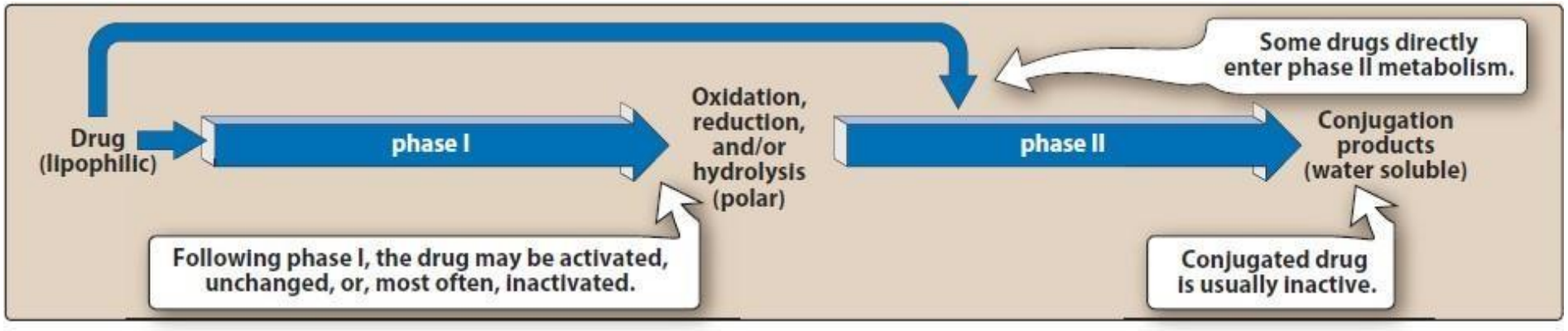
   e.g. codeine → morphine.
4. Convert **drugs** to **toxic** metabolites

   e.g. Halothane & Paracetamol ---- hepatotoxic

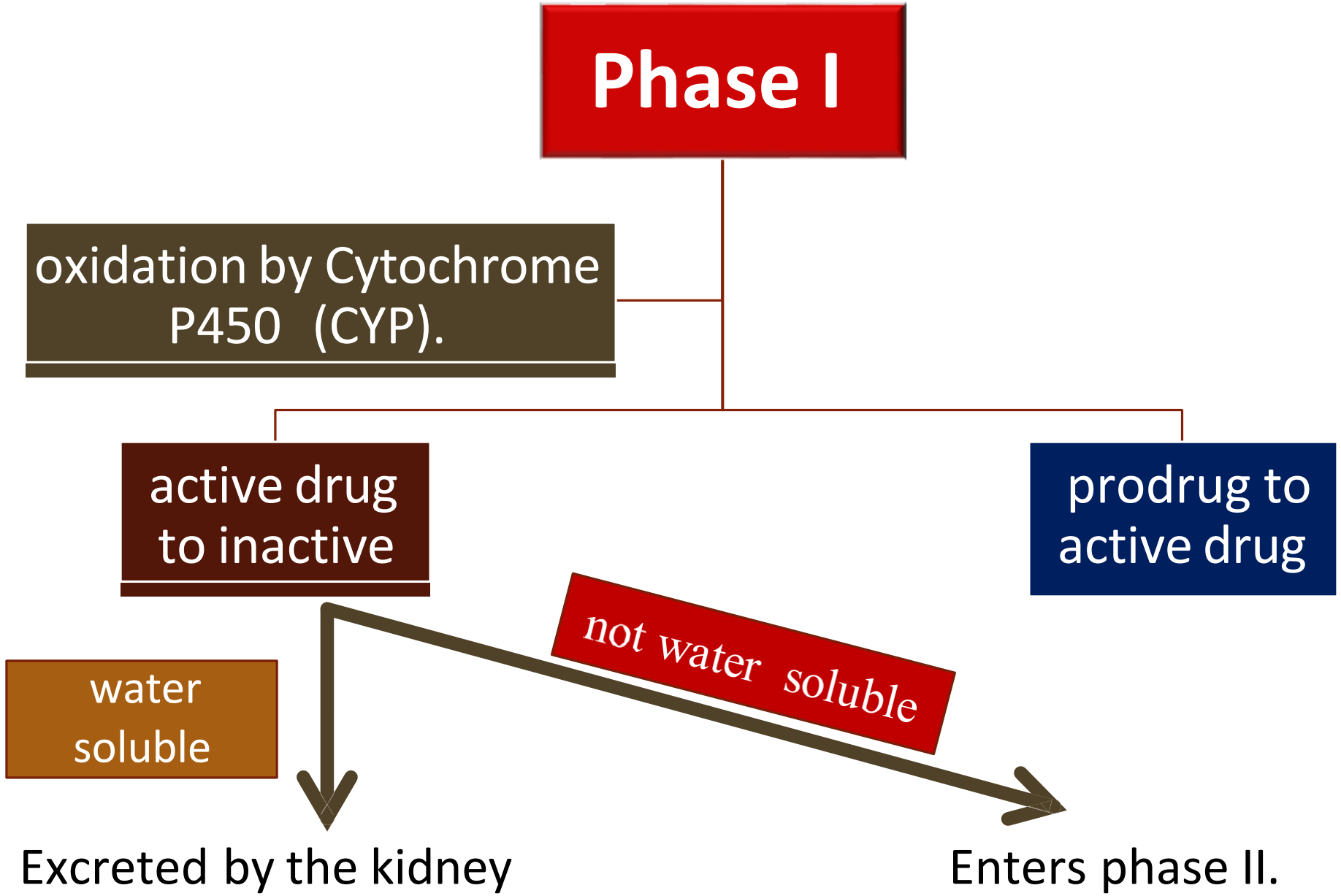
Biotransformation reaction

- **Phase I:** oxidation, reduction hydrolysis
  - Convert Lipophilic drugs into more polar (Extra)

- **Phase II:** Biosynthetic reactions "conjugation" (addition (conjugation) of large polar groups such as glucuronic acid, glutathione or sulphate to small reactive groups mostly after phase 1 metabolism) (Extra)



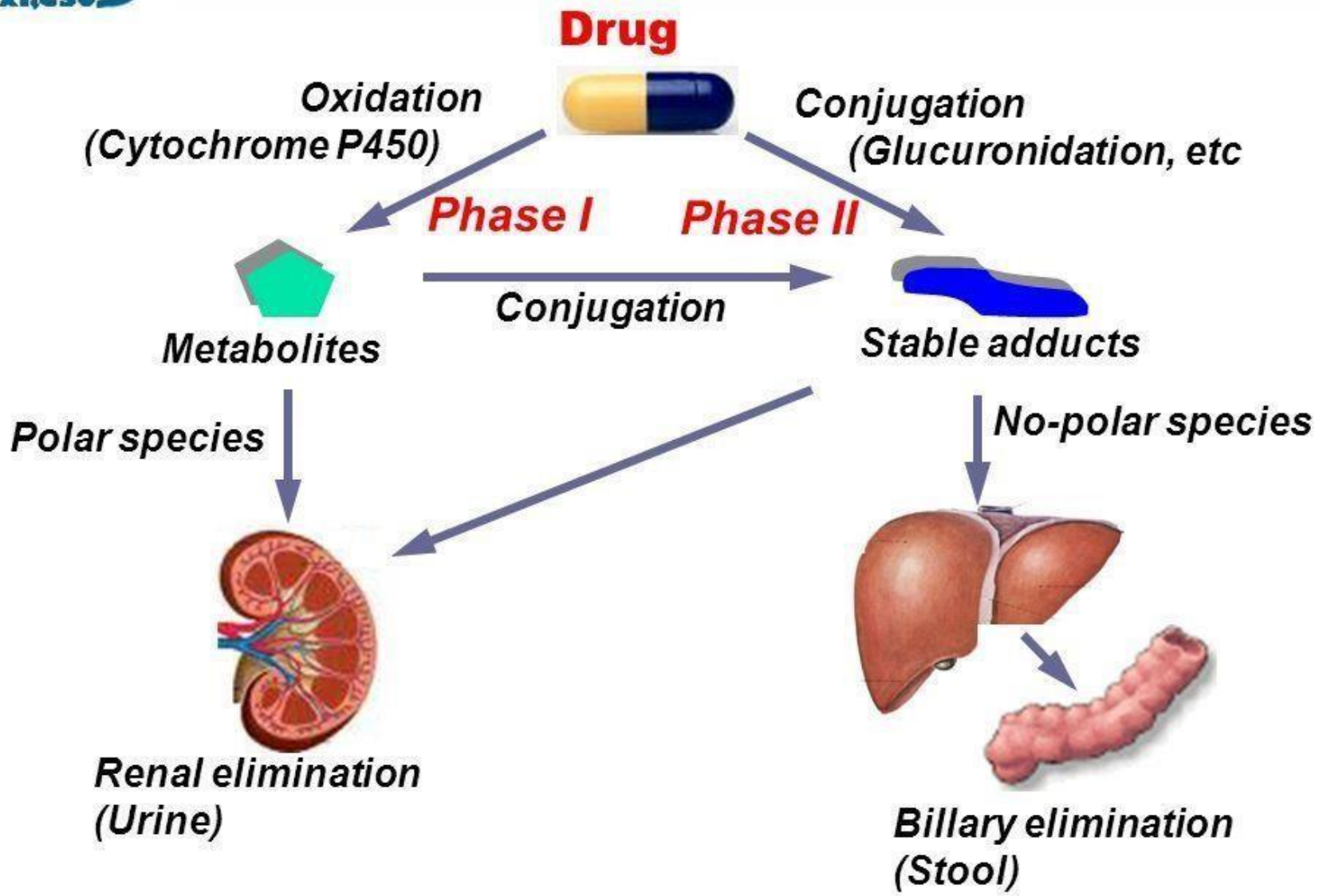
Its necessary for the drug to go through both phases ?


Phase I
oxidation by Cytochrome P450 (CYP).
active drug to inactive
prodrug to active drug
water soluble
not water soluble
Excreted by the kidney
Enters phase II.

Phase II (biosynthetic) "conjugation" reactions

- If the metabolite from phase I metabolism is sufficiently polar, it can be excreted by the kidneys, However, many phase I metabolites are still too lipophilic to be excreted
- An endogenous substrate e.g. glucuronic acid, sulfate, glutathione amino acids, or acetate is conjugated with the parent drug or its phase I metabolite.
- Highly polar – rapidly excreted in urine and feces.
- This result in formation of water soluble and rapidly eliminated conjugates..

Phases of metabolism



Factors affecting biotransformation

1. **Physiological factors** :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 induce (increase activity and number) of microsomalenzymes resulting in increased rate of metabolism of the inducing drug as well as other drugs metabolized by the same microsomal enzymes.

- D ?

- **Some inducing drugs** : Phenobarbitone, phenytoin, nicotine, rifampicin, carbamazepine.

Consequences of enzyme induction:

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

2. **Drug interactions:**
   - ❑ Rifampicin enhances metabolism of warfarin.
   - ❑ Antiepileptics increase the metabolism of each other.

3. **Prolonged use** of enzyme inducers 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 inhibit activity of microsomal enzymes resulting in decreased rate of metabolism of other drugs i.e. potentiate their pharmacological actions.

- **Some enzyme Inhibitor drugs**
  - Erythromycin, Clarithromycin, Cimetidine, Contraceptive pills

Consequences of enzyme inhibition on metabolized drugs

1) Exaggerated pharmacological actions.

2) Exaggerated adverse effects.

3) Drug interactions.