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Drug metabolism

Drug metabolism

- **Metabolism is defined as:** The irreversible biotransformation of drug in the body → typically involves making it more polar to enhance renal excretion

- Drug metabolism often converts lipophilic chemical compounds into:
  1. more hydrophilic, more water soluble
  2. have their actions decreased (become less effective) or increased (become more effective)
  3. May be converted to less toxic or more toxic metabolites or to metabolites with different type of effect or toxicity

- The metabolism of drugs takes place mainly in the liver (the smooth endoplasmic reticulum of the liver cell) . However, other organs such as the kidney, lung, intestine and placenta can also be involved in this process.

Drug metabolism

- In some occasions, the metabolite is less water soluble.
- A significant example is the acetyl metabolite of some of the sulfonamides.

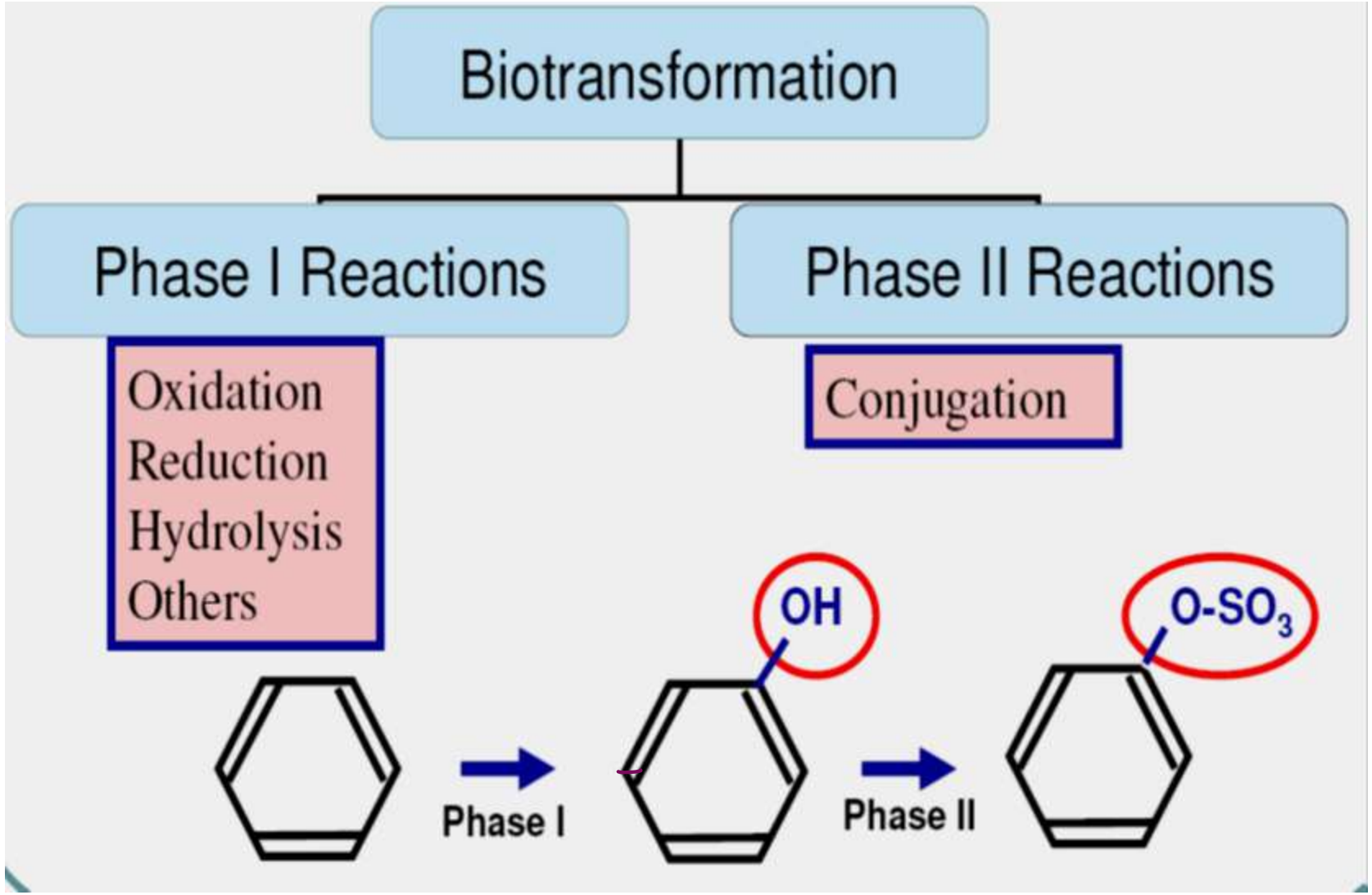
- Some of the earlier sulfonamides are acetylated to relatively insoluble metabolites which precipitated in urine, crystalluria.

تسبب حصوات فكانوا ينصحوا
المريض يشرب كميات كبيرة من السوائل
عشان يقدر يطلع sulfonamide

- Now the more commonly used sulfonamides have different elimination and solubility properties and exhibit less problems.

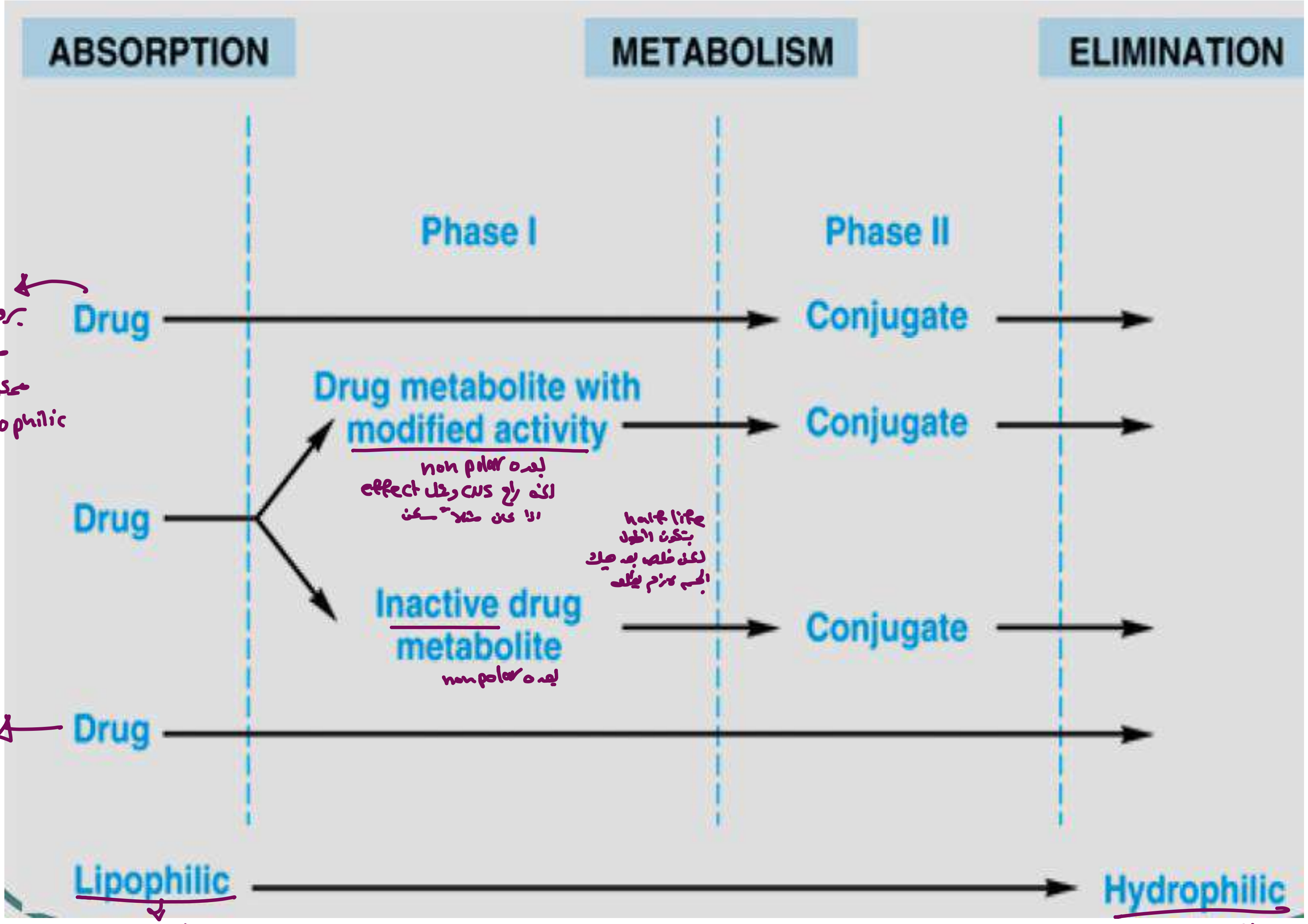
حالياً ما يستخدم بدرجة كبيرة
إلا من نوع
sulfamethoxazole
trimethoprim مع

Two types of Metabolic Reactions



بروح على phase II مباشرة

ممكن يكون فيها OH من الأصل
hydrophilic نفس الشيء



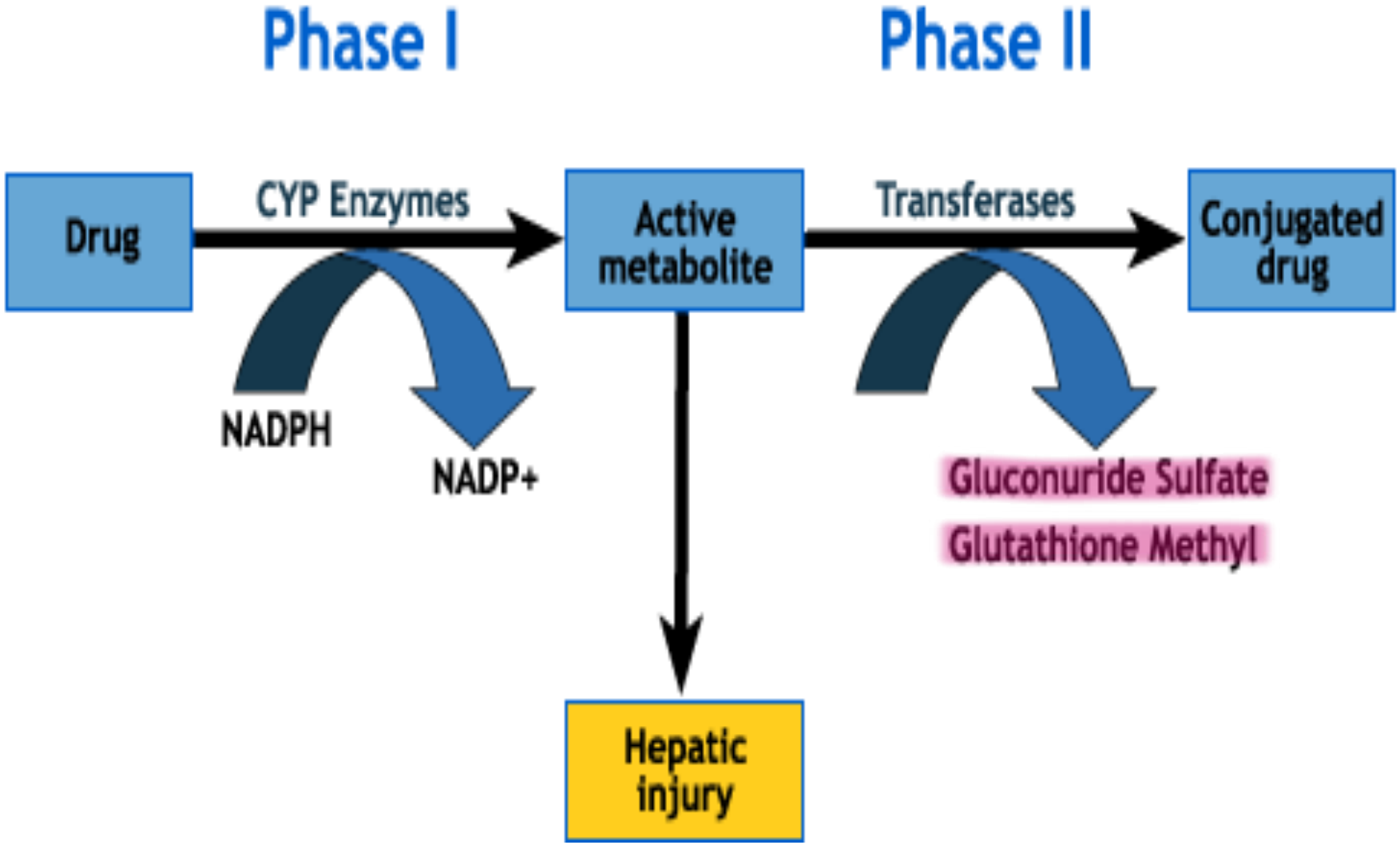
اذا كان الدواء
highly polar
ما بصير
metabolism
مثل
(metformin)

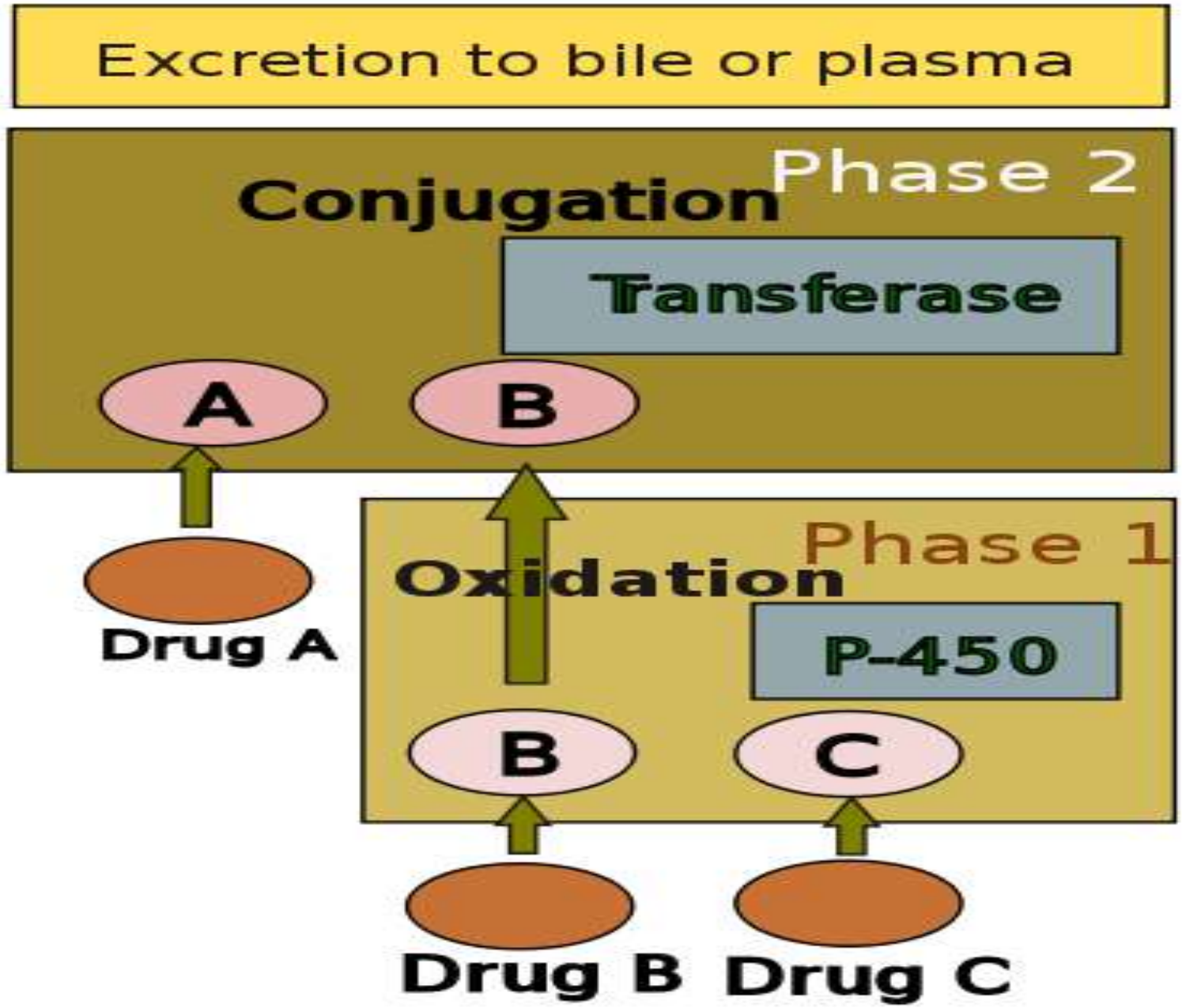
* معناته
metabolism
إنه دخل بال
physico-chemical properties

يفضل انه يصير
metabolism I and II

يفضل انه يصير
excretion مباشرة (unchanged)

Phases of metabolism




Excretion to bile or plasma
Phase 2
Conjugation
Transferase
A
B
Drug A
Phase 1
Oxidation
P-450
B
C
Drug B
Drug C

Phases of metabolism

Phase I reactions:

- Change drugs to more hydrophilic metabolites which are more readily excreted
- Introduce into the drug molecule sites for phase II reactions
- May be less toxic (but not always)
- Mostly occur in the endoplasmic reticulum (microsomes) of liver cells.
- Usually involve oxidation, reduction, hydrolysis or other reactions

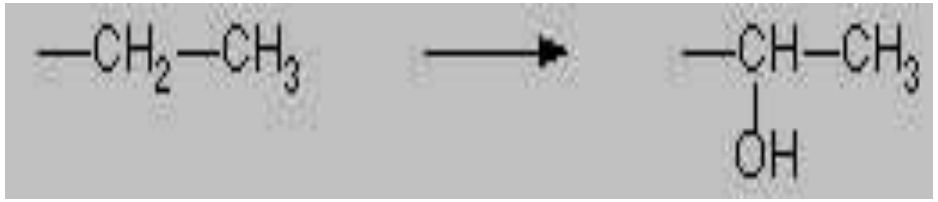
Phase I reaction

1- Oxidation

Oxidation is the addition of oxygen and/or the removal of hydrogen, carried out by oxidases . Most oxidation steps occur in the endoplasmic reticulum. These oxidative reactions typically involve a cytochrome P450, NADPH and oxygen.

Common reactions include :-

- **Alkyl group ----> alcohol**

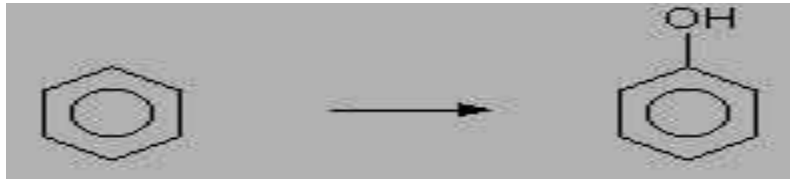


- **Aromatic ring ----> phenol**

Phases of metabolism

for example phenytoin

Oxidation at S or N



for example chlorpromazine

2.Reduction

Add a hydrogen or remove oxygen

azo (-N=N-) or nitro groups (-NO2) -----> amines (-NH2)

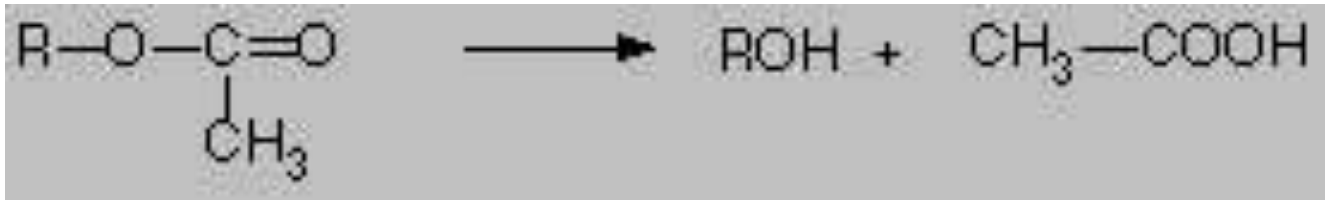
for example nitrazepam

Phases of metabolism

3.Hydrolysis

Addition of water with breakdown of molecule.

amides و **Esters ---> alcohol and acid**



- for example aspirin to salicylic acid

Phase II

1.Conjugation → على كل الاحوال تحول الدواء الى inactive and polar

Conjugation reactions covalently add large, polar endogenous molecules to parent drug or Phase I metabolite →inactive and excretable

(glucuronide, glutathione, sulfate, acetate, amino acids etc)

Phases of metabolism

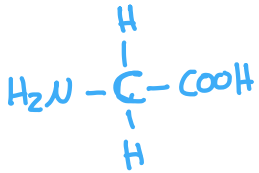
- **Glucuronidation**

This is the main conjugation reaction in the body. This occurs in the liver. Aliphatic alcohols and phenols are commonly conjugated with glucuronide. Thus hydroxylated metabolites can also be conjugated. for example morphine

- **Acylation**

Acylation, especially acetylation with the acetyl group, e.g. sulfonamides

- **Glycine**



Glycine addition (NH2CH2COOH) for example nicotinic acid

- **Sulfate**

Sulfate (-SO4) for example morphine, paracetamol

Drug metabolism

- In most cases the metabolites are inactive, however, occasionally the metabolite is also active, even to the extent that the metabolite may be the preferred compound to be administered. The original drug may take on the role of a pro-drug. For example:-

inactive

codeine ---> morphine

primidone ---> phenobarbital

- Drug metabolism can be quantitatively altered by drug interactions. This alteration can be an increase by induction of enzyme activity or a reduction by competitive inhibition.

* بعض الادوية ممكن تعمل induction أو inhibition لل microsomal enzymes

cytochrome p450 بالتالي ممكن

تأثر عال metabolism لأدوية ثانية

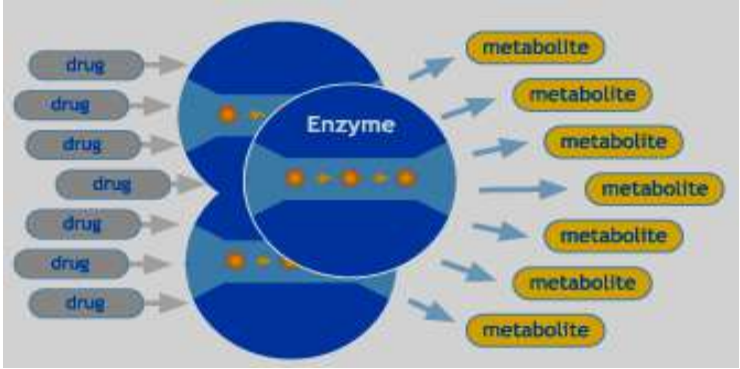
* يعني ممكن مريض الصرع ياخذ

phenytoin ← phenobarbitone

يقلل فعالية

نقص ← doses نحتاج نوازن بين.

Drug metabolism



I. Induction

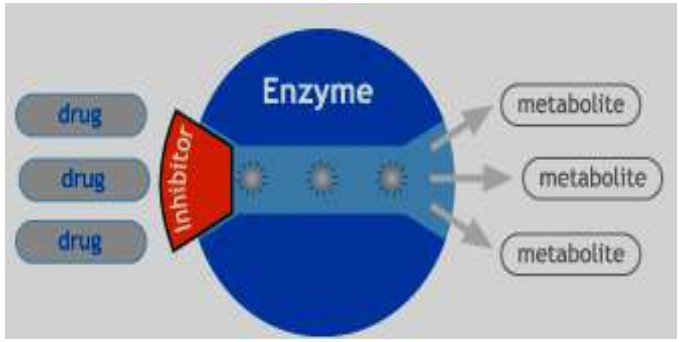
Induction ~ ↑ metabolic activity of enzyme = ↓ [drug]

E.g. Phenobarbitone will induce the metabolism of itself, phenytoin, warfarin, etc.

E.g. Cigarette smoking can cause increased elimination of theophylline.

E.g. alcohol, Dosing rates may need to be increased to maintain effective plasma concentrations.

Drug metabolism



II. Inhibition

Inhibition ~ ↓ metabolic activity of enzyme = ↑ [drug]

e.g. grapefruit juice

- For example, warfarin inhibits tolbutamide elimination which can lead to the accumulation of drug and may require a downward adjustment of dose.
- Cimetidine is a therapeutic agent (prevent ulcer) that has been found to impair the in vivo metabolism of other drugs.

Drug metabolism

Factors that can influence drug metabolism:

1. **Age:** Drugs metabolism is slower in fetal, neonatal and elderly humans than in adults.

2. **Sex:** women metabolize alcohol more slowly than men

3. **Other drugs:** Certain drugs (enzyme inducers) can increase the rate of metabolism of active drugs (enzyme induction) and thus decrease the duration and intensity of the their action. The opposite is also true (enzyme inhibition).

Drug metabolism

4. Food: Grapefruit juice contains furanocoumarins which inhibit drug metabolism by interfering with hepatic cytochrome P450.

5. Genetic variation (polymorphism):

With N-acetyltransferases (involved in Phase II reactions), individual variation creates a group of people who acetylate drugs (isoniazid) slowly (slow acetylators) and those who acetylate quickly.

(isoniazid → metabolism by Acylation)

- This variation may have dramatic consequences, as the slow acetylators are more prone to dose dependent toxicity.

- 13% of Egyptians are slow acetylators. Warfarin (bleeding) and phenytoin (ataxia) are examples

تزنح يعني المشي بخط غير مستقيم

Drug metabolism

6. **Physiological factors** that can influence drug metabolism include age, individual variation (e.g., pharmacogenetics), enterohepatic circulation, nutrition, intestinal flora, or sex differences.

7. **Pathological factors** can also influence drug metabolism, including liver, kidney, or heart diseases.

Diseases and Drug metabolism

Liver Disease:

- Acute or chronic diseases that affect liver function markedly affect hepatic metabolism of some drugs. Such conditions include **fat accumulation, alcoholic cirrhosis, biliary cirrhosis, and acute viral or drug hepatitis**. These conditions may impair hepatic drug-metabolizing enzymes, particularly microsomal oxidases, and thereby markedly affect drug elimination.
- For example, the half-life of diazepam in patients with liver cirrhosis or acute viral hepatitis is greatly increased, with a corresponding prolongation of its effect.

Renal Disease:

Chronic renal failure affect the drugs that excreted unchanged in the urine e.g Metformin will lead to lactic acidosis and so contraindicated if GFR<30ml/min per 1.73m2 body surface area

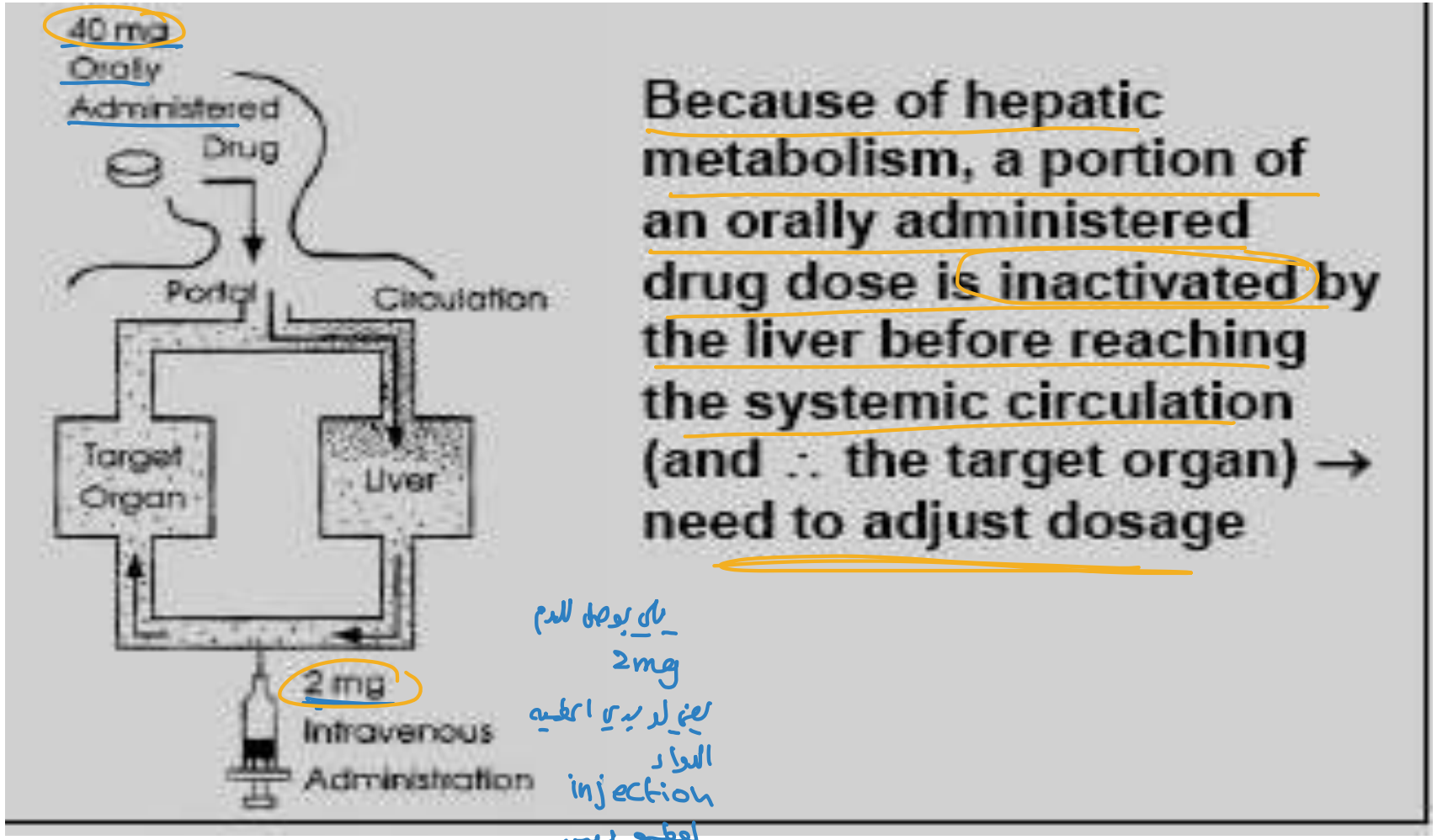
Cardiac Disease:

- Cardiac disease, by limiting blood flow to the liver, may impair disposition of those drugs whose metabolism is flow-limited.

Cardiac output ↓ → blood flow to the liver ↓ → metabolism ↓

Drug metabolism

Enterohepatic circulation:



يلي يوصل للدم
2mg
يعني لو بدي اعطيه
الدواء
injection
لعطيه بس
2mg