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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

paracetamol → more toxic (Free radicals) → glutathione conjugation

- 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.

المستقيمة

inhalational anesthetics

هذا يدخل عن طريق الرئة ويطلق منها

وهو جزء يمكن تحويله liver لا metabolism

والنتج يكون (toxic) free radicals يمكن ترتبط ببروتينات لا liver

وتعد هناك صعوبة للشخص وكلما كانت الكمية التي يصيرها metabolism أكبر يصير toxic أكثر

(30% metabolism → very toxic)
1% = → safety ↑

يوجد على الـ liver ويغيره
إذا هو polar ولا non polar
إذا كان non polar يحط على
hydroxyl group

بعد ذلك يذهب إلى الـ kidney
تعمله reabsorption ويرجع إلى
الدم ويذهب مرة ثانية على liver
يوجد بزيادة الـ polarity لأن مرة
عن طريق الـ conjugation

يعني بصيف عليه شيء بحيث أن
يخرج مرة ثانية

مثلاً
glucuronide
* sulfate

أي شيء يكون highly polar
عليه charge

هكذا نضمن أنه يخرج
الصفة irreversible
يعني أي شيء ضخمه ما
يبتلعك

سخطم الازدوية
يتصير less
effective

ليس يمكن يصير more
pro drug

أو يمكن يكون بالأصل active
وال metabolites تكون active بزيادة
كل هذا (benzodiazepines)

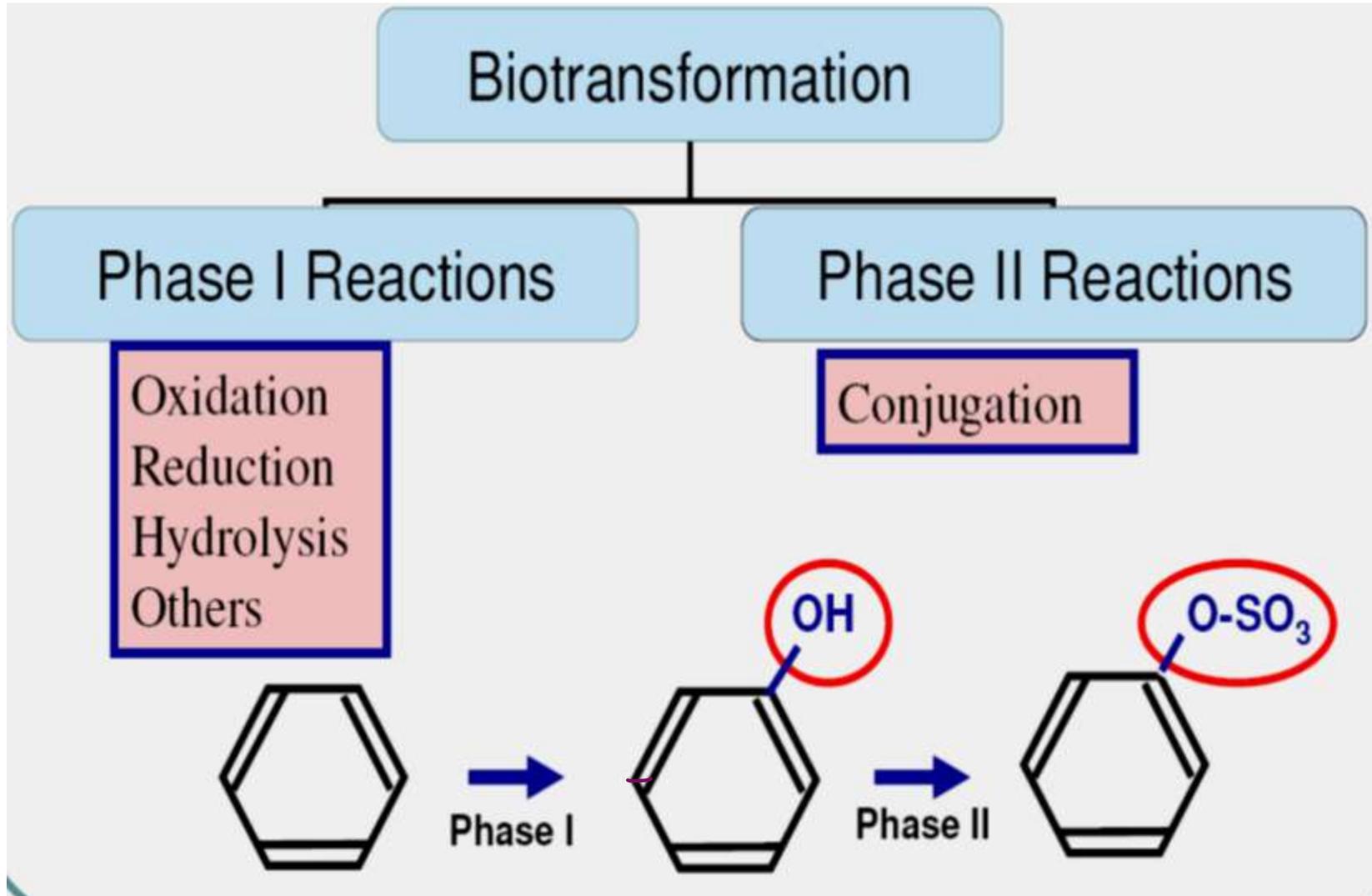
Drug metabolism

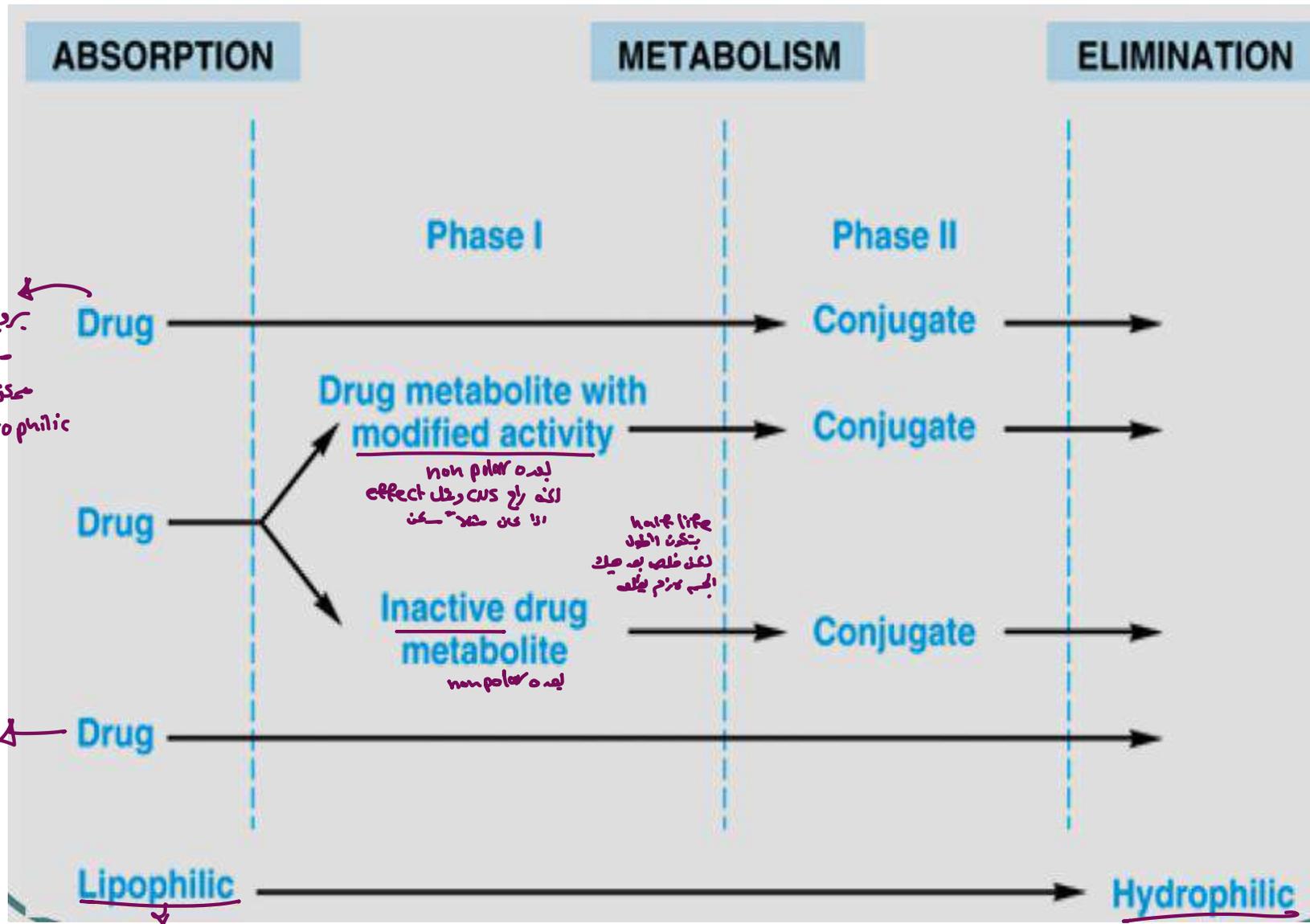
- In some occasions, the metabolite is less water soluble.
- A significant example is the acetyl metabolite of some of the sulfonamides.
- Some of the earlier sulfonamides are acetylated to relatively insoluble metabolites which precipitated in urine, crystalluria.
- Now the more commonly used sulfonamides have different elimination and solubility properties and exhibit less problems.

تسبب حصوات فكانوا ينصحوا
المرضى بشرب كميات كبيرة من السوائل
عشان يقدر يطلع sulfonamide

حالياً لا يستخدم بذكر كليس
لغاية من
sulfamethoxazole
trimethoprim

Two types of Metabolic Reactions





بروز على phase II مباشرة
 يمكن يكون فيها OH من الامل
 hydrophilic ذوب نفس

ازاي ان الوب
 highly polar
 ما بصيرك
 metabolism
 (metformin)

بفضل انه يصير
 II and I ← metabolism

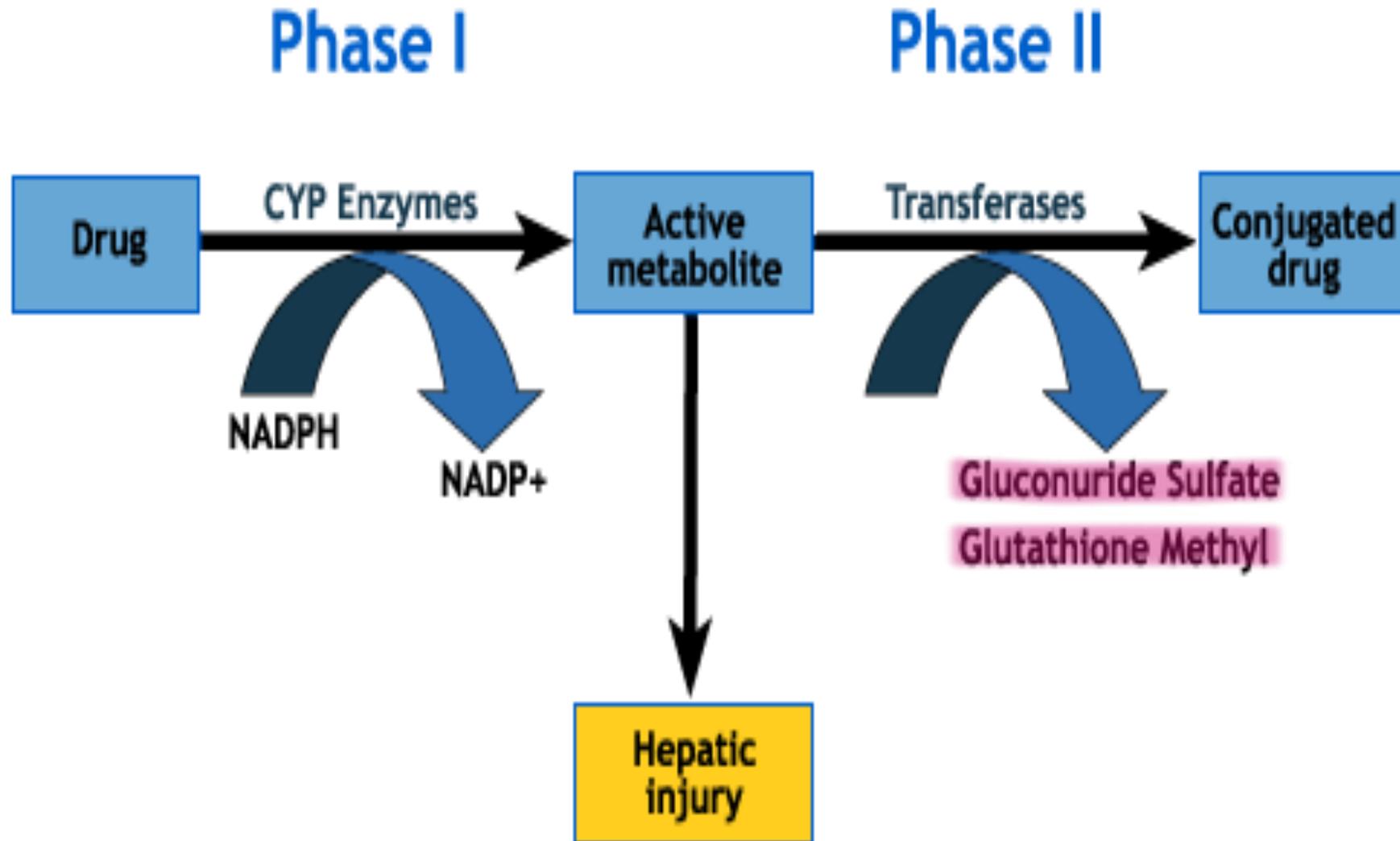
لده non polar
 لكن راج CVS وغل effect
 ولا ين صلا-كن

half life
 بتكون الطول
 لكن خلاصه بعد حياك
 الجسم موزم يطلع

* معناه
 metabolism
 ال دق دار
 physico-chemical properties

بفضل انه يصير
 excretion مباشرة
 (unchanged)

Phases of metabolism



Excretion to bile or plasma

Conjugation Phase 2

Transferase

A

B

Drug A

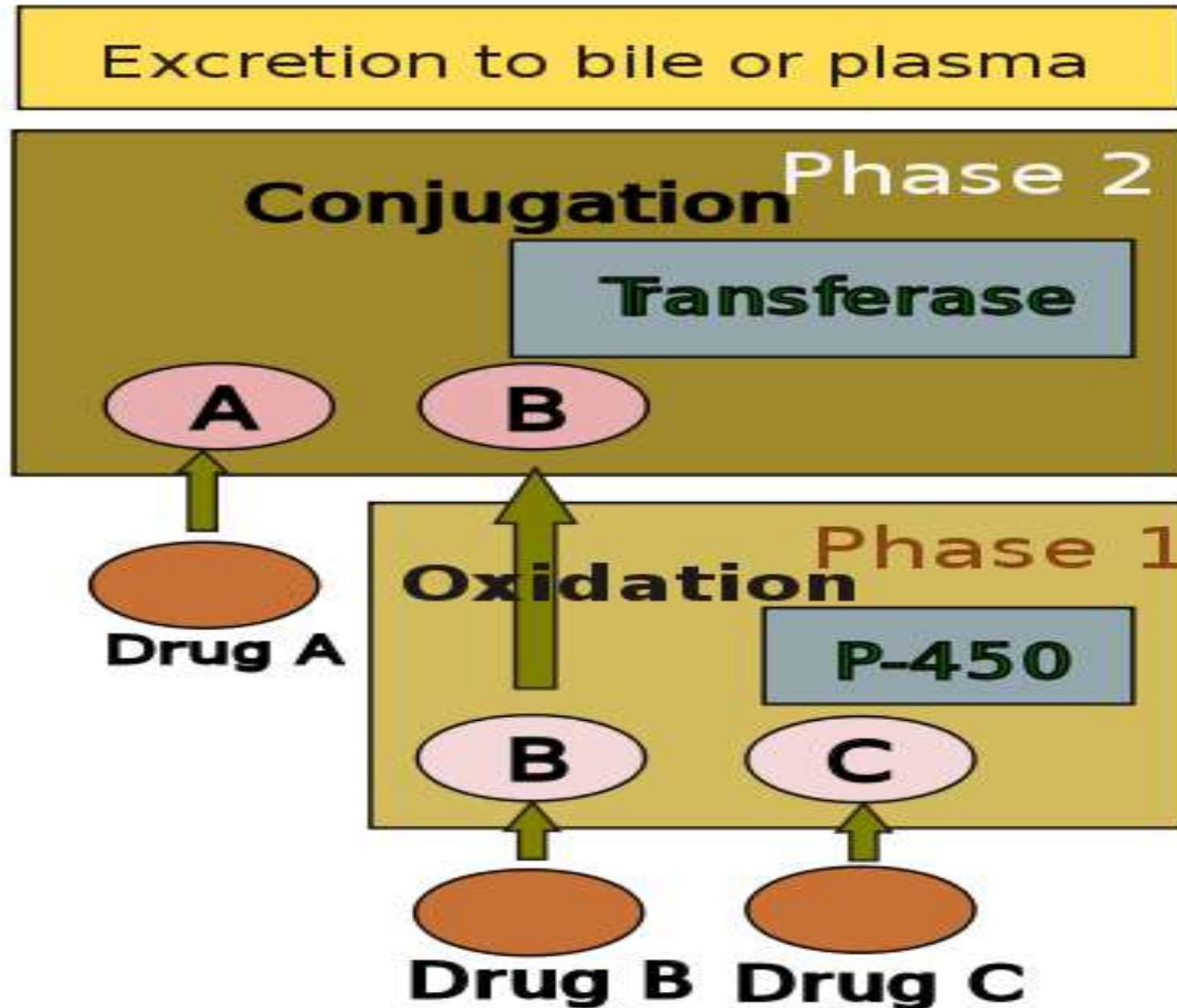
Oxidation Phase 1

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

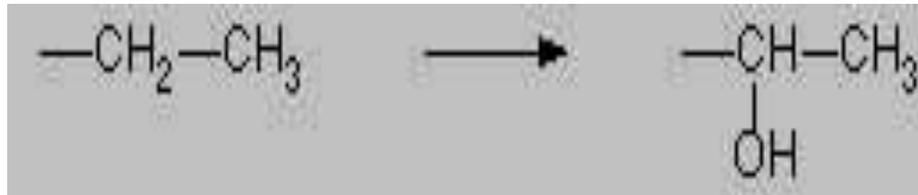
1- Oxidation

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

← الناسيل كندا
حالة يتصير NADPH
في كل الادوية تزيدها حجم
الوزن كذا في الـ cytochrome
P450



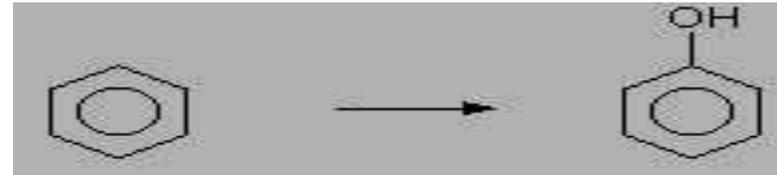
- Aromatic ring ----> phenol

لصار
polar
صار له
acidic properties

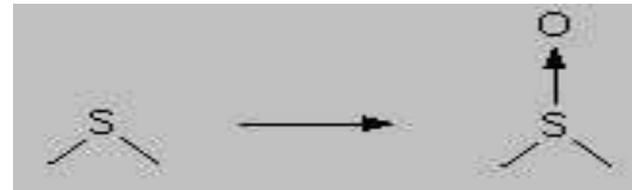
Phases of metabolism

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)

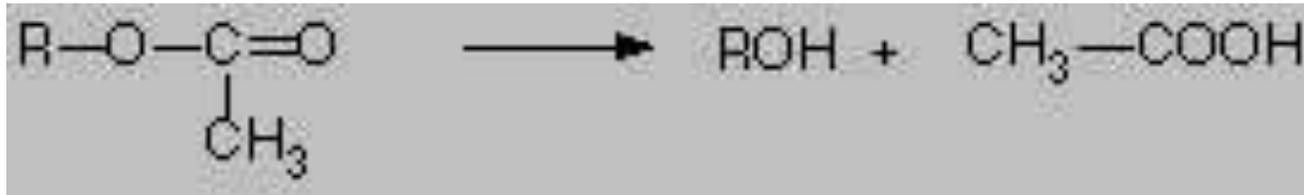
for example nitrazepam

Phases of metabolism

3. Hydrolysis

Addition of water with breakdown of molecule.

amides في Esters ---> alcohol and acid



- for example aspirin to salicylic acid

Phase II

1. Conjugation → طريق الاحوال
تحويل 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**

يُدرج من الأهل عليه OH
أو كان في phase I

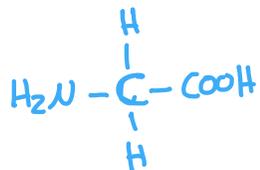
- **Acylation**

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

- **Glycine**

Glycine addition (NH₂CH₂COOH) for example **nicotinic acid**

بمناسبة Solubility! ليد
metabolism ال



- **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 يمكن تعديل
microsomal inhibition أو induction
enzymes

cytochrome P450
بالنسبة يمكن

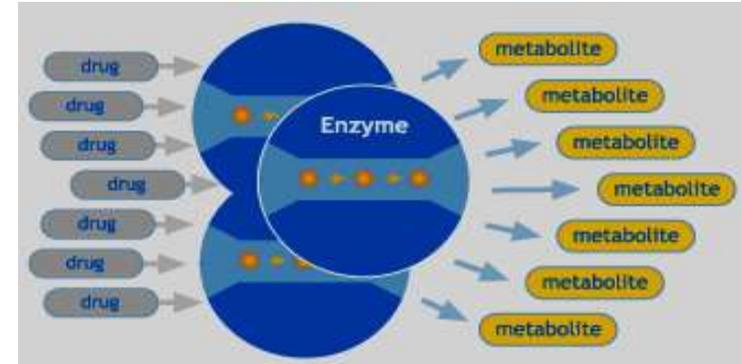
تأثيره أو metabolism أو درجة ثانية

* يعني يمكن مريض الصرع يافذ

phenytoin ← phenobarbital

يقول خالصة
↓
تلازم فائز. بين doses ← بعض

Drug metabolism



I. Induction

Induction ~ \uparrow metabolic activity of enzyme = \downarrow [drug]

↑ dose
phenytoin
warfarin

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

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

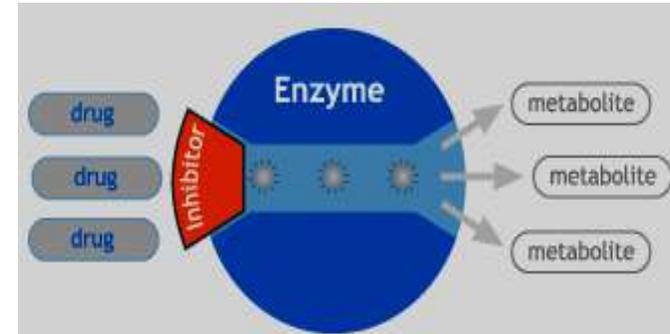
asthma

↑ dose
(ethanol)

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

Drug metabolism

II. Inhibition



Inhibition ~ \downarrow metabolic activity of enzyme = \uparrow [drug]

e.g. grapefruit juice

anticoagulant

دواء
سحر

- 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.

بزيه تركيز
tolbutamide
يعني بزيه
تبعته يصير عنده المريفق
(hypoglycemia)
لما نعطهم ح يعني
دزم نقل dose

Drug metabolism

عوامل

Factors that can influence drug metabolism:

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

↓
لأنه ليس له أعضاء
organs عندهم

→
لأنه ليست كل
أعضاء الجسم
مكتملة ويمكن
يكون في تلف
بالخلايا

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 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.

- 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

(isoniazid)
↓
metabolism by
Acylation

تدرج
يعني المصنعي بخط
غير متعدي

مع زيادة في
SaidEffecty أكثر من الناس المصريين

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.

يمكن الكبد لعمل metabolism
والبدين ينقله الى bile bladder
لهذين بين ناكل يصيرك اوزار
لا intestine يصيرك اصحاب
يرجلا liver ورجلا

يأثر أكثر ←
← سراد كان acute او chronic

Diseases and Drug metabolism

Liver Disease: *بأن أكثر*

- 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. *دعوى عالقة*
- 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. *تشجع الكبد*

لا لازم نقل من جرعة الدواء بل يصير *metabolism* في *liver*

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

براي الحالة ما يصير *فقطي المريض metformin*

Cardiac Disease:

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

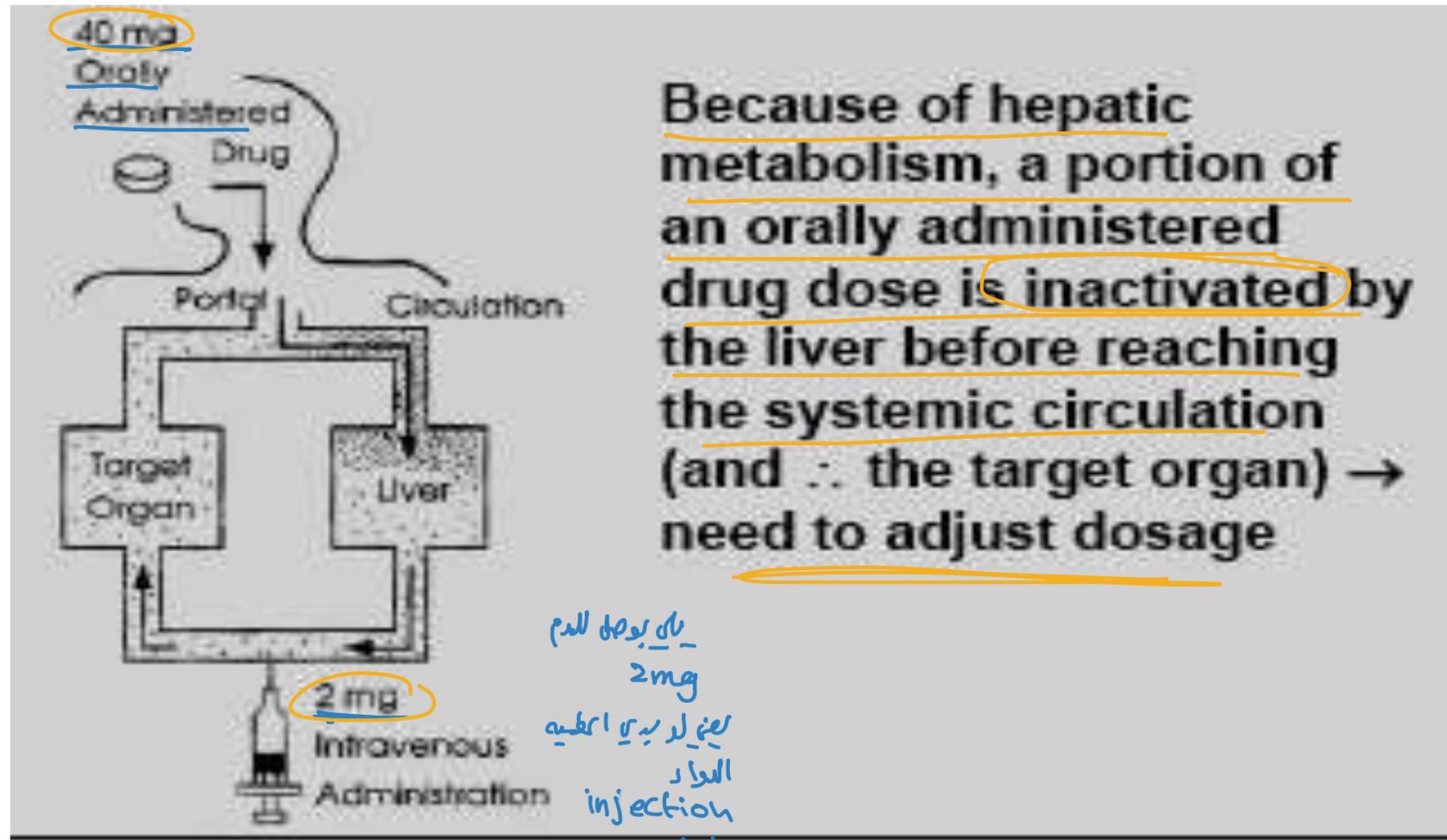
Cardiac output ↓

blood flow to the liver ↓

metabolism ↓

Drug metabolism

Enterohepatic circulation:



ياي يوصل للدم
2mg
يعني لو بدي اعطيه
الدم
injection
يعطيه بدي
2mg