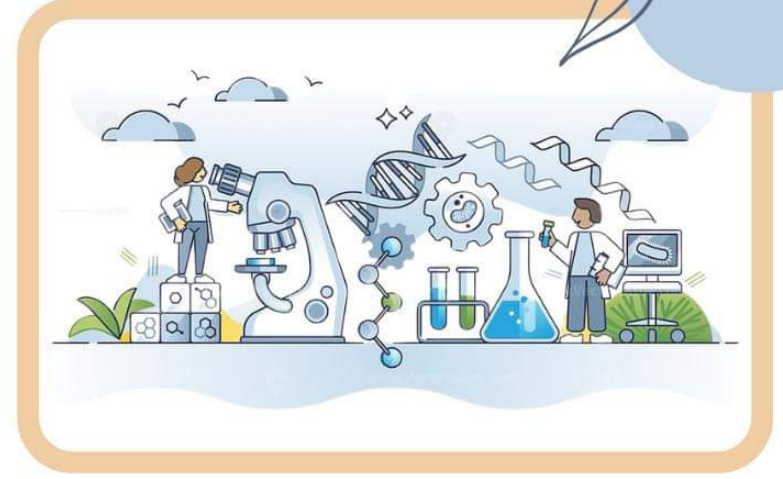


# تفريغ بيوفارما

اسم الموضوع: Metabolism

إعداد الصيدلاني / ة: ياسمين خليل



إِنَّ اللَّهَ لَا يُغَيِّرُ مَا بِقَوْمٍ حَتَّىٰ  
يُغَيِّرُوا مَا بِأَنْفُسِهِمْ

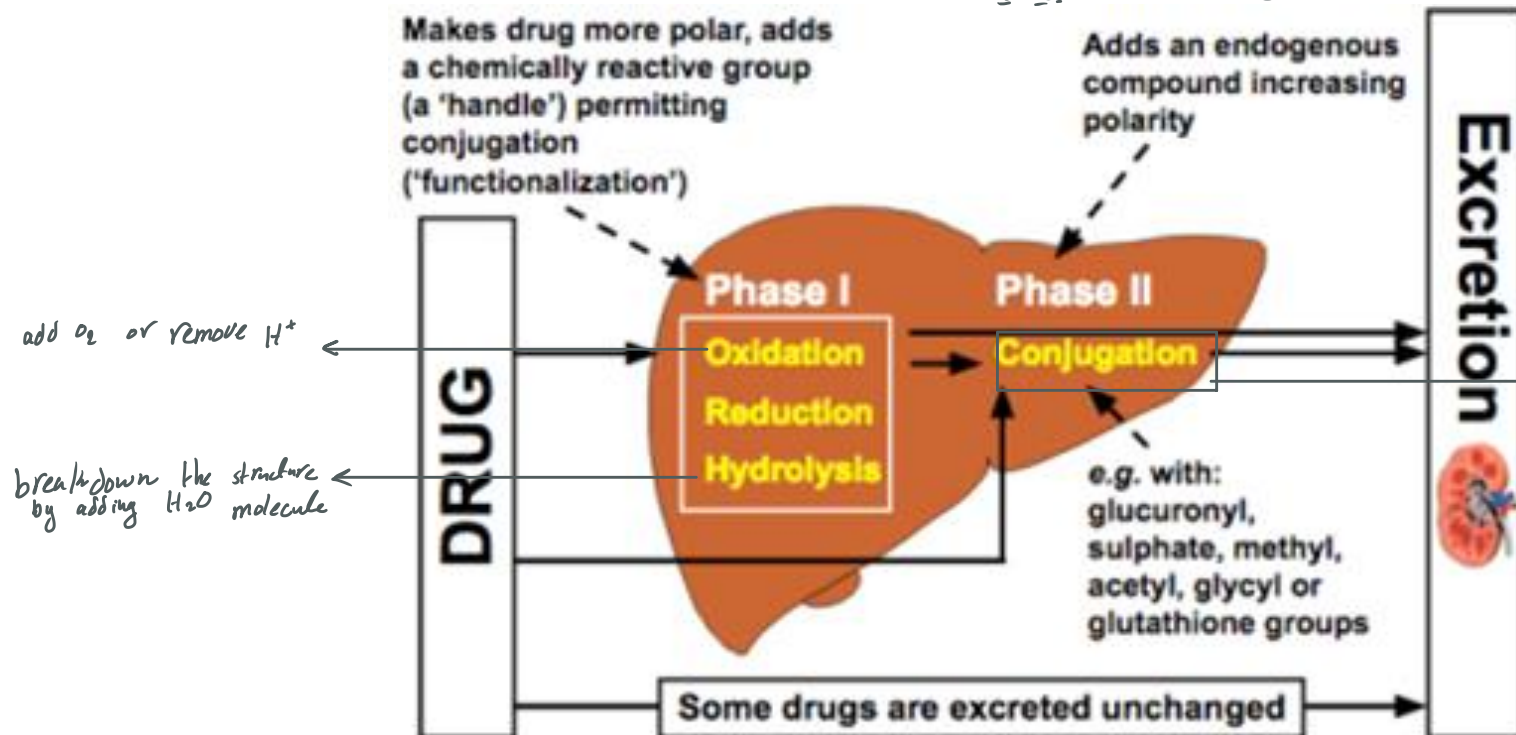


لجان الرفعات

# Drug Metabolism

Converts the drug  
from active to inactive  
and from hydrophobic to  
lipophilic [more polar]

عبارة عن تفاعلات كيميائية



في phase I كنا نضاعف ذائبت  
في حالة oxidation ، بيت لولسا (مركب)  
صا صاير ذائب في الماء رح يروح الى phase II  
و بيسير conjugation يعني الى هنا حة مركب  
الى O<sub>2</sub> الى ضيفناها في phase I ، تمام !  
بعد من رح بيسير hydrophilic

Dr. Muna Oqal

# 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:

– more hydrophilic, more water soluble

– have their actions decreased (become less effective) or increased (become more effective)

– May be converted to less toxic or more toxic metabolites or to metabolites with different type of effect or toxicity

→ are the products of metabolism

تعديل على خواص الدواء + بنية الجزيء  
لتحقيق الفائدة من الدواء

✓ التغيير بشكل  
الدواء عن حالته  
الاصولية

لما يكونه افعالنا  
من تأثير الدواء  
هو ليس شئاً  
في ذاته يغيره  
metabolism  
عشاه يوقف

active → inactive

normal drug

pro drugs

طبعاً من دايماً الدواء يتحول  
من active إلى inactive عن طريق  
metabolism  
يمكن تحول العكس وصحاحاً تحول من  
lipophilic إلى hydrophilic  
ويعرف في أدوية مسكنها قلبية بين  
مع metabolism ربع تميز سامة أكثر مثل paracetamol ...  
• المهم ناتج عملية metabolism من ثابت تمام !

• أي مكان في الجسم فيه إنزيمات ١٤

metabolism فيه

but mainly on ① liver ② gut wall  
of intestine  
الأكثر انتشارا مكان كبدية، الأمعاء

## Drug Metabolism

in general (often)

active → inactive  
hydrophobic → hydrophilic  
toxic → non toxic

- **Lipophilic substances** are not eliminated efficiently by the kidney. Consequently, most lipophilic drugs are metabolised in the liver to more polar products, which are then excreted in urine.
- The metabolism of drugs takes place mainly in the liver (the smooth endoplasmic reticulum of the liver cell), especially by the cytochrome P450 (CYP) system.
- However, other organs such as the kidney, lung, intestine and placenta can also be involved in this process.

كان فيه إنزيمات

# Drug Metabolism

بعضهم عن ذاكين من الماء، بالتالي غير ذائبن في الدم وصارح عسوا صنيع ← بالتالي ربح يتراكموا في الدم ويعملوا

• In some occasions, the metabolite is less water soluble.

- A significant example is the acetyl metabolite of some of the sulfonamides. *antibiotic for UTI*

أفعلها فيها ذائبة  
صنيفة للماد بس مع عالج metabolite  
less water soluble مع تصير

أفعلها في acetyl group

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

حصوات في حجارى ابول في بنحى الكريدها لحار؟ فذ هذا الموار يشرب كثير ماء

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

الاصول الجيدة من Sulfonamides رجت تحسنت عندها، لذائبة في الماء في يعملوا صوان بس بشكل اقل

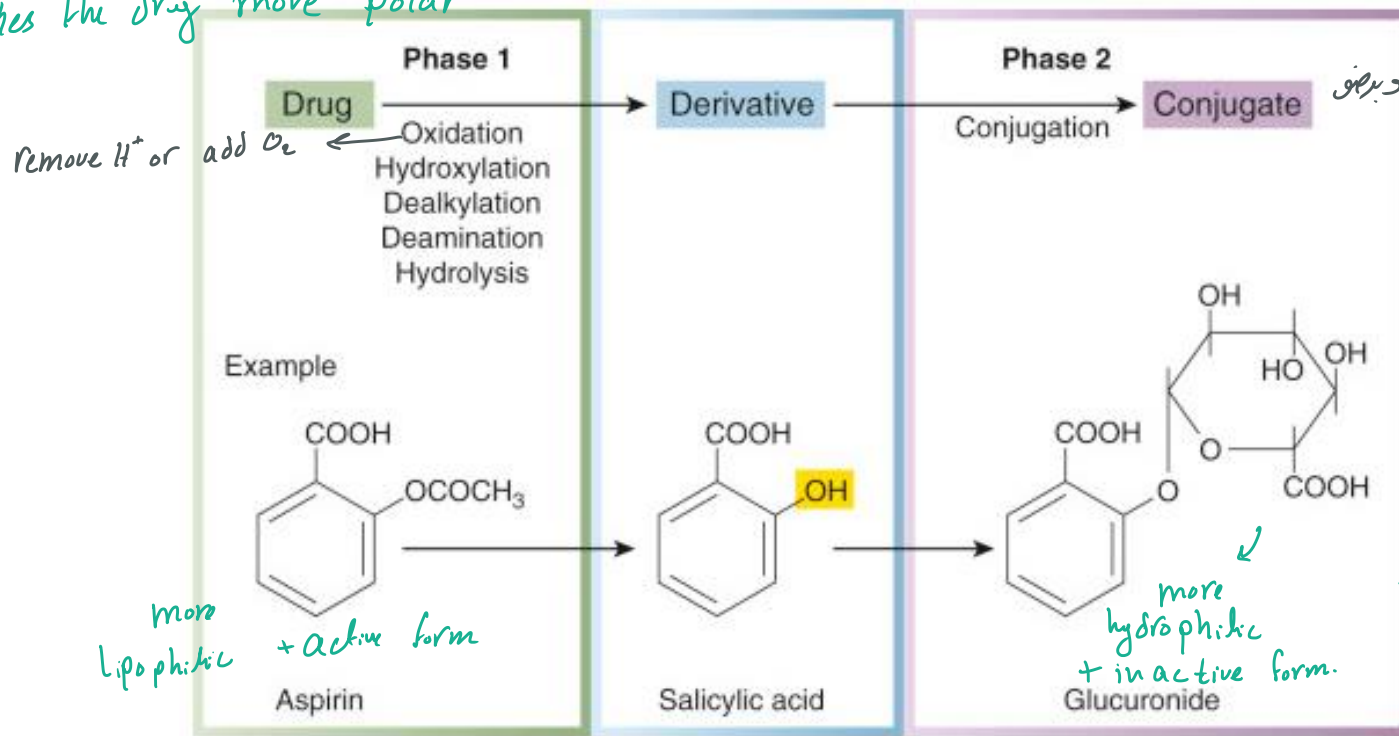
# Drug Metabolism

- Drug metabolism involves two kinds of reaction, known as **phase 1** and **phase 2**, which often occur sequentially. Both phases decrease lipid solubility, thus increasing renal elimination.

②

makes the drug more polar

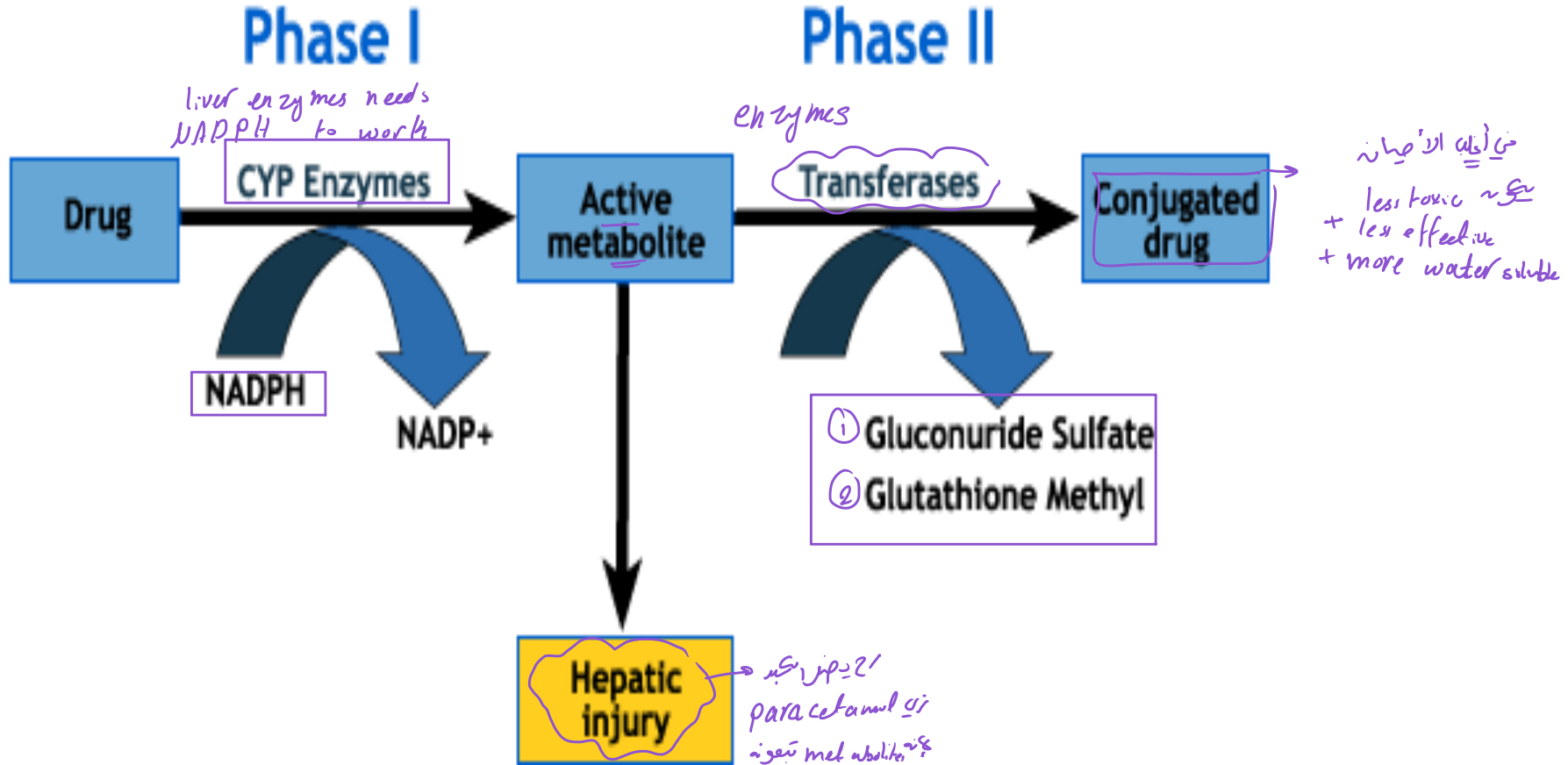
هذه كل الأدوية بتدخل في phase I و phase II ؟



The two phases of drug metabolism

لا!  
في أدوية بين phase II وفي بين I و II  
أدوية phase I و II  
يعني زي صا دة هذة الجسم بتدخل فيه  
↳ Hard drugs  
هي الأدوية (سهة طبعها)  
hydrophilic  
بالتالي صحت بها phase metabolism  
دوجودها في الدم بين

# Phases of Metabolism



**Table 11.2 Biotransformation Reactions and Pharmacologic Activity of the Metabolite**

| Reaction                                                         | Example                                                    |
|------------------------------------------------------------------|------------------------------------------------------------|
| <i>normal type of drugs</i>                                      |                                                            |
| <b>Active Drug to Inactive Metabolite</b>                        |                                                            |
| Amphetamine <i>remove amine group</i><br>Deamination →           | Phenylacetone                                              |
| Phenobarbital<br>Hydroxylation →                                 | Hydroxyphenobarbital                                       |
| <b>Active Drug to Active Metabolite</b>                          |                                                            |
| Codeine <i>remove CH<sub>3</sub></i><br>Demethylation →          | Morphine                                                   |
| Procainamide <i>add acetyl group</i><br>Acetylation →            | N-acetylprocainamide                                       |
| Phenylbutazone<br>Hydroxylation →                                | Oxyphenbutazone                                            |
| <hr/> <b>Inactive Drug to Active Metabolite</b> <i>Pro-drugs</i> |                                                            |
| Hetacillin<br>Hydrolysis →                                       | Ampicillin                                                 |
| Sulfasalazine<br>Azoreduction →                                  | Sulfapyridine + 5-aminosalicylic acid                      |
| <b>Active Drug to Reactive Intermediate</b>                      |                                                            |
| Acetaminophen<br>Aromatic Hydroxylation →                        | Reactive metabolite (hepatic necrosis)<br><i>موت الكبد</i> |
| Benzo[a]pyrene<br>Aromatic Hydroxylation →                       | Reactive metabolite (carcinogenic)                         |

اللهم اغفر لي خطيئتي  
وجهلي، وإسرافي في  
أمرّي وما أنت أعلم به  
مني، اللهم اغفر لي جدي  
وهزلي وخطأي وعمدي  
وكل ذلك عندي

# Phases of Metabolism

**Table 11.3 Some Common Drug Biotransformation Reactions**

## Phase I Reactions

### Oxidation

Aromatic hydroxylation  
Side chain hydroxylation  
N-, O-, and S-dealkylation  
Deamination  
Sulfoxidation, N-oxidation  
N-hydroxylation

### Reduction

Azoreduction  
Nitroreduction  
Alcohol dehydrogenase

### Hydrolysis

Ester hydrolysis  
Amide hydrolysis

## Phase II Reactions [transferases]

### Glucuronide conjugation

Ether glucuronide  
Ester glucuronide

Amide glucuronide → makes the drug more hydrophilic

### Peptide conjugation

### Glycine conjugation (hippurate)

Methylation → add methyl group  $\text{CH}_3$

N-methylation  
O-methylation

### Acetylation

Sulfate conjugation  
Mercapturic acid synthesis

the most common rxn ←

الترشح  
تحت

# Phases of Metabolism

## Phase 1 Reactions

- Change drugs to more hydrophilic metabolites which are more readily excreted  
*phase I و phase II پس اکثرین درین*
- Introduce into the drug molecule sites for phase II reactions  
*تغییر phase I. بعضی اوقات عصاره تغیر phase II*
- May be less toxic (but not always)  
*the main metabolism organ*
- Mostly occur in the endoplasmic reticulum (microsomes) of liver cells.
- Usually involve oxidation, reduction, hydrolysis or other reactions

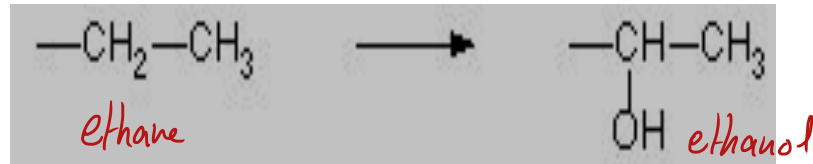
# Phase I Reaction

## 1- Oxidation

يعني إما بزيادة  $O_2$  أو نزع  $H^+$  (أو كليهما مع بعض)

- Oxidation is the addition of oxygen and/or the removal of hydrogen, carried out by oxidases.
  - Most oxidation steps occur in the endoplasmic reticulum. (1)
  - These oxidative reactions typically involve a cytochrome P450, NADPH and oxygen. (2)
  - Common reactions include :-
- Alkyl group hydroxylation ----> alcohol

ROH



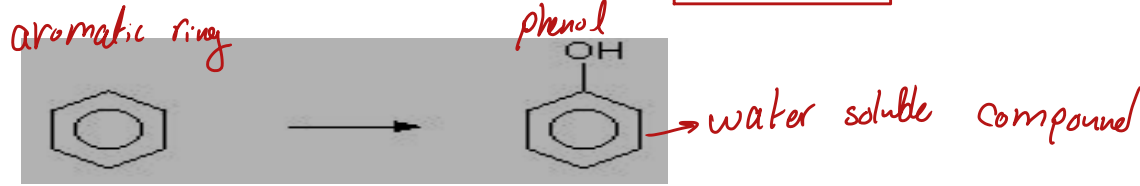
\*metabolism by oxidation examples:-

- phenytoin
- chlorpromazine

• need cyp450 enzymes  
+ NADPH +  $O_2$

# Phase I Reaction

- Hydroxylation of benzene: for example phenytoin



- Oxidation at S or N: for example chlorpromazine



## 2. Reduction →

عكس oxidation:  $H^+$  اونیون  $O_2$

- Add a hydrogen or remove oxygen: azo (-N=N-) or nitro groups (-NO<sub>2</sub>) -----> amines (-NH<sub>2</sub>)

← double bond بین دو ←

← reduction: جبرک های اکسایش ←

- For example nitrazepam

استهلاک

- Reduction is less common in phase 1 metabolism than oxidation

- warfarin is inactivated by reduction of a ketone to a hydroxyl group by CYP2A6.

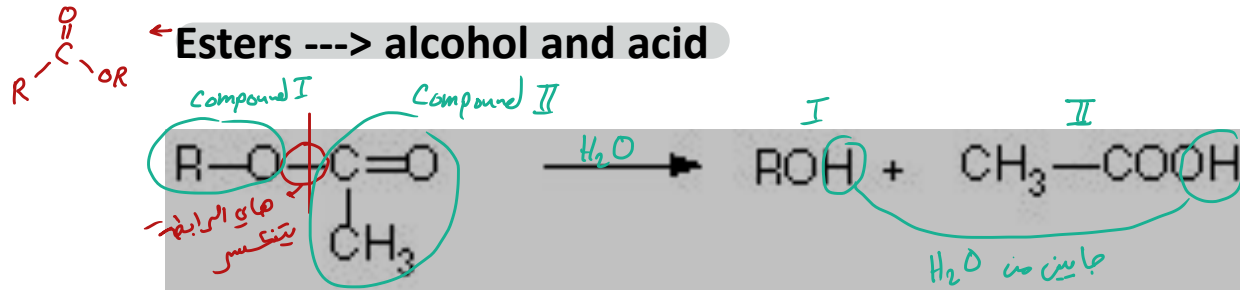
reduction metabolism  
examples:  
nitrazepam

# Phase I Reaction

تکسیر الرابطة باستخدام / إضافة  $H_2O$

## 3. Hydrolytic Reactions (Hydrolysis)

- Addition of water with breakdown of molecule.



- For example aspirin to salicylic acid

hydrolysis metabolism  
example:  
aspirin  $\rightarrow$  salicylic acid

( فَقُلْتُ اسْتَغْفِرُوا رَبَّكُمْ  
إِنَّهُ كَانَ غَفَّارًا )

# Phase 2 Reactions [Conjugation]

رابطه مرکب کبیر، محب اللاد  
صع مرکب الادواء عشانه یهیر  
الادواء عین عقال

... more ...  
لکون طریقہ انتزاعی  $\rightarrow$   $\text{transferase}$  - یتیم رابطہ مرکب کبیر الحکم بد  $\text{structure}$  یتیم الادواء عشانہ یهیر زنی صا یهیر با غلبہ الحماکات  $\text{more}$

- Phase 2 reactions are synthetic ('anabolic') and involve conjugation (i.e. attachment of a substituent group), which usually results in inactive products, although there are exceptions

➤ e.g. the active sulphate metabolite of minoxidil, a potassium channel activator used to treat severe hypertension and (as a cream) to promote hair growth.

➤ Codeine ---> morphine  
 ➤ Primidone ---> phenobarbital

→ are examples of pro-drugs than enters the body inactive but becomes active with metabolism  
 Active metabolism → more Active  
 and they have long duration of action

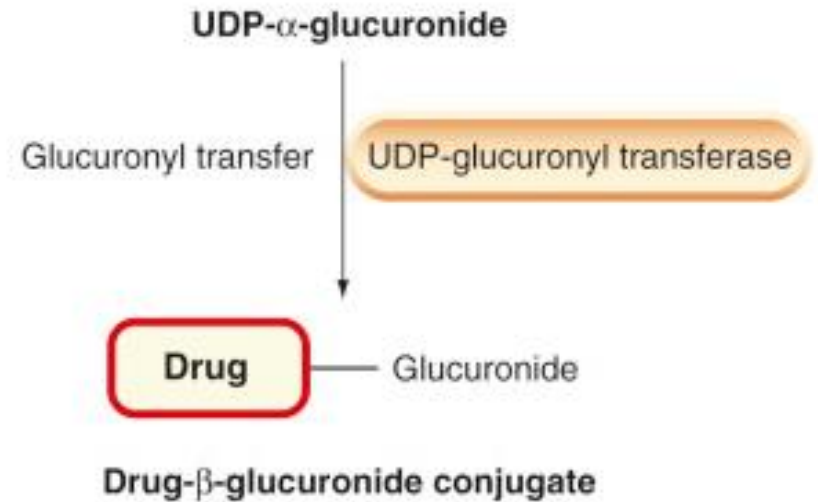
- Phase 2 reactions take place mainly in the liver. If a drug molecule or phase 1 product has a suitable 'handle' (e.g. a hydroxyl, thiol or amino group), it is susceptible to conjugation.

بیس صحت کل الادویہ یتیم فی  $\text{phase I+II}$   
فی صحتها بیس واحد منهم و فی الادویہ  
صا یتیم بائی تفاعل منهم

# Phase 2 Reactions → Occur by transferases enzymes

## 1. Conjugation <sup>بنهین المدکب مکان صاهر تفاعل فی phase I</sup> <sup>أو مکانه آخر بموجب الدواء</sup>

- Conjugation reactions **covalently** add large, polar endogenous molecules to parent drug or Phase I metabolite → inactive and excretable.
- The chemical group inserted may be glucuronyl, sulphate, methyl or acetyl.
- Acetylation and methylation reactions occur with acetyl-CoA and S-adenosyl methionine, respectively, acting as the donor groups.
- Many conjugation reactions occur in the liver, but other tissues, such as lung and kidney, are also involved.



The glucuronide conjugation reaction.  
A glucuronyl group is transferred from uridine diphosphate glucuronic acid (UDPGA) to a drug molecule.

# Phase II Reaction

## Examples

- **Glucuronidation** ⇒ Adding glucuronide molecule

- This is the main conjugation reaction in the body.

- This occurs in the liver. → هذا ينتج phase I شيفاهم نوعه

- **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 ( $\text{NH}_2\text{CH}_2\text{COOH}$ ) for example **nicotinic acid**.

- **Sulfate**

- **Sulfate** ( $-\text{SO}_4$ ) for example **morphine, paracetamol**.

sulfate + Glucuronidation

\* Drugs that pass phase I and II are?  
morphine  
sulfonamides  
nicotinic acid  
paracetamol

أي مركب  
على (OH)  
نوعه  
morphine

لما يخلع مضاد ويصير به يخلع من الجسم ع 2  
بفعل phase I وينتجان إلى OH وبعد phase II وينتجان glucuronide

# Factors Affecting Hepatic Metabolism

1. **Age:** Drugs metabolism is slower in fetal, neonatal and elderly humans than in adults. *كل رزم هر عتقم تكون أقل من الشباب لأنه حالة من انخفاض metabolism عندهم بصفة معاكسة مع الشباب.*
2. **Sex:** women metabolize alcohol more slowly than men.
3. **Some drugs:**
  - 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. *لما أعطى دواء معين بغيره metabolism بارتفاع معين أو أخذ آخر معاً فكان دواء بغيره metabolism بنفس الارتفاع فهو [drug-drug interaction] روح يأخذوا على نفس الأساس على تحييد الدواء إلى أطلاق مفعول*
  - 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. *بما كان عندى enzyme induce الزيد المجرى*
  - The opposite is also true (enzyme inhibition). *أما enzyme inhibition في أتمك المجرى والشرى تحت*  
*decrease the rate of metabolism and thus increase duration and intensity of their action.*

# Factors Affecting Hepatic Metabolism

لهوول (صلا على أدوية + مالا  
بتريد من الانزعاج اي يتكر  
الادوية بالمتالي بيل تركيز وفعال  
الادوية

## I. Induction

دوا يحفز الانزعاج ديهها فافاة كثير بالمتالي كثير  
من الادوية درج يهبط له metabolism بالمتالي حورج يهبط بتركيز الادوية؟ (دع يقل)  
Induction ~  $\uparrow$  metabolic activity of enzyme =  $\downarrow$  [drug] هاي  
لغتي تركيز

- ✓ E.g. Phenobarbitone will induce the metabolism of itself, phenytoin, warfarin, etc.
- ✓ E.g. Cigarette smoking can cause increased elimination of theophylline. ينشط الدم فنين جريه أكبر  
من التمثيل عن المدخن
- ✓ E.g. alcohol, Dosing rates may need to be increased to maintain effective plasma concentrations. يا بنزيد الجرعة أو عدد مرات أخذ الادوية بيل 3 مرات بدهير 4 مرات أو بنخليه 3 مرات بين  
لا أخذ 7mg بدل 5mg
- ✓ A number of drugs, such as rifampicin, ethanol and carbamazepine, increase the activity of microsomal oxidase and conjugating systems when administered repeatedly. عشان صيل بنزيد جرعتهم  
enzyme
- ✓ Enzyme induction can increase drug toxicity and carcinogenicity, because several phase 1 metabolites are toxic or carcinogenic. ها هي الانزعاج كما تقل الانزيم بسرعة ليعت الادوية ممكن تهبط حارة  
مثال paracetamol
- ✓ An important example is paracetamol, a drug with a highly toxic metabolite. تتابع علية metabolism

## Factors Affecting Hepatic Metabolism

- **Enzyme induction** is exploited therapeutically by administering phenobarbital to premature babies to induce glucuronyltransferase, thereby increasing bilirubin conjugation and reducing the risk of kernicterus (staining and neurological damage of the basal ganglia by bilirubin).
- The most thoroughly studied inducing agents are polycyclic aromatic hydrocarbons.

# Factors Affecting Hepatic Metabolism

## Examples of drugs that induce drug-metabolising enzymes

| Drugs inducing enzyme action | Examples of drugs with metabolism affected             |
|------------------------------|--------------------------------------------------------|
| Phenobarbital                | Warfarin                                               |
| Rifampicin                   | Oral contraceptives                                    |
| Griseofulvin                 | Corticosteroids                                        |
| Phenytoin                    | Ciclosporin                                            |
| Ethanol<br>Carbamazepine     | Drugs listed in left-hand column will also be affected |

# Factors Affecting Hepatic Metabolism

Induction عكس

أحياناً تكون سمية دواء  
تنشيط الكلى نزعات بالأسباب هو  
لما يرتفع تركيز الدواء في الدم عند  
المحدد أو المخلوون مع دواء toxic

## 2. Inhibition

→ يعني تدهور بتركيز الدواء؟ يزداد مع  
هون مع تنشيط الإنزيمات بالأنشطة metabol

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

✓ E.g. <sup>1</sup> Grapefruit juice → الكافيين الذي يشرب مع grapefruit لازم أن قل إلا الجرعة كجدة  
يعرف صاد الدواء مع يعل تنشيط الكلى نزعات يعني مع يزداد تركيز الدواء وما يتأثر بدهس toxic

✓ For example, <sup>2</sup> warfarin inhibits tolbutamide elimination which  
can lead to the accumulation of drug and may require a  
downward adjustment of dose. <sup>warfarin جرعة</sup>

✓ <sup>3</sup> Cimetidine is a therapeutic agent (<sup>H<sub>2</sub> blocker to reduce stomach acidity</sup> prevent ulcer) that has been  
found to impair the in vivo metabolism of other drugs.

• Inhibitors of P450 differ in their selectivity towards different isoforms of the enzyme, and are classified by their mechanism of action.

# Factors Affecting Hepatic Metabolism

## Examples of drugs that inhibit drug-metabolising enzymes

| Drugs inhibiting enzyme action | Drugs with metabolism affected              |
|--------------------------------|---------------------------------------------|
| Allopurinol                    | Mercaptopurine, azathioprine                |
| Chloramphenicol                | Phenytoin                                   |
| Cimetidine                     | Amiodarone, phenytoin, pethidine            |
| Ciprofloxacin                  | Theophylline                                |
| Corticosteroids                | Tricyclic antidepressants, cyclophosphamide |
| Disulfiram                     | Warfarin                                    |
| Erythromycin                   | Cyclosporin, theophylline                   |
| Monoamine oxidase inhibitors   | Pethidine                                   |
| Ritonavir                      | Saquinavir                                  |

## • Factors that can influence drug metabolism

- 3. Food:** Grapefruit juice contains furanocoumarins which inhibit drug metabolism by interfering with hepatic cytochrome P450. So it's decrease metab + increase duration and concentration of drug.

سرعة التخلص من metabolism كل شخص و حسب جيناته

عنا صلح نقل الجورة

### 4. 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 (rapid acetylators).
- This variation may have dramatic consequences, as the slow acetylators are more prone to dose dependent toxicity. منهم فرق ونحسب عنان الجورة لهم سرعة التخلص
- 13% of Egyptians are slow acetylators. Warfarin (bleeding) and phenytoin (ataxia) are examples نسبة عند ان شاربها اي عند هم metab بطيئة

• الشخص اي عنده metabolism سي بدي ازمنة الجورة بكونه سريعه يعني اهدا صاير يهزل

حقنة طول في السهم و يعمل المصنوع المفلوب تم ا دالسي مديج

دب انهم اذوا تانا المسلمين  
في كل مكان و زمان

## • Factors that can influence 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. *adults are the best*  
*male's metabolism is faster than female*

### 7. Route of administration

- A drug given parenterally, transdermally, or by inhalation may distribute within the body prior to metabolism by the liver.
- In contrast, drugs given orally are normally absorbed in the duodenal segment of the small intestine and transported via the mesenteric vessels to the hepatic portal vein and then to the liver before entering the systemic circulation. *الأدوية التي بغيرها metabolism بعد كبير، مع بكونه B A! لها علاقة أكبر، عن طريق الأدوية التي تعطي IV أو B A! لا تأخذها من أولها تدخل.*
- Drugs that are highly metabolized by the liver or by the intestinal mucosal cells demonstrate poor systemic availability when given orally which is termed first-pass effect (e.g. *Propranolol, nitroglycerin, verapamil, morphine, isoproterenol, etc*).

# Diseases and Drug Metabolism

ممكن اني بخصوني الجسم اذ يمكن  
فيه إنزيمات، روح بقم فيه metabolism.  
طبيب كين روح غششي هاي العملية لو  
العضو هاد مريضها؟

## 8. Pathological factors

- Can also influence drug metabolism, including liver, kidney, or heart diseases.

[الحمد لله الذي]

➤ **Liver Disease** → the main organ of metabolism + production of enzymes

بما خانا صا ابتلي

[بغيرنا]

- Acute or chronic diseases that affect liver function markedly affect hepatic metabolism of some drugs.

تراجع انه هو على الكبد

ضرب الكبد من الكحول

- Such conditions include **fat accumulation, alcoholic cirrhosis, biliary cirrhosis, and acute viral or drug hepatitis.**

بالتالي نظامهم المجموعات من الأدوية

- 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.

تأثيره مثلاً 12 ساعة

بين عند شخص عند مشكلة

بالكبد روح يصل 24 ساعة

# Diseases and Drug metabolism

➤ **Renal Disease** Cause kidneys are detoxification organ, which means they're responsible of excretion + metabolism of some drugs

- 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 <60ml/min per 1.73m<sup>2</sup> body surface area.

➤ **Cardiac Disease** → responsible of blood flow to the organs which have metabolism and for all the body.

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

ADME → excretion  
absorption ↓  
distribution ↓  
metabolism

# Important Highlights for Drug Metabolism

- **DRUG METABOLISM**

- Phase 1 reactions involve oxidation, reduction and hydrolysis. They:

- usually form more chemically reactive products, which can be pharmacologically active, toxic or carcinogenic.

paracetamol زى ما حكتنا عن

- often involve a monooxygenase system in which cytochrome P450 plays a key role.

- Phase 2 reactions involve conjugation (e.g. glucuronidation) of a reactive group (often inserted during phase 1 reaction) and usually lead to inactive and polar products that are readily excreted in urine.

ما ده هو هدفنا من metabolism  
عشان نخرج الدواء من الجسم بيه  
ما اعطانا مفعوله.

سبحان الله و بعمده

سبحان الله العظيم

# Important Highlights for Drug Metabolism

phase II

- Some conjugated products are excreted via bile, are reactivated in the intestine and then reabsorbed ('enterohepatic circulation').
- Induction of P450 enzymes can greatly accelerate hepatic drug metabolism. It can increase the toxicity of drugs with toxic metabolites, and is an important cause of drug-drug interaction, as is enzyme inhibition.
- Presystemic metabolism in liver or gut wall reduces the bioavailability of several drugs when they are administered by mouth.   
↳ cause of metabolism

oral, sublingual, ...