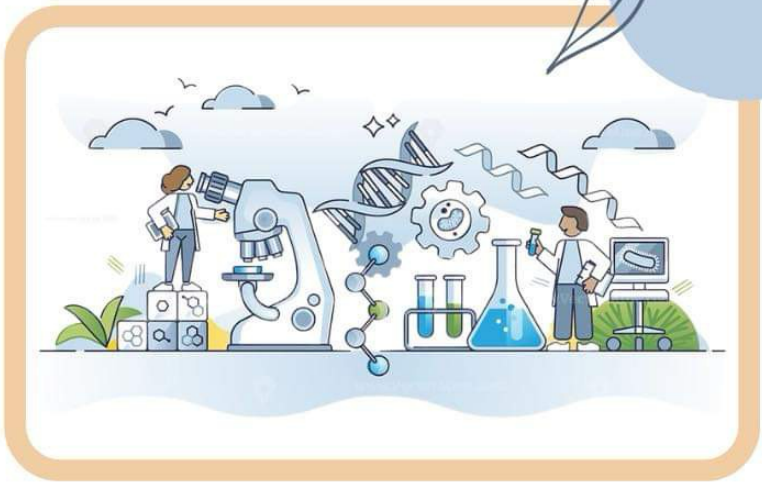
تفريغ بيوفارما



اسم الموضوع: Metabolism

إعداد الصيدلاني/ـة: ياسمين خليل 🌷

(إِنَّ اللَّهَ لَا يُغَيِّرُ مَا بِقَوْمٍ حَتَّىٰ يُغَيِّرُوا مَا بِأَنفُسِهِمْ)

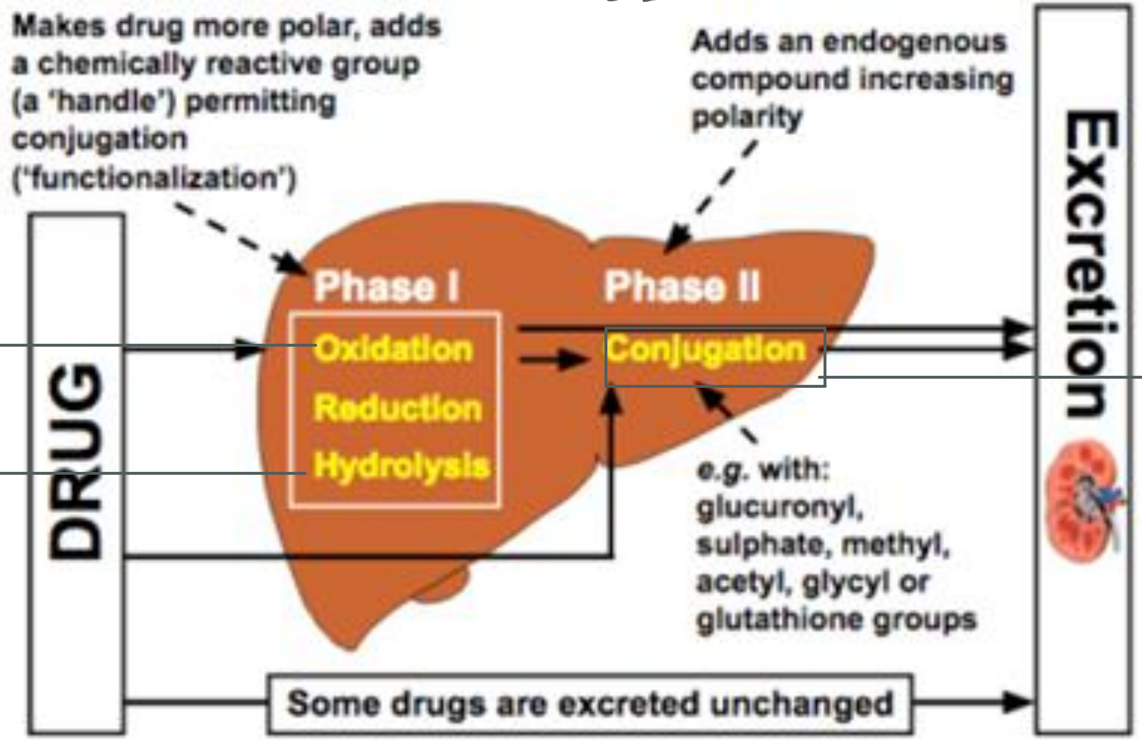
Soul Academy

لجان الدُّفعات

Drug Metabolism

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

عبارة عن تفاعلات كيميائية



Oxidation: add O_2 or remove H^+

Hydrolysis: breakdown the structure by adding H_2O molecule

في phase I كنا قلنا نضيف
① في عملية oxidation ، بس لو لسا المركب
ما صار ذائب في الماء رح يروح إلى phase II
و بصير Conjugation يعني إضافة مركب
إلى O_2 إلي ضفناها في phase I، تتم!
وبعدين رح يصير hydrophilic

Dr. Muna Oqal

Drug Metabolism

- **Metabolism is defined as:** modify on drug's properties + structure to get the benefits of drug
  - ✓ The irreversible biotransformation of drug in the body → typically involves making it more polar to enhance renal excretion

- Drug metabolism often (not always) converts lipophilic chemical compounds into:
  - more hydrophilic, more water soluble
  - have their actions decreased (become less effective (normal drug)) or increased (become more effective) → prodrugs
  - 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

active → inactive

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.

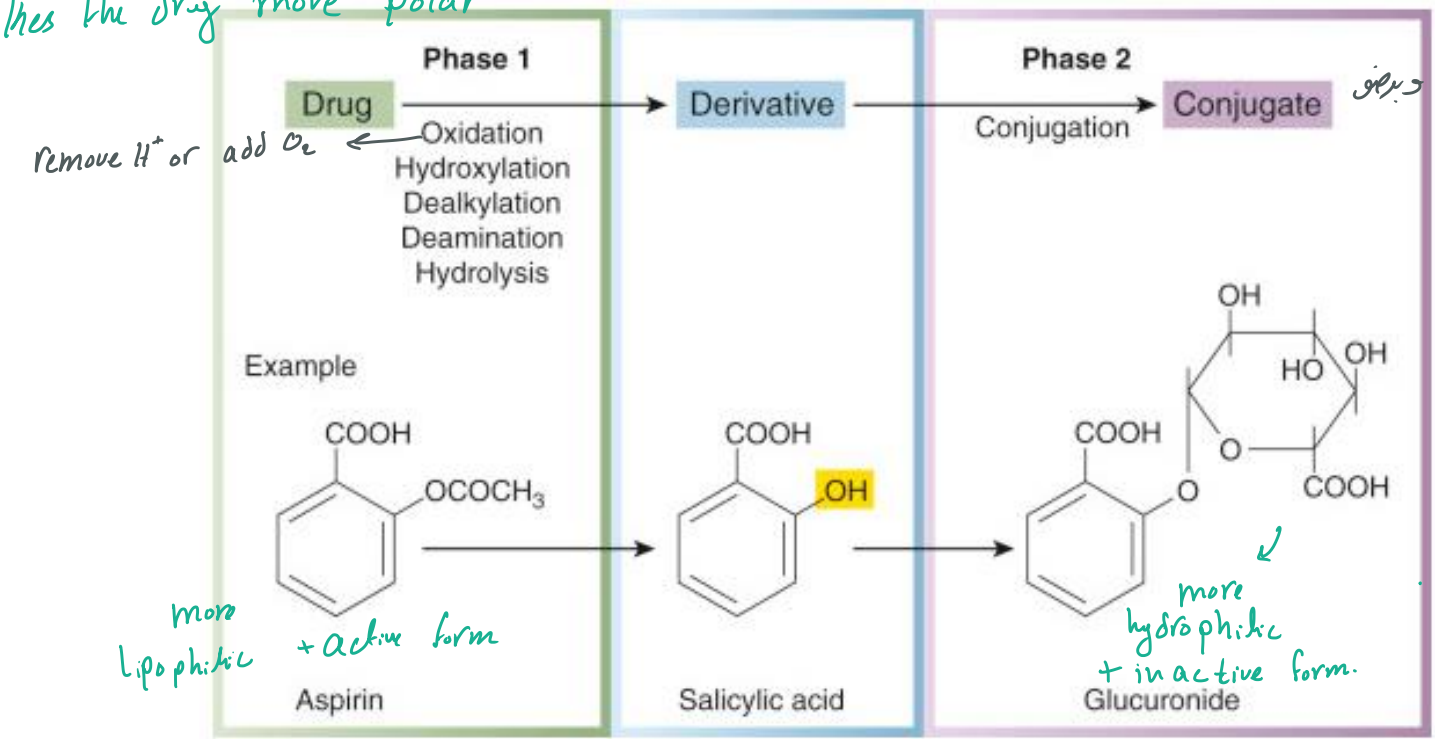
- However, other organs such as the kidney, lung, intestine and placenta can also be involved in this process.

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.

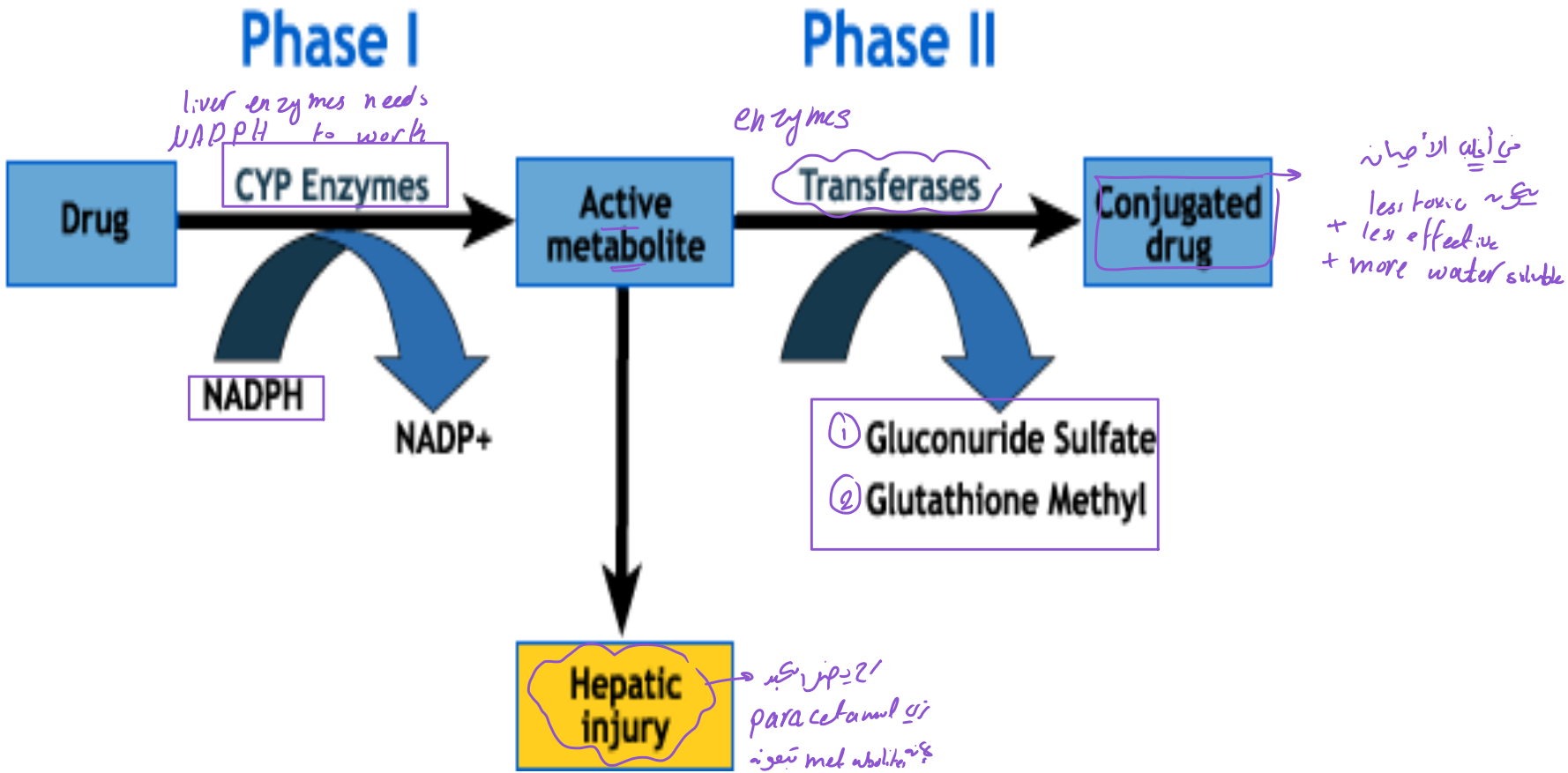
Drug Metabolism

- 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.



The two phases of drug metabolism

Phases of Metabolism



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

Table 11.2 Biotransformation Reactions and Pharmacologic Activity of the Metabolite

Reaction		Example
		Active Drug to Inactive Metabolite
Amphetamine	Deamination	Phenylacetone
Phenobarbital	Hydroxylation	Hydroxyphenobarbital
		Active Drug to Active Metabolite
Codeine	Demethylation	Morphine
Procainamide	Acetylation	N-acetylprocainamide
Phenylbutazone	Hydroxylation	Oxyphenbutazone
		Inactive Drug to Active Metabolite
Hetacillin	Hydrolysis	Ampicillin
Sulfasalazine	Azoreduction	Sulfapyridine + 5-aminosalicylic acid
		Active Drug to Reactive Intermediate
Acetaminophen	Aromatic Hydroxylation	Reactive metabolite (hepatic necrosis)
Benzo[a]pyrene	Aromatic Hydroxylation	Reactive metabolite (carcinogenic)

Phases of Metabolism

Table 11.3 Some Common Drug Biotransformation Reactions

Phase I Reactions	Phase II Reactions [transferases]
Oxidation (the most common rxn)	Glucuronide conjugation (الأسرع تحت)
Aromatic hydroxylation	Ether glucuronide
Side chain hydroxylation	Ester glucuronide
N-, O-, and S-dealkylation	Amide glucuronide → makes the drug more hydrophilic
Deamination	
Sulfoxidation, N-oxidation	Peptide conjugation
N-hydroxylation	
Reduction	Glycine conjugation (hippurate)
Azoreduction	
Nitroreduction	Methylation → add methyl group CH_3
Alcohol dehydrogenase	N-methylation
Hydrolysis	O-methylation
Ester hydrolysis	
Amide hydrolysis	Acetylation
	Sulfate conjugation
	Mercapturic acid synthesis

Phases of Metabolism

Phase 1 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

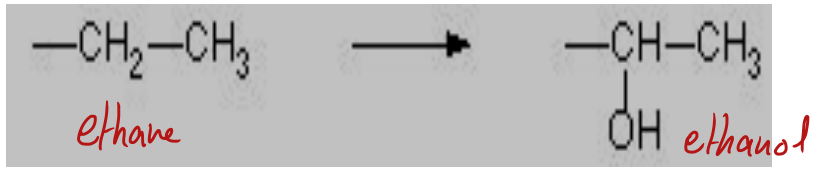
1- Oxidation

يعني يا بنضيف O_2 أو نحذف H^+ أو العمليتين 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, (2) NADPH and oxygen. (3)
- Common reactions include :-

➢ **Alkyl group hydroxylation ----> alcohol**

ROH



*metabolism by oxidation examples:-

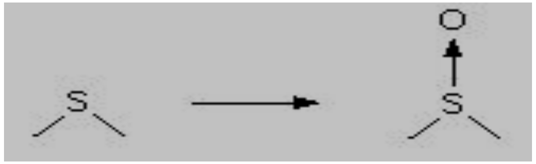
- phenytoin
- Chlorpmazine

- 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

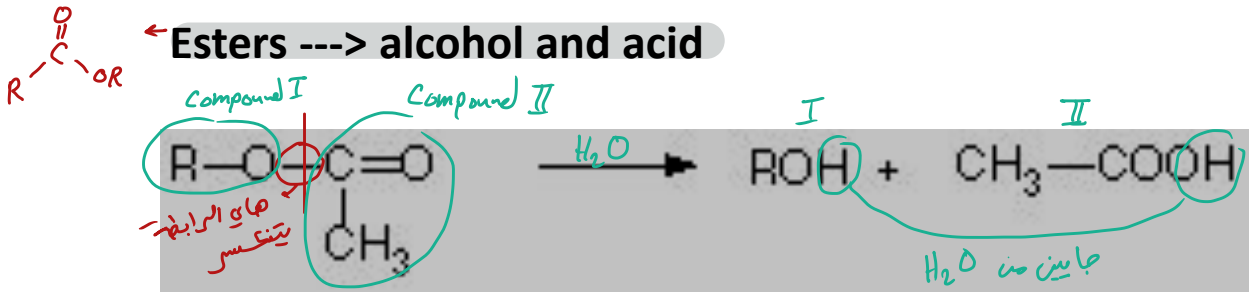
- Add a hydrogen or remove oxygen: azo (-N=N-) or nitro groups (-NO2) -----> amines (-NH2)
- For example nitrazepam
- Reduction is less common in phase 1 metabolism than oxidation
- warfarin is inactivated by reduction of a ketone to a hydroxyl group by CYP2A6.

Phase I Reaction

H_2O تكسير الرابطة باستخدام/إضافة

3. Hydrolytic Reactions (Hydrolysis)

- Addition of water with breakdown of molecule.



- For example aspirin to salicylic acid

hydrolysis metabolism
example:
aspirin → salicylic acid

(فَقُلْتُ اسْتَغْفِرُوا رَبَّكُمْ
إِنَّهُ كَانَ غَفَّارًا)

Phase 2 Reactions [Conjugation]

ربط مركب كبير محب للماء مع مركب الدواء عشان يصير الدواء غير فعّال

لعمل طريقة إنزيمات transferase تتم ربط مركب كبير الحجم بـ structure الدواء عشان يصير زي ما بصير بأغلب الحالات more polar ...

- Phase 2 reactions are synthetic ('anabolic' [بناء]) 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 that 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.

بس مش كل الأدوية بتمر في phase I+II
في منهم بس واحد منهم وفي أدوية
ما بتمر بأي تفاعل منهم

Phase 2 Reactions

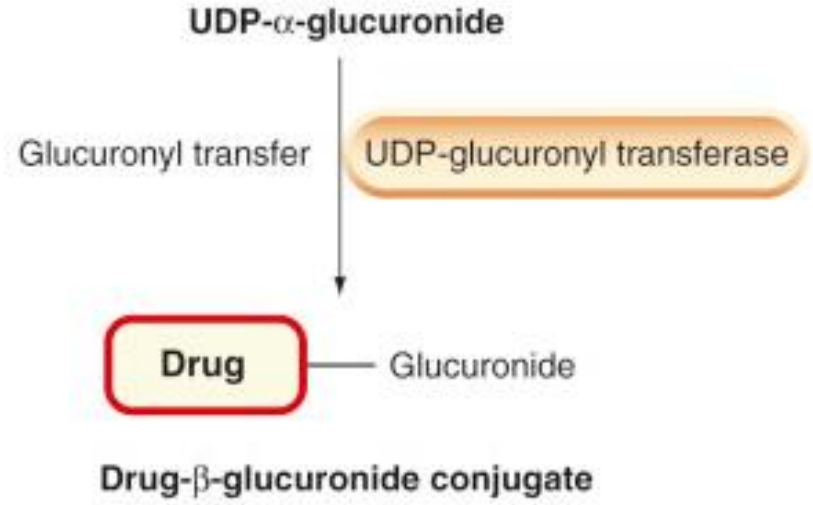
Occur by transferases enzymes

1. Conjugation

phase I بتضيف المركب وكان ما صار تفاعل في او مكانه آخر بعرجب الدواء

- 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.

phase II



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

Phase II Reaction

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

Examples

- **Glucuronidation** ⇒ Adding glucuronide molecule
  - 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.

sulfate + Glucuronidation

Factors Affecting Hepatic 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. **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.
- 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).

Decrease the rate of metabolism and thus increase duration and intensity of their action.

Factors Affecting Hepatic 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.
- ✓ A number of drugs, such as rifampicin, ethanol and carbamazepine, increase the activity of microsomal oxidase and conjugating systems when administered repeatedly.
- ✓ Enzyme induction can increase drug toxicity and carcinogenicity, because several phase 1 metabolites are toxic or carcinogenic.
- ✓ An important example is paracetamol, a drug with a highly toxic metabolite.

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 Carbamazepine	Drugs listed in left-hand column will also be affected

Factors Affecting Hepatic Metabolism

2. 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.

- 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	Ciclosporin, 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.

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

- **Factors that can influence drug metabolism**

adults are the best

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

8. Pathological factors

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

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

- 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.

Diseases and Drug metabolism

➢ Renal Disease

Cause kidneys are detoxification organs, 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^2 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
distribut
→ 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.

  – 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.

سبحان الله وبحمده
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, Sublengual, ...

اللهم ارحم عبدك أيوهم واجعله
وأهله في الفردوس وأعظم أعمالنا بالصالحات