(اللهم ارزقني قوة الحفظ وسرعة الفهم وصفاء الذهن
وأصلحني وأصلح بي الأمة)

→ Process come after drug absorption & distribution

Drug Metabolism

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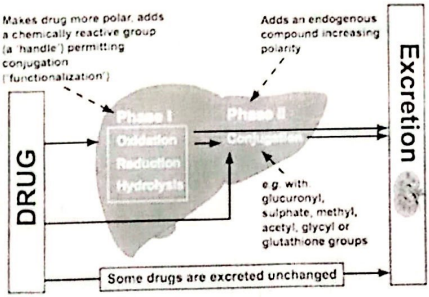
→ The main goal is to prepare drug to be excreted outside the body by Kidney, why do we need it?

because Kidney can not deal with lipophilic drug so we need to add some polar groups to convert them to more polar agent or polar compounds to can be excreted easily

Not all drug go in this Procedure. By the same way, some drugs will be transferred into Phase I & Phase II. Other drugs are already have chemical group or reactive group so they can under go to Phase II directly, other drugs can be executed without any changes



→ The Liver the Place where metabolism occur, so the goal is to make drug more Polar by add chemical reactive group for it

→ Phases of metabolism → Phase I :- is the middle to Prepare compounds to be suitable for Phase II for conjugation. In other words, Phase I is the Process to make functional group in the compound able for the next step, which includes the conjugation of the metabolite with other indigenous compounds available like a Glucuronyl, Sulphate, methyl acetyl or glycel or a glutathione groups to be excreted

- Sometimes metabolism results in less polar compound, so lipophilic compound can be converted to more hydrophilic and water soluble because it's hydrophilic, and sometimes these metabolites will become less effective & their action decreases. or in other side these metabolites become more effective & their action increases
- These metabolites can be less toxic or more toxic than parent drug or the origin drug with different type of effect or toxicity

8/9/

Drug Metabolism

- **Metabolism is defined as:**
  - ✓ The irreversible biotransformation of drug in the body → typically involves making it more polar to enhance renal excretion (it is a typical way to make it more polar, but it's not always the case)
- 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

Note Lipophilic substances are not eliminated efficiently by kidney. Consequently, most lipophilic drug are metabolised to more polar product, which are then excreted in urine. Drug are metabolised predominantly in the liver, especially by cytochrome P450 (CYP) system.

Drug Metabolism

- **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. But sometimes other processes or other organs can contribute to drug metabolism, like Kidney (morphine, Paracetamole are metabolized in Kidney) and in kidney there are enzymes for drug metabolism.
- However, other organs such as the kidney, lung, intestine and placenta can also be involved in this process.

5-aminosalicylic acid — Azoreductase (Bacteria)

metabolism can be in:
- Liver
- Kidney (metabolism of morphine & Paracetamol)
- Lung (metabolism of Propofol)
- intestine
- Placenta

• يساعدوا ال Liver لكن metabolism تحدث بشكل أساسي في Liver مثلاً ال lung تساعد في metabolism of Propofol & metabolism of theophylline وهكذا

Drug Metabolism

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

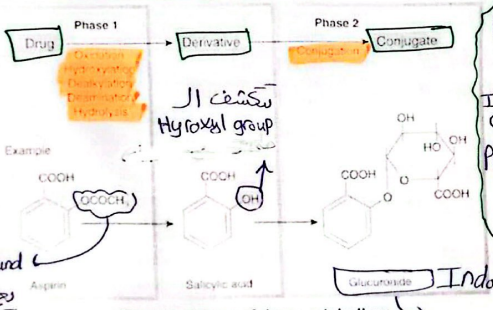
- Some of the earlier sulfonamides are acetylated to relatively insoluble metabolites which precipitated in urine, crystalluria.

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

acylated كانوا (old sulfonamide) ← sulfonamide هو earlier version ال
Precipitation in urine لـ يحدث insoluble metabolites يعطي تحكم Acylation و ال
. Crystalluria فتسبب
more properties حيث different elimination و العم new sulfonamide لكن
less problems و أكثر solubility properties . و العم less precipitation العم

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

Drug تغير ← Phase I
Suitable حتى يصير
Indogenous انه يرتبط بال Compound
Phas II reaction الي تشمل
Drug ال صير حتى
more Polar & excrete outside the body

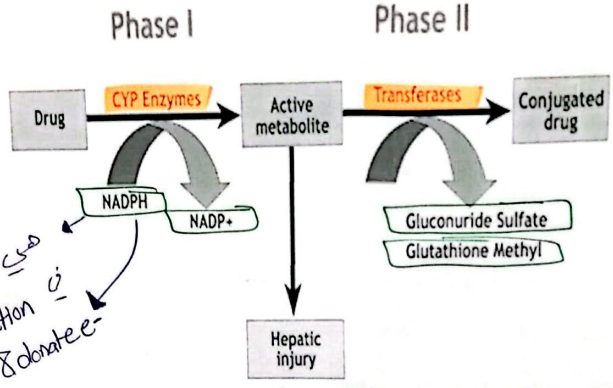
Indogenous sugar component

Drug ال water solubility يزيد

Hydrolysis of ester bond يحصل وجود ester compound في وجود H^+

Aspirin (acetyl Salicylic acid) → Salicylic acid + acetic acid → Glucuronide

Phases of Metabolism



في الإنجليزي تسمى Biotransformation لأن Can accept & donate e-

↳ Sometimes this active metabolite is toxic & affects the hepatic tissue & cause hepatic necro & hepatic injury

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)

Drug → metabolite → conjugated drug

maybe the drug is active & metabolite is inactive or both are active or drug is inactive & metabolite is active or metabolite is toxic

To target colon ←

- Deamination is Process in Phase I
- Loratadine هو Active و desloratadine (Active) فشركات الأدوية كتير بتعمل وتصنع Desloratadine من البداية وتعطيه as drug حيث ال Activity اله عالية

Phases of Metabolism

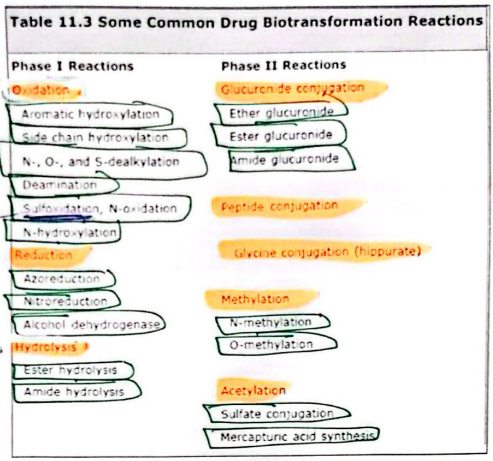


Table 11.3 Some Common Drug Biotransformation Reactions

Phase I Reactions	Phase II Reactions
Oxidation	Glucuronide conjugation
Aromatic hydroxylation	Ether glucuronide
Side chain hydroxylation	Ester glucuronide
N-, O-, and S-dealkylation	Amide glucuronide
Deamination	
Sulfoxidation, N-oxidation	Peptide conjugation
N-hydroxylation	
Reduction	Glycine conjugation (hippurate)
Azoreduction	
Nitroreduction	Methylation
Alcohol dehydrogenase	N-methylation
Hydrolysis	O-methylation
Ester hydrolysis	
Amide hydrolysis	Acetylation
	Sulfate conjugation
	Mercapturic acid synthesis

oxygen ← sulfur ارتباط

Phases of Metabolism

Phase 1 Reactions

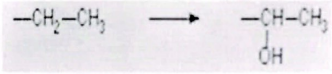
- Change drugs to more hydrophilic metabolites which are more readily excreted
- Introduce into the drug molecule sites for phase II reactions
- May be less toxic (but not always)
- Mostly occur in the endoplasmic reticulum (microsomes) of liver cells.
- Usually involve oxidation, reduction, hydrolysis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

Phase I Reaction

1- Oxidation

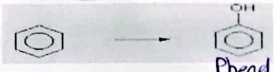
- Oxidation is the addition of oxygen and/or the removal of hydrogen, carried out by oxidases.
- Most oxidation steps occur in the endoplasmic reticulum.
- These oxidative reactions typically involve a cytochrome P450, NADPH and oxygen.
- Common reactions include :-

➢ Alkyl group hydroxylation ----> alcohol



Phase I Reaction

➢ Hydroxylation of benzene: for example phenytoin

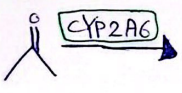


Phenol

➢ Oxidation at S or N: for example chlorpromazine

2. Reduction (oxidation ممكن)

- 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.

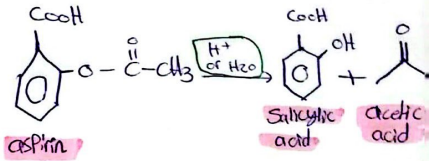


warfarin alcohol warfarin (inactive)

- The degration of drug not only in the body also outside body

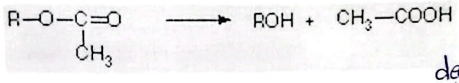
Phase I Reaction

3. Hydrolytic Reactions (Hydrolysis)



- Addition of water with breakdown of molecule.

  Esters ---> alcohol and acid



في دواء الـ Aspirin وجود الرطوبة يعمل الـ degradation ينتج acetic acid فتظهر رائحة

- For example aspirin to salicylic acid

Note Hydrolysis (e.g. aspirin) occurs in Plasma and in many tissue. Both ester and (less readily) amide bonds are susceptible to hydrolytic cleavage. Reduction is less common in Phase I metabolism than oxidation.
But warfarin is inactivated by reduction of Ketone to hydroxyl group by CYP2A6

Phase 2 Reactions

- 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

- 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.

Note 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.

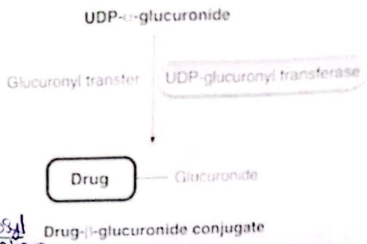
Phase 2 Reactions

1. Conjugation

- 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.

by acetyl CoA (Donor group)

by S-adenosyl methionine (Donor group)



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

Phase II Reaction

Examples

- **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 (NH_2CH_2COOH) for example nicotinic acid.
- **Sulfate**
  - Sulfate (-SO_4) for example morphine, paracetamol.

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).

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

↱ Can help in getting rid of toxins

- **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.

• الـ Induction بيعمل ع Phenobarbital بالـ Hepatic metabolism أو بيزود الـ Glucuronyltransferase اللي بتعمل Conjugation with bilirubin فبيقلل الـ risk of bilirubin accumulation فبيقلل الـ Neurological damage in basal ganglia

Factors Affecting Hepatic Metabolism

Examples of drugs that induce drug-metabolising enzymes

Drugs inducing enzyme action	Examples of drugs with metabolism affected
Phenobarbital	Warfarin (↑ metabolism)
Rifampicin	Oral contraceptives (↑ metabolism)
Griseofulvin	Corticosteroids (↑ metabolism)
Phenytoin	Ciclosporin (↑ metabolism)
ethanol	Drugs listed in left-hand column will also be affected
Carbamazepine	

Not taken with alcohol

• warfarin has too many interaction (كثير تداخل)

Factors Affecting Hepatic 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.
- 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**

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 (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

toxicity of drug ← low metabolism ← Slow acetylator بعض الناس

- **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.
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).*

Bioavailability تقل first Pass-metabolism تدخل الدم قبل تصل & orally drug ال
small intestine → metabolism يحصل وممكن

Diseases and Drug Metabolism

8. Pathological factors

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

➢ **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.

metabolism الـ Half-life of diazepam يزداد مع Viral hepatitis الـ
والباقي مع تمثل داخل الـ

Diseases and Drug metabolism

➢ **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<60ml/min per 1.73m^2 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.

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.

note Liver cells transfer various substances, including drugs, from Plasma to bile by transport systems similar to those of the renal tubule; these include organic cation transporters (OSTs), organic anion transporters (OATs) & P-glycoproteins (P-gps). Various hydrophilic drug conjugates (particularly glucuronides) are concentrated in bile & delivered to the intestine, where the glucuronide can be hydrolysed, regenerating active drug; free drug can then be reabsorbed & cycle repeated, a process referred to enterohepatic circulation. The result is "reservoir" of recirculating drug that can amount amount to about 20% of total drug in the body, prolonging drug action. Examples where this is important include morphine.

Important Highlights for Drug Metabolism

- 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.