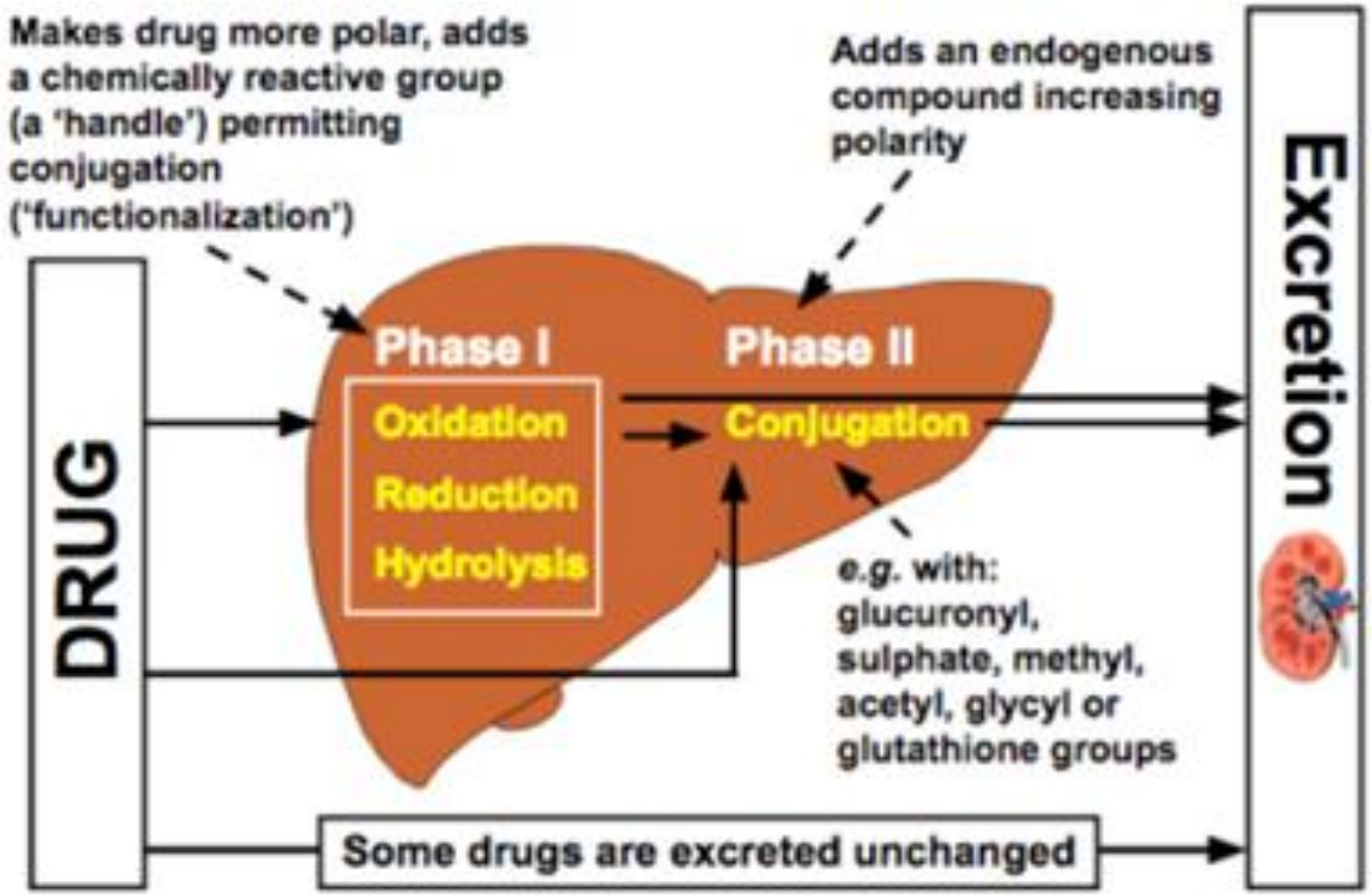
Drug Metabolism



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

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.

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

Drug Metabolism

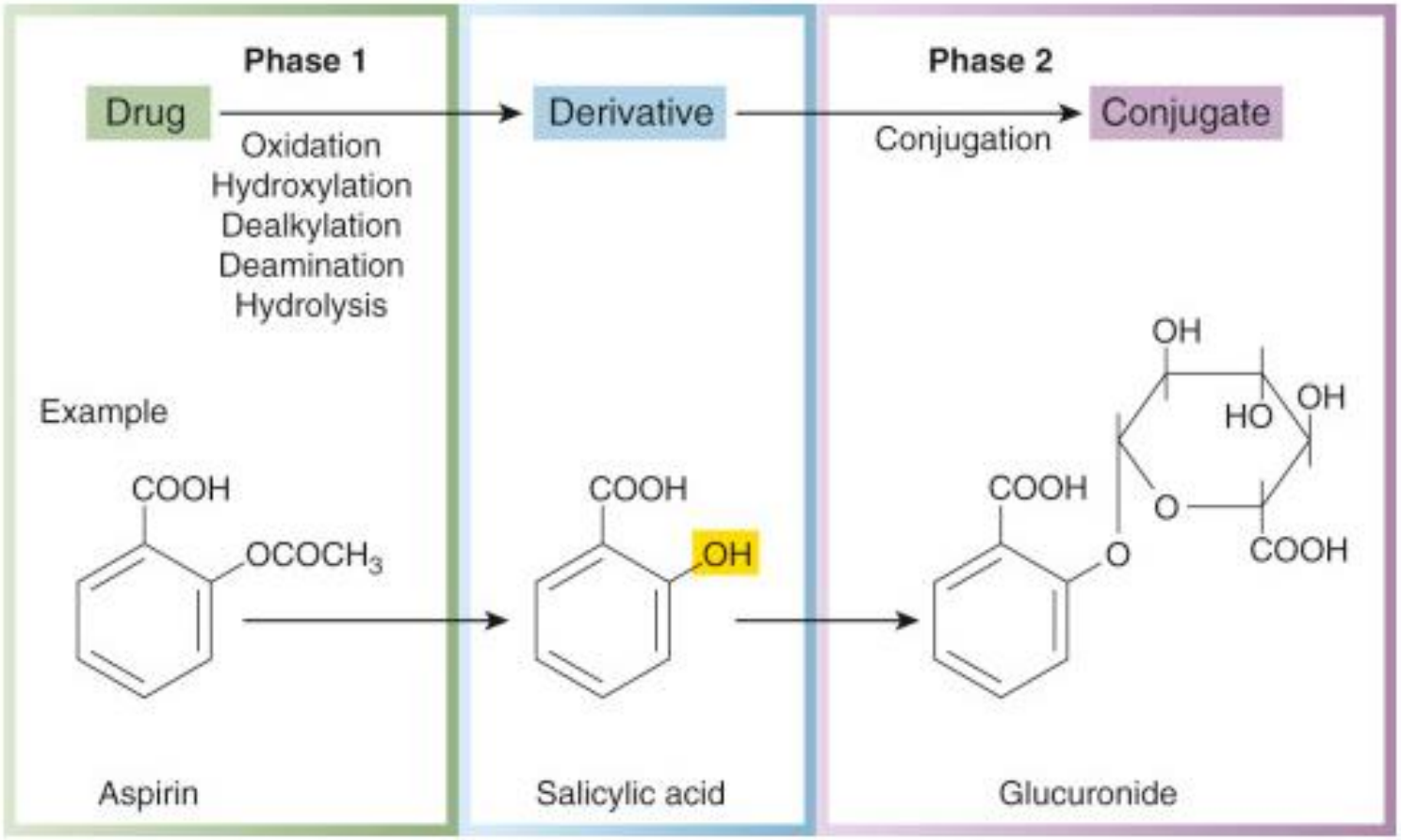
- In some occasions, the metabolite is less water soluble.
- A significant example is the acetyl metabolite of some of the sulfonamides.

- 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

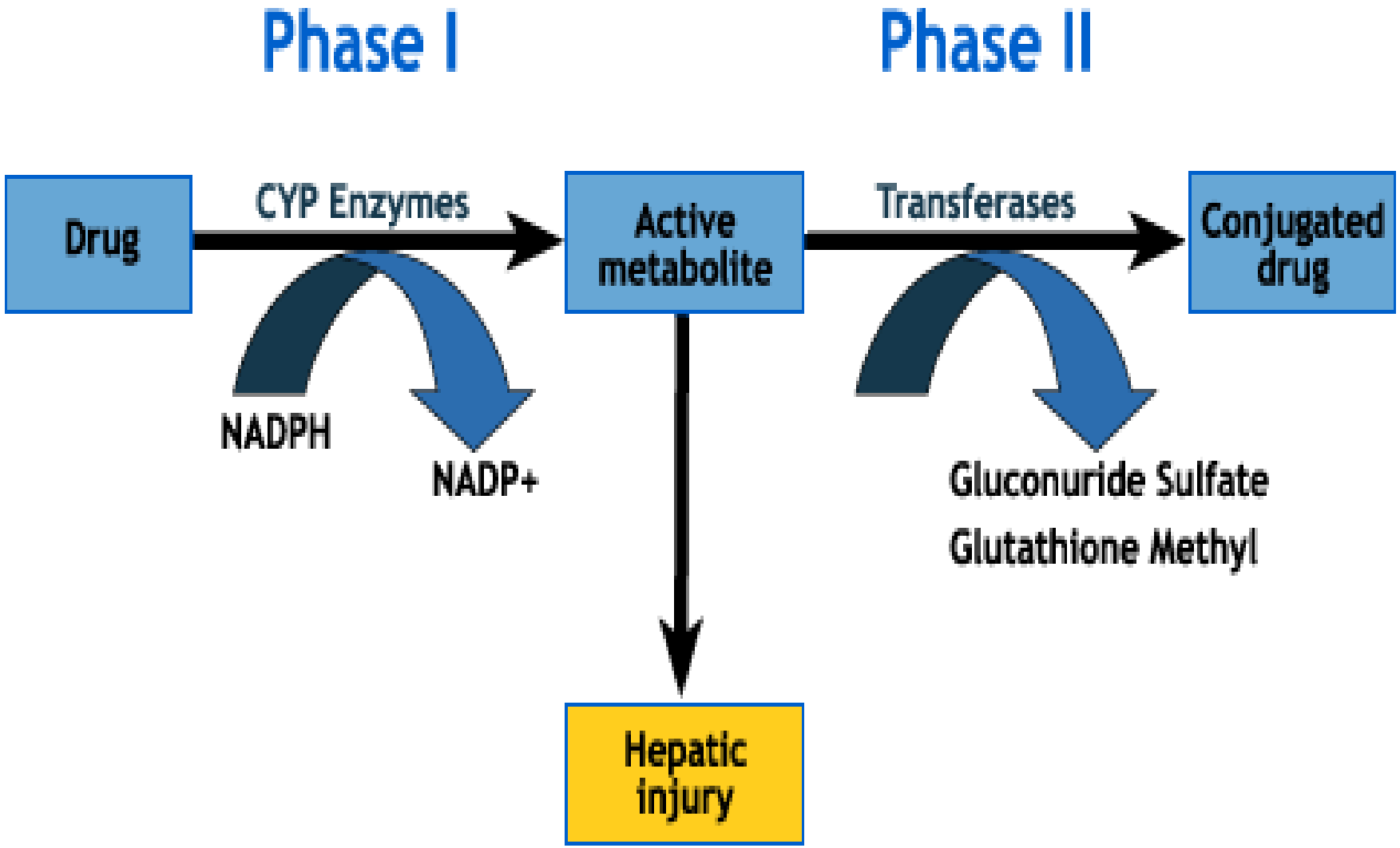


Table 11.2 Biotransformation Reactions and Pharmacologic Activity of the Metabolite

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**
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

Phases of Metabolism

Phase 1 Reactions

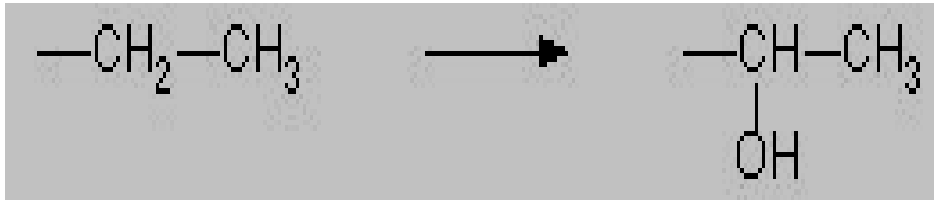
- Change drugs to more hydrophilic metabolites which are more readily excreted
- Introduce into the drug molecule sites for phase II reactions
- May be less toxic (but not always)
- Mostly occur in the endoplasmic reticulum (microsomes) of liver cells.
- Usually involve oxidation, reduction, hydrolysis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

Phase I Reaction

1- Oxidation

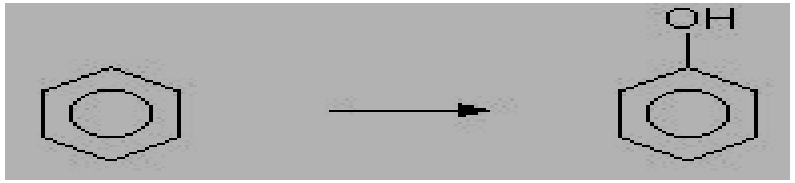
- Oxidation is the addition of oxygen and/or the removal of hydrogen, carried out by oxidases.
- Most oxidation steps occur in the endoplasmic reticulum.
- These oxidative reactions typically involve a cytochrome P450, NADPH and oxygen.
- Common reactions include :-

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

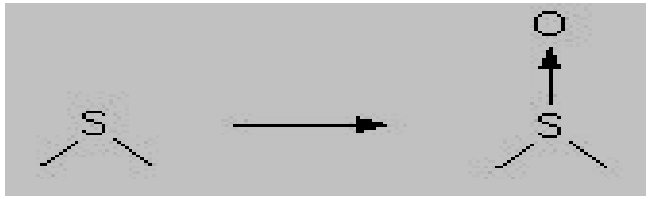


Phase I Reaction

- **Hydroxylation of benzene:** for example phenytoin



- **Oxidation at S or N**: for example chlorpromazine



2. Reduction

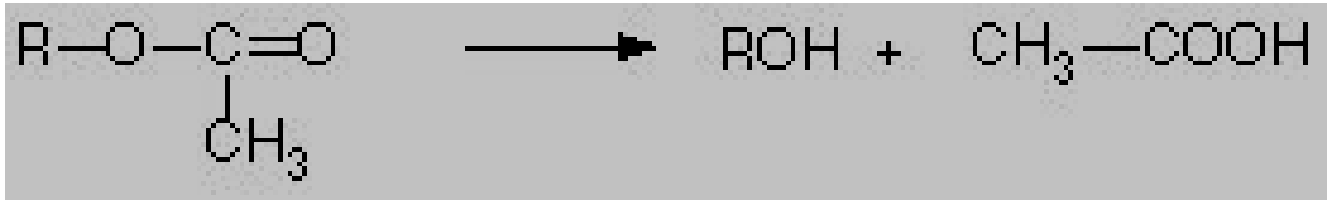
- Add a hydrogen or remove oxygen: azo (-N=N-) or nitro groups (-NO2) -----> amines (-NH2)
- For example nitrazepam
- Reduction is less common in phase 1 metabolism than oxidation
- warfarin is inactivated by reduction of a ketone to a hydroxyl group by CYP2A6.

Phase I Reaction

3. Hydrolytic Reactions (Hydrolysis)

- Addition of water with breakdown of molecule.

  Esters ---> alcohol and acid



- For example aspirin to salicylic acid

Phase 2 Reactions

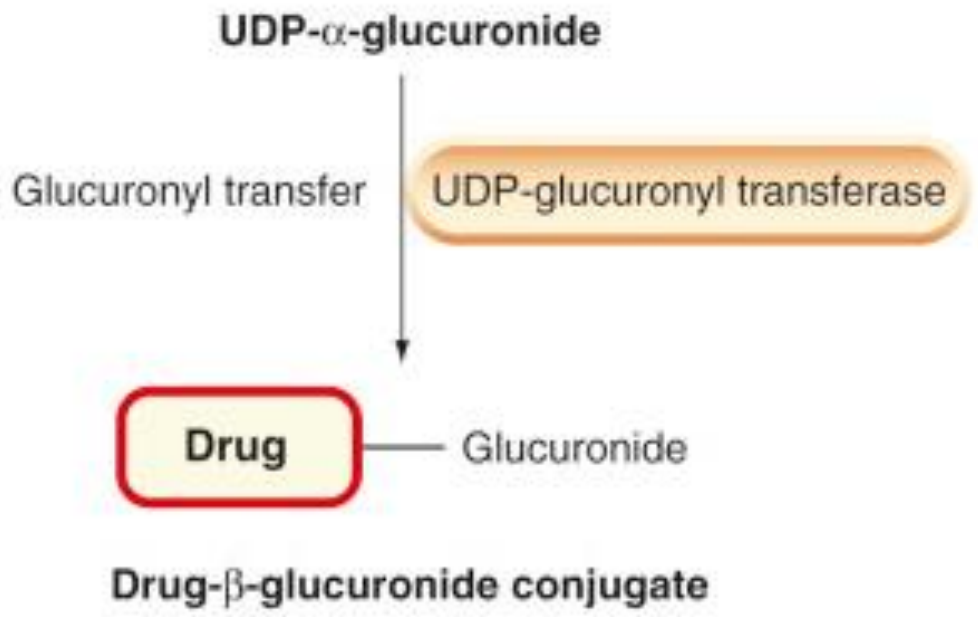
- Phase 2 reactions are synthetic (‘anabolic’) and involve conjugation (i.e. attachment of a substituent group), which usually results in inactive products, although there are exceptions
  - e.g. the active sulphate metabolite of minoxidil, a potassium channel activator used to treat severe hypertension 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.

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.



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

- **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.

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

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).*

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.

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.

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.