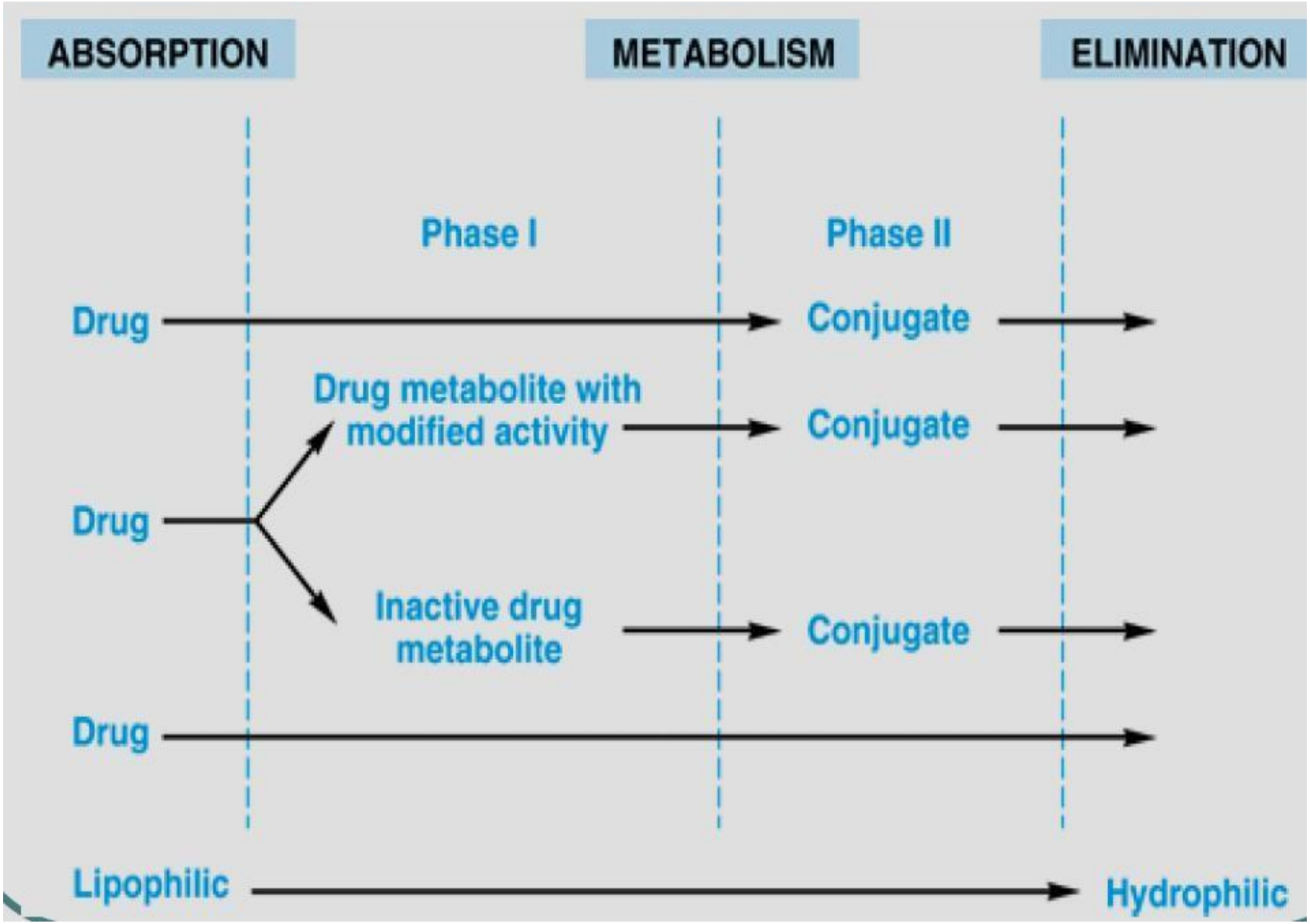
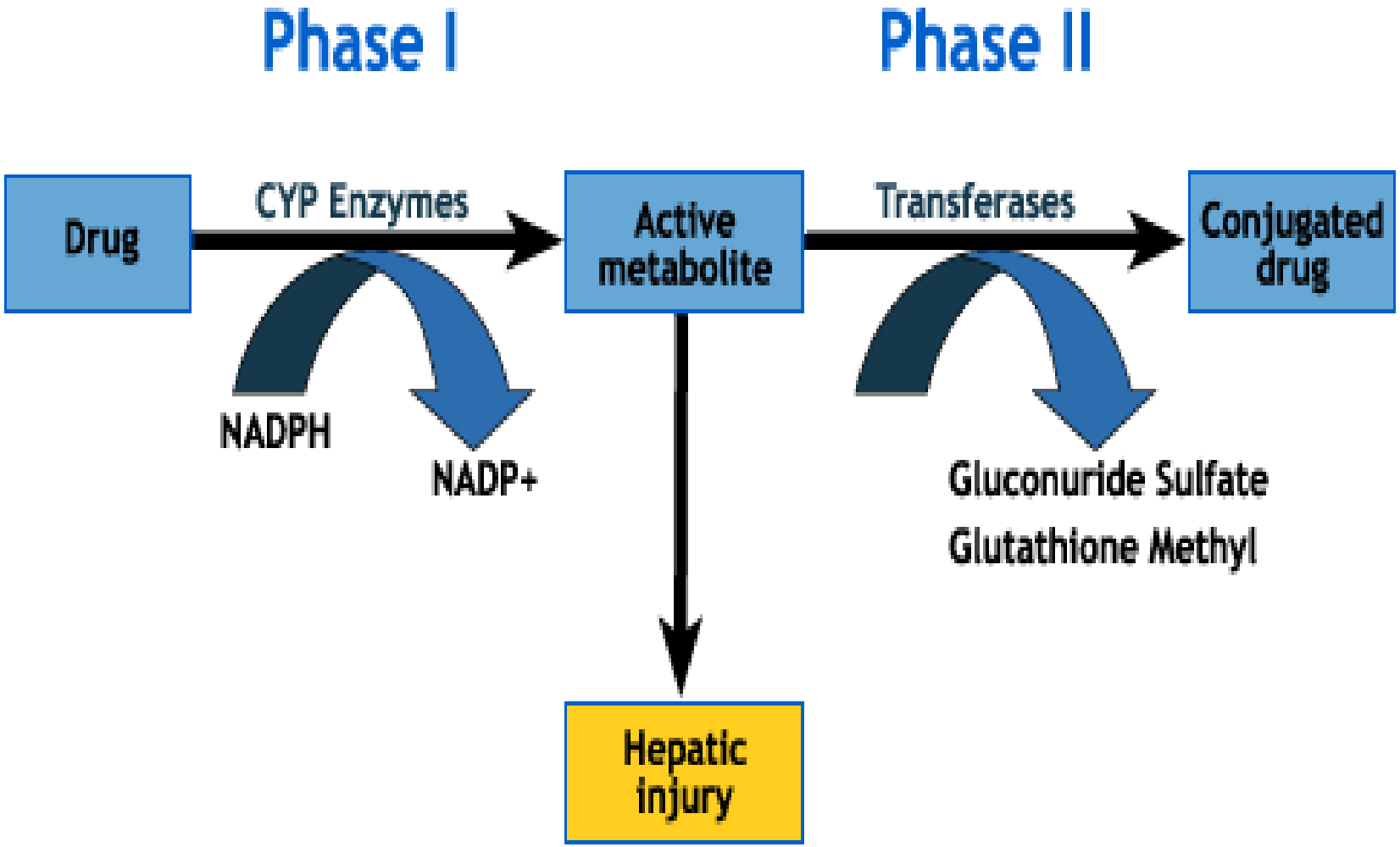
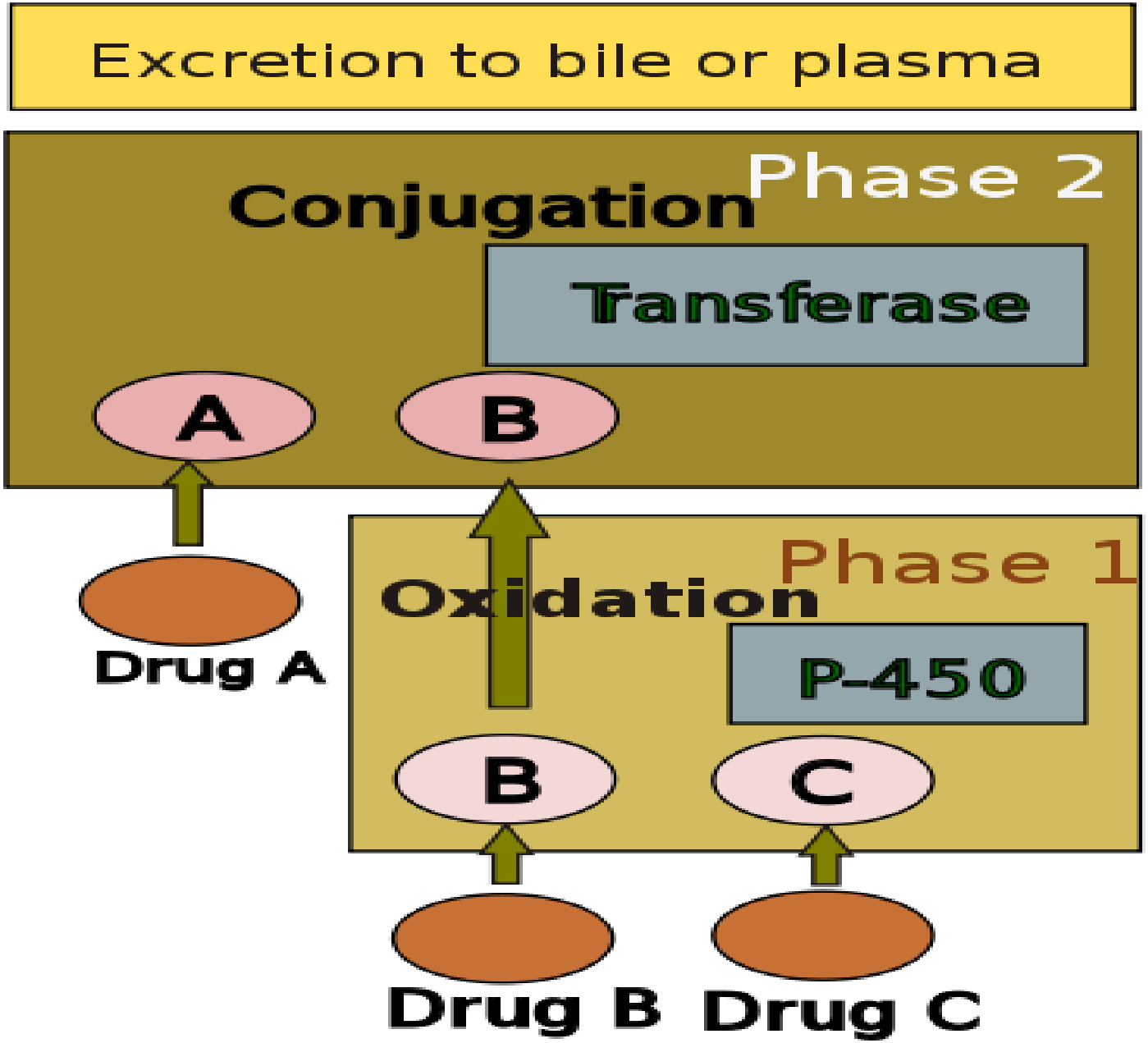

ABSORPTION
METABOLISM
ELIMINATION
Phase I
Phase II
Drug
Conjugate
Drug metabolite with modified activity
Conjugate
Drug
Inactive drug metabolite
Conjugate
Drug
Lipophilic
Hydrophilic

Phases of metabolism:




Excretion to bile or plasma
Phase 2
Conjugation
Transferase
A
B
Phase 1
Oxidation
P-450
B
C
Drug A
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 reactions:

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.

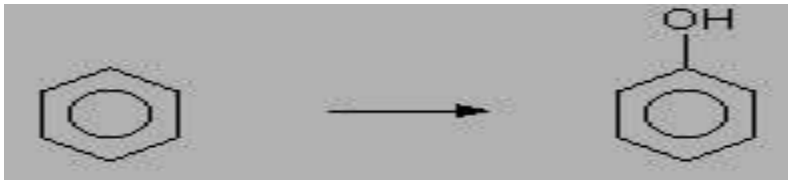
Common reactions include :-

- **Alkyl group ----> alcohol**



- **Aromatic ring ----> phenol**

Phases of metabolism (Cont.):



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)

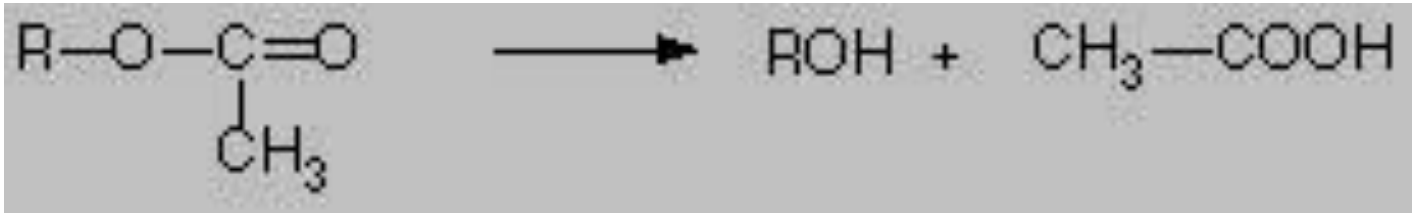
for example nitrazepam

Phases of metabolism (Cont.):

3.Hydrolysis

Addition of water with breakdown of molecule.

Esters ---> alcohol and acid



- for example aspirin to salicylic acid

Phase II

1.Conjugation

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 (Cont.):

- **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 (NH2CH2COOH) for example nicotinic acid

- **Sulfate**

Sulfate (-SO4) for example morphine, paracetamol

Drug metabolism (Cont.):

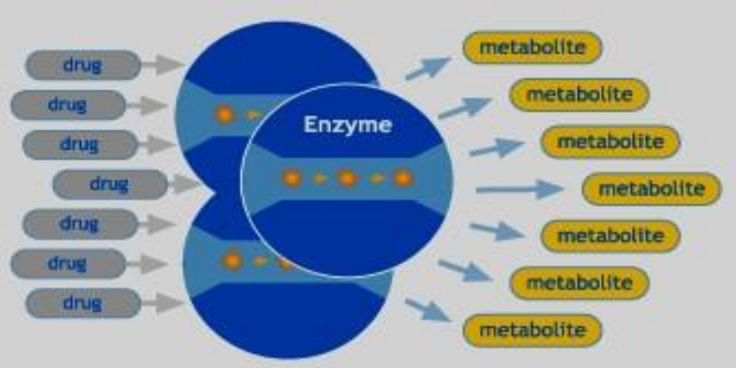
- In most cases the metabolites are inactive, however, occasionally the metabolite is also active, even to the extent that the metabolite may be the preferred compound to be administered. The original drug may take on the role of a pro-drug. For example:-

  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.

Drug metabolism (Cont.):



I. Induction

Induction ~ ↑ metabolic activity of enzyme = ↓ [drug]

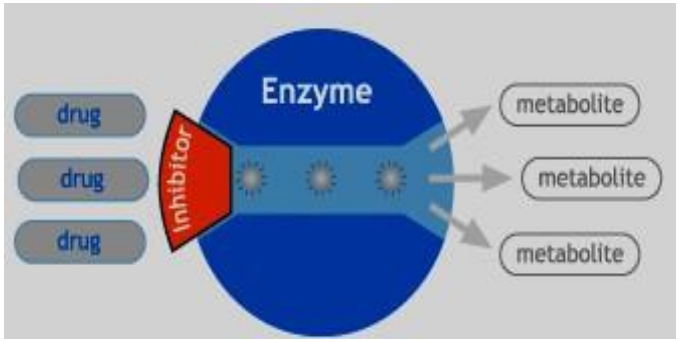
E.g. Phenobarbitone will induce the metabolism of itself, phenytoin, warfarin, etc.

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.

Drug metabolism (Cont.):



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.

Drug metabolism (Cont.):

Factors that can influence drug 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. **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 the their action. The opposite is also true (enzyme inhibition).

Drug metabolism (Cont.):

4. **Food:** Grapefruit juice contains furanocoumarins which inhibit drug metabolism by interfering with hepatic cytochrome P450.

5. Genetic variation (polymorphism):

With Nacetyltransferases (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

Drug metabolism (Cont.):

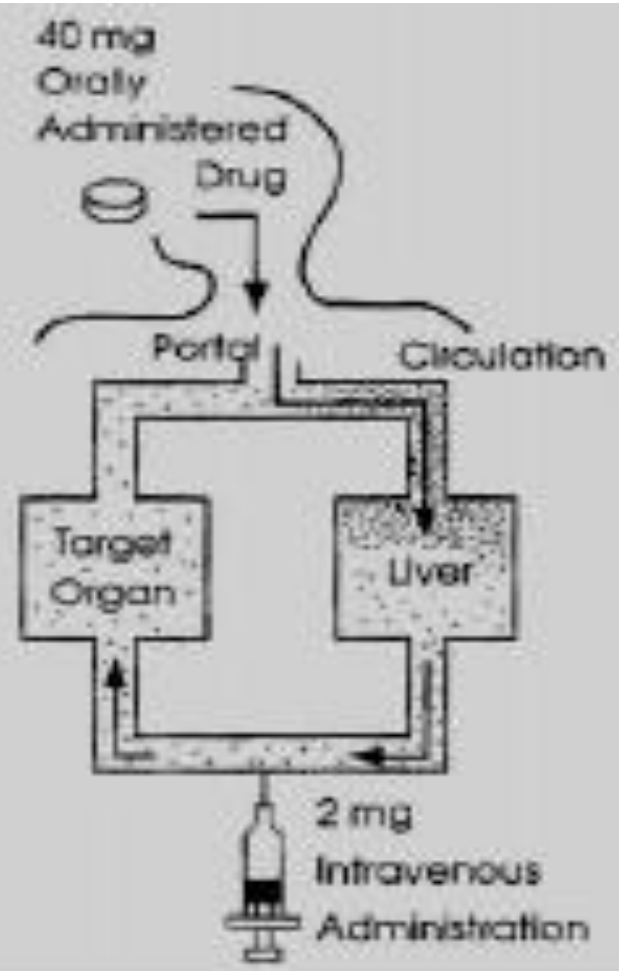
6. **Physiological factors** that can influence drug metabolism include age,individual variation (e.g., pharmacogenetics), enterohepatic circulation,

nutrition, intestinal flora, or sex differences.

7. **Pathological factors** can also influence drug metabolism, including liver, kidney, or heart diseases.

Drug metabolism (Cont.):

Enterohepatic circulation:



Because of hepatic metabolism, a portion of an orally administered drug dose is inactivated by the liver before reaching the systemic circulation (and ∴ the target organ) → need to adjust dosage

Diseases and Drug Metabolism:

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.

Cardiac Disease:

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

Excretion

The irreversible loss of drug from the body

- primarily via kidney and bile (feces, sweat, saliva, tears, expired air & breast milk to lesser degrees)

NOTE: **Excretion ≠ Elimination**

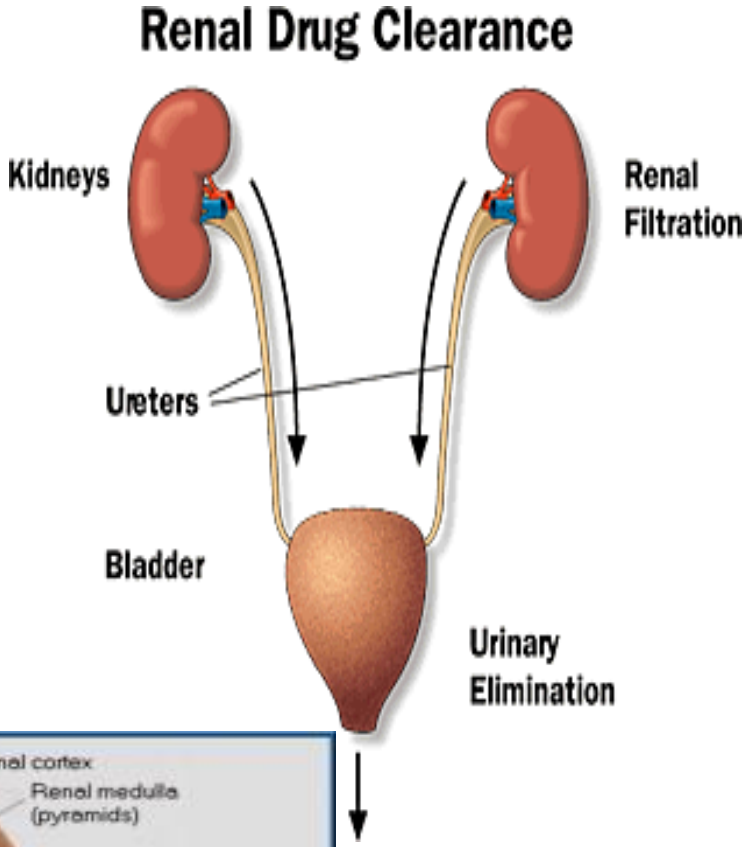
Excretion:	irreversible loss of drug from body
Elimination:	irreversible loss of parent drug by metabolism and/or excretion

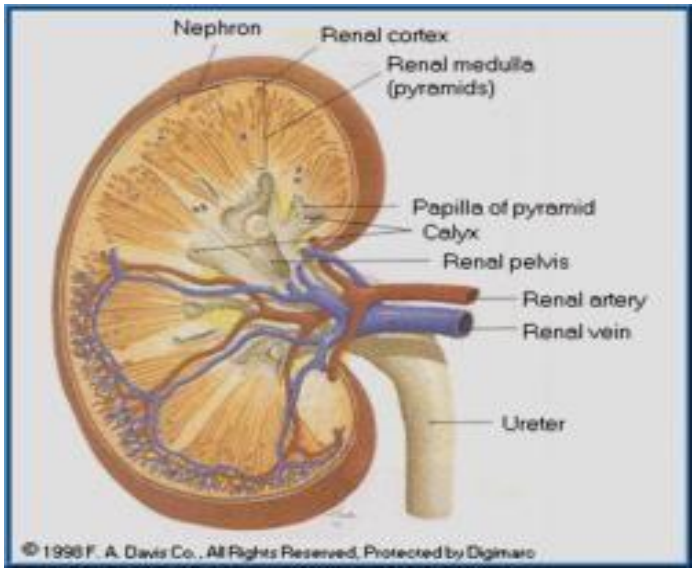
∴ **Elimination = *Metabolism &/or Excretion***

Drug excretion:

1. Renal excretion:

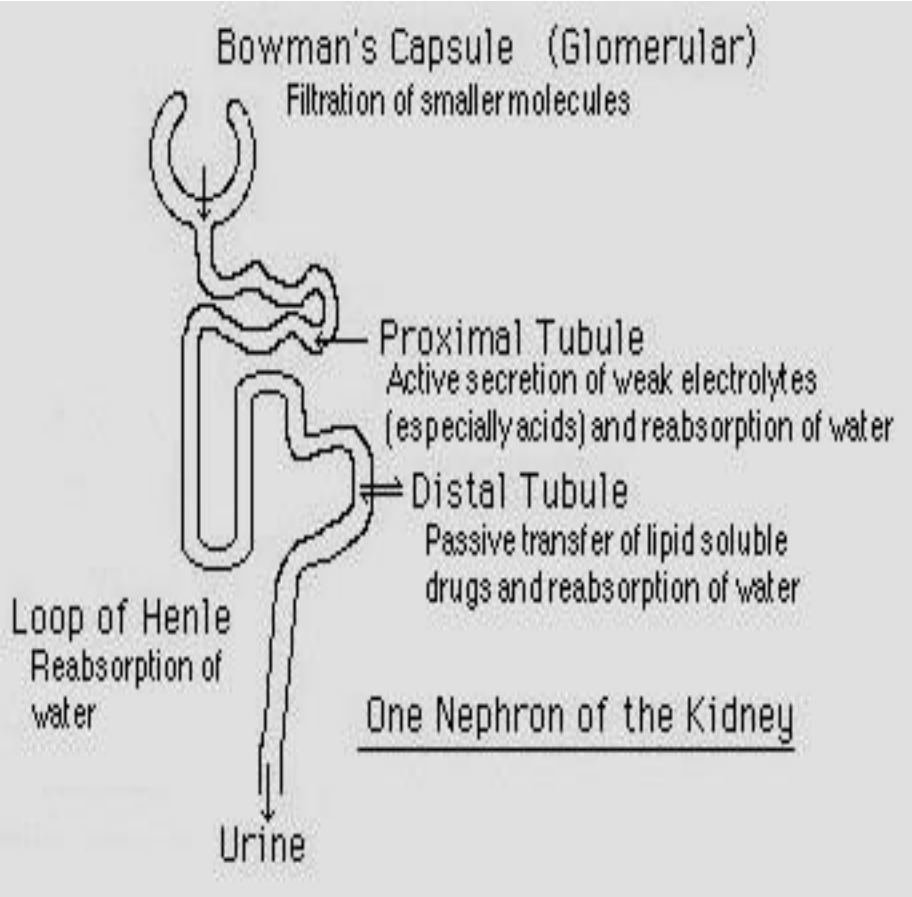
-The major organ for the excretion of drugs is the KIDNEY. The functional unit of the kidney is the nephron in which there are three major processes to consider:-





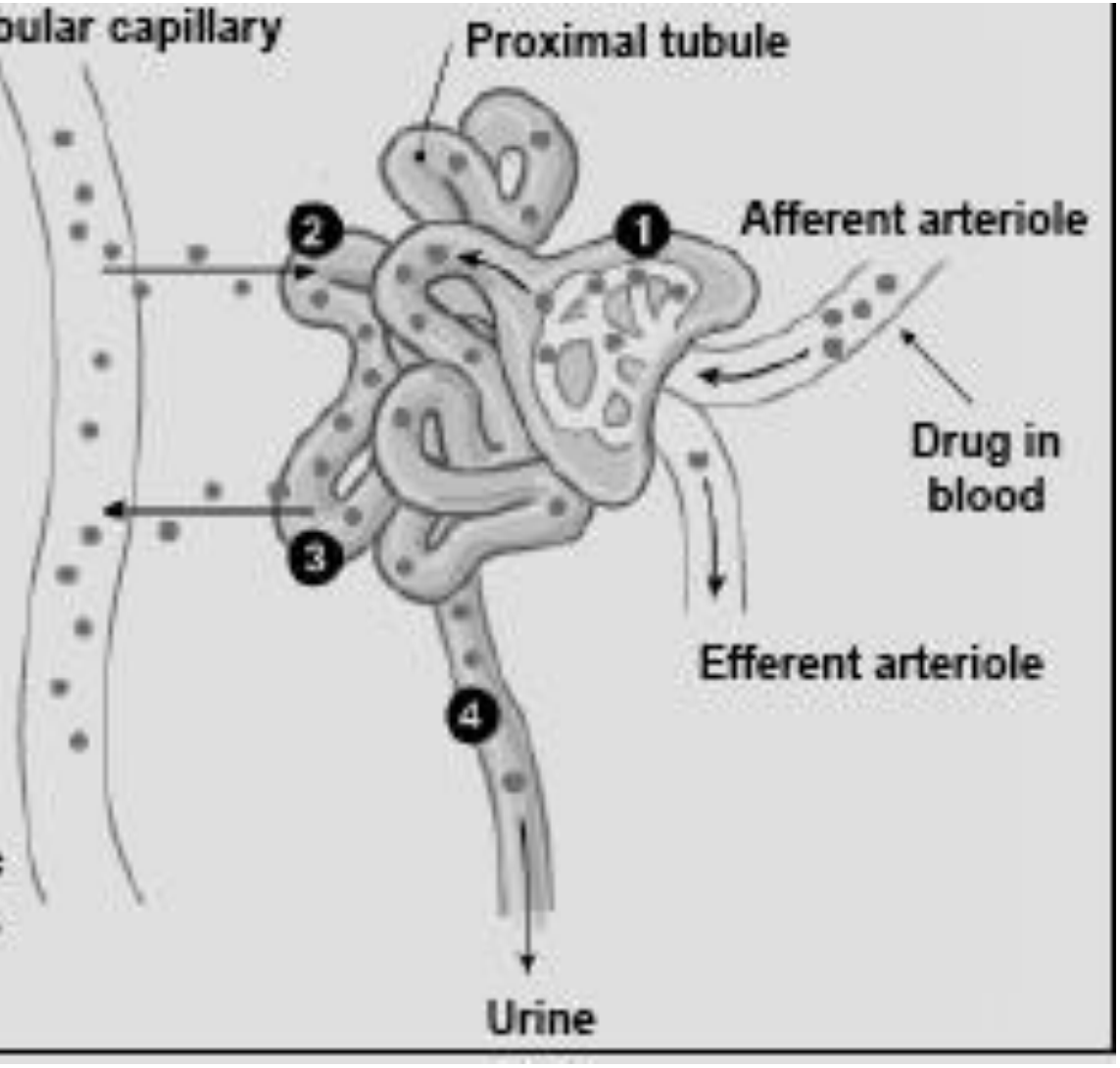
Drug excretion (Cont.):

1) Passive glomerular filtration
2) Active tubular secretion
3) Passive tubular re-absorption



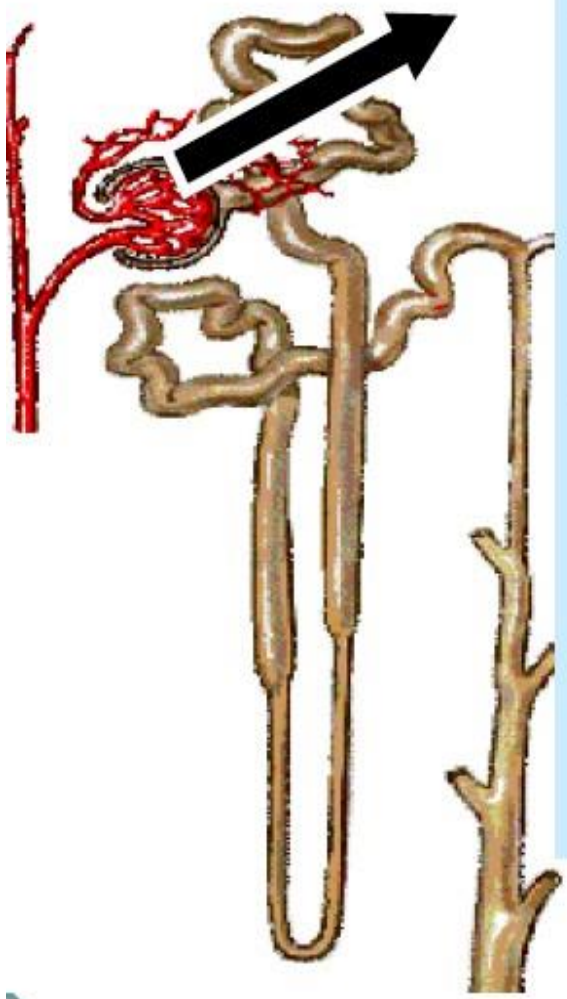
Renal excretion:

1. Passive Glomerular Filtration: free drug <20kDa
2. Active Tubular Secretion: separate transport systems for weak acids and bases
3. Passive Tubular Reabsorption: conc. gradient drives diffusion of uncharged drug back into systemic circulation – urine pH is key



Drug excretion (Cont.):

1) Glomerular filtration



- In the glomerulus all molecules (including drugs) of low molecular weight (less than 2000) are readily filtered out of the blood unless they are tightly bound to plasma protein (albumin).
- This filtration rate is often measured by determining the renal clearance of inulin. Inulin is readily filtered in the glomerular, and is not subject to tubular secretion or re-absorption. Thus inulin clearance is equal to the glomerular filtration rate.

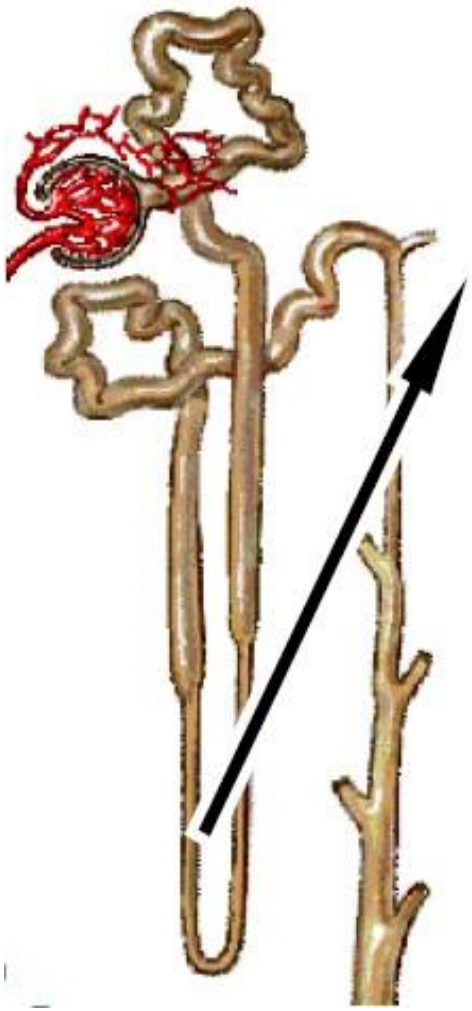
Drug excretion (Cont.):

2)Tubular secretion



- Only less than 20% of renal plasma flow is filtered through the glomerulus, leaving at least 80% to pass on to the peritubular capillaries of the proximal tubule.
- There, drug molecules are transferred to the tubular lumen by two non-selective carriers (one transports acidic drugs, while the other handles organic bases.
- This is active transport and therefore:
- It can secrete all of the drug (even if it is bound to plasma protein) making it the most effective mechanism of renal elimination .
- **Penicillin**, for example being 80% protein-bound is cleared only slowly by filtration, but almost completely removed by proximal tubular secretion
- Competitive inhibition of the secretion of one compound by another may occur (inhibition of penicillin excretion by probenecid).

Drug excretion (Cont.):



- In the loop of Henle, 99% of the filtered water is re-absorbed.
- All solutes (including drugs) in the lumen are therefore significantly concentrated.
- When the drugs reach the distal tubule, their high luminal concentration favours their re-absorption

Drug excretion (Cont.):

3)Tubular re-absorption



- In the distal tubule there is passive excretion and re-absorption of lipid soluble drugs. Filtered lipophilic drugs are extensively reabsorbed. Thus if a drug is non-ionized or in the unionized form it maybe readily reabsorbed.
- Many drugs are either weak bases or acids and therefore the pH of the filtrate can greatly influence the extent of tubular re-absorption for many drugs.
  - When urine is acidic weak acid drugs tend to be reabsorbed.
  - Alternatively when urine is more alkaline, weak bases are more extensively reabsorbed.

(continued)

3)Tubular re-absorption



Urine pH varies from 4.5 to 8.0 depending on the diet (e.g. meat can cause a more acidic urine) or drugs (which can increase or decrease urine pH).

In drug overdose it is possible to increase the excretion of some drugs by suitable adjustment of urine pH.

In overdoses with weak acids (pentobarbital, aspirin) injecting sodium bicarbonate increases drug excretion.

In overdoses with weak bases (codeine, amphetamine) ammonium chloride lowers pH and increases ionization of bases

Drug excretion (Cont.):

Renal clearance:

- One method of quantitatively describing the renal excretion of drugs is by means of the renal clearance value for the drug.
- Renal clearance can be used to investigate the mechanism of drug excretion:

A- If the drug is filtered but not secreted or reabsorbed the renal clearance will be about 120 ml/min in normal subjects.

B- If the renal clearance is less than 120 ml/min then we can assume that at least two processes are in operation, glomerular filtration and tubular re-absorption.

C- If the renal clearance is greater than 120 ml/min then tubular secretion must be contributing to the elimination process.

Drug excretion (Cont.):

Renal clearance is then:-

$$CL_{renal} = \frac{\text{filtration rate} + \text{secretion rate} - \text{reabsorption rate}}{Cp}$$

$$\text{Renal Clearance} = \frac{\text{Rate of Excretion}}{\text{Plasma Concentration}}$$

Factors Altering Renal Drug Clearance:

Renal drug clearance is lower [therefore you must reduce dose] in:

- Elderly and Newborn
- Women (20%) than men
- Kidney and Heart Disease
- Patients taking drugs which block secretion (aspirin,probenecid)

Drug excretion (Cont.):

Hemodialysis:

- Hemodialysis or `artificial kidney' therapy is used in renal failure to remove toxic waste material normally removed by the kidneys.

- In the procedure blood is diverted externally and allowed to flow across a semi-permeable membrane that is bathed with an aqueous isotonic solution. Nitrogenous waste products and some drugs will diffuse from the blood, thus these compounds will be eliminated.

- This technique is particularly important with drugs which:-

1) have good water solubility;
2) are not tightly bound to plasma protein;
3) are smaller molecular weight; and
4) have a small apparent volume of distribution.

- Drugs which are tightly bound or extensively stored or distributed into tissues are poorly removed by this process.

Haemodialysis

