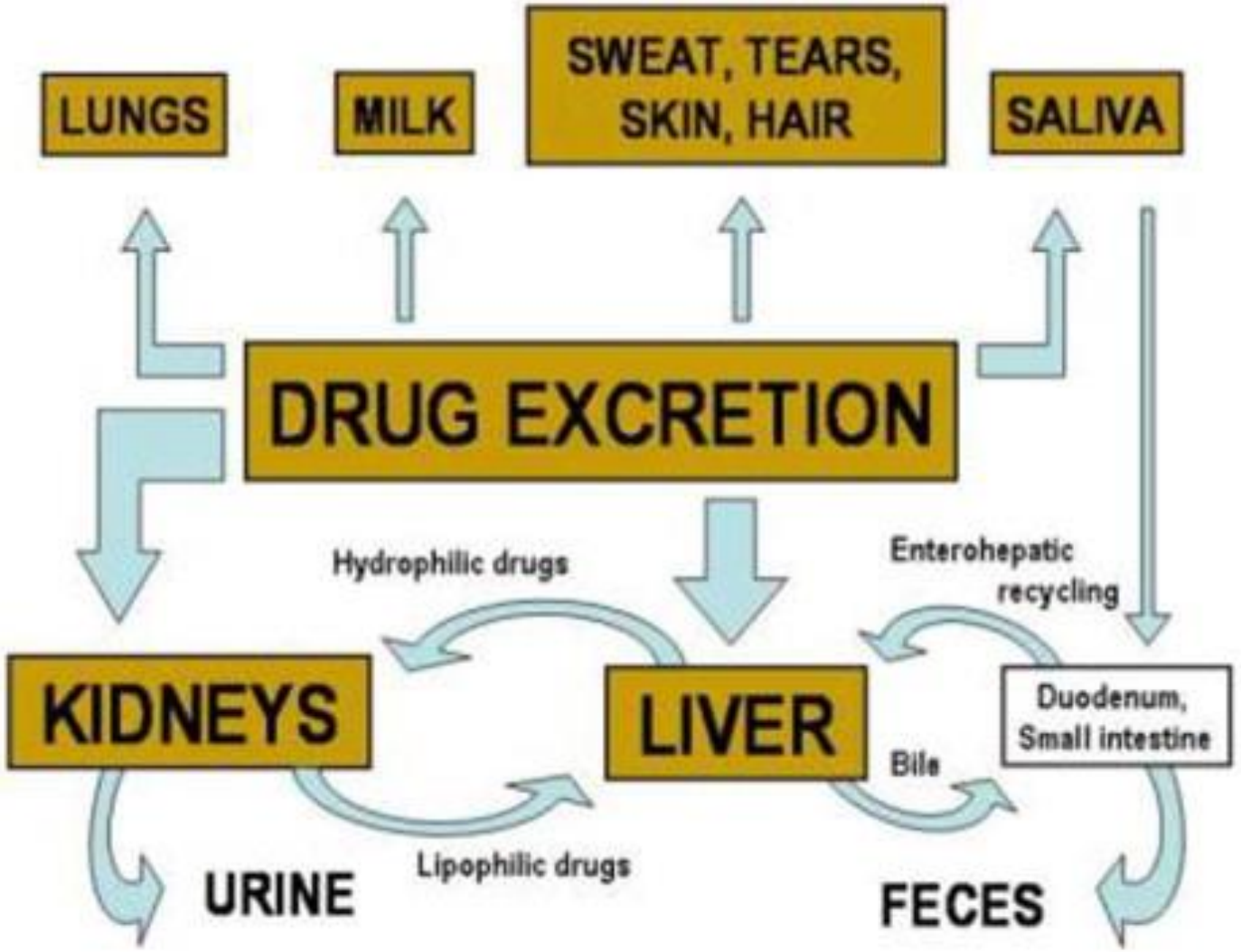
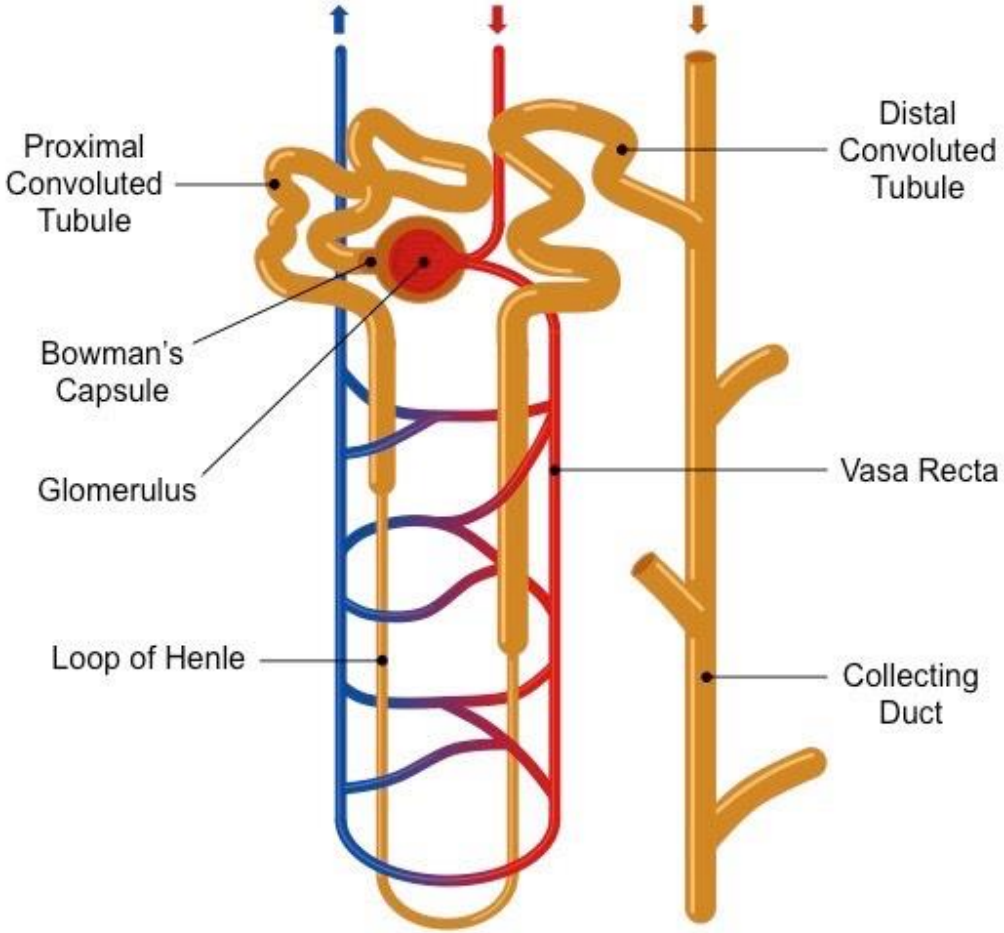
Excretion of Drugs





Introduction

- Drug elimination is the irreversible loss of drug from the body.
- It occurs by two processes: *metabolism* and *excretion* .
- Metabolism consists of anabolism and catabolism, that is, respectively, the build-up and breakdown of substances by enzymic conversion of one chemical entity to another within the body, whereas excretion consists of elimination from the body of drug or drug metabolites.
- The main excretory routes are:

➢The kidneys

➢The hepatobiliary system

➢The lungs (important for volatile/gaseous anaesthetics)

Introduction

- Most drugs leave the body in the urine, either unchanged or as polar metabolites.
- Some drugs are secreted into bile via the liver, but most of these are then reabsorbed from the intestine.
- There are, however, instances (e.g. **rifampicin**) where faecal loss accounts for the elimination of a substantial fraction of unchanged drug in healthy individuals, and faecal elimination of drugs such as **digoxin** that are normally excreted in urine becomes progressively more important in patients with advancing renal impairment.
- Excretion via the lungs occurs only with highly volatile or gaseous agents (e.g. general anaesthetics).

Introduction

- Small amounts of some drugs are also excreted in secretions such as milk or sweat.
- Elimination by these routes is quantitatively negligible compared with renal excretion, although excretion into milk can sometimes be important because of effects on the baby Lipophilic substances are not eliminated efficiently by the kidney.
- Consequently, most lipophilic drugs are metabolised to more polar products, which are then excreted in urine

Drug Excretion

- *Drug excretion* is the removal of the intact drug.
- Nonvolatile drugs are excreted mainly by renal excretion, a process in which the drug passes through the kidney to the bladder and ultimately into the urine.
- Other pathways for drug excretion may include the excretion of drug into bile, sweat, saliva, milk (via lactation), or other body fluids.
- Volatile drugs, such as gaseous anesthetics or drugs with high volatility, are excreted via the lungs into expired air

Drug Excretion

- Elimination of drugs by the kidneys is best quantified by the renal clearance ($CL_{ren,}$).
- This is defined as the volume of plasma containing the amount of substance that is removed from the body by the kidneys in unit time.
- It is calculated from the plasma concentration, C_p , the urinary concentration, C_u , and the rate of flow of urine, V_u , by the equation:

$CL_{ren}=(Cu \times Vu)/C_p$.

CL_{ren} varies greatly for different drugs, from less than 1 mL/min to the theoretical maximum set by the renal plasma flow, which is approximately 700 mL/min, measured by p -aminohippuric acid (PAH) clearance (renal extraction of PAH approaches 100%).

Drug Excretion

- Drugs differ greatly in the rate at which they are excreted by the kidney, ranging from penicillin, which is (like PAH) cleared from the blood almost completely on a single transit through the kidney, to amiodarone and risedronate, which are cleared extremely slowly.
- Most drugs fall between these extremes.

Drug Excretion

Renal clearance:

- One method of quantitatively describing the renal excretion of drugs is by means of the renal clearance value for the drug.
- So 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.

Factors Altering Renal Drug Clearance

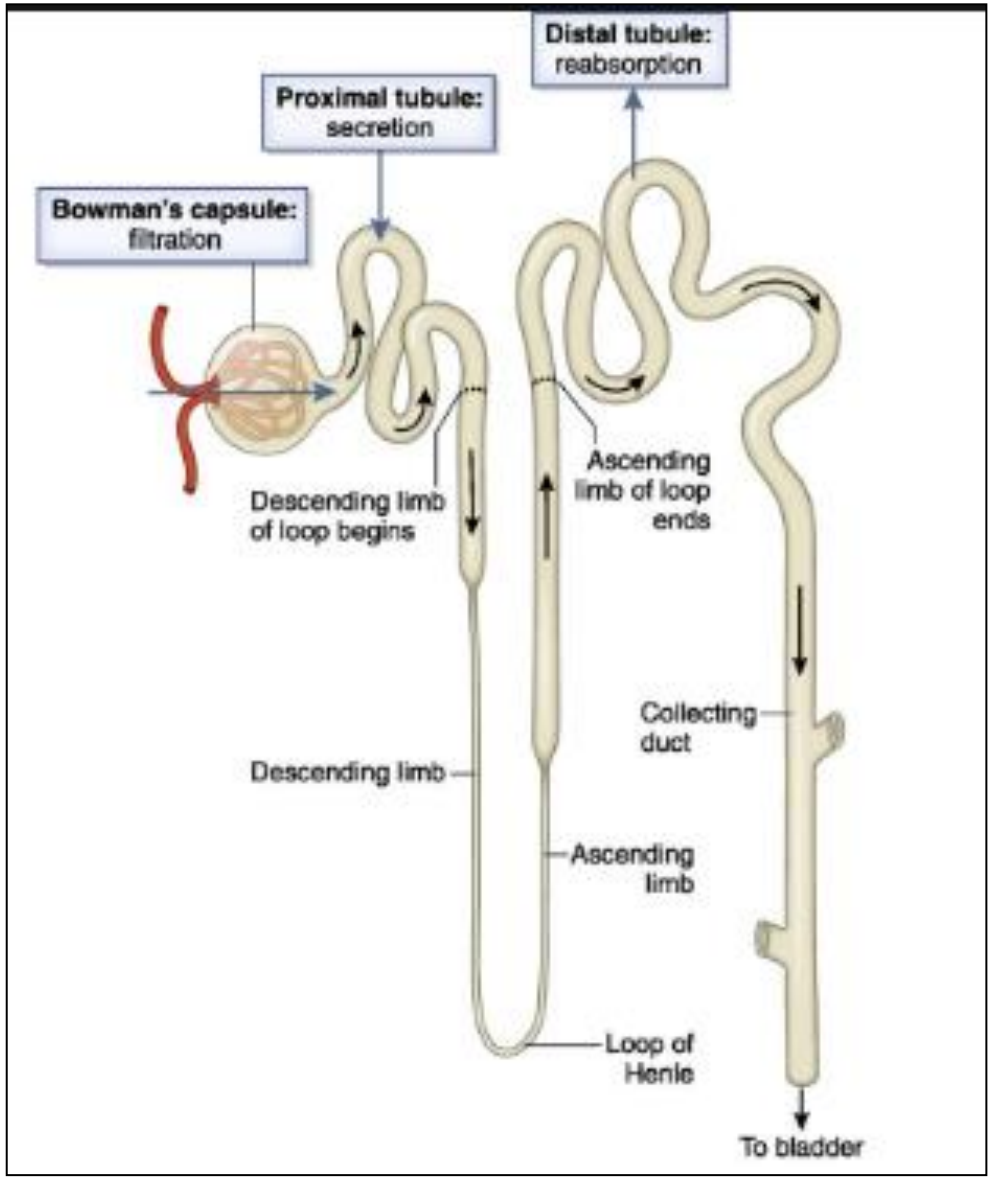
Renal drug clearance is lower [therefore you must reduce dose] in:

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

Drug Excretion

- 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 fundamental processes account for renal drug excretion:

1. Glomerular filtration
2. Active tubular secretion
3. Passive tubular reabsorption (diffusion from the concentrated tubular fluid back across tubular epithelium).



Drug Excretion

1) **Passive glomerular filtration**:

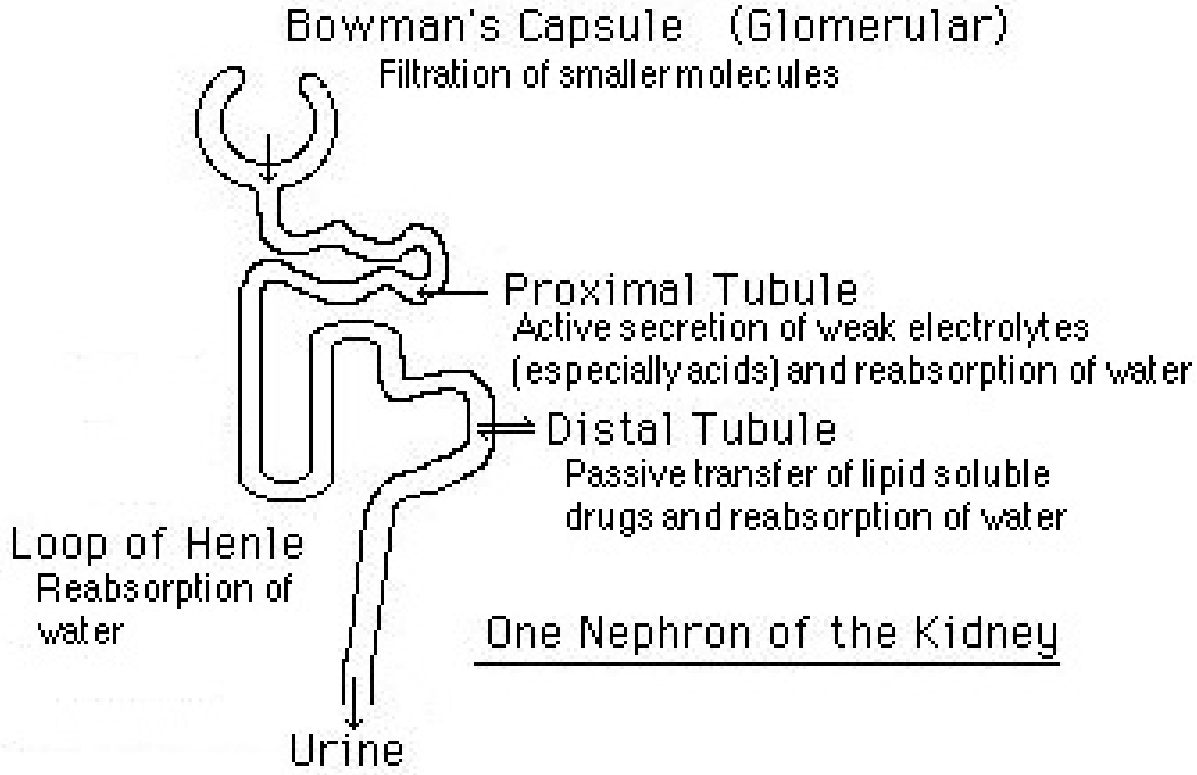
free dug < 20kDa

2) Active tubular secretion:

separate transport systems for weak acids and bases

3) Passive tubular re-absorption:

Conc. gradient drives diffusion of unchanged drug back into systemic circulation- urine pH is the key



Drug Excretion

1. Glomerular filtration

- In the glomerulus all drug molecules of low molecular weight (less than 20 kDa to pass into the glomerular filtrate (are readily filtered out of the blood unless they are tightly bound to plasma proteins (albumin 68 kDa)).
- If a drug binds to plasma albumin, only free drug is filtered. If, like warfarin, a drug is approximately 98% bound to albumin, the concentration in the filtrate is only 2% of that in plasma, and clearance by filtration is correspondingly reduced.

- The filtration rate is often measured by determining the renal clearance of creatinine.
- Creatinine is readily filtered in the glomerular and is not subject to tubular secretion or reabsorption. So its clearance is equal to the glomerular filtration rate

Drug Excretion

2. Tubular secretion

- Only less than 20% of renal plasma flow is filtered through the glomerulus, leaving at least 80% to pass to the peritubular capillaries of the proximal tubule.
- Two non-selective carriers (OAT and OCT) are responsible for transferring the drug to the tubular lumen (one for acidic and one for basic drugs; respectively)
- The process is active and so:
- It can transport all of the drug (even if it is bound to plasma protein) making it the most effective renal elimination mechanism.
- Penicillin, 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 excretion of penicillin by probenecid)

Drug Excretion

- In the loop of Henle, 99% of the filtered water is reabsorbed.
- All solutes (including drugs) in the lumen are therefore significantly concentrated.
- When the drugs reach the distal tubules their high luminal concentration favors their reabsorption

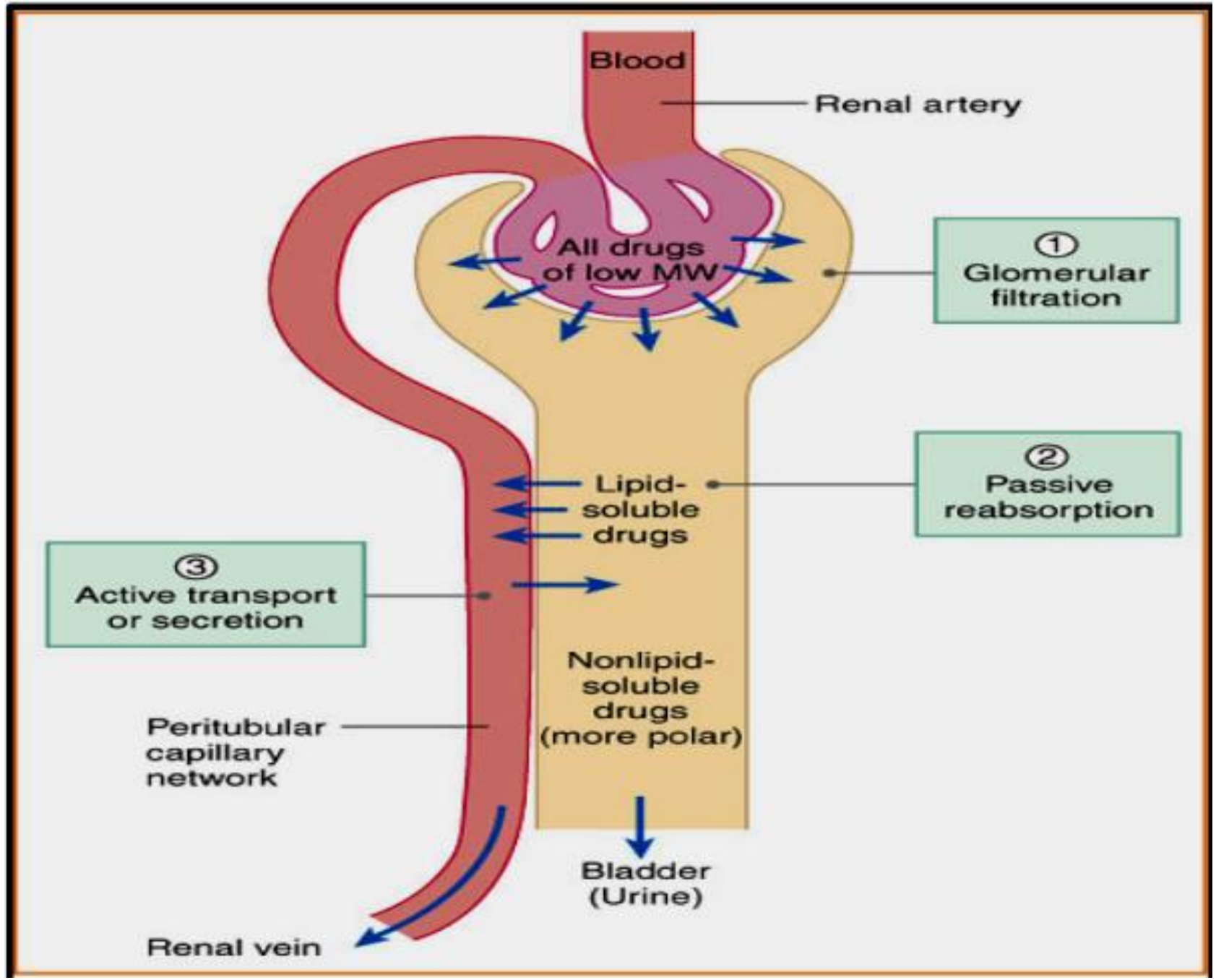
3. Tubular reabsorption

In the distal tubules there is passive excretion and reabsorption of lipid soluble drugs. Filtered lipophilic drugs are extensively reabsorbed. Thus, if the drug is non-ionized or in its unionized form it maybe readily absorbed.

Drug Excretion

- **Tubular reabsorption**
- Many drugs are either weak acids or bases and therefore the pH of the filtrate can greatly influence the extent of tubular reabsorption of 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

- Urine pH varies from 4.5 to 8.0 depending on the diet (e.g. meat can cause more acidic urine) or drugs (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
- Weak acid overdose (Aspirin or phenobarbital), we can increase renal excretion by injection of sodium bicarbonate
- While in weak bases overdose (codeine and amphetamine), ammonium chloride will lower the urine pH and increase the ionization of the bases


Blood
Renal artery
All drugs of low MW
① Glomerular filtration
② Passive reabsorption
Lipid-soluble drugs
③ Active transport or secretion
Nonlipid-soluble drugs (more polar)
Peritubular capillary network
Bladder (Urine)
Renal vein

Main Highlights

- Most drugs, unless highly bound to plasma protein, cross the glomerular filter freely.
- Many drugs, especially weak acids and weak bases, are actively secreted into the renal tubule and rapidly excreted.
- Lipid-soluble drugs are passively reabsorbed along with water by diffusion across the tubular barrier, so are not efficiently excreted in the urine.
- Because of pH partition, weak acids are more rapidly excreted in alkaline urine, and vice versa.
- Several important drugs are removed predominantly by renal excretion, and are liable to cause toxicity in elderly persons and patients with renal disease.

Drug Excretion

Hemodialysis:

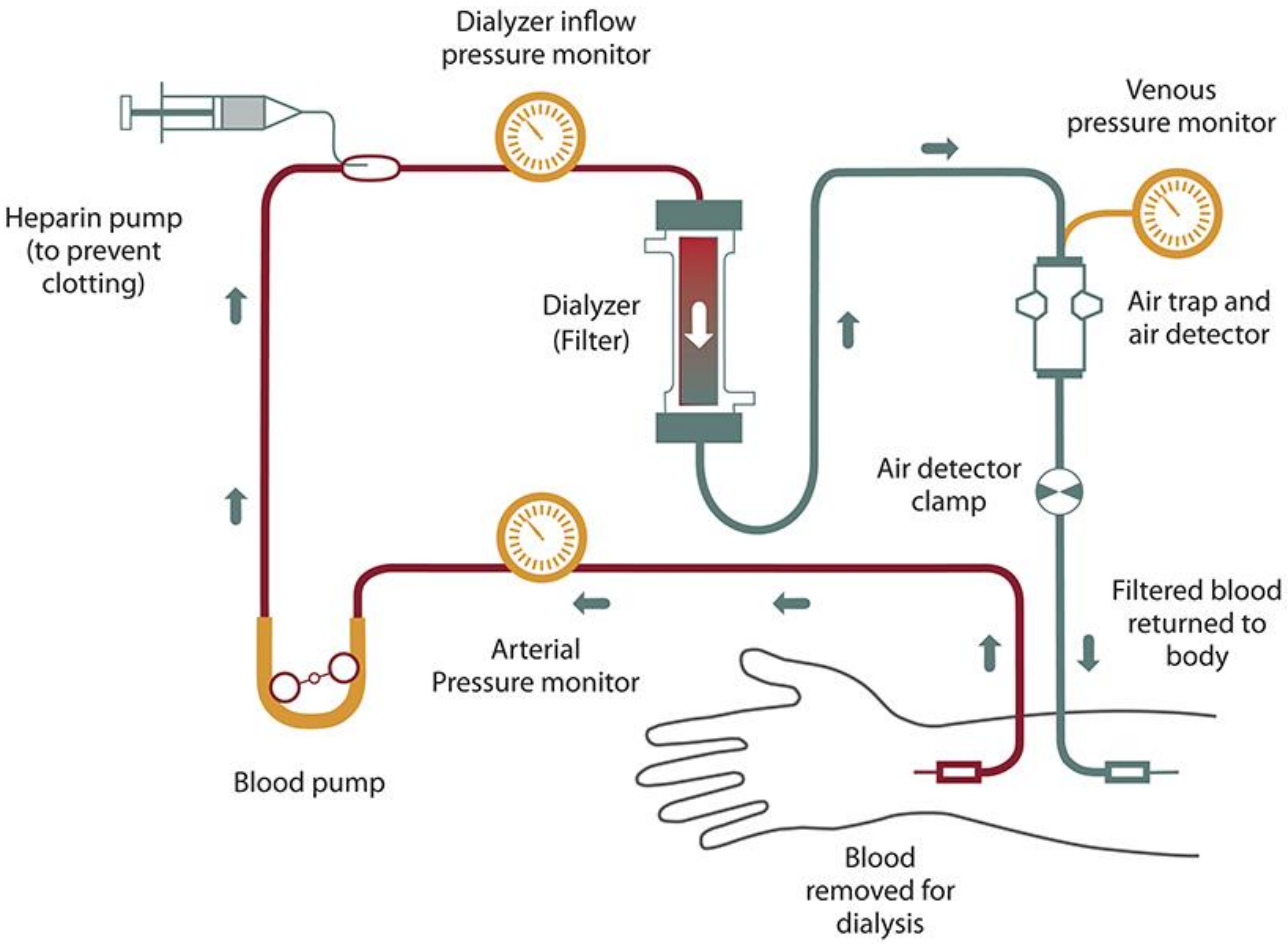
- Hemodialysis, also spelled haemodialysis, or simply dialysis or `artificial kidney' therapy is used in renal failure to remove toxic waste material from the blood which are normally removed by the kidneys.
- In the procedure blood is diverted externally and allowed to flow across a semi-permeable membrane 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.

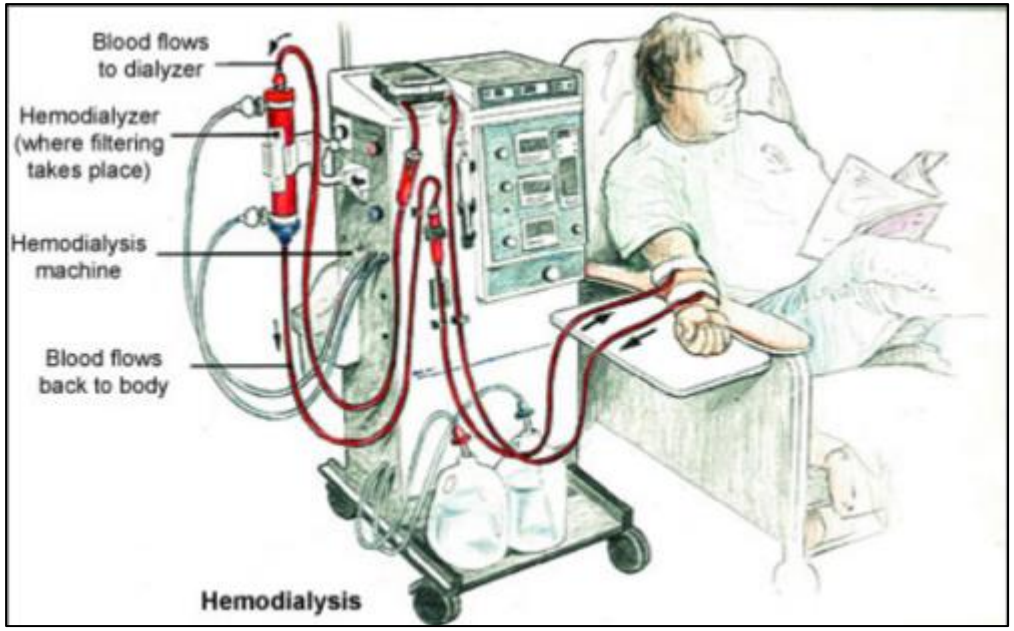
- **This technique is particularly important with drugs which:-**

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.**

Hemodialysis





Drug Excretion

2. Hepatobiliary excretion:

Fecal excretion: Elimination of toxicants in the feces occurs from two processes:

A- Excretion in bile:

- Some heavy metals are excreted into the bile, e.g., arsenic, lead, and mercury. However, the most likely substances to be excreted via the bile are comparatively large, ionized molecules, such as large molecular weight (greater than 300) conjugates e.g. morphine and chloramphenicol (as glucuronide).

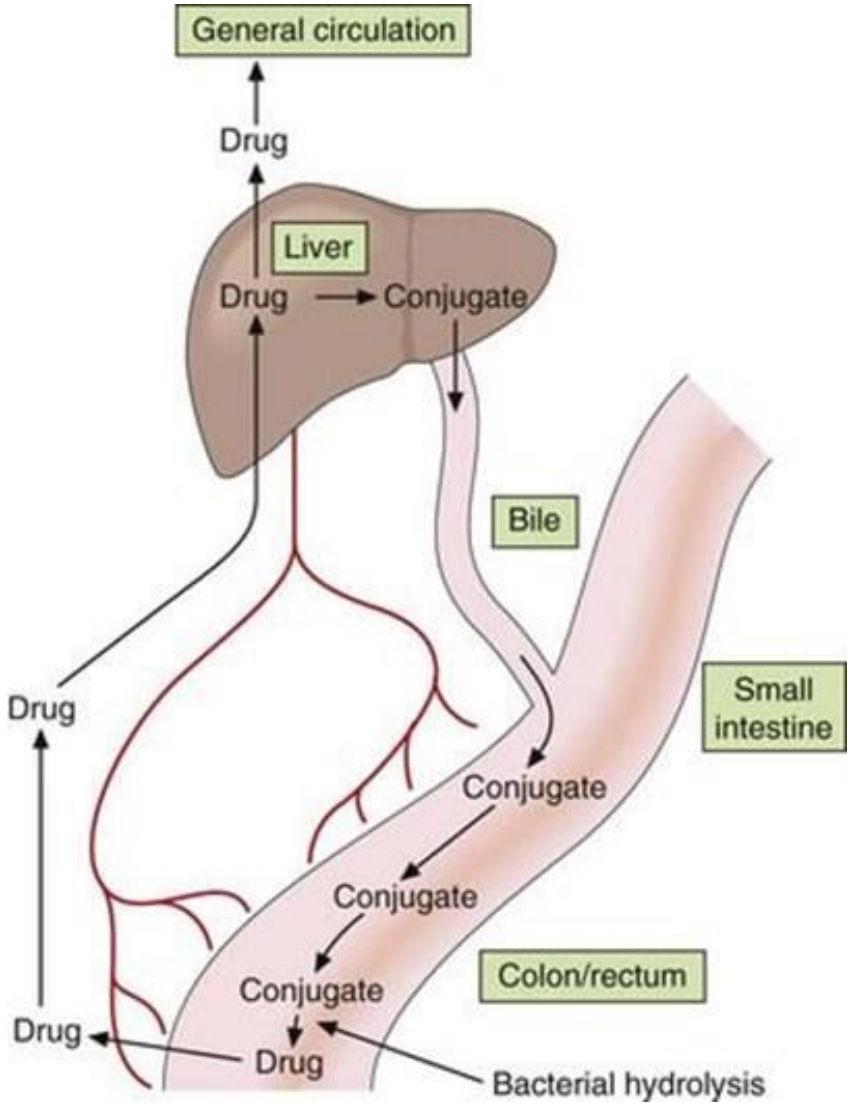
- The biliary secretion is active since bile/plasma concentrations maybe as high as 50/1. There can also be competition between compounds.

Drug Excretion

- Once a substance has been excreted by the liver into the bile, and subsequently into the intestinal tract, it can then be eliminated from the body in the feces, or it may be reabsorbed.

- Since most of the substances excreted in the bile are water-soluble, they are not likely to be reabsorbed as such. However, enzymes in the intestinal flora are capable of hydrolyzing some glucuronide and sulfate conjugates, which can release the less-polar compounds that may then be reabsorbed. This process is known as the **enterohepatic circulation.**

- The effect of this enterohepatic circulation is to prolong the life ($t_{1/2}$) of the drug in the body.



Enterohepatic circulation

Enterohepatic circulation

- Some drugs are extracted so efficiently by the liver or gut wall that the amount reaching the systemic circulation is considerably less than the amount absorbed.
- This is known as presystemic (or first-pass) metabolism and reduces bioavailability, even when a drug is well absorbed.
- Presystemic metabolism is important for many therapeutic drugs and is a problem because: A much larger dose of the drug is needed when it is taken by mouth than when it is given parenterally

Examples of drugs that undergo substantial pre-systemic (“first-pass”) elimination

- Aspirin
- Glyceryl trinitrate
- Isosorbide dinitrate
- Levodopa
- Lidocaine
- Metoprolol
- Morphine
- Propranolol
- Salbutamol
- Verapamil

Drug Excretion

• Another way that drugs can be eliminated via the feces is by:

B- Direct intestinal excretion:

- Orally administered drugs may be excreted in the feces if they are incompletely absorbed or not absorbed at all (e.g. Cholestyramine)
- Increasing the lipid content of the intestinal tract can enhance intestinal excretion of some lipophilic substances. For this reason, mineral oil is sometimes added to the diet to help eliminate toxic substances, which are known to be excreted directly into the intestinal tract.

Drug Excretion

Drugs may be excreted by passive diffusion from:

3. Pulmonary excretion:

- The lung is the major organ of excretion for gaseous and volatile substances. Most of the gaseous anesthetics are extensively eliminated in expired air. Some of the ingested ethanol is excreted by exhalation.

4. Salivary excretion:

- Drug excretion into saliva appears to be dependent on pH partition and protein binding.
- In some instances, salivary secretion is responsible for localized side effects.

➢For example, excretion of antibiotics may cause black hairy tongue,

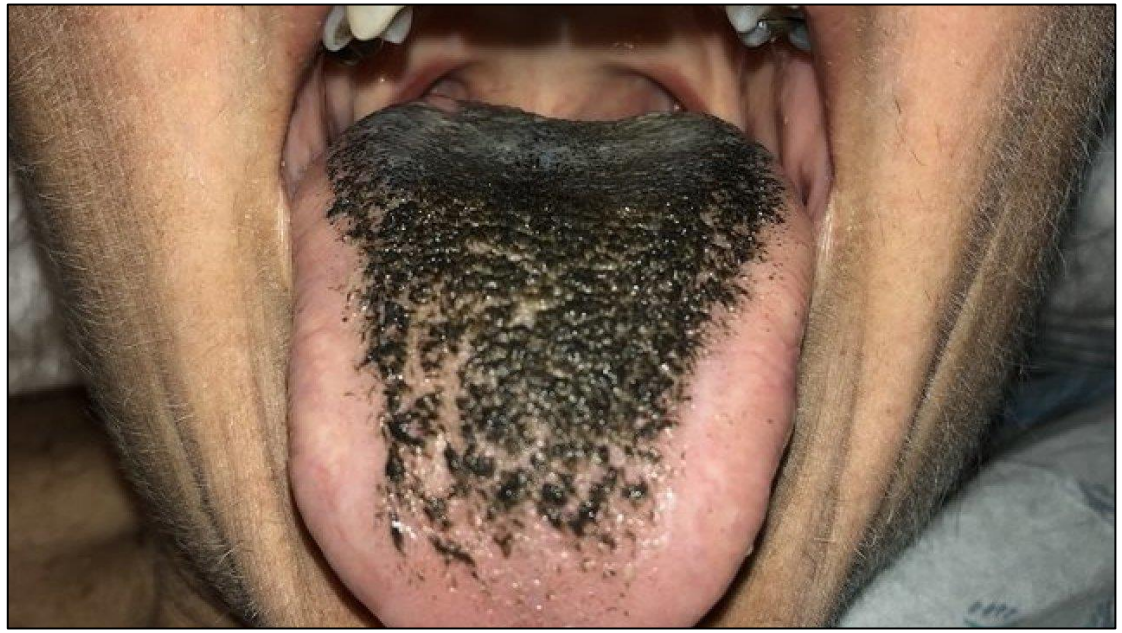
➢Gingival hyperplasia can be a side effect of phenytoin.

➢Superinfection from antibiotics.

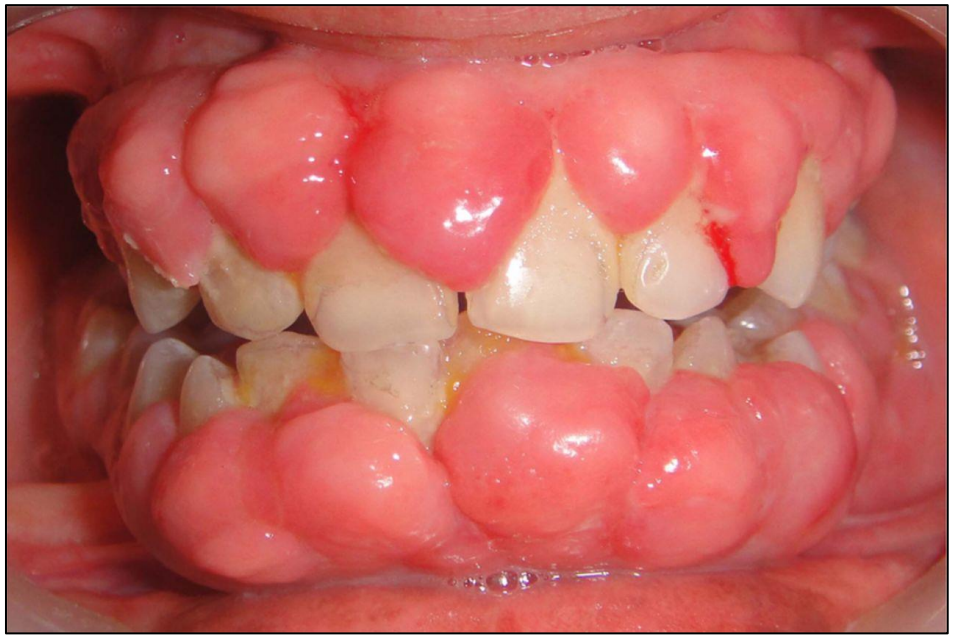
➢Dental mottling upon tetracycline ingestion.

Black hairy tongue is caused by excretion of antibiotic as:

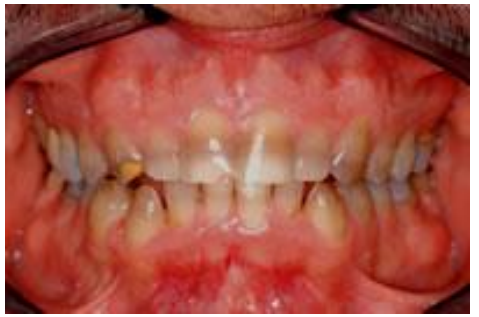
- Penicillin
- Erythromycin
- Doxycycline, and
- Neomycin



Gingival hyperplasia
which is caused as a side effect of Phenytoin



Dental mottling upon tetracycline ingestion



Drug Excretion

5. Skin excretion:

- Iodine, bromine, benzoic acid, salicylic acid, lead, arsenic, mercury , iron and alcohol are examples of compounds that excreted in sweat.
- Neonatal jaundice result from sulfonamide interaction with bilirubin.

6. Mammary excretion:

- Both basic substances and lipid-soluble compounds can be excreted into milk.
- Basic substances can be concentrated in milk since milk is more acidic (pH ~ 6.5) than blood plasma.
- Since milk contains 3-4% lipids, lipid-soluble drugs can diffuse along with fats from plasma into the mammary gland and thus can be present in mother's milk.
- Substances that are chemically similar to calcium can also be excreted into milk along with calcium.
- Ethanol and tetracycline enter the milk by diffusion through membrane pores (of mammary alveolar cells).
- Mothers smoking more than 20 to 30 cigarettes a day may induce nausea, vomiting, abdominal cramps and diarrhea in the infant.

Questions