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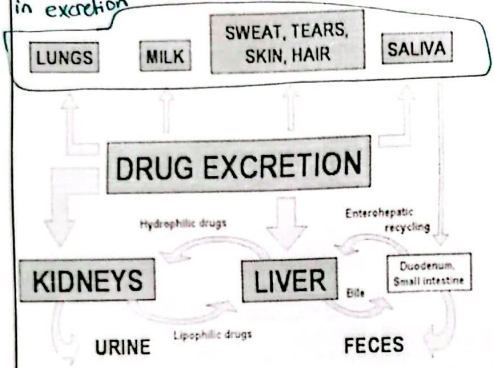
If the drug is lipophilic it will go to liver first for metabolism to convert it to Polar form then to Kidney

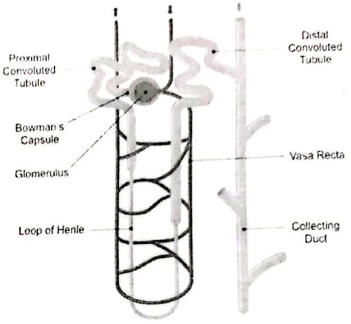
→ mainly occurs in Kidney

→ Process or irreversible Process that drug excreted outside the body via Urine

Excretion of Drugs

Other organs Contribute with Kidney in excretion





- Liver Can excret compounds in the Bile, then bile go to small intestine and in small intestine there is a conjugation, after that either go in feces or reabsorption then return to liver.
- Enterohepatic → when drug go with bile to small intestine [between liver and small intestine]

Introduction

- other [organs] contribute to excretion, maybe drug go with feces directly Without completely or Partially reabsorption. (reabsorption) Feces
- 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)

↓ or maybe excretion in Saliva, then after swallow it, it will go with feces

lungs important in excretion for volatile & gases

excretion in milk

• Digoxin يجي له excretion طالعة في الـ urine
لكن من بعاني من Renal imfairment سيصبح الـ excretion في الـ Feces

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

Renal excretion يلي ← most important في most common

• Lipophilic can be excreted in milk

لكن في الـ Kidney الـ lipophilic لا يجي excretion الـ بكفاءة

• الـ Lipophilic drugs يجي لهم reabsorption
و ما رح يرجعوا الـ plasma و رح يرجعوا الـ urine

الفرق بين Drug elimination و Drug excretion ؟ 8/2/2023

Elimination يعني يطلع خارج الجسم 6 بعمله Changing أو metabolite ويخرج خارج الجسم

Excretion هو removal of drug without changing يعني بدون ما يحدث له metabolism

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

note: Drug elimination refers to irreversible removal of drug from the body by all routes of elimination

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:

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

- لو صار Filtration و Secretion لل Drug مثل ما يحدث في Penicillin رح يزيد Cu ثم ↑CL_{ren}

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%).

- ال Drug رح يوصل من خلال afferent artery الى Glomerulus Part و Bowman's Capsule ورح يصير ال Filtration لل Drug وبعدها يحمل ال Drug 6 ويعتمد هنا أيضاً ع rate of urine flow
Cu Vu

Cu → Concentration of drug in urine

Vu → flow of urine

- أي شي بأثر ع هذه ال 3 variable (Cu, Vu, CP) سيؤثر ع CL_{ren}

لو زادت ال Dose يعني ↑Cu رح يأثر ع CL_{ren} لكن لو صار Reabsorption بالتالي ↓Cu وثم ↓CL_{ren}

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.

Extremes ← معظم الأدوية تتراوح بين هذه ال

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. Drug filtrated but without secretion or reabsorption

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. Drug filtrated & reabsorbed

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

• في عمليتين بصيرا معصيا اللي صار: Reabsorption و Secretion

يعني Afferent artery قال Filtration ما بصير لهم Drugs فضي بصير efferent artery عنا و بصير Secretion لا Drug من efferent artery ... فيه Reabsorption in distal tubule وبعدين CH وبزداد الموجودة Proximal tubule لا

To remember !

Reabsorption will ↓ CL_{ren}
Secretion will ↑ CL_{ren}

- Drug binding to Protein such as albumin that will affect filtration

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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 (Renal function impairment, Kidney injury)
- Patients taking drugs which block secretion (aspirin, probenecid)

For who we must reduce dose?

بسبب قلة Kidney Blood flow فيقل ال Concentration فيقل Clren

When renal Clearance is low we must reduce dose

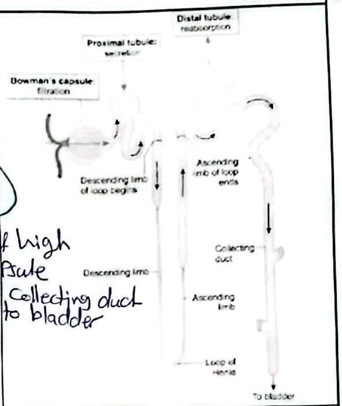
Active tubular secretion: كل drug صار لها filtration ال ما كمل ل Efferent artery فيه هنا ما بقى لحق وصل Proximal tubule صار secretion ال Drug تم كمل وطلع ع Bladder

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: (Important) (There is millions of nephrons)

1. Glomerular filtration → Conc. & Pressure in afferent high So it will filtrate to bowman's Capsule to reach then Collecting duct to bladder
2. Active tubular secretion
3. Passive tubular reabsorption (diffusion from the concentrated tubular fluid back across tubular epithelium).

Drug يصير تركيزه صونه آخر من Blood وال Drug هو lipophilic فيتنقل من high conc ↓ low conc.



Note: GFR depends on your age, race, gender, body size.

The urine will be sent to laboratory, where a test called an ACR (Albumin-to-creatinine ratio) is done. An ACR shows whether you have a type of Protein called albumin in your urine

✓ Reabsorption occur from tubular fluid to blood

Note Dalton (Da) is an alternate name for atomic mass unit, and Kilodalton (KDa) is 1,000 daltons. Thus a Peptide with mass of 64 KDa has a molecular weight of 64,000 grams per mole

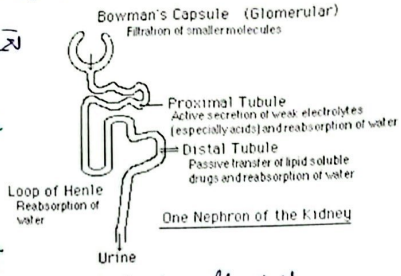
→ Protein-Drug will not Pass

Drug Excretion

1) **Passive glomerular filtration:** (From blood to bowman's Capsule)
free dug < 20kDa
(20 Dalton) (Particle size of drug)

2) **Active tubular secretion:**
separate transport systems for weak acids and bases
Reabsorption of water

3) **Passive tubular re-absorption:**
Conc. gradient drives diffusion of unchanged drug back into systemic circulation- urine pH is the key



Drug conc. is higher in tubular fluid than its conc in blood

→ Direction of moving tubular fluid to Blood

Note If your GFR number is below 60 for 3 monthes (Above 60 with signs of Kidney damage Chowing Protein in urine is sign of Kidney damag)
You may have Kidney disease.

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)). Plasma Protein
- 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

secretion or reabsorption Highly filtered

Clearance of Creatinine = GFR

Note Creatinine is a waste Product that comes from normal wear and tear on muscles of body. Everyone has Creatinine in their bloodstream.
GFR is a routine lab that can be found on your blood work report. GFR is a calculation that includes your creatinine, along with your age, gender, race and weight. your GFR number will help your healthcare Provider if you have Kidney disease

Note one of these, the OAT, transports acidic drug in their negatively 8/2/2023
Charged anionic form (as well as various endogenous acids, such as: uric acid)
while an OCT handles organic bases in their Protonated cationic
form. The OAT Carrier can transfert drug molecules against an
electrochemical gradient and can therefor reduce the Plasma Concentration
nearly to Zero, whereas OCT facilitates transport down electrochemical
gradient.

Drug Excretion

• no filtration for drugs bind to Protein, but there is secretion for them

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: OAT for acidic drugs, OCT for basic drugs
- 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)

↳ inhibit secretion of Penicillin, so Clren of Penicillin will decrease

Note Because at least 80% of drug delivered to Kidney is Presented to the Carrier, tubular secretion is theoretically the most effective mechanism of renal drug elimination. unLike glomerular filtration, Carrier-mediated transport can achieve maximal drug clearance even when most drug bound to Plasma Protein.

Drug Excretion

not contribute too much with drug

↳ mostly contribute with water reabsorption

- In the loop of Henle, 99% of the filtered water is reabsorbed.
- All solutes (including drugs) in the lumen are therefore significantly concentrated. Volume of liquids ال يقل يكون
- 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.

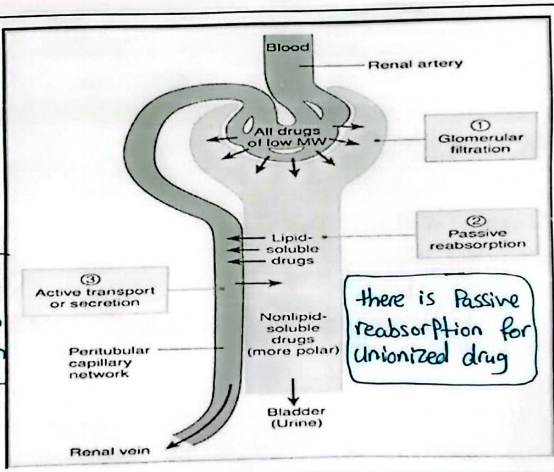
Drug Excretion

- **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 (we can increas PH to decrease reabsorPtion)
- While in weak bases overdose (codeine and amphetamine), ammonium chloride will lower the urine pH and increase the ionization of the bases

will be Highly reabsorPtion & go blood & ↑ toxicity

• لو عنا Unionized basic drug فال Reabsorption تكون عالي
فرح يزداد ال Plasma conc of drug فبنروح بنعدل PH فيصبح ionized
وما رح يصير ReabsorPtion

هاي الرسمة مهمة جداً



there is Passive reabsorPtion for Unionized drug

No filtration for bound drug, but only secretion

Carrier في الك اشي لل Basic drug واشي لل Acidic drug

• هون بالرسمة بوضح انه بيجي ال Blood لل nephron رح يصير filtration لل Drug اللي هم Low Mw وال Drugs اللي ما طلعت أو اللي كانت Bound رح يكملوا مع ال Artery ويصير الها Active transport or secretion

وبطلعوا 6 دقي حالة كان Lipophilic drug رح يصير الهم Passive reabsorPtion
ثم المتبقي من اللي صارلهم filtration و Secretion رح يروحوا ع Collecting duct
ثم ع Bladder ثم إلى Urine

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: → Depends on Passive diffusion

- 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.

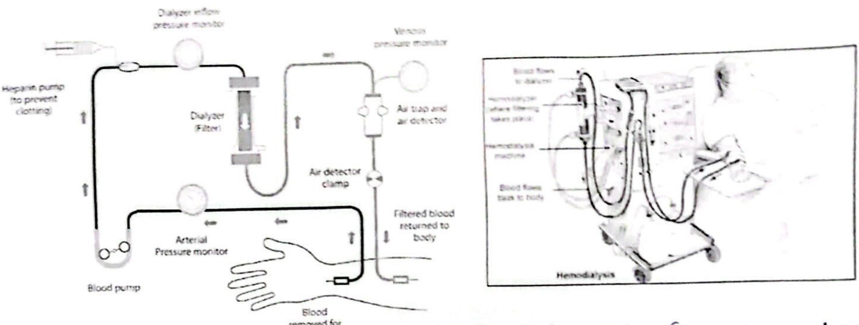
↓MW
↑ diffusion

Concentration كل ما كان الفرق بال كل ما كانت العملية more efficent

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

toxic compound — Hemodialysis — Blood — tube — Dialysate — Waste Product — Fresh media — Blood Flow — Patient — toxins

Hemodialysis



• في بعض الأحيان نعطي المريض Heparin عن طريق Pump
موجودة لحتى ما يصير Clotting أثناء عملية Hemodialysis

Drug Excretion

2. Hepatobiliary excretion:

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

A- Excretion in bile:

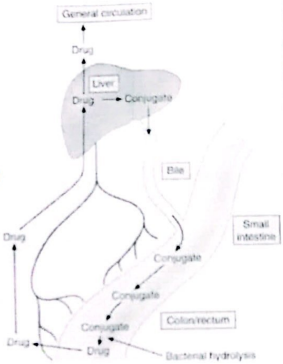
- Some heavy metals are excreted into the bile, e.g., arsenic, lead, and mercury. However, the most likely substances to be excreted via the bile are comparatively large, ionized molecules, such as large molecular weight (greater than 300) conjugates e.g. morphine and chloramphenicol (as glucuronide).

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

← كل ما كان الفرق بينهم عالي مثلاً 50/1
فـ رح تزيد الـ efficiency للـ biliary secretions

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 (1) partition (2) and protein binding.
- In some instances, salivary secretion is responsible for localized side effects.

➢ For example, excretion of antibiotics may cause black hairy tongue, (1)

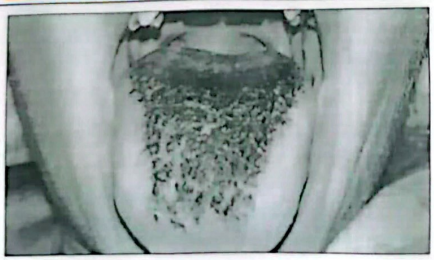
(2) ➢ Gingival hyperplasia can be a side effect of phenytoin.

(3) ➢ Superinfection from antibiotics.

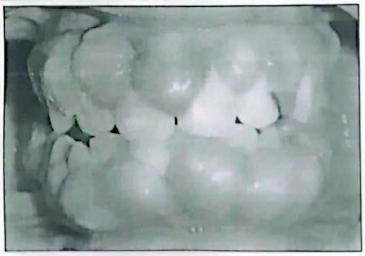
(4) ➢ Dental mottling upon tetracycline ingestion.

Black hairy tongue is caused by excretion of antibiotic as:

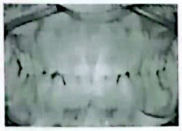
- Penicillin
- Erythromycin
- Doxycycline, and
- Neomycin



Gingival hyperplasia which is caused as a side effect of Phenytoin



Dental mottling upon tetracycline ingestion



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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.

• Lipid soluble drug فالـ Lipids عـ بحتوي milk الـ
عـ mammary gland الـ Plasma من Fats الـ عـ Diffusion بعمل
الـ milk الـ

• Basic drug is more soluble in milk because milk is acidic

• Calcium, ethanol, tetracycline enter milk by diffusion So they can appear in milk

Questions