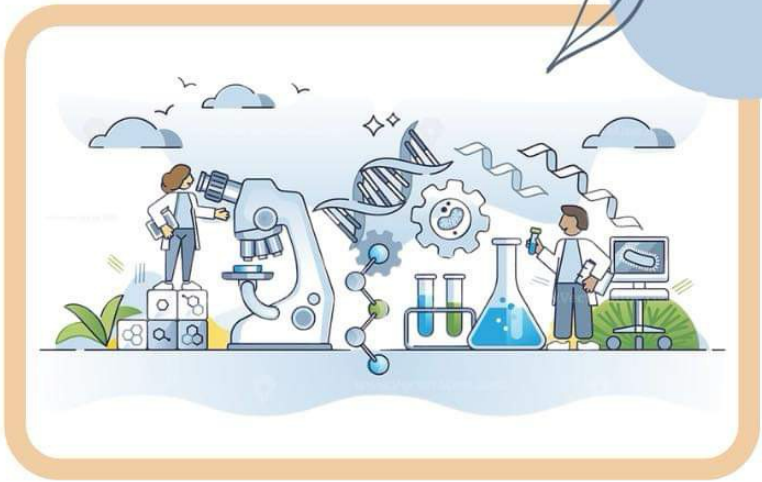
تفريغ بيوفارما



اسم الموضوع: Excretion of drugs

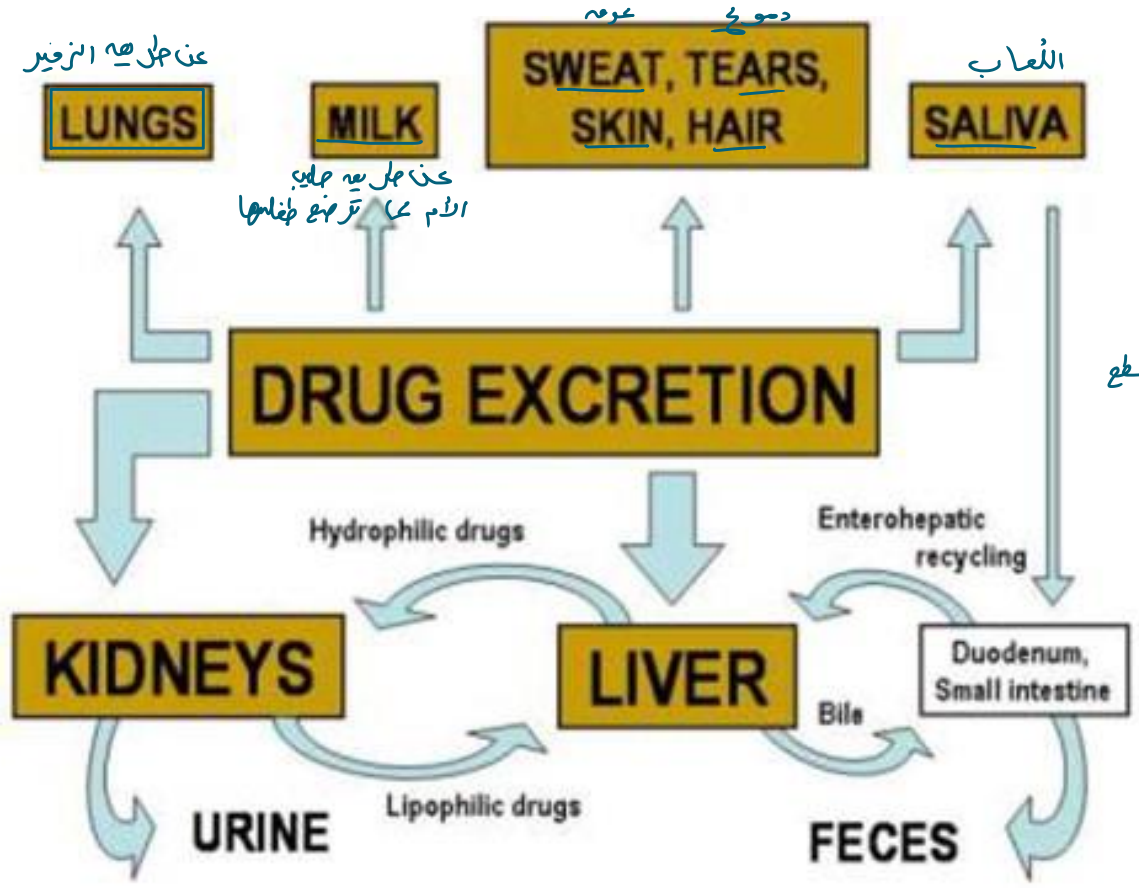
إعداد الصيدلاني/ـة: ياسمين خليل 🌷

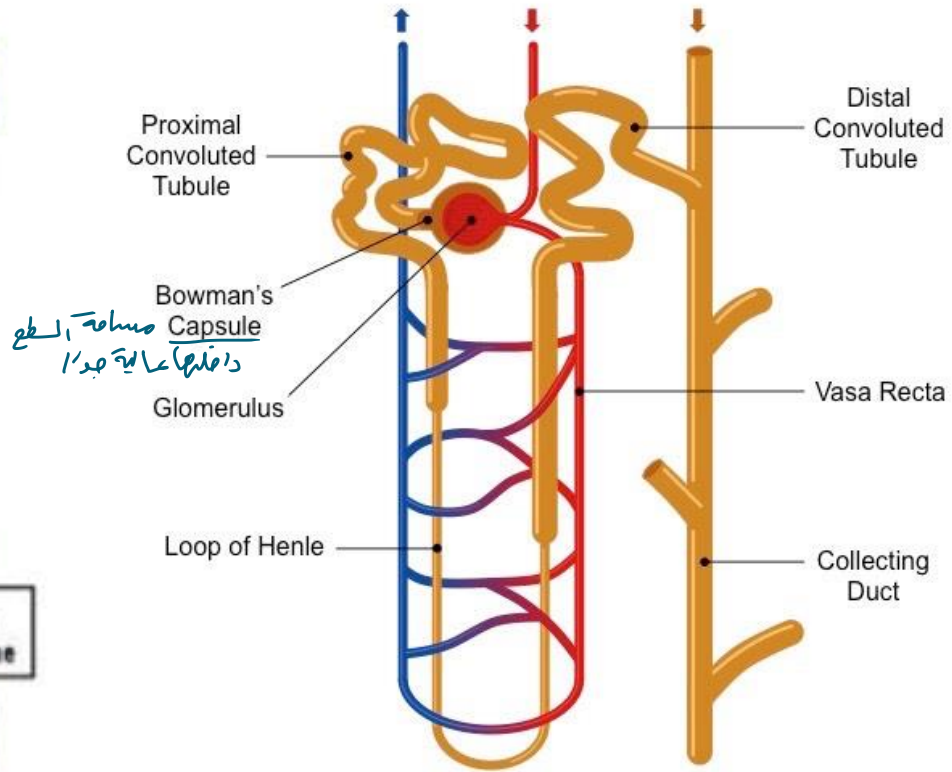
بسم الله الرحمن الرحيم

Soul Academy

لجان الدُّفعات

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

non-polar

- 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.

إذا تم إفراز مواد الجسم بحالتها وصعب تصويفها، فهيك رح يتم إعادة إمتصاصها

- 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.

← ممكن أفراد يكونوا عندهم مرض معين بالذات في الكلى، رح يأخر الإفراز بالتالي رح يضل الدواء داخل الجسم وممكن يعمي

- Excretion via the lungs occurs only with highly volatile or gaseous agents (e.g. general anaesthetics).

non-volatile أما ← يتم إفرازها by kidneys

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

Polar + inactive form of drug = excreted from the body

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

اللهم اغفر لي صغيري
وكبيري وسري وعلني
وما أنت أعلم به مني

- بنقدر نقيس الدواء وكمية البول للمتكون للدم للكلى عن طريق إنه نأخذ أكثر من عينة بول (urin sample) وبأوقات مختلفة وبكل مرة نقيس كم عندها دواء في البول وبرضو بنقدر نعرف الدواء عبارة Filtration أو reabsorption أو secretion من خلال هاي الطريقة كمان ، الحين اسم هاي العملية هو؟

renal clearance (CL_{ren})

وهو عبارة عن مجموع طرح إخراج الدواء من الدم للكلى ناقص طريقة رجوع الدواء من الكلى للدم محسوبة كل تركيز الدواء في البلازما

C_p [reabsorption] [Filtration + secretion]

وعنا 3 إحتمالات للناتج بعد الحساب ، وكل الناتج تتركز حول رقم 120 ml/min وهاي الناتج عندنا منها وظائف الكلى عندهم سليمة :

- لو كان الناتج أكبر من 120 ← reabsorption + secretion + Filtration
- لو كان الناتج يساوي 120 ← Filtration
- لو كان الناتج أقل من 120 ← reabsorption + Filtration

[مشروع سلايدات لقدام]

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:

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

تركيز الدواء في plasma

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%).

لا إله إلا أنت سبحانك إني كنت من الظالمين

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.

filtration + reabsorption too

Factors Altering Renal Drug Clearance

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

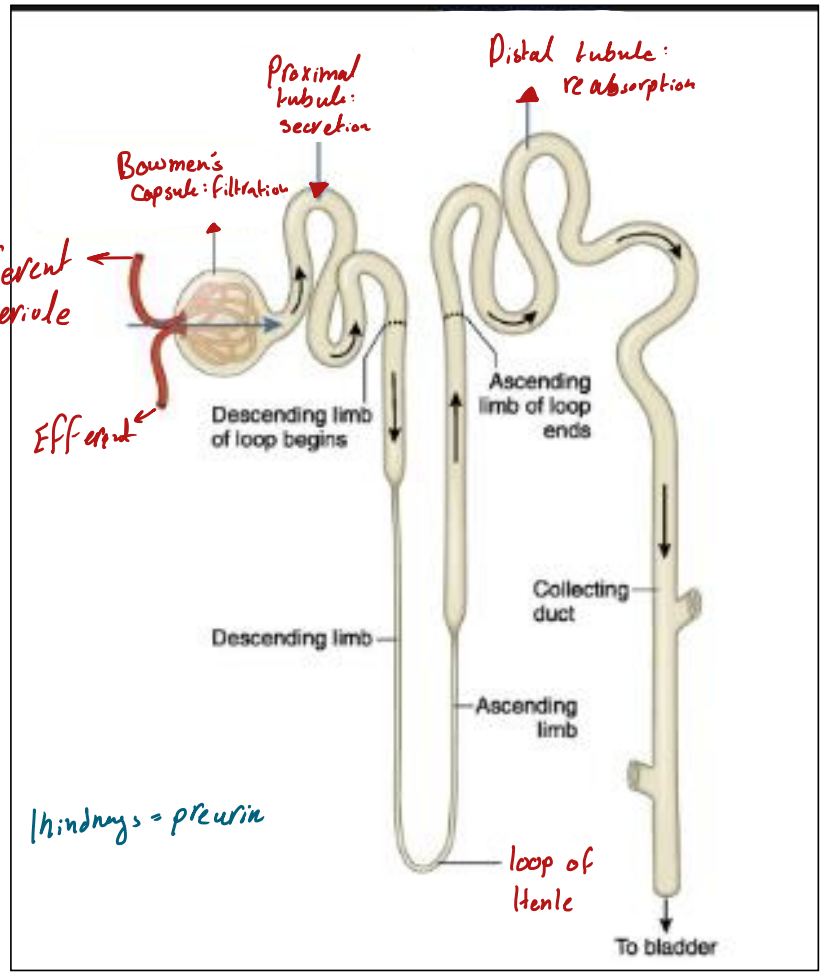
- Elderly and Newborn
- Women (20%) than men
- Kidney and Heart Disease
- Patients taking drugs which block secretion (aspirin, probenecid)

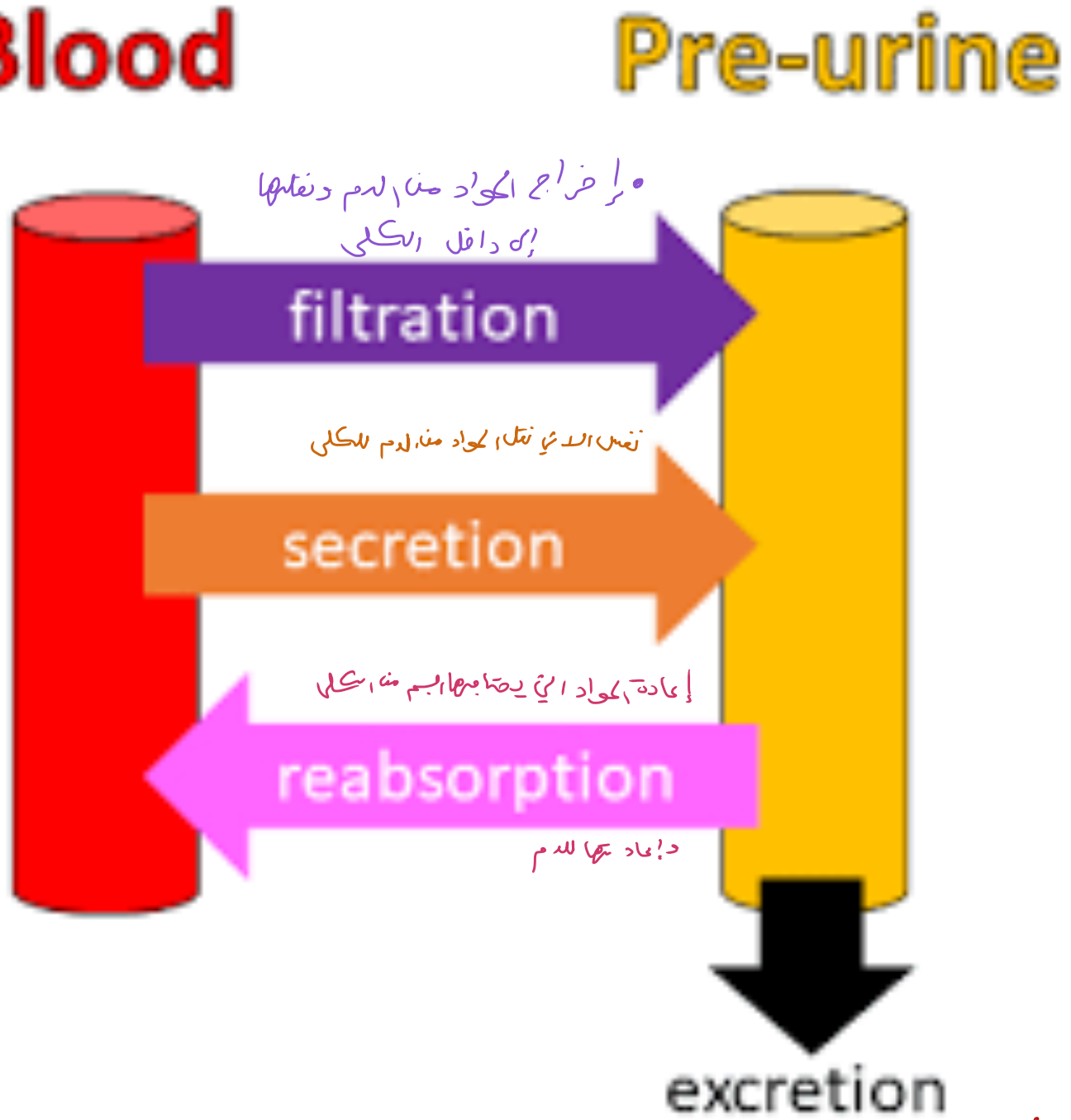
حسبنا الله سيؤتينا الله من فضله ، إنا إلى الله راغبون

Drug Excretion

- The **major** organ for the excretion of drugs is the **KIDNEY**. 90% of excretion
- 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).





• إخراج المواد من الدم ونقلها إلى داخل الكلى

نفس الشيء نقل المواد من الدم للكلى

إعادة المواد التي يحتاجها الجسم من الكلى

وإعادتها للدم

اللهم ارزقه الحسنين الجنة

Drug Excretion

no energy is needed ← glomerulus [هاي التشعبات داخل محفظة بومان]

1) Passive glomerular filtration:

free dug < 20kDa

① ②

شروط مرور المواد بهاي الطريقة
انه الدواء يكون مش مرتبط مع بروتين
كأنه لو مرتبط، رح يكون حجمه كبير ← [free drug]
X < 20 kDa بالتالي الحجم المسموح هو

أصلو حجم الدواء كبير فبنحتاج هاي الطريقة

needs ATP + carrier

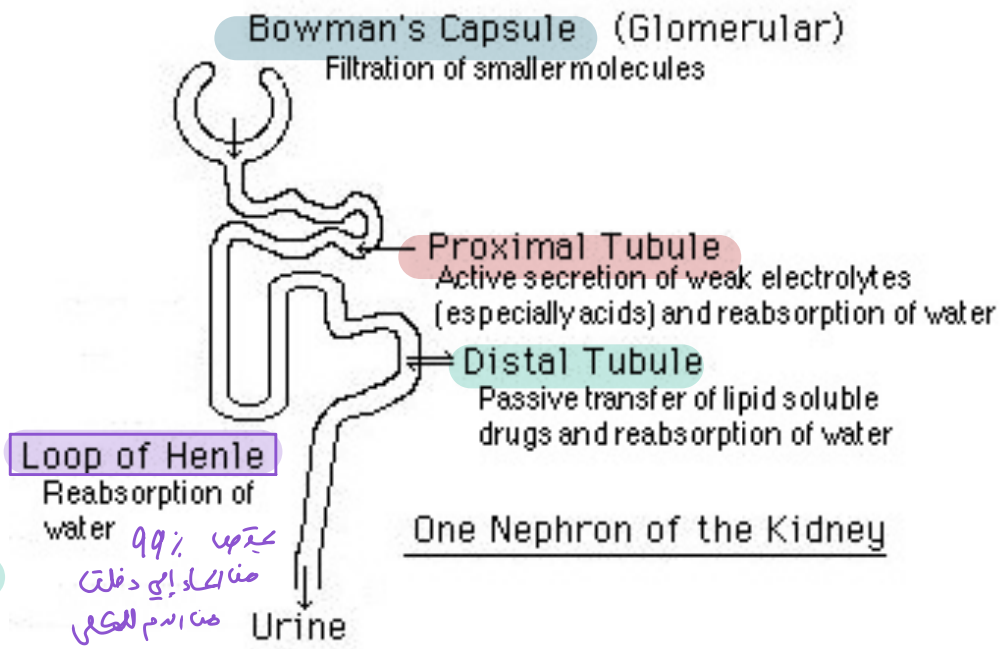
2) Active tubular secretion:

separate transport systems for weak acids and bases on proximal tubule

ATP صفة دايمًا ما بنحتاج

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

- Inulin is completely filtrated

Drug Excretion

20% filtration
80% secretion
لـ مسؤول أكثر عن إفراغ الأدوية من الدم للنفرون من filtration

2. Tubular secretion

Active: needs ATP + carriers for acidic/basic drugs

filtration

- 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:

يعني انه صرفنا طاقة في الكبد قادرة تنقل أدوية مرتبطة مع بروتين

- 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

لحاجتنا نخلّي penicillin من الدم مع يصير له جزء صغير filtration و الجزء الأكبر Active secretion والسبب إنه مرتبط مع بروتين في يحتاج نقل مع طاقة secretion مع يصير له

- Competitive inhibition of the secretion of one compound by another may occur (inhibition of excretion of penicillin by probenecid)

زي تشابك الأنزيمات كما شكينا النواقل بصير عليها أزمة أدوية في بصير Competitive inhibition

في عنا carriers للأدوية الحمضية والأدوية القاعدية تمام!
بين النواقل تتبعون الأدوية الحمضية non-selective يعني تتقبل الأدوية الحمضية صغير أو كبيرة او متوسطة بحجم أو حجم و النواقل العضية كذلك non-selective

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.

non-polar [lipo-philic]
= reabsorption

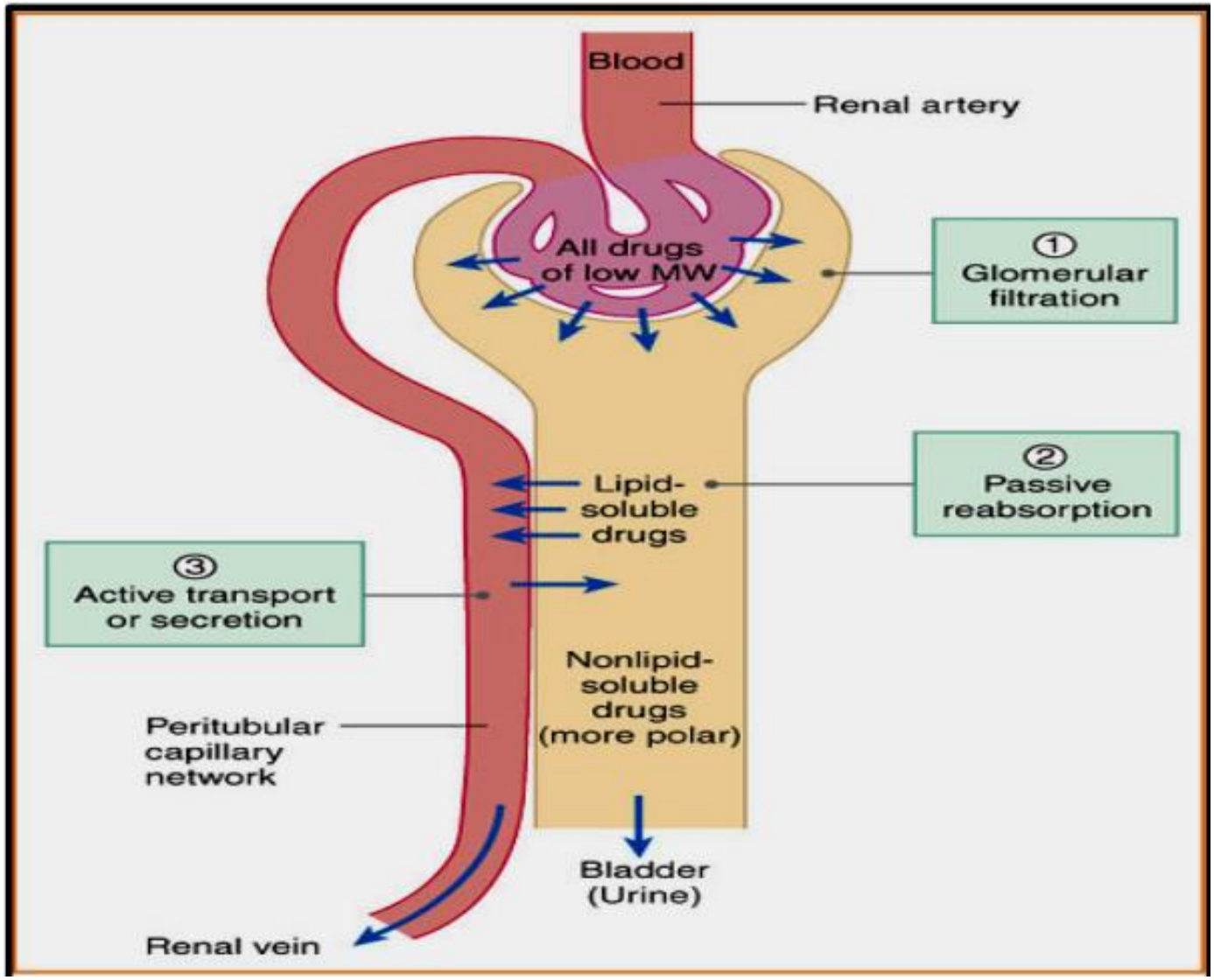
unionized form

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 → base urin + weak acid drugs = ionized → excretion
- While in weak bases overdose (codeine and amphetamine), ammonium chloride will lower the urine pH and increase the ionization of the bases

acid

اللهم إني أسألك الجنة
و أعوذ بك من النار



Main Highlights

د. أعنا الارتباط بعل صوية بانم الدواء يكون بشكل طبيعي

- 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. والعكس صحيح

  ↳ unionized يكونهم
- Several important drugs are removed predominantly by renal excretion, and are liable to cause toxicity in elderly persons and patients with renal disease. الأشخاص الكبار في العمر أو اللي عندهم أمراض في الكلى عافانا الله و إياكم، عندهم عملية excretion أكيد مش زي الشخص في عمر الشباب أو شخص كلاية سليمة، عشان هيك مهم نسأل الدكتور اللي بيعالجنا يجي على الصيدلية إذا صح أمراض على أدوية عشان نقدر نحدد الجرعات والتكرار ... الخ

الحمد لله الذي عافانا

عسيل الكلى [غسيل الدم]

Drug Excretion

Hemodialysis:

كلية صناعية ، اسمها هيك لأنه عمليات غسيل الكلى (الدم) بتكون خارجية مش من الكلية ذاتها

- 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.

تعيس وظيفة الكلى السليمة

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

• هل غسيل الكلى بنظف الدم من كل أنواع ؟ wastes

وهاي حضاتها المواد إلي بتتنظف من الدم ←

1. Have good water solubility
2. Are not tightly bound to plasma protein — صابوبير لبروتين
3. Are smaller molecular weight; and
4. Have a small apparent volume of distribution.

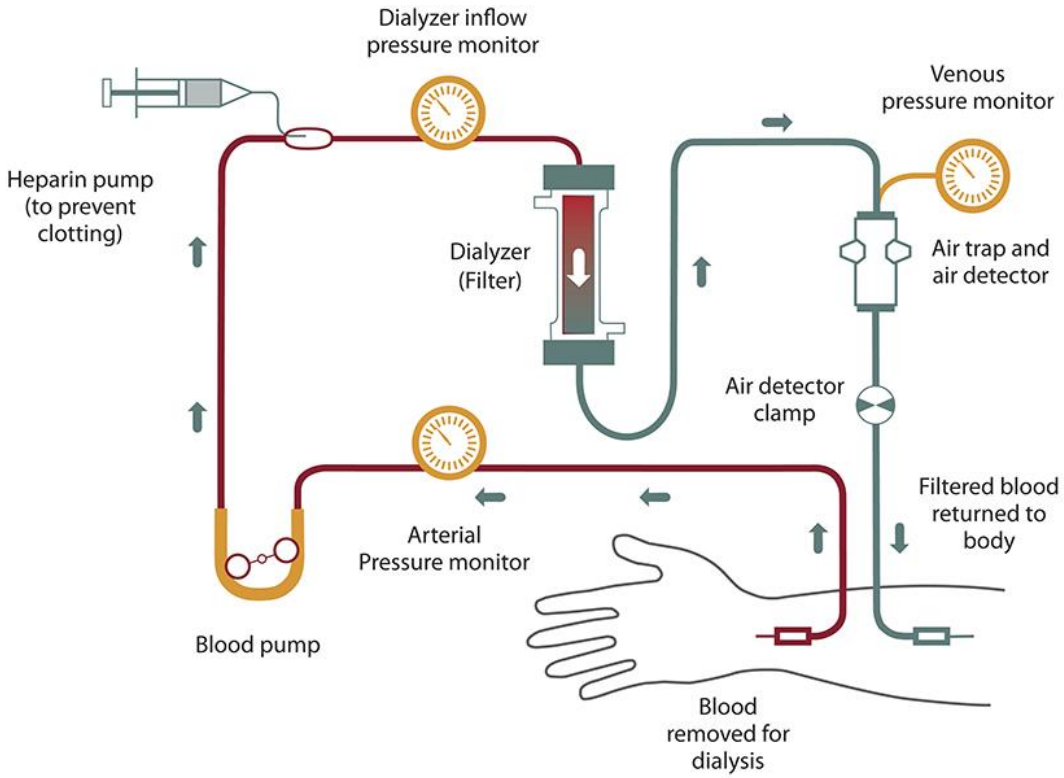
← ممكنا قبل عن ولا كما تكون قليلة بتكون توزيع الدواء في plasma بس

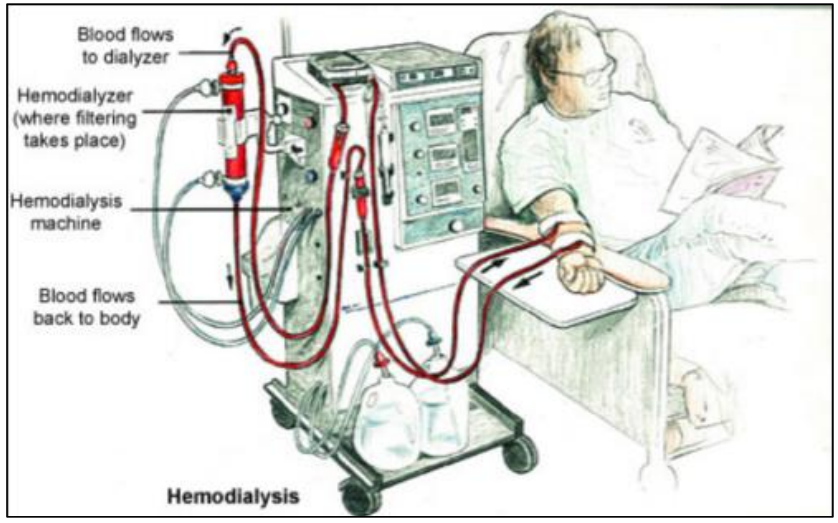
عشان صيغ لرياضات ولا كبيرة رح تكون مرتبطة في بروتينات الأنسجة وصاتغسل

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

Hemodialysis

نحقن في وريد الكوديفا أنبوبين، واحد منهم يسحب الدم الجهان
والثاني يرجع الدم الـ fresh للوريد والجسم





اللهم أصلحني واجعلني مصلح/ـة

Drug Excretion

2. Hepatobiliary excretion:

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

by feces

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).

(3) (1) (2) (4)

وبعدين جوه بيتعرضوا لـ hydrolysis عن طريق normal flora في الأمعاء فبتتحول water-soluble وبترجع تتمتص تاني

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

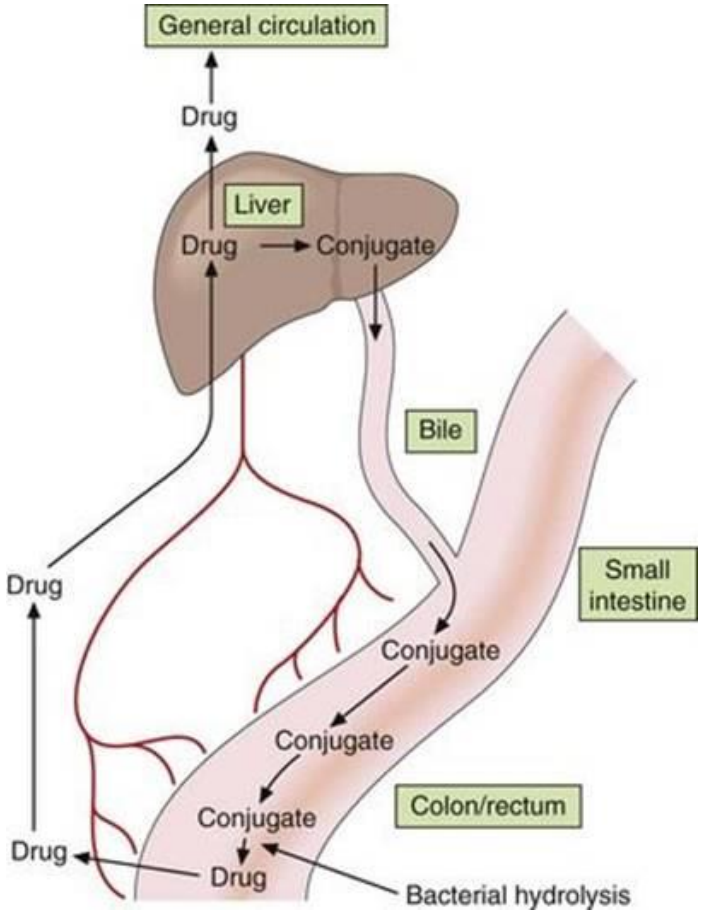
عشان الإفراز هاي ليه؟ Active
بدي أنقل الدواء من الدم إلى bile علمًا إن تركيز الدواء أكثر بكثير من الدم يعني اتنقل الدواء من المنطقة ذات تركيز قليل لمنطقة ذات تركيز عالي وهاي Active transport
50 جزيء دوا مقابل 1 جزيء دم في البداية.

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

يروح تقلل من فعالية
الدواء و B.A يكون للدم
بعد الأخذ

اللهم إني أسألك توبة قبل الموت، و شهادة عند الموت
و مغفرة بعد الموت، و عفوًا عند الحساب و أمانًا
من العذاب و نصيبًا من الجنة

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: → for volatile drugs [from liquid to gas]

- 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. [Inhalation]

- الأدوية أو المخدرات التي يتم إخراجها الجسم عن طريق التنفس
يتطلع من الجسم بهواي الطريقة

4. Salivary excretion: خروج الدواء عن طريق اللعاب

- Drug excretion into saliva appears to be dependent on pH partition and protein binding.

صعادلة عشان يخترق على الحواجز والجلتات حيط اللعاب

↳ non highly binding

- In some instances, salivary secretion is responsible for localized side effects.

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

زي ما بيصير مع بعض المضادات الحيوية

➢ Gingival hyperplasia can be a side effect of phenytoin.

يعني جرعة المضادات صارت كبيرة زيادة

➢ Superinfection from antibiotics.

➢ Dental mottling upon tetracycline ingestion.

discoloration يعطل الأسنان عن طريق اللعاب ويحلل

صحتو لما بيتم إعطاءه للأطفال تحت 8

Black hairy tongue is caused by excretion of antibiotic as:

- Penicillin
- Erythromycin
- Doxycycline, and
- Neomycin

لسانه عليه
زي شعر أسود

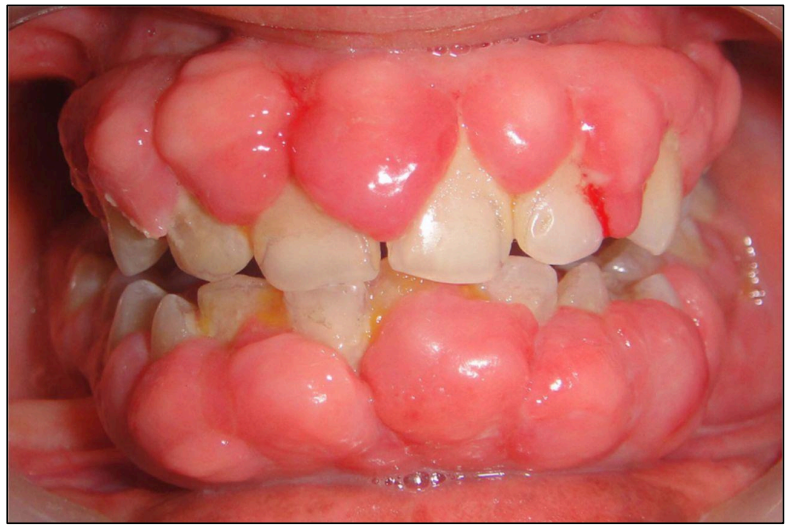
وهاد نتيجة وجود
المواد بيعملوها
في اللعاب وعزوجه
عن طريقها

مثل هاي
الأدوية (مضادات)

Gingival hyperplasia تضخم اللثة

which is caused as a side effect of

Phenytoin



Dental mottling upon tetracycline ingestion

Cause discoloration
Can't be given to children under 8 years C

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.

🔻اللهم اغفر لي وارحمني واهدني وعافني وأعفُ عني ولا تكلني إلى نفسي طرفة عين واجعلني خير للأمة ولا تبتليني في ديني وارزقني ووالديّ والمسلمين والمسلمات جنات الفردوس نتنعم بها حيث نشاء

🔻اللهم ارزق عبادك المظلومين النصر والعزة ، اللهم أعز أهل غزة كما أعزوا الإسلام ،اللهم أكرمهم في حياتهم قبل دخولهم الجنة كما جعلوا دينهم ثغرهم ، وأجعل نتاج صبرهم الحسنى وزيادة (رؤية وجه رب العالمين)

🔻اللهم أرحم عبدك أيهم واغفرله وعافه وأعفُ عنا واجعل الجنة داره ، وحور العين زوجه ، وأسكن أهله معه في الجنة ،واجعله من أصحاب اليمين في عليين وإيانا أجمعين

🔻وما تنسوا الدعاء لأهلنا في اليمين ولبنان والسودان وكل مسلم مستضعف في الأرض