جامعة الملك سعود
King Saud University

PHARMACO

Team 434

Foundation Block

4-GENERAL PHARMACOLOGY (excretion)

Color Index

Red: Important Notes.

Orange: Further Explanation.

Purple: Additional Notes.

By the end of this lecture, students should be able to:

- Identify main and minor routes of Excretion including renal elimination and biliary excretion
- Describe enterohepatic circulation and its consequences on duration of drugs.
- Describe some pharmacokinetics terms including clearance of drugs.
- Biological half-life (t ½), multiple dosing, steady state levels, maintenance dose and Loading dose.

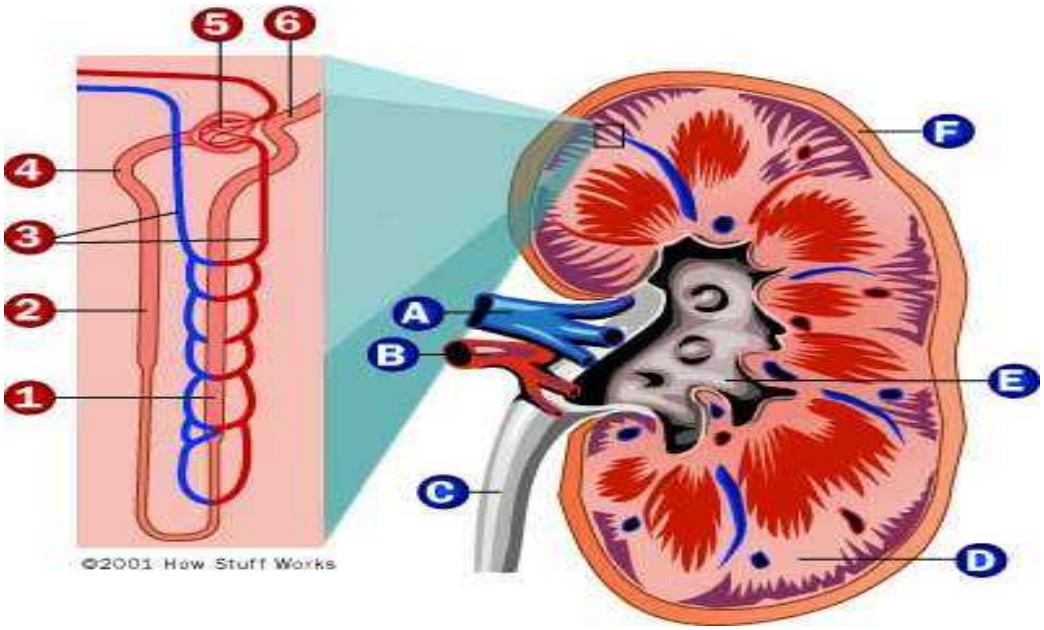
ROUTES OF EXCRETION

Main Routes of Excretion

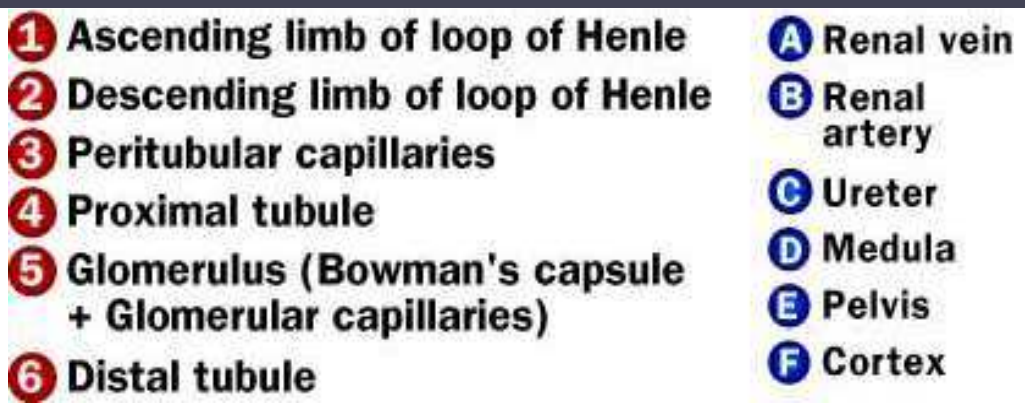
- Renal Excretion
- Biliary Excretion

Minor Routes of Excretion.

- Exhaled air (Exhalation)
- Salivary
- Sweat

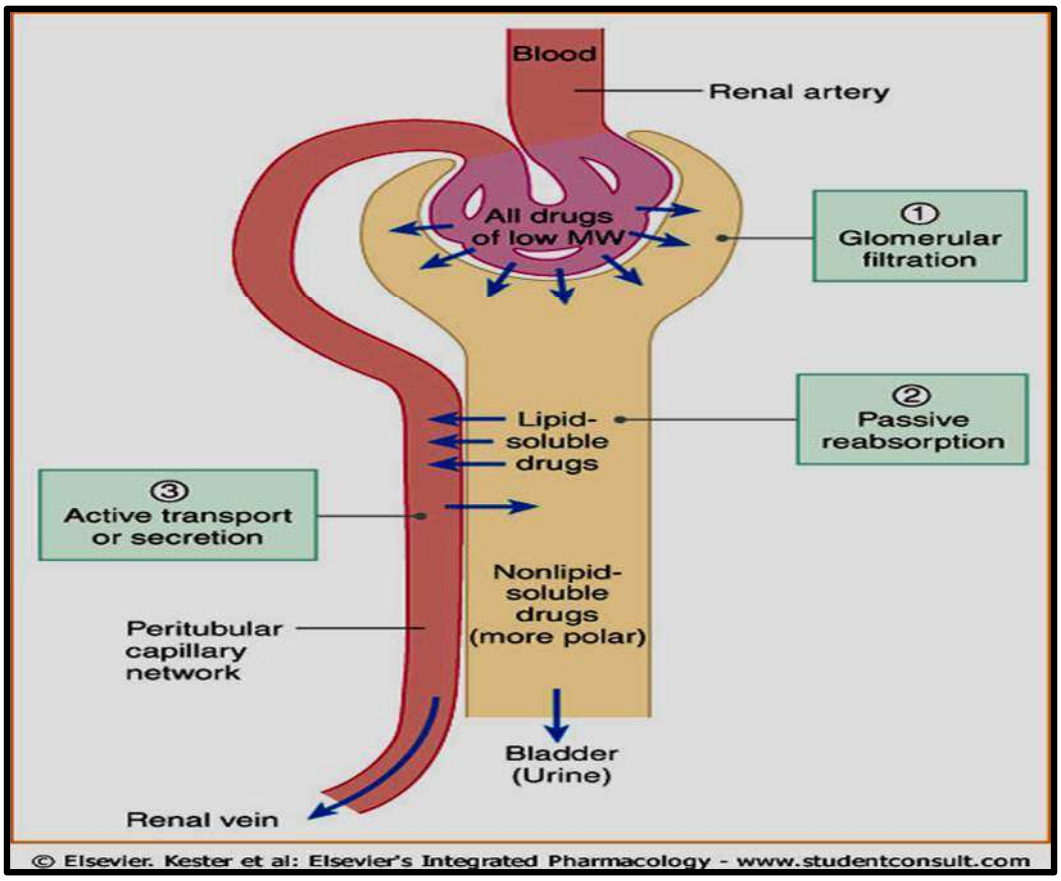


- Milk
- Tear

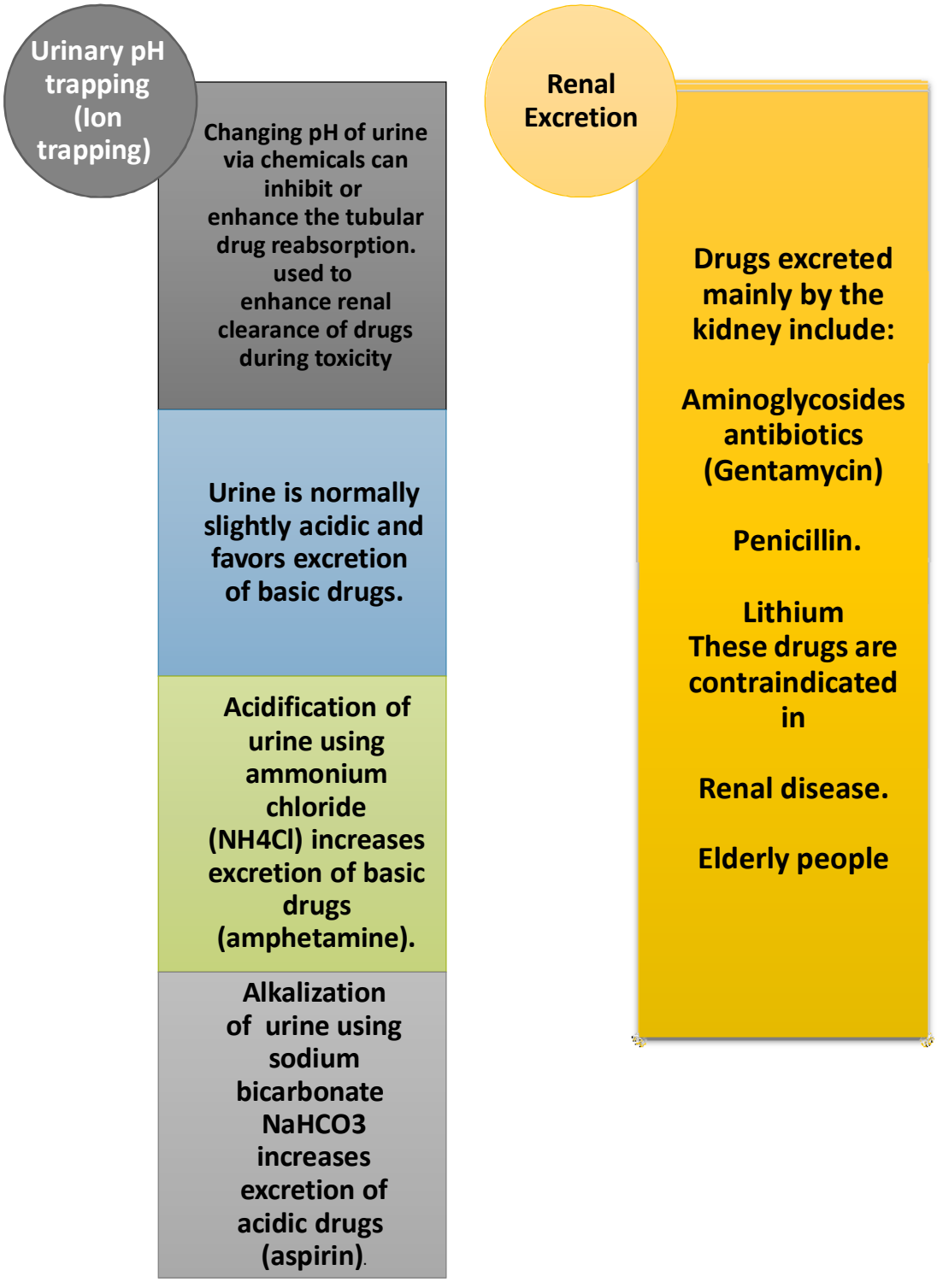

1 Ascending limb of loop of Henle
2 Descending limb of loop of Henle
3 Peritubular capillaries
4 Proximal tubule
5 Glomerulus (Bowman's capsule + Glomerular capillaries)
6 Distal tubule
A Renal vein
B Renal artery
C Ureter
D Medula
E Pelvis
F Cortex

Renal Excretion includes

1. Glomerular filtration.
2. Passive tubular reabsorption.
3. Active tubular secretion.



PHARMACOLOGY: EXCRETION


Urinary pH trapping (Ion trapping)
Changing pH of urine via chemicals can inhibit or enhance the tubular drug reabsorption. used to enhance renal clearance of drugs during toxicity
Urine is normally slightly acidic and favors excretion of basic drugs.
Acidification of urine using ammonium chloride (NH4Cl) increases excretion of basic drugs (amphetamine).
Alkalization of urine using sodium bicarbonate NaHCO3 increases excretion of acidic drugs (aspirin).
Renal Excretion
Drugs excreted mainly by the kidney include:
Aminoglycosides antibiotics (Gentamycin)
Penicillin.
Lithium
These drugs are contraindicated in
Renal disease.
Elderly people

Glomerular filtration (GFR):

- Dpends upon renal blood flow (600 ml/min)
- Glomerular filtration occurs to Low MW drugs
- Only free drugs (unbound to plasma proteins) are filtered.

Tubular secretion:

- occurs mainly in proximal tubules; increases drug conc. in lumen
- organic anionic and cationic tranporters mediate active secretion of anioinc and cationic drugs.
- can transport drugs against conc. gradients.
- Passive diffusion occurs for uncharged drugs.
- Penicillin is an example of actively secreted drug.

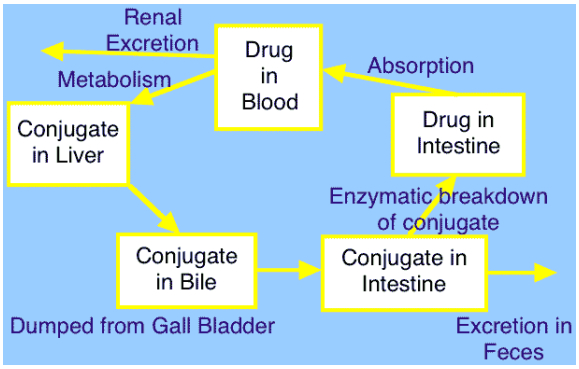
Passive tubular reabsorption

- In distal convoluted tubules & collecting ducts.
- Passive diffusion of unionized, lipophilic drugs
- Lipophilic drugs can be reabsorbed back into blood circulation and urinary excretion will be Low.
- Ionized drugs are poorly reabsorbed & so urinary excretion will be High.

BILIARY EXCRETION

- Occurs to few drugs that are excreted into feces.
- Such drugs are secreted from the liver into bile by active transporters, then into duodenum.
- Some drugs undergo Enterohepatic circulation back into systemic circulation.

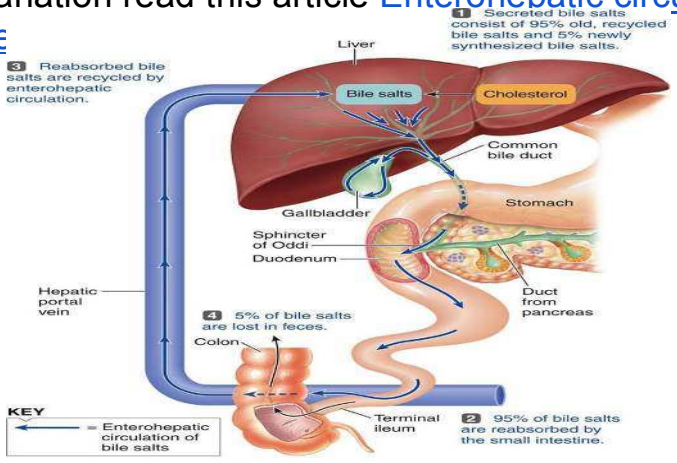
Plasma ⟶ Hepatocytes ⟶ Bile.
For more explanation read this article Biliary excretion



ENTEROHEPATIC CIRCULATION

- Drugs excreted in the bile in the form of *Glucouronides* will be hydrolyzed in intestine by bacterial flora liberating free drugs that can be reabsorbed back if lipid soluble.
- This prolongs the action of the drug. e.g. Digoxin, morphine, thyroxine.

For more explanation read this article Enterohepatic circulation and watch this video The Ente



PLASMA HALF-LIFE (T ½):

- **It is the time required for the plasma concentration of a drug to fall to half of its initial concentration.**
- **It is a measure of duration of action.**
- **Helps to determine the dosing interval**

Drugs of short plasma half life

- **Penicillin, tubocurarine.**

Drugs of long plasma half life

- **Digoxin, thyroxine, arsenic.**

FACTORS THAT MAY INCREASE HALF-LIFE (T ½):

Decreased metabolism

- **Liver disease.**
- **Liver enzyme inhibitors.**

Decreased clearance

- **Renal disease.**
- **Congestive heart failure.**

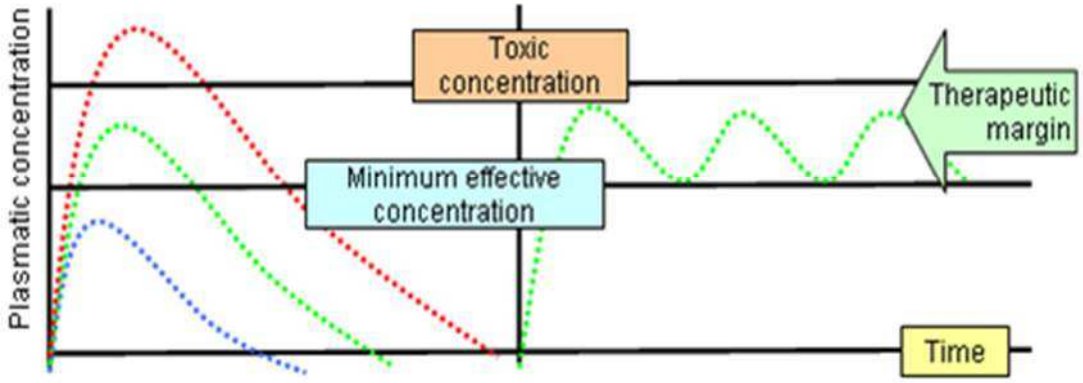
High binding of drugs

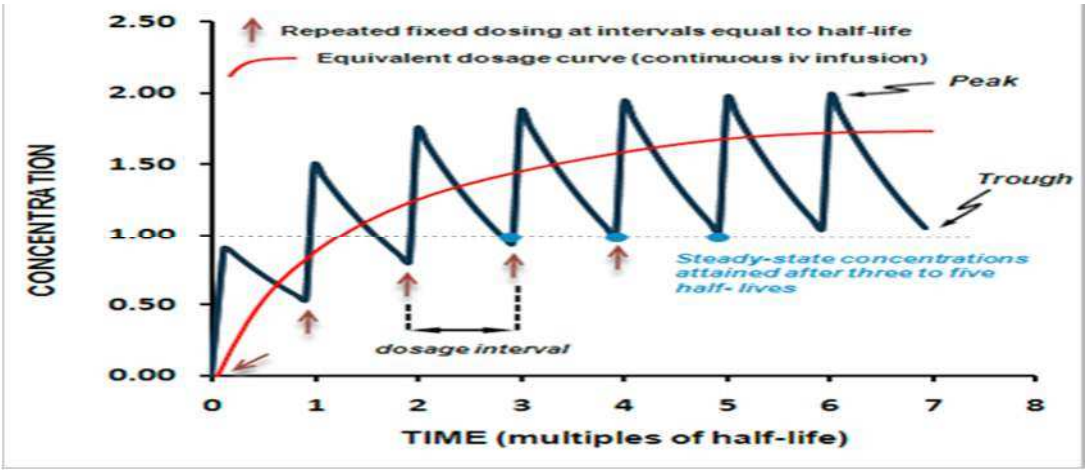
- **Plasma proteins.**
- **Tissue binding.** Enterohepatic recycling

STEADY STATE LEVELS.

- **A state at which the plasma concentration of the drug remains constant.**
- **Rate of drug administration = Rate of drug elimination.**

In most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion to maintain a steady-state concentration of drug associated with the therapeutic window (the range between effective and toxic levels of drugs).





Loading dose	**Maintenance doses**
is the large initial dose that is given till the required therapeutic plasma level is rapidly reached.	Are the doses required to maintain the steady state level and therapeutic level of the drug.
After administration of drug the plasma concentration decreases due to distribution of drugs to other tissues.	These doses balance the amount of drug lost during metabolism and clearance
Initial loading doses are drugs are given in order to achieve rapid therapeutic level. These doses balances the drug distribution.	The patient needs to take regular doses of a drug such as amoxycillin (500 mg) 8 hourly to maintain the therapuatic level.

CLINICAL APPLICATIONS OF LOADING DOSE

- A loading dose may be desirable if the time required to attain steady state of drug (4 elimination $t_{1/2}$ values) is long and rapid relief is required in the condition being treated.
- For example, the $t_{1/2}$ of lidocaine (treating arrythmia) is usually 1-2 hours. Arrhythmias after myocardial infarction are life-threatening, and one cannot wait 4-8 hours to achieve a therapeutic concentration.
- Use of a loading dose of lidocaine in the coronary care unit is standard.

LOADING DOSE VS. MAINTENANCE DOSE

MCQs

1. The two most important sites for drug elimination:

A) Pulmonary and liver
B) Liver and gastrointestinal tract
C) Kidney and liver
D) Skin and liver

2..... of renal blood flow represents GFR:

A) 10%
B) 15%
C) 20%
D) 25%

3. Which of the following will have low concentration in the urine?

A) Ionized drugs
B) Hydrophobic drugs
C) Water-soluble drugs
D) Hydrophilic drugs
E) Both A+B

4. Passive tubular re-absorption happens in:
A) Glomerulus
B) Proximal convoluted tubules
C) Distal convoluted tubules
D) Collecting ducts
E) Both C+D

5. A person attempted suicide by taking an Overdose of penicillin (Pka: 2.74). Which of the following you should give this person to eliminate the excess of penicillin by excreting it in the urine?
A) Ammonium chloride to acidify the urine
B) Ammonium chloride to alkalize the urine
C) Sodium bicarbonate to acidify the urine
D) Sodium bicarbonate to alkalize the urine

6. Which of the following increases when the lipid-soluble drugs undergo the enterohepatic circulation?
A) The drug's pH
B) The duration of action
C) The rate of excretion
D) The rate of metabolism

7. Digoxin (long t1/2) should be prescribed in:
A) Few doses a day
B) Many doses a day
C) No doses at all
D) Both A+C

8. Half-life is decreased when there is:
A) A liver disease
B) A lot of microsomal inhibitors
C) A low plasma protein binding
D) A congestive heart failure
E) Both A+B

9. The maintenance doses balance the amount of drug lost during:
A) Absorption
B) Distribution
C) Metabolism
D) Excretion
E) Both C+D

10. Steady state levels are maintained when:
A) Rate of drug absorption = rate of drug excretion
B) Rate of drug administration = rate of drug absorption
C) Rate of drug administration = rate of drug metabolism
D) Rate of drug administration = rate of drug excretion

Answers: 1:C | 2:C | 3:B | 4:E | 5:D | 6:B | 7:A | 8:C | 9:E | 10:D

Done by Pharmacology Team

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