

# EXCRETION OF DRUGS

Ali Alhoshani, B.Pharm, Ph.D.

[ahoshani@ksu.edu.sa](mailto:ahoshani@ksu.edu.sa)

Office: 2B 84

# Excretion



By the end of this lecture, you should:

- Identify major 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 ( $t_{1/2}$ ), multiple dosing, steady state levels, maintenance dose and Loading dose.

# Excretion



## □ Major Routes of Excretion

- Renal Excretion
- Biliary Excretion

## □ Minor Routes of Excretion

- Pulmonary excretion.
- Salivary excretion.
- Mammary excretion via milk.
- Skin / Dermal excretion via sweat.
- Tears

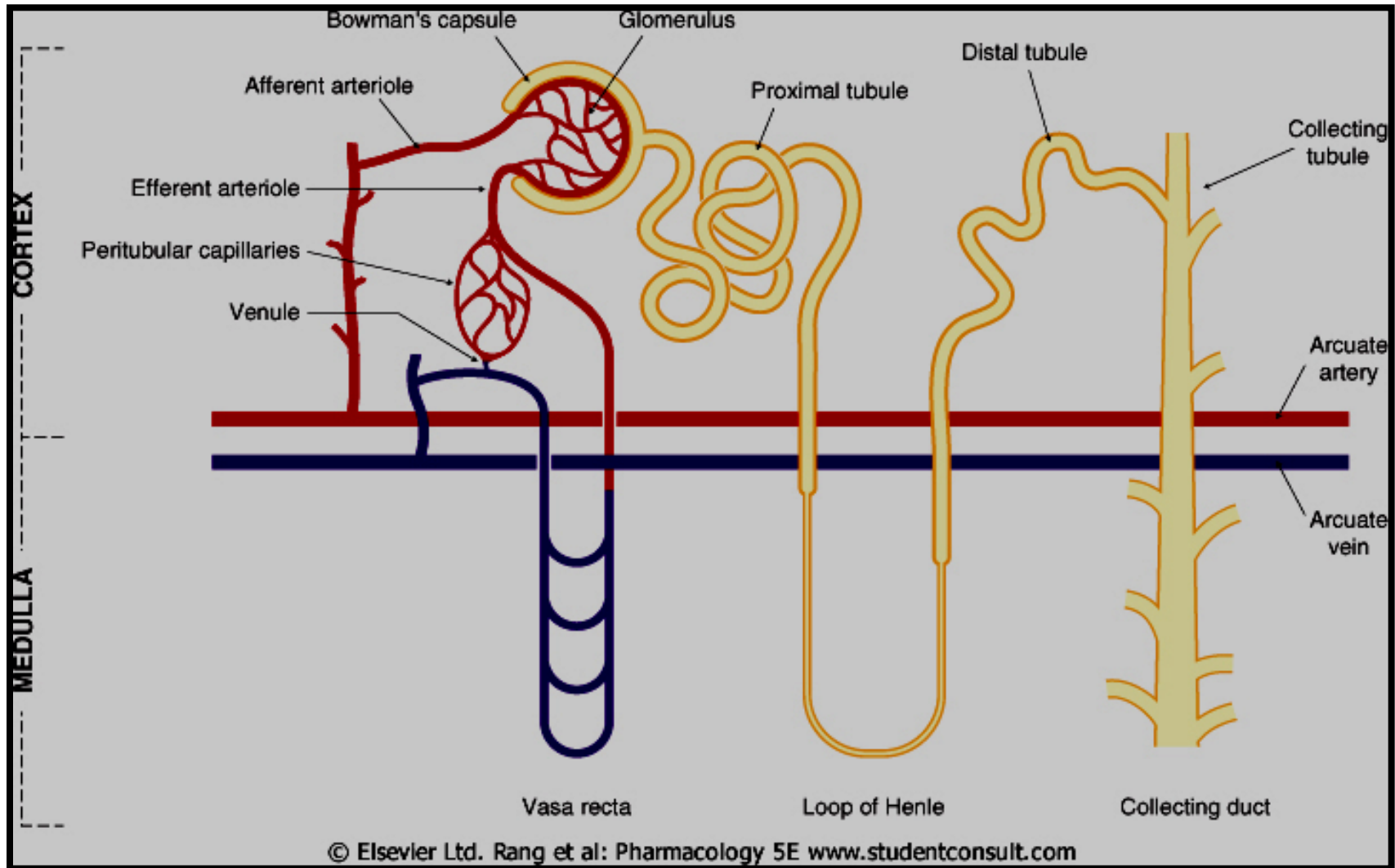
# Renal Excretion



## Structure of kidney

- The structure unit of kidney is nephron
- That consists of :
  - ▣ Glomerulus
  - ▣ Proximal convoluted tubules
  - ▣ Loop of Henle
  - ▣ Distal convoluted tubules
  - ▣ Collecting ducts

# Kidney



# Renal Excretion includes



The principle processes that determine the urinary excretion of drugs are:

- ❑ Glomerular filtration.
- ❑ Passive tubular reabsorption.
- ❑ Active tubular secretion.

# Renal Excretion includes



## □ Glomerular filtration

- Depends upon renal blood flow (600 ml/min)
- GFR 20% of renal blood flow = 125 ml/min.
- Glomerular filtration occurs to
  - Low molecular weight drugs
  - Only free drugs (unbound to plasma proteins) are filtered.

# Renal Excretion includes

- 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 excretion in urine will be low.
  - ▣ Ionized drugs are poorly reabsorbed & so urinary excretion will be high.



# Renal Excretion includes

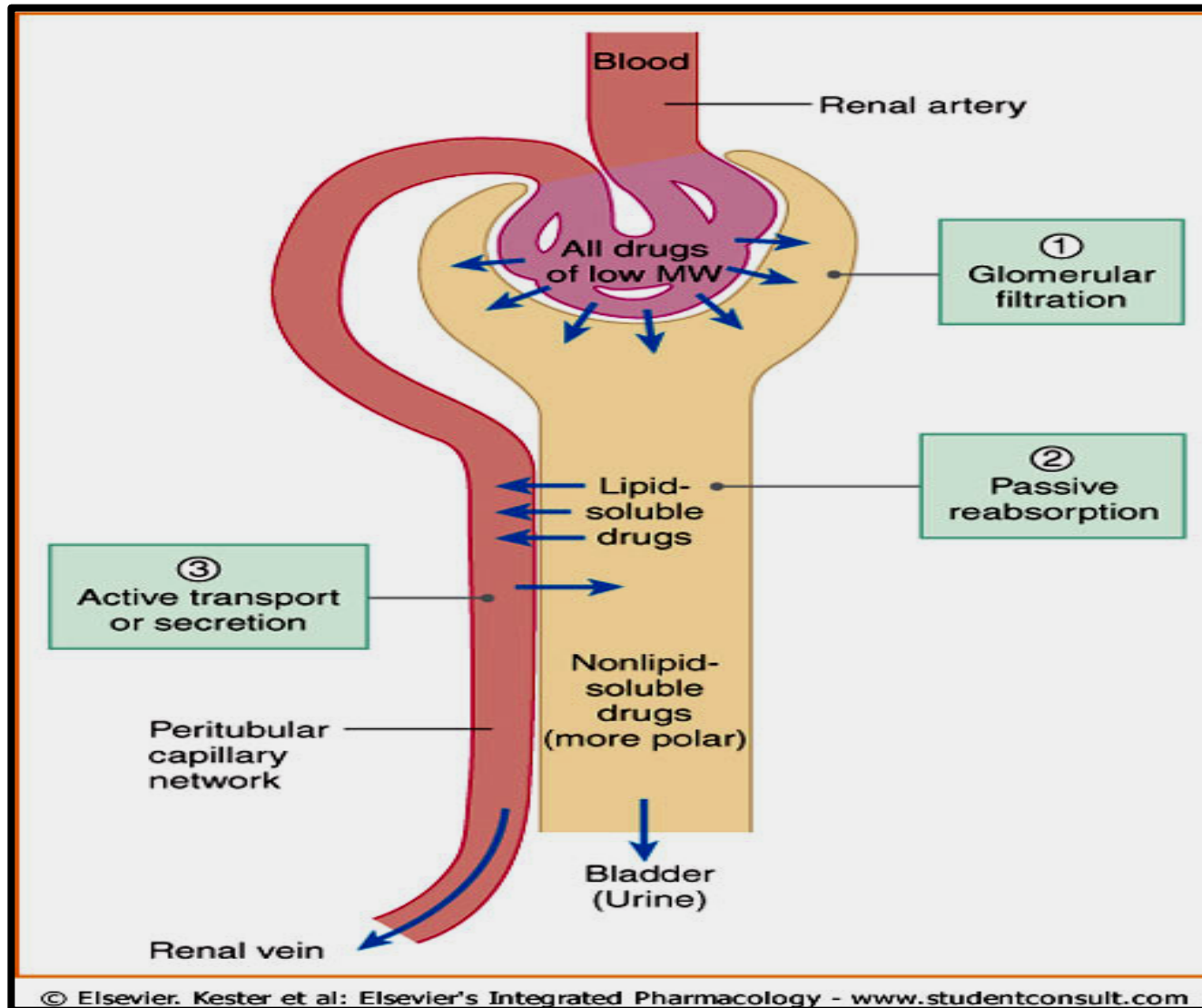
---

- Active tubular secretion.
  - ▣ Occurs mainly in proximal tubules; increases drug concentration in lumen
  - ▣ Organic anionic and cationic transporters mediate active secretion of anionic and cationic drugs.
  - ▣ Can transport drugs against conc. gradients.
    - Penicillin is an example of actively secreted drug.

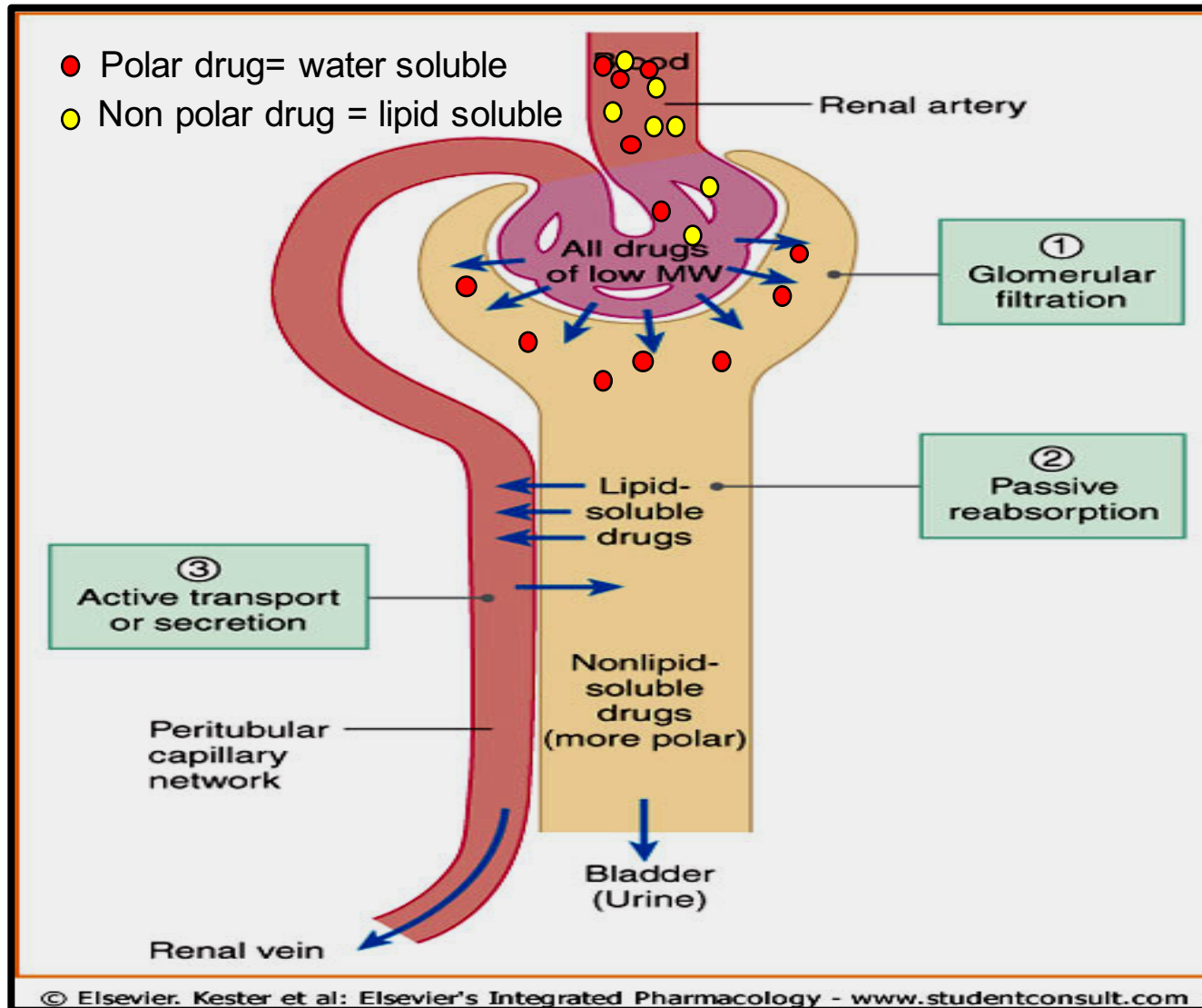
# Renal Excretion includes

- Active tubular secretion.
  - System for Acidic drugs.
    - Salicylates
    - Sulphonamides
    - Penicillin
    - Transport of acidic drugs is blocked by probenecid
  - System for Basic drugs
    - Morphine
    - Atropine
    - Quinine
    - Neostigmine

# Renal Excretion includes



# Renal Excretion includes



# Urinary pH trapping (Ion trapping)

---

- Changing pH of urine by chemicals can inhibit or enhance the drug reabsorption from renal tubules back into blood circulation.
- Ion trapping is used to enhance renal clearance of drugs during toxicity.
- Urine is normally slightly acidic and favors excretion of basic drugs.

# Urinary pH trapping (Ion trapping)

- Acidification of urine using ammonium chloride ( $\text{NH}_4\text{Cl}$ ) increases excretion of basic drugs as amphetamine.
- Alkalinization of urine using sodium bicarbonate ( $\text{NaHCO}_3$ ) increases excretion of acidic drugs as aspirin.

# Renal Excretion



Drugs excreted mainly by the kidney include:

- Aminoglycosides antibiotics (as gentamycin)
- Penicillin
- Lithium

These drugs should be prescribed carefully in

- patients with renal disease.
- Elderly people

# 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 blood circulation



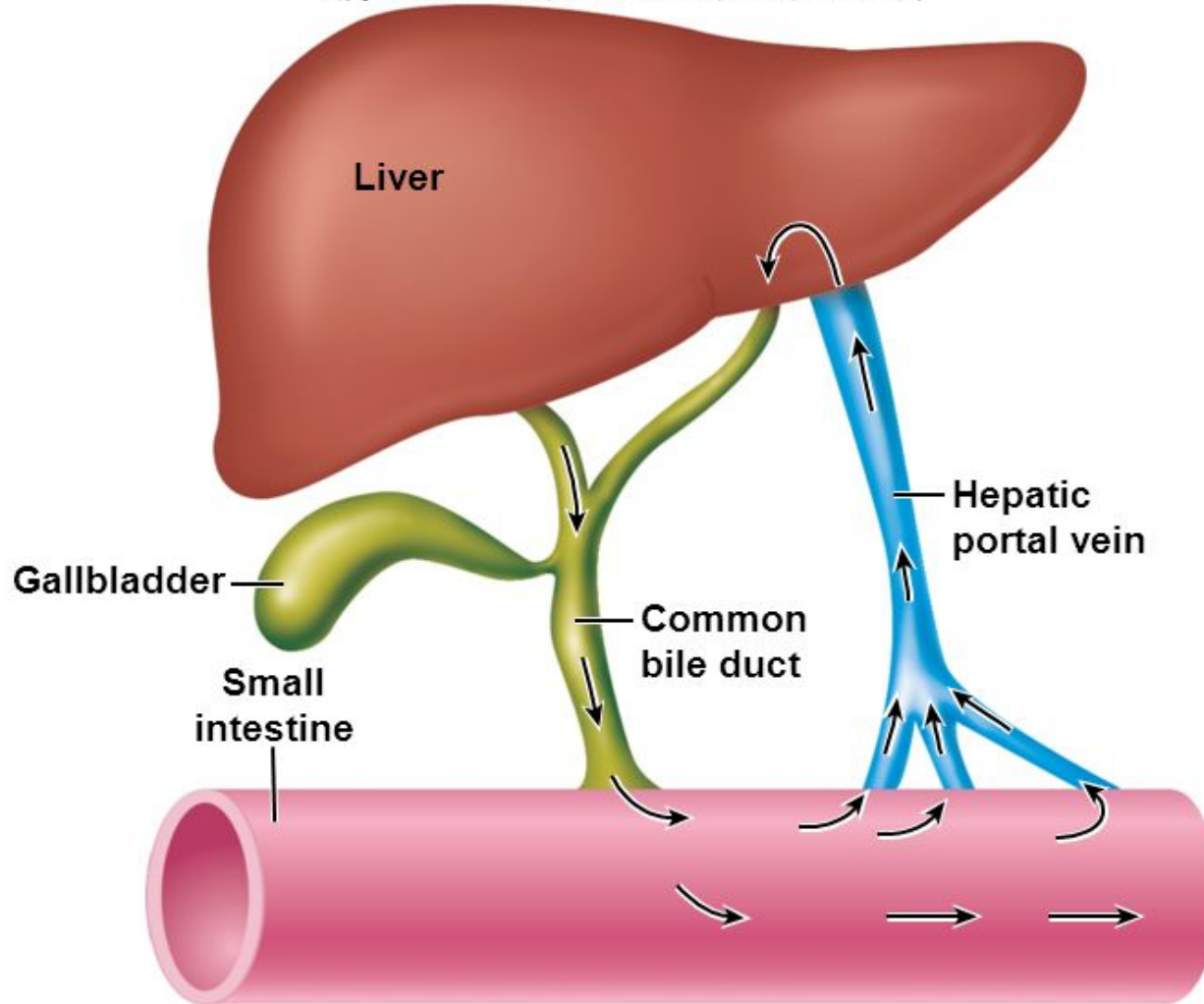
# Enterohepatic circulation



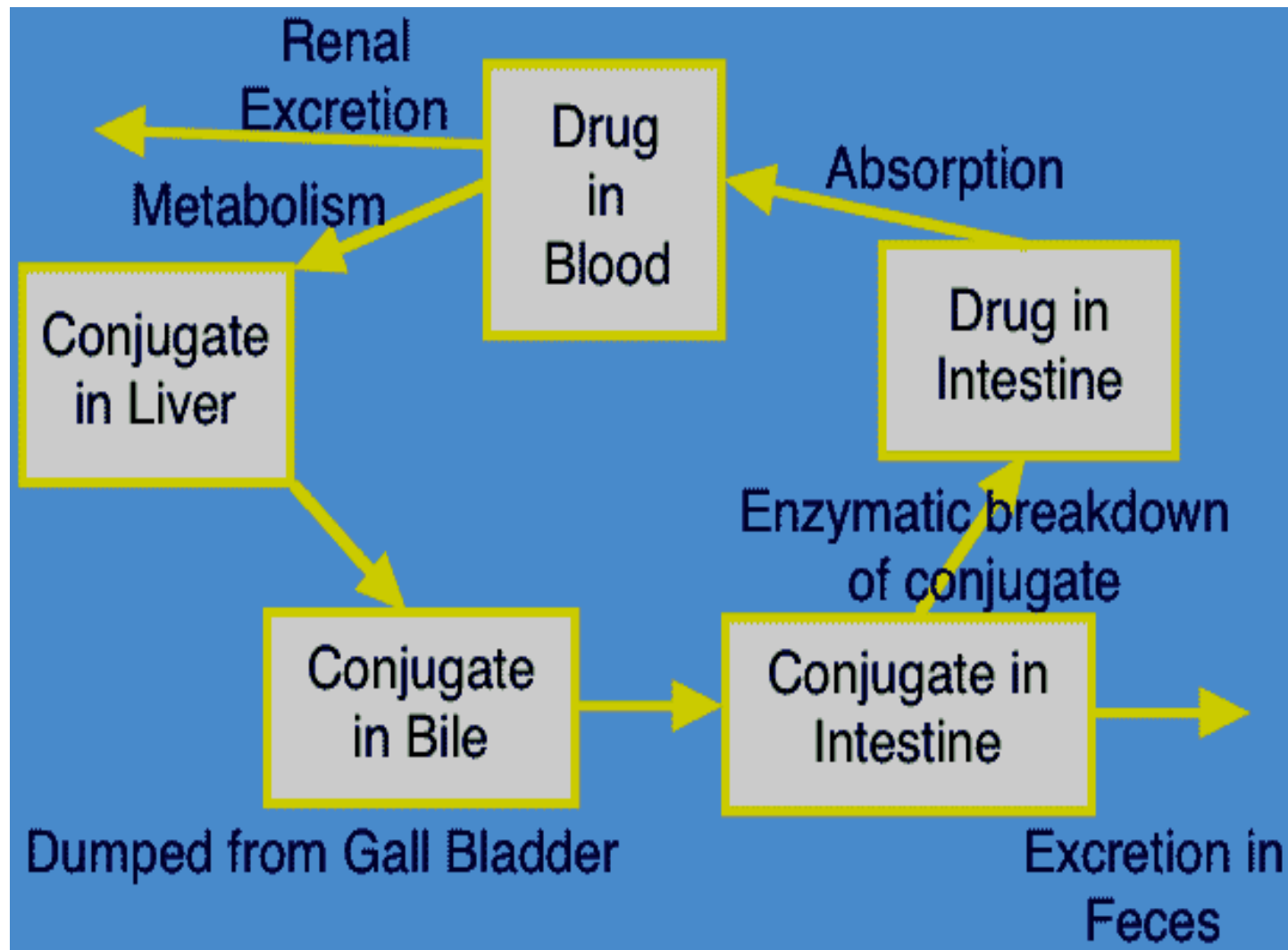
- Drugs excreted in the **bile** in the form of **glucuronides** will be hydrolyzed in intestine by bacterial flora liberating free drugs that can be reabsorbed back into blood if the drugs are lipid soluble.
- This prolongs the duration of action of drugs e.g. digoxin, morphine, thyroxine.

# Enterohepatic circulation

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.



# Excretion



# Plasma half-life ( $t_{1/2}$ )

---

- Is the time required for the plasma concentration of a drug to fall to half of its initial concentration.
- Is a measure of duration of action.
- Determine the dosing interval

## Drugs of short plasma half life

- Penicillin, tubocurarine.

## Drugs of long plasma half life

- Digoxin, Thyroxine.

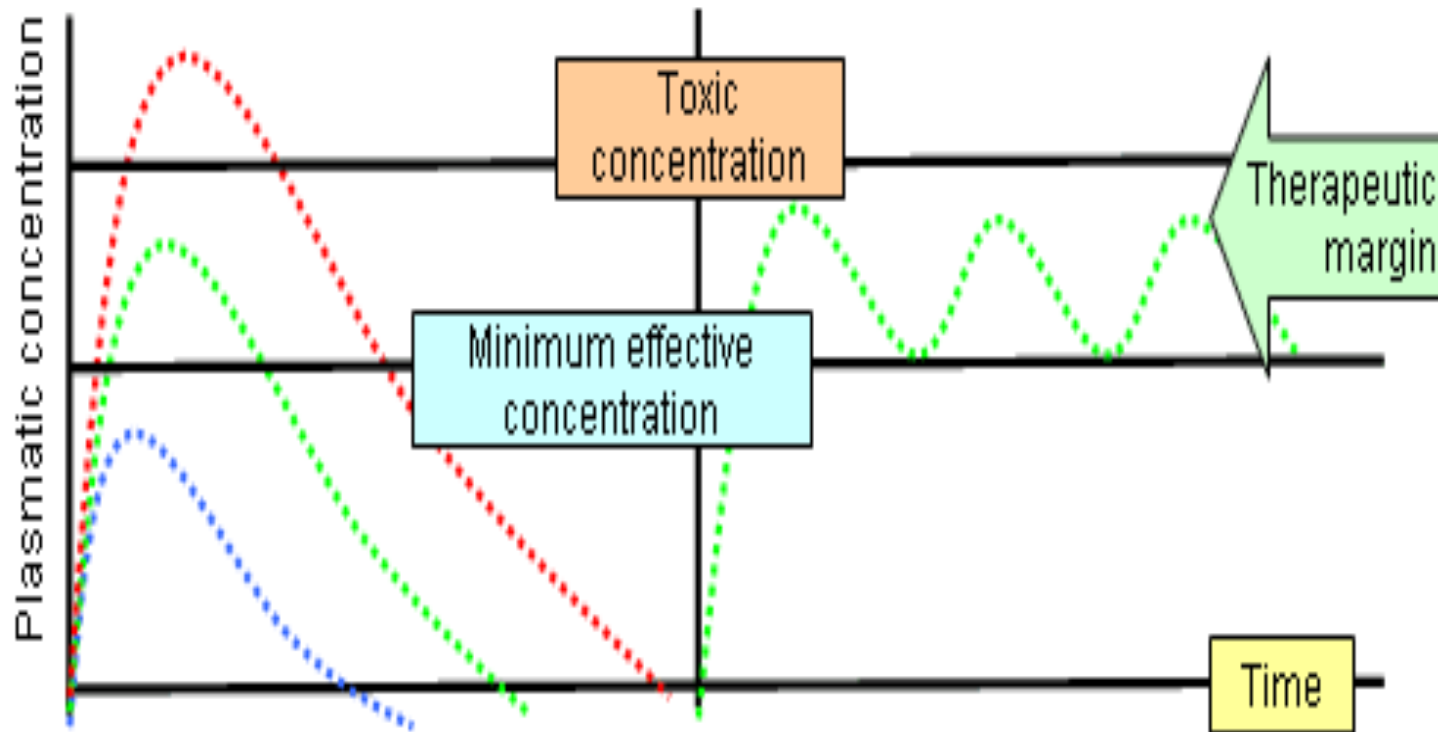
# Factors May Increase Plasma half-life ( $t_{1/2}$ )

- **Decreased metabolism**
  - ▣ Liver disease.
  - ▣ Microsomal inhibitors.
- **Decreased clearance**
  - ▣ Renal disease.
  - ▣ Congestive heart failure.
- **High binding of drugs**
  - ▣ Plasma proteins.
  - ▣ Tissue binding.
- **Enterohepatic recycling**

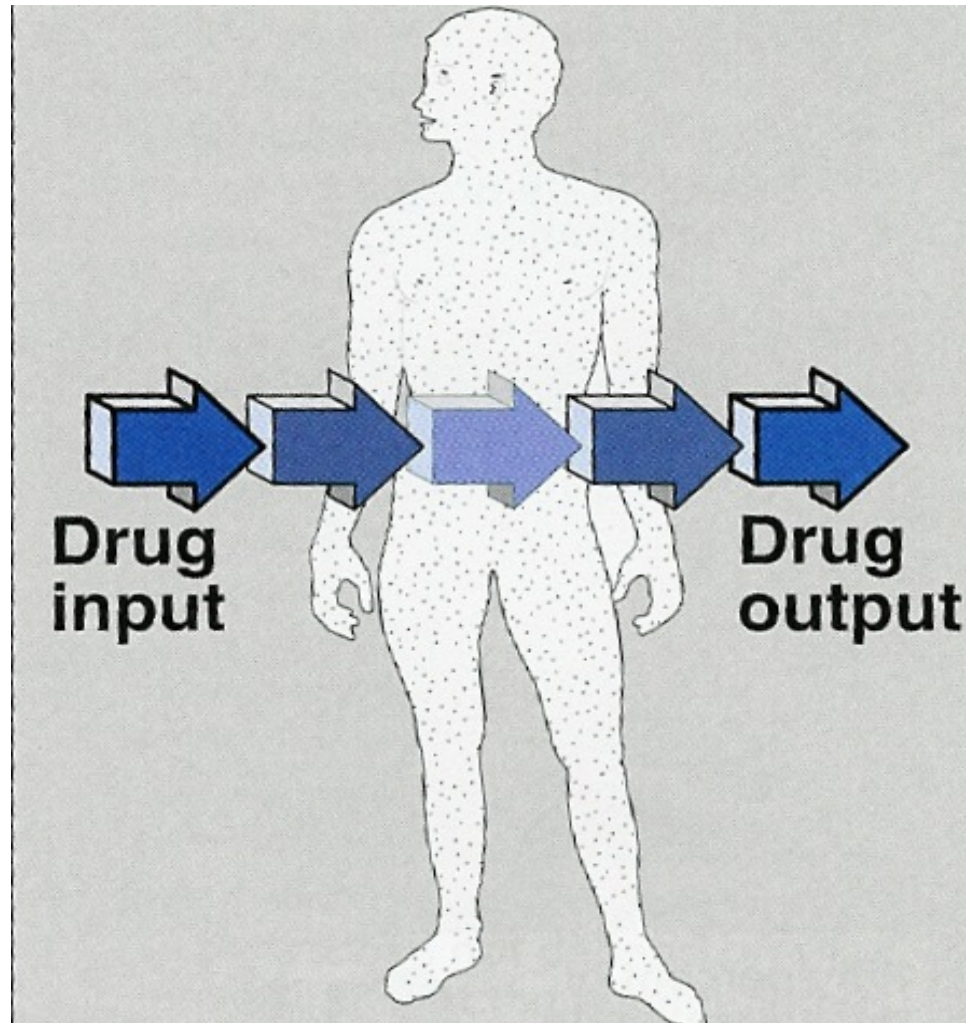
# Steady State

- ▣ A state at which the therapeutic plasma concentration of the drug (mg/ml) remains constant with the therapeutic window (the range between effective and toxic levels of drugs).
- ▣ At steady state:  
rate of drug administration = elimination rate

# Therapeutic Window



# Steady State





# Steady State

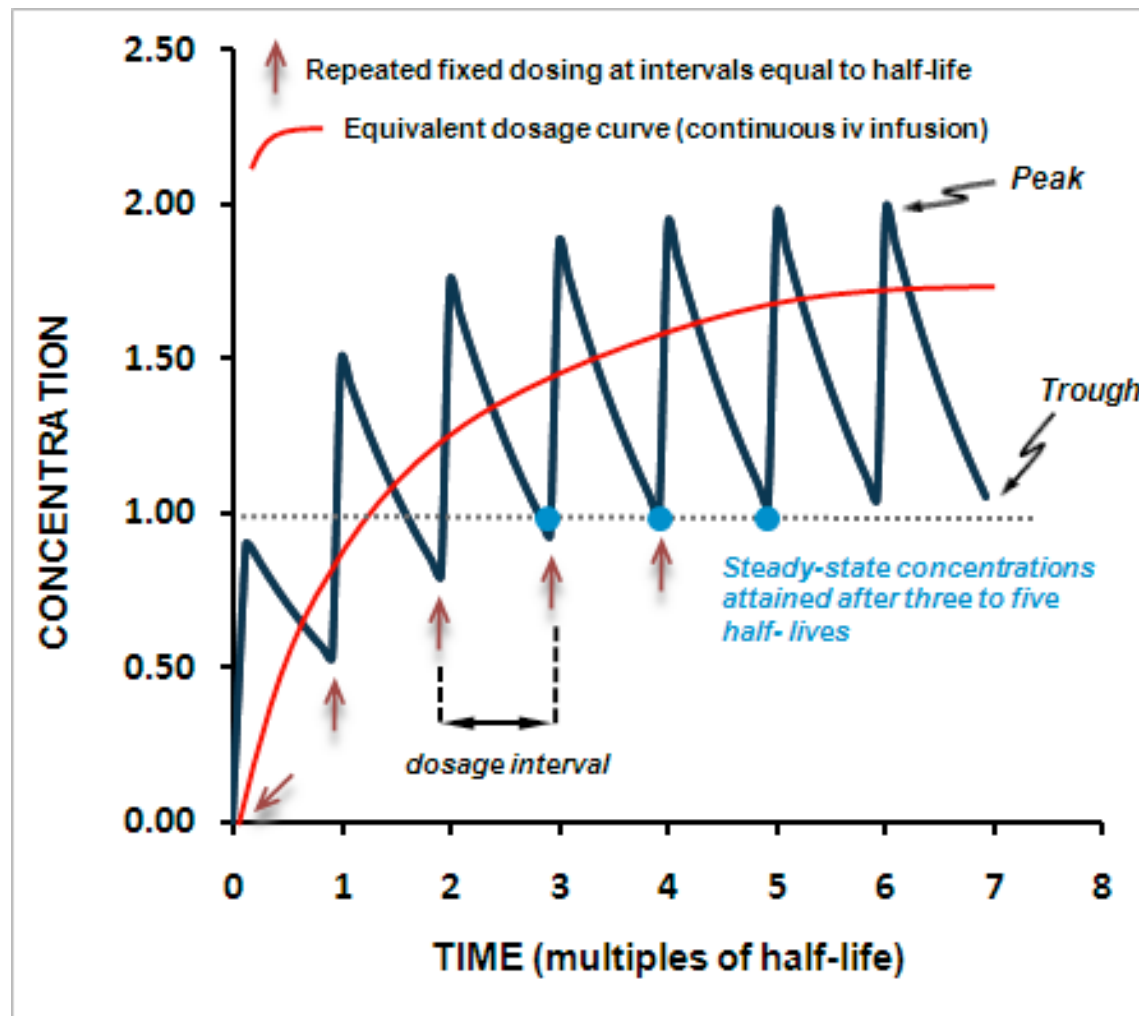


How many half-lives would be necessary to reach steady state?

**Steady state concentration is attained after 3-5 half lives**

**E.g. Morphine**

# Steady State Level



# Loading Dose



- is the large initial dose that is given to achieve rapid therapeutic plasma level.
- After administration of the drug, the plasma concentration decreases due to distribution of drug to other tissues.
- These doses balances the drug distribution.
- This is important for drugs with long halve lives.

# Clinical Application 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.
- E.g.  $t_{1/2}$  of lidocaine (antiarrhythmic drug) 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.

# Maintenance Doses

- are the doses required to maintain the therapeutic level of the drug constant or the steady state of the drug.
- These doses balance the amount of drug lost during metabolism and clearance.
- The patient needs to take regular doses of a drug such as **amoxicillin ( 500 mg) / 8 hours to maintain the therapeutic level.**

# Summary

---

- Polar drugs are readily excreted and poorly reabsorbed.
- Lipid soluble drugs are reabsorbed back and excretion will be low
- Acidic drugs are best excreted in alkaline urine (*sodium bicarbonate*).
- Basic drugs are best excreted in acidic urine (*ammonium chloride*).
- Enterohepatic circulation prolongs half life of the drug.

# Questions

