Excretion of Drugs

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Excretion of Drugs

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

- **Identify the main and minor routes of excretion including renal elimination and biliary excretion**
- **Describe the enterohepatic circulation and its consequences on duration of actions of drugs.**
- **Describe pharmacokinetics terms including clearance of drugs, half-life (t ½), steady state levels, maintenance dose and loading dose.**

Routes of Excretion

Main Routes of Excretion

- **Renal Excretion**
- **Biliary Excretion**

Minor Routes of Excretion

- **Pulmonary excretion (Exhalation).**
- **Salivary excretion.**
- **Mammary excretion via milk.**
- **Skin / Dermal excretion via sweat.**
- **Tears**

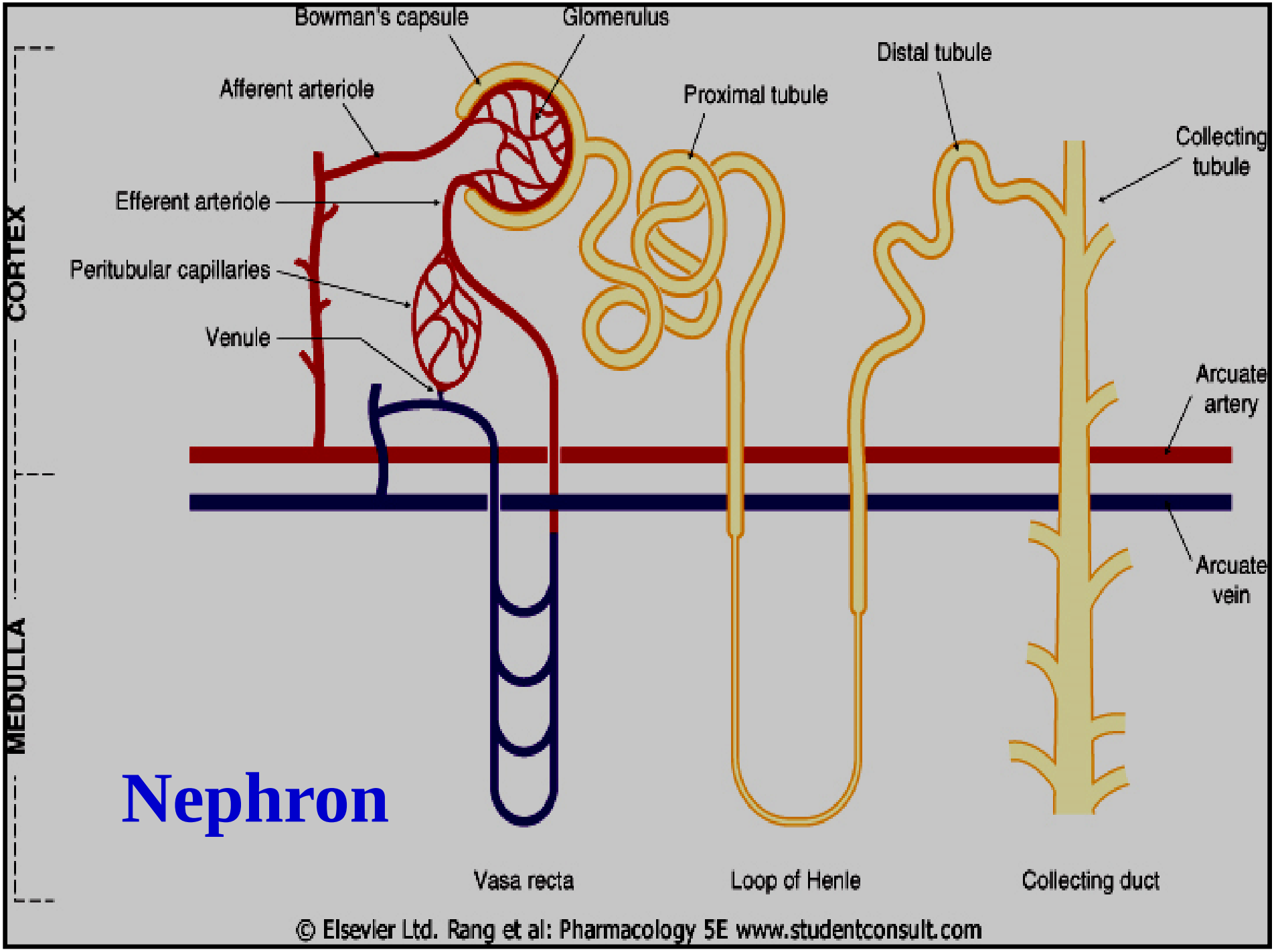
Renal Excretion

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**


Bowman's capsule
Glomerulus
Distal tubule
Afferent arteriole
Proximal tubule
Collecting tubule
Efferent arteriole
Peritubular capillaries
Venule
Arcuate artery
Arcuate vein
CORTEX
MEDULLA
Nephron
Vasa recta
Loop of Henle
Collecting duct
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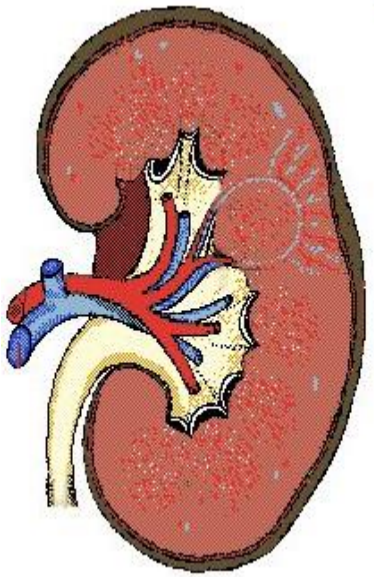
Renal Excretion includes

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

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



Glomerular filtration (GFR):

- **Depends upon renal blood flow (600 ml/min)**
- **Glomerular filtration rate (GFR) is about 20% of renal blood flow = 125 ml/min.**
- **<u>Glomerular filtration occurs to:</u>**
  - **Low molecular weight drugs**
  - **Only free drugs (unbound to plasma proteins)**

  are filtered while bound drugs are not filtered.

Active tubular secretion:

- **occurs mainly in proximal tubules; increases drug concentration in tubular 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.**

Transporters for acidic drugs.

- Salicylates
- Sulphonamides
- Penicillin

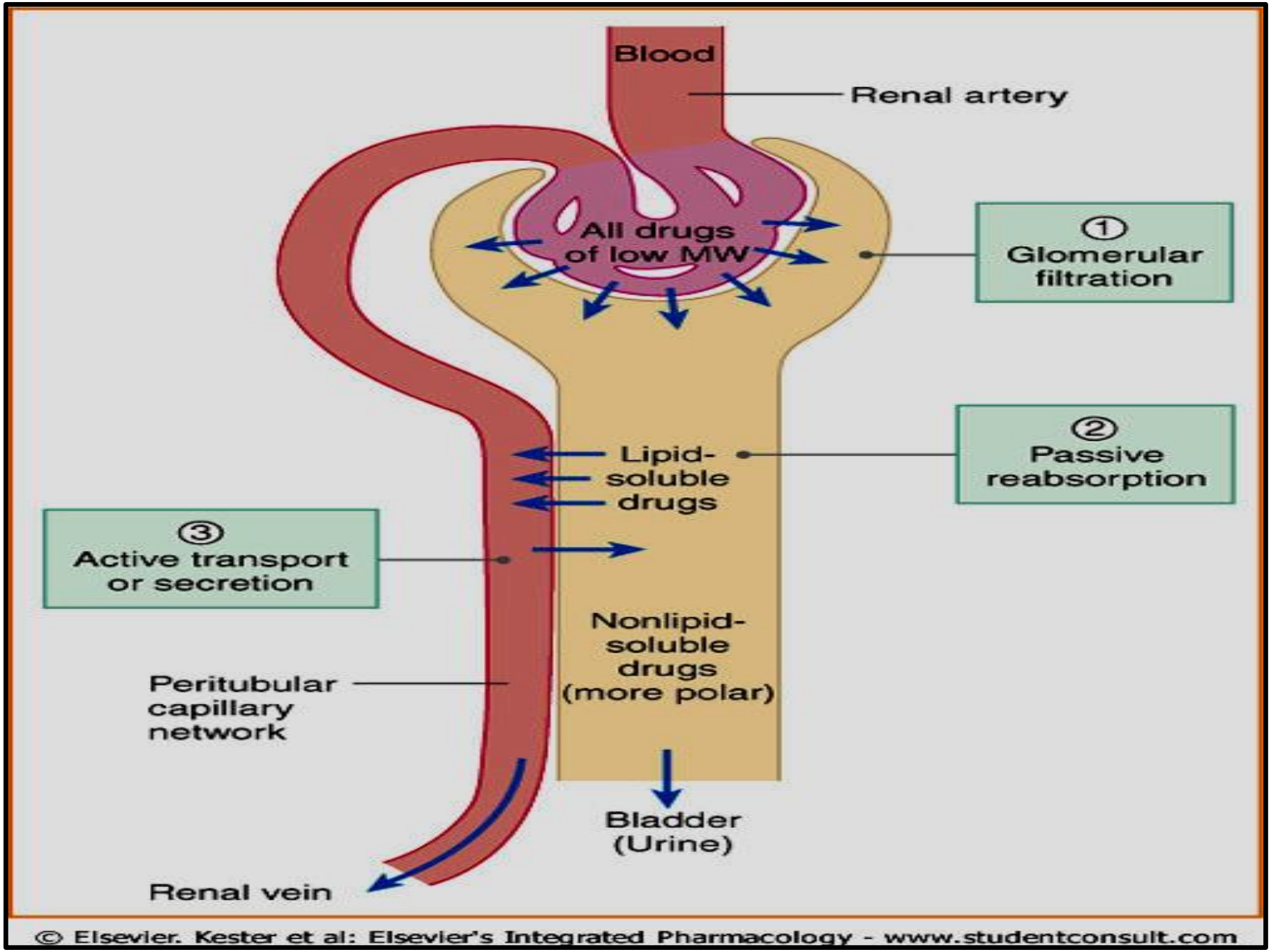
Transport of acidic drugs is blocked by probenecid

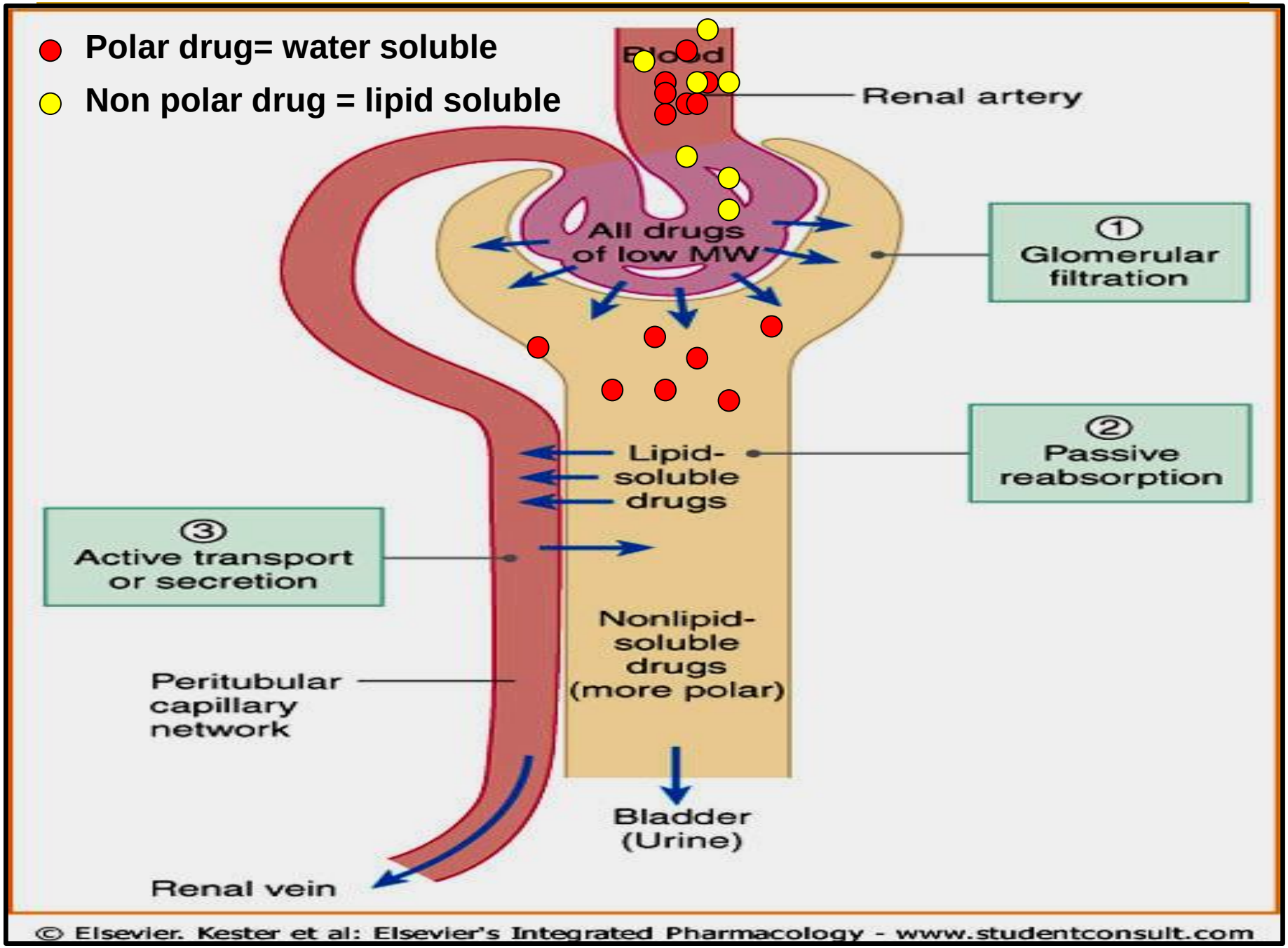
Transporters for basic drugs

- Morphine
- Atropine
- Quinine
- Neostigmine

Passive tubular re-absorption

- **In distal convoluted tubules & collecting ducts.**
- **Passive diffusion of unionized, lipophilic drugs**
- **Lipophilic drugs can be reabsorbed back from tubular lumen to blood circulation and excretion in urine will be low.**
- **Ionized drugs are poorly reabsorbed & so urinary excretion will be high.**




Polar drug= water soluble
Non polar drug = lipid soluble
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
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Urinary pH trapping (Ion trapping)

- **Changing the pH of urine by chemicals can inhibit or enhance the renal excretion of drugs.**
- **Urine is normally slightly acidic and favors excretion of basic drugs.**

Urinary pH trapping (Ion trapping)

- **Acidification of urine using ammonium chloride (NH4Cl) increases excretion of basic drugs as amphetamine.**
- **Alkalinization of urine using sodium bicarbonate $NaHCO_3$ increases excretion of acidic drugs as aspirin.**
- **Ion trapping is used to enhance renal clearance of drugs during toxicity.**

Renal Excretion

Drugs excreted mainly by the kidney include:

- **Aminoglycosides antibiotics (as gentamycin)**
- **B-lactam antibiotics as penicillin**
- **Lithium**

These drugs should be prescribed carefully in

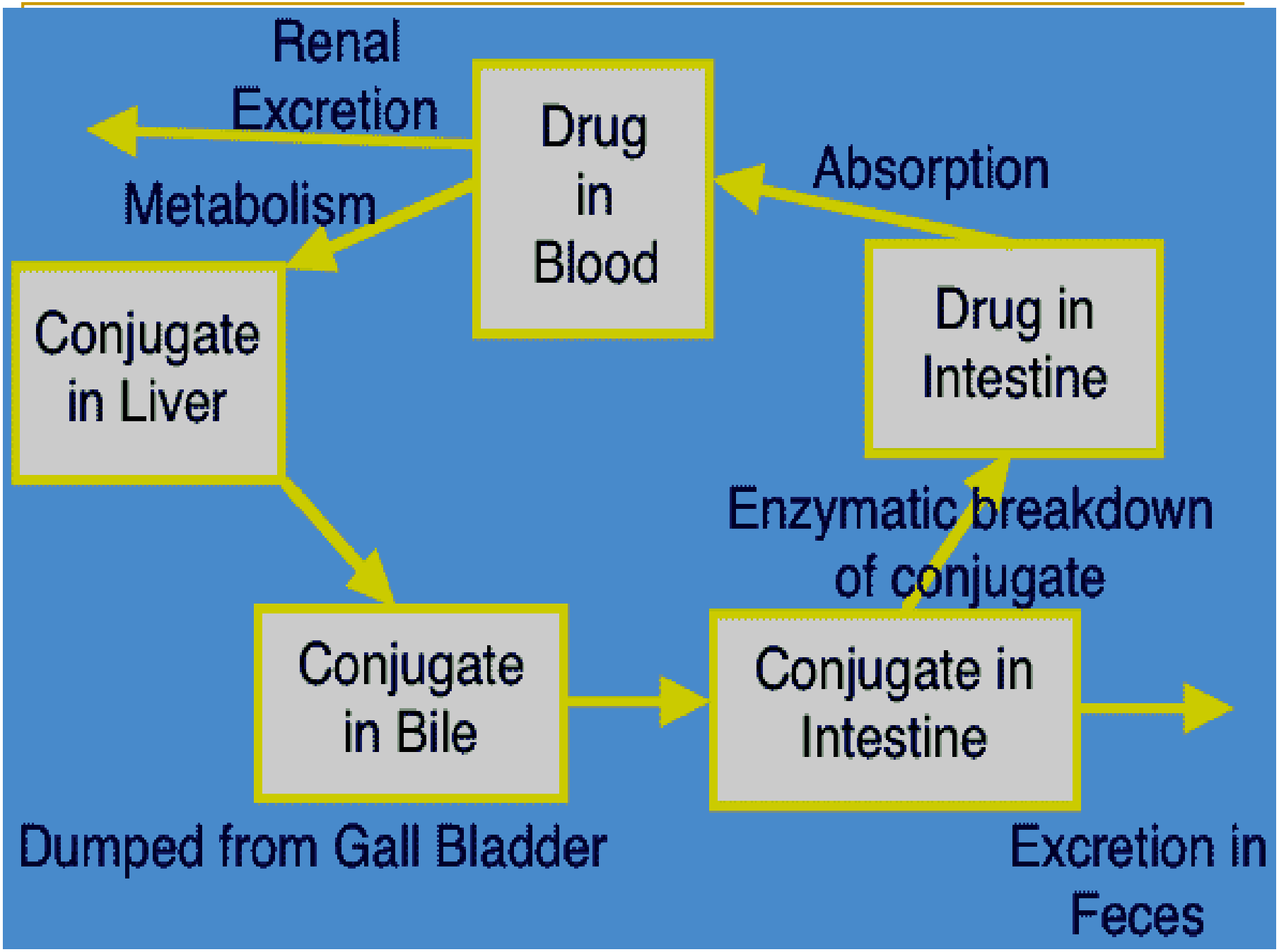
- **patients with renal disease.**
- **Elderly people**

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 from intestine back into systemic blood circulation.**

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 into blood if drugs are lipid soluble.**
- **This prolongs the duration of action of drugs e.g. digoxin, morphine, thyroxine.**


Renal Excretion
Drug in Blood
Absorption
Metabolism
Conjugate in Liver
Drug in Intestine
Enzymatic breakdown of conjugate
Conjugate in Bile
Conjugate in Intestine
Dumped from Gall Bladder
Excretion in Feces

Plasma half-life (t ½)

- **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 G, tubocurarine.**

Drugs of long plasma half life

- **Digoxin, thyroxine.**

Factors that may increase half-life (t ½)

Decreased metabolism

- **Liver disease.**
- **Microsomal inhibitors.**

Decreased clearance

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

High binding of drugs

- **Plasma proteins.**
- **Tissue binding.**

Enterohepatic recycling

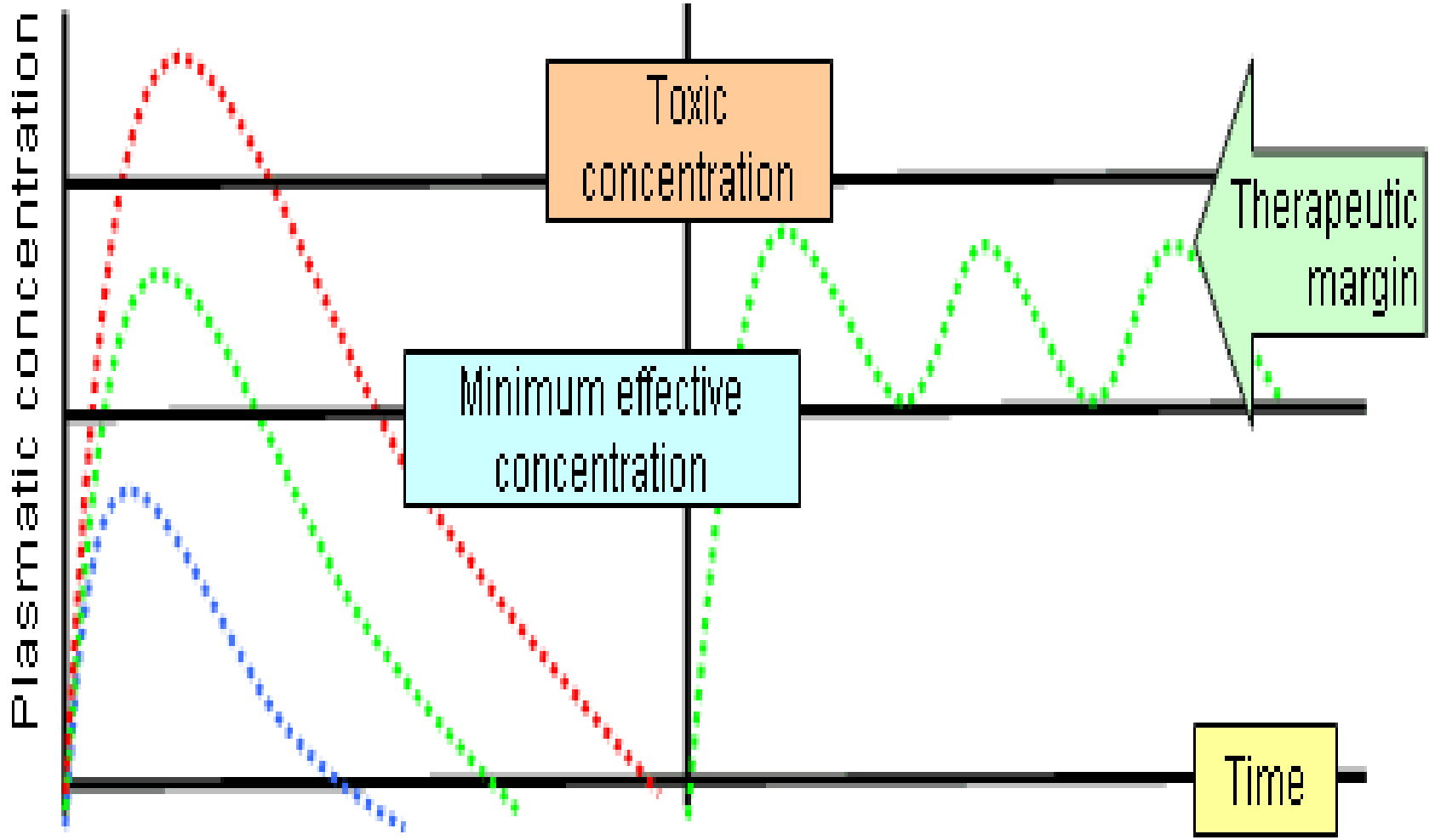
Steady state level.

- A state at which the therapeutic plasma concentration of the drug (mg/ml) remains constant within the therapeutic window

- **Therapeutic window:**

the range between the effective and the toxic level of the drug.

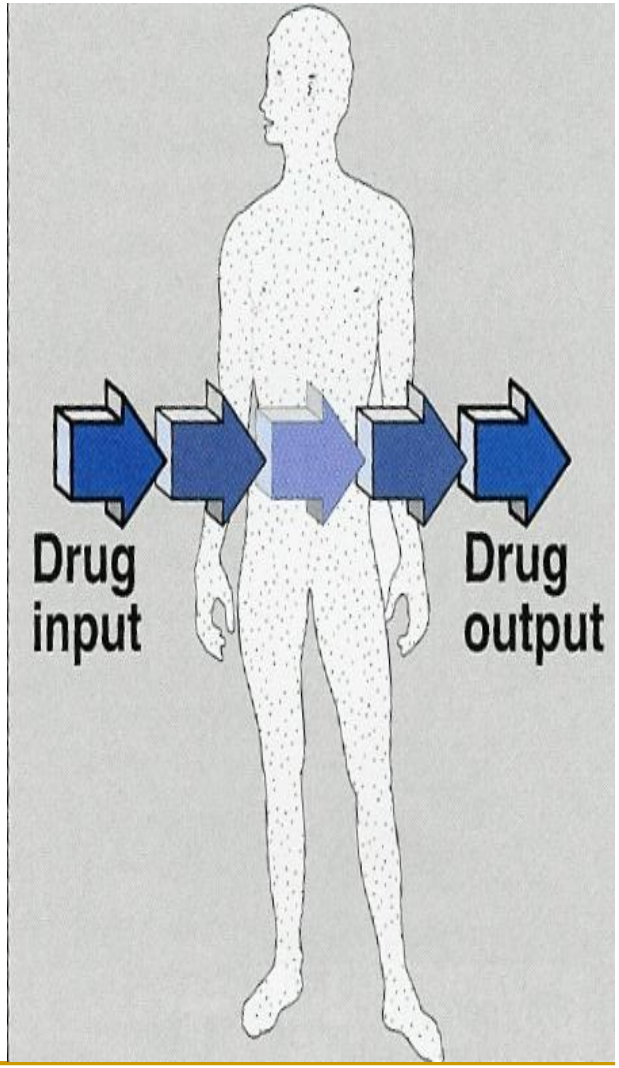
Therapeutic window



Steady state of a drug

Steady-state: the amount of drug eliminated equals the amount of drug administered

rate of drug administration = rate of drug elimination



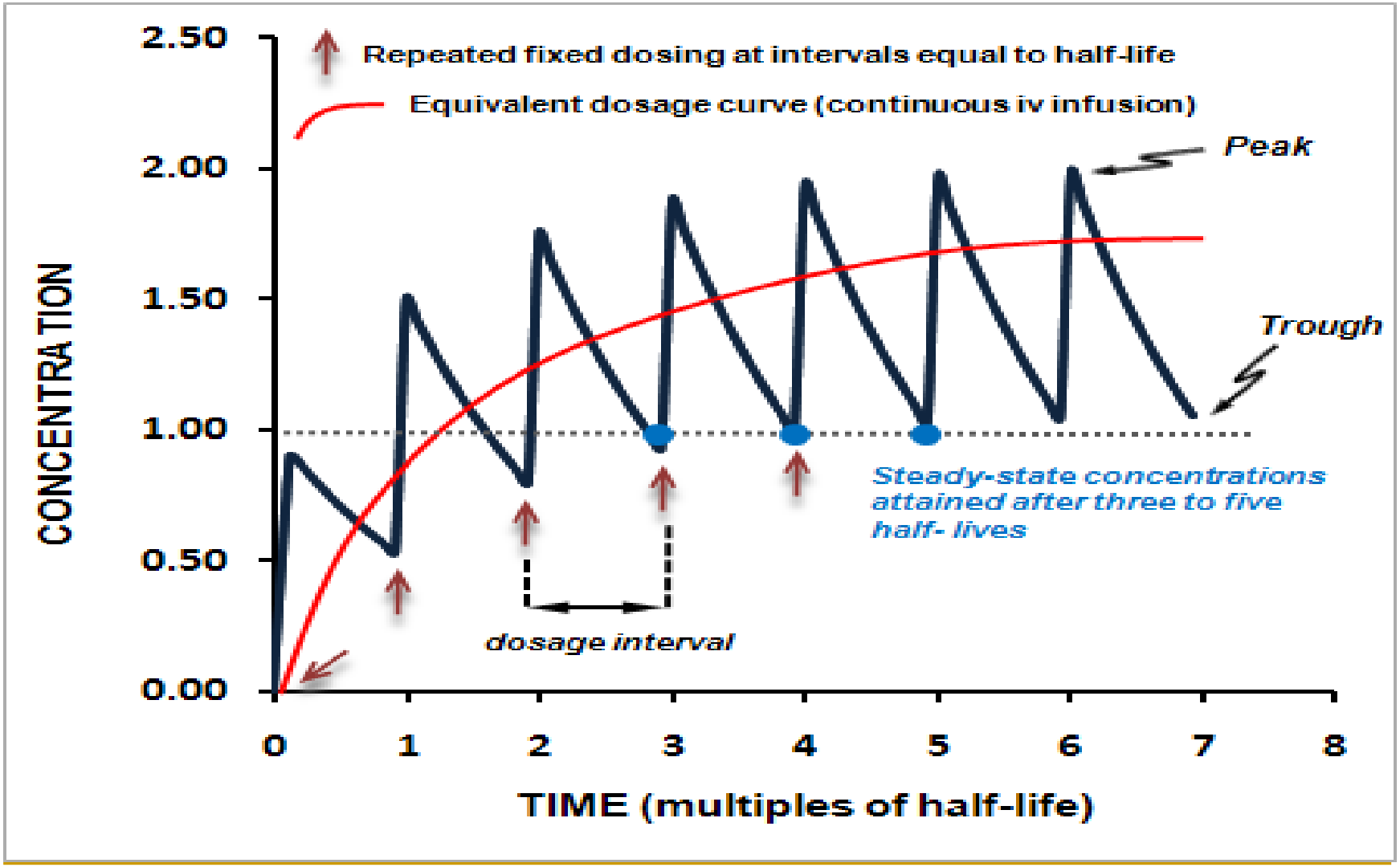
How many half-lives would be necessary to reach steady state?

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

$t_{1/2}$ can be used to predict how long it will take from the start of dosing to reach steady-state levels during multiple dosing.

No. of $t_{1/2}$	**Concentration achieved (% of steady conc.)**	
0		**100%**
1		**50 %**
2	**(50+100)**	**75%**
3	**(75+100)**	**87.5%**
4	**(87.5+100)**	**94%**
5	**(94+100)**	**97%**

Steady state levels



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.**

Loading dose =Vd x required plasma drug concentration

Clinical applications of loading dose

- A loading dose may be desirable if the **time required to attain steady state of drug is long** and **rapid relief is required** in the condition being treated.

- **e.g. lidocaine** is antiarrhythmic drug with t1/2 of around 1-2 hours.

Clinical applications of loading dose

- Arrhythmias after myocardial infarction are life-threatening, and one cannot wait more several hours to achieve a therapeutic concentration.

  Steady state= 3-5 X 2 hour = 6-10 hours

- 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.**
- **Maintenance dose =**

  Clearance x required Plasma concentration

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?