



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 ($t_{1/2}$), 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**

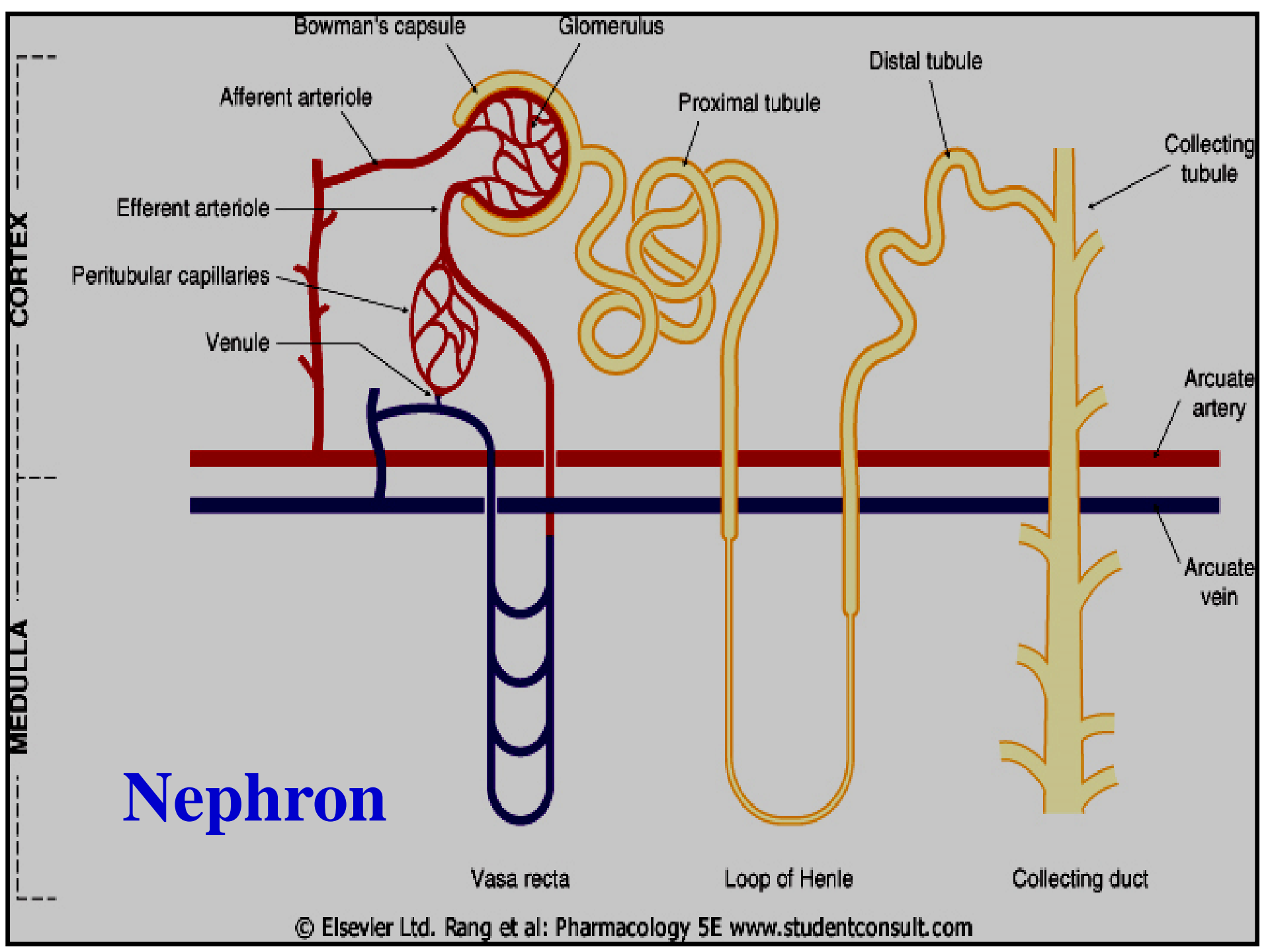
Renal Excretion

Structure of kidney

The structure unit of kidney is nephron

That consists of :

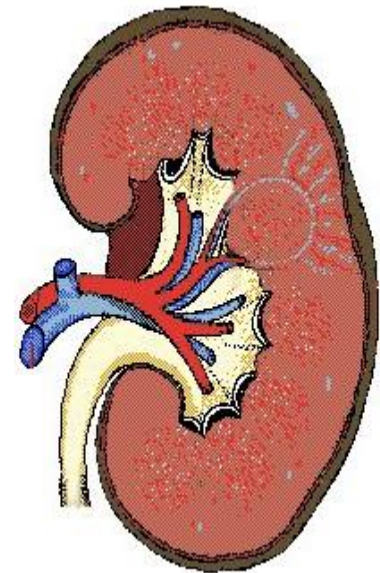
- ❑ Glomerulus**
 - ❑ Proximal convoluted tubules**
 - ❑ Loop of Henle**
 - ❑ Distal convoluted tubules**
 - ❑ Collecting ducts**
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Renal Excretion includes

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.
- ❑ Glomerular filtration occurs to:
 - ❑ 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**

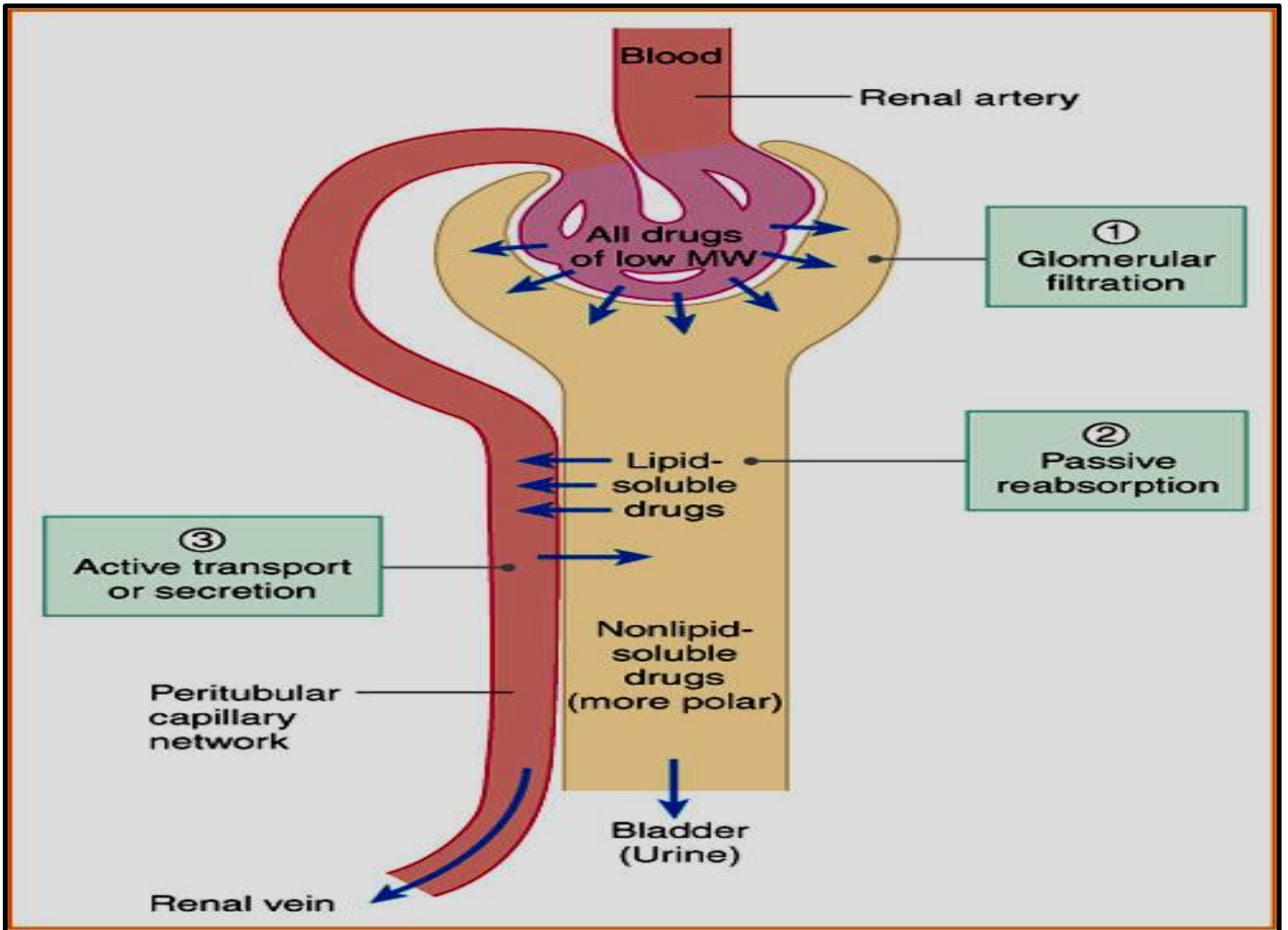
Transport of acidic drugs is blocked by probenecid

Transporters for basic drugs

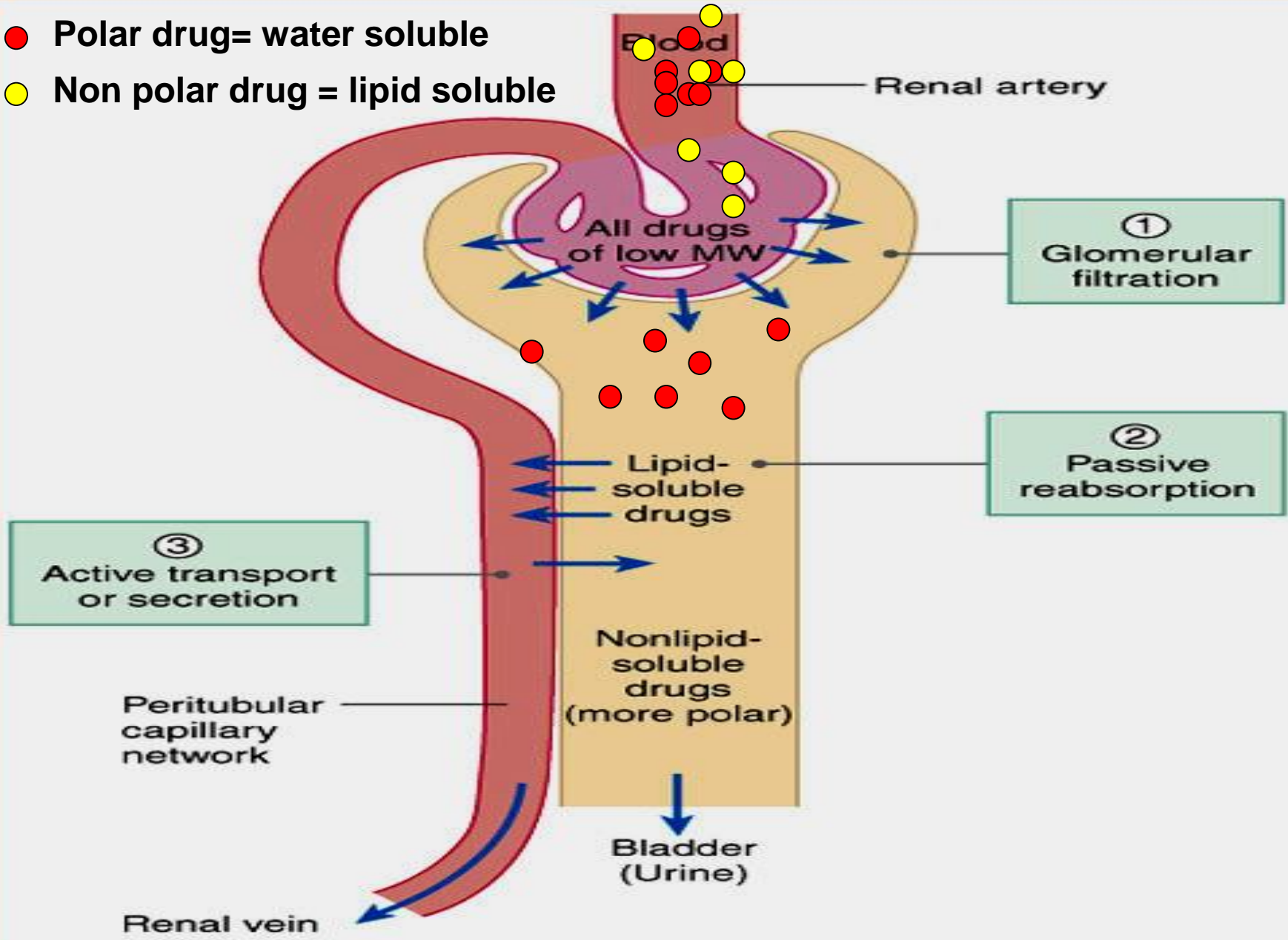
- **Morphine**
- **Atropine**
- **Quinine**
- **Neostigmine**

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



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 (NH_4Cl) 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.
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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

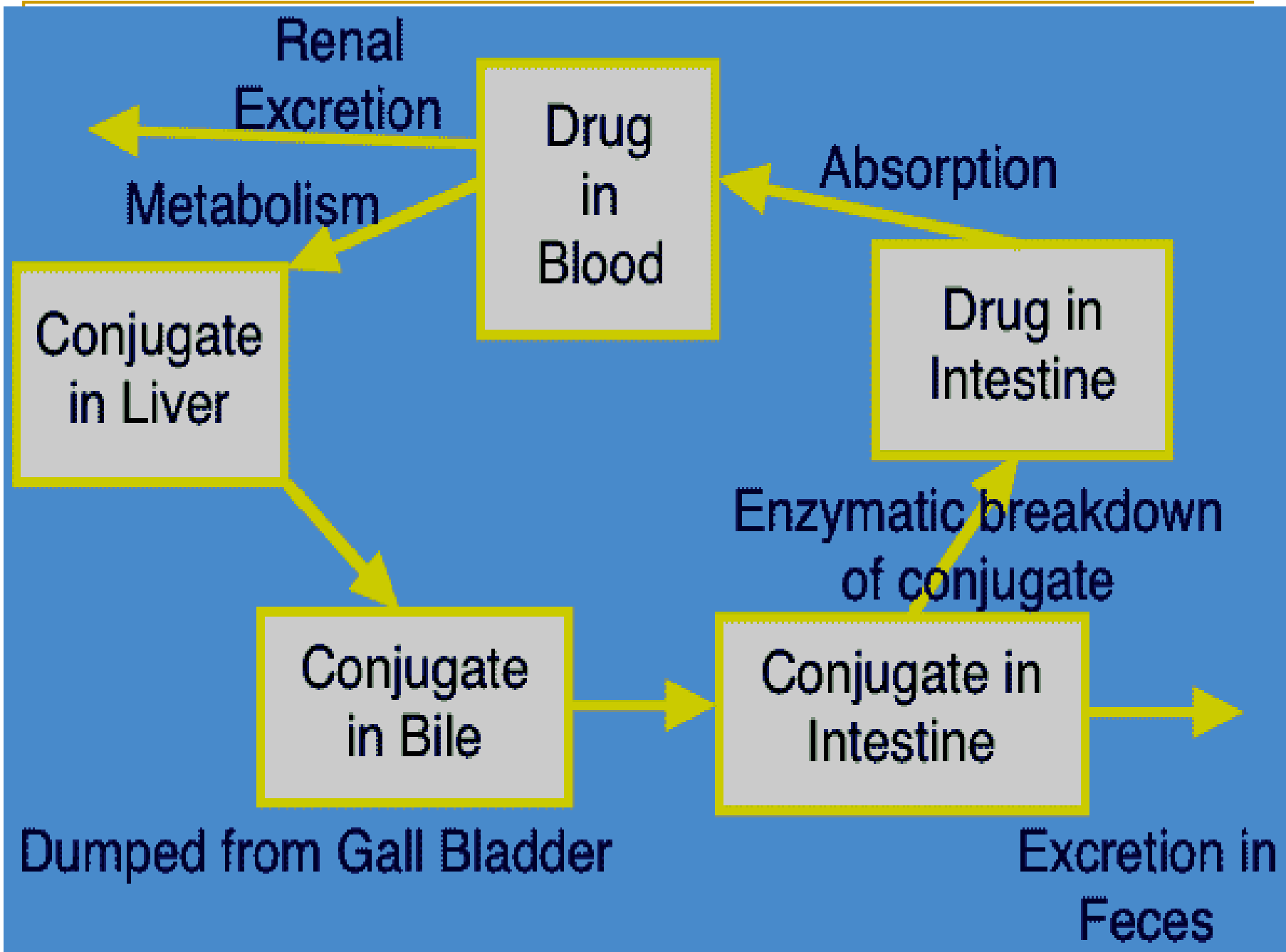
- **patients with renal disease.**
- **Elderly people**

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 **glucuronides** 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.**



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 G, tubocurarine.**

Drugs of long plasma half life

- **Digoxin, thyroxine.**

Factors that may increase 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

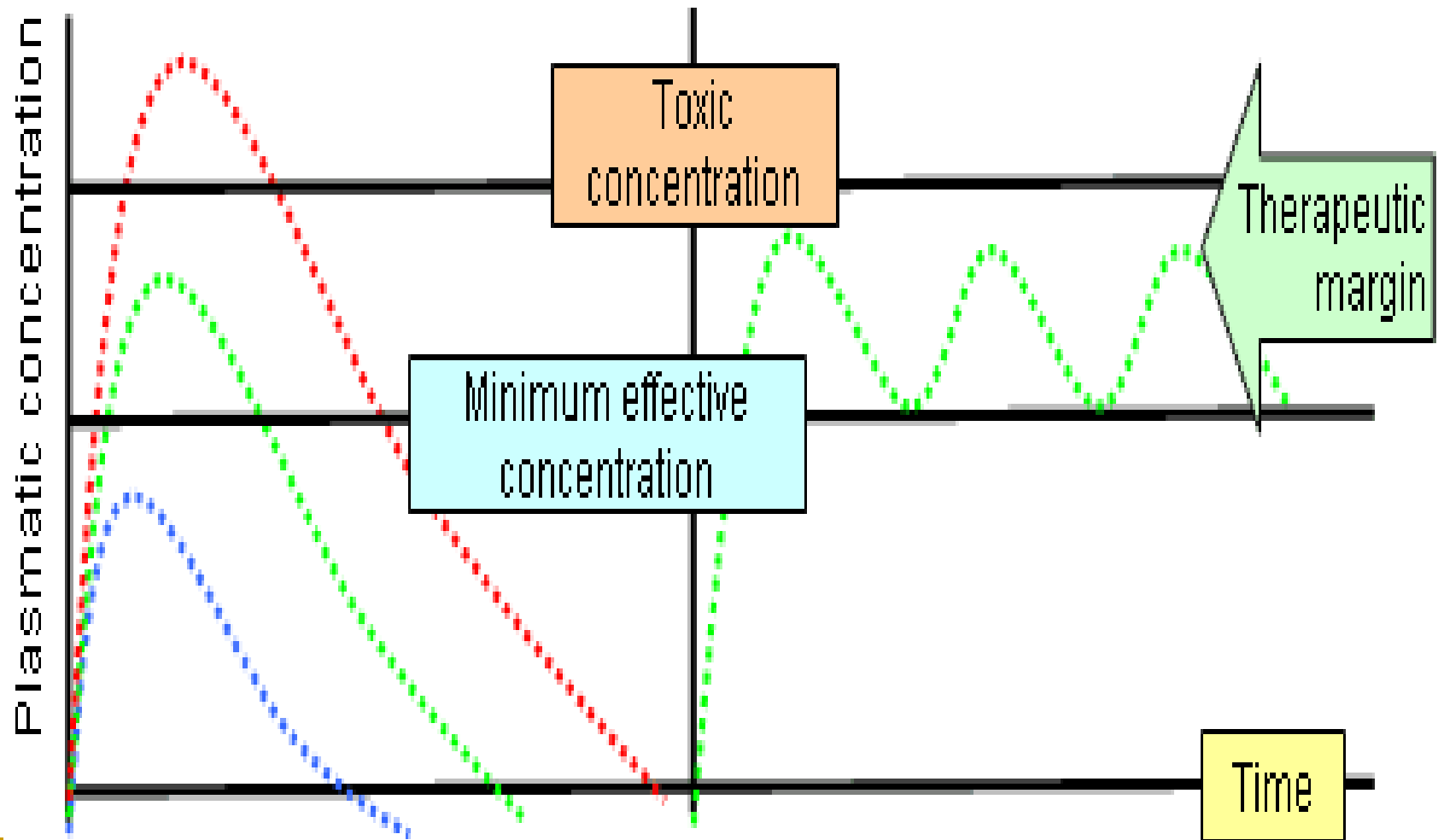
Steady state level.

- ❑ 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.

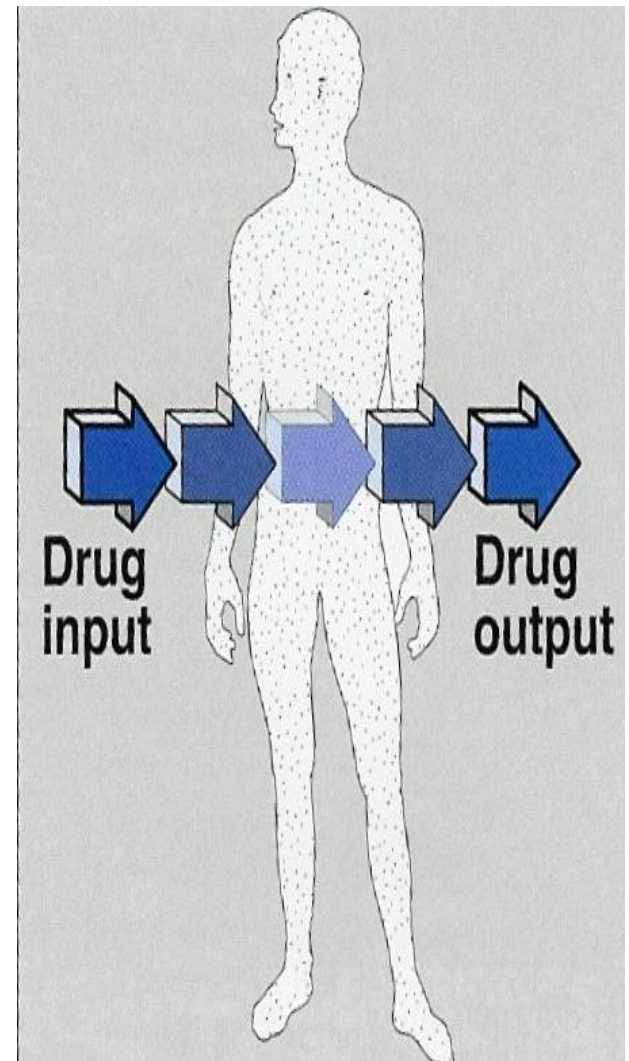
Therapeutic window



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



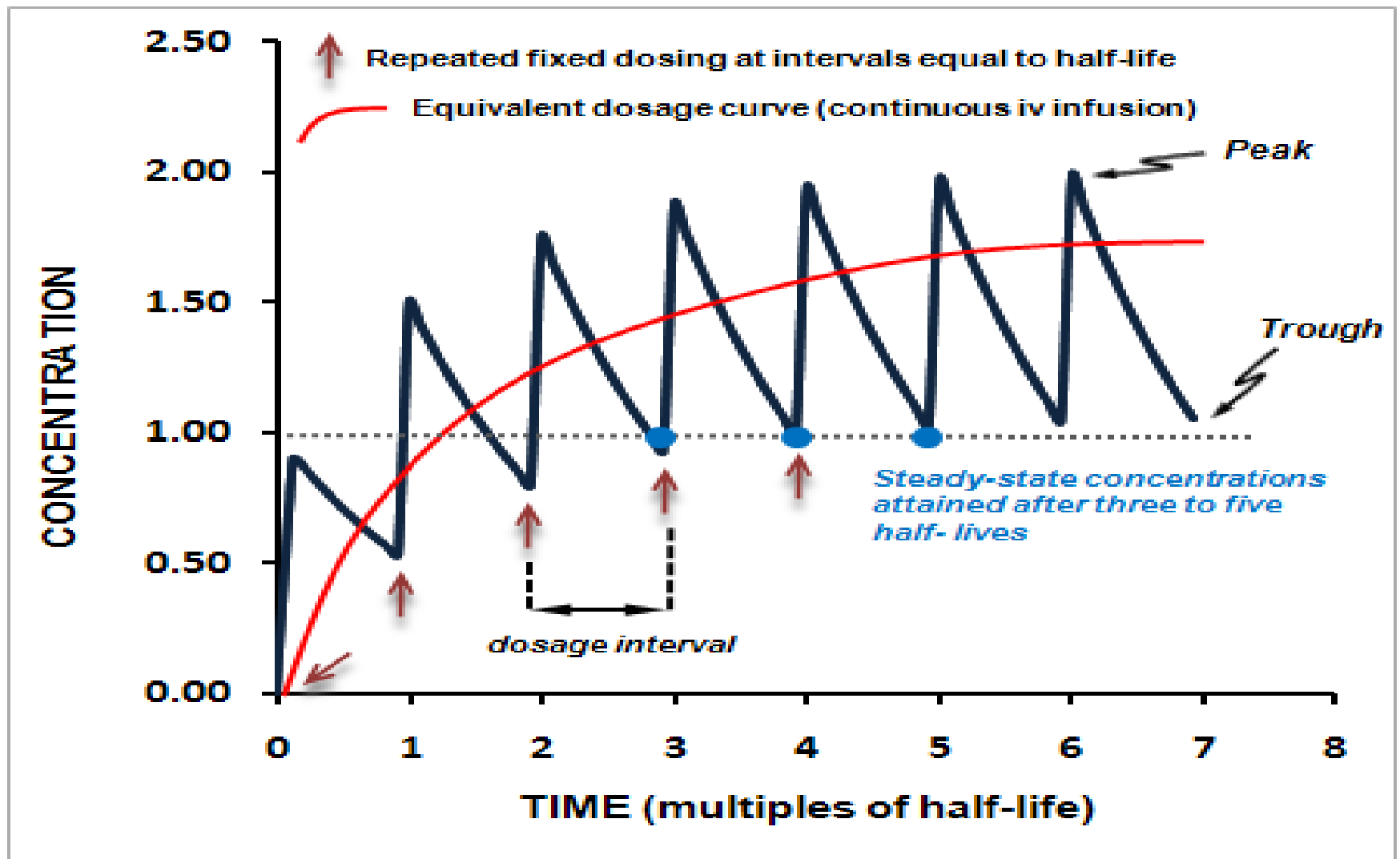
How many half-lives would be necessary to reach steady state?

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 = $V_d \times$ 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 $t_{1/2}$ of around 1-2 hours.
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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= $3-5 \times 2 \text{ hour} = 6-10 \text{ hours}$

- Use of a loading dose of lidocaine in the coronary care unit is standard.
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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
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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.
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Questions?

