EXCRETION OF DRUGS

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(Slides are adopted and modified from Prof. Hanan Hajar)

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 ½), multiple dosing, steady state levels, maintenance dose and loading dose.

Excretion

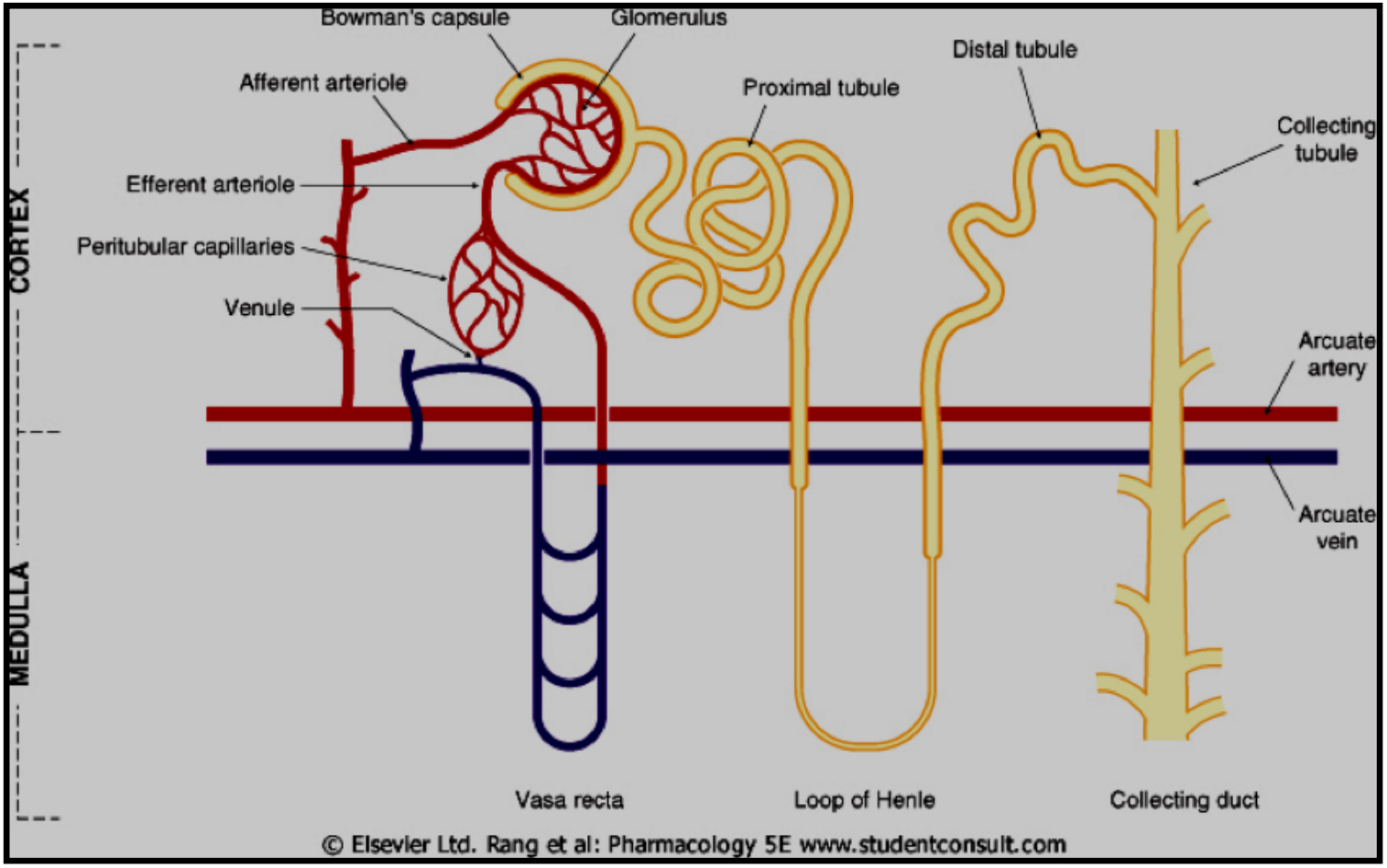
- **Major Routes of Excretion**
  - Renal Excretion
  - Biliary Excretion
- **Minor Routes of Excretion**
  - Pulmonary excretion.
  - Salivary excretion.
  - Mammary excretion via milk.
  - Skin / Dermal excretion via sweat.
  - Tears

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


Bowman's capsule
Glomerulus
Afferent arteriole
Proximal tubule
Distal tubule
Collecting tubule
Efferent arteriole
Peritubular capillaries
Venule
CORTEX
MEDULLA
Arcuate artery
Arcuate vein
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:

Renal Excretion= Filtration – Reabsorption + Secretion

- 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.

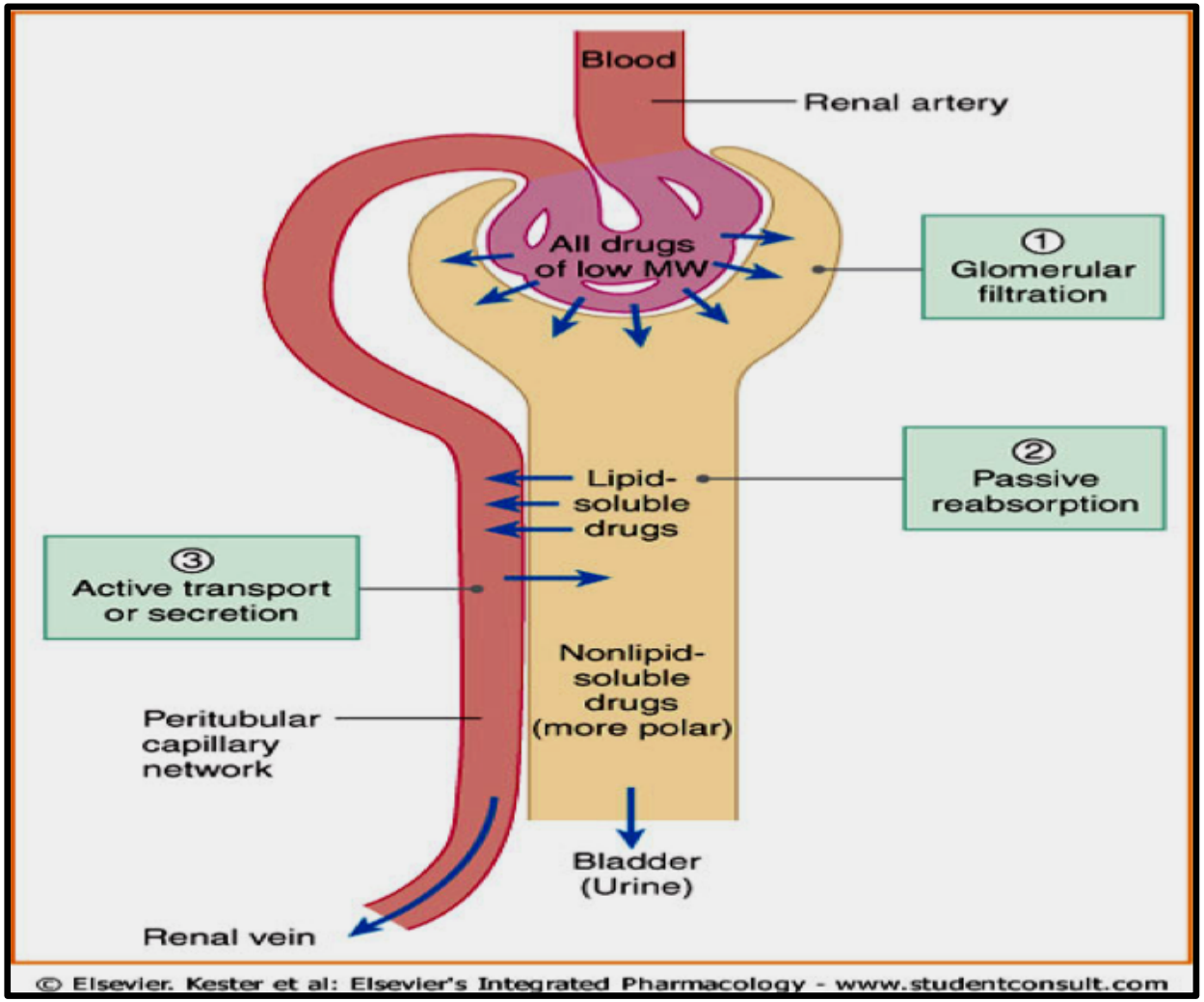
Renal Excretion includes

- 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.

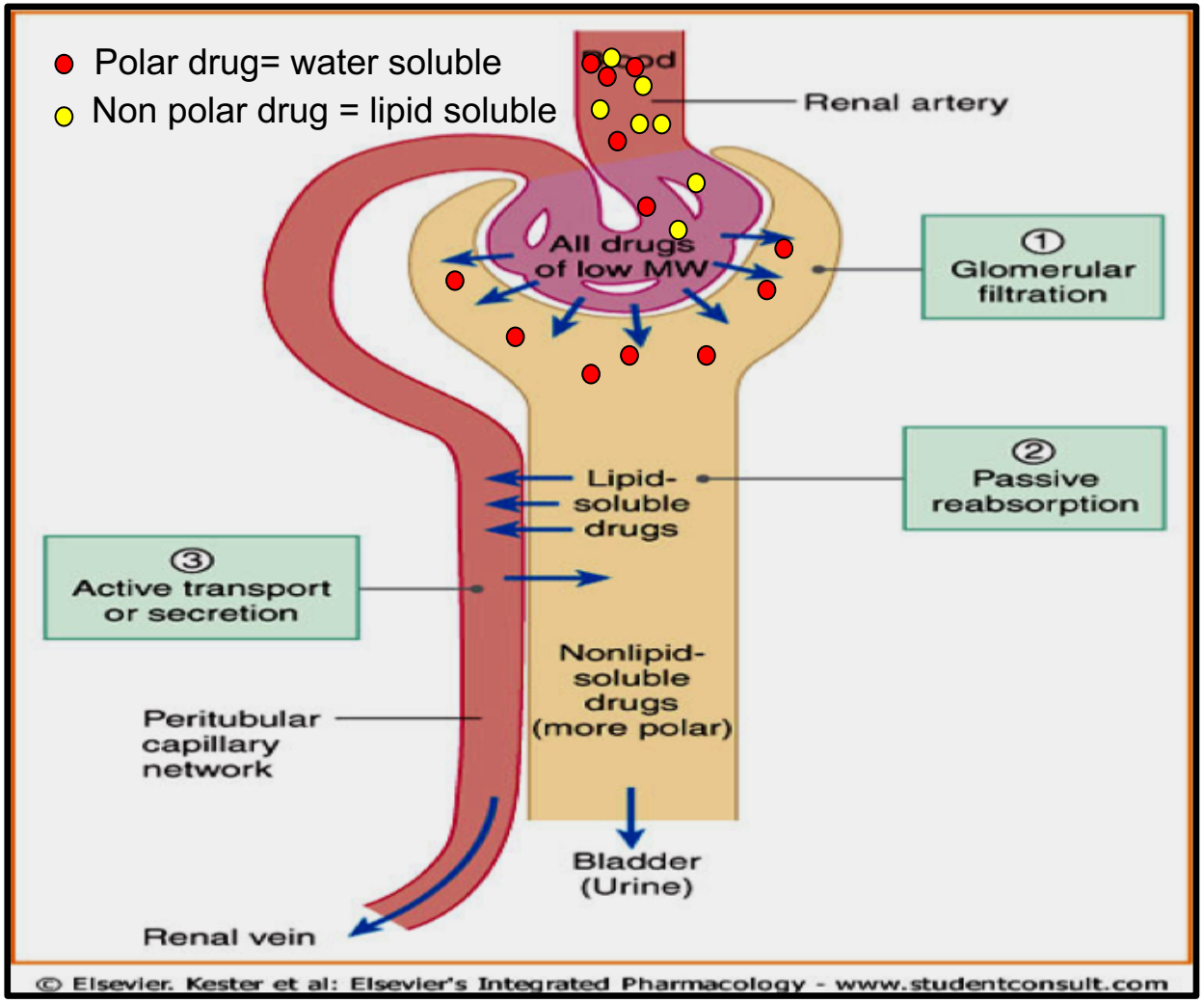
Renal Excretion includes

- 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 (NH4Cl) increases excretion of basic drugs as amphetamine.

- Alkalinization of urine using sodium bicarbonate ($NaHCO_3$) 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

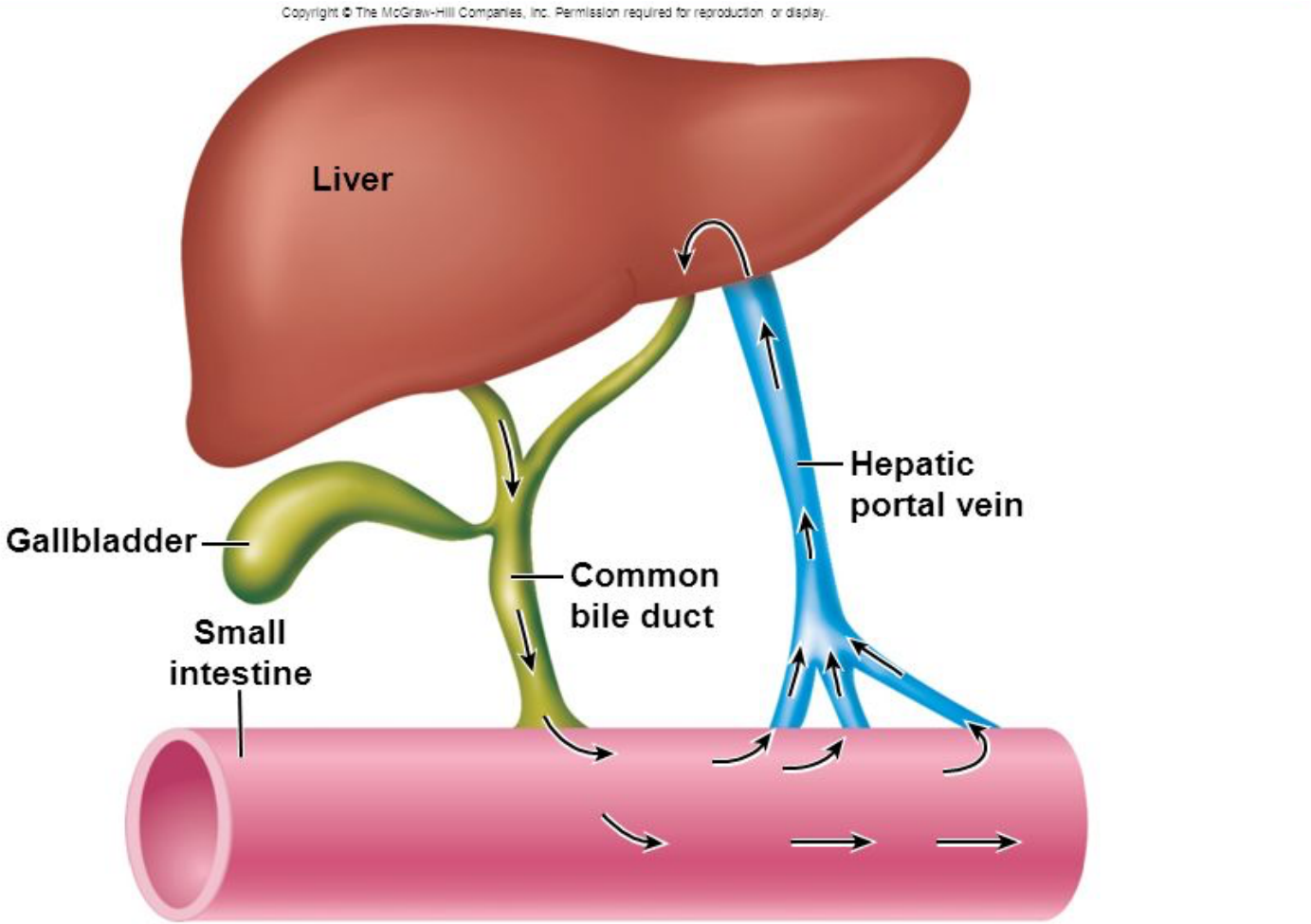
Biliary Excretion

- 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

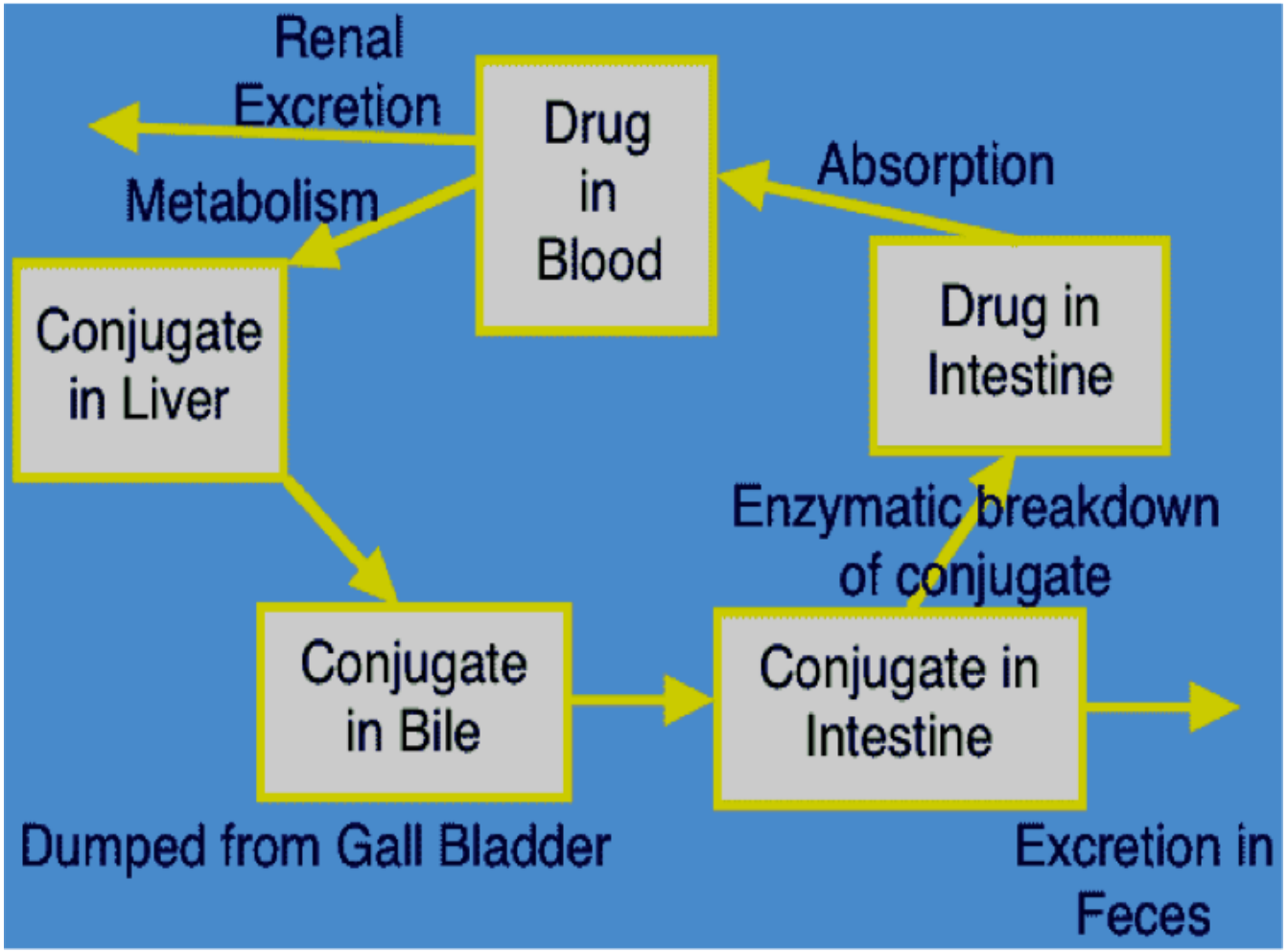
Enterohepatic circulation

- Drugs excreted in the bile in the form of glucouronides 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



Excretion


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, tubocurarine.

Drugs of long plasma half life

- Digoxin, Thyroxine.

Factors May Increase Plasma half-life (t ½)

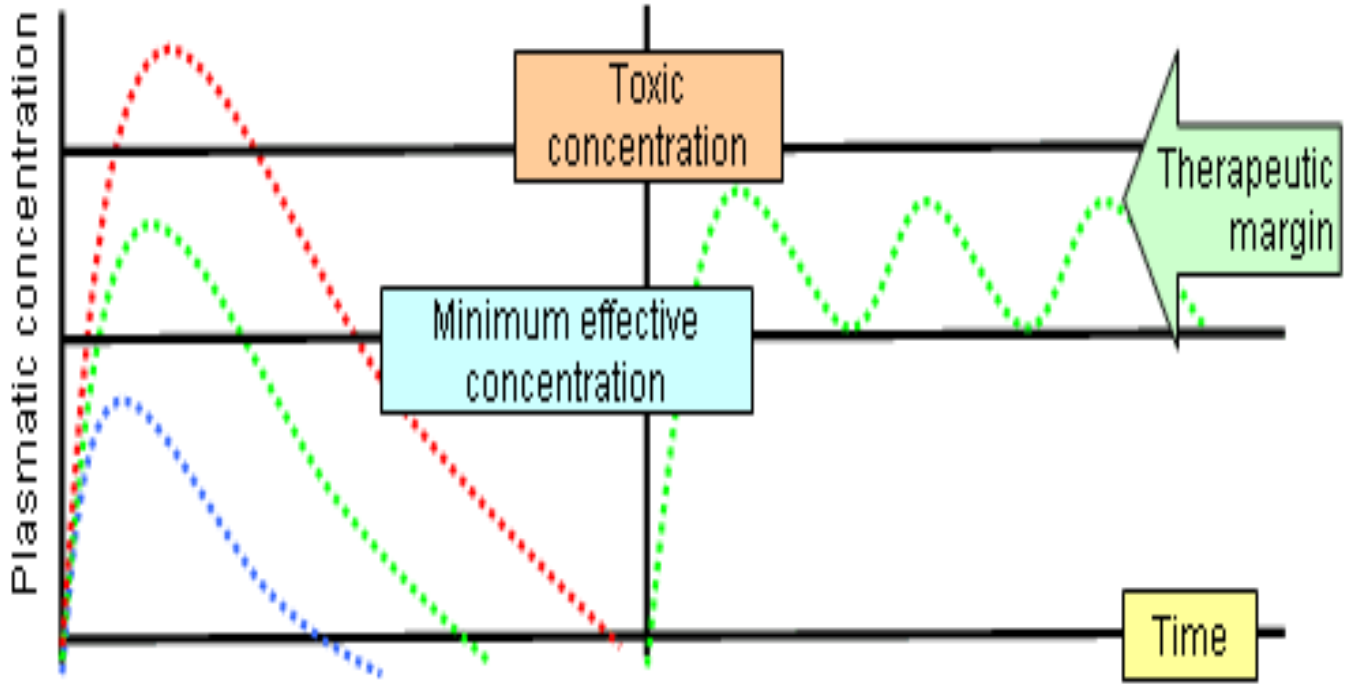
- Decreased metabolism
  - Liver disease.
  - Microsomal inhibitors.
- Decreased clearance
  - Renal disease.
  - Congestive heart failure.
- High binding of drugs
  - Plasma proteins.
  - Tissue binding.
- Enterohepatic recycling

Steady State

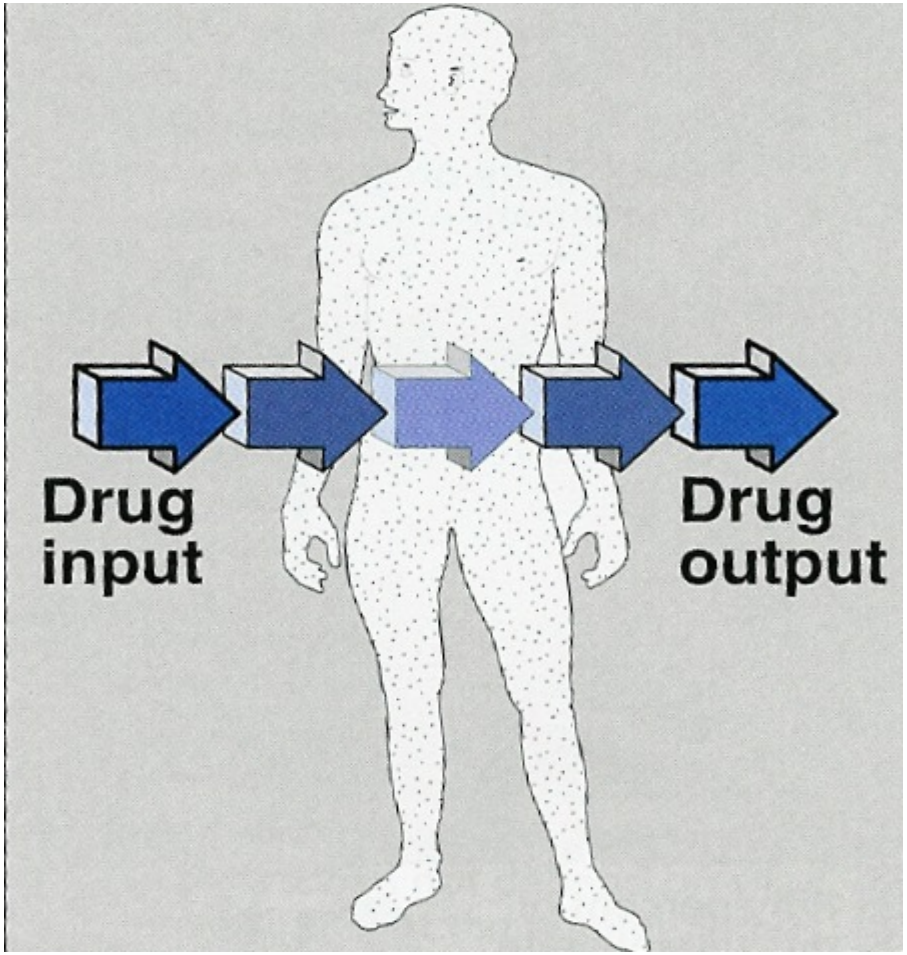
- A state at which the therapeutic plasma concentration of the drug (mg/ml) remains constant with the therapeutic window (the range between effective and toxic levels of drugs).
- At steady state:

rate of drug administration = elimination rate

Therapeutic Window



Steady State



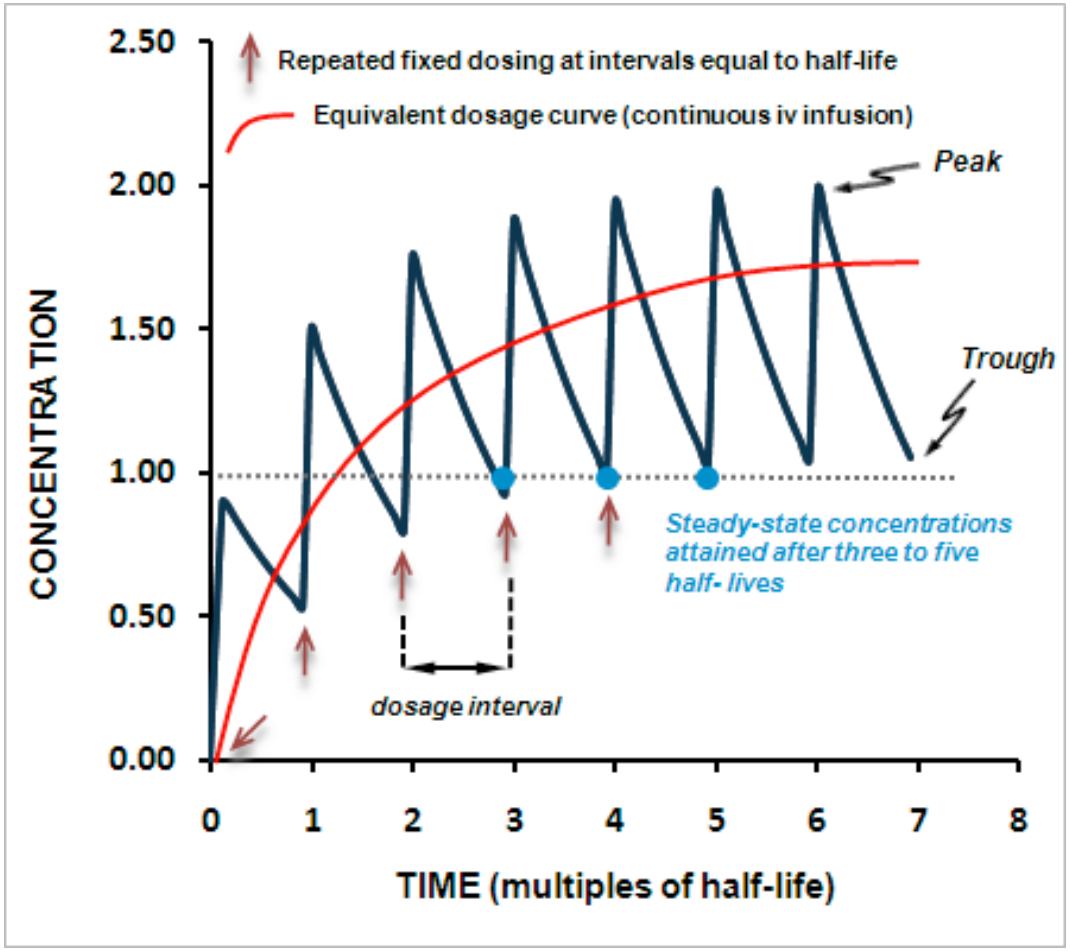
Steady State

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

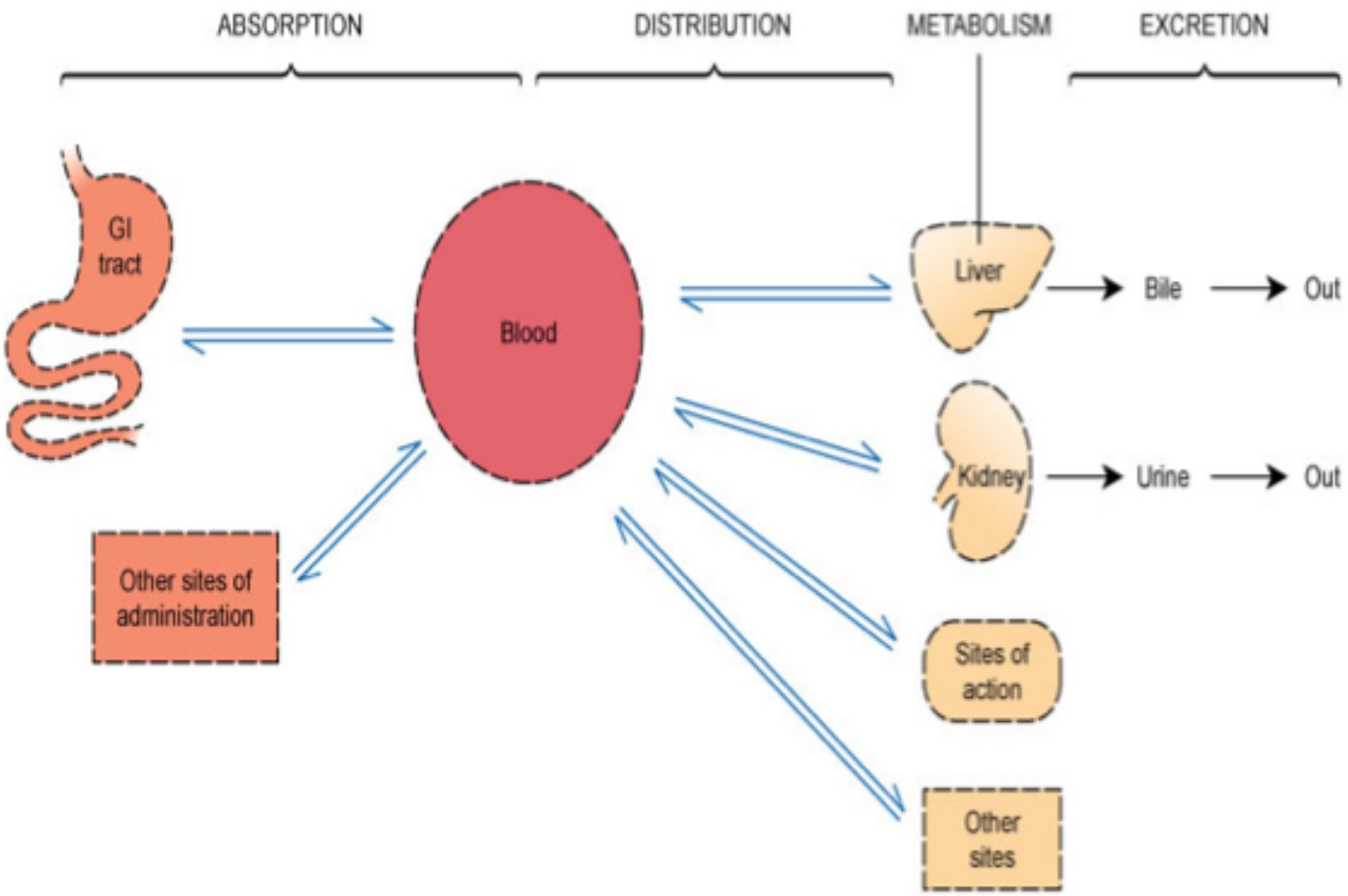
- A loading dose may be desirable if the time required to attain steady state of drug (4 elimination t1/2 values) is long and rapid relief is required in the condition being treated.
- E.g. t1/2 of lidocaine (antiarrhythmic drug) is usually 1-2 hours. Arrhythmias after myocardial infarction are life-threatening, 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.


ABSORPTION
DISTRIBUTION
METABOLISM
EXCRETION
GI tract
Blood
Liver
Bile
Out
Kidney
Urine
Out
Other sites of administration
Sites of action
Other sites

Questions