Excretion of Drugs

OUTLINE

- Main and minor routes of Excretion.
- Renal Elimination.
- Biliary Excretion
- Enterohepatic Circulation.
- Clearance of drugs

Excretion of Drugs

OUTLINE

- Half-life (t ½).
- Multiple dosing.
- Steady state levels.
- Maintenance dose.
- Loading dose.

Routes of Excretion

Main Routes of Excretion

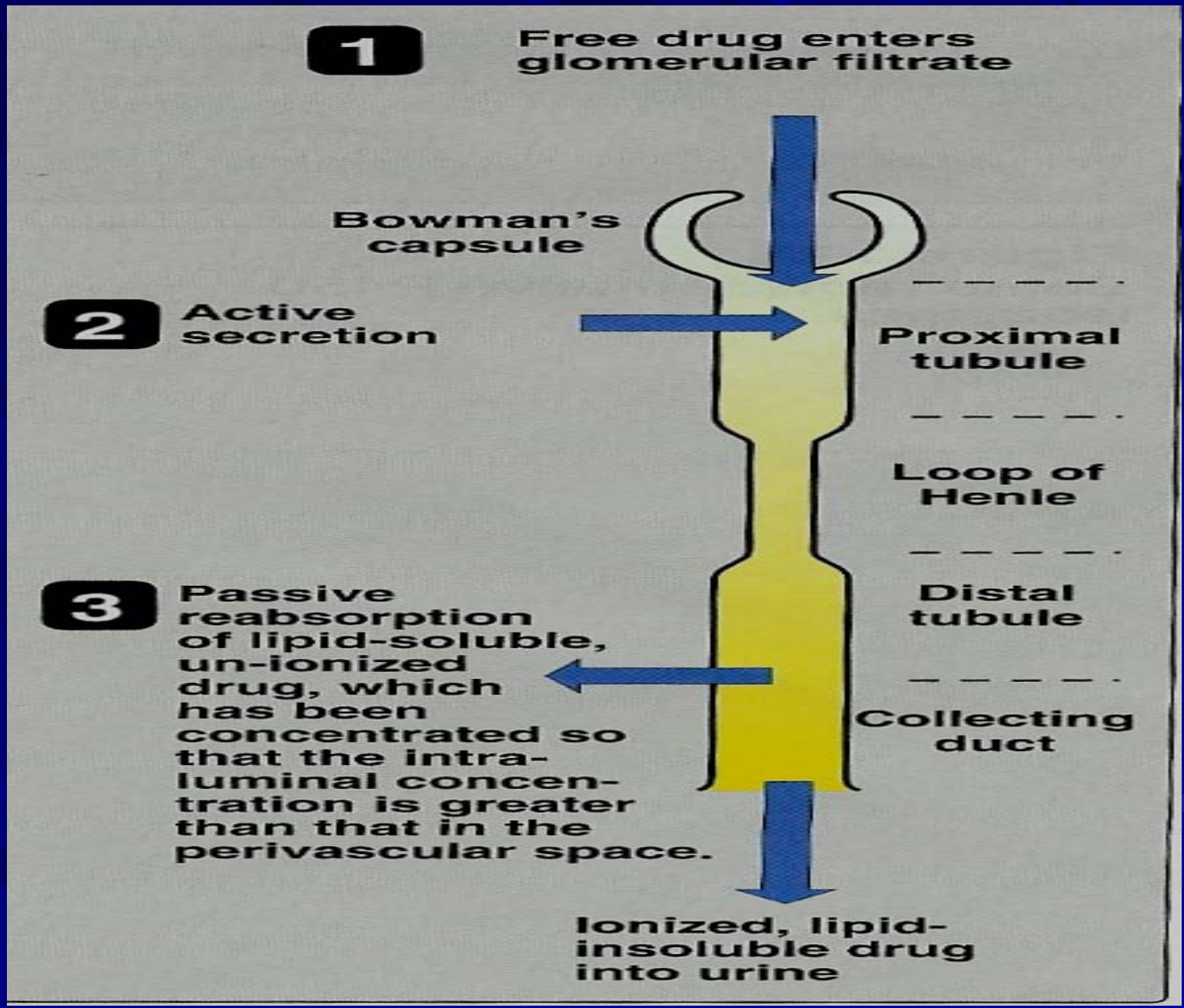
1. Renal Excretion
2. Biliary Excretion

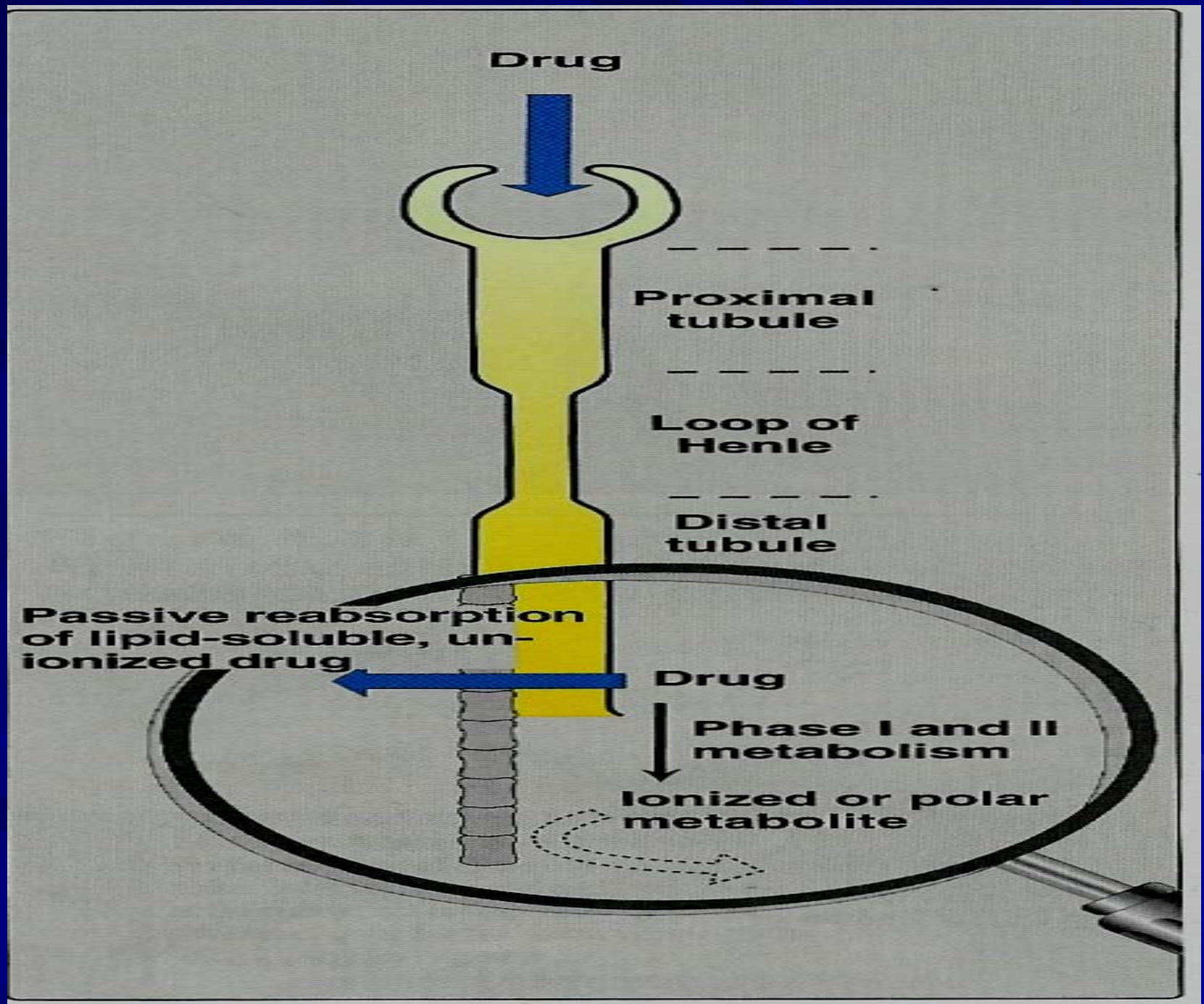
Minor Routes of Excretion.

1. Exhaled air (Exhalation)
2. Salivary
3. Sweat
4. Milk
5. Tears

Renal Excretion includes

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


1
Free drug enters glomerular filtrate
Bowman's capsule
2
Active secretion
Proximal tubule
Loop of Henle
Distal tubule
3
Passive reabsorption of lipid-soluble, un-ionized drug, which has been concentrated so that the intra-luminal concen-tration is greater than that in the perivascular space.
Collecting duct
Ionized, lipid-insoluble drug into urine


Drug
Proximal tubule
Loop of Henle
Distal tubule
Passive reabsorption of lipid-soluble, un-ionized drug
Drug
Phase I and II metabolism
Ionized or polar metabolite

Glomerular filtration.

- RPF = 600 ml/min
- GFR 20% of RPF = 125 ml/min.
- Only free drugs (unbound to plasma proteins).
- Low MW drugs

Active tubular secretion

Mainly in proximal tubules

Characters ?

1. Selective.
2. Require energy.
3. Can transport drugs against conc. gradients.
4. Clearance to plasma protein bound drugs.

Types ?

1. System for Acidic drugs.
2. System for Basic drugs

1. System for Acidic drugs.

- Penicillin
- Uric acid
- Salicylates
- Sulphonamides

Blocked by probenecid

2. System for Basic drugs

- Atropine
- Morphine
- Quinine
- Neostigmine
- Catecholamines

Passive tubular reabsorption.

- In distal convoluted tubules & collecting ducts.
- Passive diffusion
- Lipid soluble form of the drug (Non ionized) can be reabsorbed back into systemic circulation and excretion will be low.
- Ionized drugs are poorly reabsorbed & so excretion is high

Drugs excreted by kidney are

Gentamycin

Penicillin

Dose should be reduced in

Elderly

Renal failure

Ion trapping (Forced diuresis)

Alteration of the pH of urine may be used to minimize the renal reabsorption & increase clearance.

- Urine is normally slightly acidic & favors excretion of basic drugs.
- Acidification of urine increases excretion of basic drugs.
- Alkalization of urine increases excretion of acidic drugs.

Acidification of urine

- Ammonium chloride (NH_4Cl)

Alkalinization of urine

- sodium bicarbonate ($NaHCO_3$)

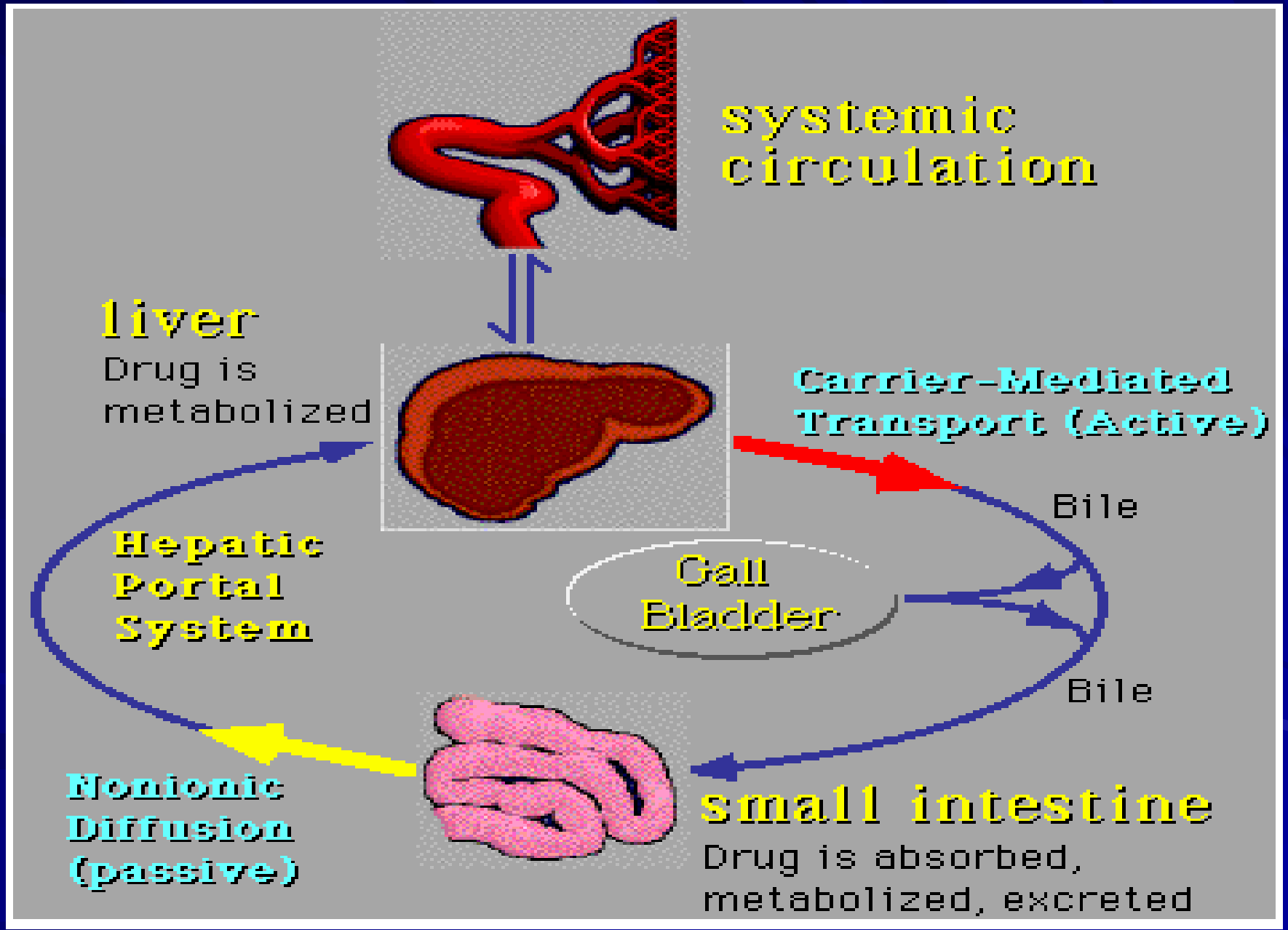
Biliary Excretion

- Plays a role in the removal of conjugated metabolites particularly glucouronides.

Enterohepatic circulation

- Drugs excreted in the bile as 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.

Enterohepatic circulation



DRUG CLEARANCE

a rate of elimination of drug by all routes to the. concentration of a drug in plasma)

$$\text{Clearance (ml / min)} = \frac{\text{Rate of elimination (mg / min)}}{\text{conc. Of drug in plasma (mg / ml)}}$$

$$CL_{total} = CL_{renal} + CL_{hepatic} + CL_{others}$$

RENAL CLEARANCE

A rate of elimination of a drug in urine relative to its serum concentration

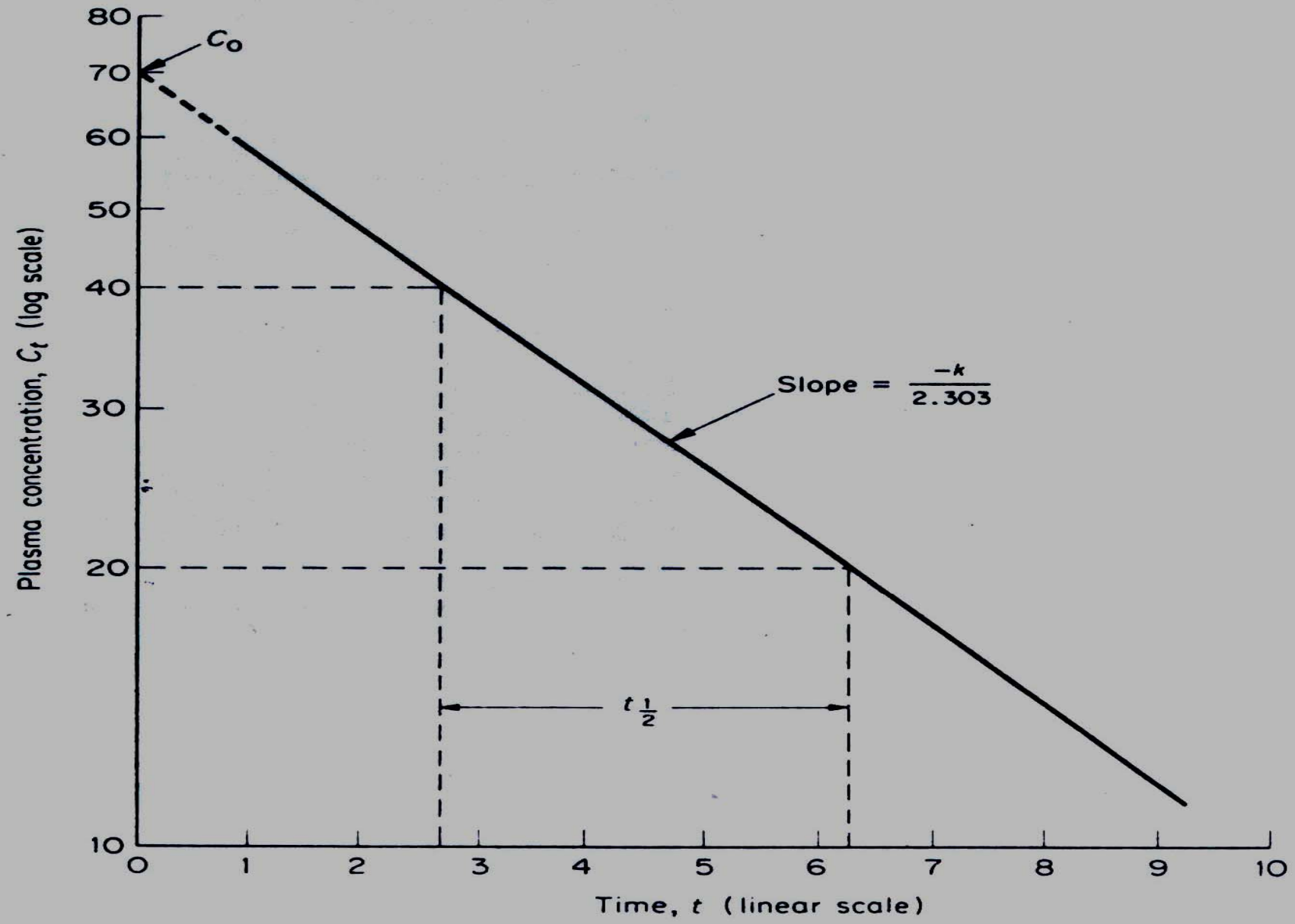
Clearance

- Units are L/h or L/h/kg
- Cl total= ke. Vd
- Ke = is elimination rate constant
- Used for determination of maintenance dose

Plasma Half-Life (t ½)

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

$$t\,½ = \frac{0.693}{ke} = \frac{Vd \;\; X\; 0.693}{CL}$$


80
70
60
50
40
30
20
10
C_o
Plasma concentration, C_t (log scale)
Slope = $\frac{-k}{2.303}$
$t_{\frac{1}{2}}$
0
1
2
3
4
5
6
7
8
9
10
Time, t (linear scale)

Drugs of short plasma half life has short duration of action.

Drugs of long plasma half life has long duration of action.

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

Loading dose

is the large initial dose that is given till the required therapeutic plasma level is rapidly reached.

Loading dose (mg) = Vd (L) x Desired plasma conc. (mg / L)

Calculate loading dose required for drug if you know that

- target concentration =10 mg/L
- Vd =0.75 L/kg
- Patient weight is 75 kg

Vd = 0.75x75= 56.25 L

Loading dose (mg) = Vd X conc

= 10 mg/L X 56.25 =565 mg

Maintenance doses

are the doses required to maintain the therapeutic level of the drug. These doses balance the clearance of the drug.

Maintenance dose (mg / min) =
CL X desired steady state conc.

Units of CL are L/h or L/h/kg

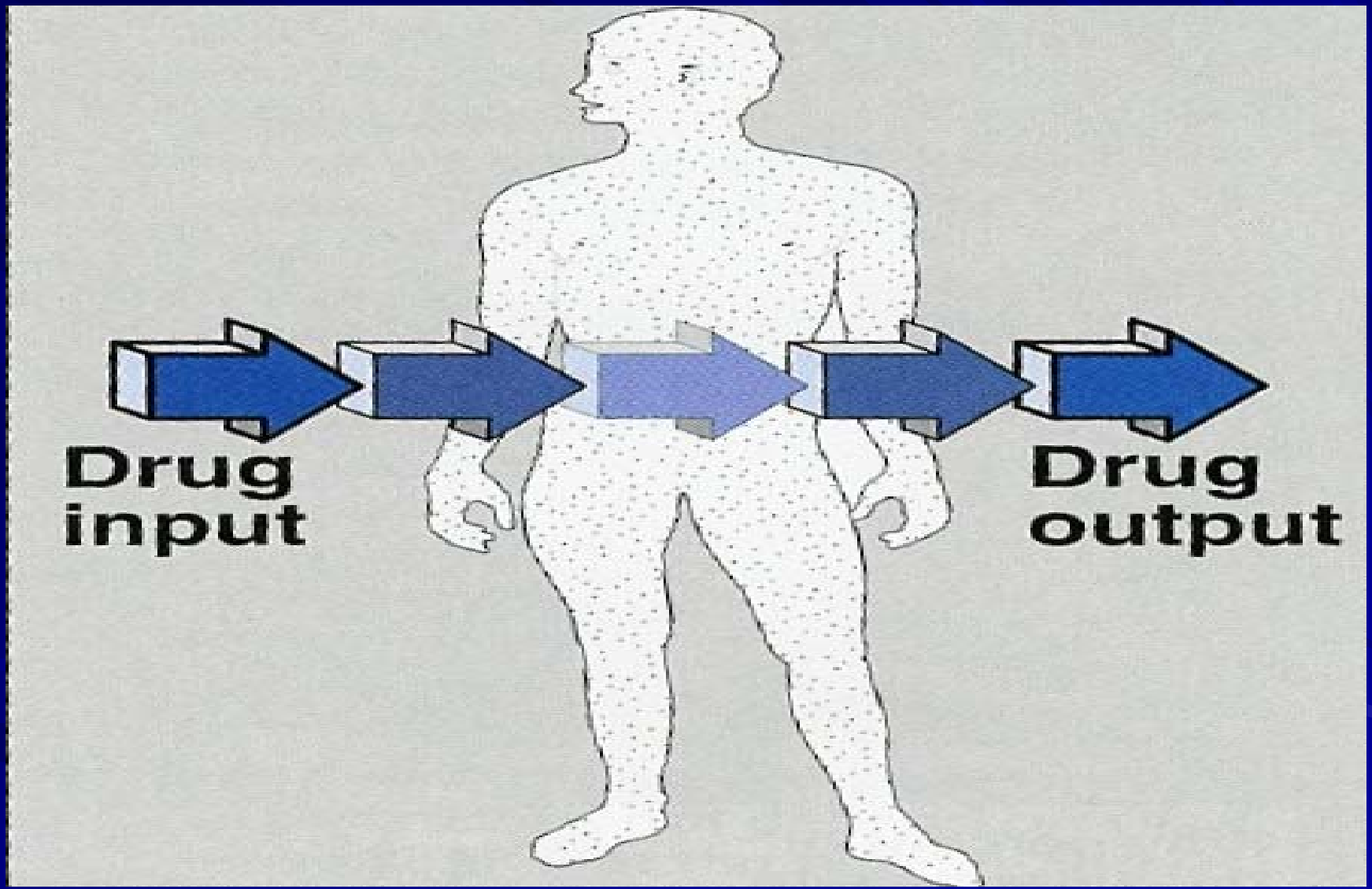
For maintenance dose, unit is mg/h

Total daily maintenance dose= multiply by 24 h

Steady state levels.

- A state at which the plasma concentration of the drug remains constant.
- Rate of drug administration = Rate of drug elimination.
- Steady state is reached after five half-lives.

Steady state of a drug



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