Excretion of Drugs

OUTLINE

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

Excretion of Drugs

OUTLINE

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

Routes of Excretion

Main Routes of Excretion

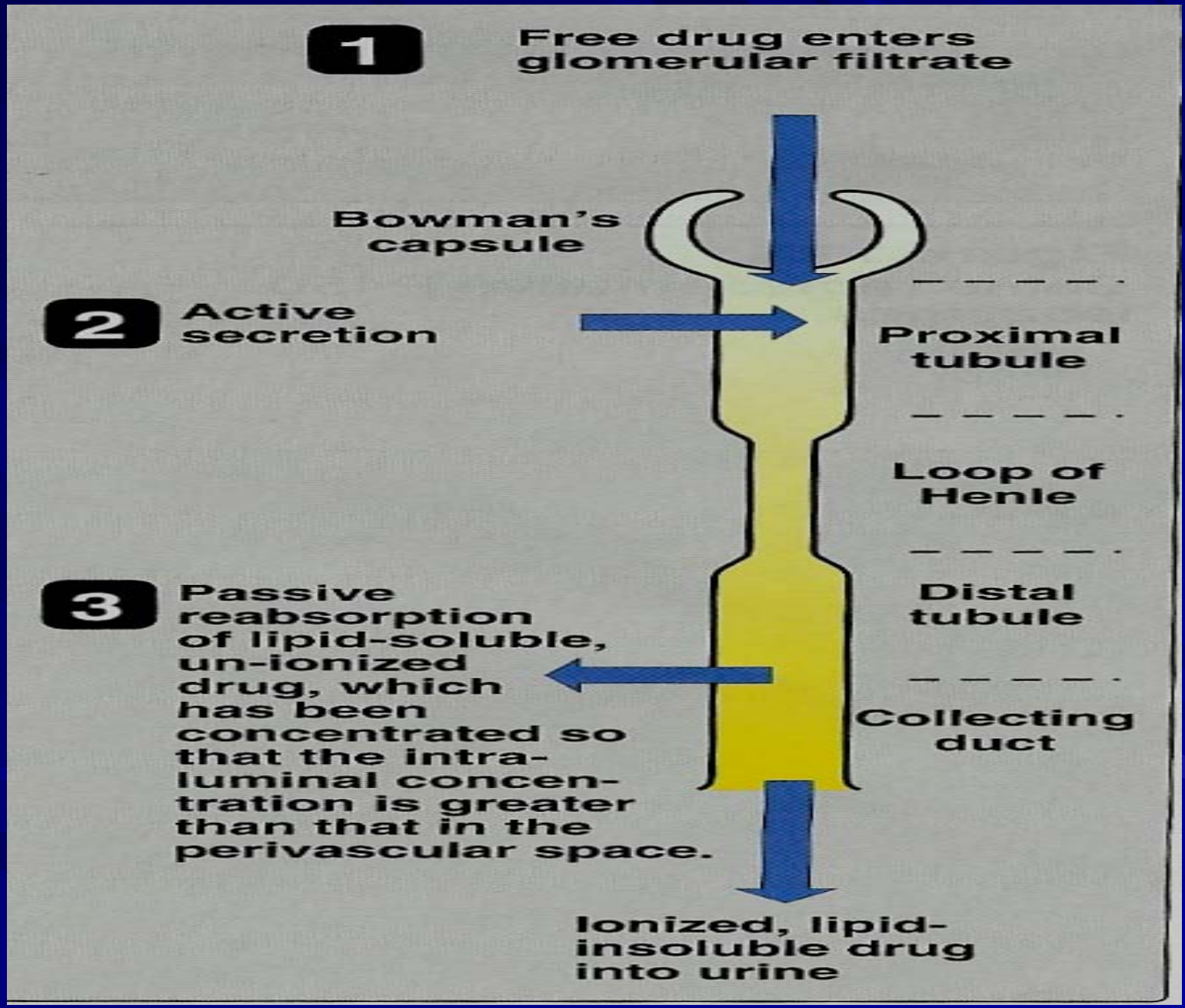
1. Renal Excretion
2. Biliary Excretion

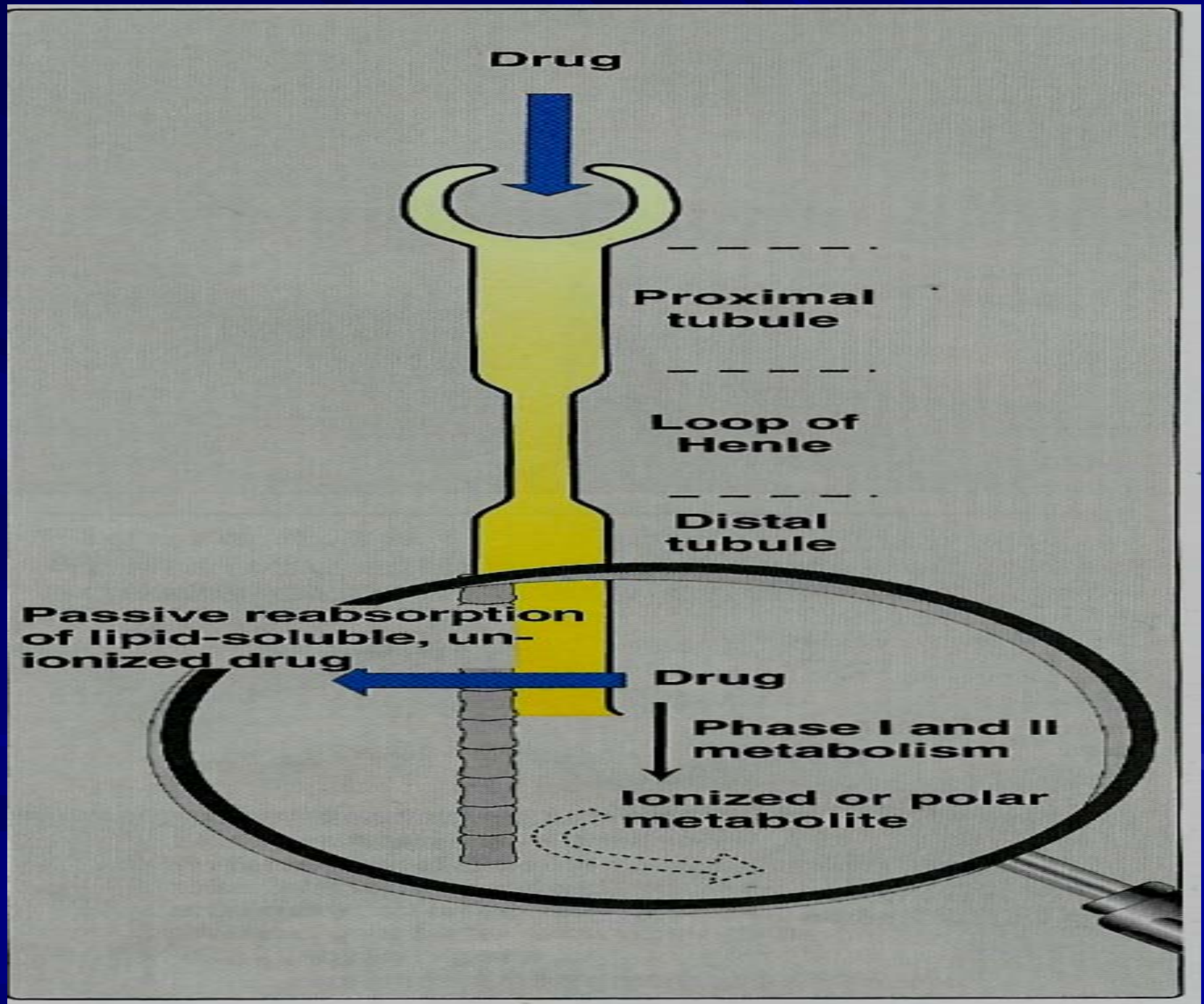
Minor Routes of Excretion.

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. Non 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
   - Salicylates
   - Sulphonamides
   - Glucouronide conjugate
   - Sulphate conjugate

   Blocked by probenecid

2. **System for Basic drugs**
   - Atropine
   - Morphine
   - Catecholamines
   - Quinine
   - Neostigmine

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 ?????.
- Ionized drugs are poorly reabsorbed & so excretion is ?????.
- Renal excretion = (G.F) + (T.S) – (T.R)

Renal Excretion

Examples (mainly excreted by the kidney)

- Aminoglycosides antibiotics (Gentamycin),
- Penicillin.

Contraindicated ?

- Renal disease.
- Elderly

Ion trapping

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

- **Urine is normally slightly acidic & favors excretion of ????? drugs.**
- **Acidification of urine increases excretion of basic drugs (amphetamine).**
- **Alkalization of urine increases excretion of acidic drugs (aspirin, barbiturates).**

Acidification of urine

- Ammonium chloride (NH_4Cl)

Alkalinization of urine

- sodium bicarbonate ($NaHCO_3$)

Biliary Excretion

- Is important for some drugs that are metabolized in the liver.
- e.g. Digitoxin
- Max. $CL_{hepatic}$ = Hepatic blood flow (1500 ml / min)
- Plays a role in the removal of conjugated metabolites particularly glucouronides.

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 if lipid soluble.

This prolongs the action of the drug.

- e.g. morphine, thyroxine.

DRUG CLEARANCE

a rate of elimination of drug by all routes to the concentration of a drug in a biological fluid (blood or plasma).

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

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

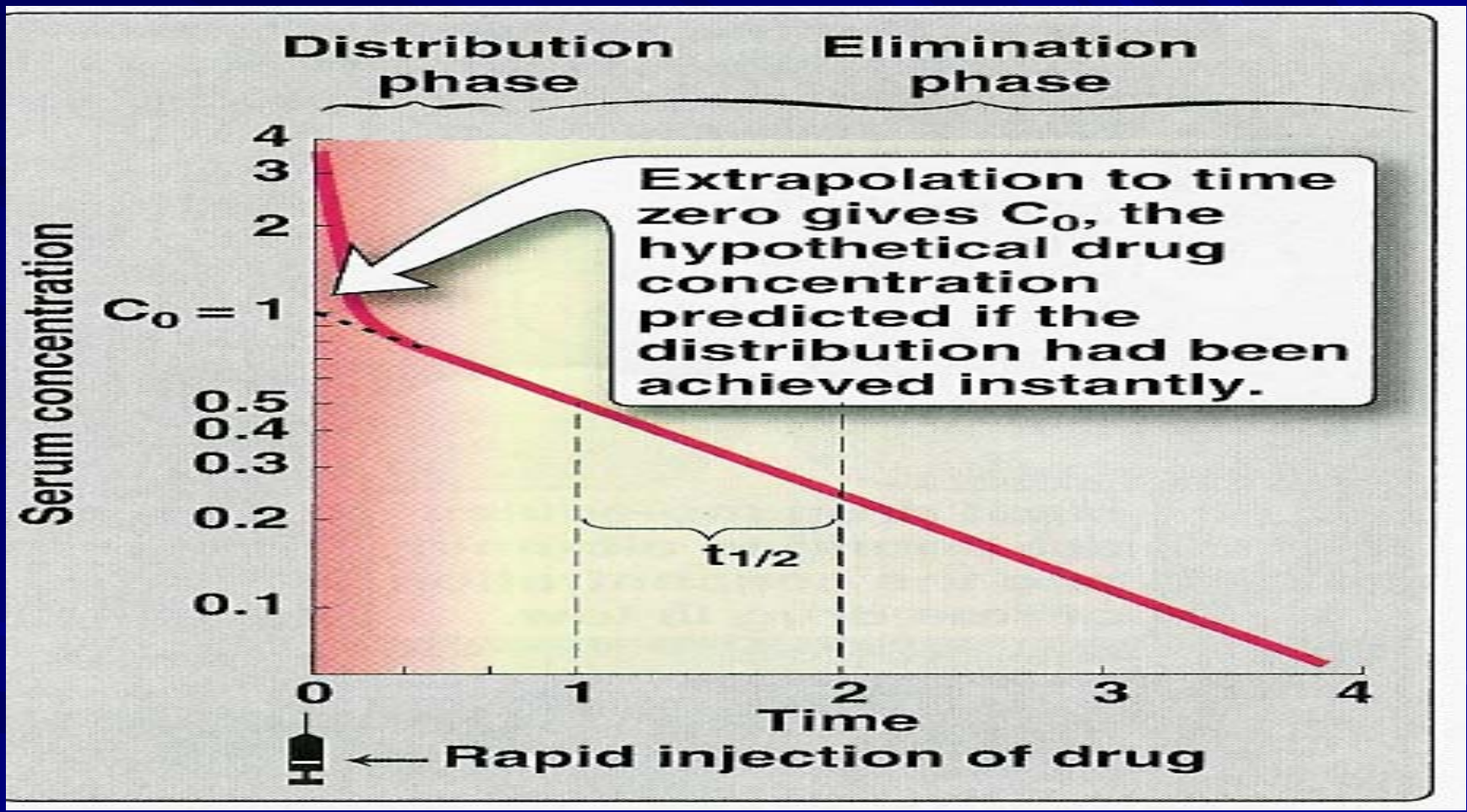
RENAL CLEARANCE

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

Biological Half-Life (t ½)•

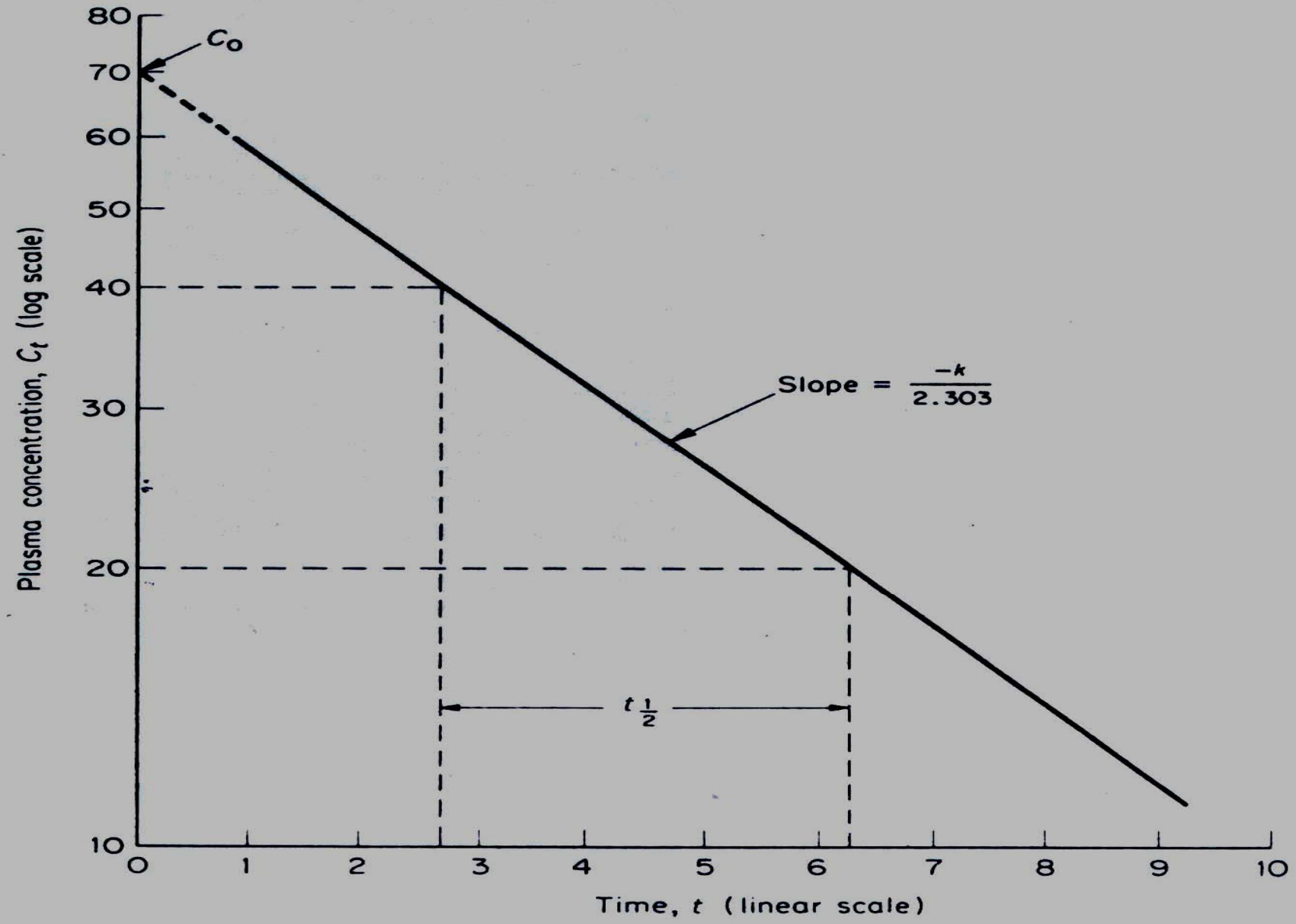
- T ½ is the time required to change the total amount of drug in the body by one-half.
- Is a measure of duration of action.
- Half-life α (t ½ α) is related to distribution phase.
- Half-life β (t ½ β) is related to elimination phase and is generally longer than t ½ α.

Half life of a drug



Plasma Half-Life (t ½)

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


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

- short duration of action.
- Benzyl penicillin, tubocurarine.
- Drugs with very short half life are given by constant I/V infusion for a prolong effect.

Drugs of long plasma half life

- Long duration of action.
- Digoxin, thyroxine, arsenic.

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 Plasma conc. (mg / L)

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) =

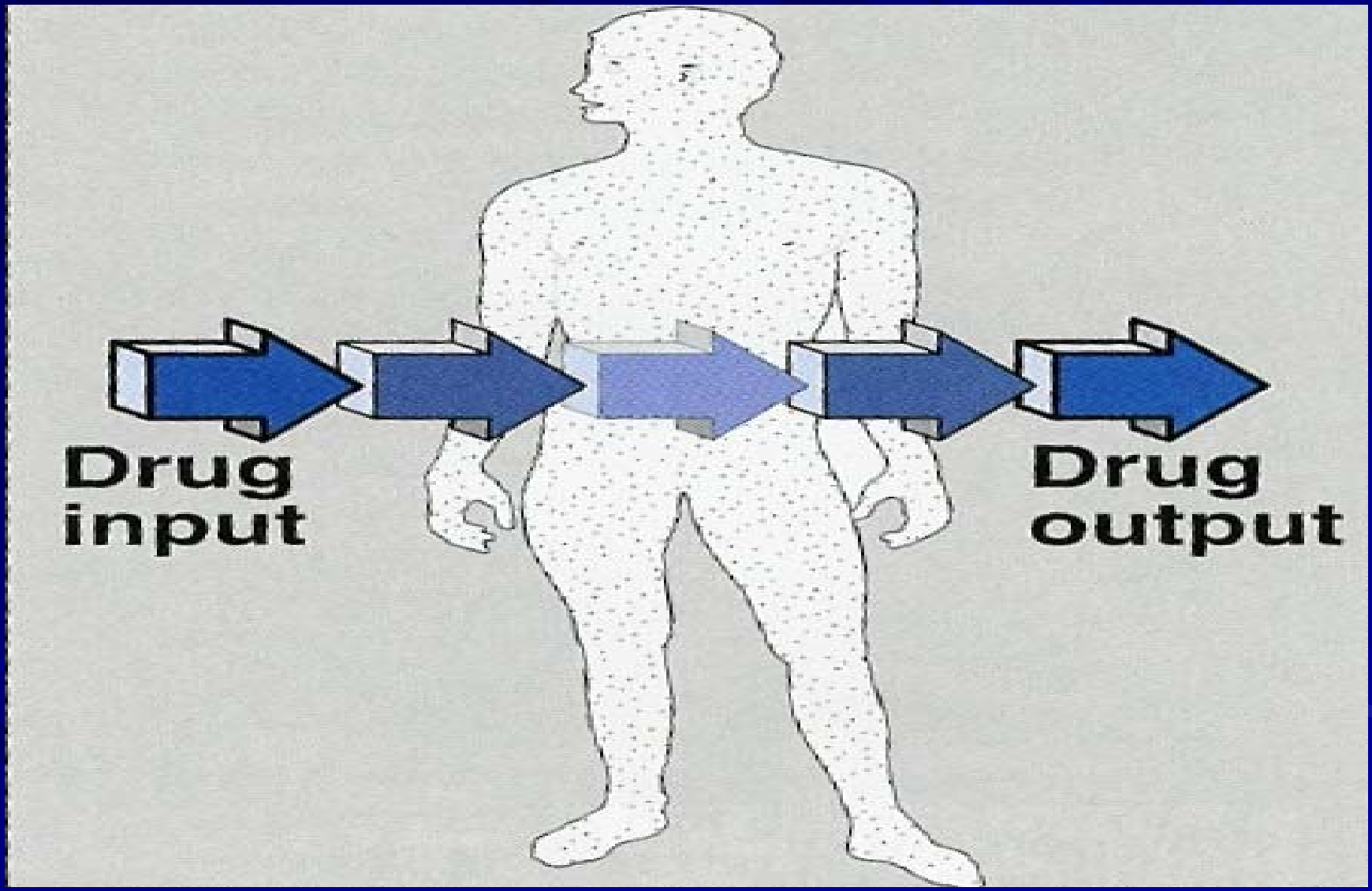
CL (ml / min) x Plasma conc. (mg / ml)

Steady state levels.

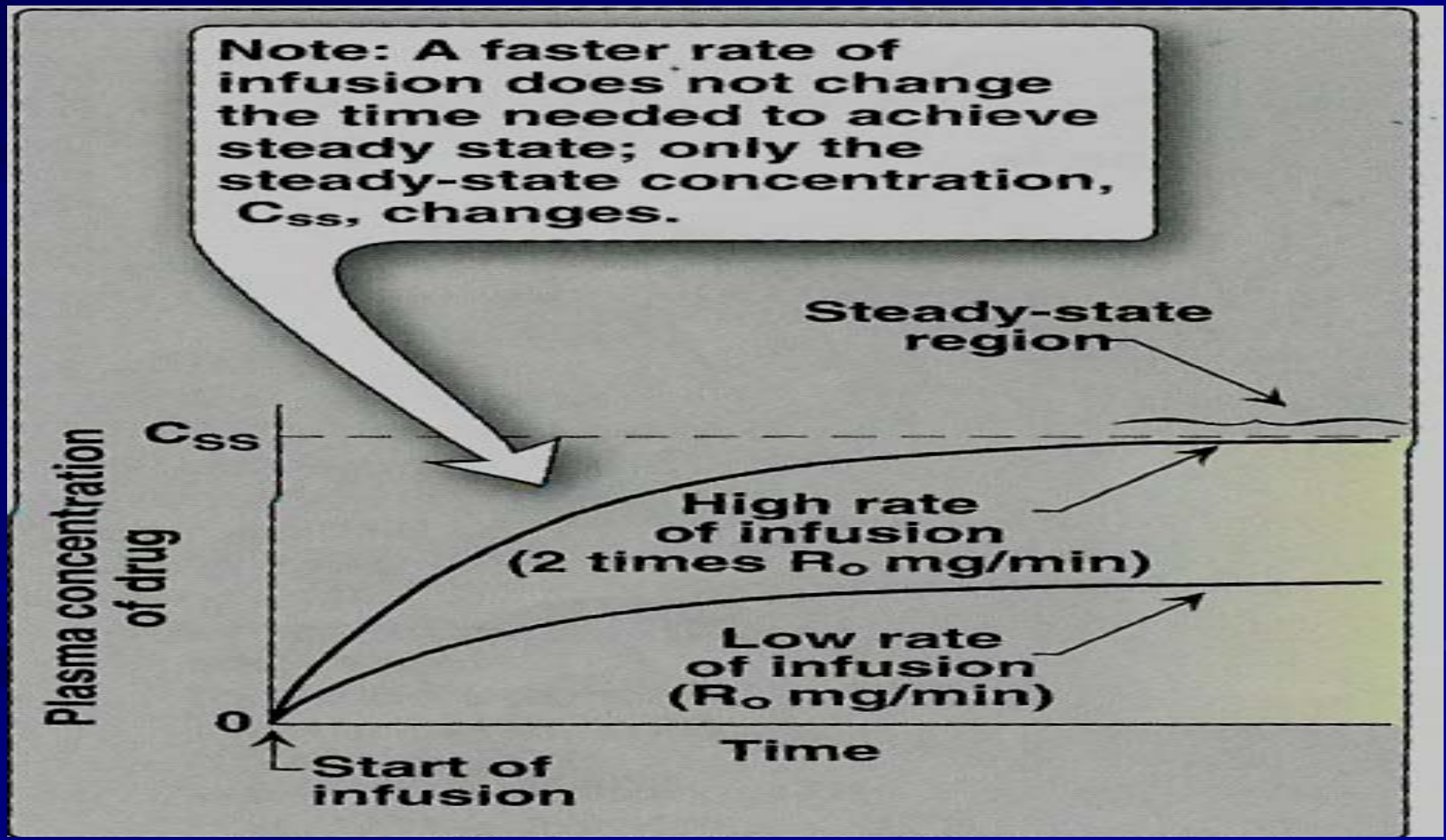
- A state at which the plasma concentration of the drug remains constant.

- Rate of drug administration = Rate of drug elimination.

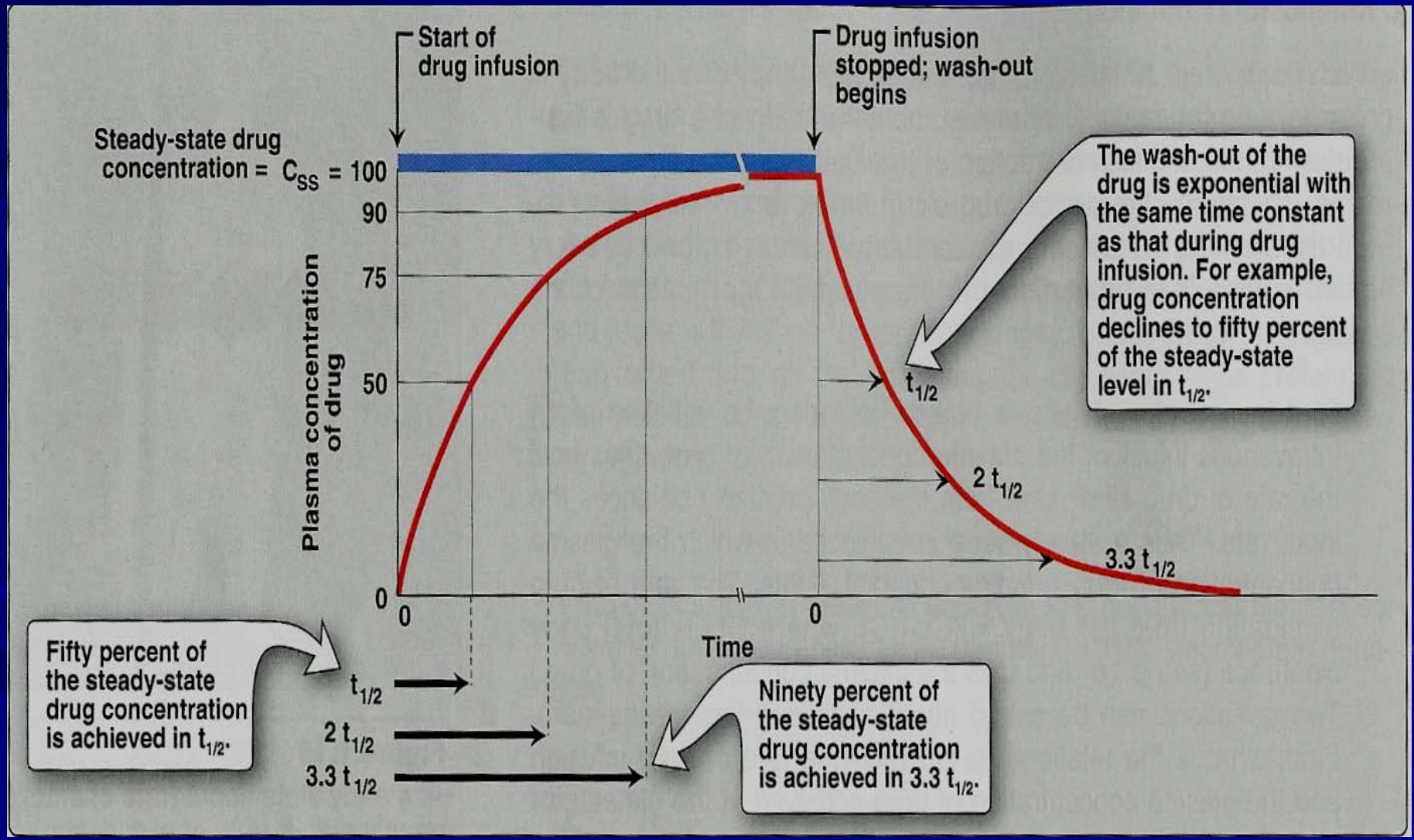
Steady state of a drug



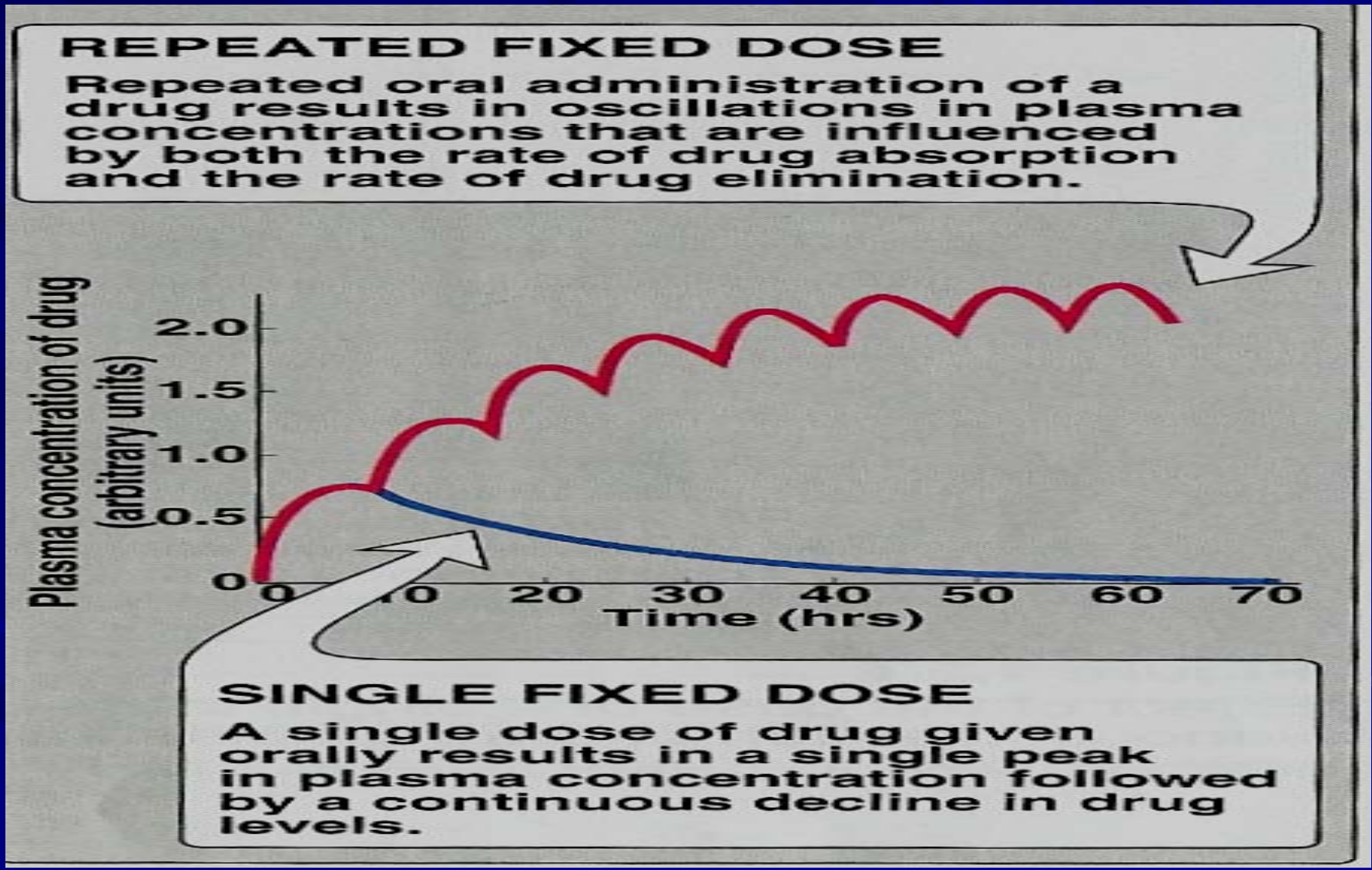
Rate of infusion on steady state

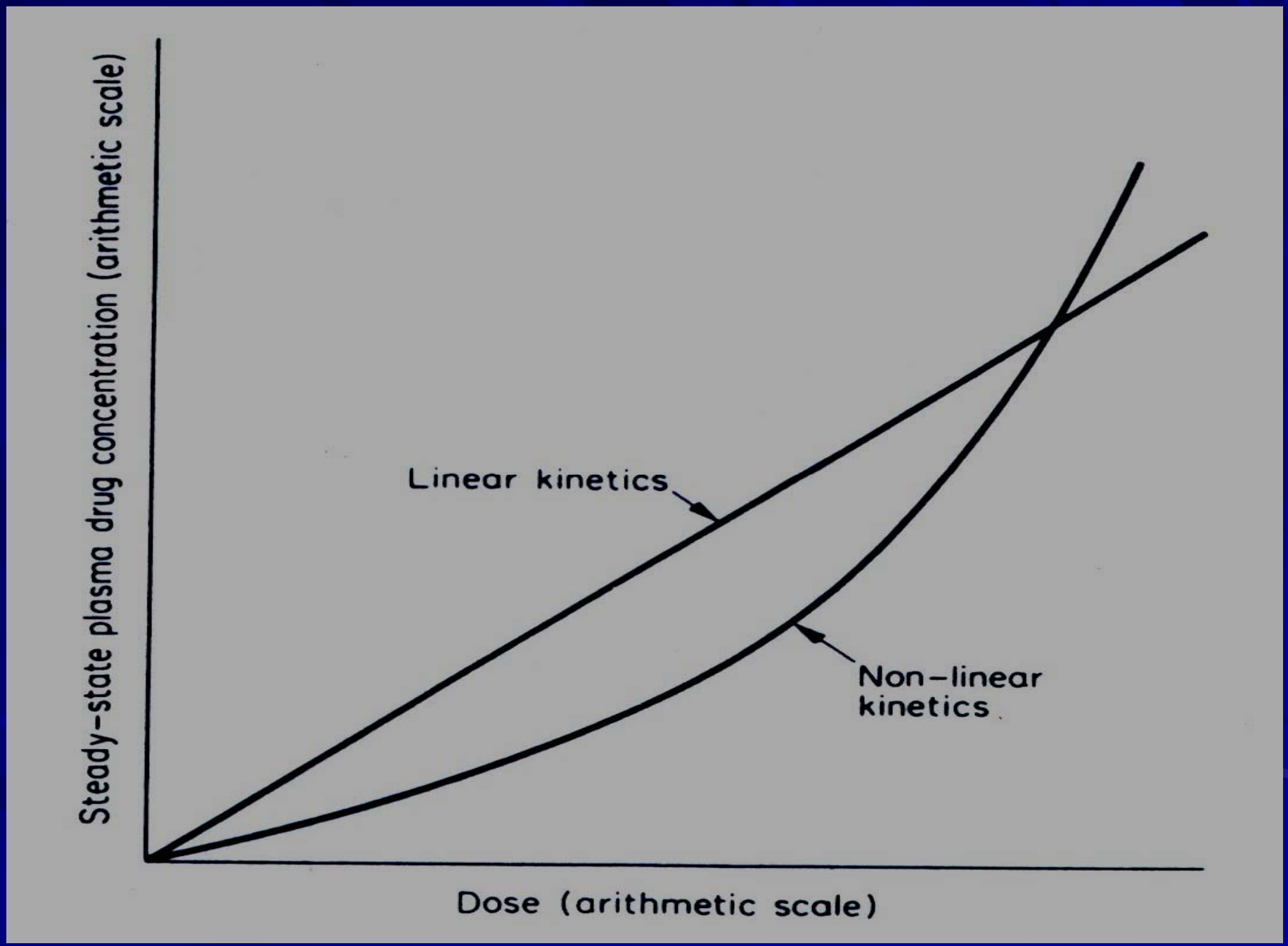


Rate of attainment of steady state of a drug in plasma



Effect of repeated oral administration of drug on plasma conc.




Steady-state plasma drug concentration (arithmetic scale)
Linear kinetics
Non-linear kinetics
Dose (arithmetic scale)

Order of Reaction

- First order (linear kinetics).
- Zero order (nonlinear kinetics).

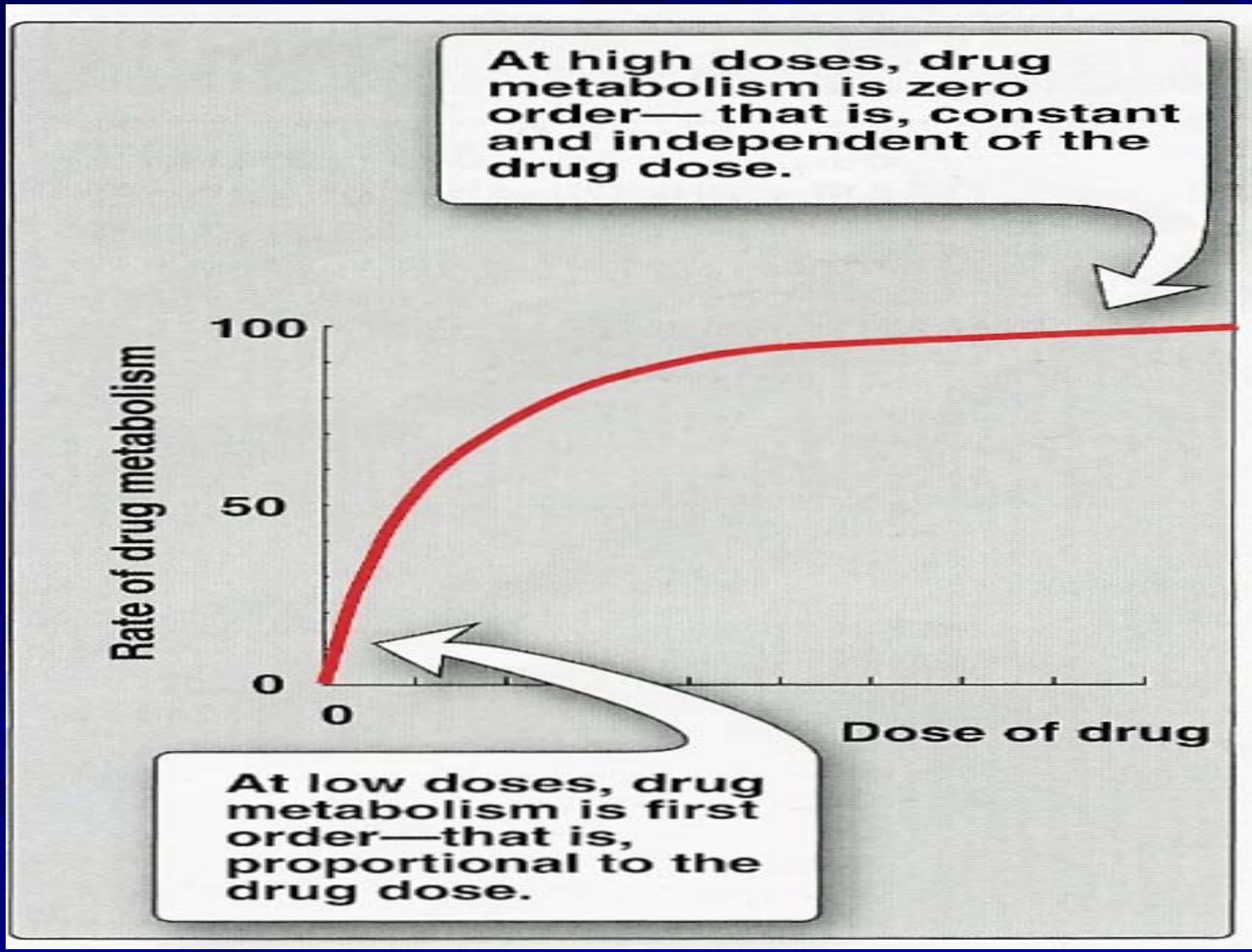
Kinetics of excretion

First-Order or Linear Kinetics

- Most drugs.
- Amount of drug excrete in urine is directly dependent on the dose.
- Half-life is constant, dose - independent.
- Area under the curve is proportional to the dose.
- Steady state is reached after five half-lives.

Zero-Order or Nonlinear kinetics.

- Reaction proceeds at a constant rate.
- Half-life is variable, dose-dependent.
- Little change in dose may lead to toxicity.
- Change in drug formulation can produce toxic effects.
- Few drugs such as ethanol, phenytoin.
- More liable to competitive drug interactions.
- Few drugs such as ethanol, phenytoin.


At high doses, drug metabolism is zero order— that is, constant and independent of the drug dose.
Rate of drug metabolism
100
50
0
0
Dose of drug
At low doses, drug metabolism is first order—that is, proportional to the drug dose.