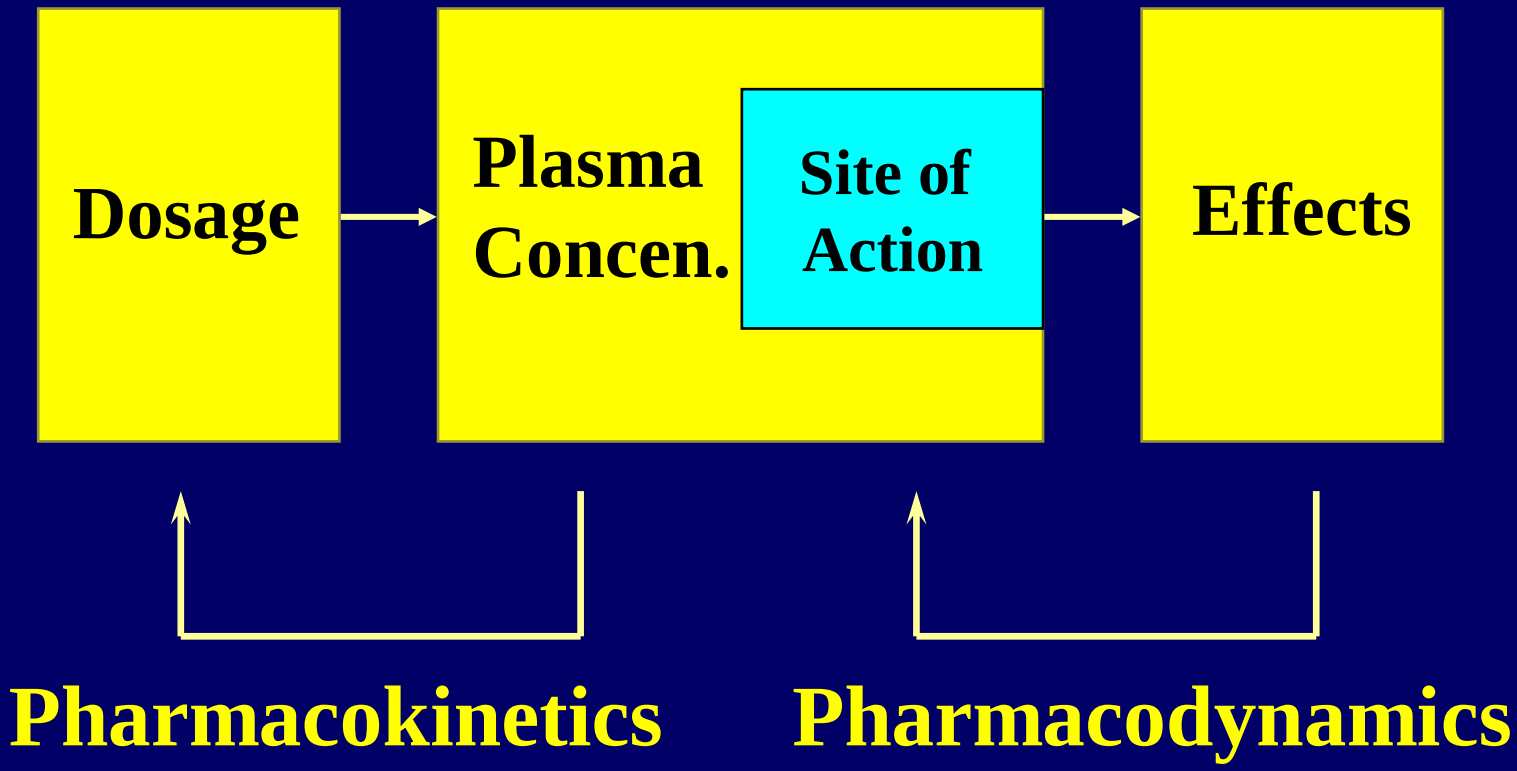
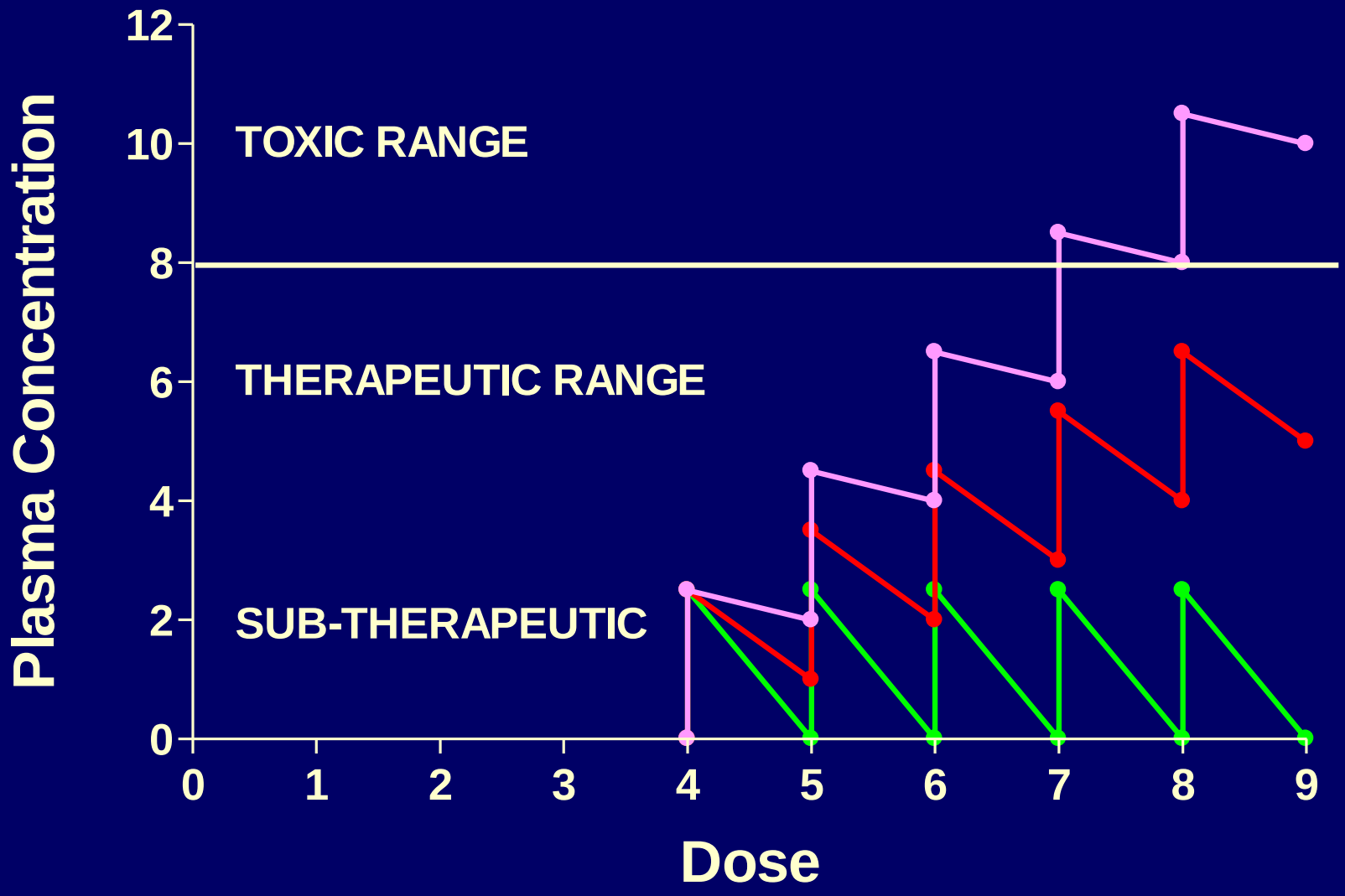
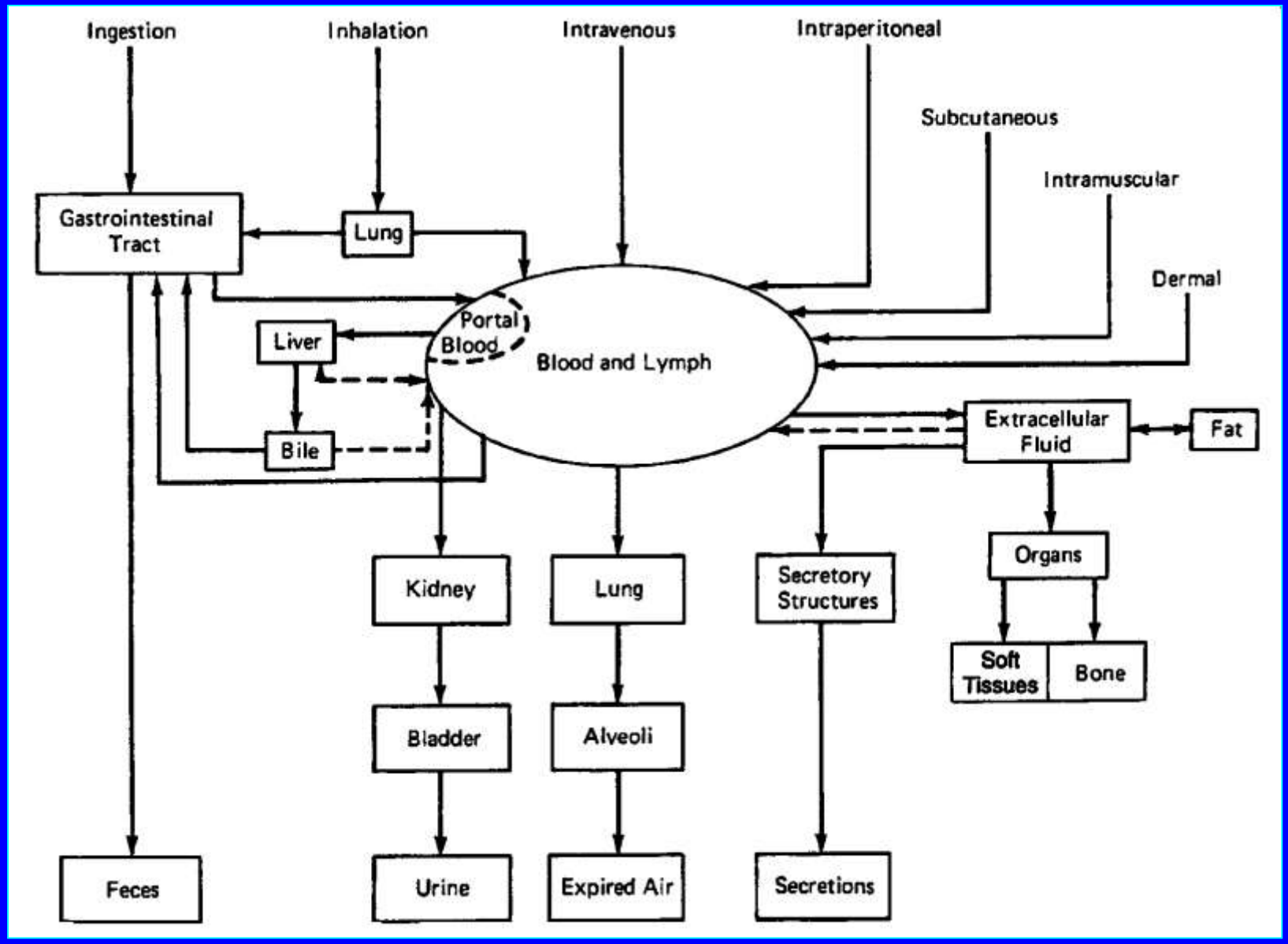
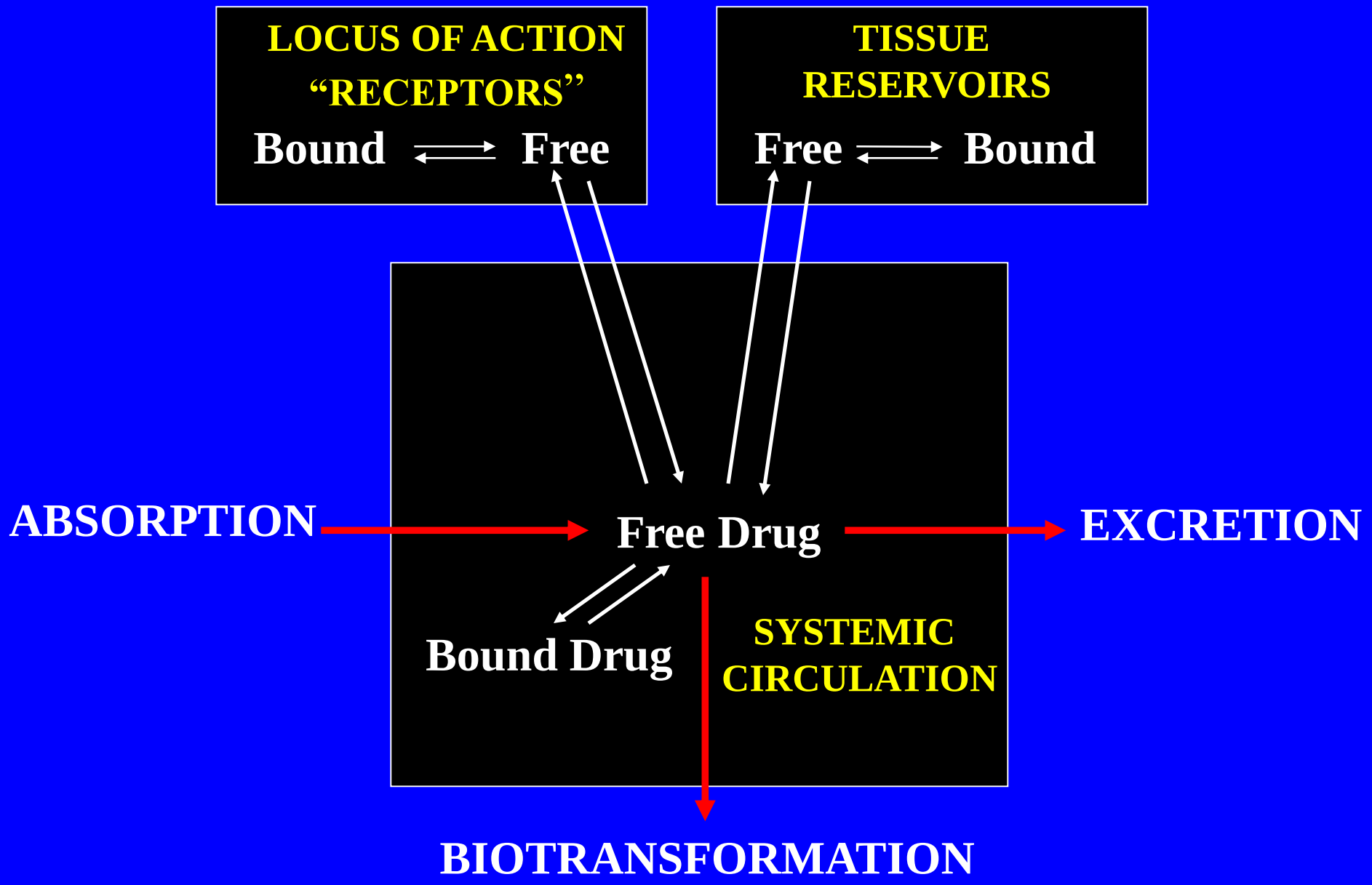

Dosage
Plasma Concen.
Site of Action
Effects
Pharmacokinetics
Pharmacodynamics


Plasma Concentration
12
10
8
6
4
2
0
TOXIC RANGE
THERAPEUTIC RANGE
SUB-THERAPEUTIC
0
1
2
3
4
5
6
7
8
9
Dose

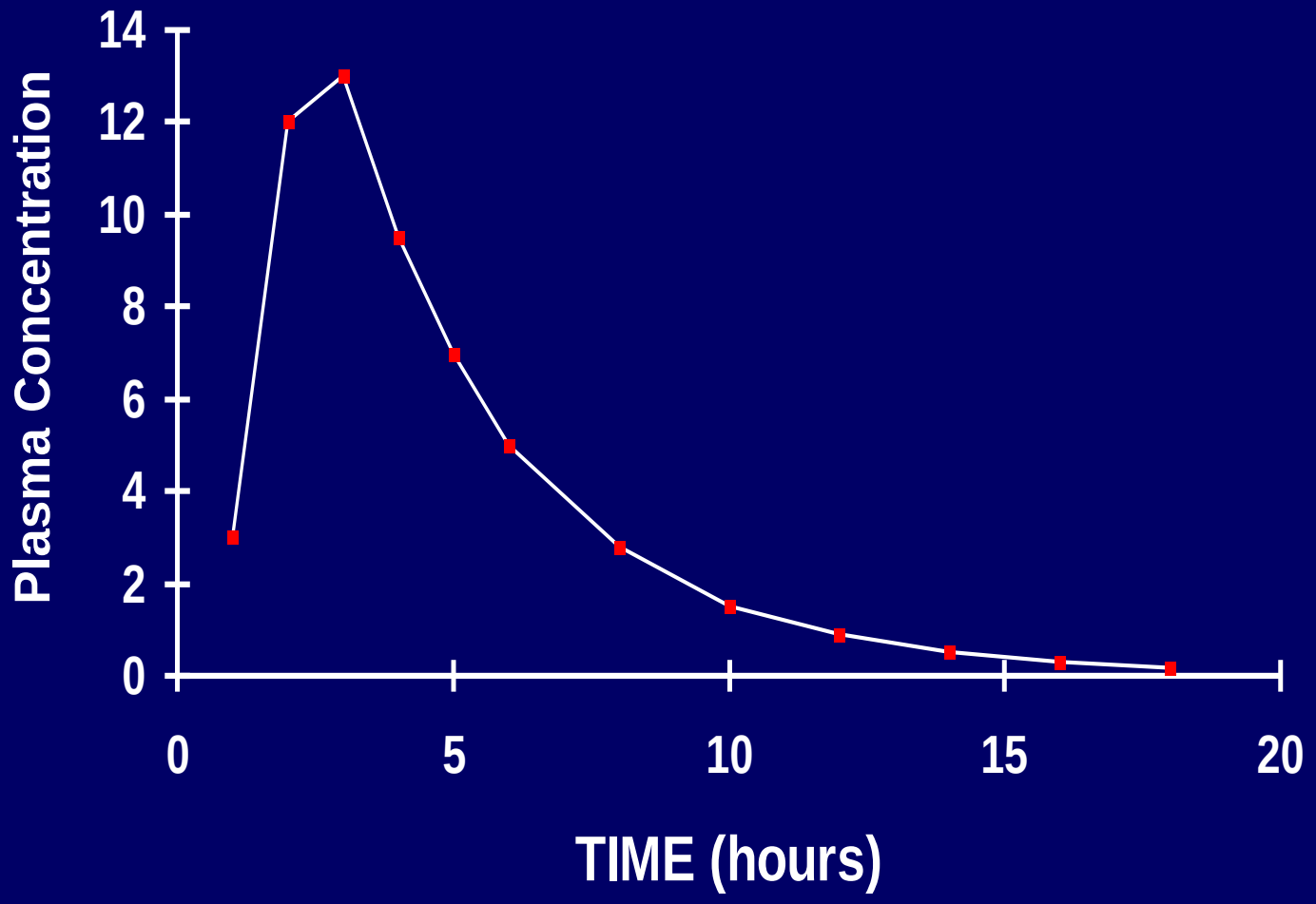
DISPOSITION OF DRUGS

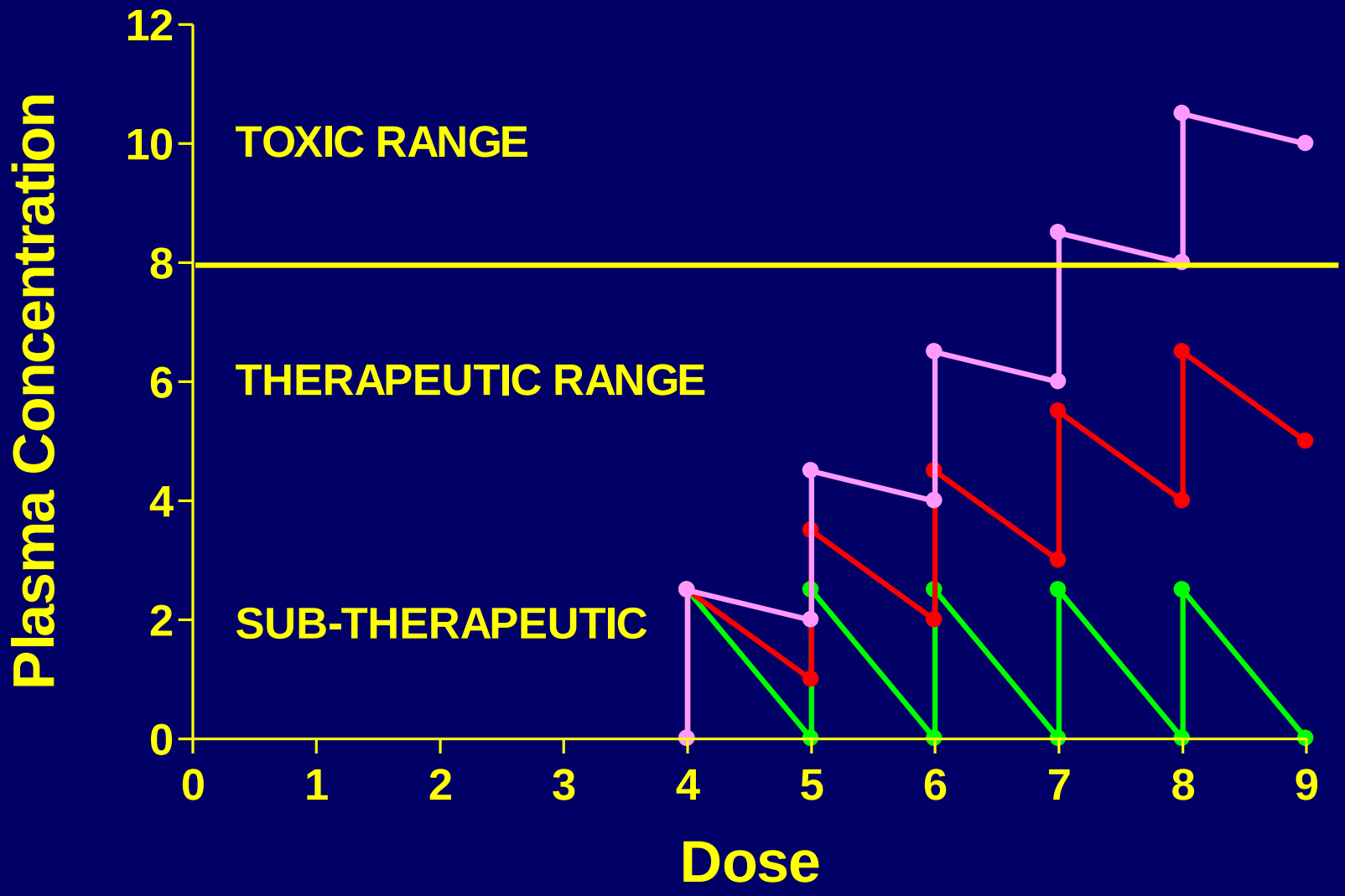


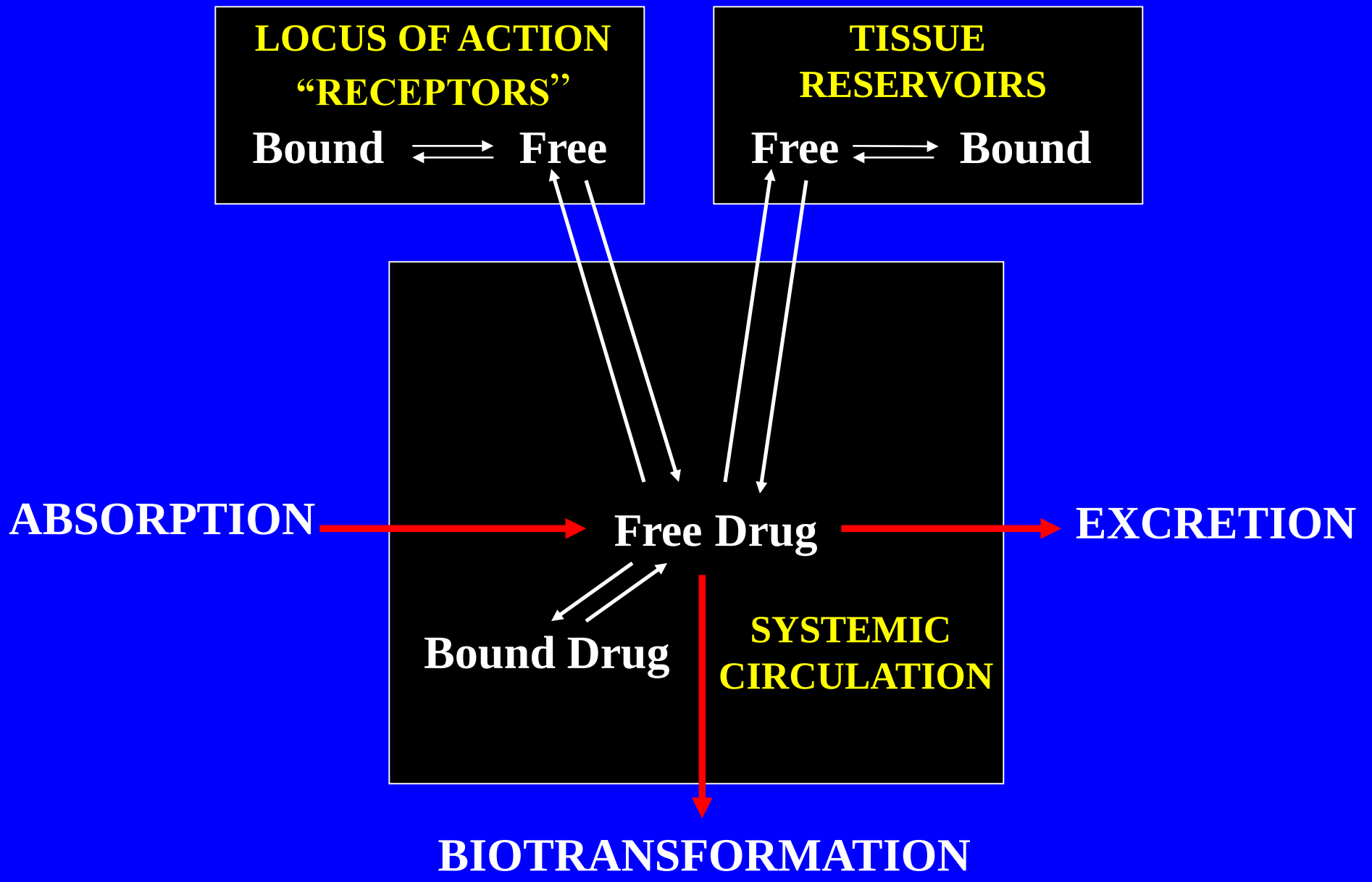
The disposition of chemicals entering the body (from C.D. Klaassen, *Casarett and Doull's Toxicology*, 5th ed., New York: McGraw-Hill, 1996).


LOCUS OF ACTION
"RECEPTORS"
Bound ⇌ Free
TISSUE
RESERVOIRS
Free ⇌ Bound
ABSORPTION
Free Drug
EXCRETION
Bound Drug
SYSTEMIC
CIRCULATION
BIOTRANSFORMATION

Plasma concentration vs. time profile of a single dose of a drug ingested orally




Plasma Concentration
12
10
8
6
4
2
0
TOXIC RANGE
THERAPEUTIC RANGE
SUB-THERAPEUTIC
0
1
2
3
4
5
6
7
8
9
Dose


LOCUS OF ACTION
"RECEPTORS"
Bound ⇌ Free
TISSUE
RESERVOIRS
Free ⇌ Bound
ABSORPTION
Free Drug
EXCRETION
Bound Drug
SYSTEMIC
CIRCULATION
BIOTRANSFORMATION

Bioavailability

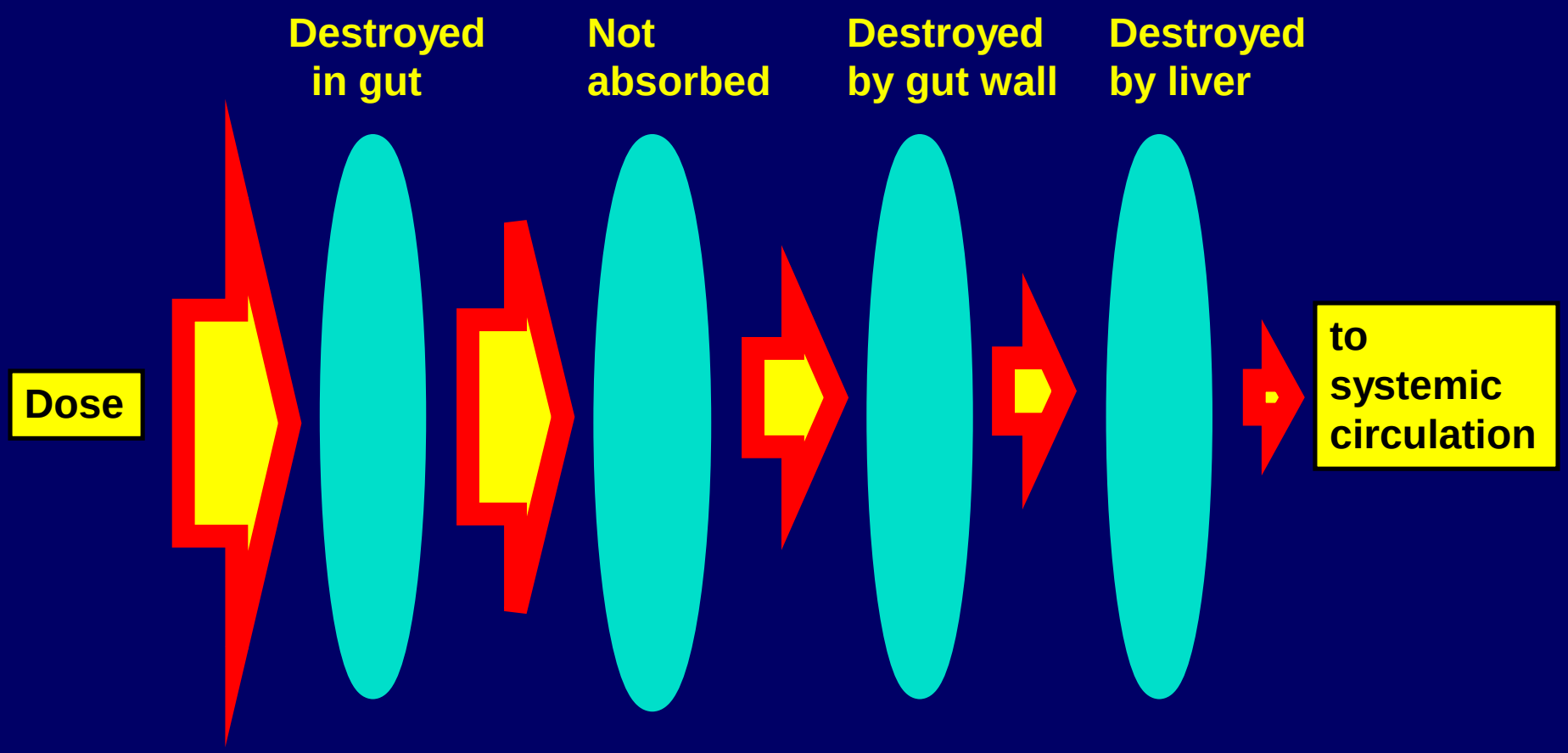
Definition: the fraction of the administered dose reaching the systemic circulation

for i.v.: 100%
for non i.v.: ranges from 0 to 100%

e.g. lidocaine bioavailability 35% due to destruction in gastric acid and liver metabolism

First Pass Effect

Bioavailability



PRINCIPLE

For drugs taken by routes other than the i.v. route, the extent of absorption and the **bioavailability** must be understood in order to determine what dose will induce the desired therapeutic effect. It will also explain why the same dose may cause a therapeutic effect by one route but a toxic or no effect by another.

PRINCIPLE

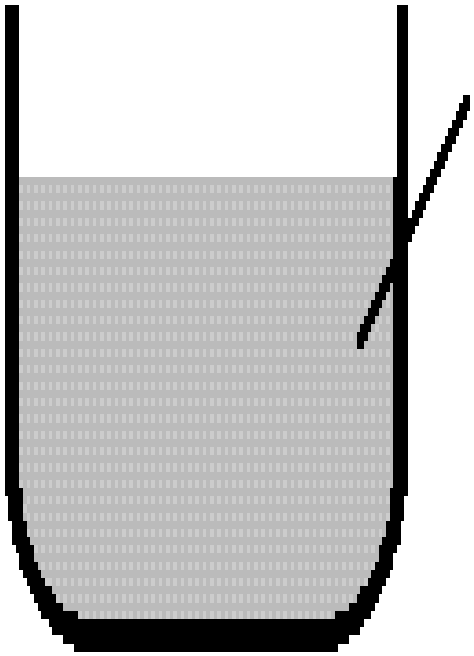
Drugs appear to distribute in the body as if it were a single compartment. The magnitude of the drug's distribution is given by the apparent volume of distribution (V_d).

Vd = Amount of drug in body ÷ Concentration in Plasma

(Apparent) Volume of Distribution:

Volume into which a drug *appears* to distribute with a concentration equal to its plasma concentration

Drug concentration in beaker:



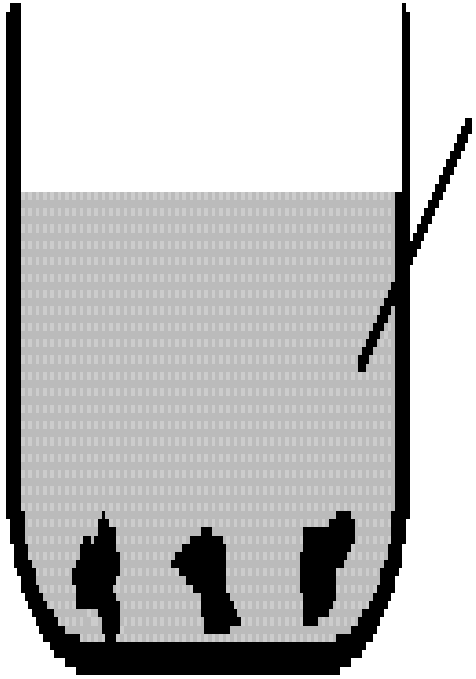
Dose = 10 mg

Cp^0 = 20 mg/L

Apparent

Volume = 500 ml

With charcoal in beaker:



Dose = 10 mg

Cp^0 = 2 mg/L

Apparent

Volume = 5000 ml

Examples of apparent Vd's for some drugs

Drug	L/Kg	L/70 kg
Sulfisoxazole	0.16	11.2
Phenytoin	0.63	44.1
Phenobarbital	0.55	38.5
Diazepam	2.4	168
Digoxin	7	490

Elimination of drugs from the body

MAJOR

KIDNEY
filtration
secretion
(reabsorption)

LIVER
metabolism
secretion

MINOR

LUNGS
exhalation

OTHERS
mother's milk
sweat, saliva etc.

Elimination by the Kidney

- **Excretion - major**

  1) glomerular filtration

  glomerular structure, size constraints, protein binding

  2) tubular reabsorption/secretion

  - acidification/alkalinization,

  - active transport, competitive/saturable, organic acids/bases

  - protein binding

- **Metabolism - minor**

Elimination by the Liver

- Metabolism - major

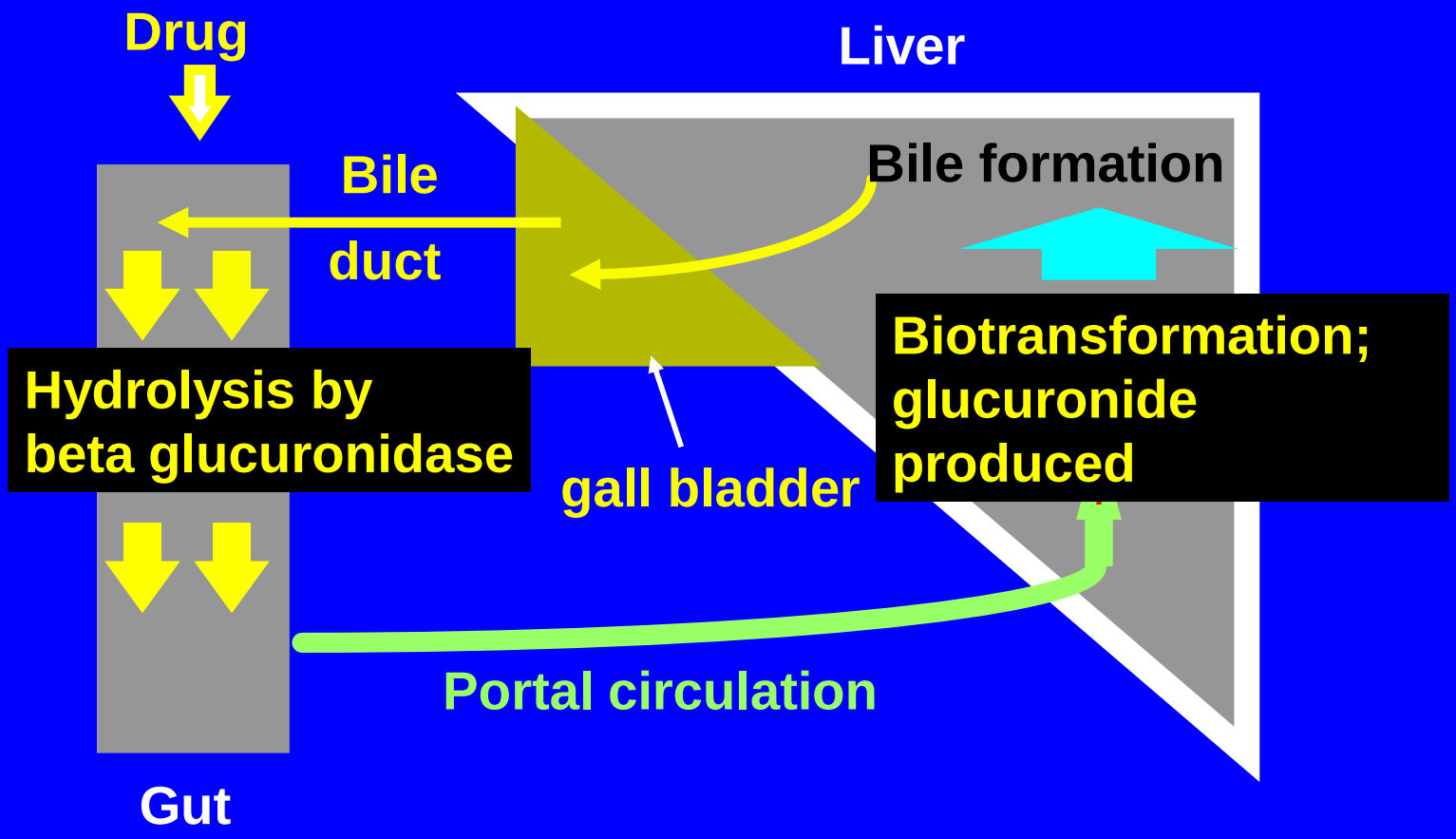
  1) Phase I and II reactions

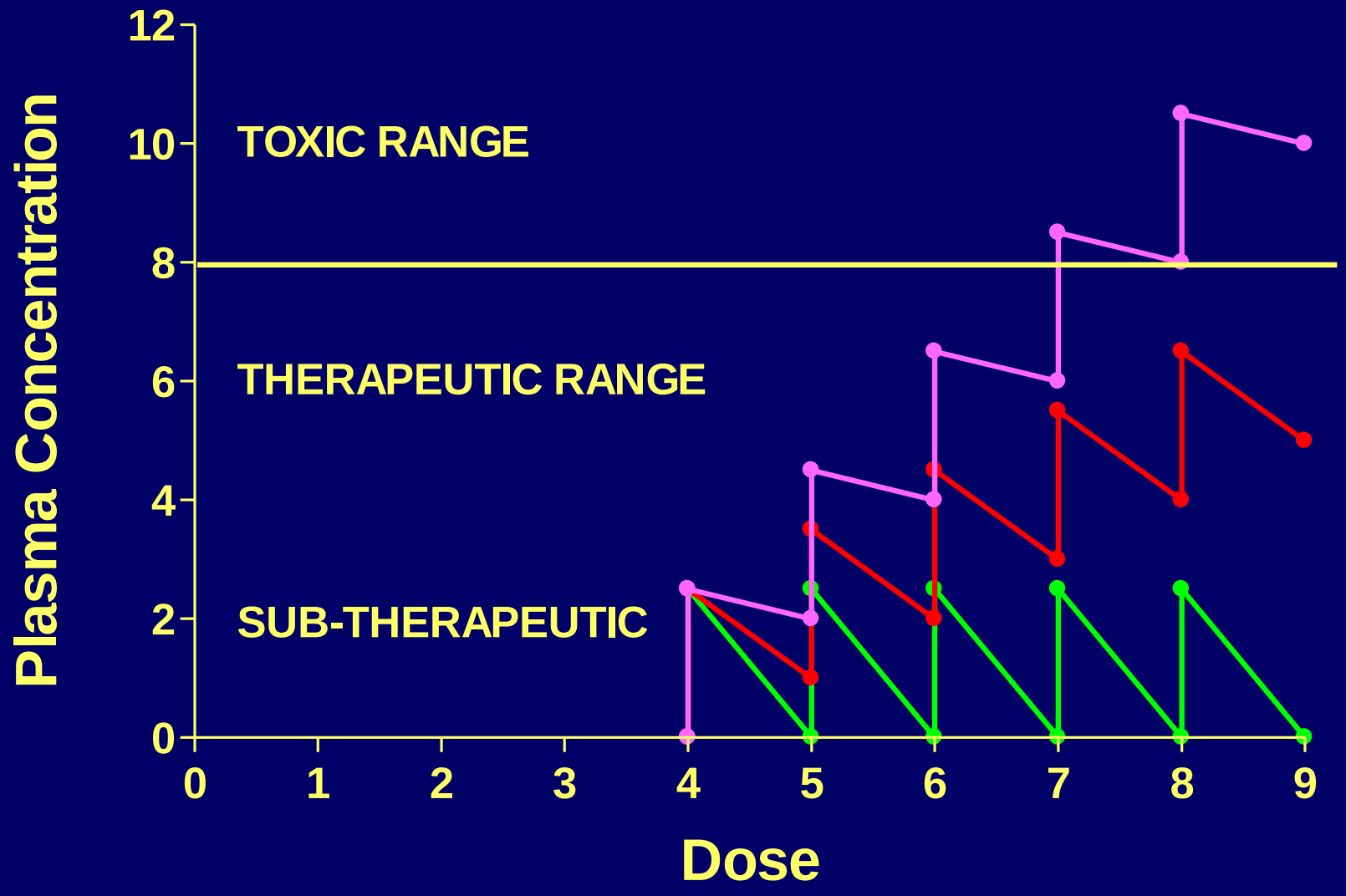
  2) Function: change a lipid soluble to more water soluble molecule to excrete in kidney

  3) Possibility of active metabolites with same or different properties as parent molecule

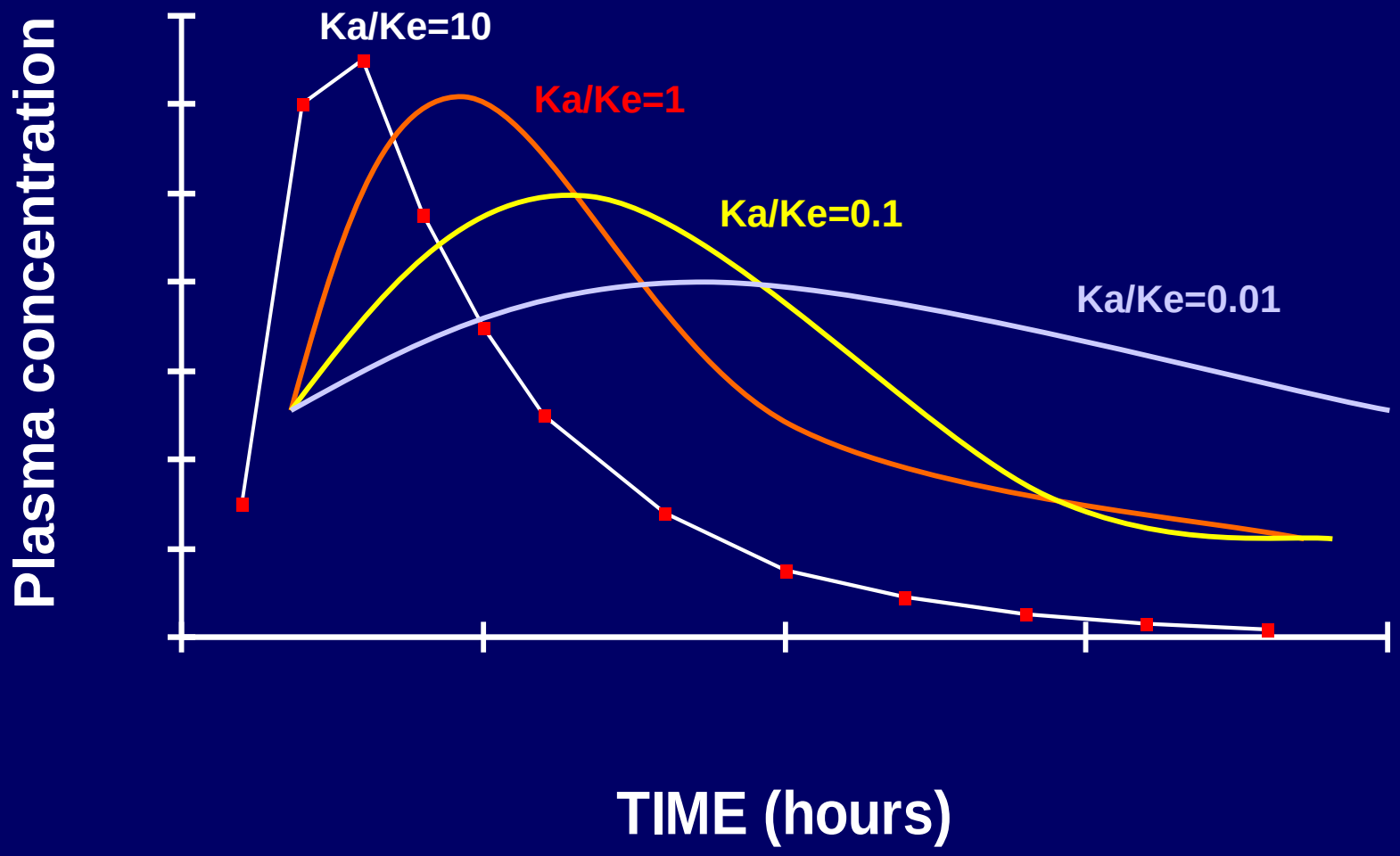
- Biliary Secretion – active transport, 4 categories

The enterohepatic shunt




Plasma Concentration
12
10
8
6
4
2
0
TOXIC RANGE
THERAPEUTIC RANGE
SUB-THERAPEUTIC
0
1
2
3
4
5
6
7
8
9
Dose

Influence of Variations in Relative Rates of Absorption and Elimination on Plasma Concentration of an Orally Administered Drug



Elimination

- **Zero order:** constant rate of elimination irrespective of plasma concentration.

- **First order:** rate of elimination proportional to plasma concentration. Constant ***Fraction*** of drug eliminated per unit time.

Rate of elimination ∝ Amount

Rate of elimination = K x Amount

Zero Order Elimination
Pharmacokinetics of Ethanol

- Ethanol is distributed in total body water.
- Mild intoxication at 1 mg/ml in plasma.
- How much should be ingested to reach it?

  Answer: 42 g or 56 ml of pure ethanol (V_dxC)

  Or 120 ml of a strong alcoholic drink like whiskey
- Ethanol has a constant elimination rate = 10 ml/h
- To maintain mild intoxication, at what rate must ethanol be taken now?

  at 10 ml/h of pure ethanol, or 20 ml/h of drink.

Rarely Done → DRUNKENNESS → Coma → Death

First Order Elimination

$dA/dt \propto A$

$DA/dt = -k \cdot A$

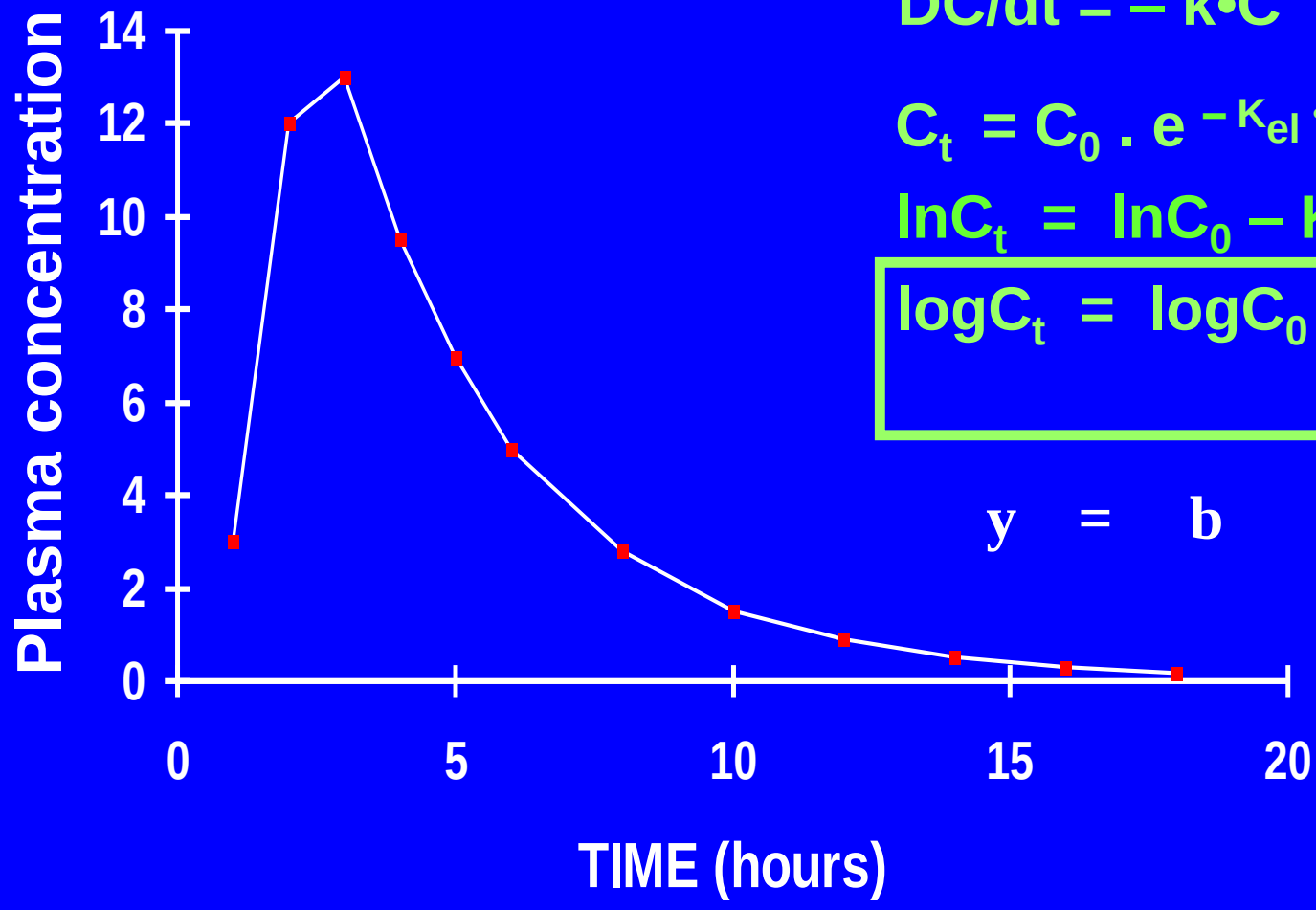
$DC/dt = -k \cdot C$

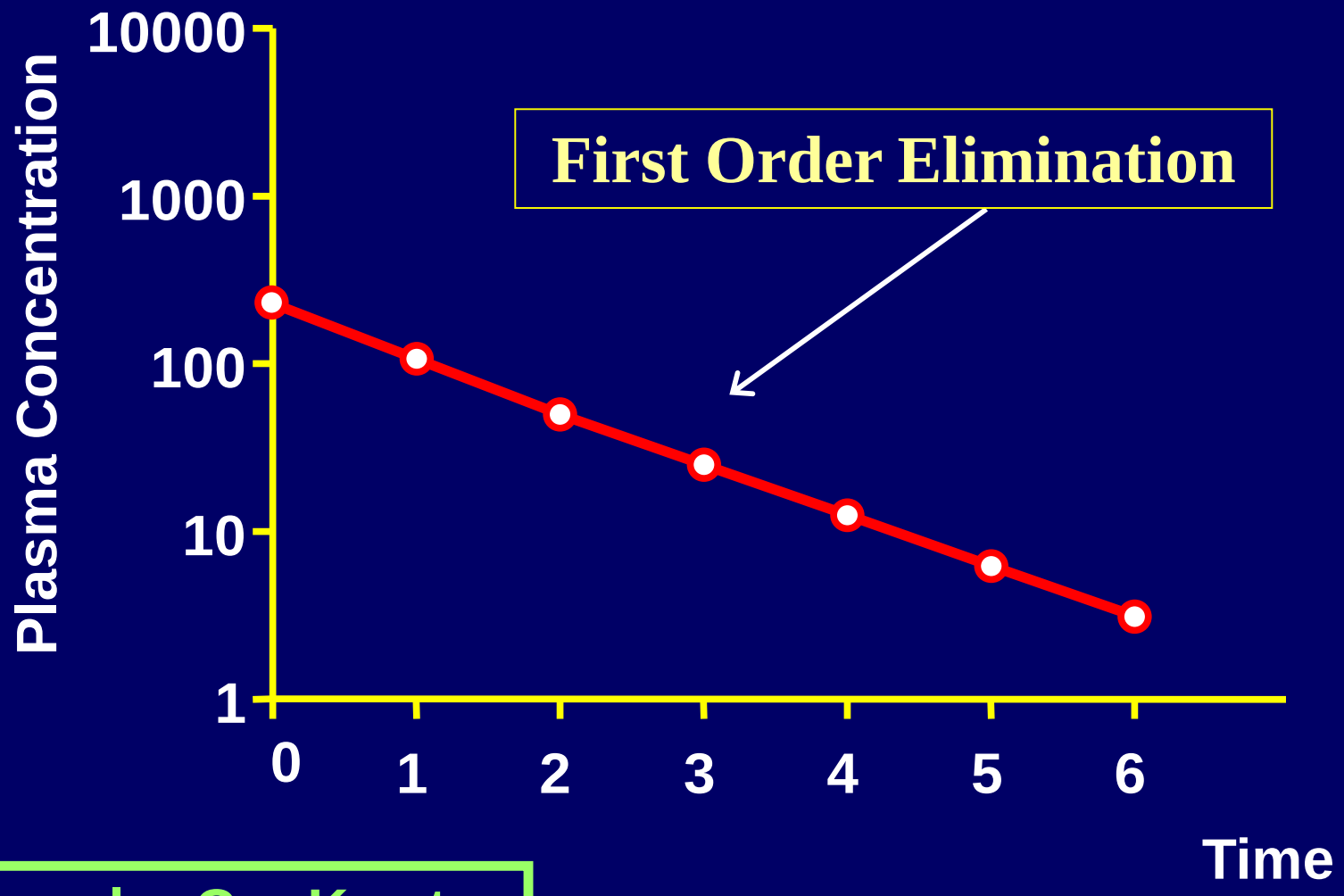
$C_t = C_0 \cdot e^{-K_{el} \cdot t}$

$\ln C_t = \ln C_0 - K_{el} \cdot t$

$$\log C_t = \log C_0 - \frac{K_{el}}{2.3} \cdot t$$

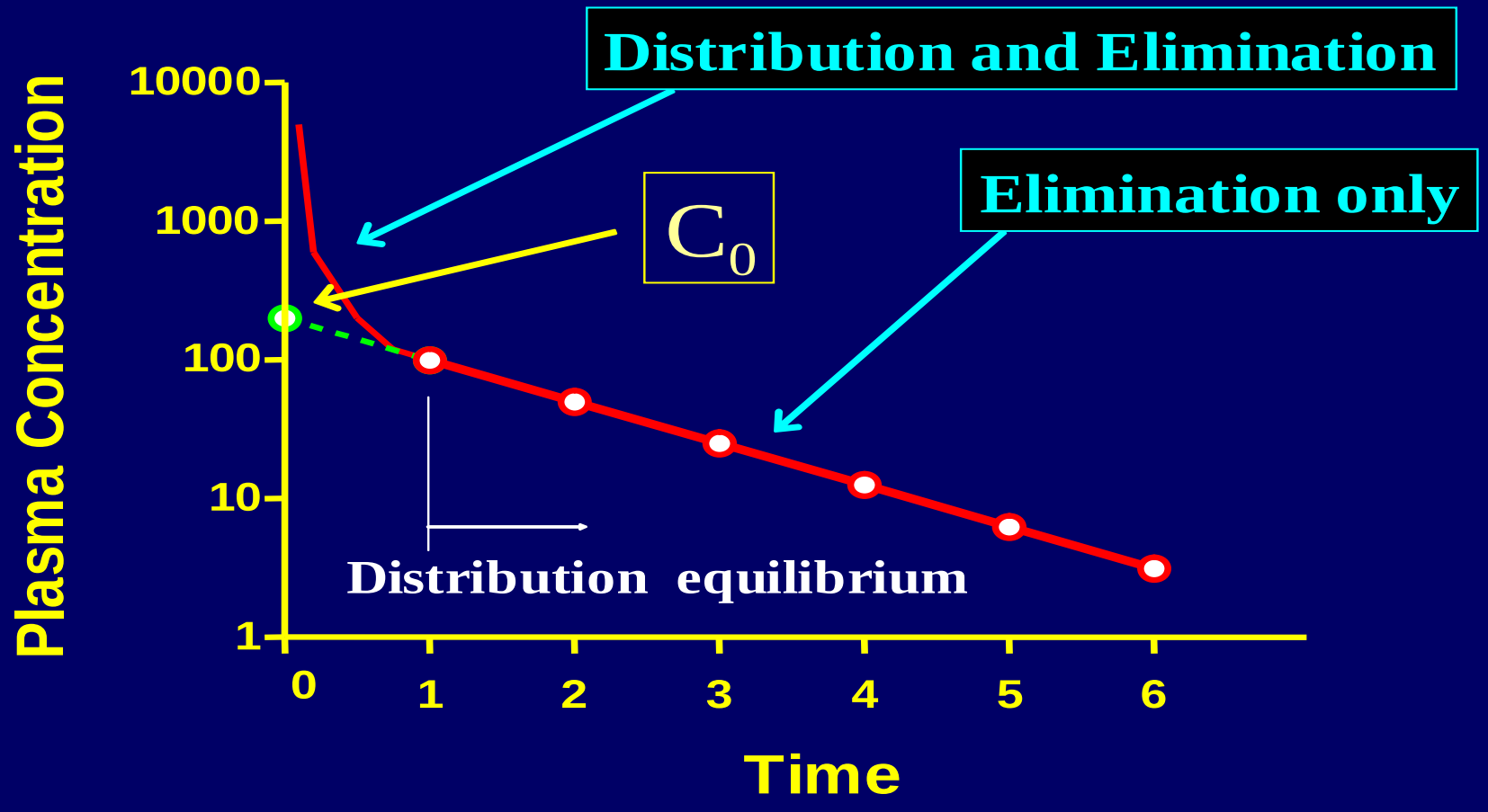
$y = b - a.x$

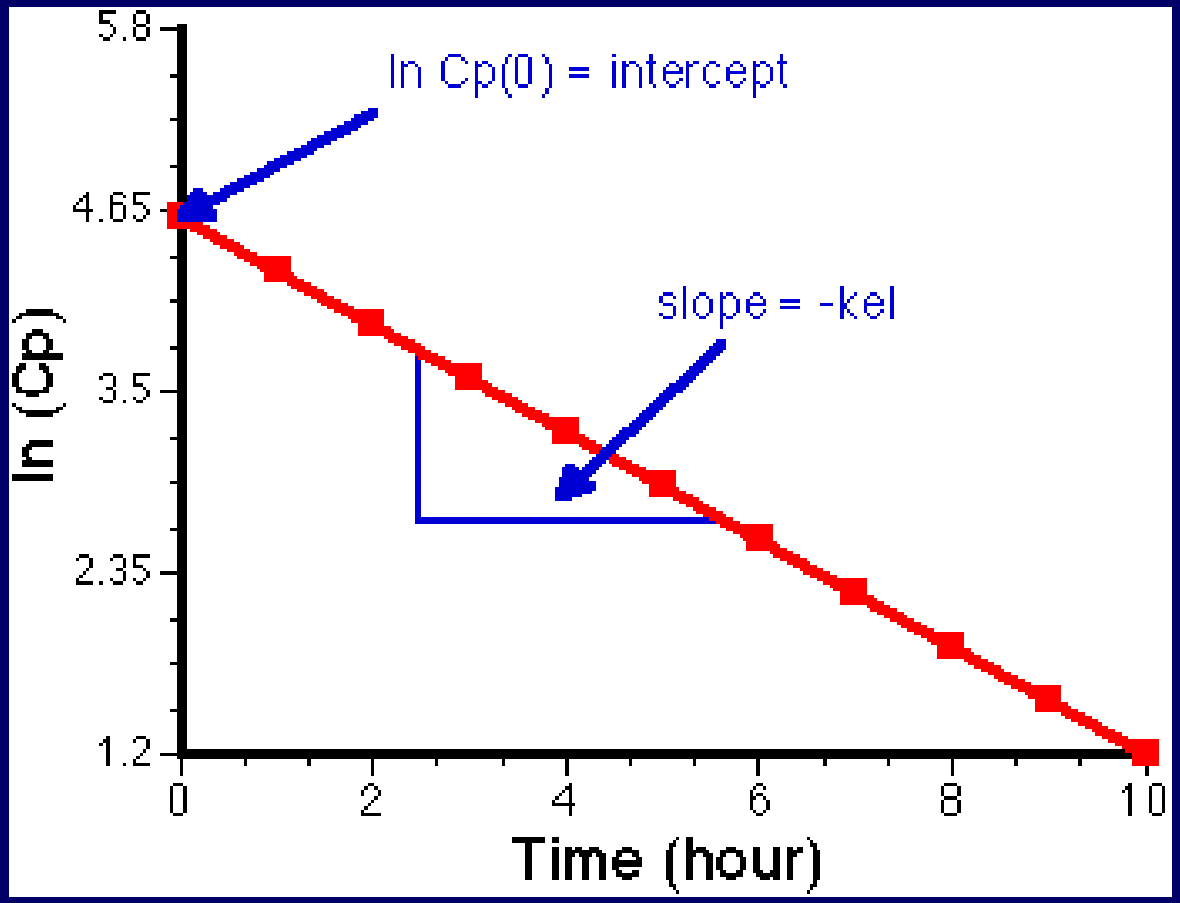




$$\log C_t = \log C_0 - \frac{K_{el} \cdot t}{2.303}$$

Plasma Concentration Profile after a Single I.V. Injection

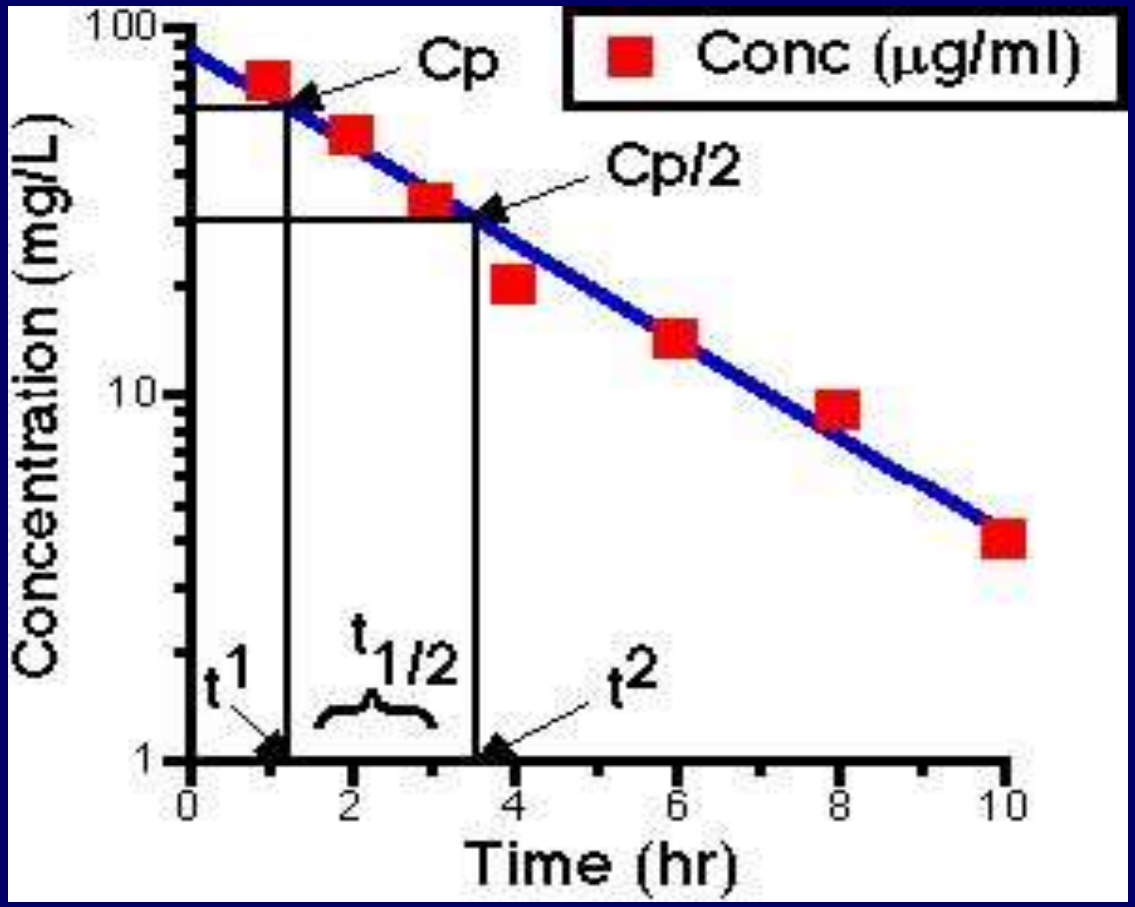




$$\ln C_t = \ln C_o - K_{el}.t$$

$$V_d = \text{Dose}/C_0$$

When t = 0, C = C_0, i.e., the concentration at time zero when distribution is complete and elimination has not started yet. Use this value and the dose to calculate V_d.



$$\ln C_t = \ln C_0 - K_{el}.t$$

$$t1/2 = 0.693/K_{el}$$

When C_t = ½ C_0, then $K_{el}.t$ = 0.693. This is the time for the plasma concentration to reach half the original, i.e., the half-life of elimination.

PRINCIPLE

Elimination of drugs from the body usually follows first order kinetics with a characteristic half-life (t1/2) and fractional rate constant (K_{el}).

First Order Elimination

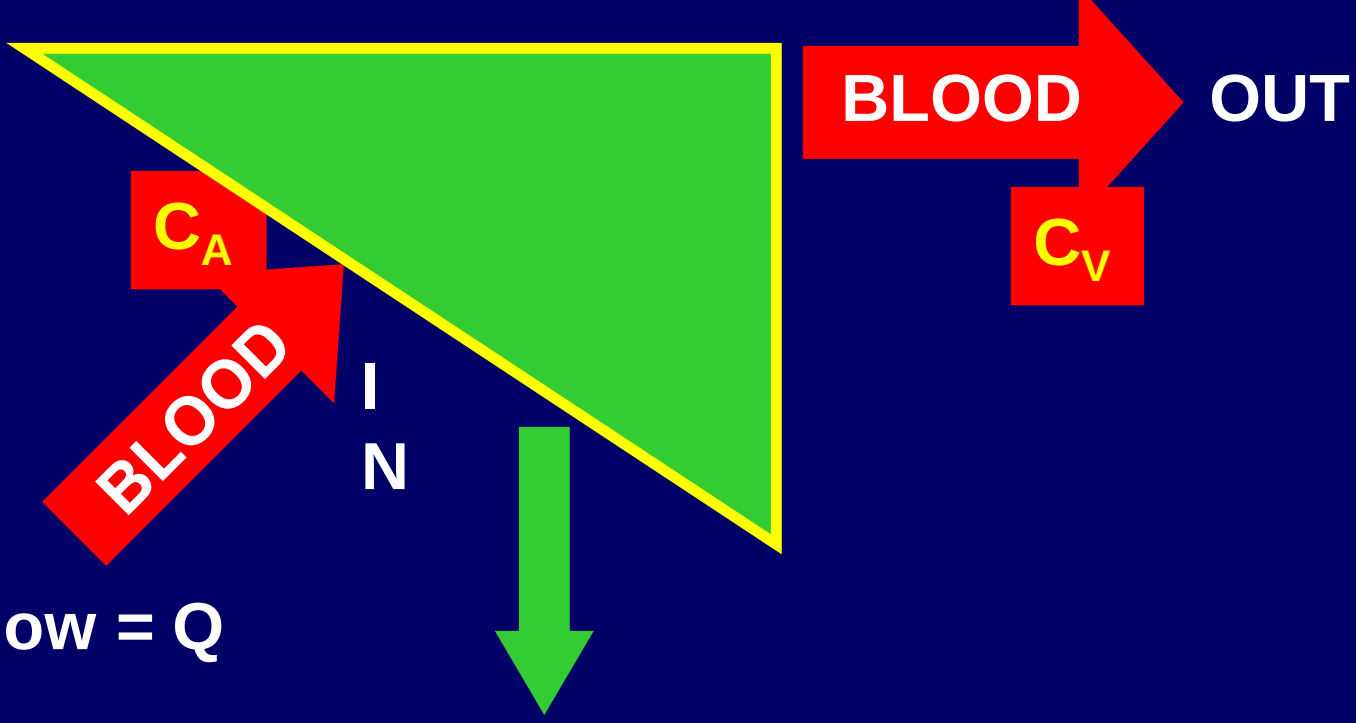
- **Clearance:** volume of plasma cleared of drug per unit time.

  Clearance = Rate of elimination ÷ plasma conc.

- **Half-life of elimination**: time for plasma conc. to decrease by half.

  Useful in estimating:

  - time to reach steady state concentration.
  - time for plasma concentration to fall after dosing is stopped.



Blood Flow = Q

Rate of Elimination = $QC_A - QC_V = Q(C_A - C_V)$

Liver Clearance = $Q(C_A - C_V)/C_A =$ $\boxed{Q \times EF}$ SIMILARLY FOR OTHER ORGANS

Renal Clearance = $U_x \cdot \dot{V}/P_x$

Total Body Clearance = $CL_{liver} + CL_{kidney} + CL_{lungs} + CL_x$

Rate of elimination = K_{el} x Amount in body

Rate of elimination = CL x Plasma Concentration

Therefore,

K_{el} x Amount = CL x Concentration

↓

$K_{el} = CL/V_d$

↓

$0.693/t1/2 = CL/V_d$

↓

$t1/2 = 0.693 \times V_d/CL$

PRINCIPLE

The half-life of elimination of a drug (and its residence in the body) depends on its clearance and its volume of distribution

$t_{1/2}$ is proportional to V_d

$t_{1/2}$ is inversely proportional to CL

$$t_{1/2} = 0.693 \times V_d/CL$$

Multiple dosing

- On continuous steady administration of a drug, plasma concentration will rise fast at first then more slowly and reach a plateau, where:

rate of administration = rate of elimination

ie. steady state is reached.

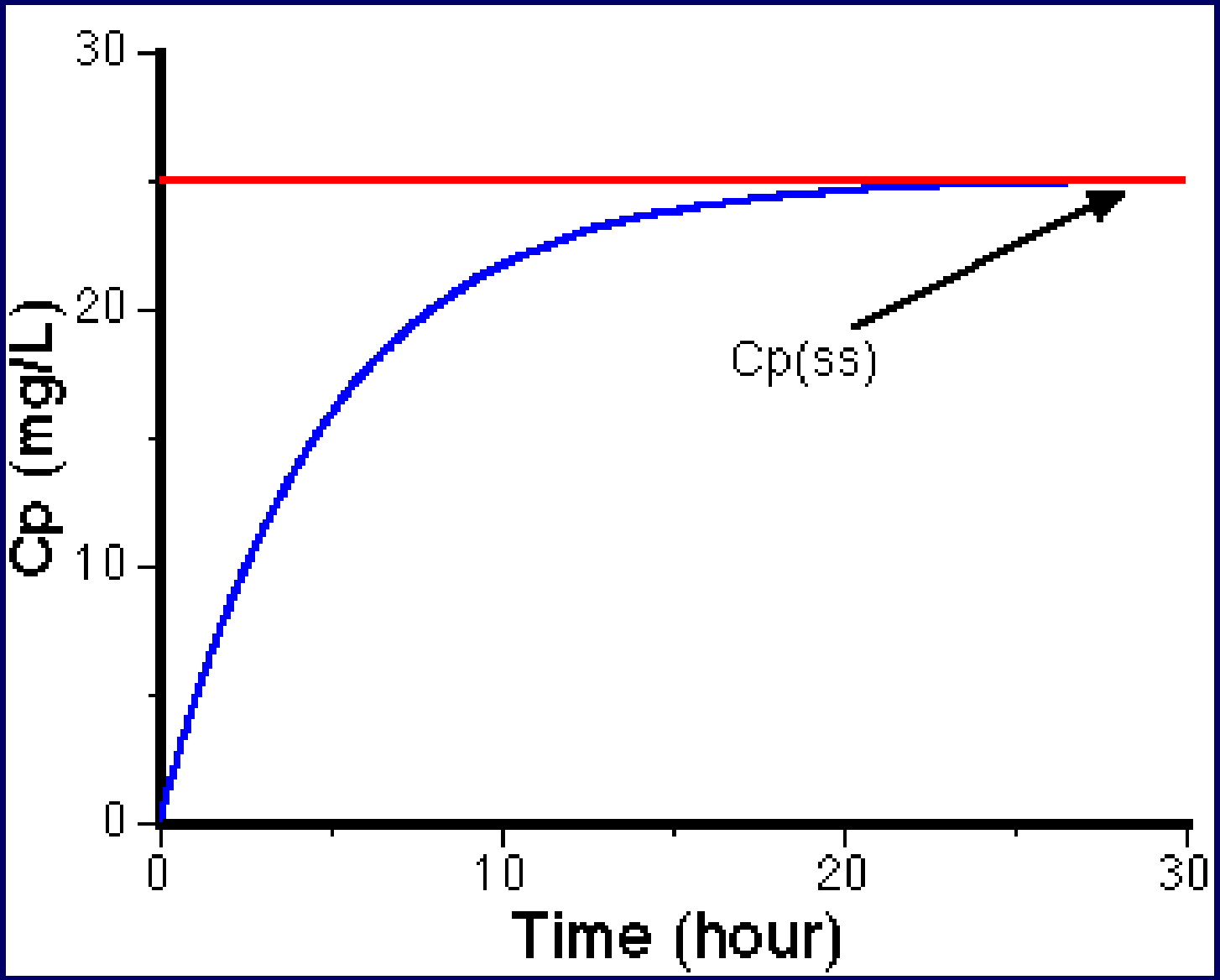
- Therefore, at steady state:

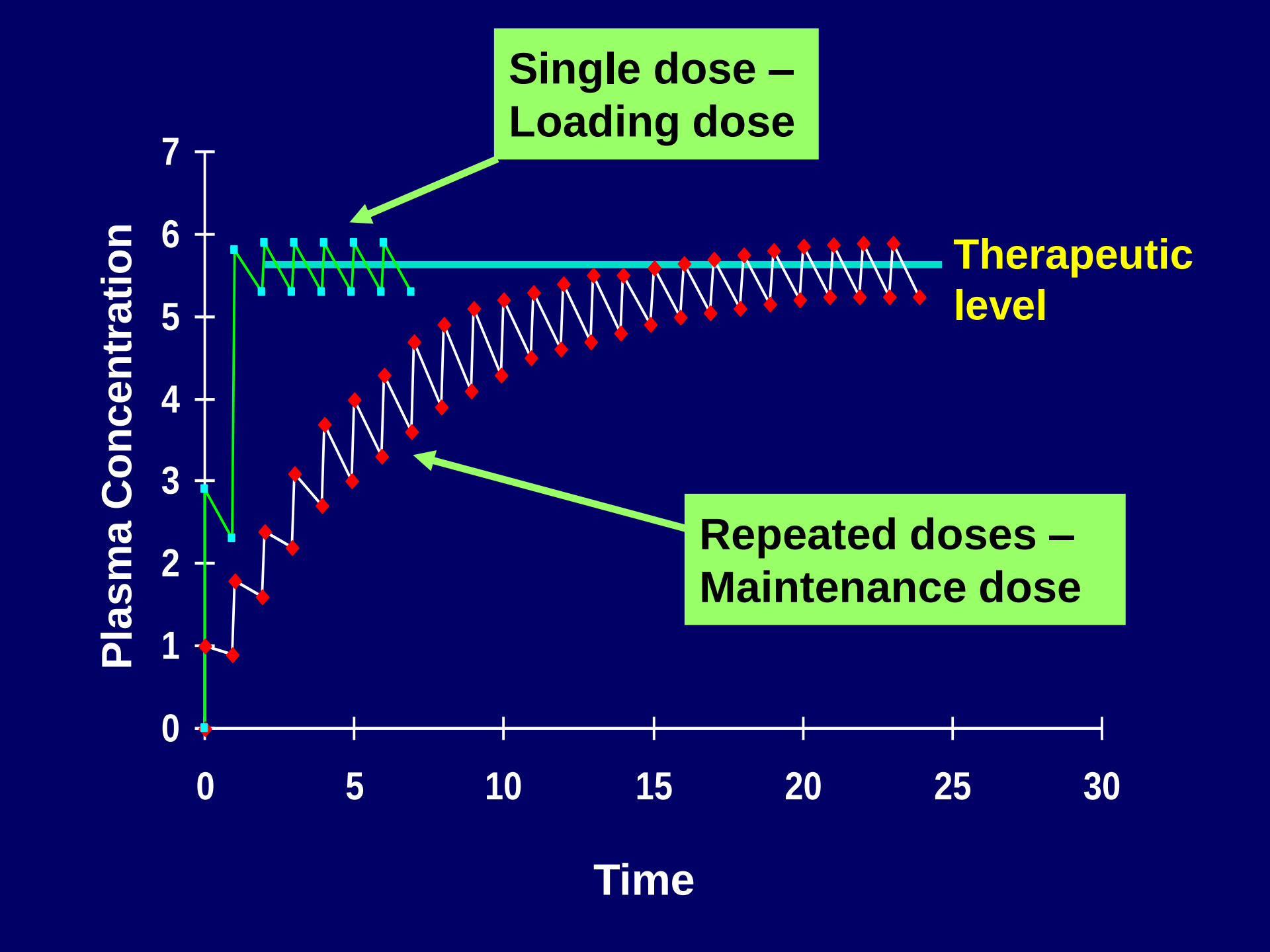
Dose (Rate of Administration) **= clearance x plasma conc.**

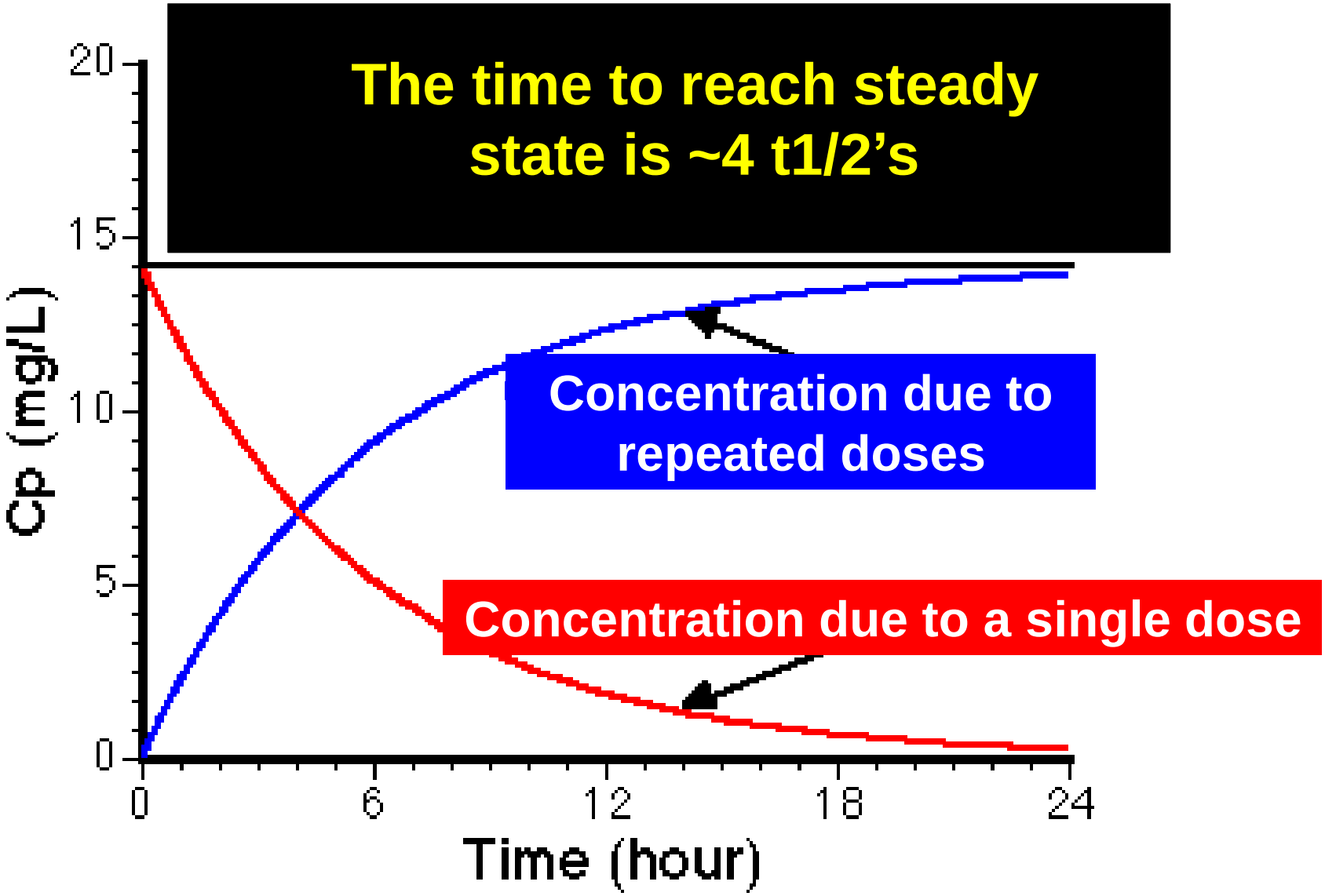
Or

If you aim at a target plasma level and you know the clearance, you can calculate the dose required.

Constant Rate of Administration (i.v.)



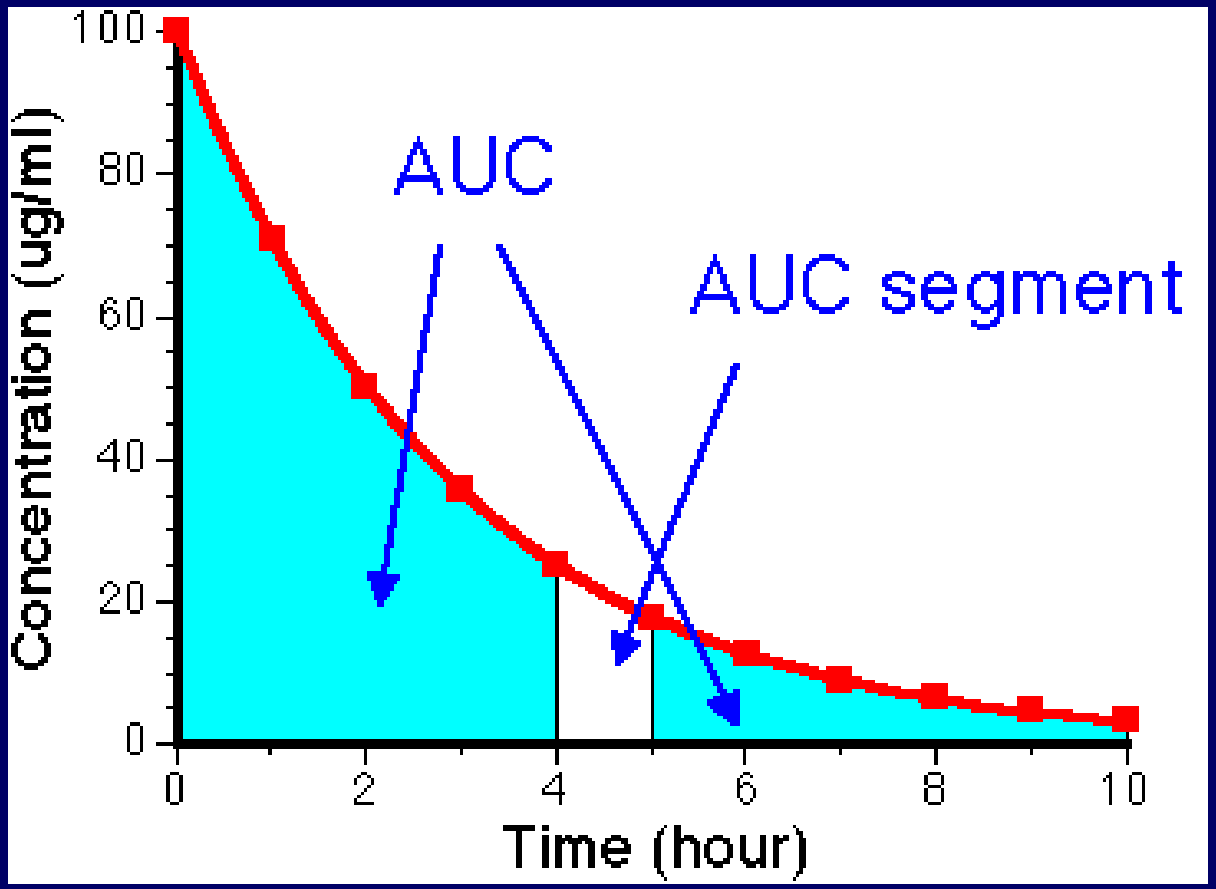

Single dose –
Loading dose
Therapeutic
level
Repeated doses –
Maintenance dose
Plasma Concentration
0
1
2
3
4
5
6
7
0
5
10
15
20
25
30
Time


The time to reach steady state is ~4 t1/2's
Concentration due to repeated doses
Concentration due to a single dose
Cp (mg/L)
Time (hour)
0
5
10
15
20
0
6
12
18
24

Pharmacokinetic parameters

Get equation of regression line; from it get K_{el}, C_0 , and AUC

- **Volume of distribution $V_d = DOSE / C_0$**
- **Plasma clearance $Cl = K_{el} . V_d$**
- **plasma half-life $t1/2 = 0.693 / K_{el}$**
- **Bioavailability $(AUC)_x / (AUC)_{iv}$**



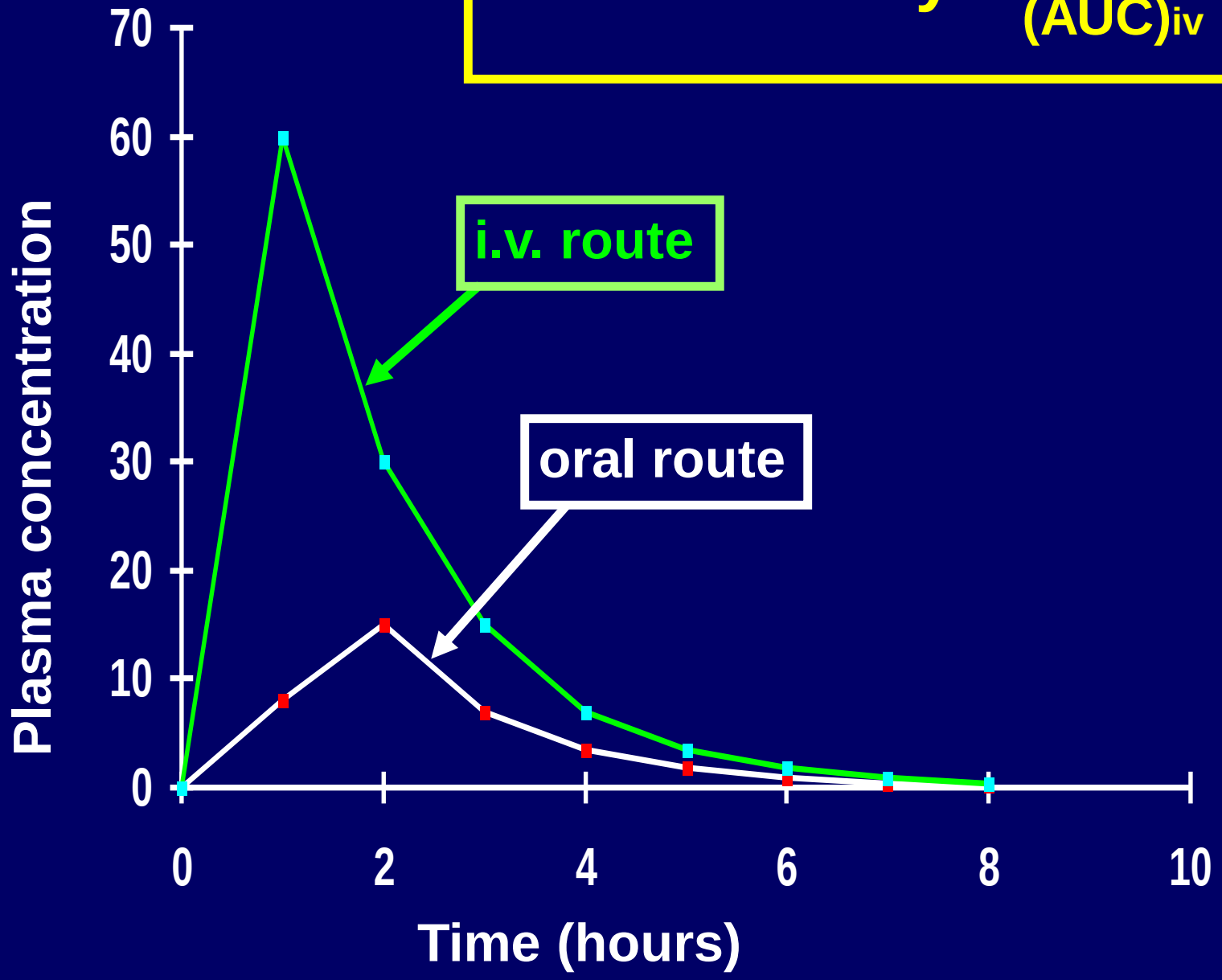
$dC/dt = CL \times C$

$dC = CL \times C \times dt$

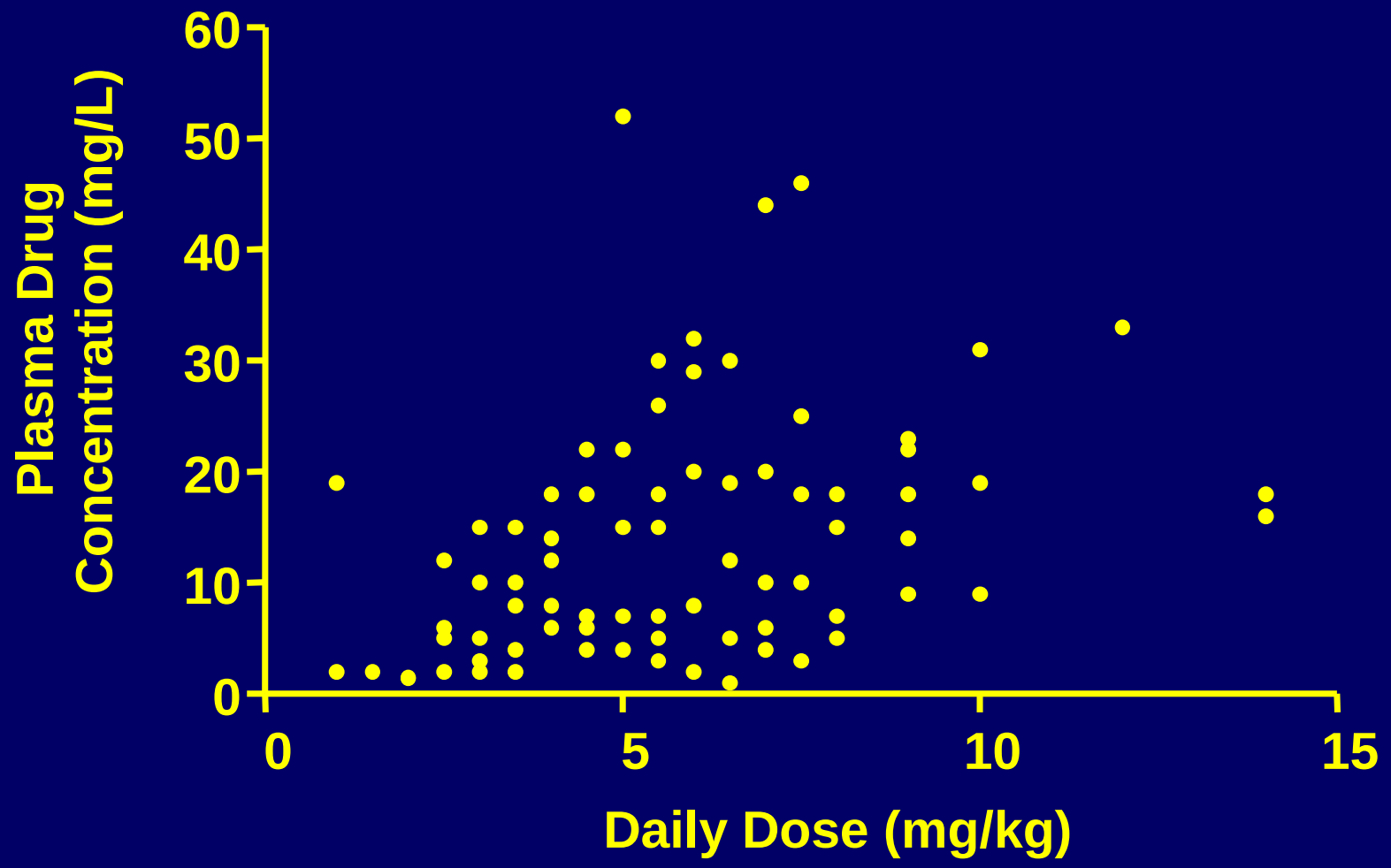
But C x dt = small area under the curve. For total amount eliminated (which is the total given, or the dose, if i.v.), add all the small areas = AUC.

Dose = CL x AUC and Dose x F = CL x AUC

$$\text{Bioavailability} = \frac{(AUC)_o}{(AUC)_{iv}}$$



Variability in Pharmacokinetics



PRINCIPLE

The absorption, distribution and elimination of a drug are qualitatively similar in all individuals. However, for several reasons, the quantitative aspects may differ considerably. Each person must be considered individually and doses adjusted accordingly.