Basic Pharmacology

- pharmacodynamics – the study of the efects of the drugs on receptors, reactions; principles of action

- pharmacokinetics - the study of the movement of drugs through the body in time. (absorption, distribution, metabolism, excretion)

Pharmacokinetics

Action of a drug requires presence of a certain concentration in the fluid bathing the target tissue.

The magnitude of response (good or bad) depends on concentration of the drug at the site of action

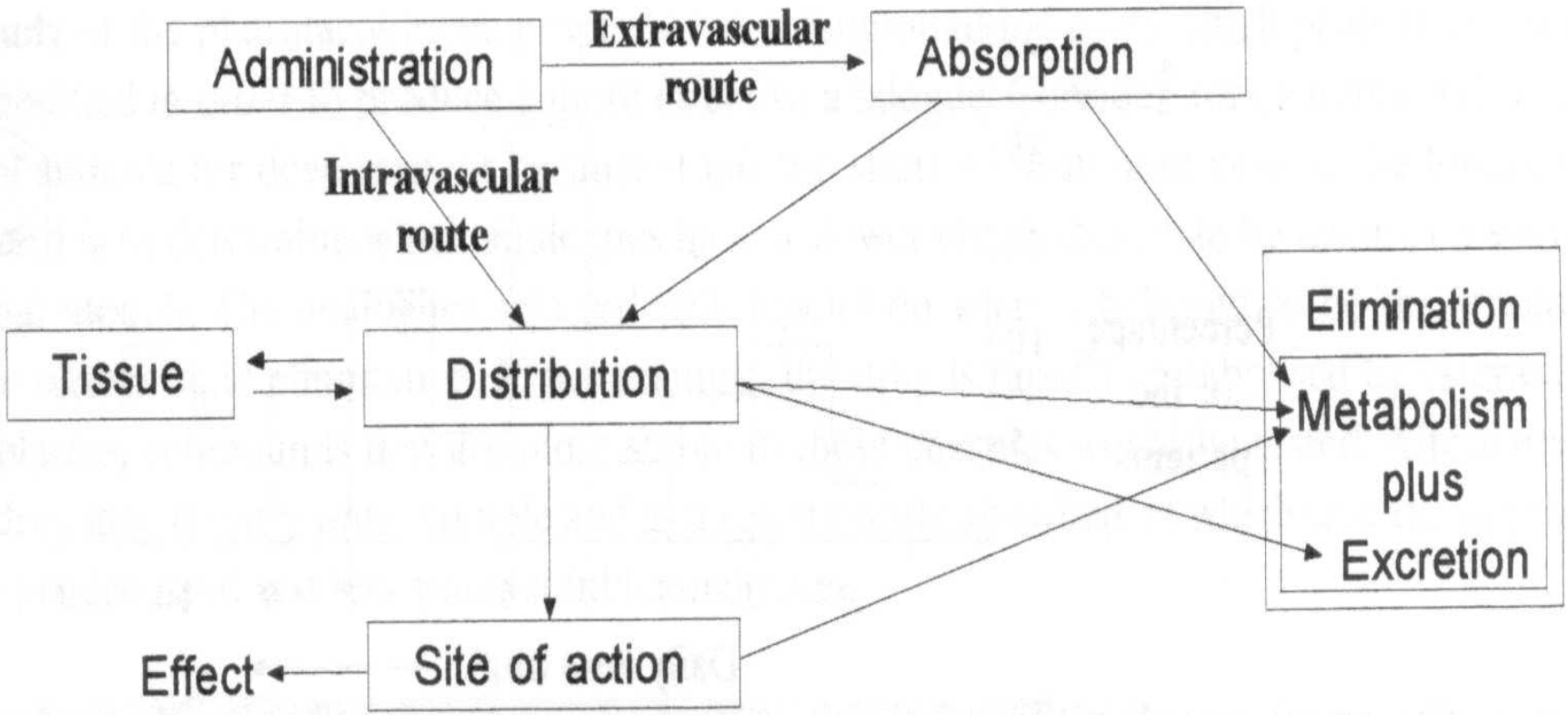
Pharmacokinetics deals with the processes of

absorption, **A**
distribution, **D**
metabolism **M**
excretion of the drug **E**

A, **D** } **invasion**
M, **E** } **elimination**
invasion + **elimination** } **“ADME“**

And their relationship with their biological (pharmacological) effect

„WHAT DOES ORGANISM DO WITH THE DRUG“



The general stages and their relationships in the life cycle of a drug after administration.

What does influence the movements of the drug in the body?

physico-chemical properties

lipophilic/hydrophilic pr
structure, pKa, charge…
AH ⇆ A- + H+ B

Ionized compounds tend to be *less* lipid soluble.
Non-Ionized compounds tend to be *more* lipid soluble.

permeation across the membr

lipophilic – difusion (pa
hydrophilic – through the pores
active transport

bonds of the drugs to:

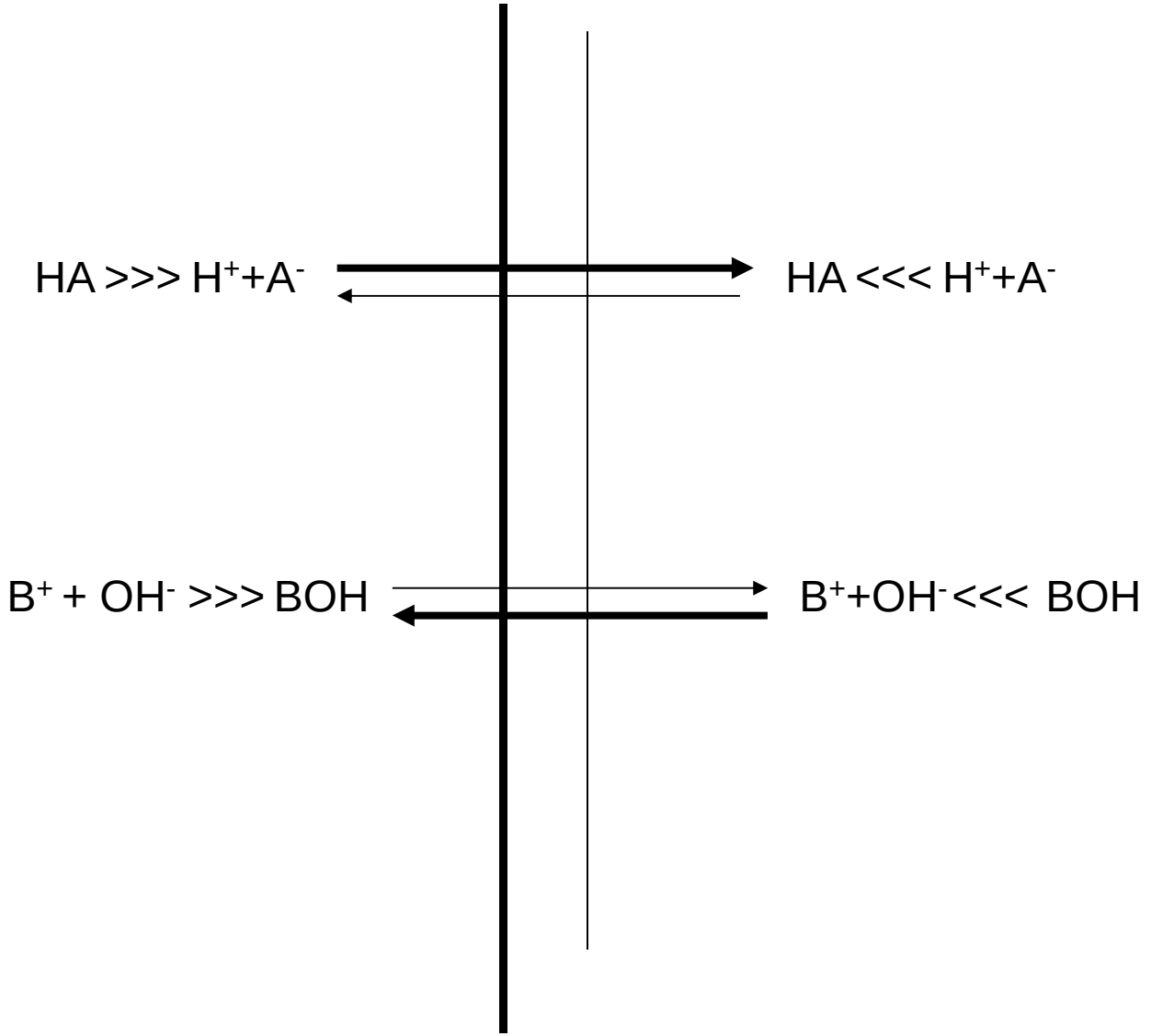
plasma proteins
blood cells in the circulation
tissue
receptors

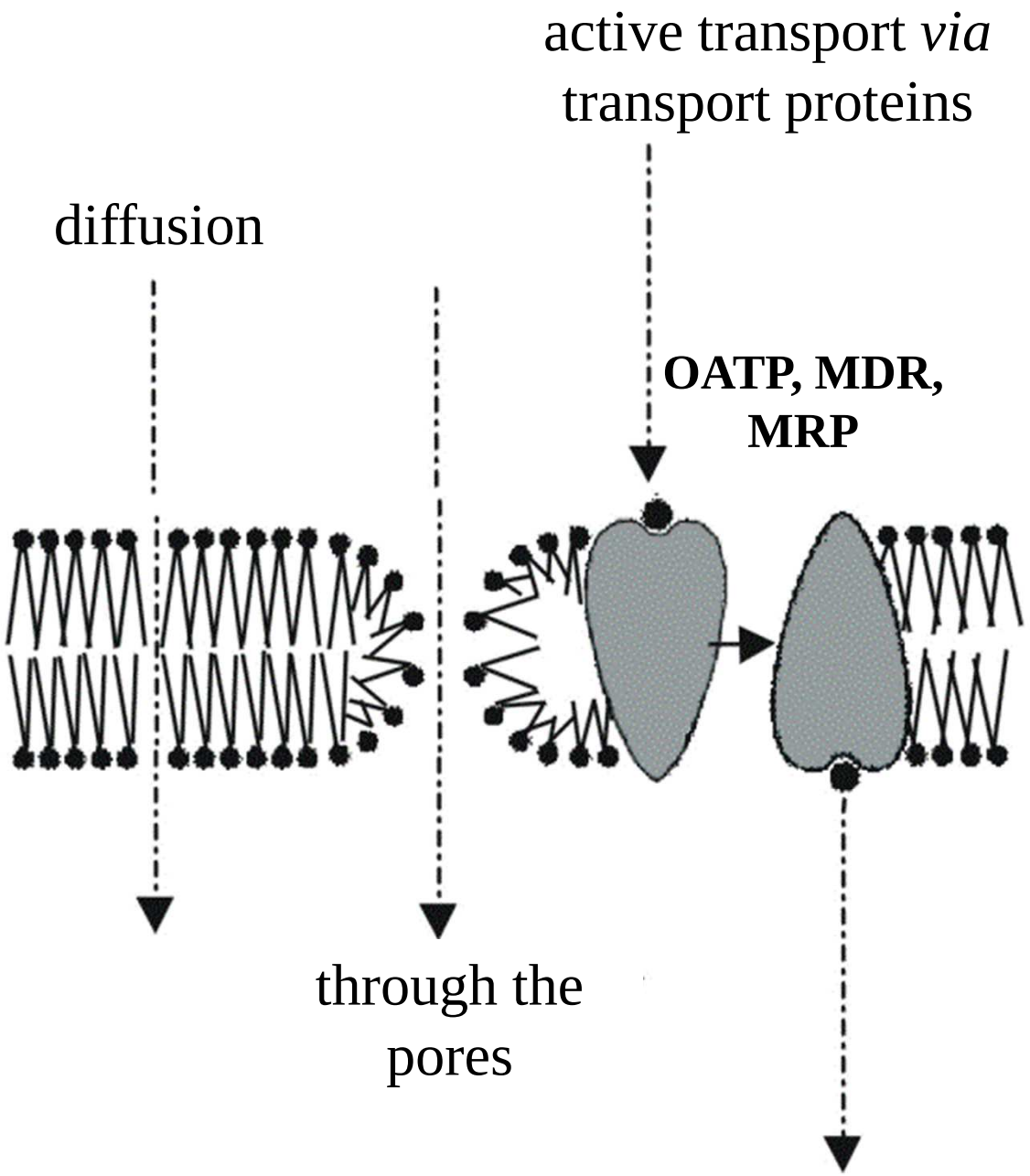
perfusion of the tissues

a) brain, heart, liver, kidney
b) fat tissue

Stomach pH 1-2

Parietal cells + endothelium of vessels
7.2-7.4




active transport *via*
transport proteins
diffusion
OATP, MDR,
MRP
through the
pores

ABSORPTION

Absorption – permeation of the soluted drug into the body fluids from the site of administration – necessary for the general (systhemic) effect

Local effect – on the skin, mucous membranes…
mouth, rectum, vagina

- absorption is fault, can cause difficulties, adverse effects)

(local aenesthetics, corticosteroids)

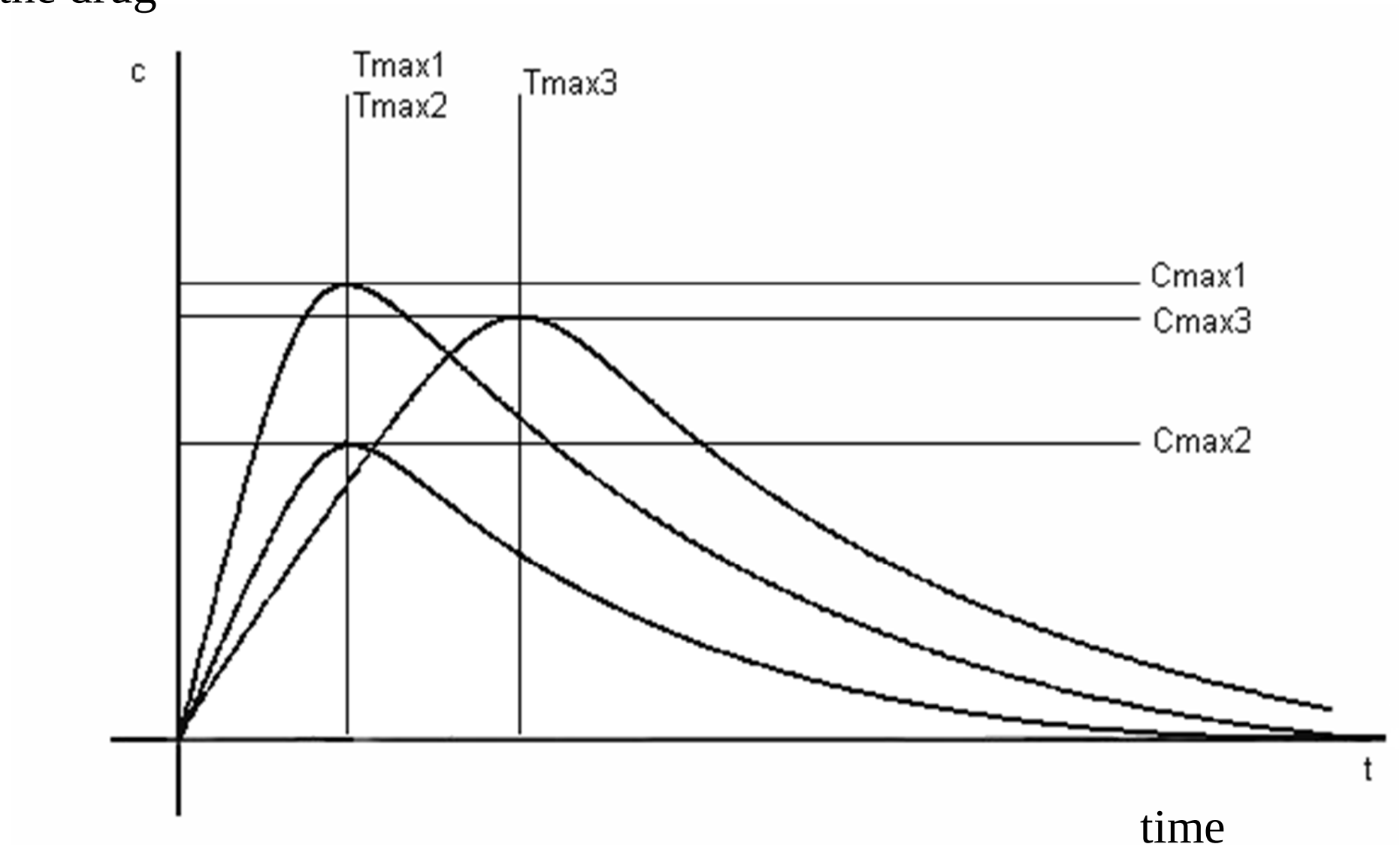
Rate and extent of absorption are described by the parameters :

C max - max. concentration of the drug in the plasma after single administration

T max - time after administration, when is Cmax

F - bioavailability (extent of absorption)

Plasmatic concentration of the drug

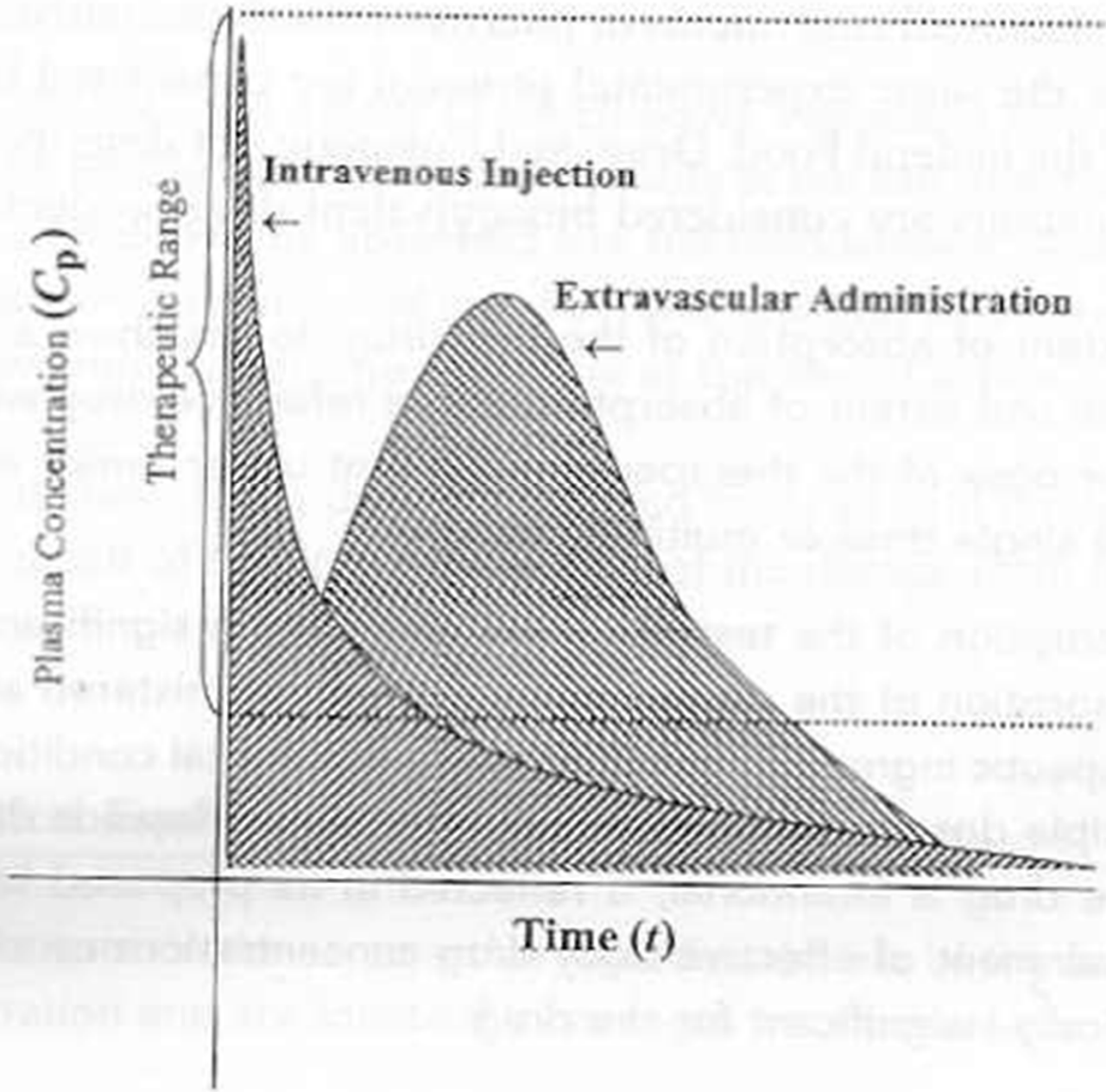


Bioavailability

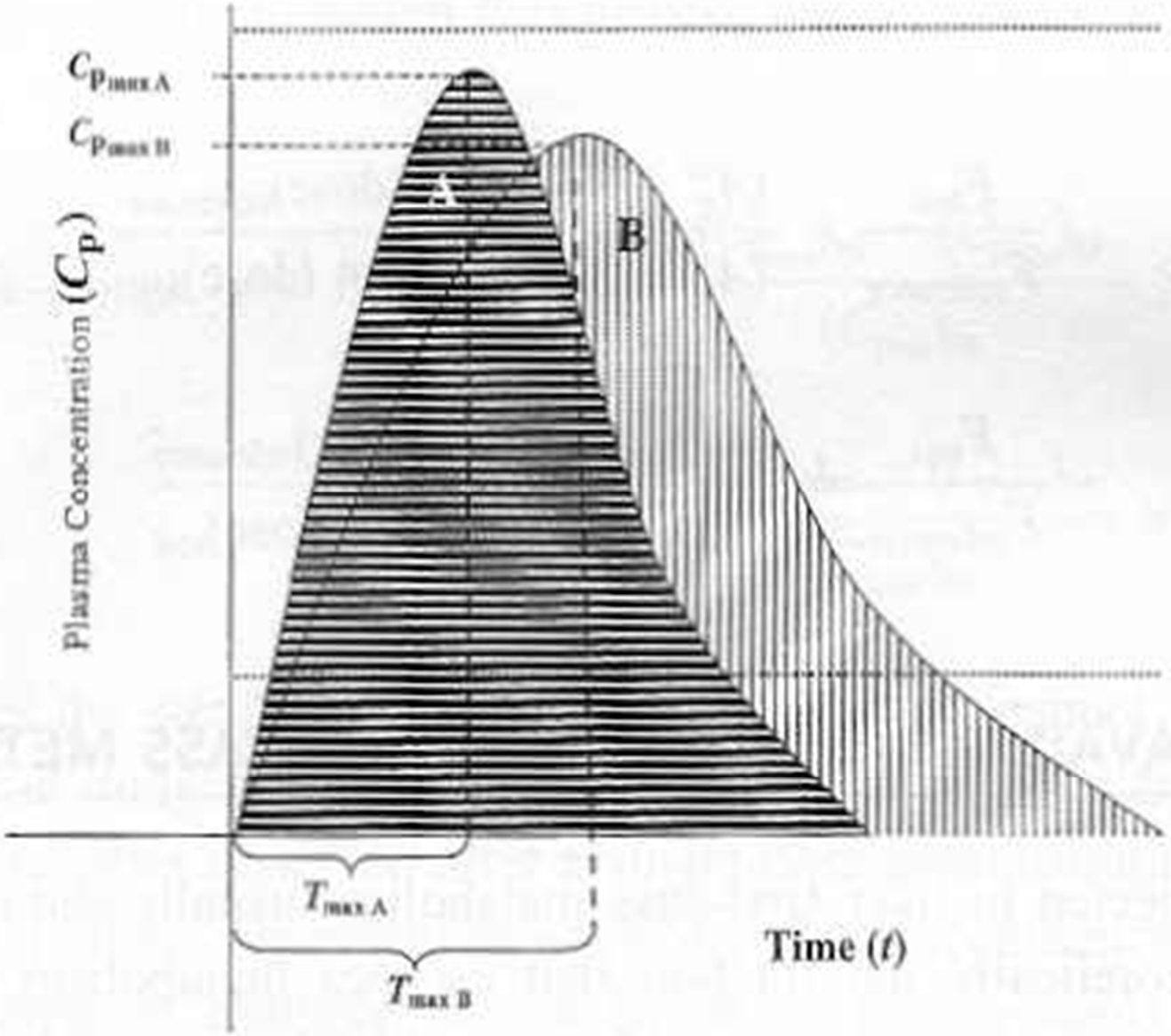
- The fraction of the dose of a drug (F) that enters the general circulatory system,

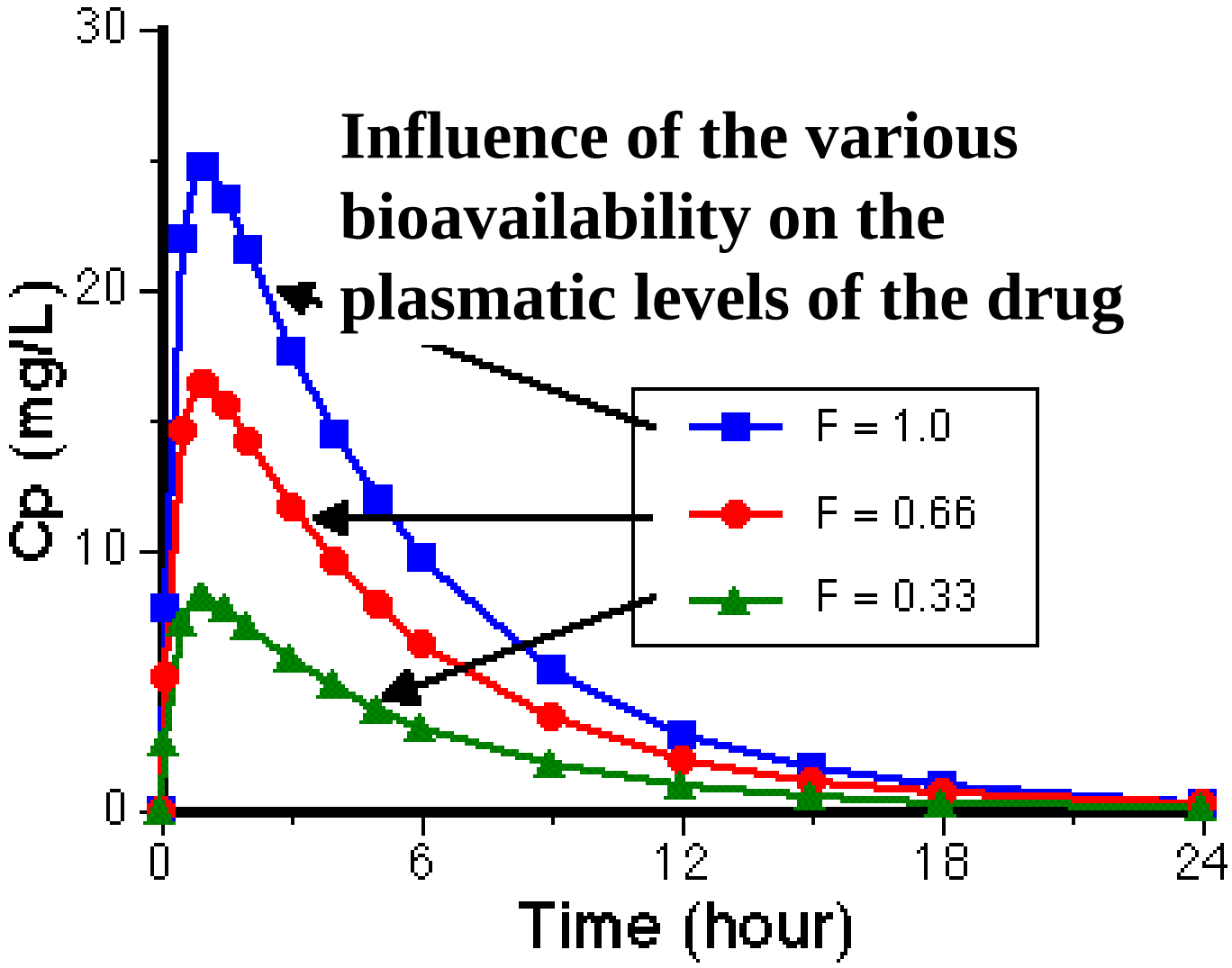
  $$F = \frac{\text{amt. of drug that enters systemic circul}}{\text{Dose administered}}.$$

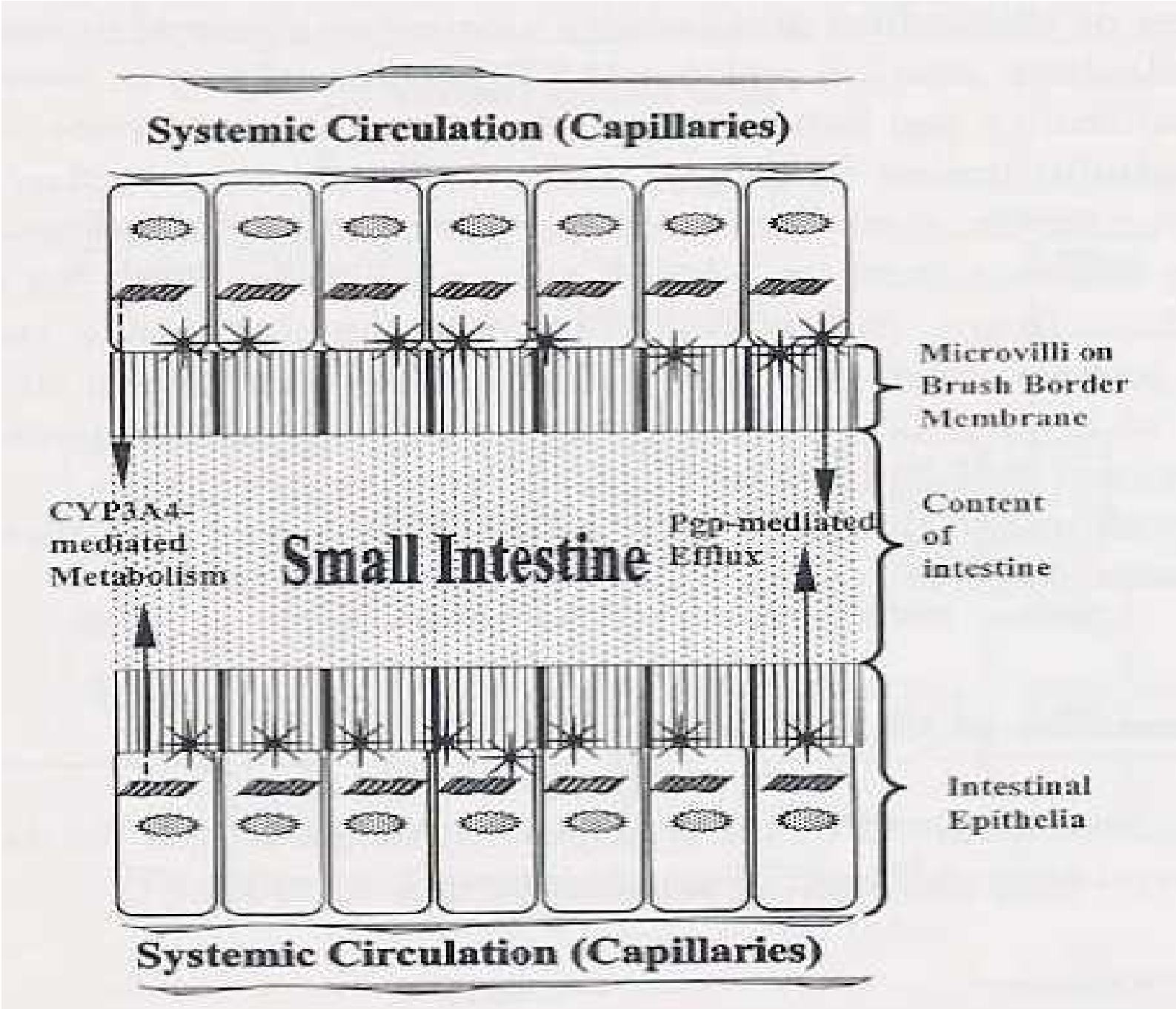
$$F = AUC_{p.o.} / AUC_{i.v.}$$


Intravenous Injection
Extravascular Administration
Therapeutic Range
Plasma Concentration (C_p)
Time (t)

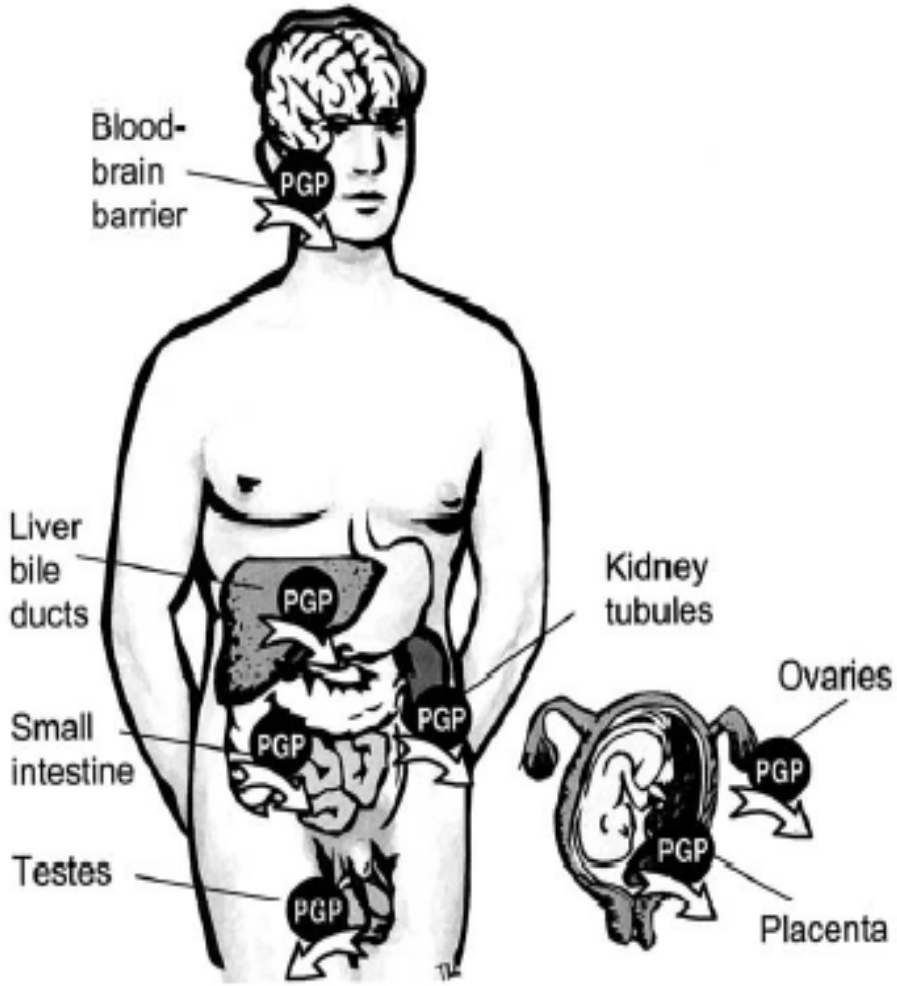
Relative bioavailability



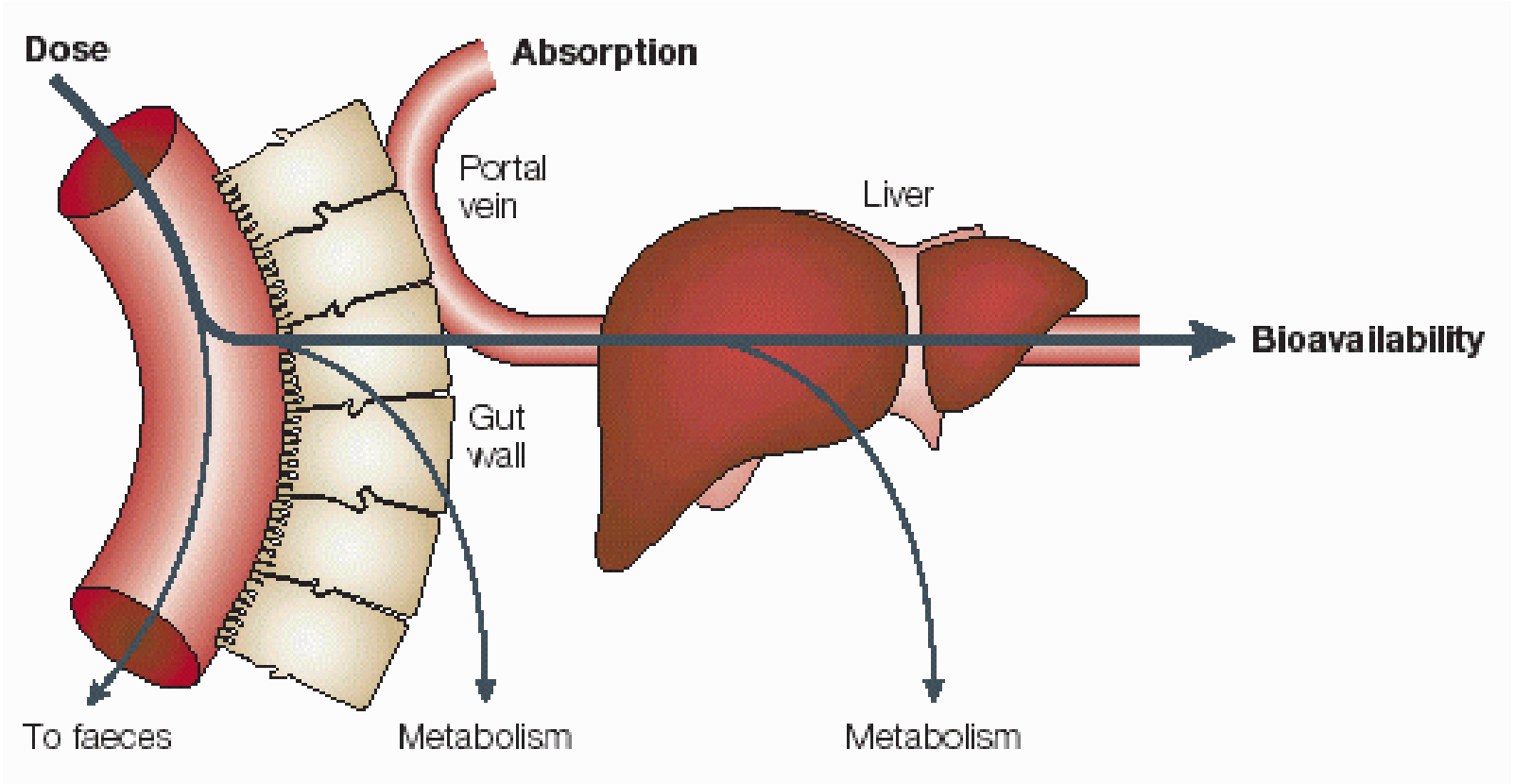

Influence of the various bioavailability on the plasmatic levels of the drug
Cp (mg/L)
30
20
10
0
0
6
12
18
24
Time (hour)
F = 1.0
F = 0.66
F = 0.33

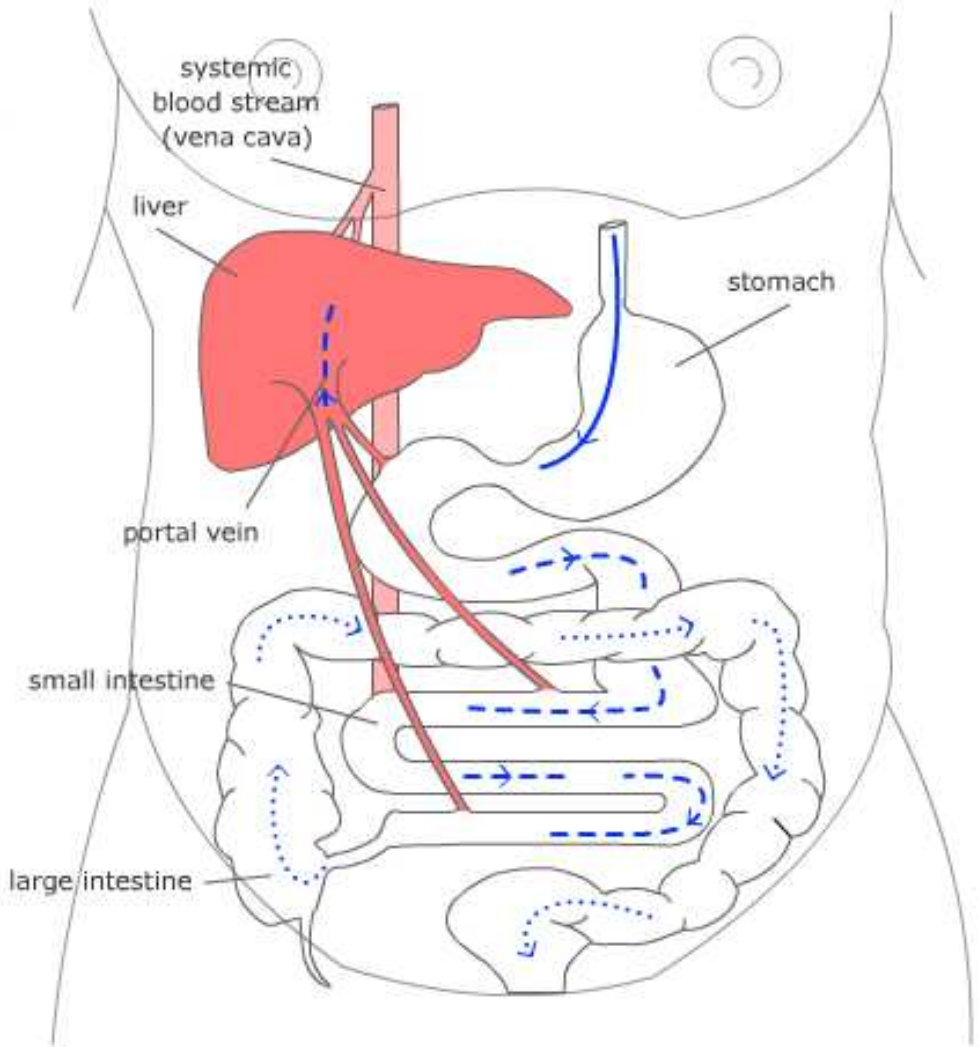

Systemic Circulation (Capillaries)
Microvilli on
Brush Border
Membrane
CYP3A4-
mediated
Metabolism
Small Intestine
Pgp-mediated
Efflux
Content
of
intestine
Intestinal
Epithelia
Systemic Circulation (Capillaries)

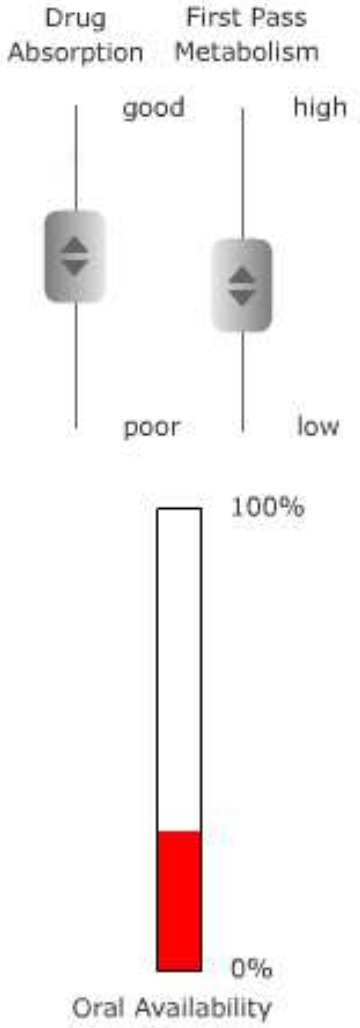
- P-glycoprotein
  - Resistance on chemotherapeutics
  - i. saquinavir



First pass effect, presysthemic elimination







Other factors influencing the absorption

gender, body weight, plasma volume, gastric amptying rate,

age - pH, bile, enzyme levels and activity

Patophysiological state – liver disseases, inflammation

simultaneously eaten meal –

acceleration/decelaration

chemical incompatibilities

function of the GIT

Distribution

= permeation from the body blood to the tissues and site of the action
Is dynamic process

rate - depends on:
bond (with the plasmatic proteins)
permeation across the membrabes
blood perfusion through the organ

state - distribution equilibrium; the the proportion of the free (unbounded) fractions of the drug in the blood and in the tissues are the same

Barriers – the distribution is limited

blood-brain barrier („leaky areas“ – area postrema), placental barrier…

A bound drug has no effect!

- **Amount bound depends on**:
- 1) free drug concentration
- 2) the protein concentration
- 3) affinity for binding sites

$$\% \text{ bound: } \frac{[\text{bound drug}]}{[\text{bound drug}] + [\text{free drug}]} \times 100$$

Volume of Distribution

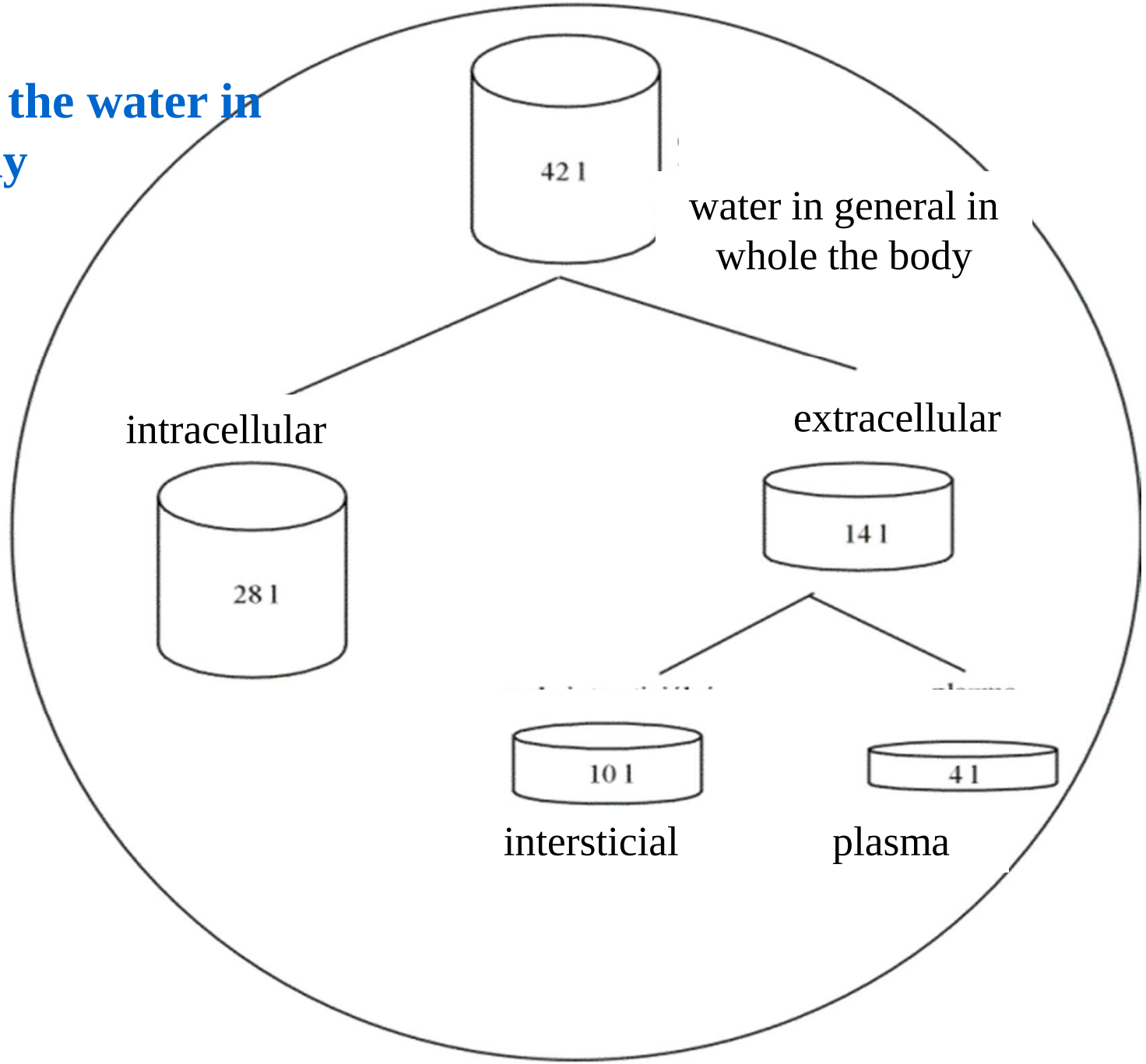
Volume of distribution – apparent, hypotethical
the proportion of the quantity of the drug and reached plasmatic concentration

- $C = D/V_d$
  - V_d is the apparent volume of distribution
  - C= Conc of drug in plasma at some time
  - D = Total quantity (dose) of drug in system

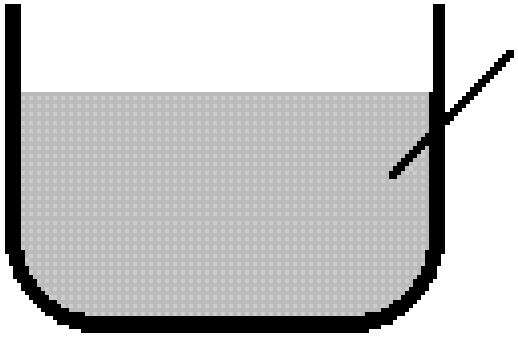
V_d gives one as estimate of how well the drug is distributed.

Value < 0.071 L/kg indicate the drug is mainly in the circulatory system. Values > 0.071 L/kg indicate the drug has gotten into specific tissues.

Volumes of the water in human body

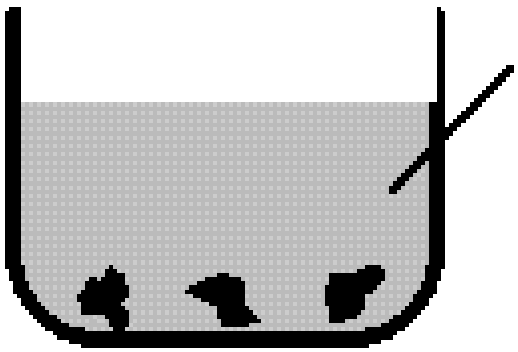


Drug concentration in beaker:

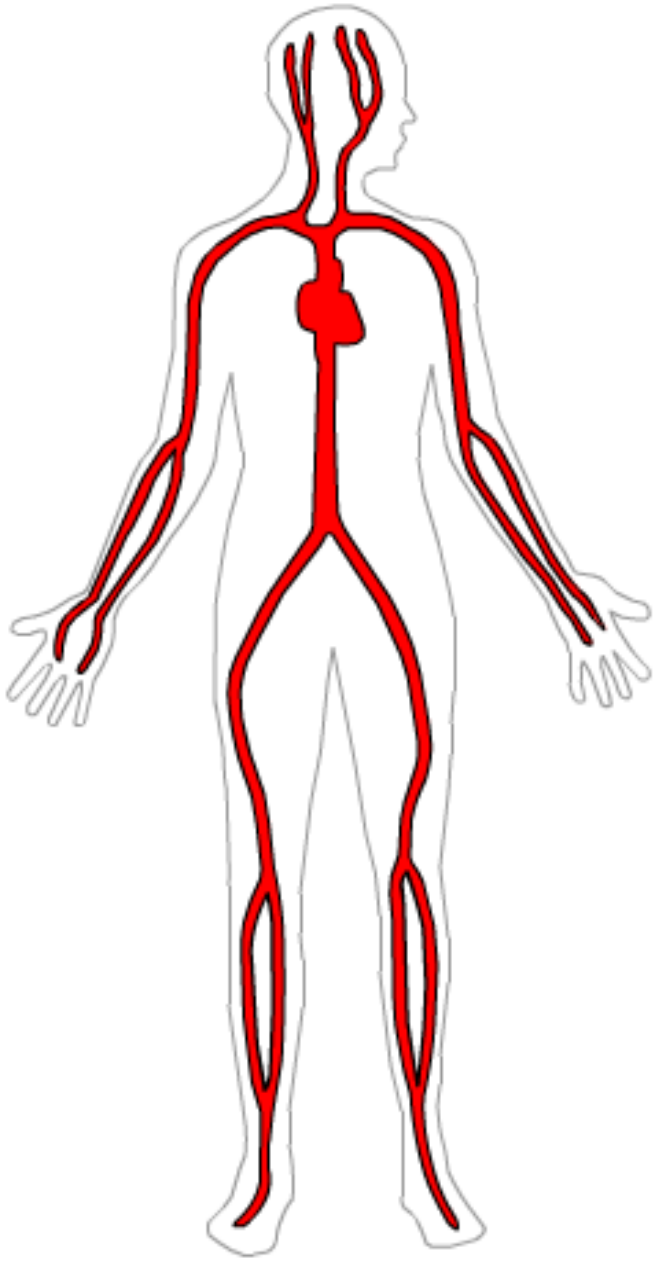


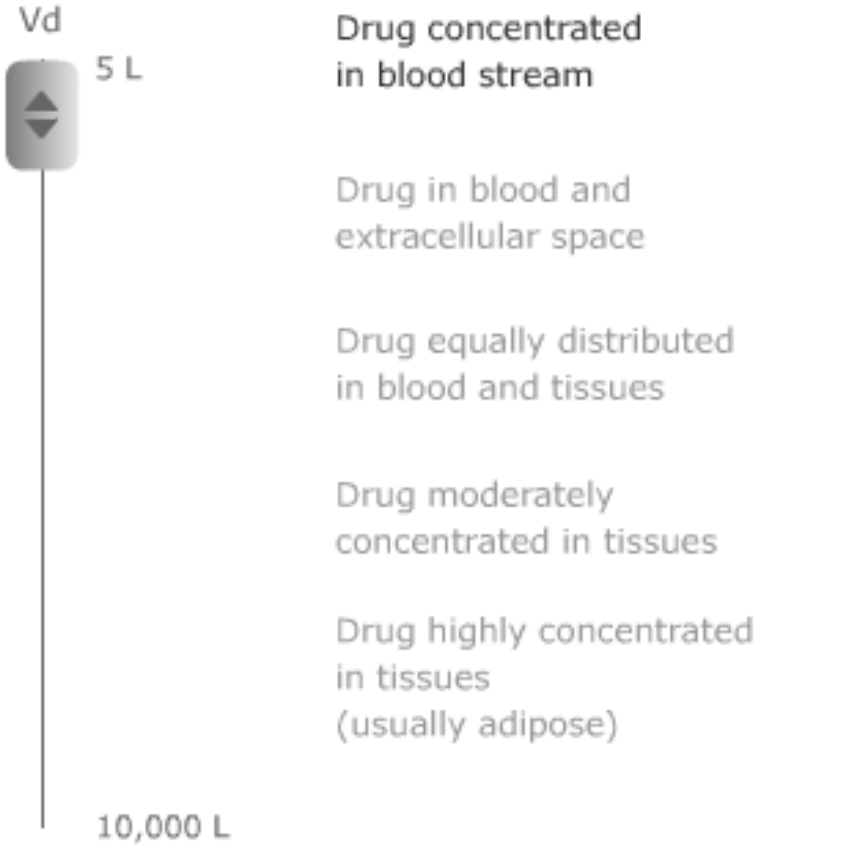
Dose = 10 mg
Cp^0 = 20 mg/L
Apparent
Volume = 500 ml

With charcoal in beaker:



Dose = 10 mg
Cp^0 = 2 mg/L
Apparent
Volume = 5000 ml





Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

$$Vd = \frac{Ab}{Cp}$$

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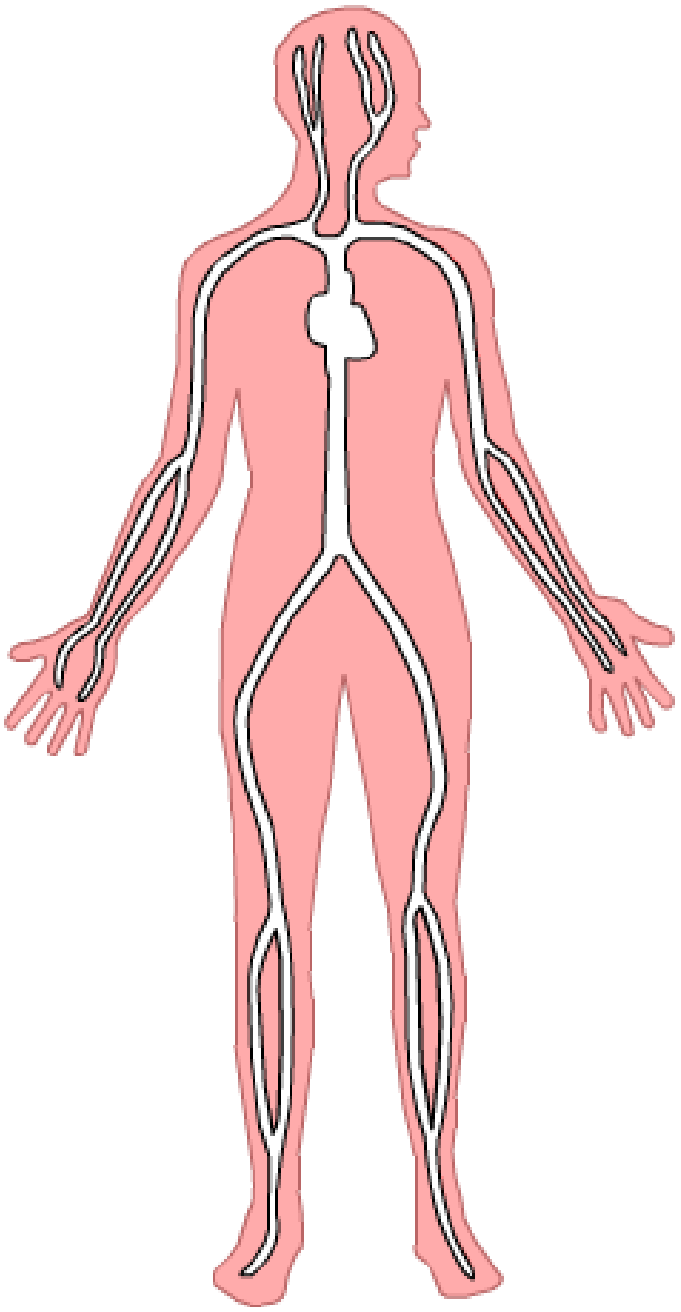

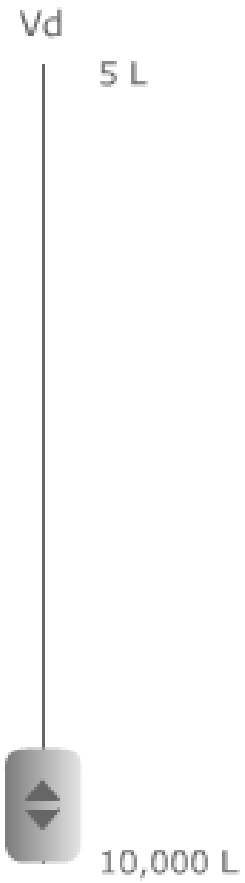

Drug concentrated in blood stream

Drug in blood and extracellular space

Drug equally distributed in blood and tissues

Drug moderately concentrated in tissues

Drug highly concentrated in tissues (usually adipose)

Amount in body = Vd x plasma concentration

$$Ab = Vd \times Cp$$

$$Vd = \frac{Ab}{Cp}$$

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Perfusion through the organs

organ	perfusion rate (ml/min/g tkáně)	% heart output
brain	0.5	14
fat	0.03	4
heart	0.6	4
kidney	4.0	22
liver	0.8	27
musculature	0.025	15
skin	0.024	6

ELIMINATION

- Kinetics of the first order

  = rate of elimination is descending with the descending concentration in the blood

  (linear kinetics)

- Kinetics of the zero order

  = rate of elimination is constant (nonlinear kinetics)

Types of Kinetics Commonly Seen

- **Zero Order Kinetics**

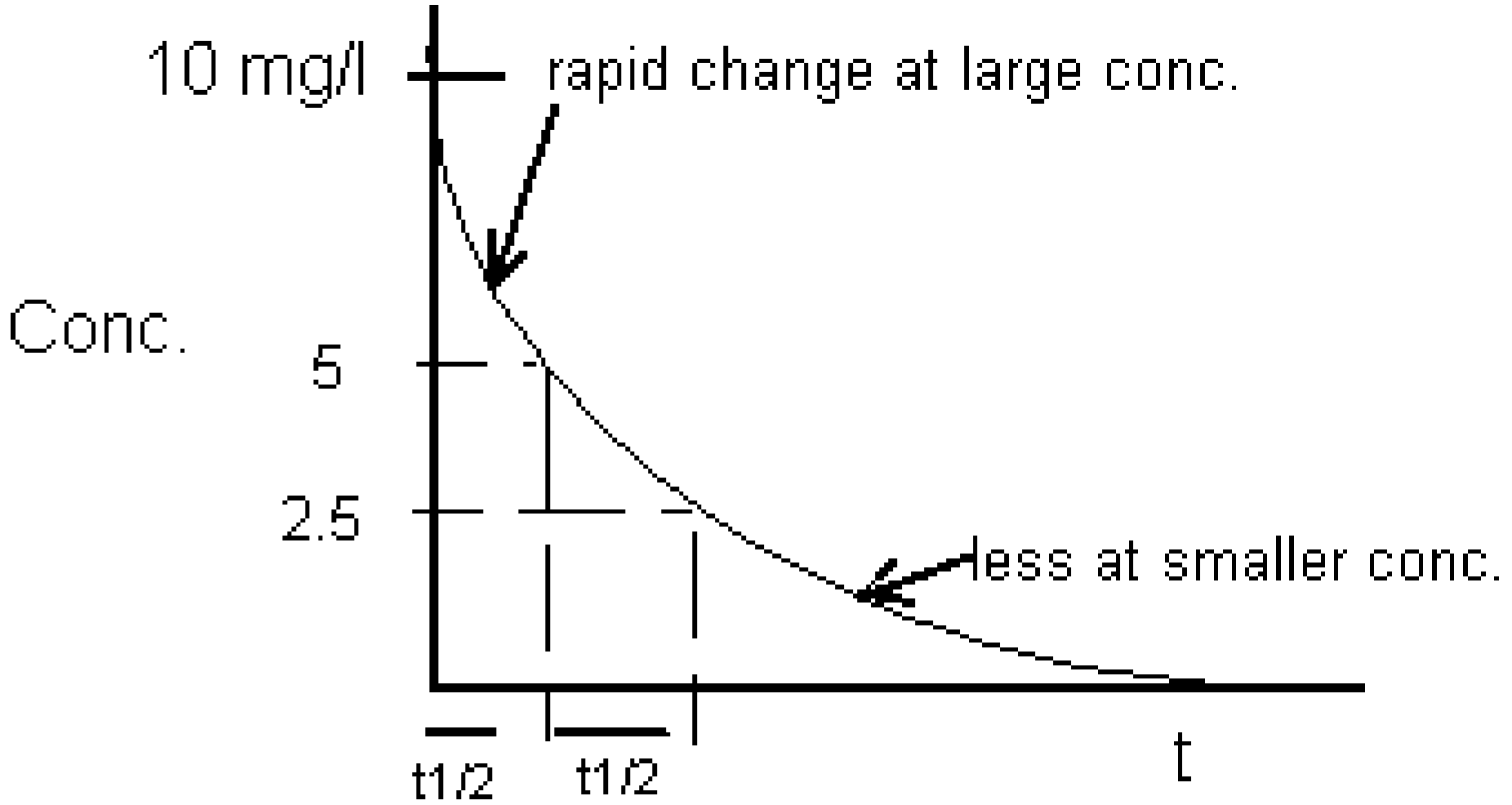
- Rate = k
- C = Co - kt

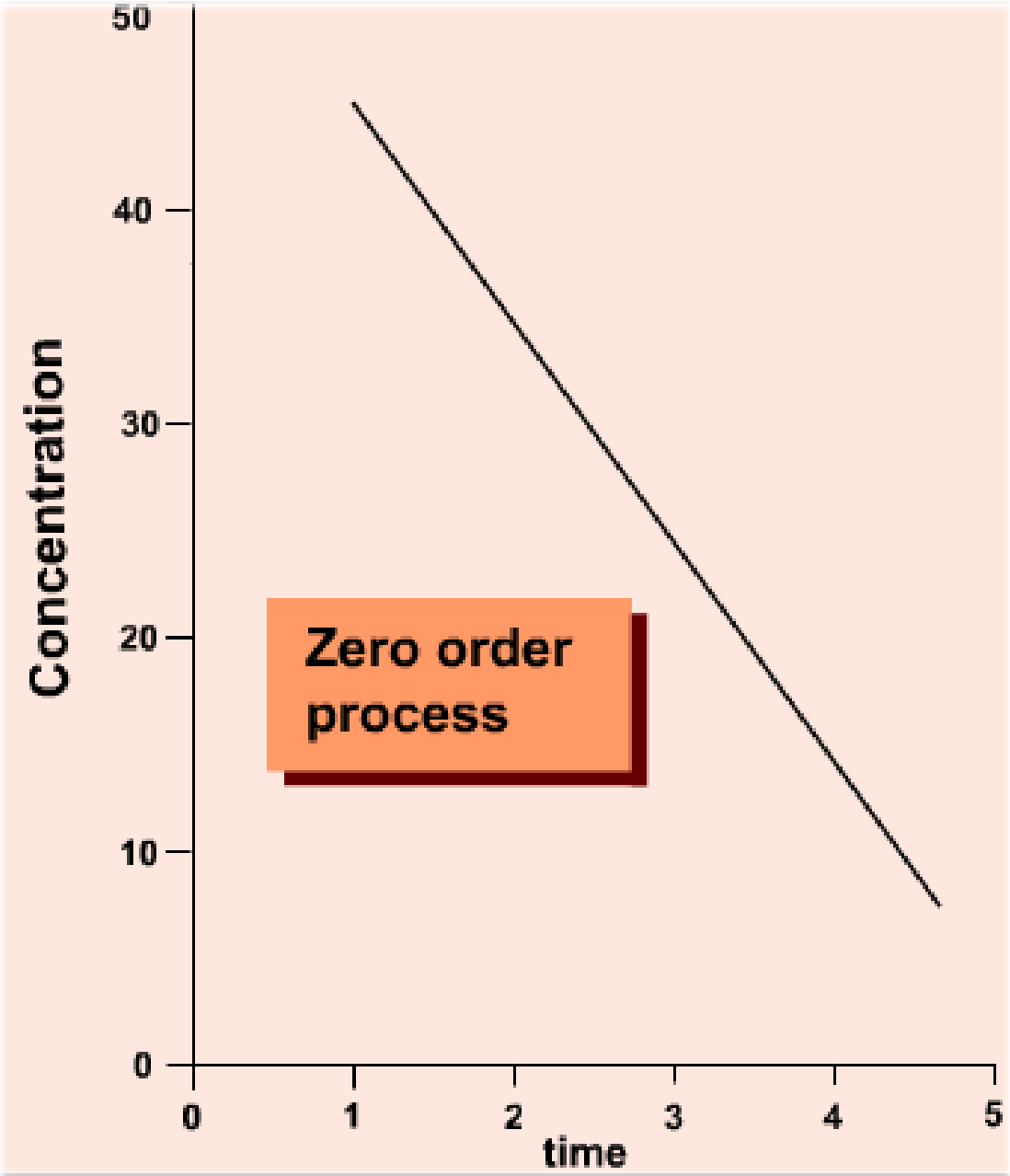
- C vs. t graph is LINEAR

First Order Kinetics

- Rate = k C
- $C = C_o e^{-kt}$

- C vs. t graph is NOT linear, decaying exponential.
- Log C vs. time graph is linear.


10 mg/l
rapid change at large conc.
Conc.
5
2.5
less at smaller conc.
t1/2
t1/2
t


50
40
30
20
10
0
Concentration
Zero order process
0
1
2
3
4
5
time

ELIMINATION

Biotransformation – metabolism

mostly in the liver,

kidney, gut, but also in other organs and tissues

Enzymatic

- **biodegradation**
- **bioactivation (prodrug)**

enalapril-enalaprilate

codein-morphine

bromhexin - ambroxol

1. Phase : oxidation, hydrolysis

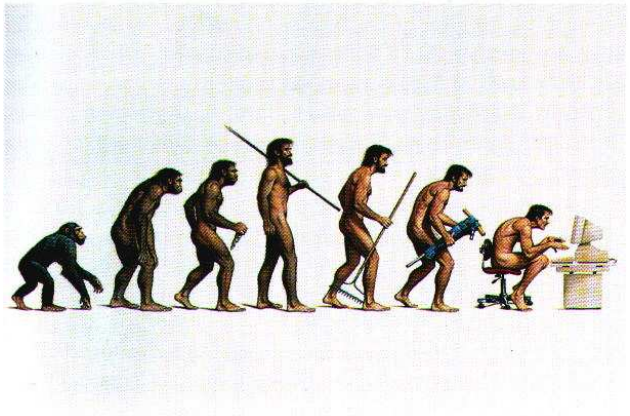
Cytochrom P450, dehydrogenases

2. Phase : conjugation – metabolites are more soluble in the water

Metabolite - effective („more / less / in other way“)

- ineffective

- toxic



men

plants

animals

CYP 450

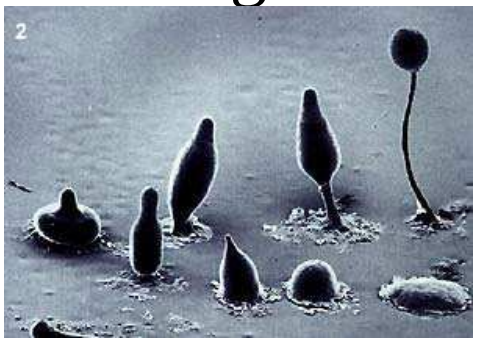
molluscs

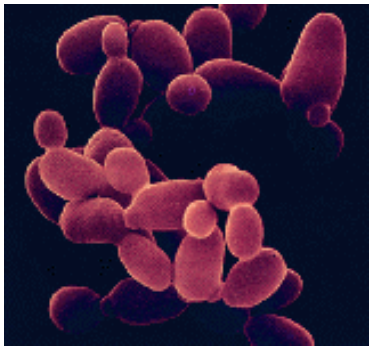
insect

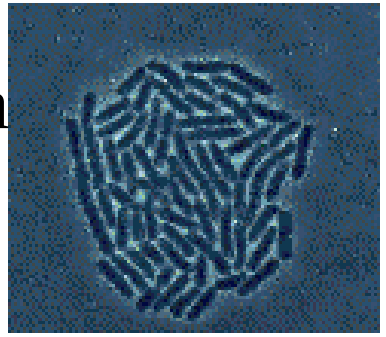
funghi

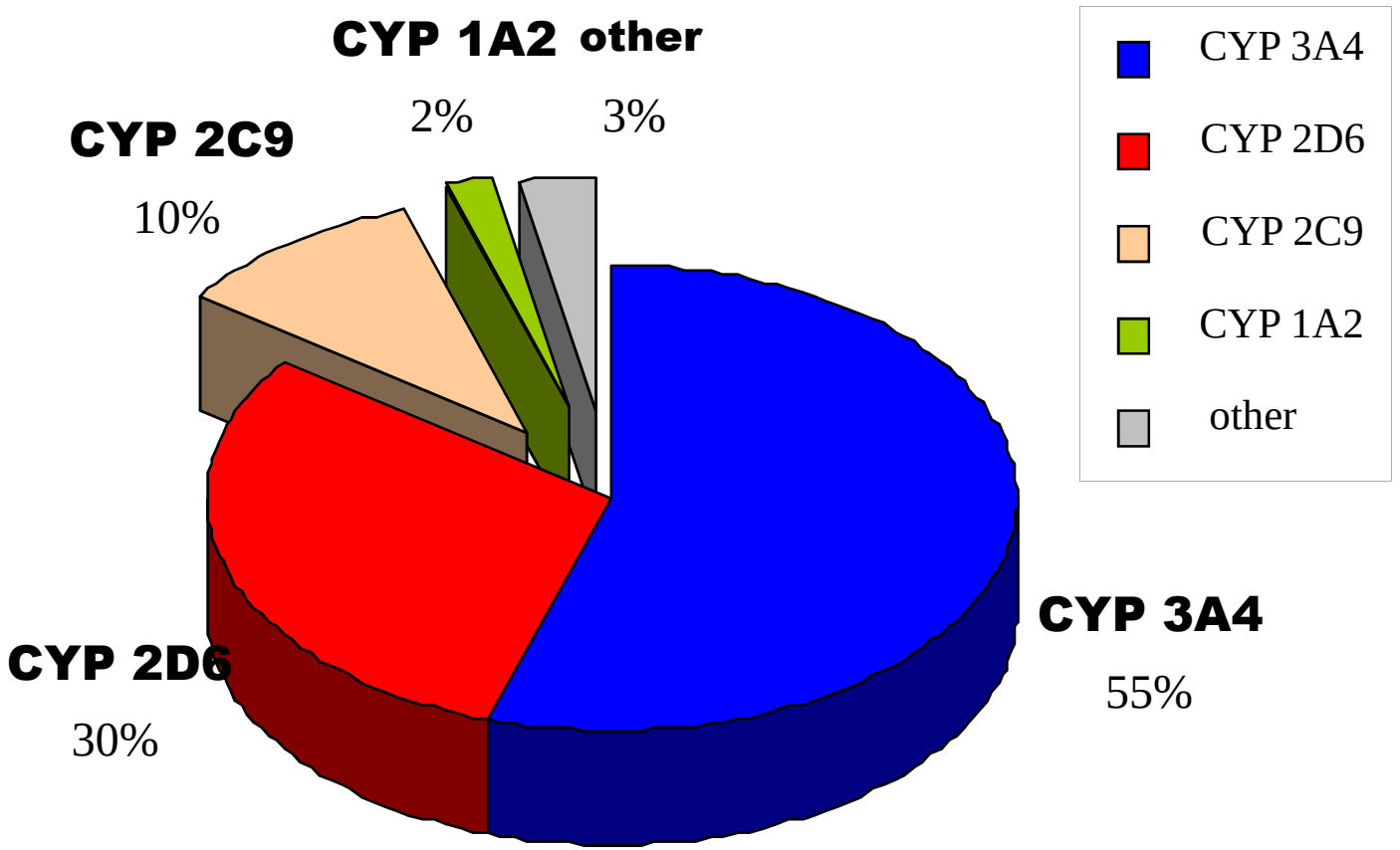
yeast

bacteria







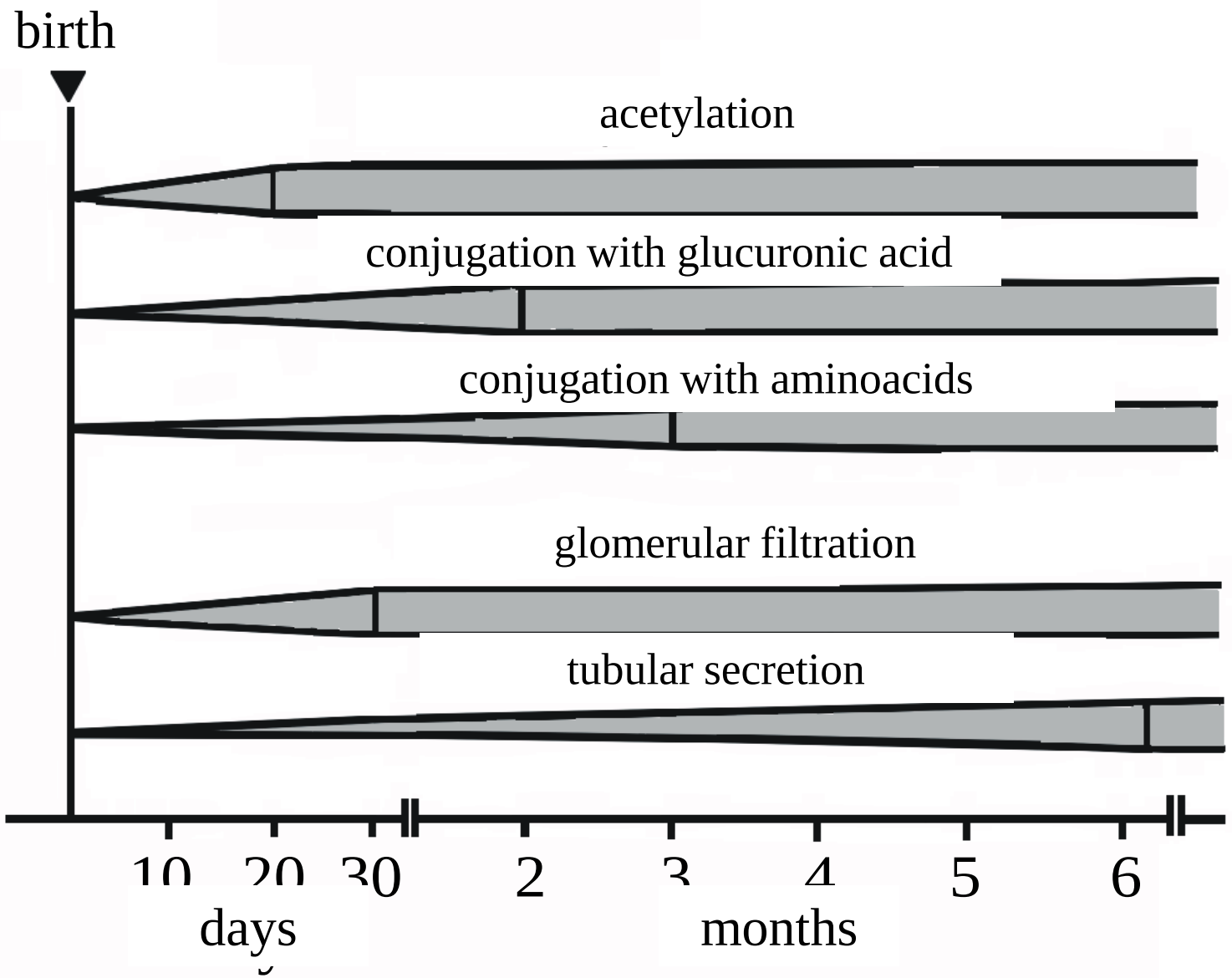

CYP 1A2
2%
other
3%
CYP 2C9
10%
CYP 2D6
30%
CYP 3A4
55%
CYP 3A4
CYP 2D6
CYP 2C9
CYP 1A2
other

INDUCERS of CYP 450

- dexamethason
- phenobarbital
- rifampicine
- phenytoin
- St. John`s Wort *(Hypericum perforatum)*
- *Ginkgo biloba*

INHIBITORS of CYP 450

- antidepresives (fluoxetin, fluvoxamin, paroxetin)
- quinine, quinidine
- chloramphenicol, erythromycin
- ketoconazol, itraconazol
- grapefruit juice


birth
acetylation
conjugation with glucuronic acid
conjugation with aminoacids
glomerular filtration
tubular secretion
10
20
30
2
3
4
5
6
days
months

Excretion

Kidney (urine)

liver (bile)

lungh (air)

saliva, skin, hair, breast milk...

Kidney

- MW < 60.000 D (MW albumin = 68.000 D)
- tubular secretion
  - organic acids
    - furosemid
    - thiazide diuretics
    - penicilins
    - glucuronides
  - organic bases
    - Morphine
    - Atropine
    - Histamine…
- tubular reabsorption

acidification

acetazolamid (inhibitor of CA)
ammonium chloride

alcalization

sodium bicarbonate

Liver

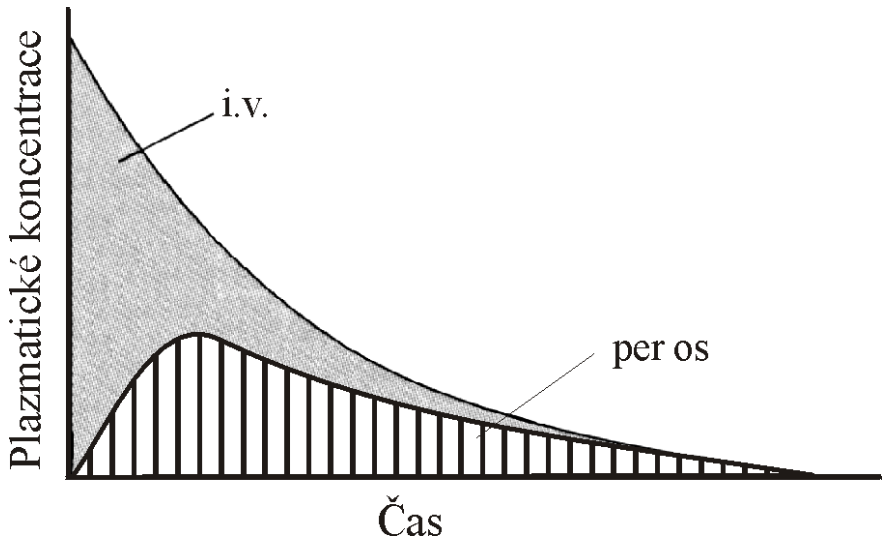
Billiar excretion, clearance.

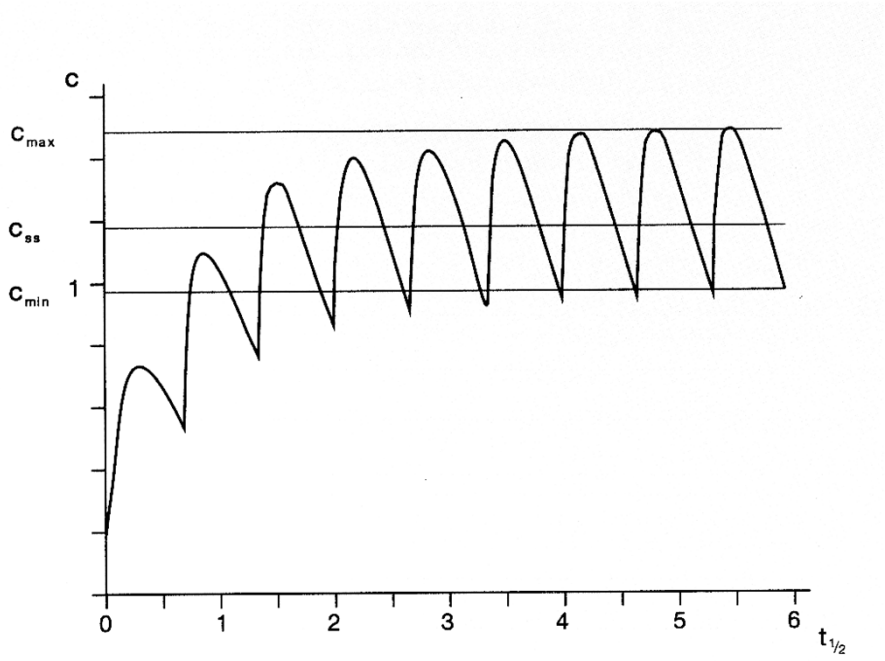
enterohepatic circulation

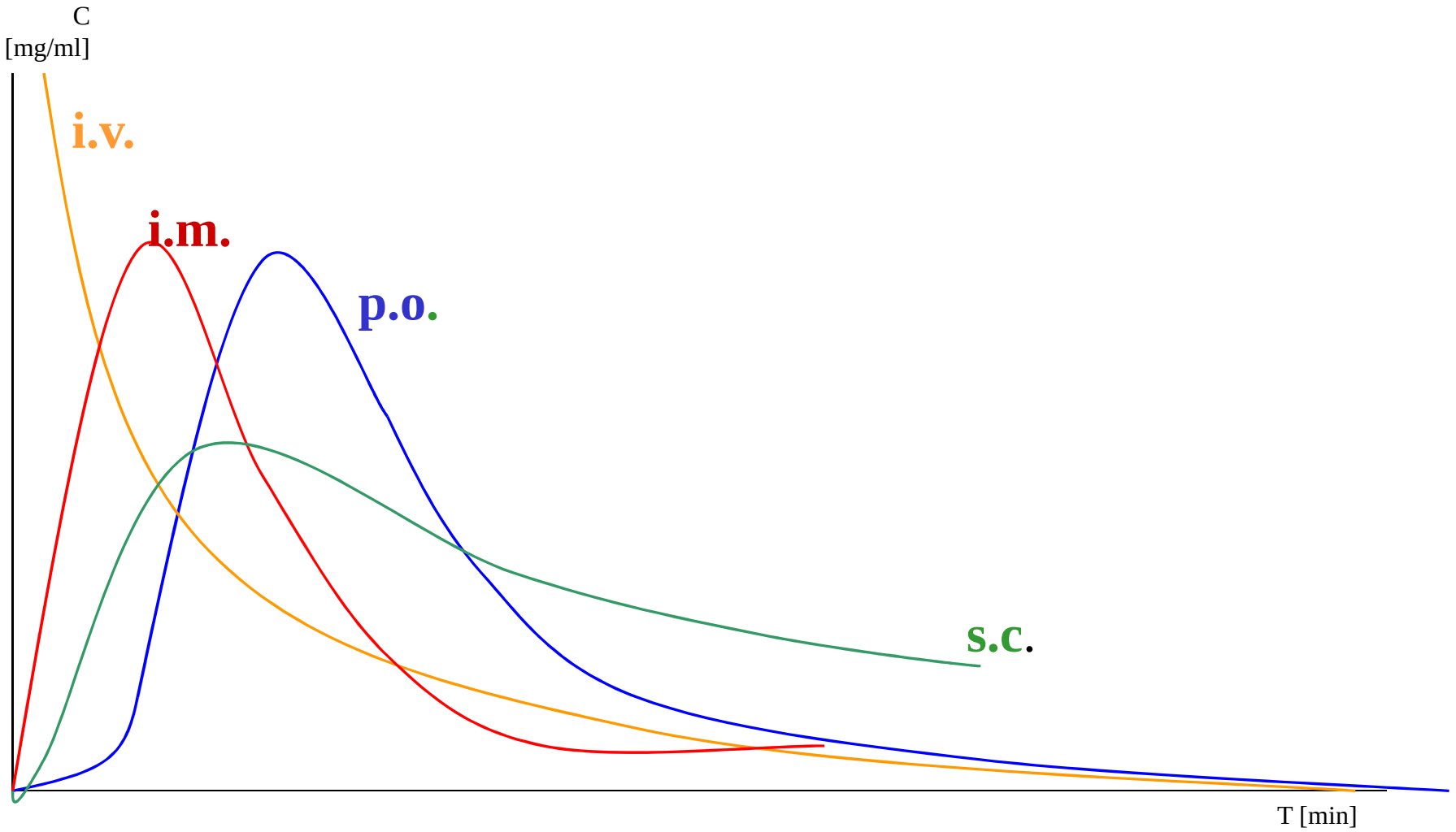
Pharmacokinetic parameters in practice

Mathematical description of the pharmacokinetic processes

When evaluating pharmacokinetics, we have to know plasmatic concentration of the drugs administered






C
[mg/ml]
i.v.
i.m.
p.o.
s.c.
T [min]

Single- dose administration

- after administration the concentration increases depending on the absorption rate and extent

.

- **Tmax**

- **Cmax**.

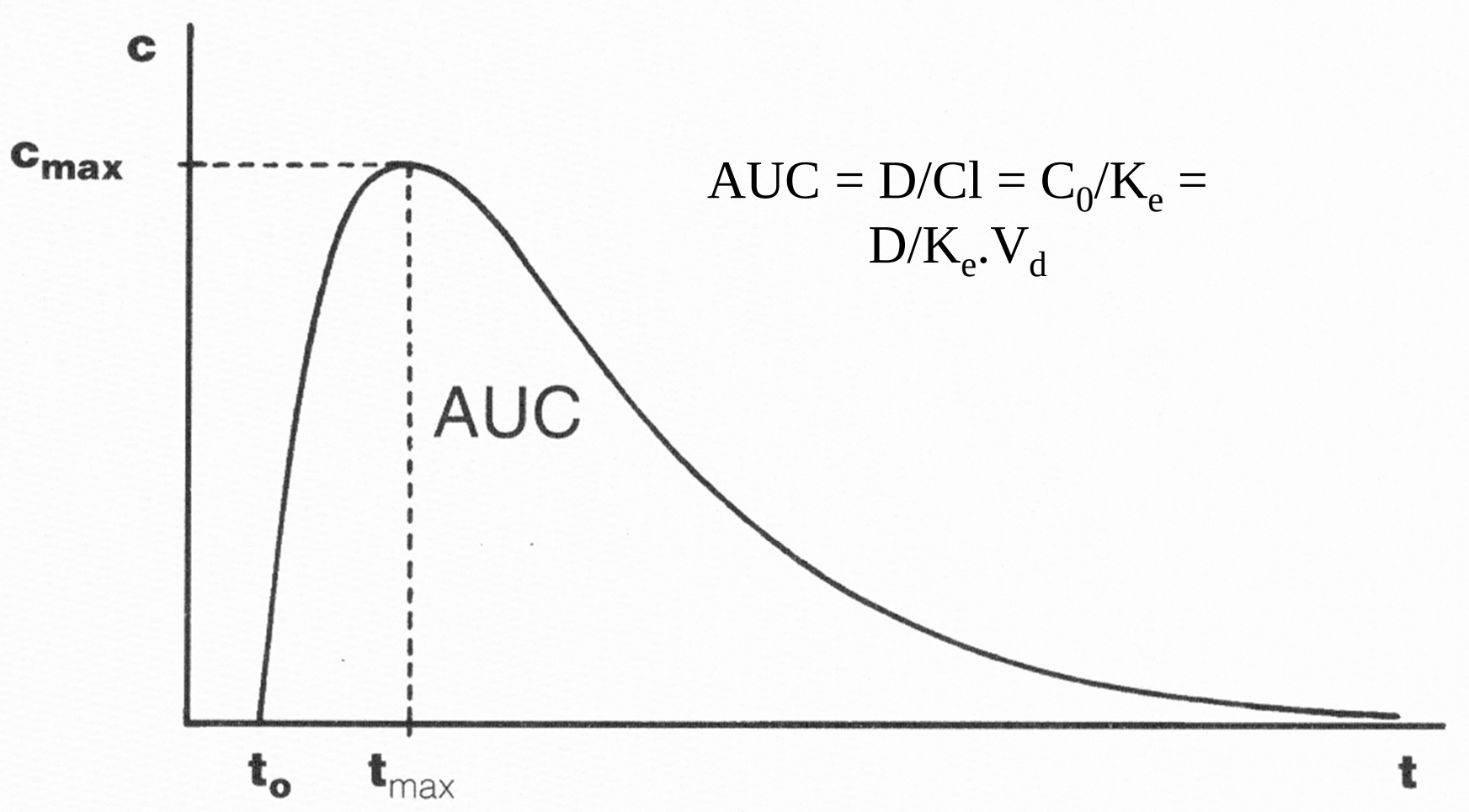
-F

AUC

Area under the concentration curve

- For IV bolus, the AUC represents the total amount of drug that reaches the circulatory system in a given time.

$$\text{Dose} = CL_T \, AUC$$



$$AUC = D/Cl = C_0/K_e = D/K_e.V_d$$

Bioavailability

- The fraction of the dose of a drug (F) that enters the general circulatory system,

  $$F = \frac{\text{amt. of drug that enters systemic circul}}{\text{Dose administered}}.$$

Bioavailability

- A concept for oral administration
- Useful to compare two different drugs or different dosage forms of same drug

- Rate of absorption depends (in part) on rate of dissolution
- Also first-pass metabolism is a determining factor

Bioavailability

Extravascular route - 0-100% (resp. 0-1).

Intravenous - 100% = 1

If F is 0-20% = 0-0,2 – not suitable route of administration (in spite of that fact, some drugs are administered, even if the F is 2-5 % SET, bisphosphonates).

F = AUCpo/AUCiv

(same drug, same dose, same patient)

Example: Therapeutic dose of the morphine i.v. is 10 mg. It`s bioavailability after p.o. admin. is 1/6 that is 16 %. If the same effect needed, the dose for the p.o. route of admin has to be 6-times higher - 60 mg.

Distribution

Volume of distribution

- $V_d = D/C$
  - V_d is the apparent volume of distribution
  - C= Conc of drug in plasma at some time
  - D = Total quantity (dose) of drug in system

Vd = hypothetical volume, apparent

Vd can has values about 50000 litres (antimalarics).

1) Get know, how the drug is distributed

Drug	**V_D**	**Comments**
Warfarin	8L	Reflects a high degree of plasma protein binding.
Theophylline, Ethanol	30L	Represents distribution in total body water.
Chloroquine	15000L	Shows highly lipophilic molecules which sequester into total body fat
NXY-059	8L	Highly-charged hydrophilic molecule.

2) If the rapid reaching of the effective level of the drug in plasma after single dose is needed, it`s possible to calculate the initial dose

3) For considering the influence of the haemodialysis and hemoperfusion on the pharmacokinetics of the drug (overdosing, forensic toxicology)

(the drugs with extremely high Vd can not be eliminated in this way)

Elimination (first order)

Elimination constant $k_e = \ln c_1 - \ln c_2 / t_2 - t_1$

Half-life of the elimination – the drug is completely eliminated after 4-5 $t_{0,5}$ **(1 t 0.5 = 50 %, 2 t 0.5 = 75 %, 3 t 0.5 = 87.5 %**

4t 0,5 = 93.75 %)

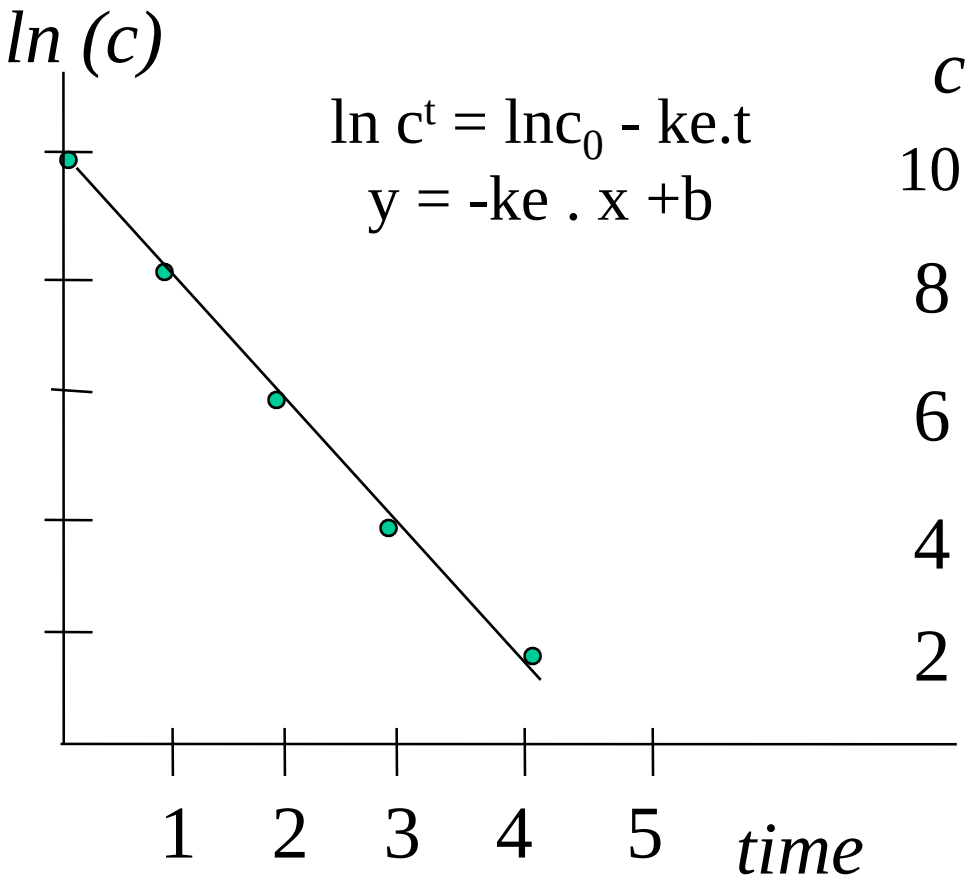
$t_{0,5} = \ln 2 / ke = 0,7 / k_e$

clearance $Cl_{TOT} = D/AUC = k_e Vd$

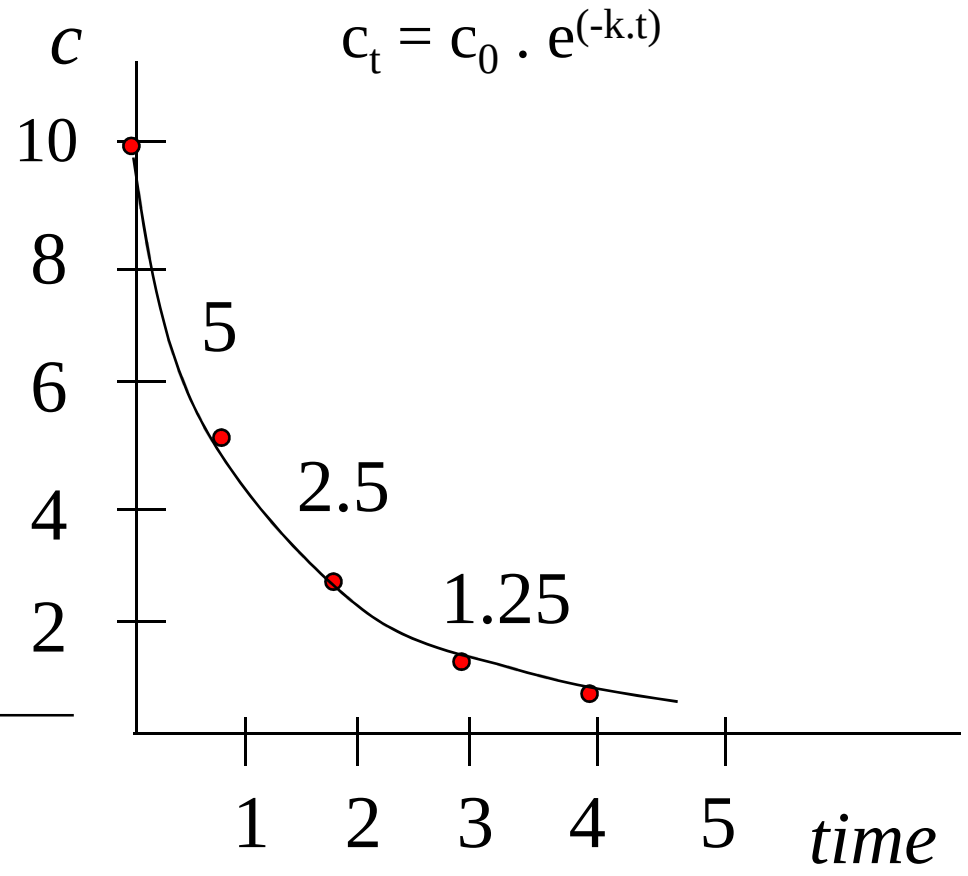
Volume of the blood in a defined region of the body that is cleared of a drug in a unit time

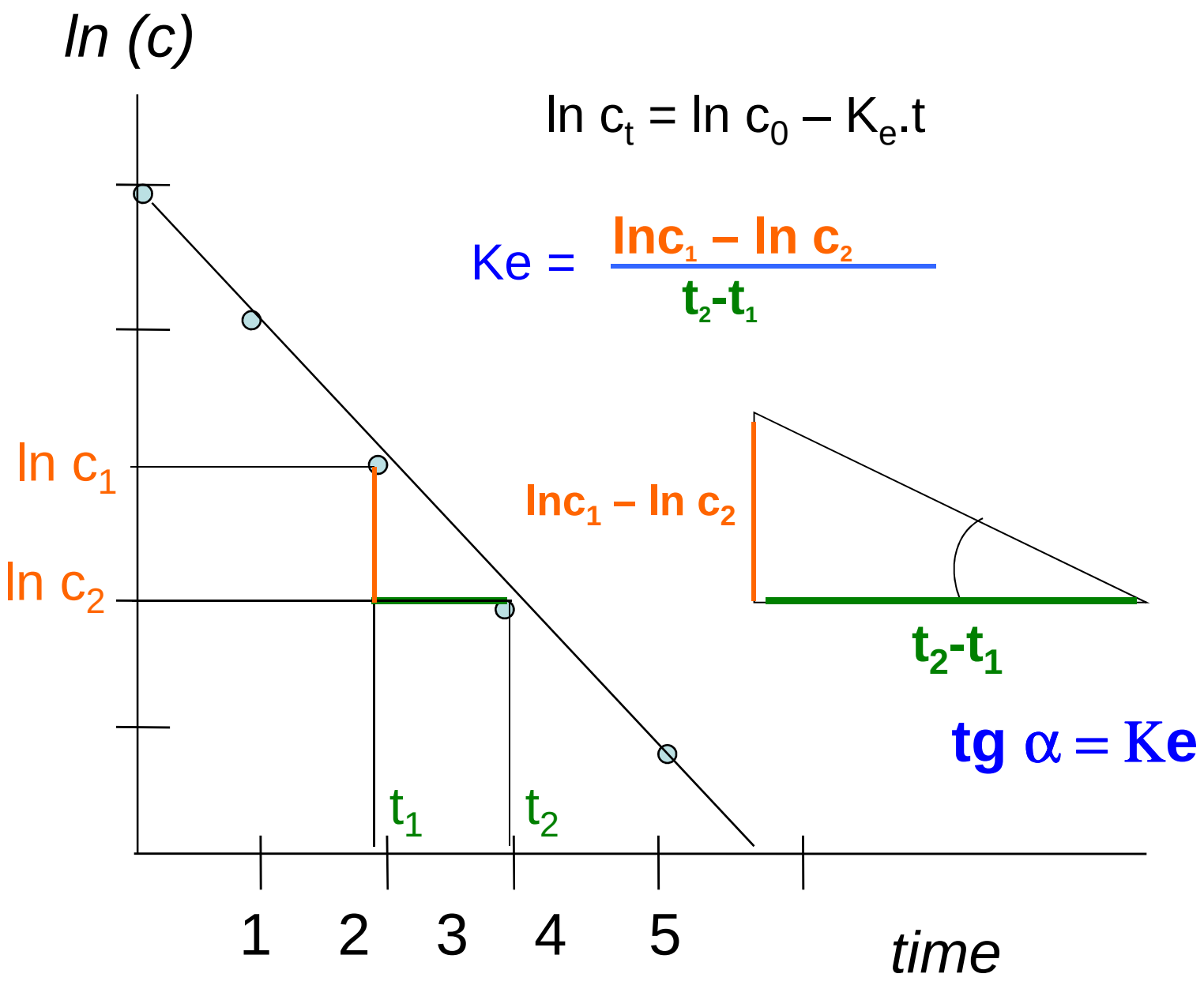
Kinetics of elimination of the 1st order –

semilog plot
(i.v. admin)



Normal plot
(i.v. admin)

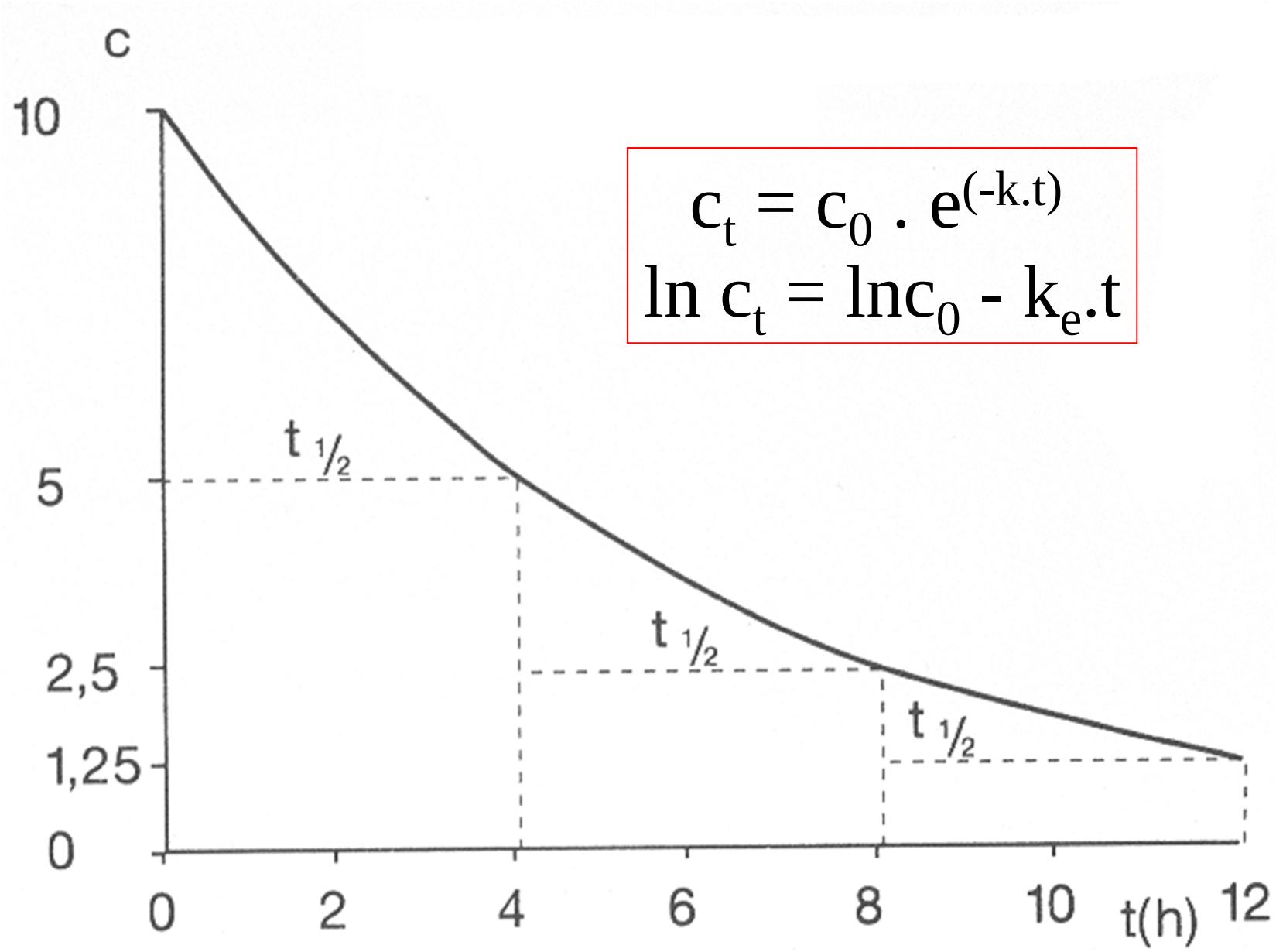



ln (c)
ln c_t = ln c_0 – K_e.t
Ke = $\frac{\ln c_1 - \ln c_2}{t_2 - t_1}$
ln c_1
ln c_2
$\ln c_1 - \ln c_2$
$t_2 - t_1$
tg α = Ke
t_1
t_2
1
2
3
4
5
time

Half-Life

- $C = C_o \ e^{-kt}$
- $C/Co = 0.50$ in the time of 1 half-life

- Thus: $0.50 = e^{-k t}$
- $\ln 0.50 = -k\, t_{½}$
- $-0.693 = -k\, t_{½}$
- $t_{1/2} = 0.693 / k$



$$c_t = c_0 \cdot e^{(-k.t)}$$

$$\ln c_t = \ln c_0 - k_e.t$$

Clearance

- Volume of blood that is cleared of a drug in a unit time.
- Clearance is a more useful concept in reality than $t_{1/2}$ or k_{el} since it takes into account blood flow rate
- Clearance varies with body weight
- Also varies with degree of protein binding

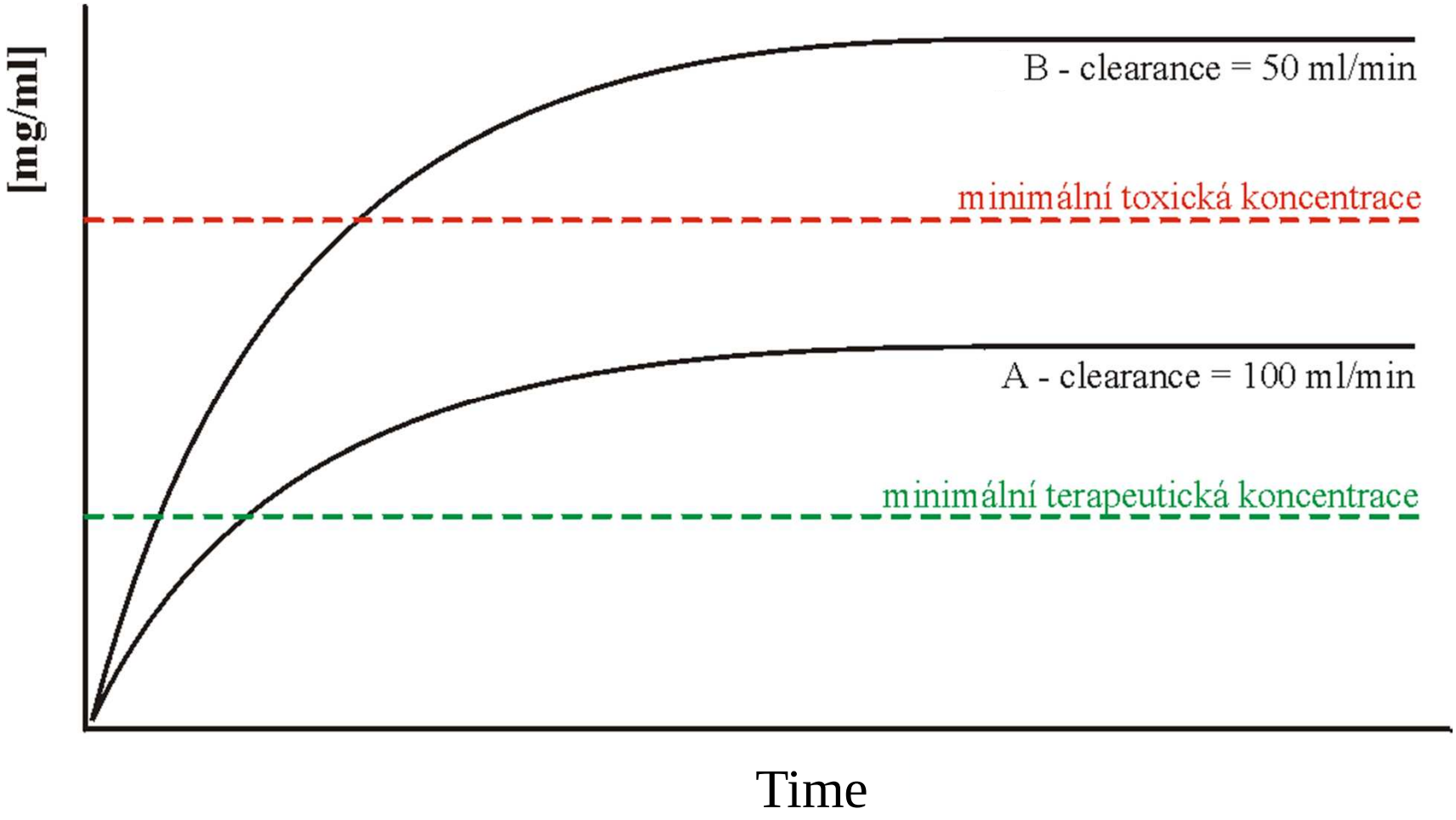
i.v. infusion

- Continual drug administration

- Administration of the drug e.g. by the infusion pump

- if lasts longer, the plasma concentration of the drug increases until the elimination rate become equal to the drug intake – plasmatic concentration is steady - the plateau state (Css).

I.v. infusion


[mg/ml]
B - clearance = 50 ml/min
minimální toxická koncentrace
A - clearance = 100 ml/min
minimální terapeutická koncentrace
Time

I.v. infuion

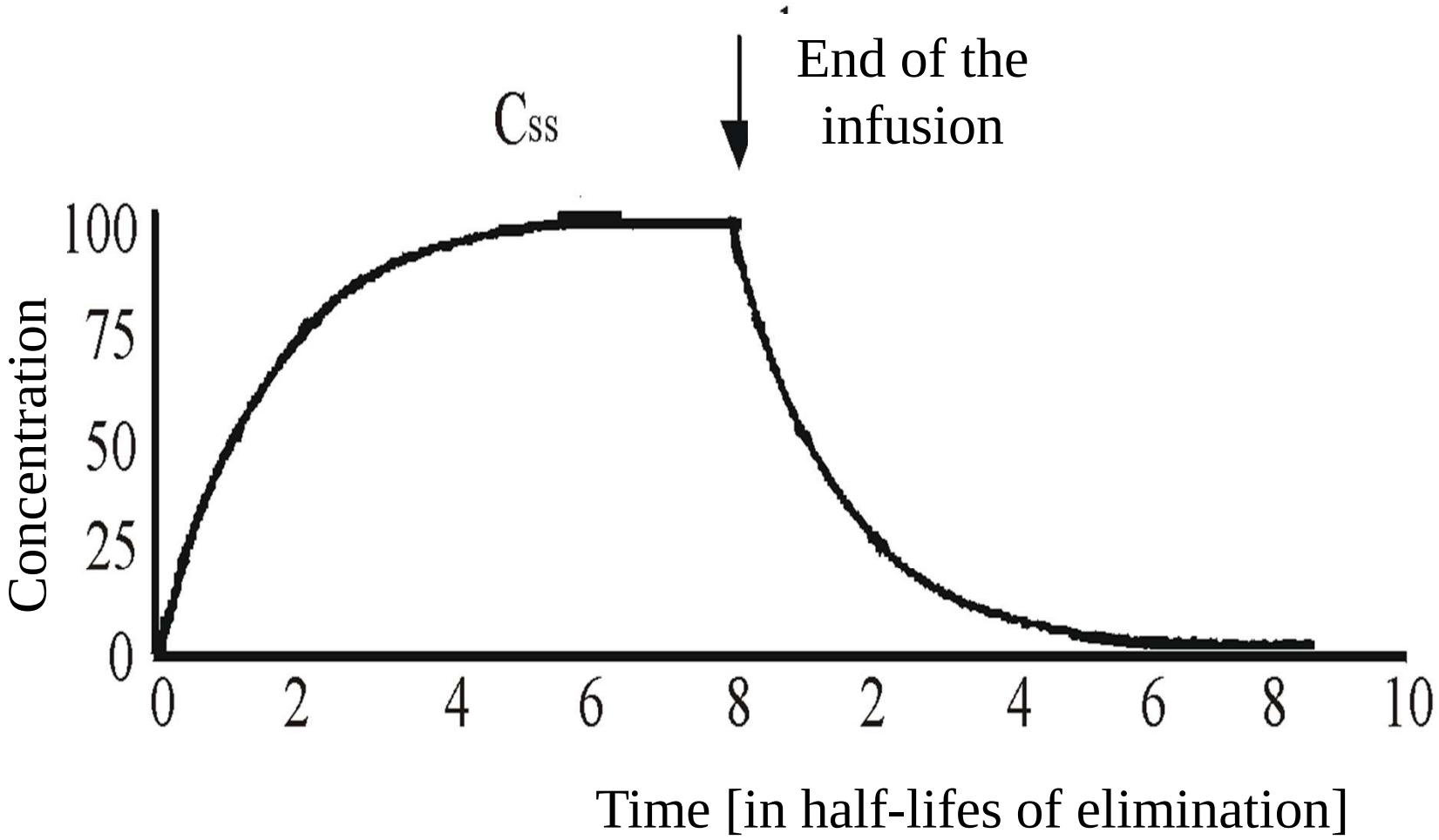
In steady state holds generally:

Drug is already bound to all of the bonding sites = distribution is finished.

The amount of the eliminated drug is equal to the administered dose in the same time interval.

Inflow rate [mg/min] = elimination rate [mg/min] (1)

i.v. infusion


End of the infusion
Css
Concentration
100
75
50
25
0
0
2
4
6
8
2
4
6
8
10
Time [in half-lifes of elimination]

Repeated drug administration

intra- (repeated i.v. injections) or **extravascular** (e.g.p.o.).

Accumulation of the drug

-If the interval between the doses is too short and the drug is not eliminated

Steady state - Elimination rate is equal to the „inflow rate“ – dose per hour

inflow rate [mg/min] = Cl x Css

Instead of Css is denominated average concentration in steady state (**Cssplateau**), what is average concentration calculated from the concentrations oserved during 1 interval between doses.

Repeated drug administration

The equation is usually modified by the factors:

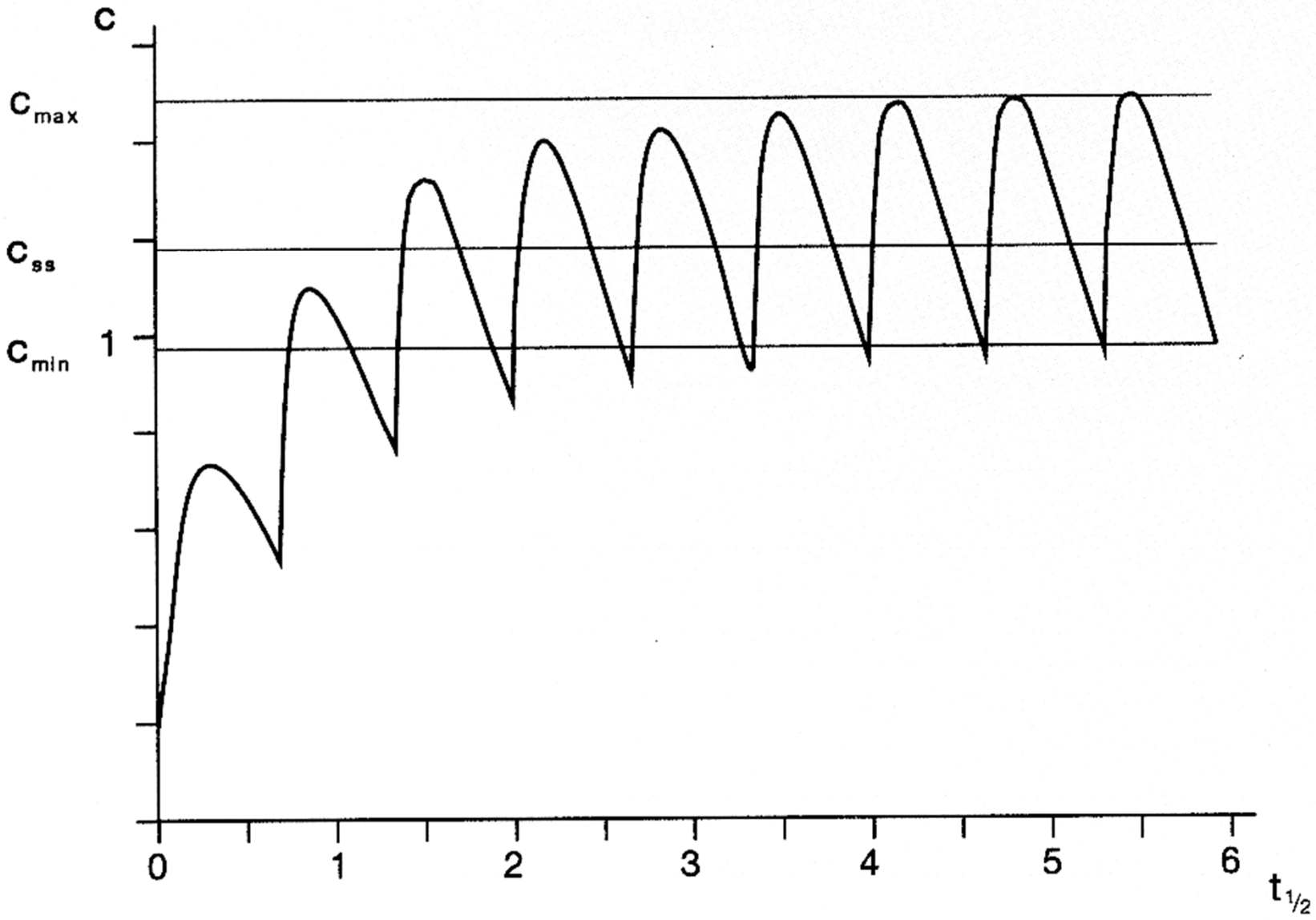
1) F – bioavailibility

2) τ –dosing interval - the concentration fluctuates from the **Cminplato to the Cmaxplato** during 1 dosing interval

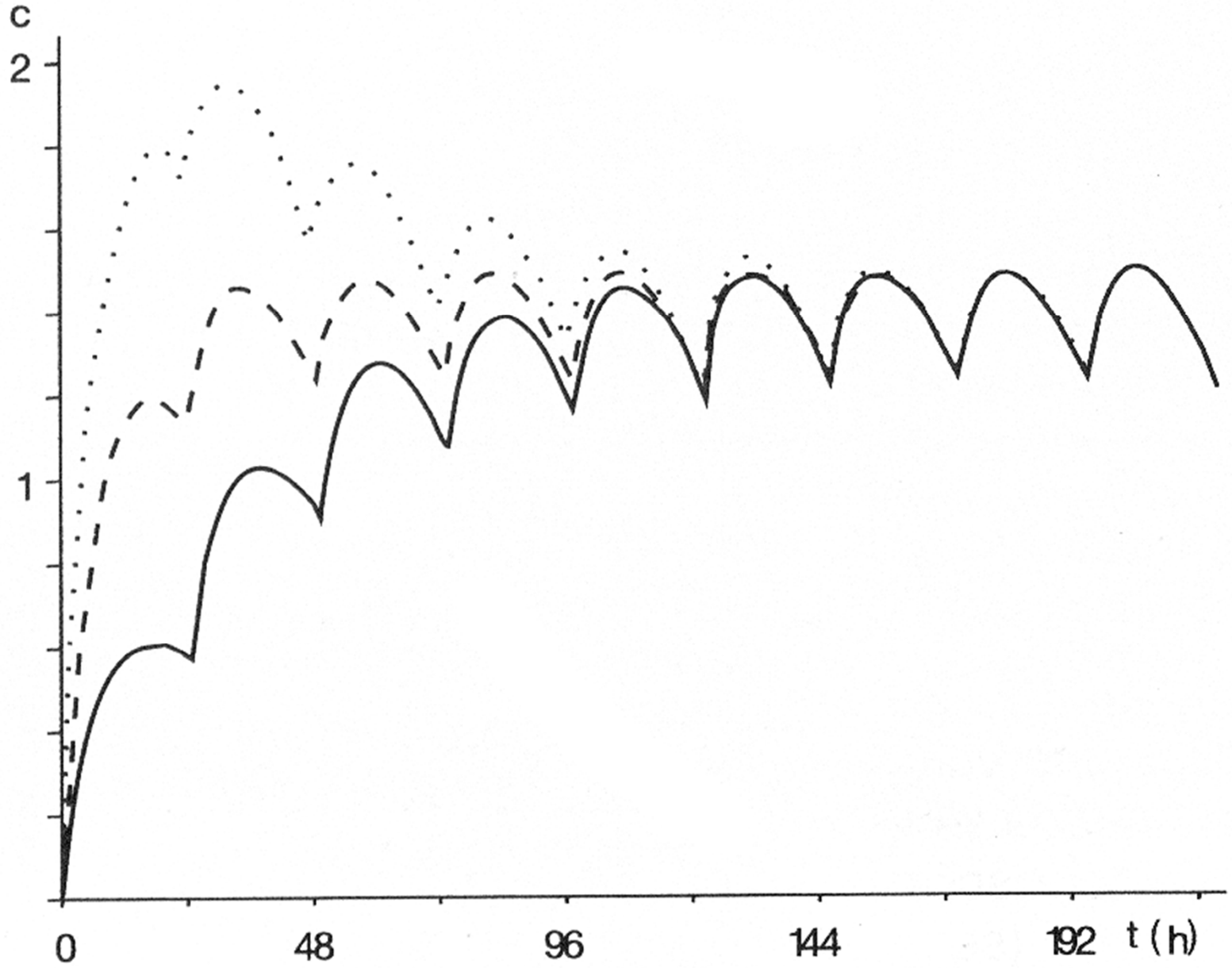
The fluctuation is proportional to the dosing interval

$$\frac{D \times F}{\tau} = Cl \times C_{ss\ plateau}$$

Repeated drug administration



Repeated drug administration



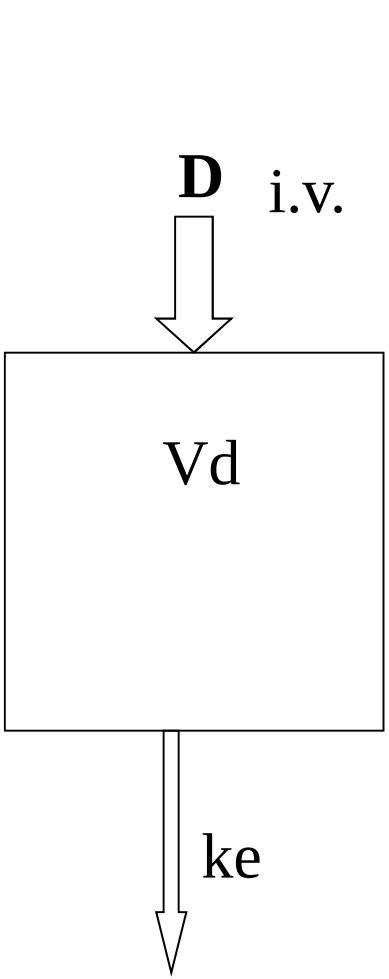
The Compartment Model

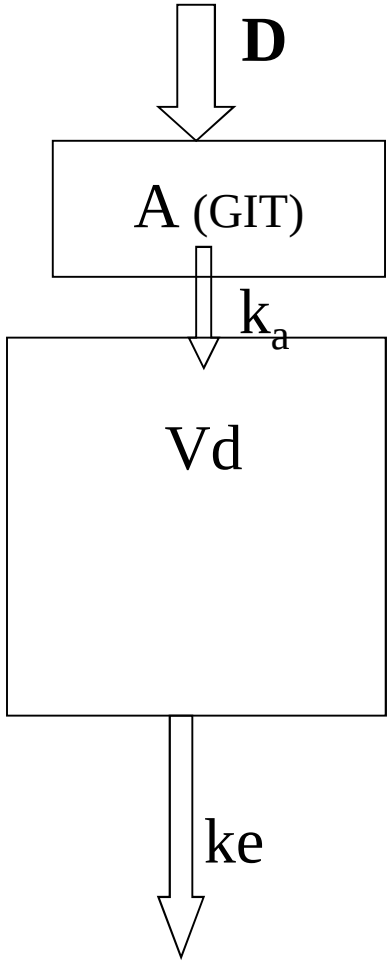
Body = a series of interconnected well-stirred compartments within which the [drug] remains fairly constant.

Movement BETWEEN compartments is important in determining when and for how long a drug will be present in body.

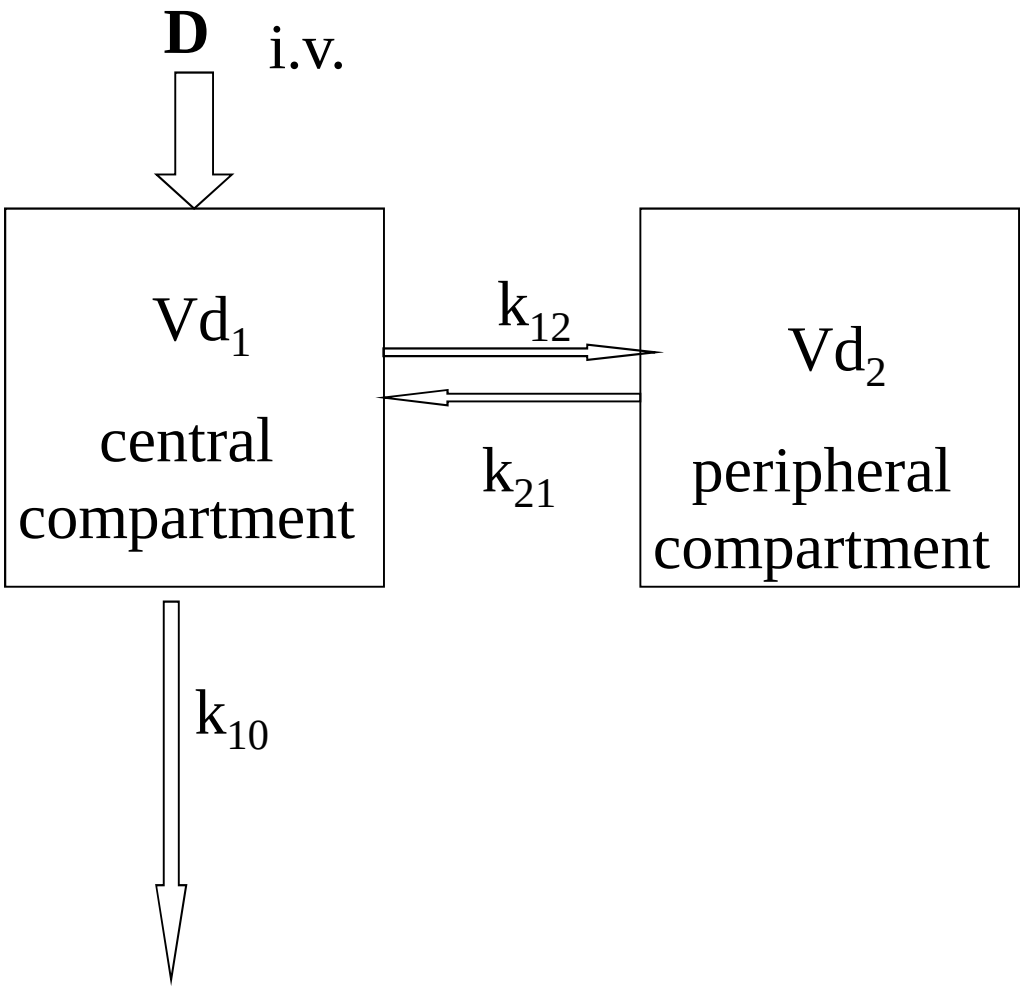
The Compartment Model

1- compartment model

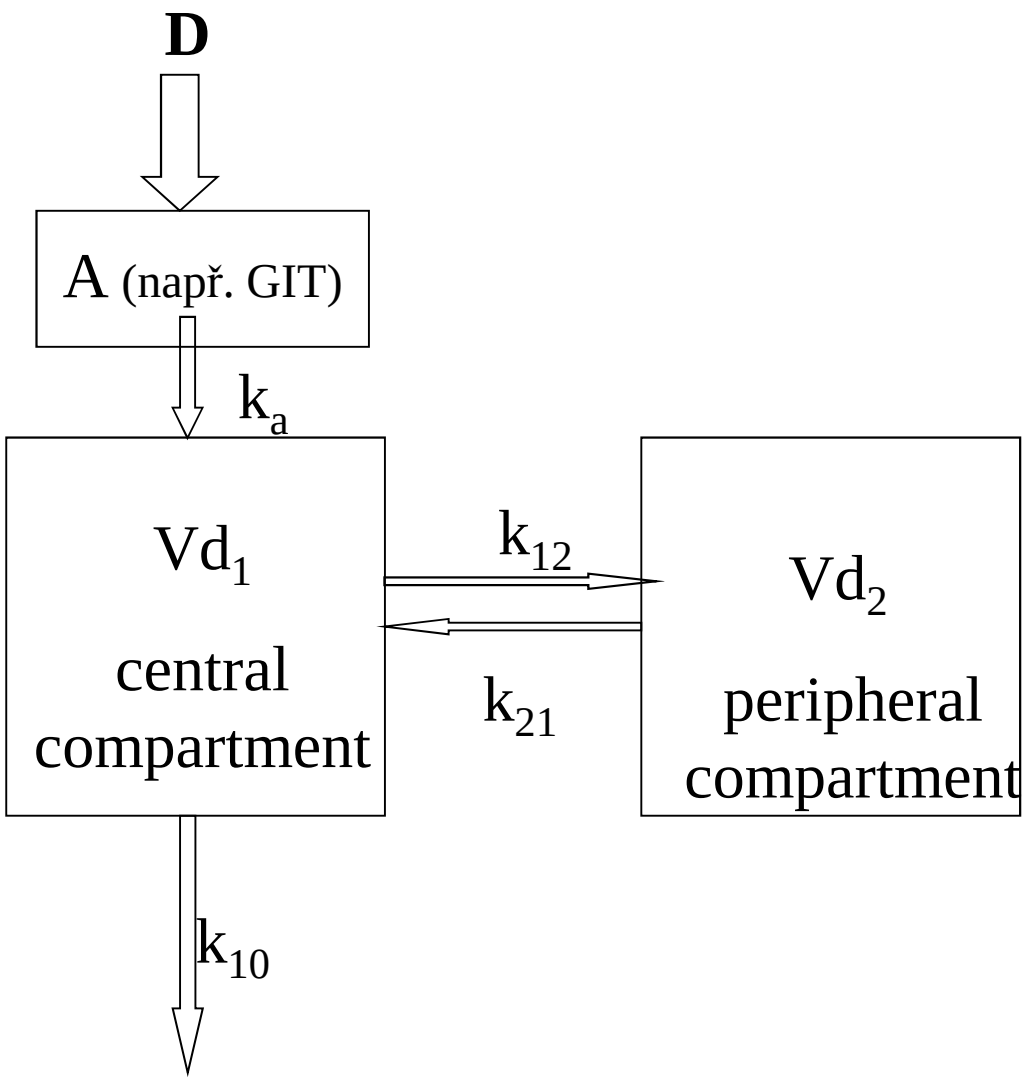




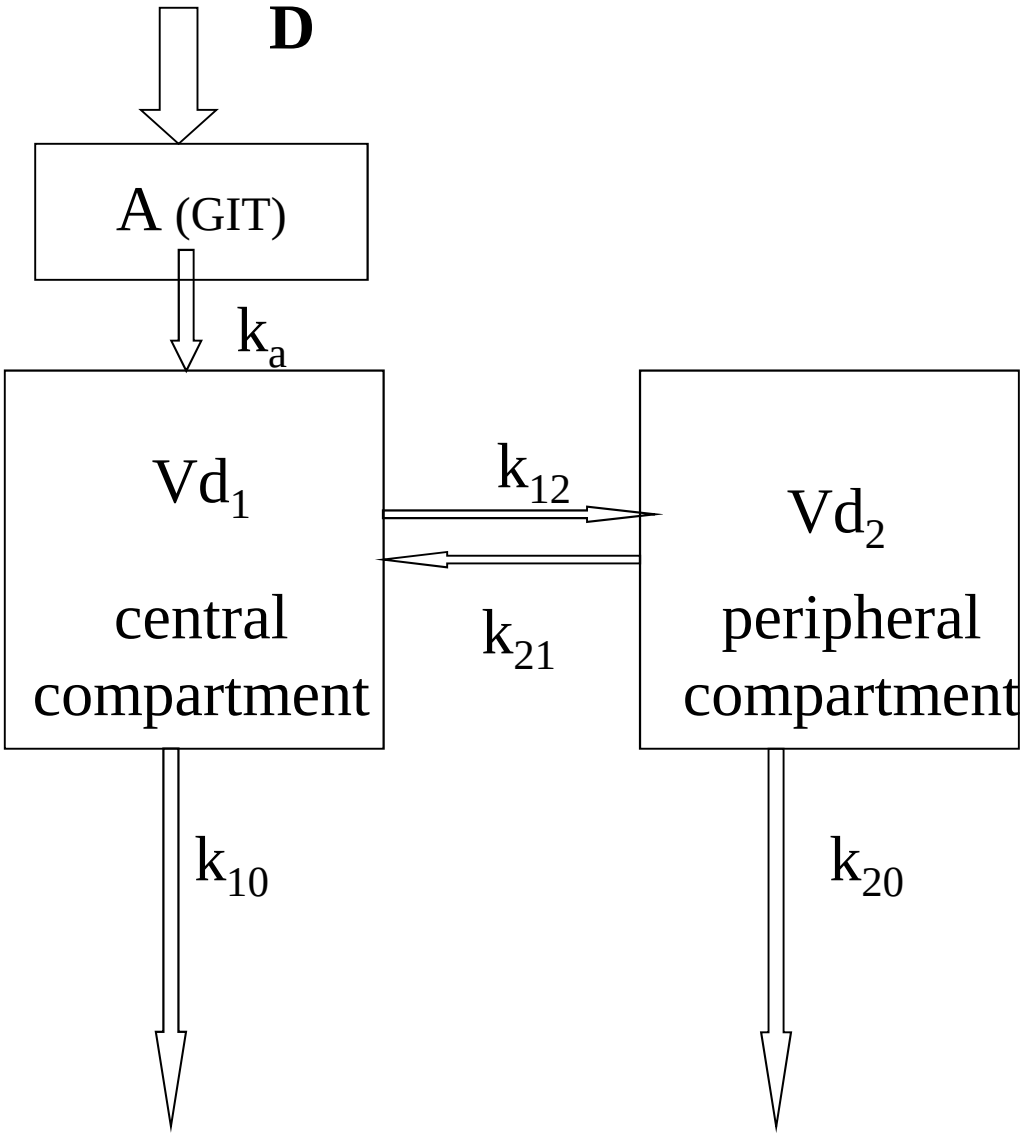
2- compartment model

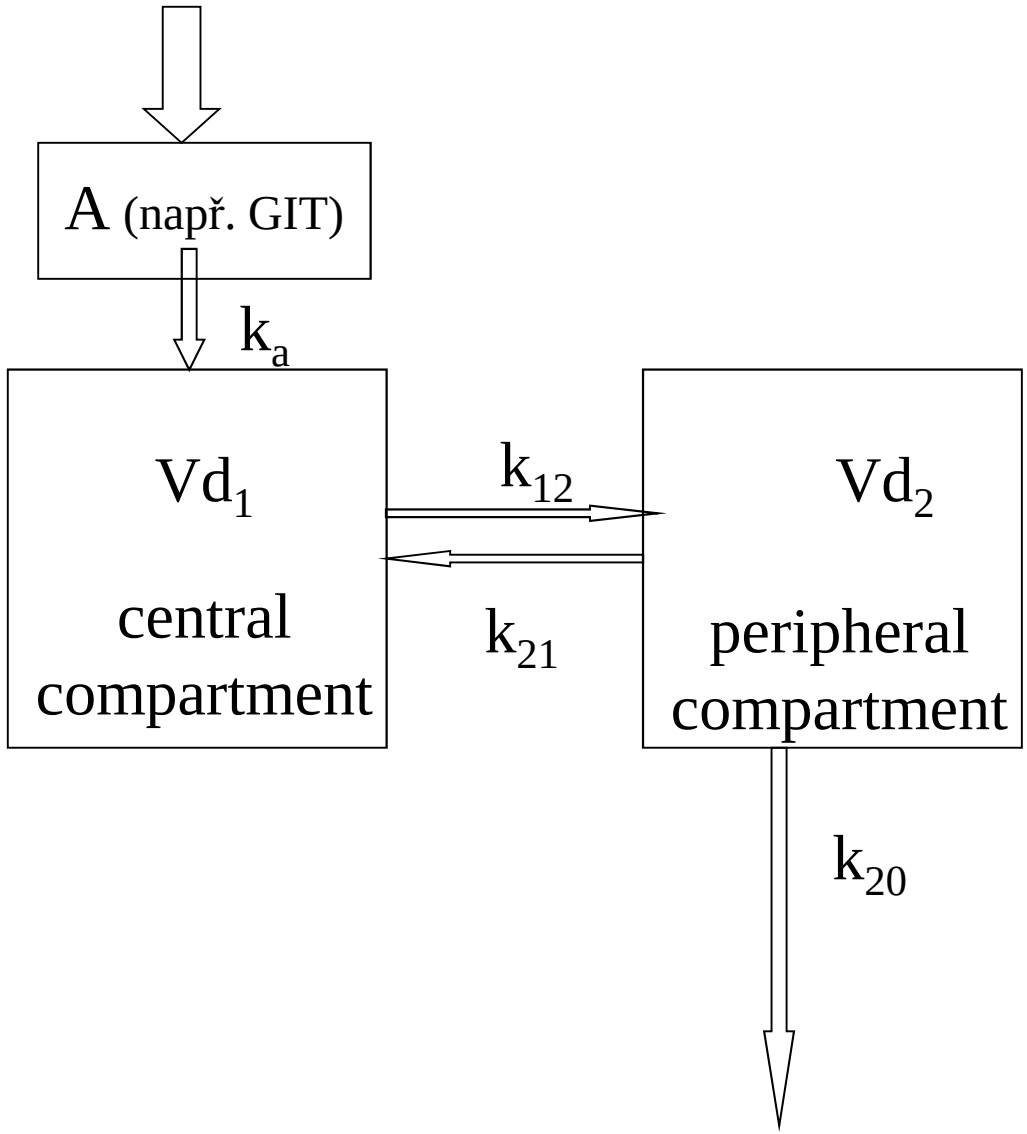


2- compartment model



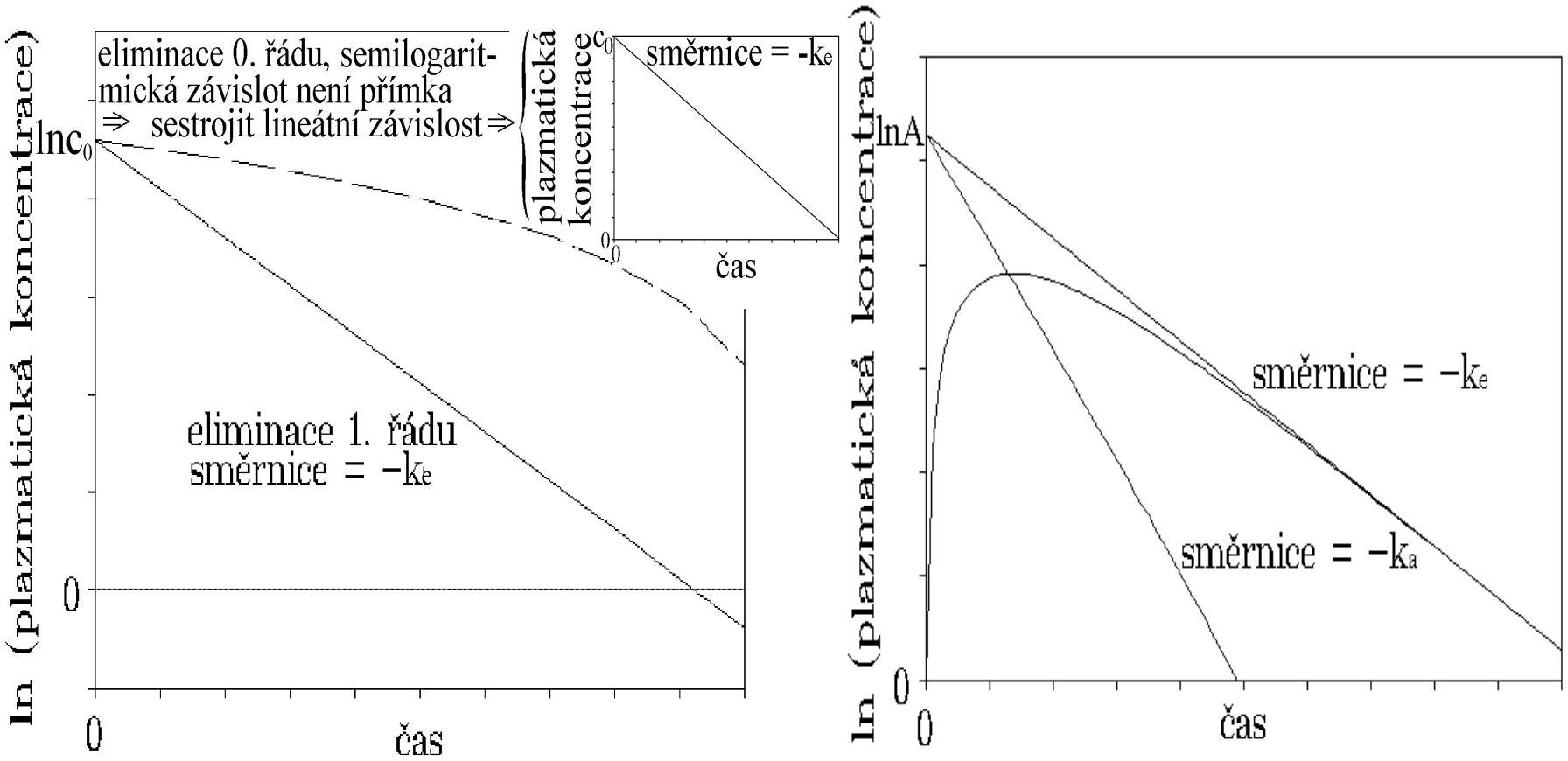
2- compartment model




A (např. GIT)
k_a
Vd_1
central compartment
k_{12}
k_{21}
Vd_2
peripheral compartment
k_{20}

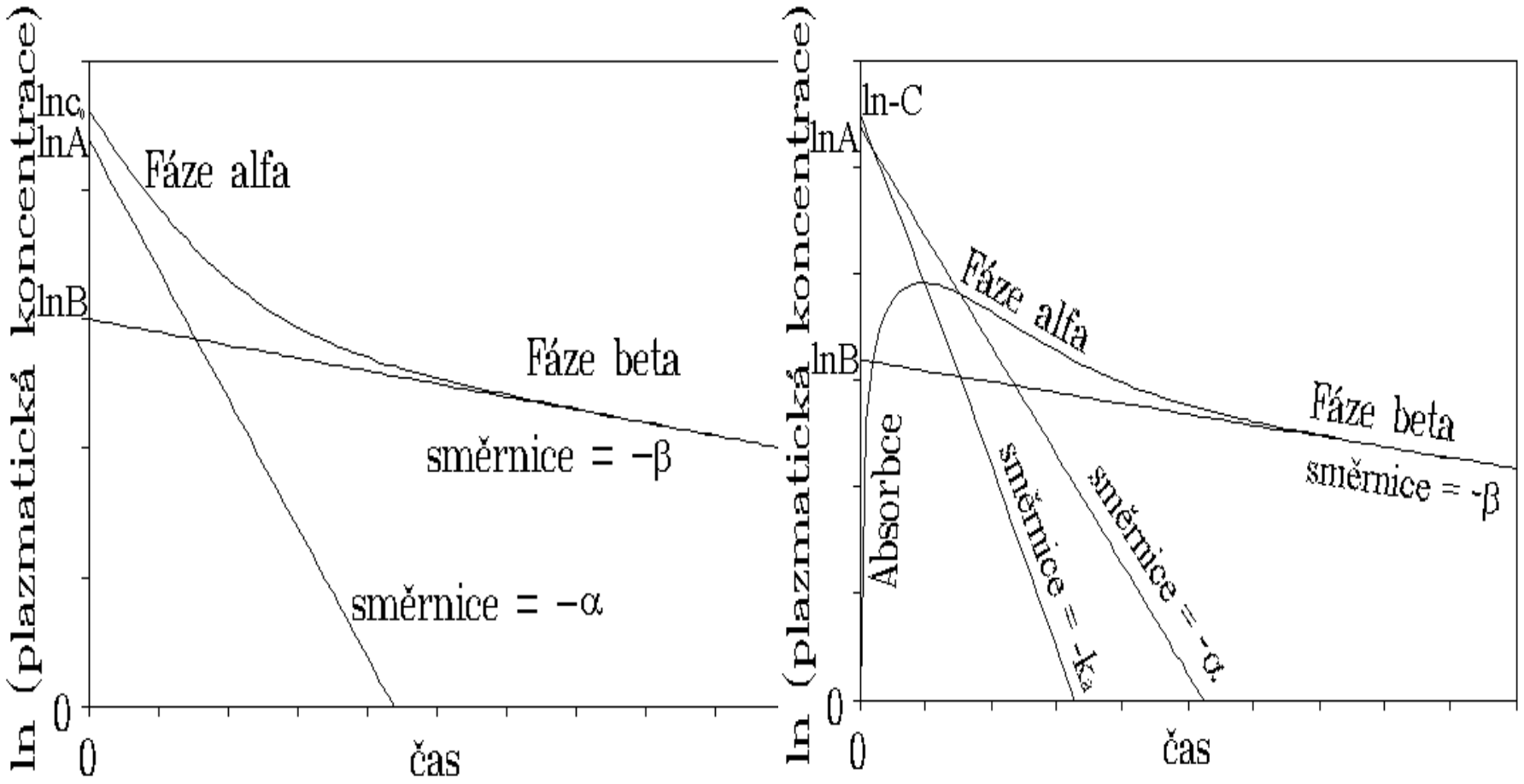
1- compartment model

Intravascular administration Extravascular application



2- compartment model

Intravascular administration Extravascular application



Basic pharmacokinetic parameters

- C_{max}
- T_{max} - time to reach C_{max}
- k_a = absorption constant
- k_e = elimination constant $= \dfrac{\ln c_1 - \ln c_2}{t_2 - t_1}$ $[h^{-1}]$
- $t_{1/2} = \dfrac{\ln 2}{k_e}$ [h]
- $V_d = \dfrac{F.\,D}{c_0} = \dfrac{F.\,D}{AUC.k_e}$ [l]
- $Cl = Cl_{ren} + Cl_{hep} + Cl_{pl} \ldots + Cl_i$ $[l\,.h^{-1}]$
- $AUC = D/\,Cl = C_0 / K_e = D/\,k_e.V_d$ $[mg.\,l^{-1}\,.h]$