- **Pharmacokinetic principles**
- **Drug absorption, distribution, metabolism and elimination**

Jan Juřica, PharmD., Ph.D.

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)**

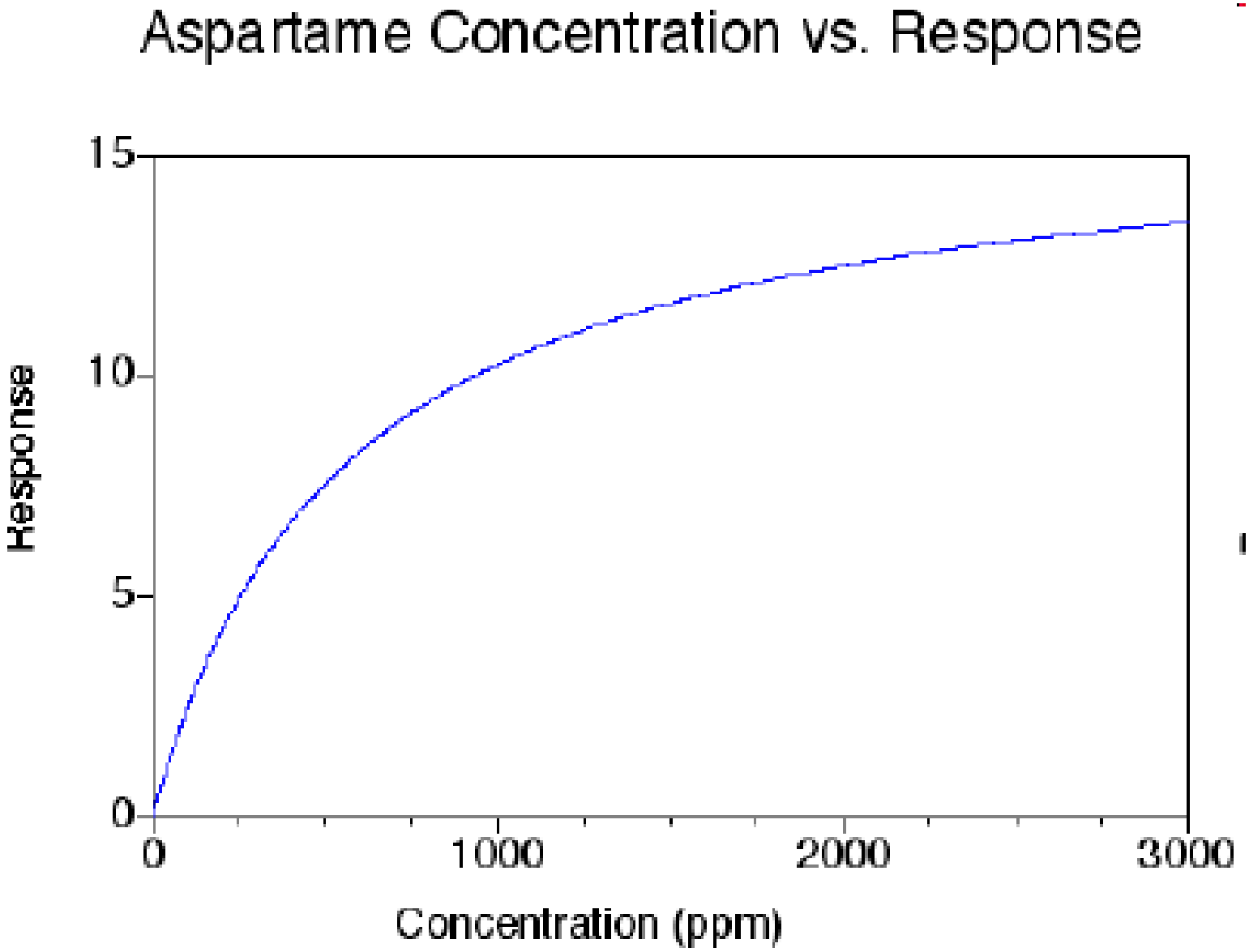
- **Concentration-response relationship**

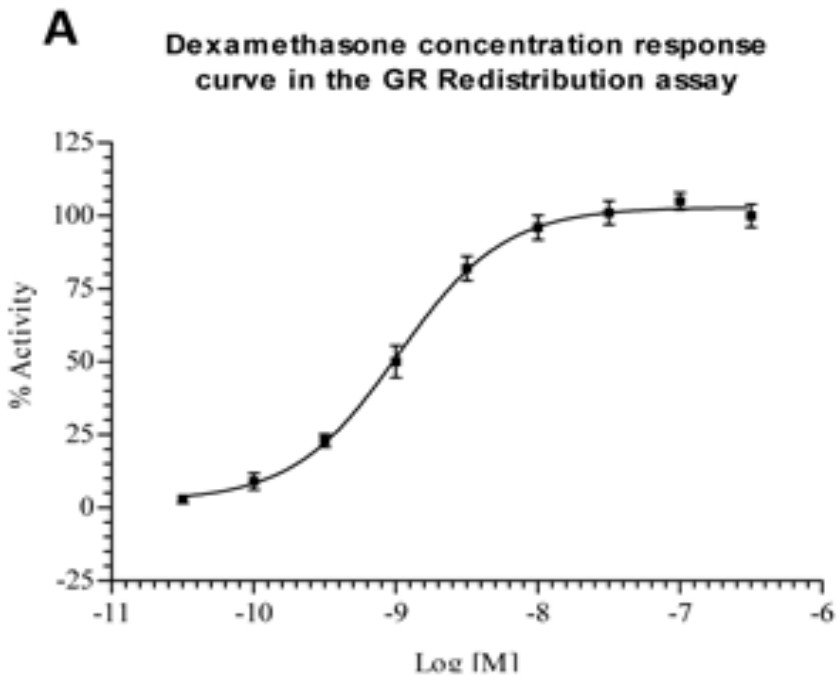
in vitro systems - simple interaction described with a few mathematical equations

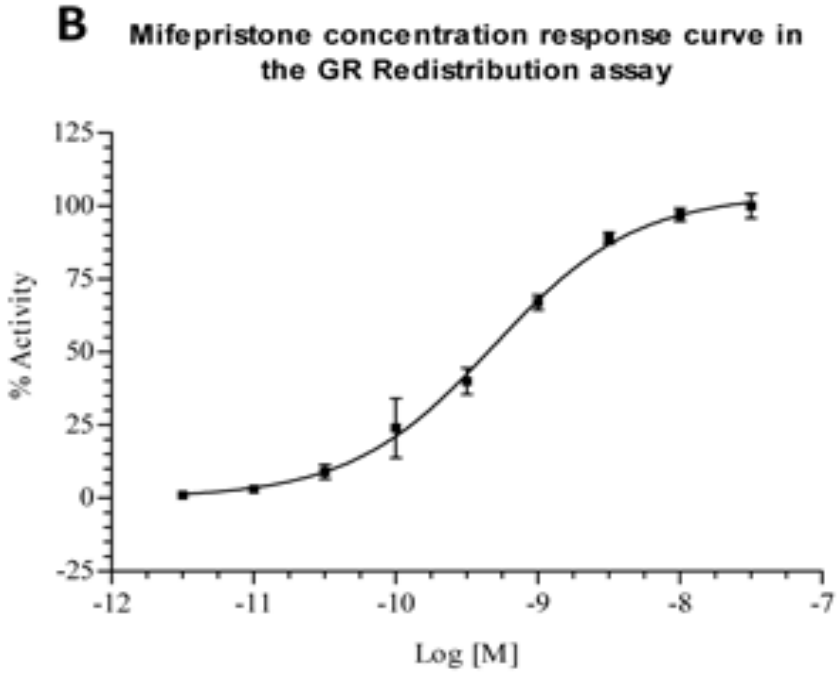
in vivo - not so clear and simple due to many biochemical linkages, feedbacks etc.

At low conc. – eff. proportional to the concentration

At higher conc. – eff. not proportional, disminished


Aspartame Concentration vs. Response
15
10
5
0
Response
0
1000
2000
3000
Concentration (ppm)





A log concentration - response curve

- usually sigmoidal
- between 10 % and 90 % of maximal response approximates to a straight line + usually occurs over two orders of magnitude of concentration

Pharmacokinetics

Occupation theory: The intensity of pharmacological response (E) is proportional to the conentration of reversible drug-receptor complex

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

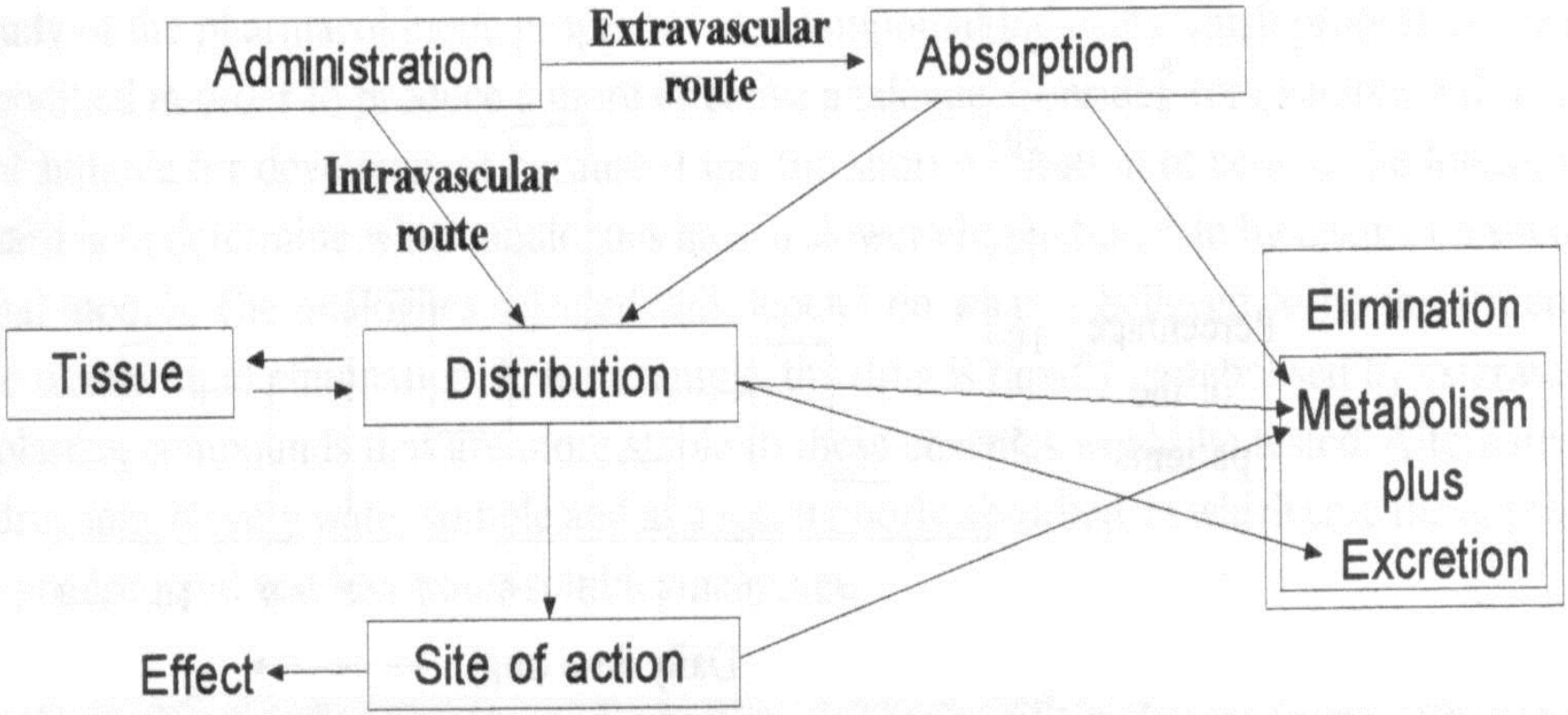
Pharmacokinetics deals with the processes of

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

invasion
elimination
"ADME"

And their relationship with their biological (pharmacological) effect

„WHAT DOES ORGANISM DO WITH THE DRUG"

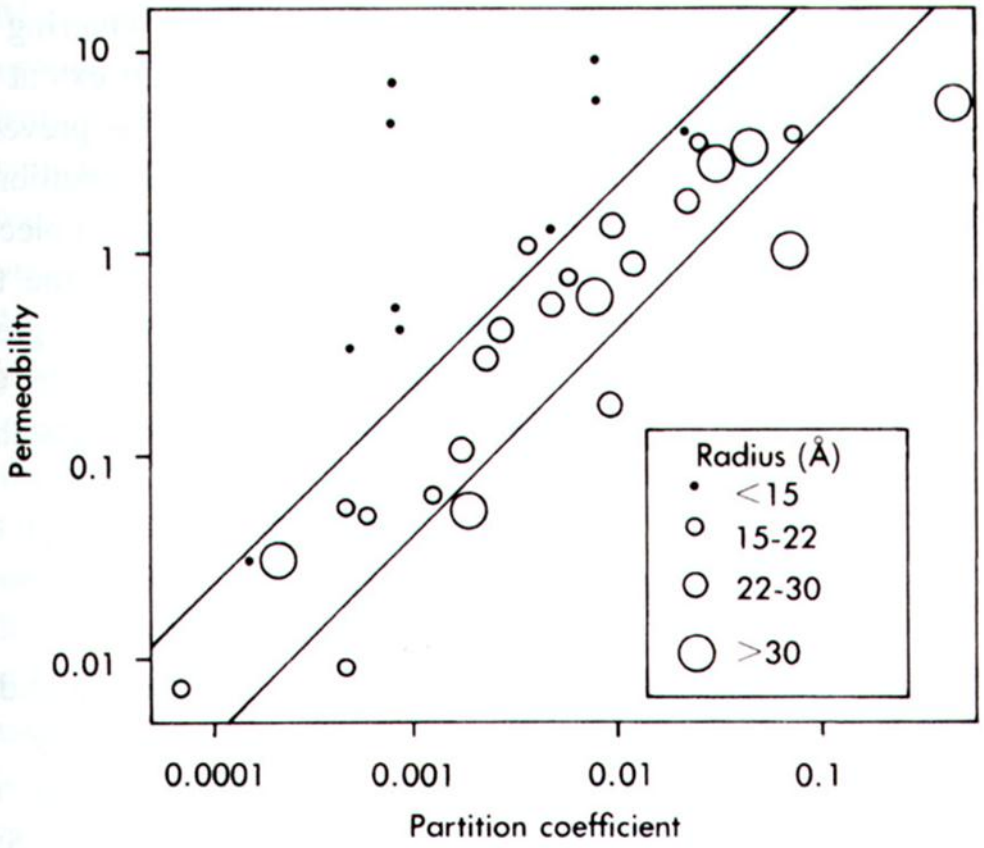


The general stages and their relationships in the life cycle of a drug after administration.

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

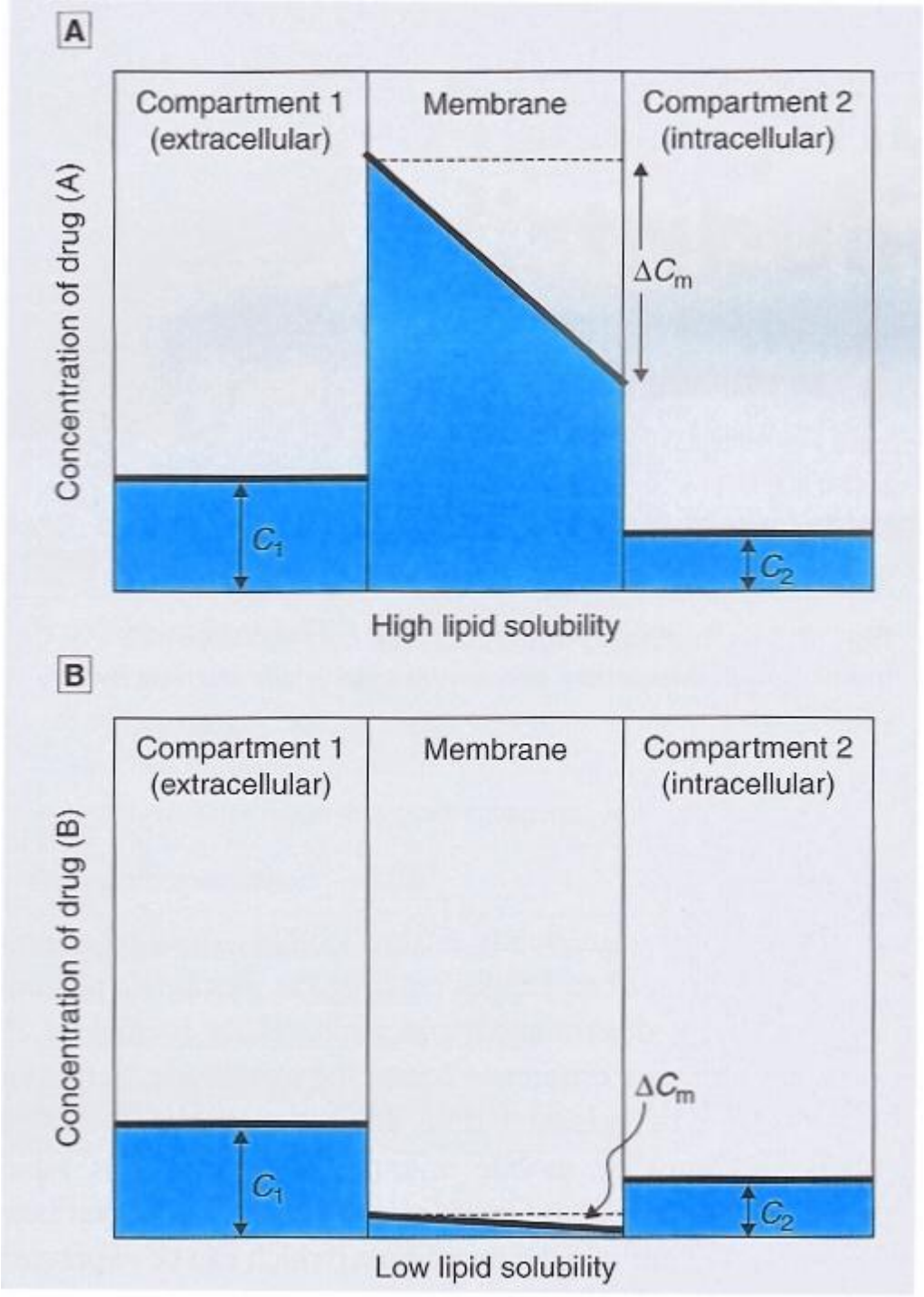
physico-chemical properties

lipophilic/hydrophilic properties, molecule structure, pKa, charge…



Ionized compounds tend to be *less* lipid soluble.

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


A
Compartment 1
(extracellular)
Membrane
Compartment 2
(intracellular)
Concentration of drug (A)
ΔC_m
C_1
C_2
High lipid solubility
B
Compartment 1
(extracellular)
Membrane
Compartment 2
(intracellular)
Concentration of drug (B)
ΔC_m
C_1
C_2
Low lipid solubility

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

physico-chemical properties

lipophilic/hydrophilic properties, molecule structure, pKa, charge…

AH ⇆ A- + H+ B + H+ ⇆ BH+

permeation across the membranes

lipophilic – difusion (passive)

hydrophilic – through the pores

active transport

bonds of the drugs to:

plasma proteins

blood cells in the circulation

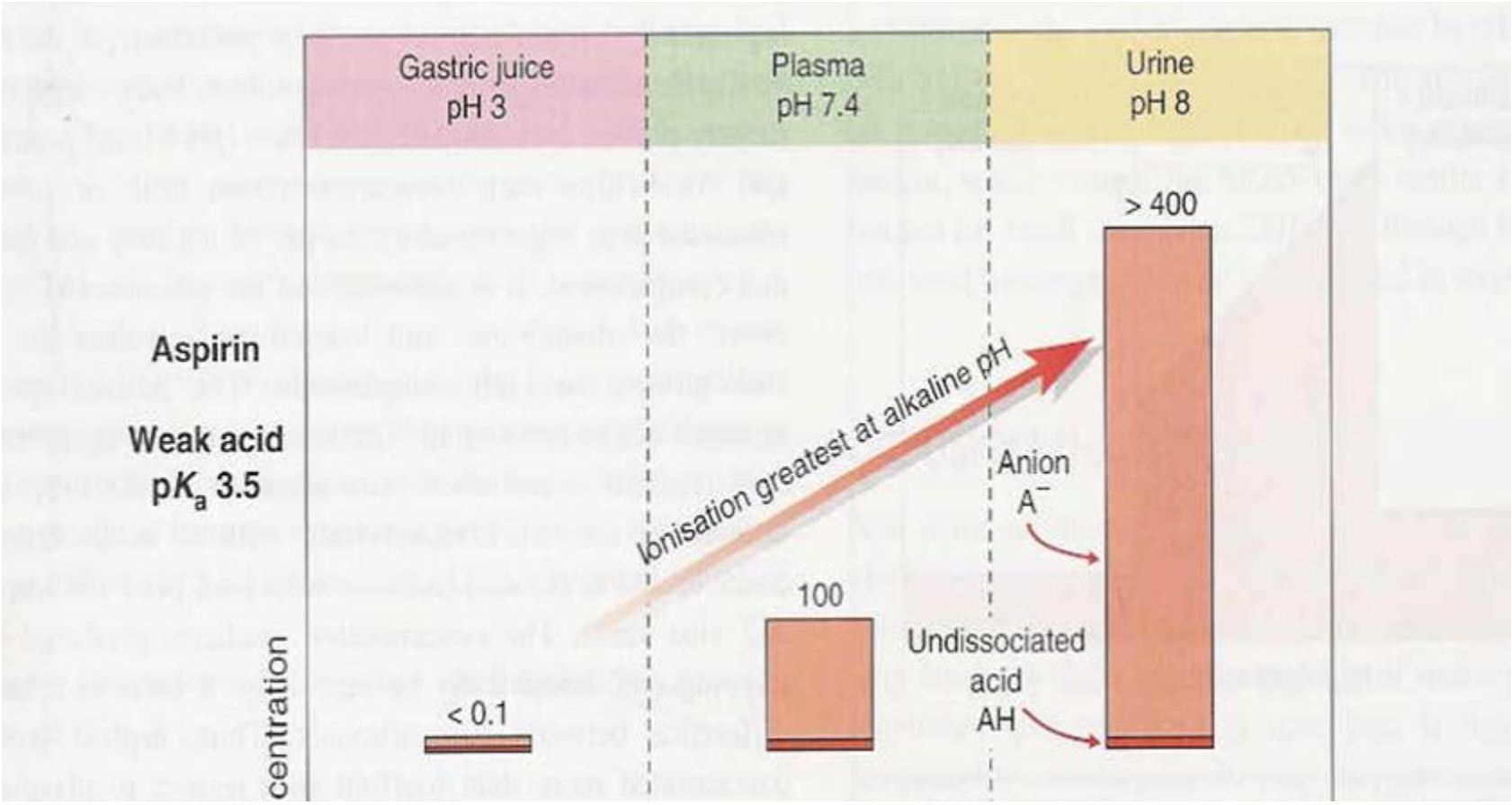
tissue

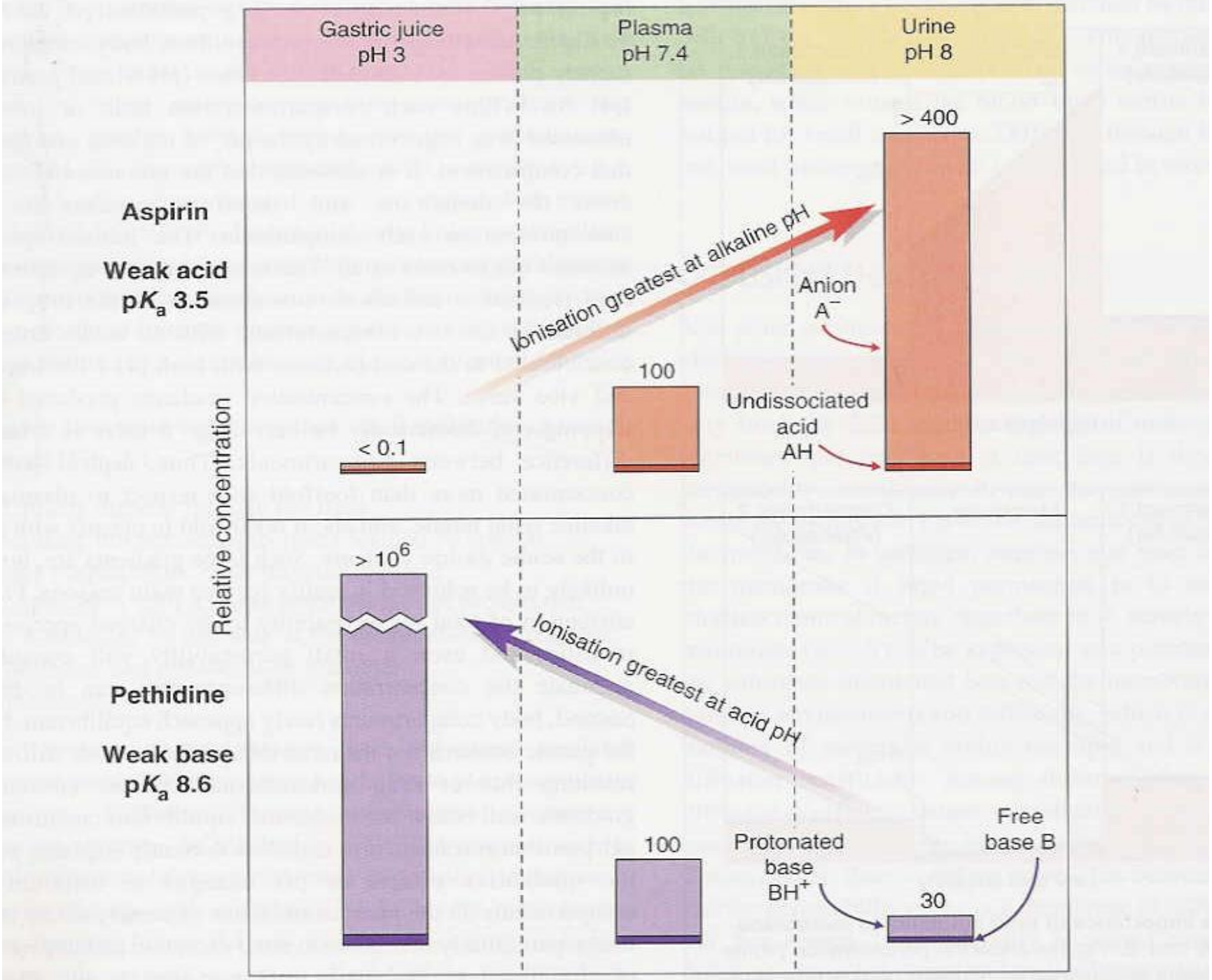
receptors

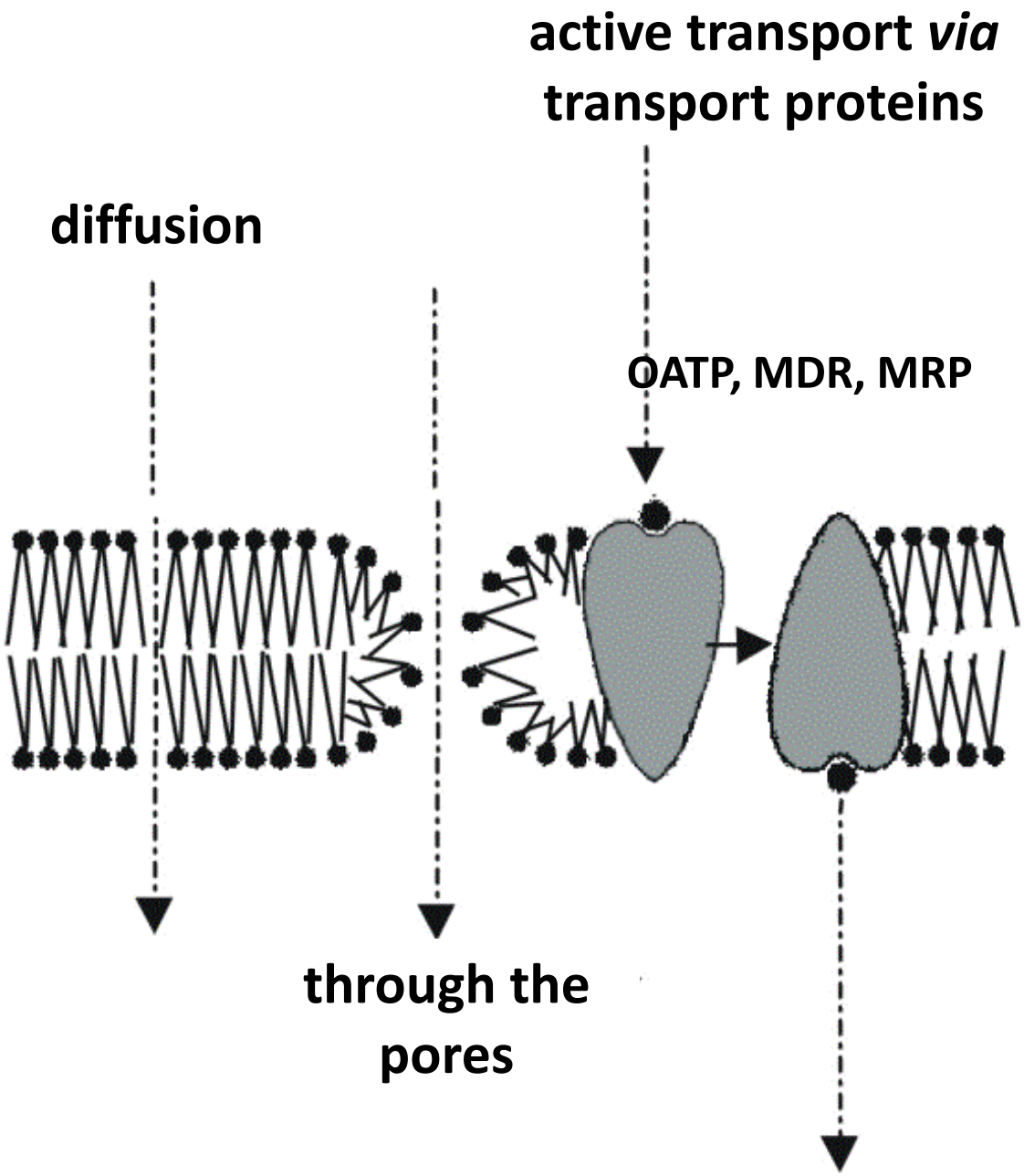
perfusion of the tissues

a) brain, heart, liver, kidney

b) fat tissue


Gastric juice
pH 3
Plasma
pH 7.4
Urine
pH 8
Aspirin
Weak acid
pK_a 3.5
centration
> 400
Ionisation greatest at alkaline pH
Anion
A^-
100
Undissociated
acid
AH
< 0.1


Gastric juice
pH 3
Plasma
pH 7.4
Urine
pH 8
Aspirin
Weak acid
pK_a 3.5
> 400
Ionisation greatest at alkaline pH
Anion
A^-
100
Undissociated
acid
AH
< 0.1
Relative concentration
> 10^6
Ionisation greatest at acid pH
Pethidine
Weak base
pK_a 8.6
100
Protonated
base
BH^+
Free
base B
30


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

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

physico-chemical properties

lipophilic/hydrophilic properties, molecule structure, pKa, charge…

AH ⇆ A- + H+ B + H+ ⇆ BH+

permeation across the membranes

lipophilic – difusion (passive)

hydrophilic – through the pores

active transport

bonds of the drugs to:

plasma proteins

tissue

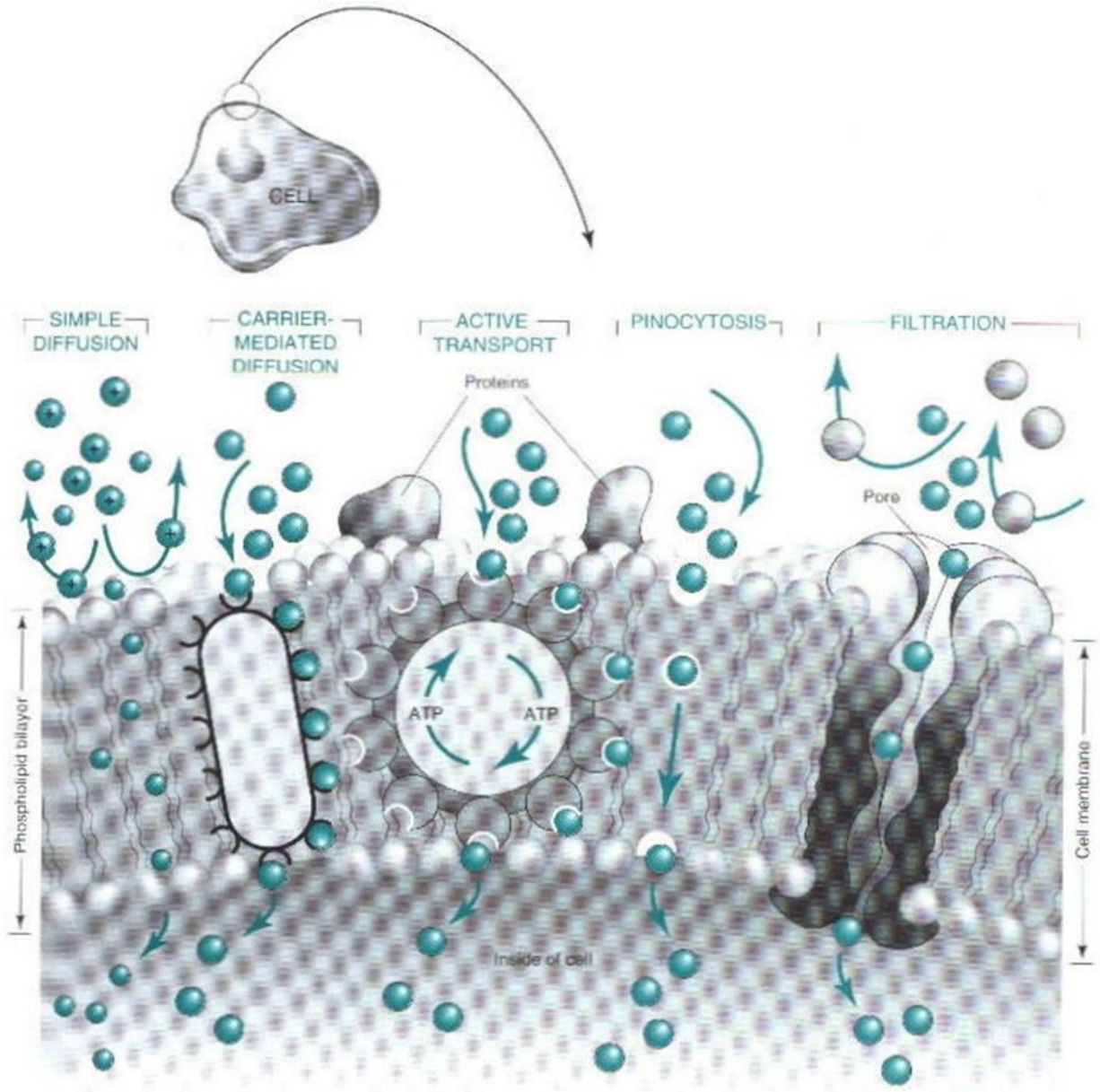
blood cells in the circulation

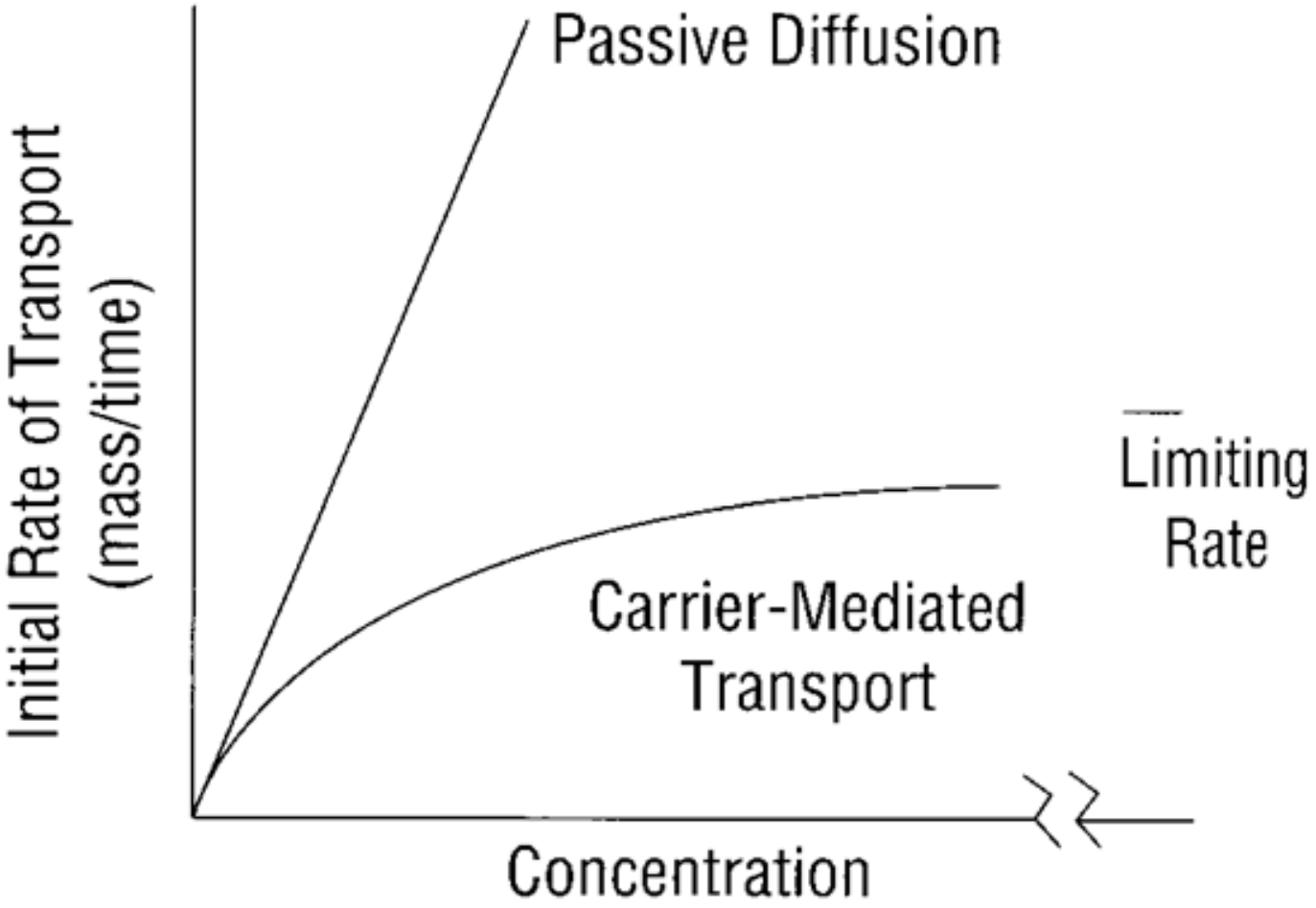
receptors

perfusion of the tissues

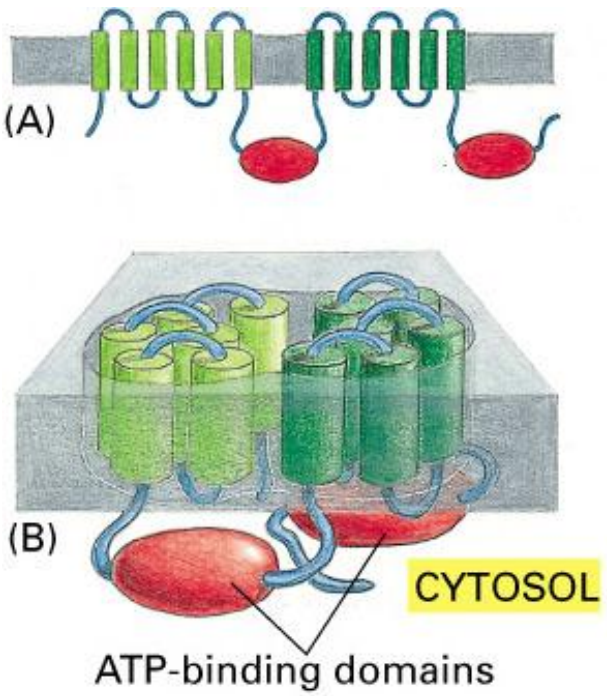
a) brain, heart, liver, kidney

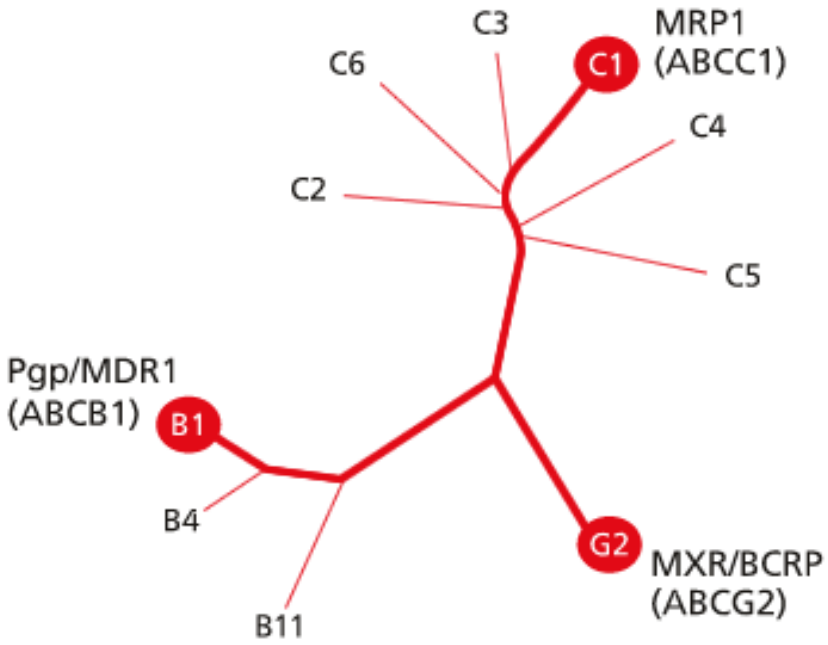
b) fat tissue


CELL
SIMPLE DIFFUSION
CARRIER-MEDIATED DIFFUSION
ACTIVE TRANSPORT
PINOCYTOSIS
FILTRATION
Proteins
Pore
ATP
ATP
Phospholipid bilayer
Cell membrane
Inside of cell


Passive Diffusion
Initial Rate of Transport
(mass/time)
Limiting
Rate
Carrier-Mediated
Transport
Concentration

ABC - ATP-BINDING CASSETTE

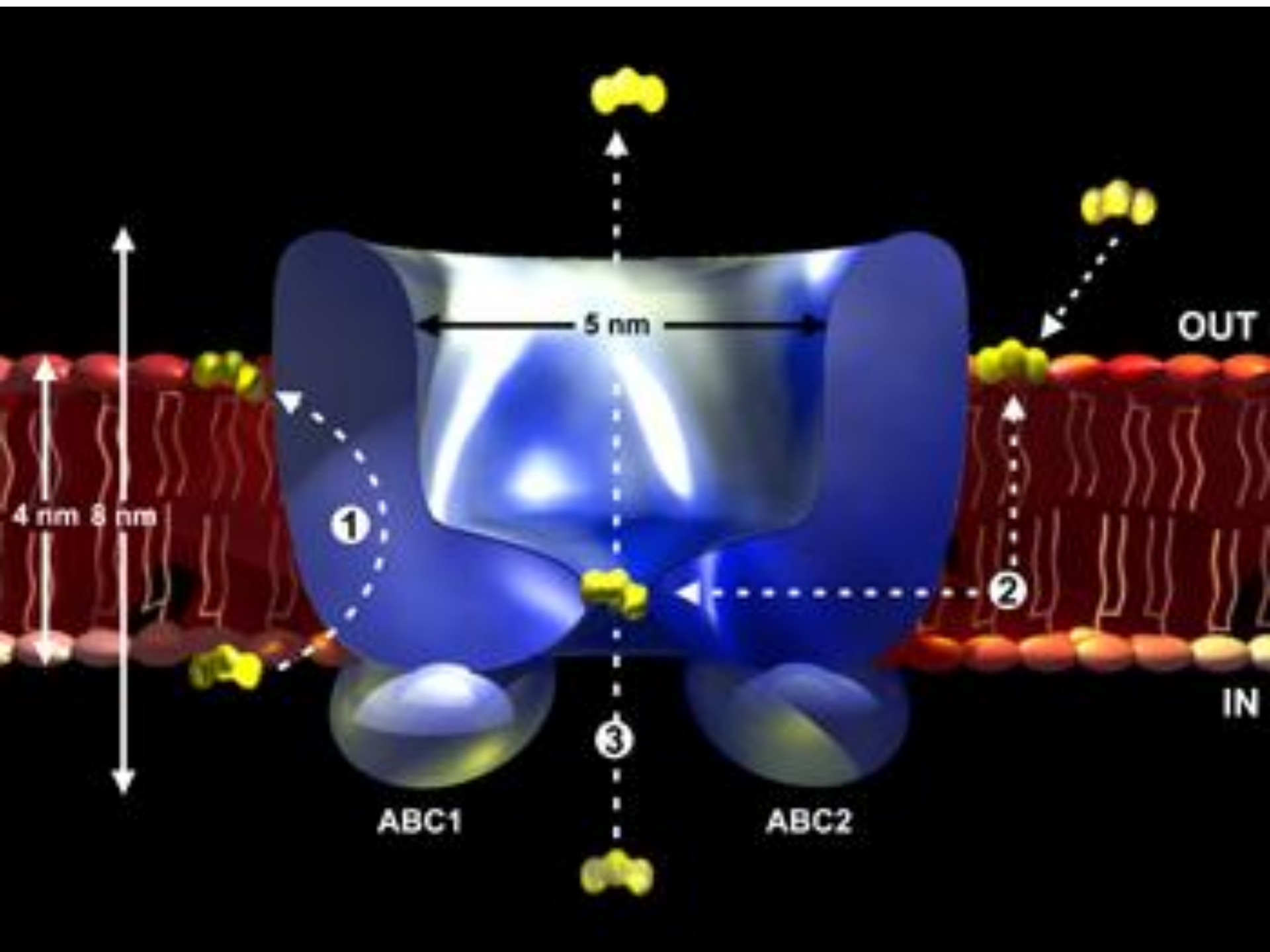


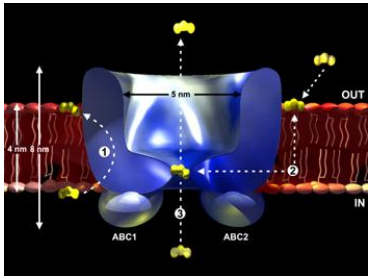


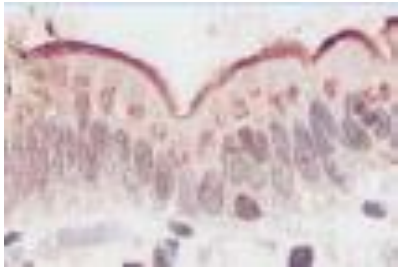
ABC - **A**TP-**B**INDING **C**ASSETTE

- **MDR - multi drug resistance**
- **MRP - multidrug resistance asociated protein**
- **MXR - mitoxantrone resistance protein**

- **Pgp - P-glykoproteinová pumpa**


5 nm
OUT
4 nm 8 nm
1
2
3
IN
ABC1
ABC2



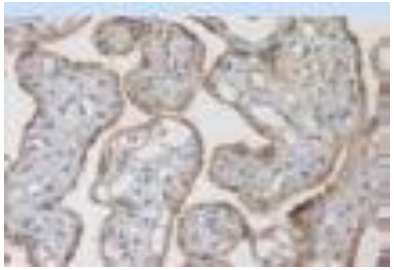


GIT

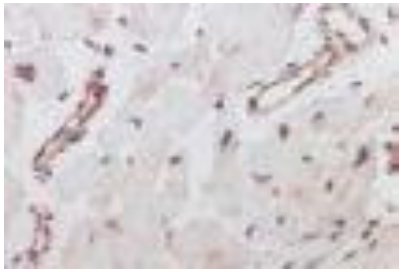
liver

brain

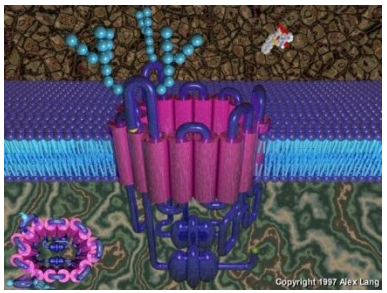
kidney



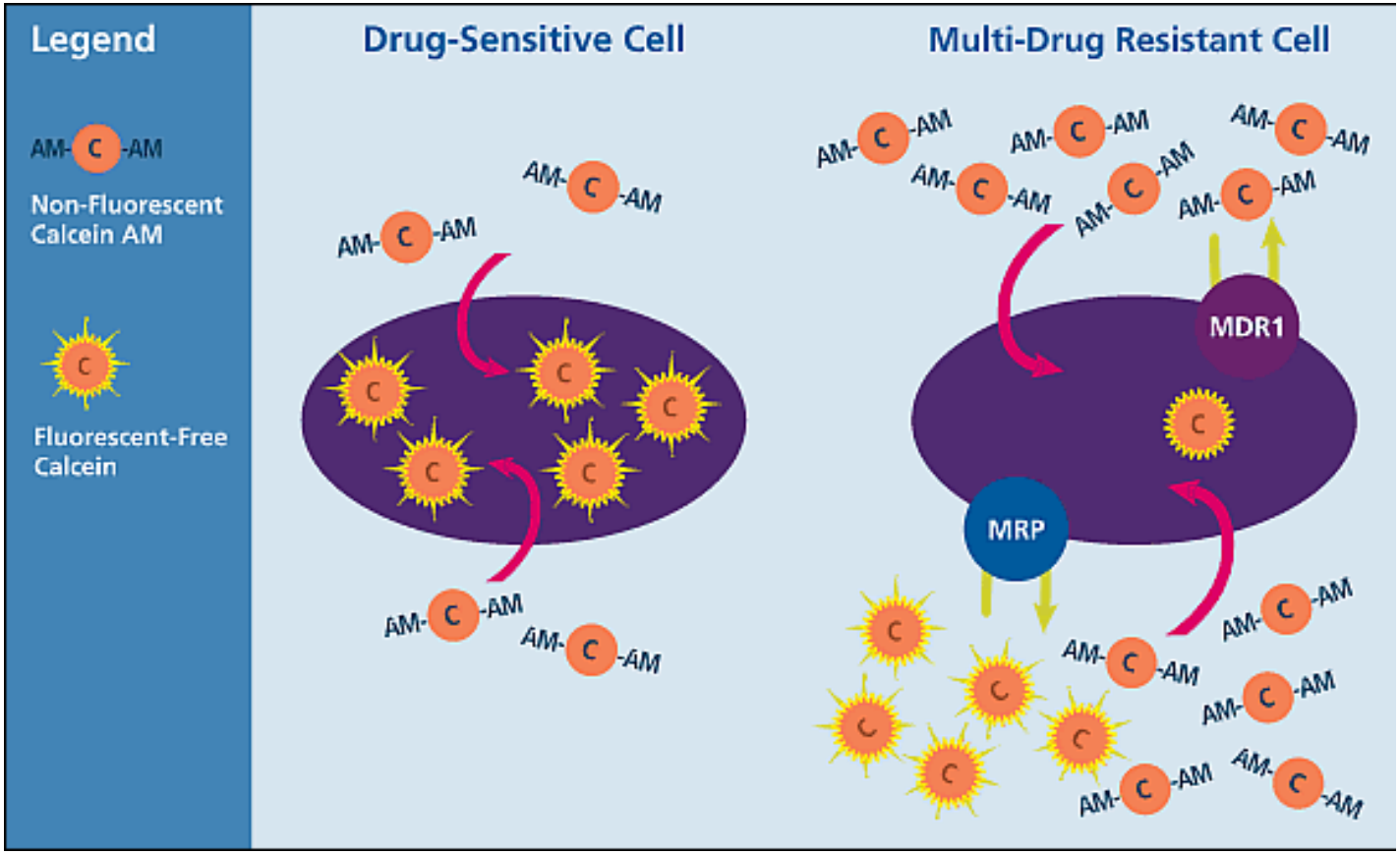
placenta



hearth



- P-glycoprotein
  - Resistence on chemotherapy



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

physico-chemical properties

lipophilic/hydrophilic properties, molecule structure, pKa, charge…

AH ⇆ A- + H+ B + H+ ⇆ BH+

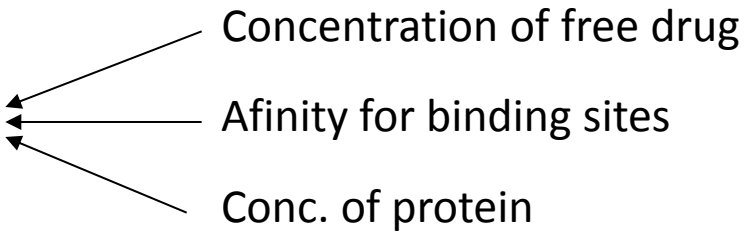
permeation across the membranes

lipophilic – difusion (passive)

hydrophilic – through the pores

active transport

bonds of the drugs to:



plasma proteins

tissue

blood cells in the circulation

receptors

perfusion of the tissues

a) brain, heart, liver, kidney

b) fat tissue

- plasma proteins
- tissue
- blood cells in the circulation
- receptors

- most of acidic drugs (at pH of 7.4= anions) are bound on albumin:
  - salicylates, sulfonamides, penicillins

- most of alcalic + neutral drugs (at pH of 7.4= cations) are bound on α_1- acidic gylcoprotein and lipoproteins:
  - quinidine, digitoxine, TCA, cyclosporine A

- Bonds with plsama proteins are
  - reversible
  - dynamic
  - competitive

drug	% bound
caffein	10
digoxine	23
gentamycine	50
phenytoin	87
digitoxine	95
diazepam	96
warfarin	98
tolbutamide	99

A bound drug has no effect!

Amount bound depends on:

1) free drug concentration
2) the protein (binding sites) concentration
3) affinity for binding sites

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

Bonds in peripheral tissues

- specific for some of the drugs
  - tetracycline antibiotics - hydroxyapatit
  - chloramfenicol – skin
  - grisefulvin - skin
  - arsenic – in hair

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)

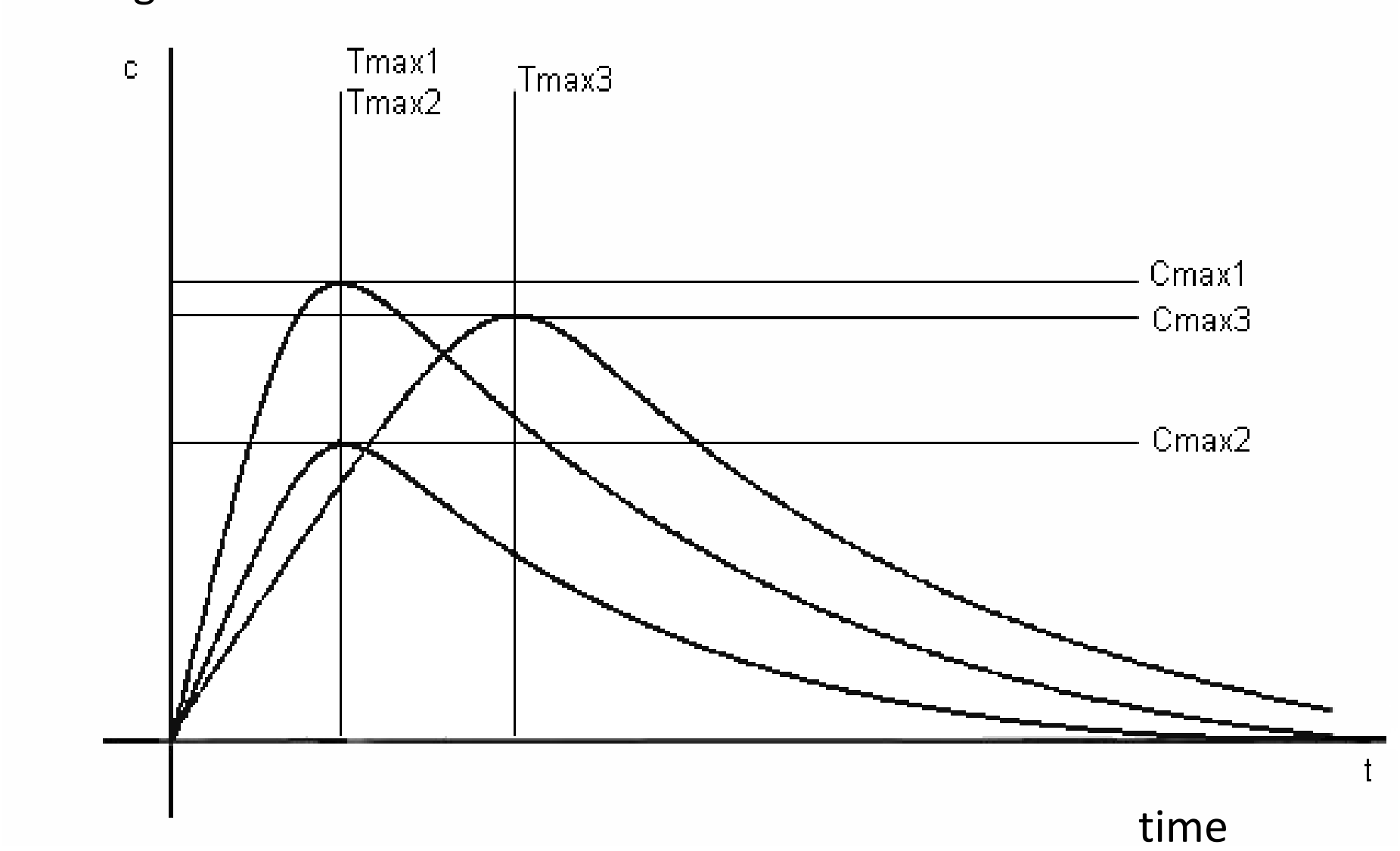
Rate and extent of absorption are described by the parameters :

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,

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

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

Bioavailability

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

Intravenous - 100% = 1

If F is 0-20% = 0-0,2 – not suitable route of administration

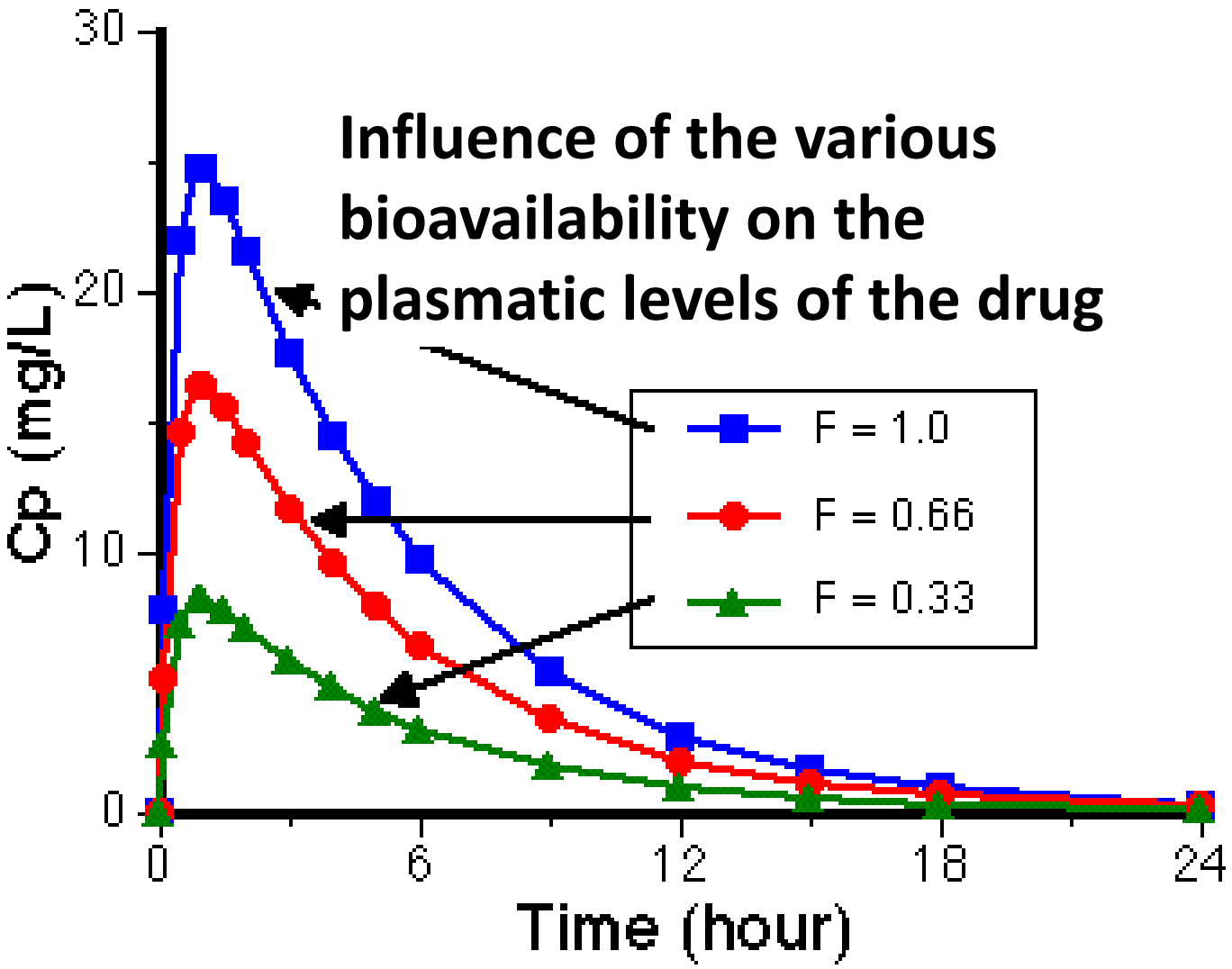
(in spite of that fact, some drugs are administered, even if the F < 2-5 %, such as SET, bisphosphonates).

F = AUCpo/AUCiv

(the same drug, same dose, same patient)

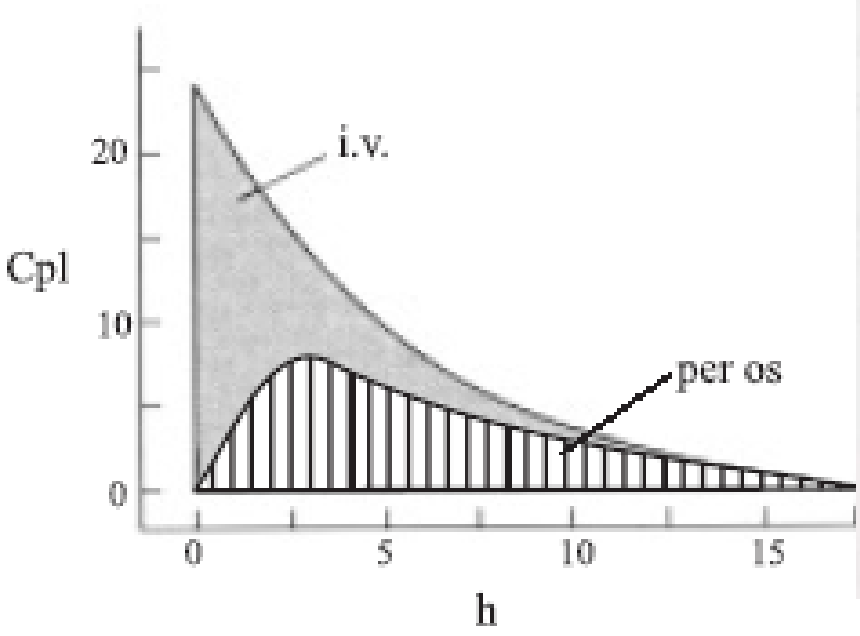
Bioavailability

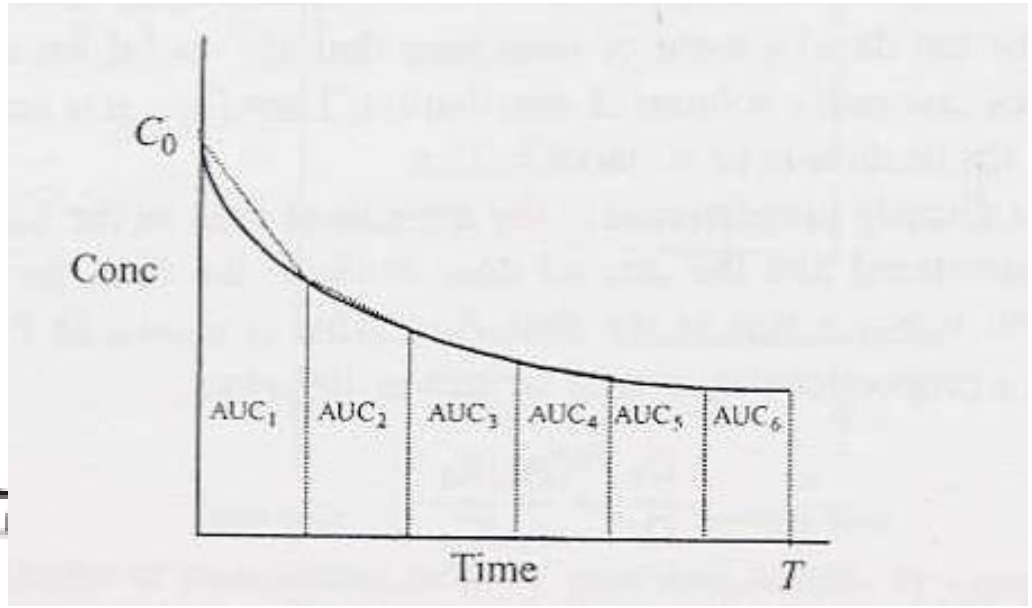
- A concept for oral (extravascular) administration
- Useful to compare two different drugs or different dosage forms of same drug
- depends, in part, on rate of dissolution (which in turn is dependent on chemical structure, pH, partition coefficient, surface area of absorbing region, etc.) Also first-pass metabolism is a determining factor


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

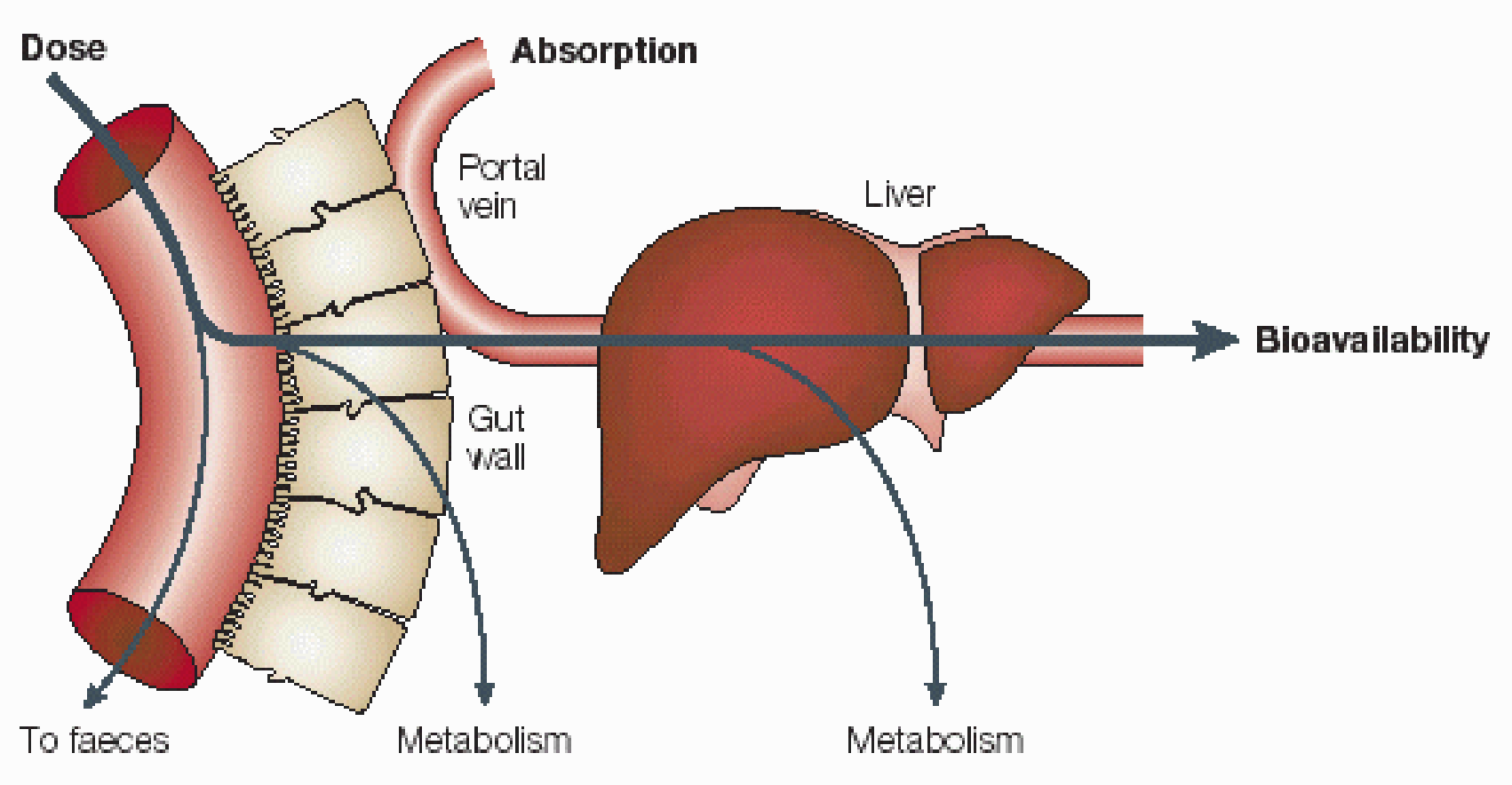
Area under curve (AUC)

- Is a measure of bioavailability





First pass effect, presysthemic elimination

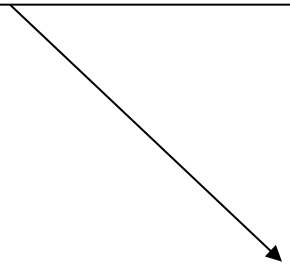


Factors influencing absorption

Drug-dosage form– tbl./ sol./ supp./ TTS/tbl.subling.

Way of administration

Physico-chemical properties of drugs



- absorptive surface area
- concentration gradient
- ionization, lipofility
- interactions

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

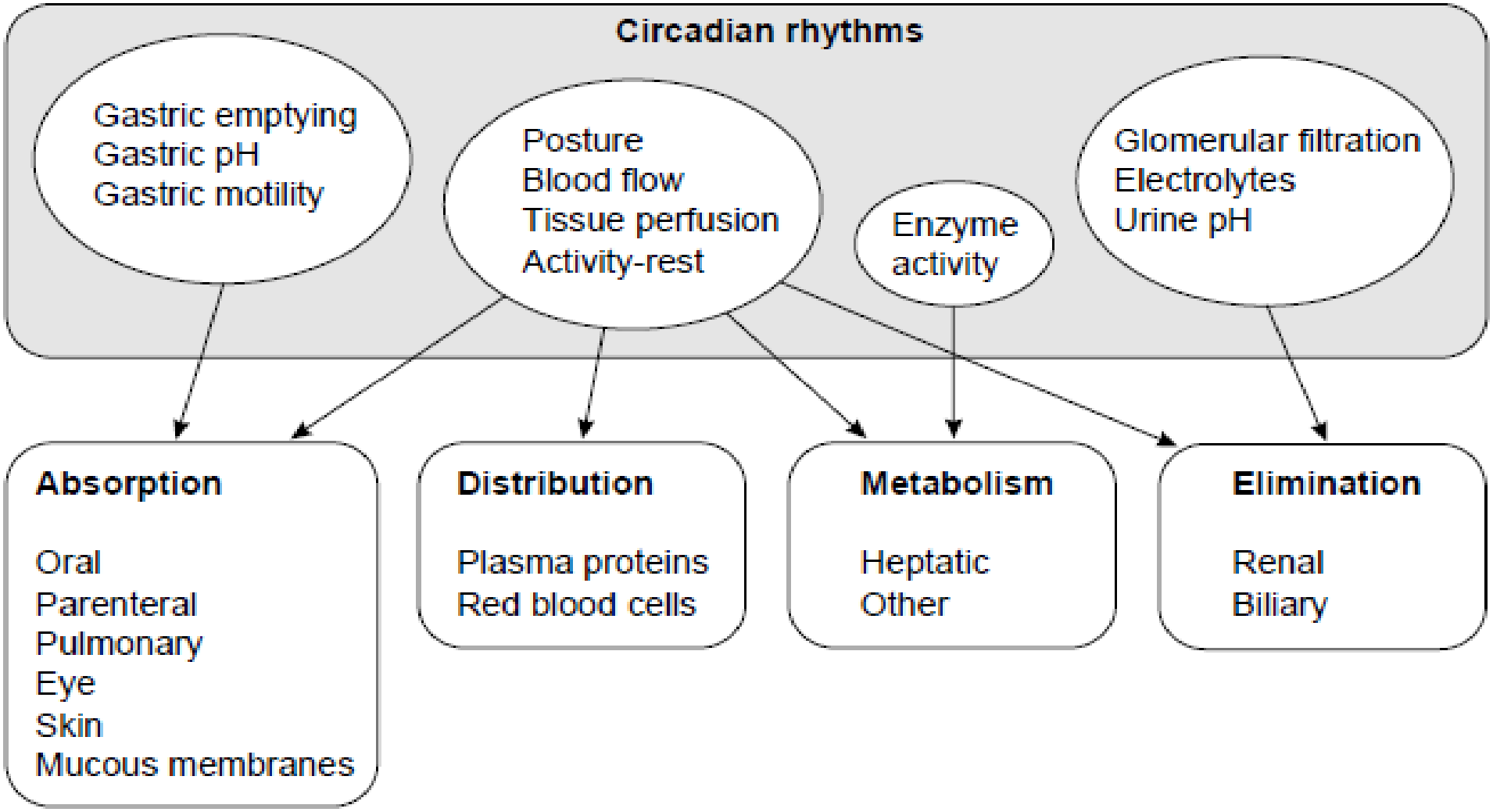
simultaneously eaten meal –

acceleration/decelaration

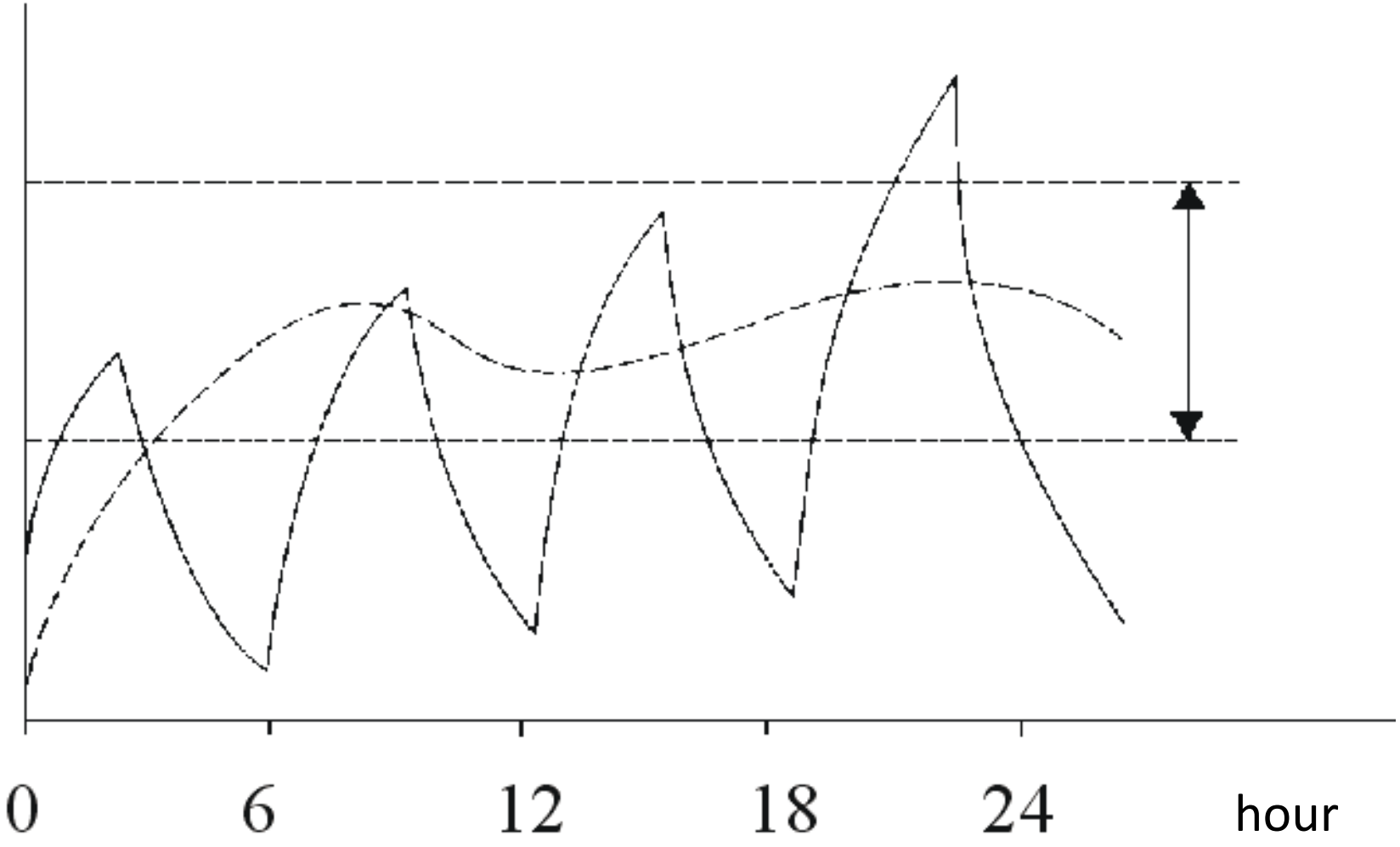
chemical incompatibilities

function of the GIT

Factors affecting pharmacokinetics



Drug dosage forms of the 1st and 2 nd generations



Distribution

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

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

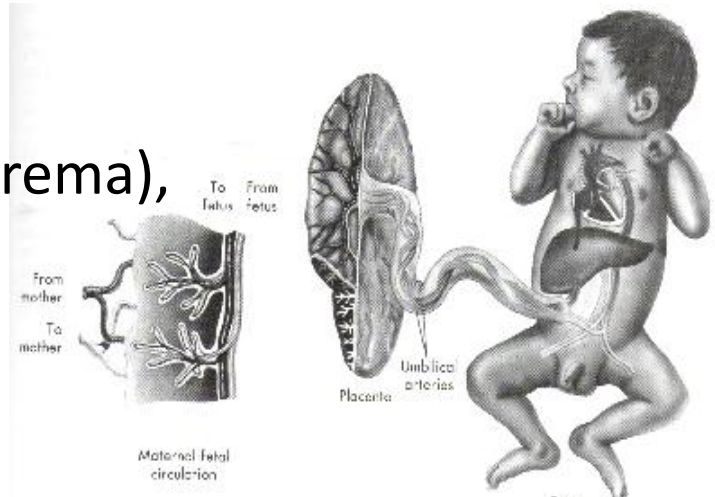
state - distribution equilibrium; the the proportion of the free (unbounded) fractions of the drug in the blood and in the tissues are the same

Barriers – the distribution is limited

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

penicilines X aminoglycosides

placental barrier…



Volume of Distribution

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

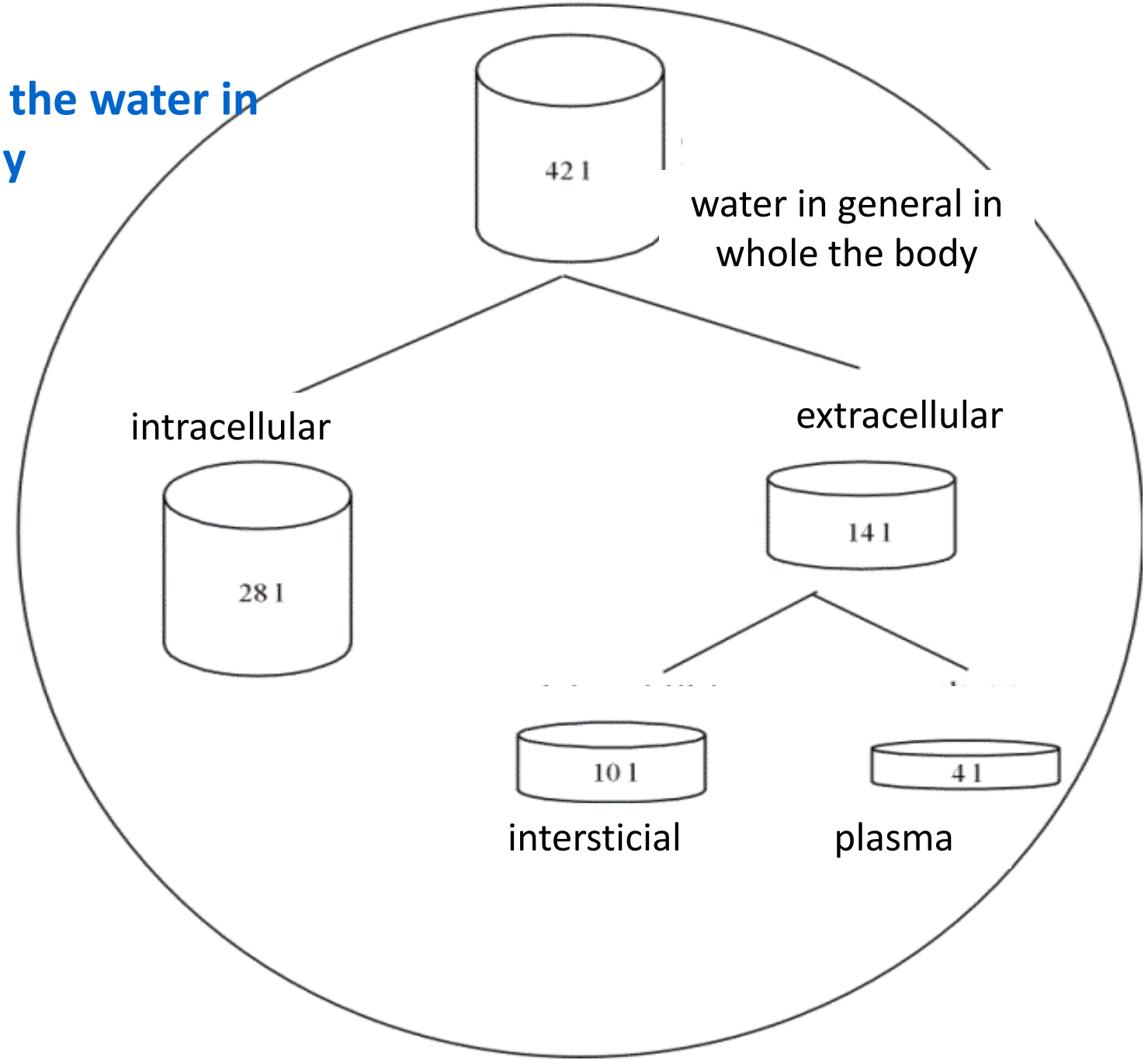
$V_d = D/C$

- 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

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



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 = biotransformation + excretion

- 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

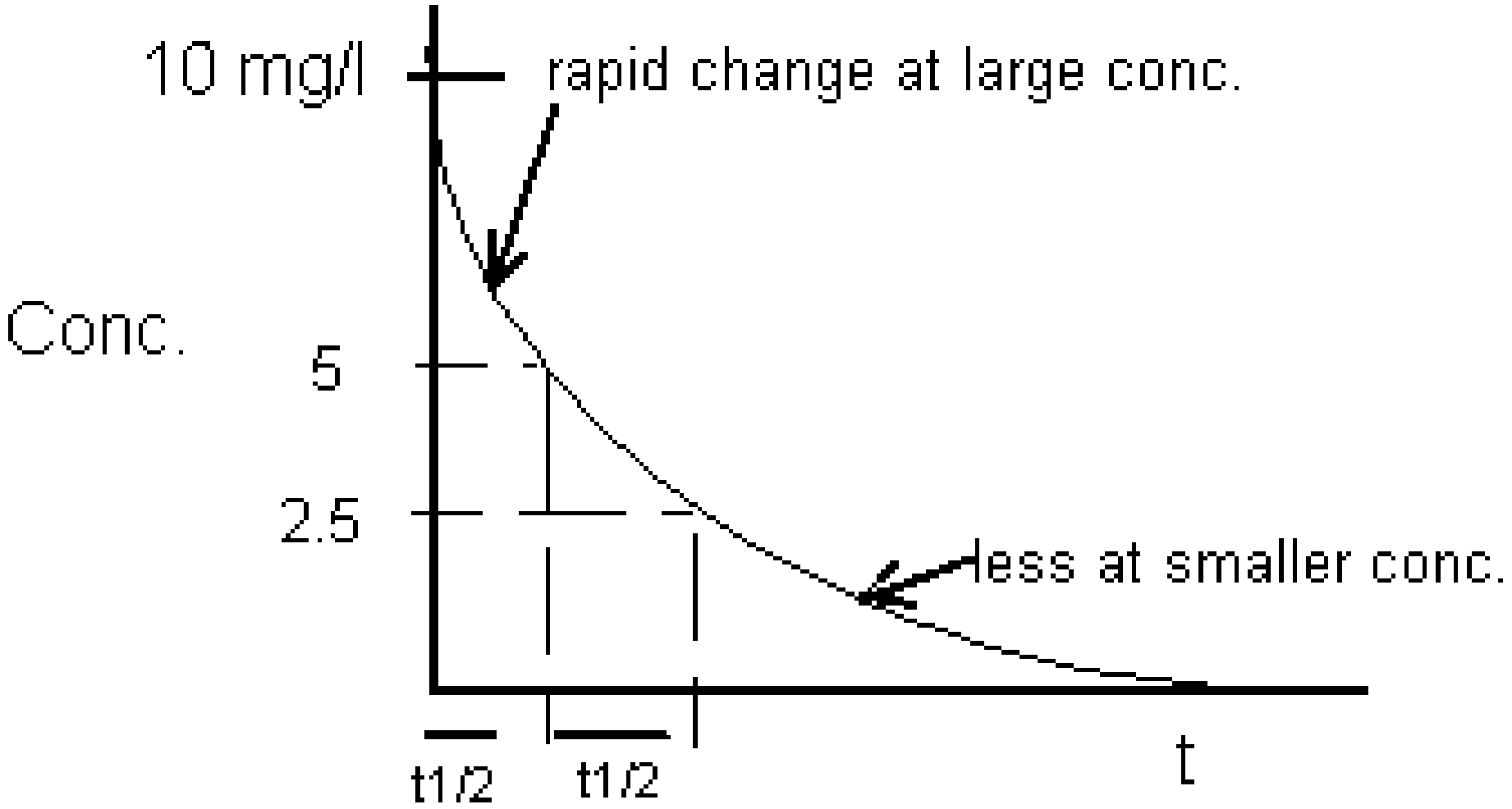
- C vs. t graph is LINEAR

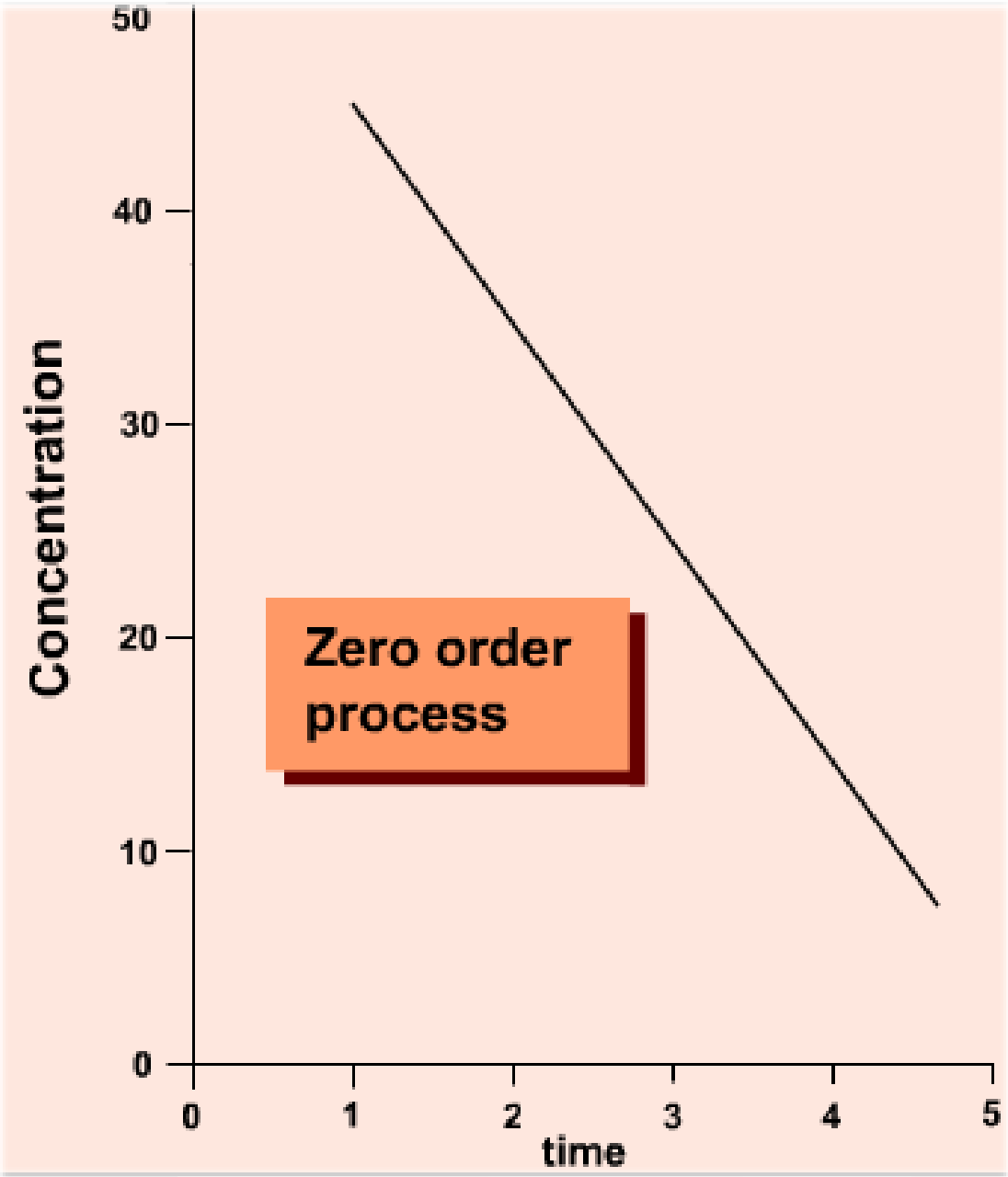
First Order Kinetics

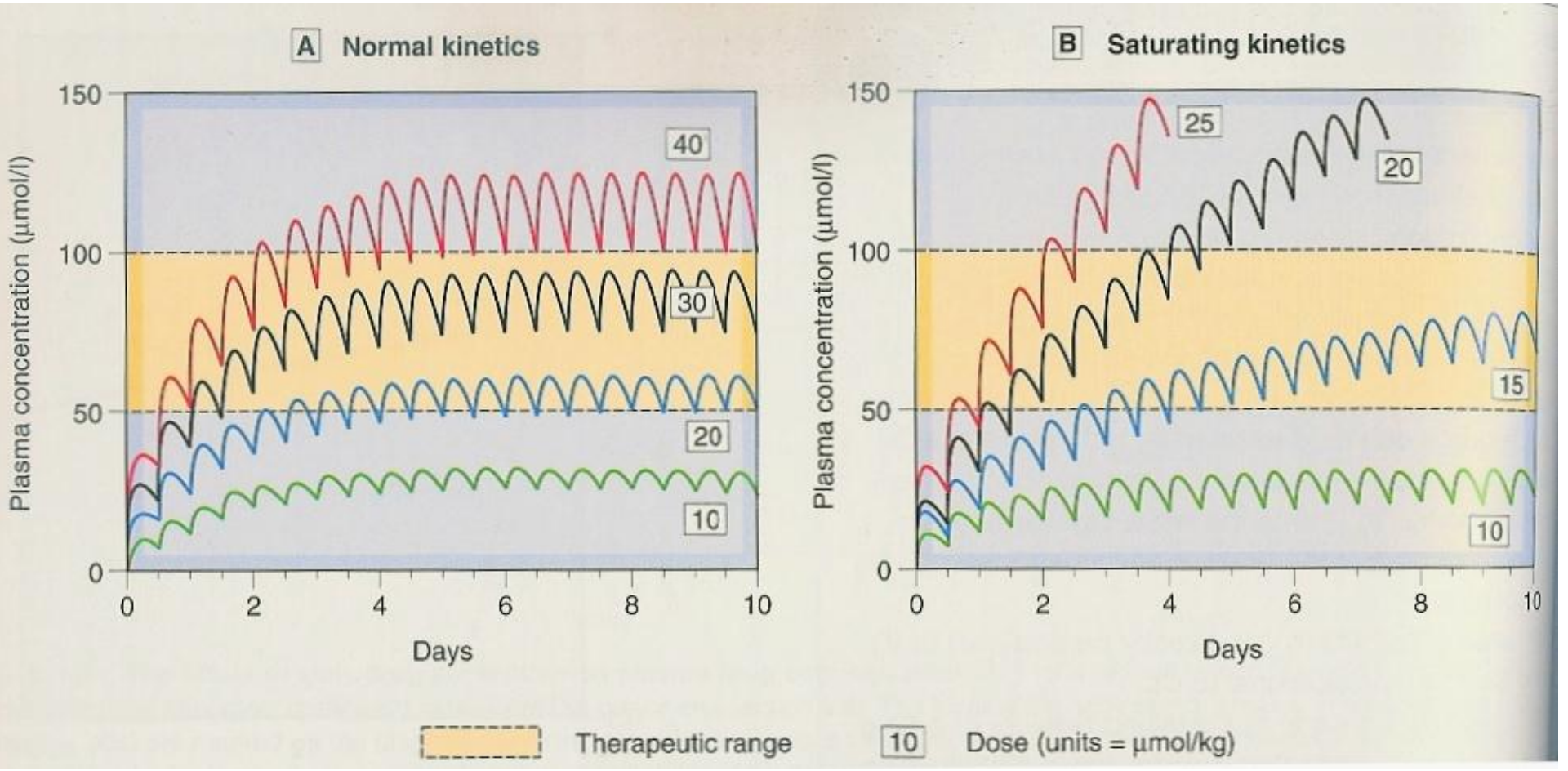
- Rate = k C
- $C = C_o e^{-kt}$

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

First Order Kinetics




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


A Normal kinetics
Plasma concentration (µmol/l)
150
100
50
0
0
2
4
6
8
10
Days
40
30
20
10
B Saturating kinetics
Plasma concentration (µmol/l)
150
100
50
0
0
2
4
6
8
10
Days
25
20
15
10
Therapeutic range
10
Dose (units = µmol/kg)

ELIMINATION

Biotransformation – metabolism

Sites of biotransformation

anywhere, where the enzymes are present: plasma, kidney, lungh
GIT, brain, but especially **liver**

Enzymatic

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

enalapril-enalaprilate

codein-morphine

bromhexin - ambroxol

1. Phase : oxidation, hydrolysis

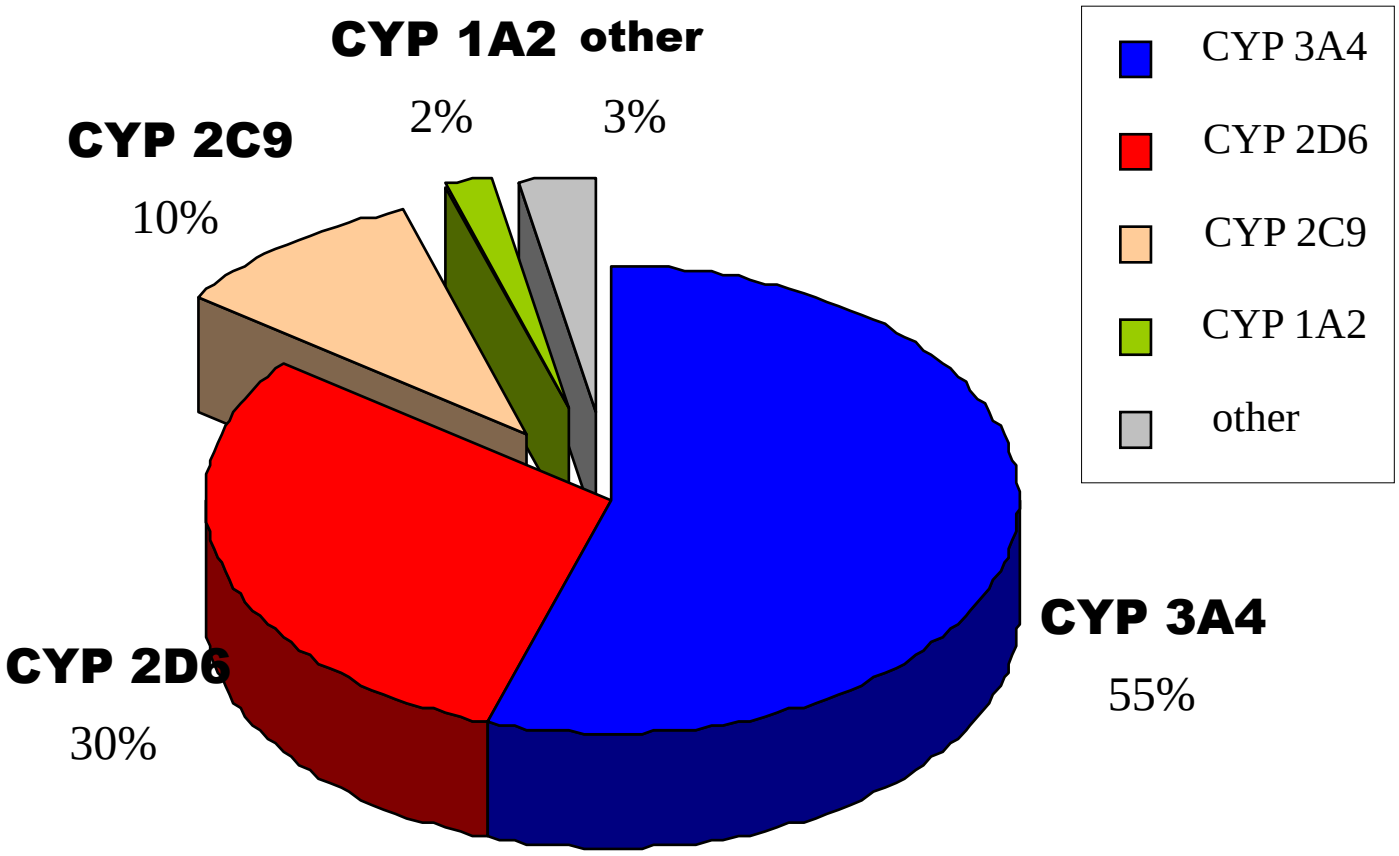
Cytochrom P450, dehydrogenases

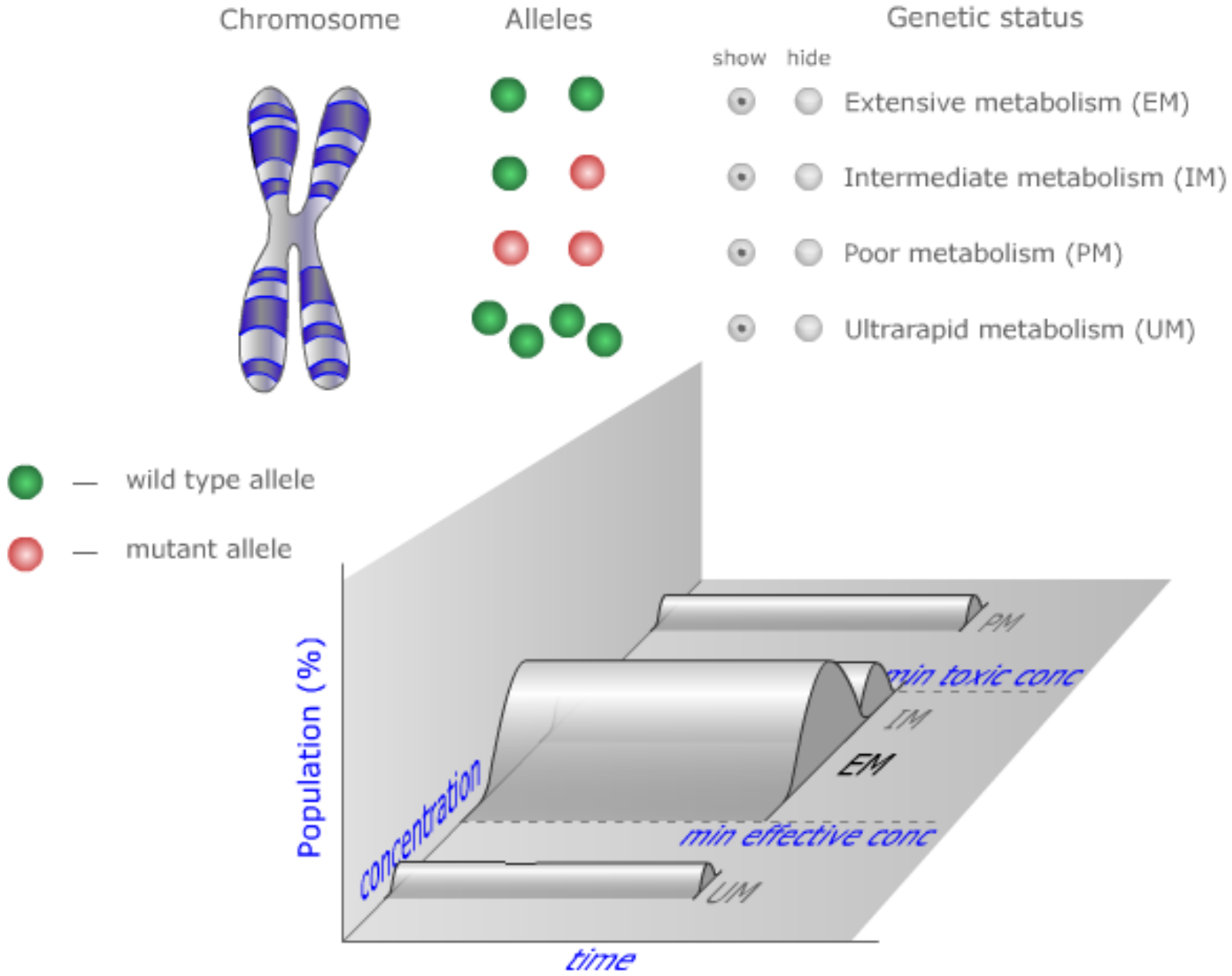
2. Phase : conjugation – metabolites are more soluble in the water

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

- ineffective

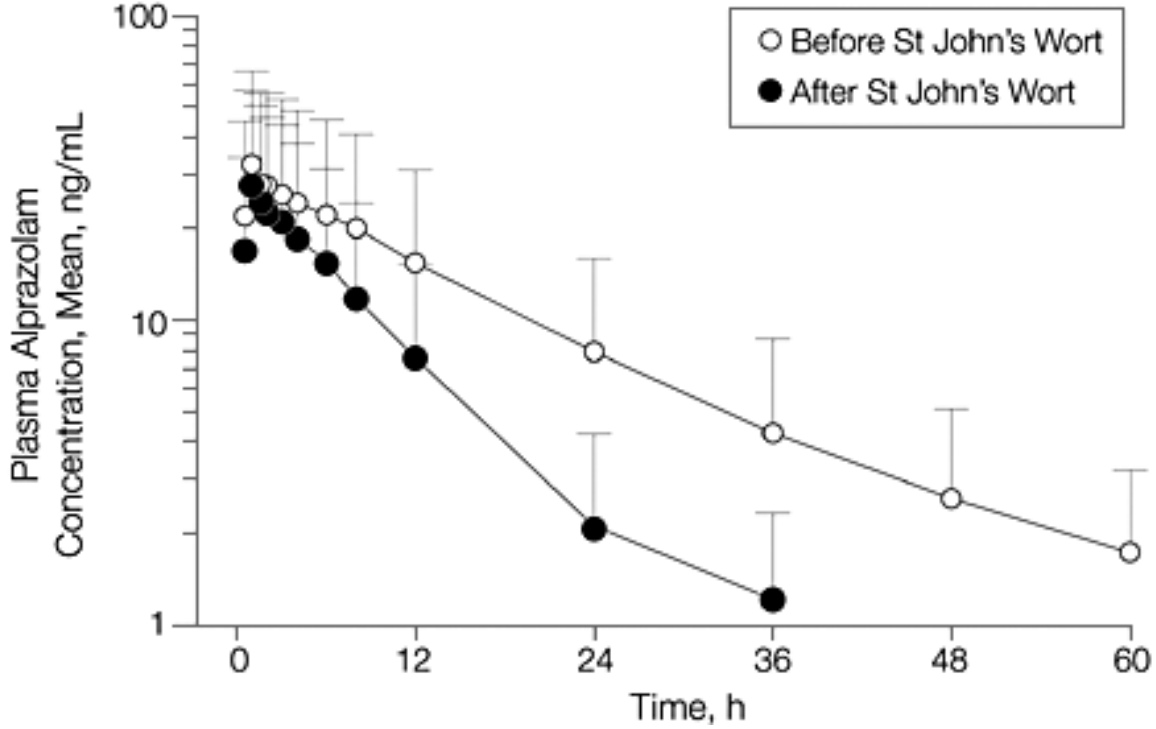
- toxic


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


Chromosome
Alleles
Genetic status
show
hide
Extensive metabolism (EM)
Intermediate metabolism (IM)
Poor metabolism (PM)
Ultrarapid metabolism (UM)
— wild type allele
— mutant allele
Population (%)
concentration
time
PM
min toxic conc
IM
EM
min effective conc
UM

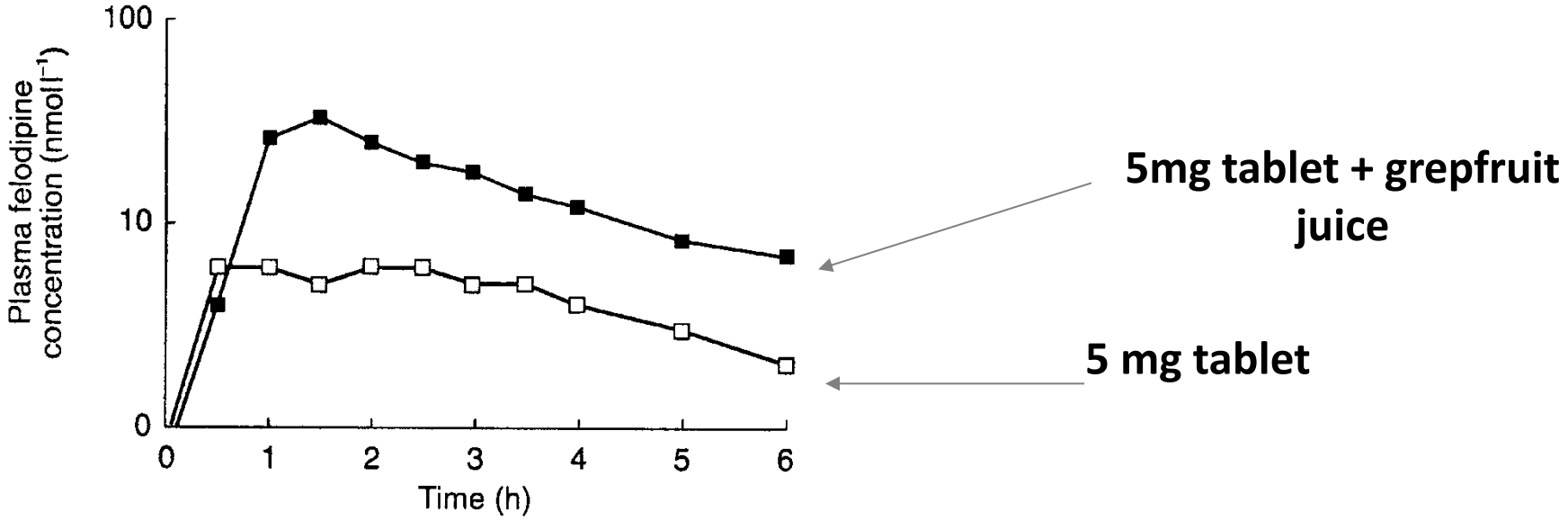
INDUCERS of CYP 450

- dexamethason
- phenobarbital
- rifampicine
- ph
- St
- *Gi*



INHIBITORS of CYP 450

- antidepressants (fluoxetine, fluvoxamine, paroxetine)
- quinine, quinidine
- chloramphenicol, erythromycin



Phase I of biotransformation

hydroxylation $-CH_2CH_3 \rightarrow -CH_2CH_2OH$

oxidation $-CH_2OH \rightarrow -CHO \rightarrow -COOH$

O-dealkylation $-CH_2OHCH_2 \rightarrow -CH_2OH + -CHO$

N-dealkylation $-N(CH_3)_2 \rightarrow -NHCH_3 + CH_3OH$

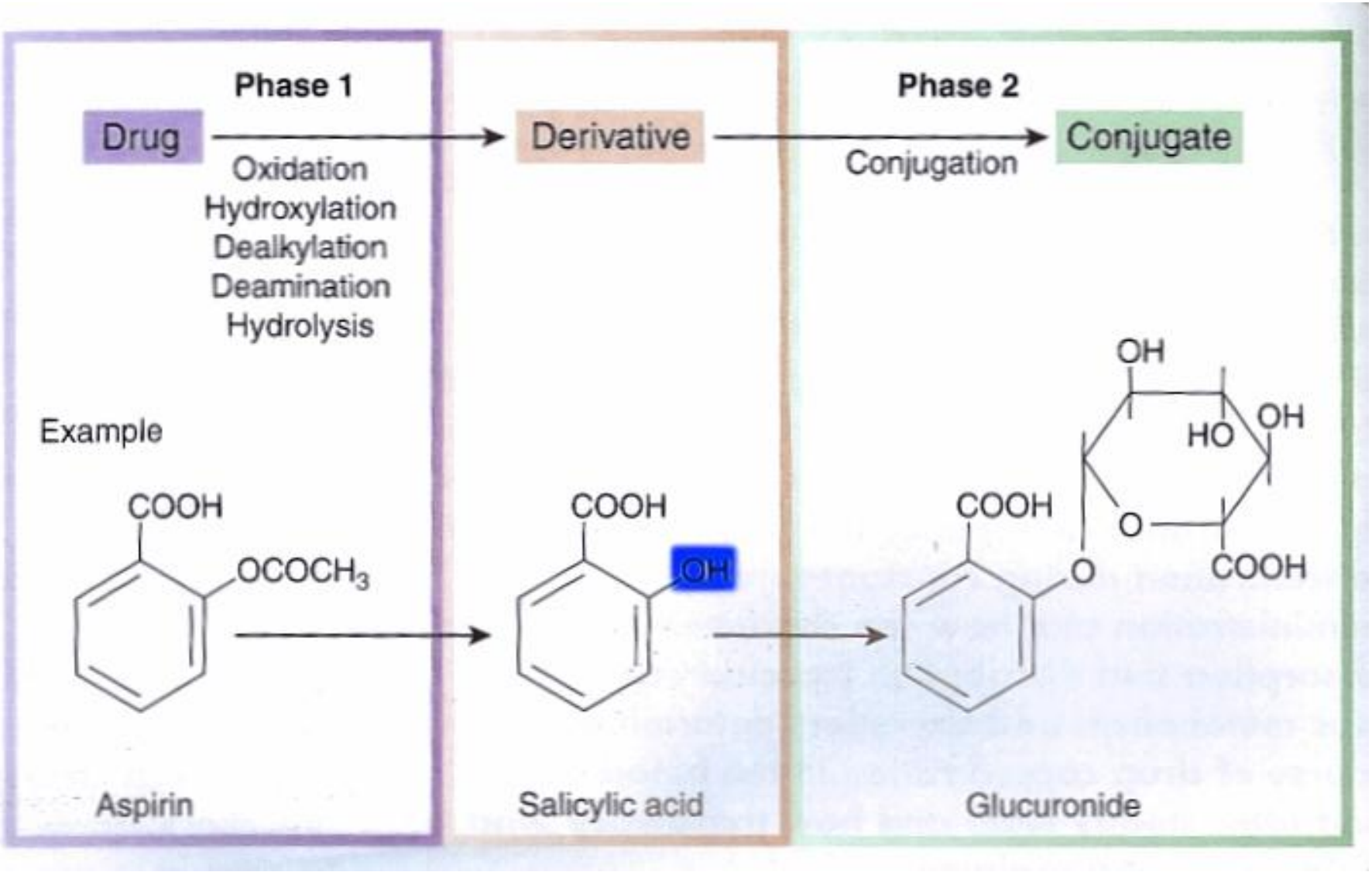
N-oxidation $-NH_2 \rightarrow -NHOH$

oxidative deamination $-CH_2CHCH_3 \rightarrow -CHCOCH_3 + NH_3$

NH_2

Other non-microsomal biotransformations

- hydrolysis of esters in plasma (suxamethonium by cholinesterase)
- dehydrogenation of alcoholic and aldehydic group in cytosol in the liver (ethanol)
- MAO in mitochondria (tyramine, noradrenaline, dopamine, amines)
- xanthinoxidase (6-merkaptopurine, uric acid)
- enzymes with distinct function (tyrosine-hydroxylase, dopa-decarboxylase, etc.)


Phase 1
Drug
Oxidation
Hydroxylation
Dealkylation
Deamination
Hydrolysis
Derivative
Phase 2
Conjugation
Conjugate
Example
COOH
OCOCH3
COOH
OH
OH
HO
OH
COOH
O
O
COOH
Aspirin
Salicylic acid
Glucuronide

Phase II of biotransformation

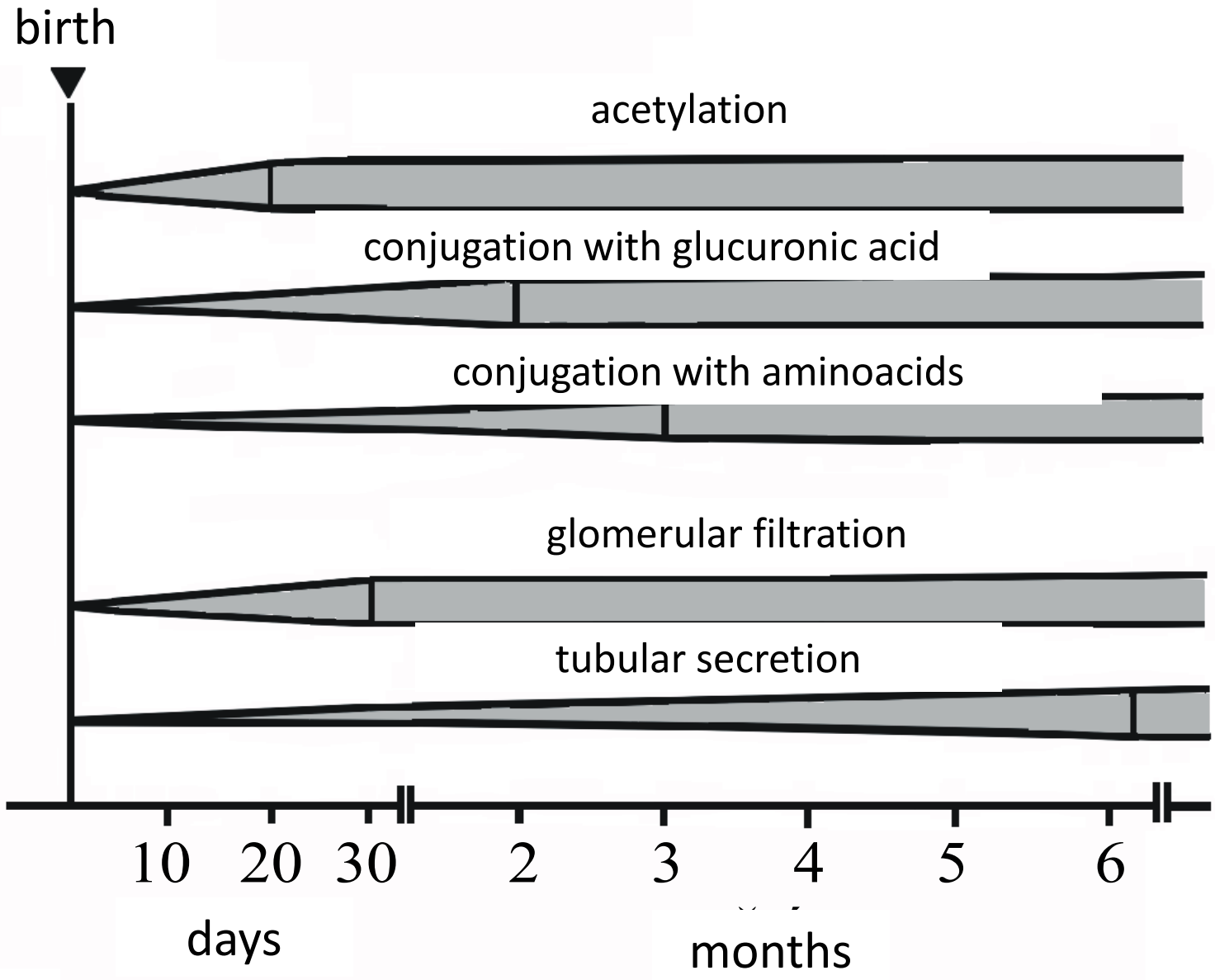
CONJUGATION

Glucuronides -OH, -SH, -COOH, -CONH wih glucuronyl acid (UDP- GlcUAc)

Sulphates: with -OH functional group

Acetylates: acetyl CoA with NH_2, -$CONH_2$, s aminoacid- group

with gluthathion with -halogen- or -nitrate functional groups, epoxides sulphates


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)

tubular excretion

x tubular reabsorption

liver (bile)

lungh (air)

saliva, skin, hair, breast milk...

Clearance Cl

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

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

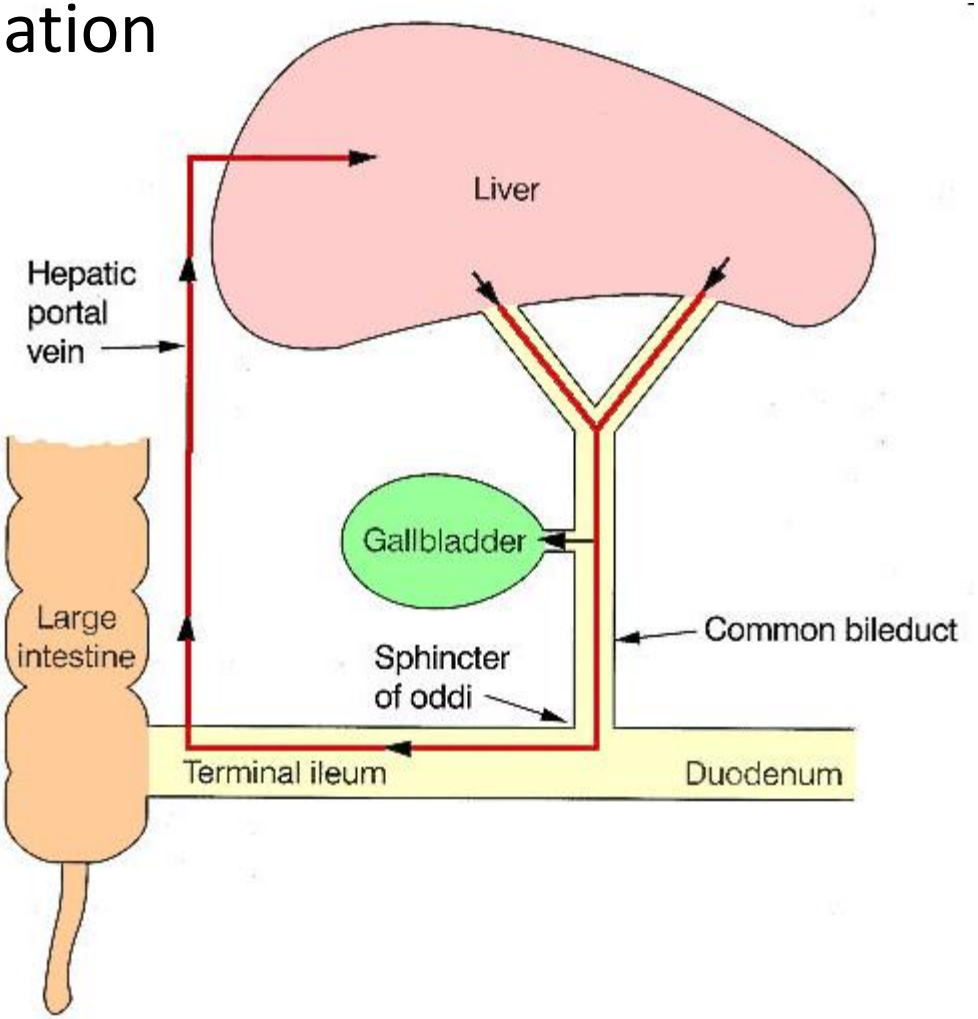
alcalization

sodium bicarbonate

Liver

Billiar excretion, clearance.

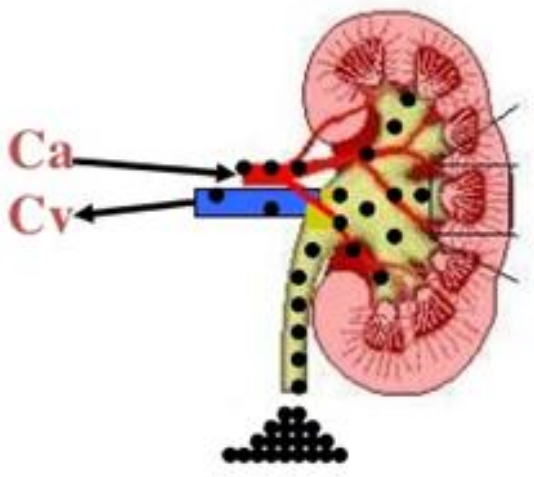
enterohepatic circulation



Extraction ratio E_R

= proportion of the drug removed durring the passage through the organ

$$E_R = c_a\text{-}c_v/c_a$$



Mean residence time MRT

= The average total time molecules of a given dose spend in the body. Thus, this can only be measured after instantaneous administration.

Non-compartment PK

$$MRT = AUMC/AUC$$

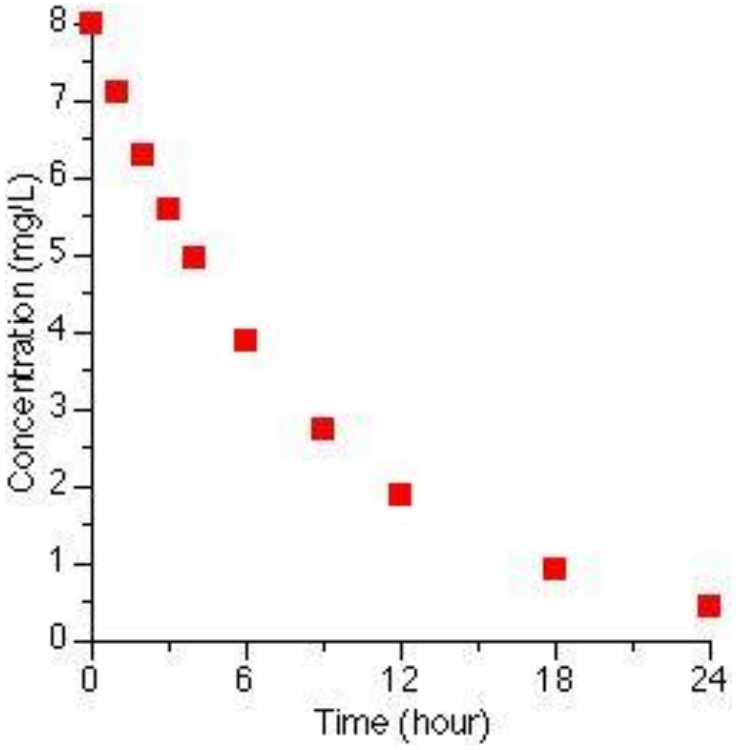
Mean residence time AUMC

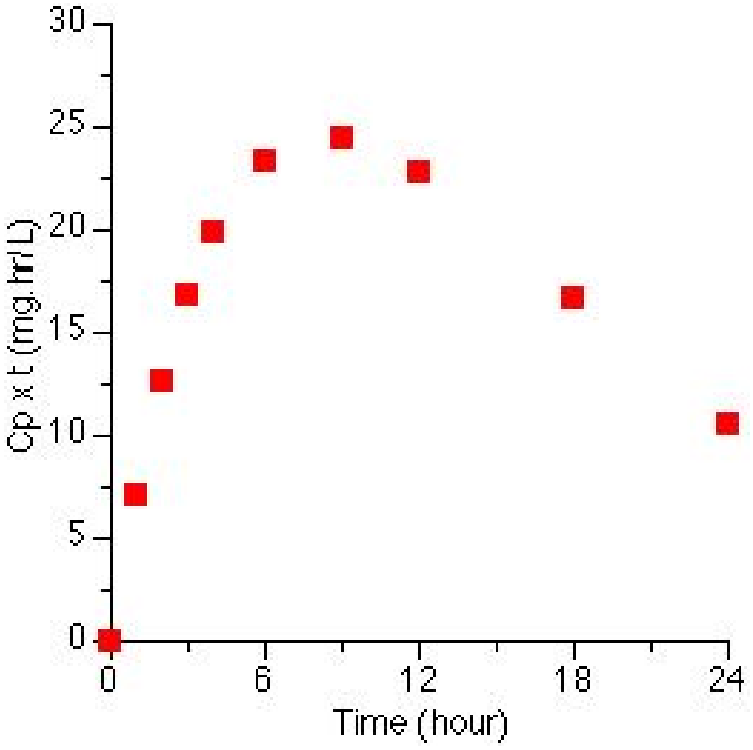
= AUMC is a measure of the'concentration - time' average of the profile,

(AUC is a measure of the'concentration' average of the profile)

= their ratio yield MRT, a measure of the 'time average' of the profile

Mean residence time AUMC





Mean residence time

$$MRT = \frac{1+1+2+2+3+3+4+4+5+5}{10}$$

$$MRT = 3$$

PHARMACOKINETIC PARAMETERS

PRIMARY

- **Bioavailability (F)**
- **Volume of distribution (Vd)**
- **Clearance (Cl)**

SECONDARY

- elimination half-life ($T_{1/2}$)
- elimination constant (Ke)
- AUC (area under the curve)
- Cumulative index
- Extraction ratio

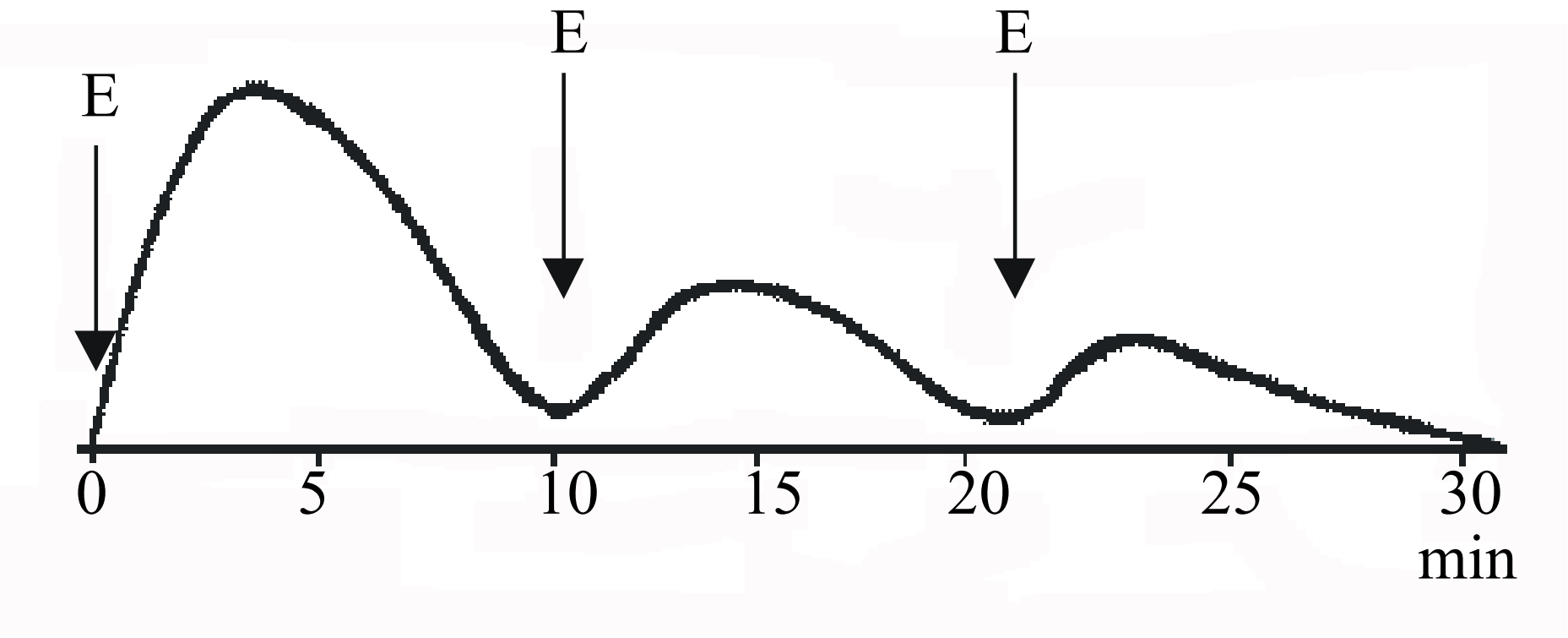
Repeated administration

- increase in effect – accumulation
  senzitization

- decrease in effect
  - tolerance - changes at the site of receptor
    - chnges in pharmacokinetics
  - tachyphylaxis
  - resistence – „tolerance“ to the drugs inhibiting cell. growth or cytotoxic drugs
    cytostatics, antiinfectives, antiseptics

- drug dependance

Tachyphylaxis after repeted ephedrine administration (decrease ineffect on blood pressure)



E = ephedrine administration

BASIC PHARMACOKINETIC PARAMETERS

- C (Co, Cmax) concentration in plasma
- Tmax time to reach Cmax
- V_d volume of distribution
- Cl clearence (Cl_{lungh} , CL_{kid} , Cl_{liv} , Cl_{tot})
- t 0,5 abs half-life of absorption
- $t_{0,5}$ ($t_{1/2}$ el, $t_{50\%}$ el) half-life of elimination
- AUC Area Under the Curve

  total amount of the drug during its presence in the body

- F [%] bioavailability