- **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)**

Pharmacokinetics

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

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

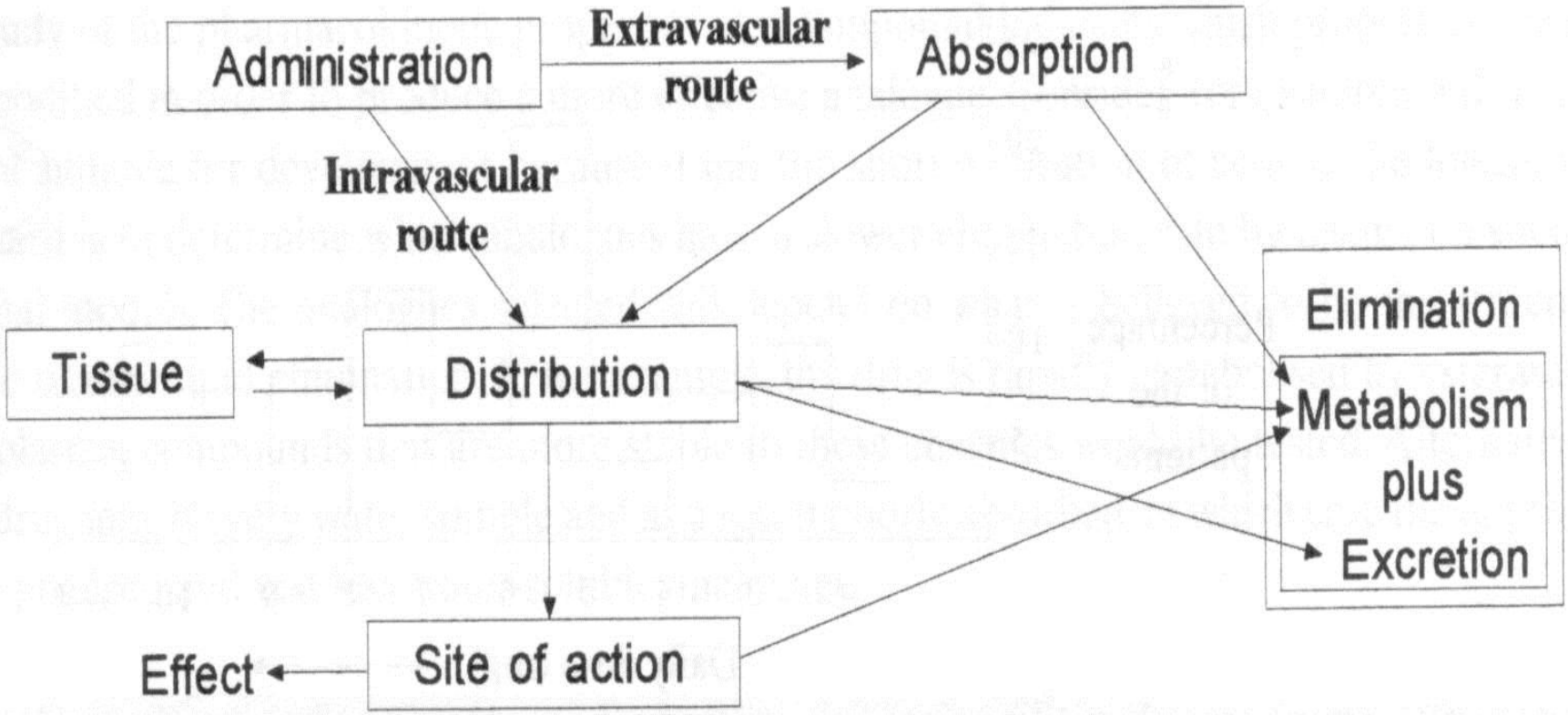
Pharmacokinetics deals with the processes of

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"

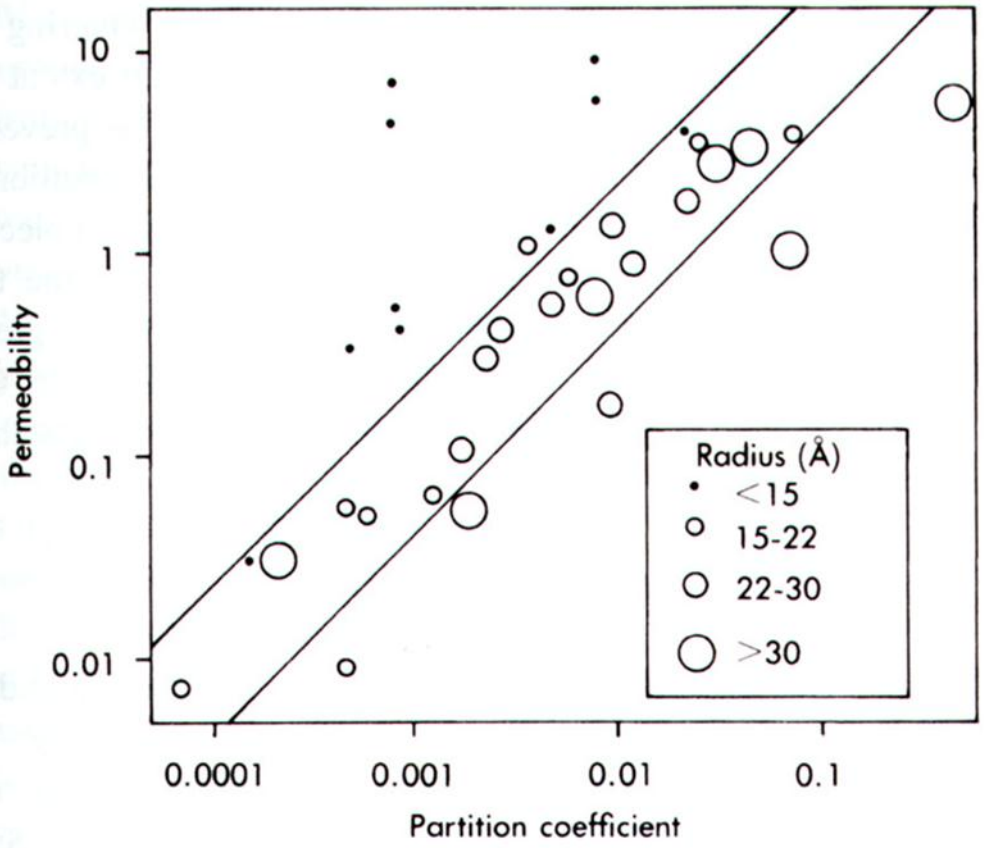


The general stages and their relationships in the life cycle of a drug after administration.

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

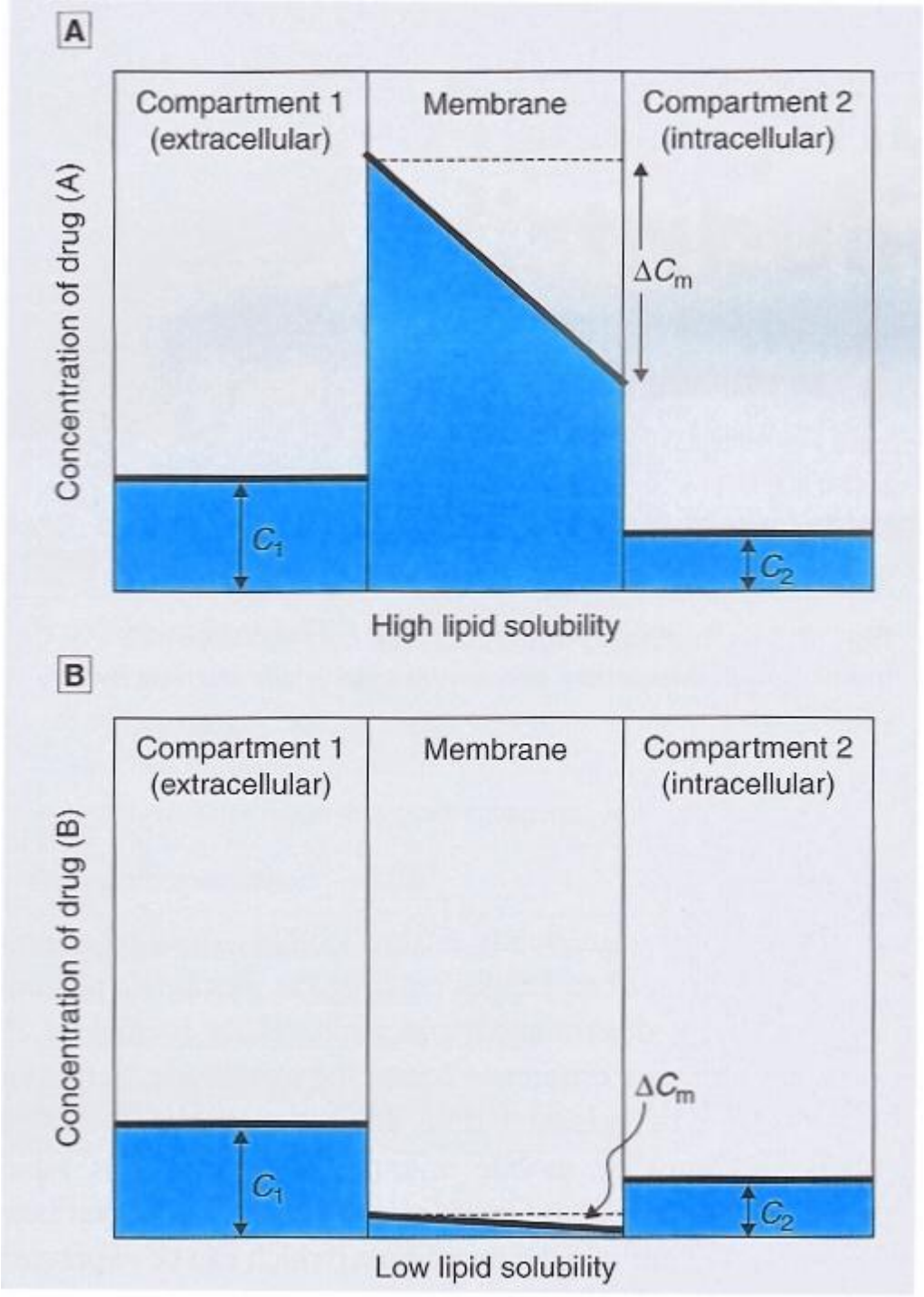
physico-chemical properties

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?

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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

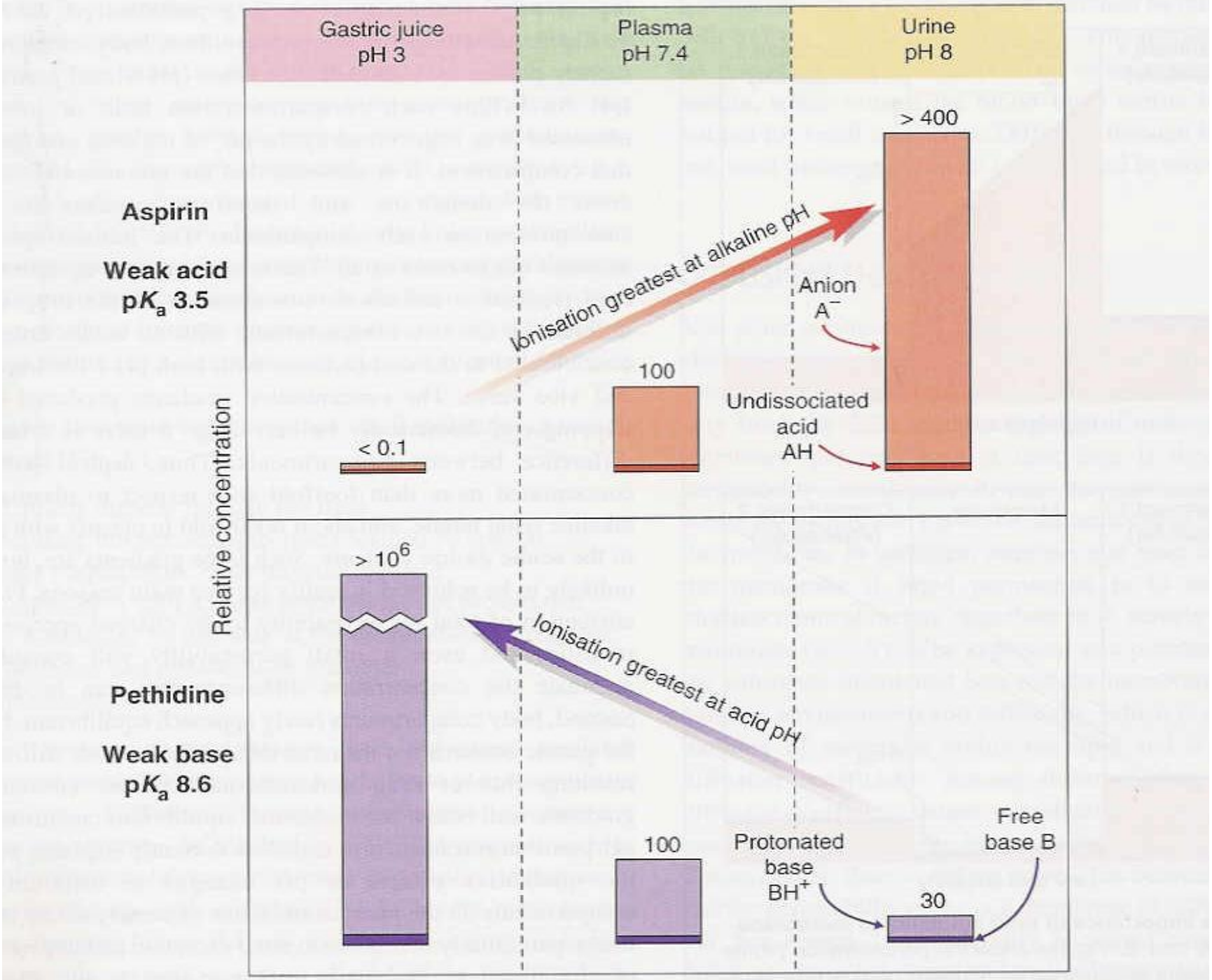
tissue

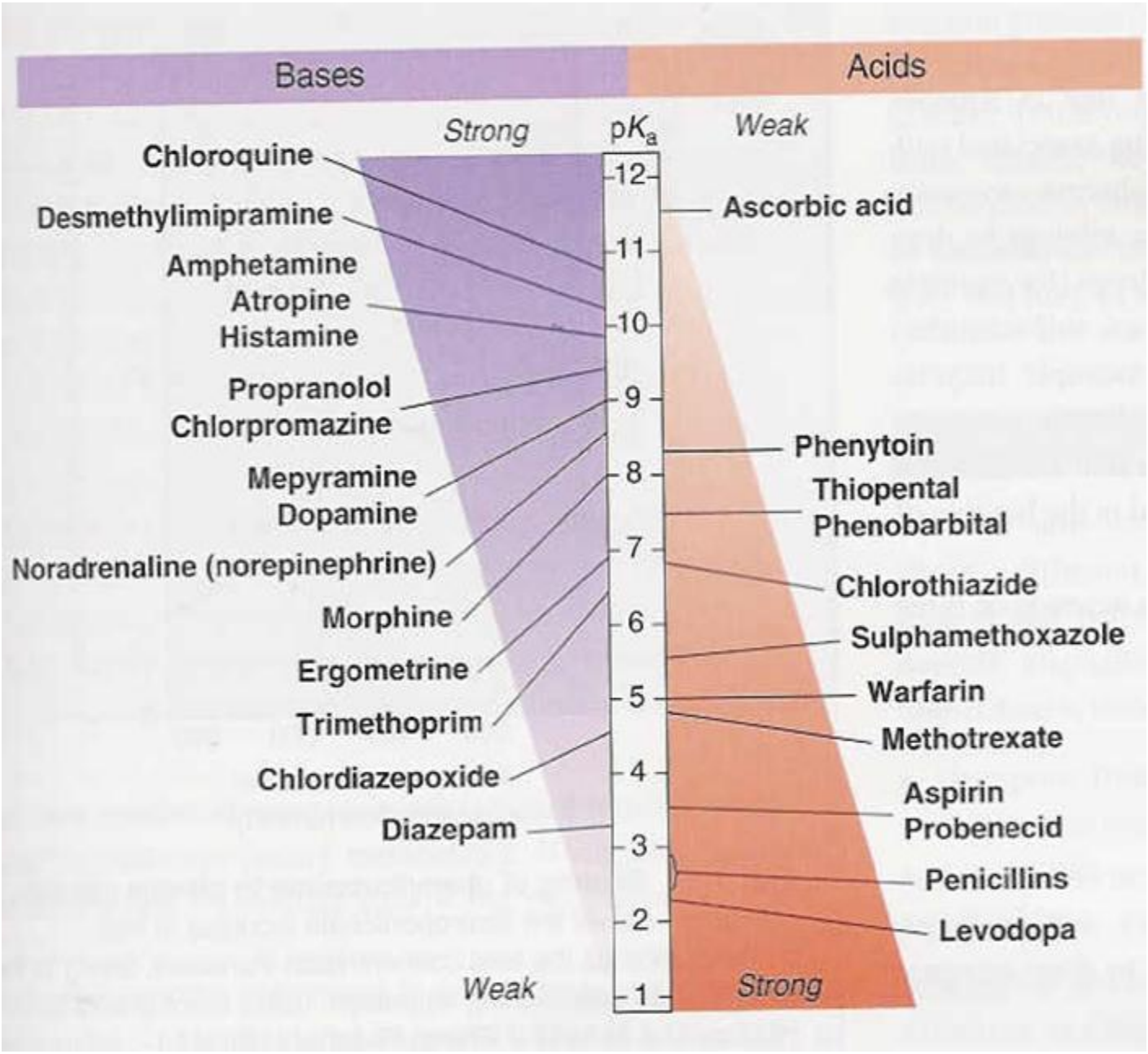
receptors

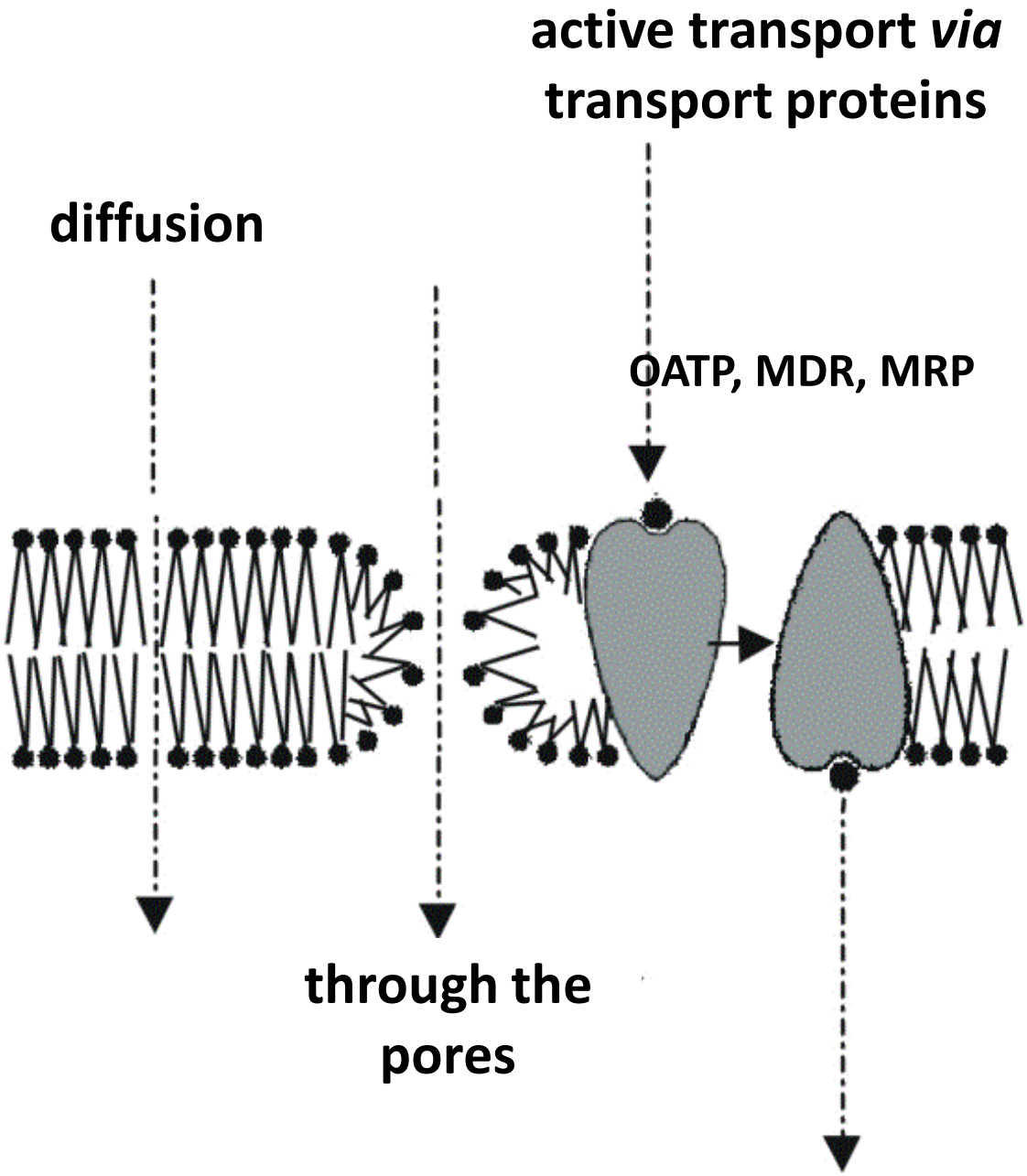
perfusion of the tissues

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
> 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


Bases
Acids
Strong
pKa
Weak
Chloroquine
Desmethylimipramine
Amphetamine
Atropine
Histamine
Propranolol
Chlorpromazine
Mepyramine
Dopamine
Noradrenaline (norepinephrine)
Morphine
Ergometrine
Trimethoprim
Chlordiazepoxide
Diazepam
12
11
10
9
8
7
6
5
4
3
2
1
Ascorbic acid
Phenytoin
Thiopental
Phenobarbital
Chlorothiazide
Sulphamethoxazole
Warfarin
Methotrexate
Aspirin
Probenecid
Penicillins
Levodopa
Weak
Strong


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

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

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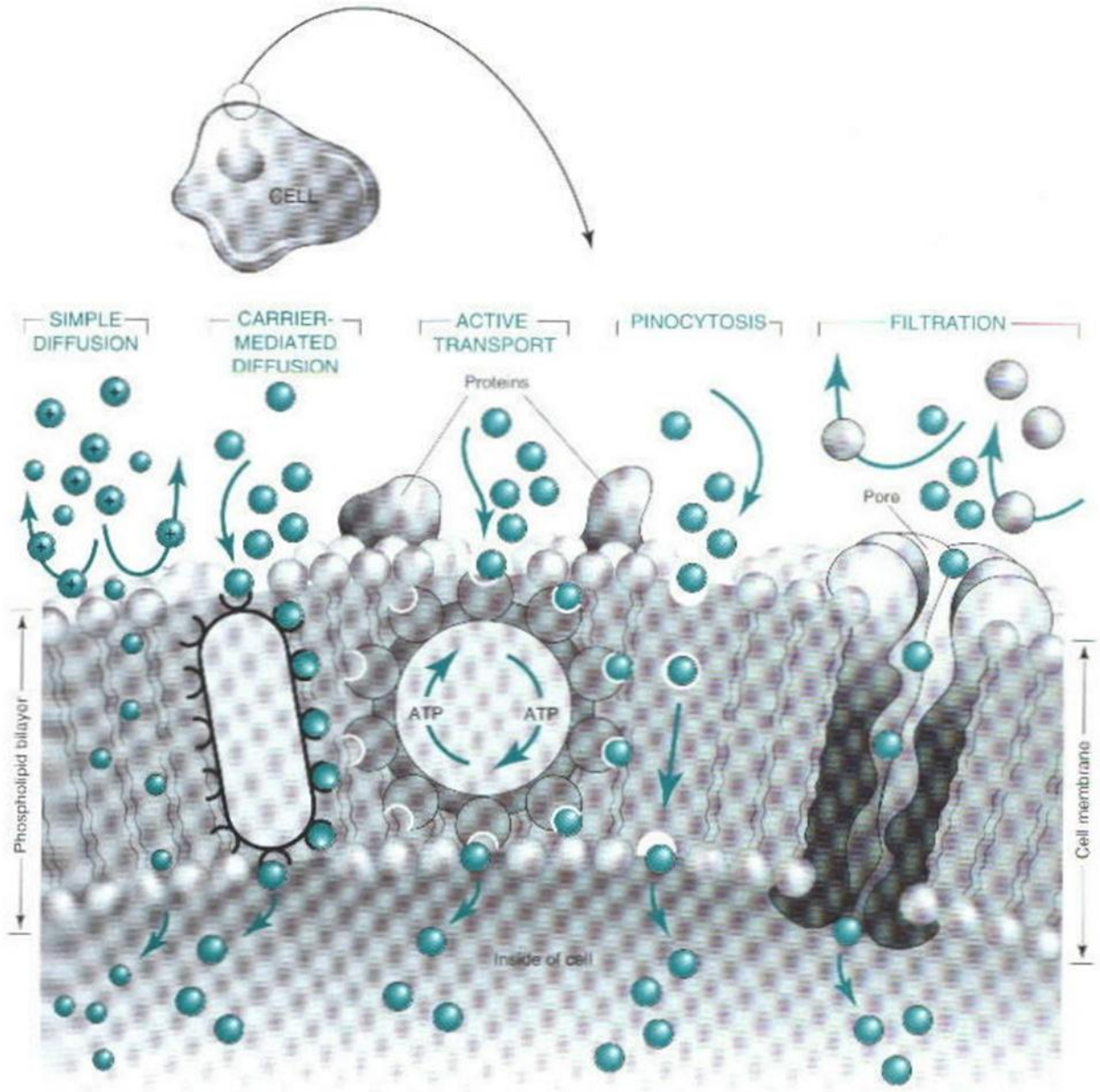
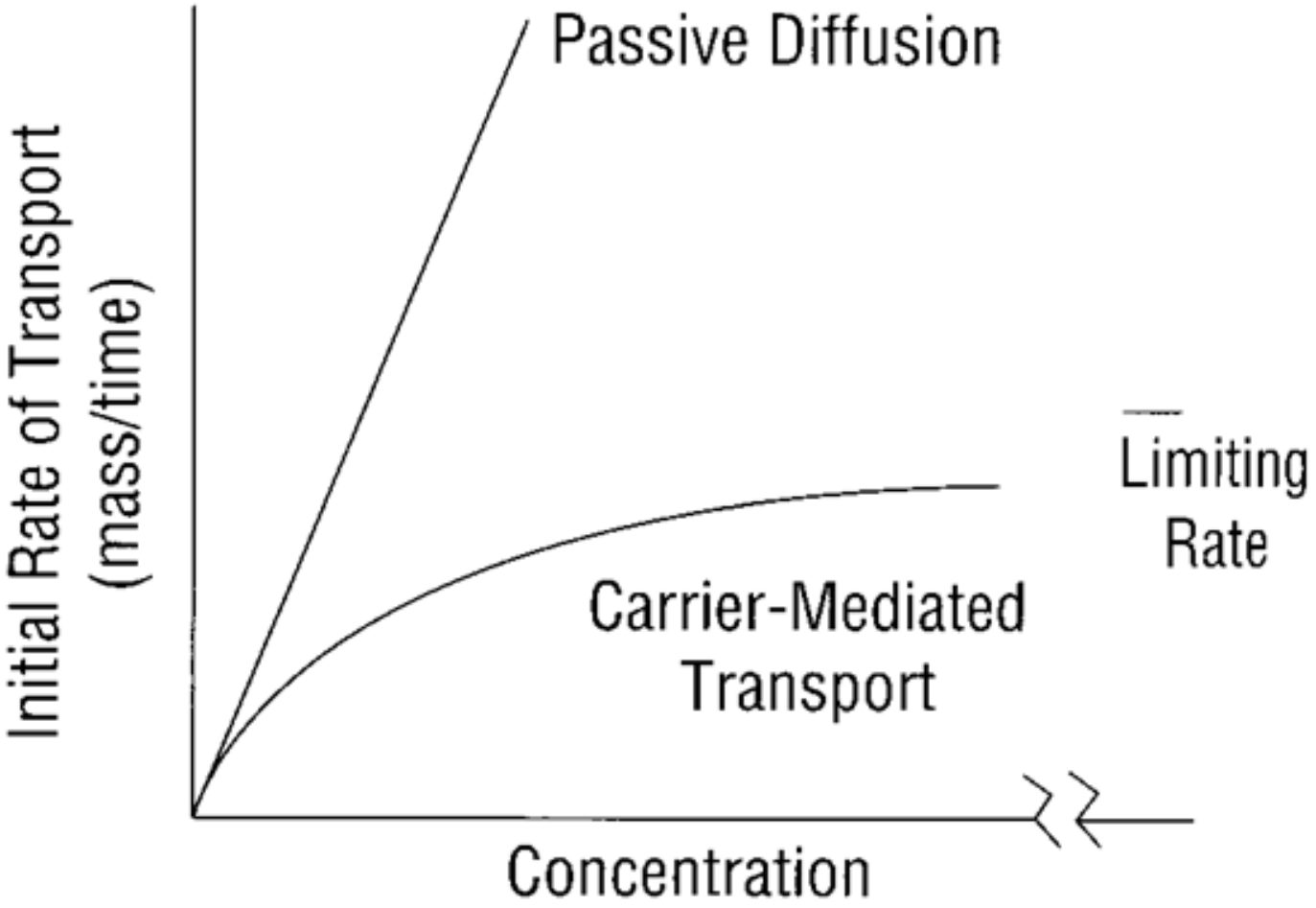
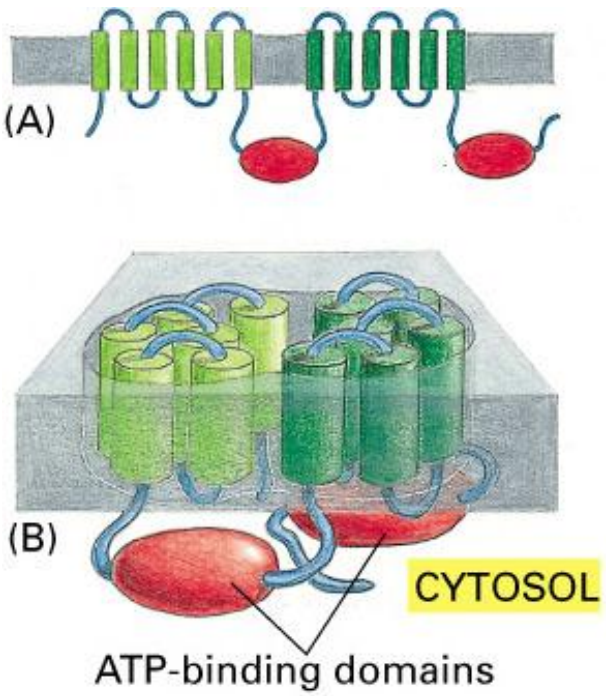
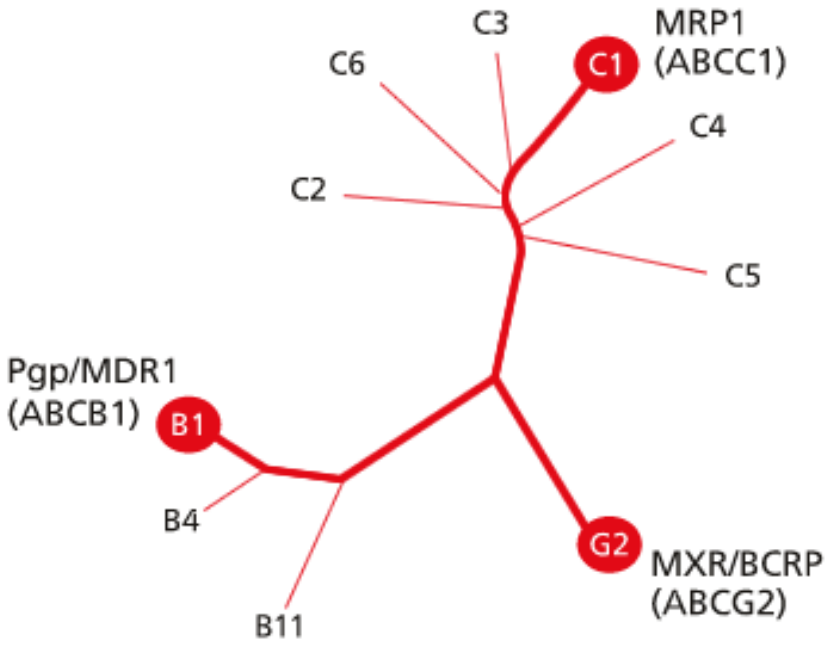

CELL
SIMPLE DIFFUSION
CARRIER-MEDIATED DIFFUSION
ACTIVE TRANSPORT
PINOCYTOSIS
FILTRATION
Proteins
Pore
ATP
ATP
Phospholipid bilayer
Cell membrane
Inside of cell


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**

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bonds of the drug

plasma prot

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blood cells in t

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perfusion of the tissues

a) brain, heart, liver, kidney

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A bound drug has no effect !!!

- 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)

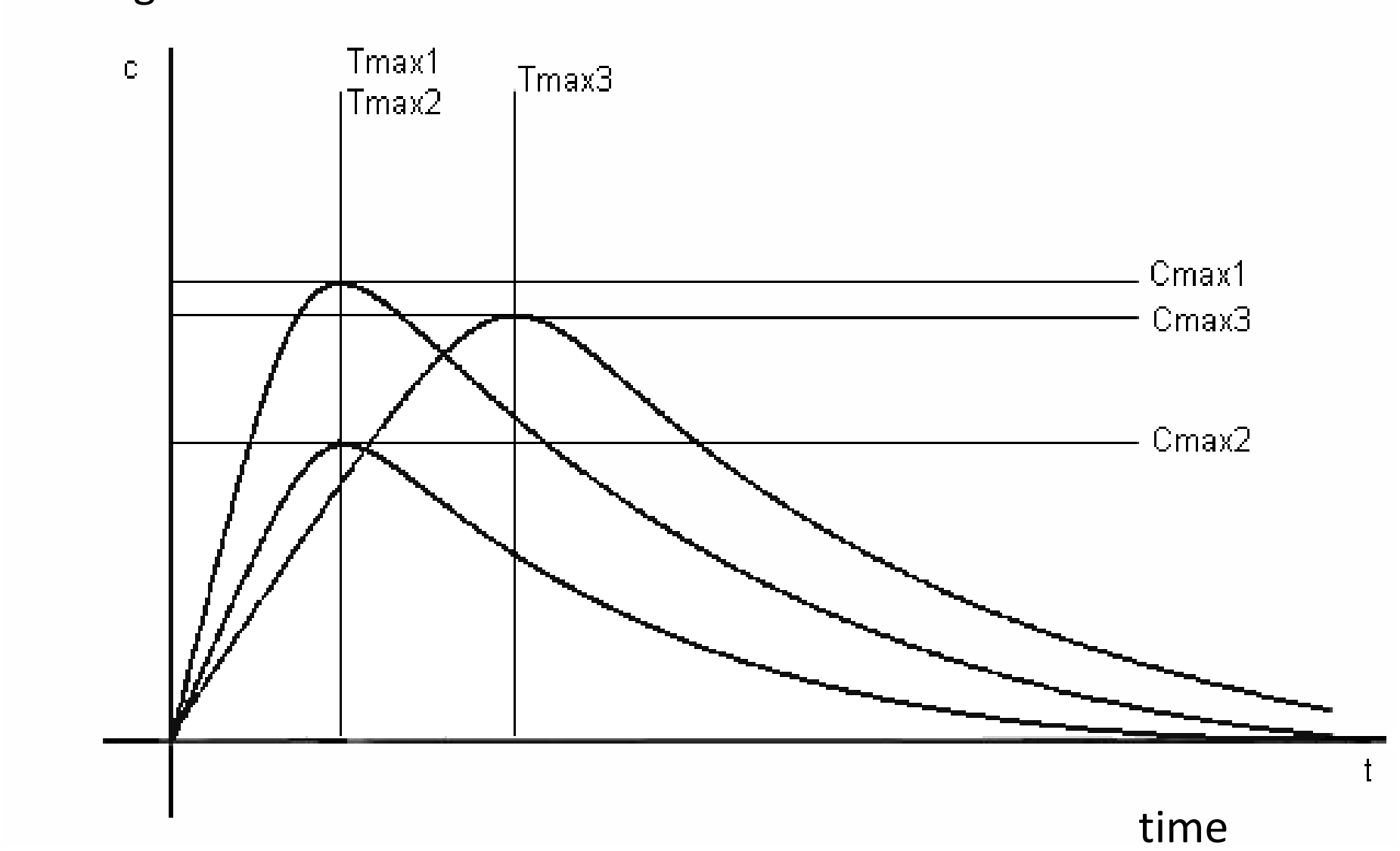
Rate and extent of absorption are described by the parameters :

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

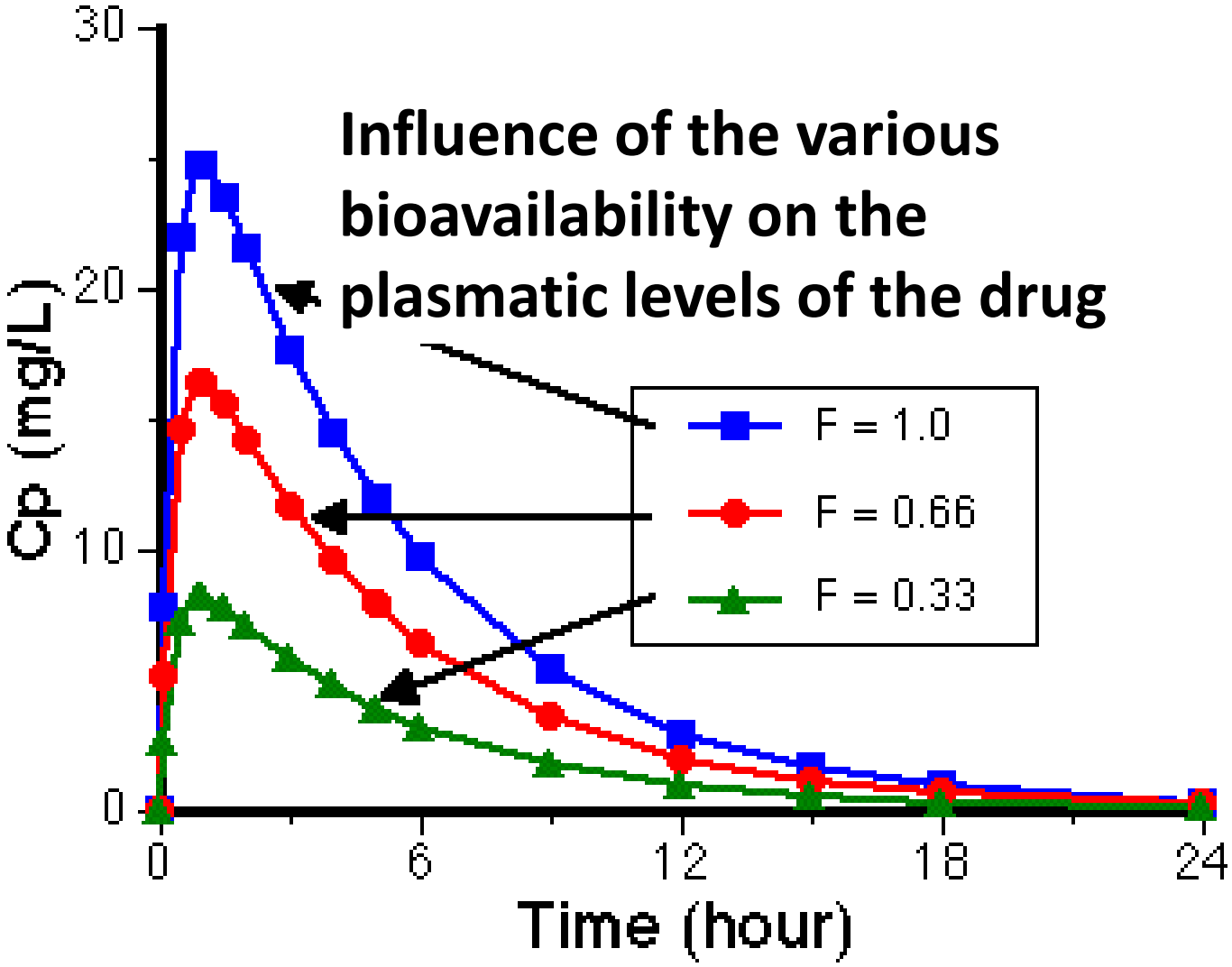
(in spite of that fact, some drugs are administered, even if the F < 2-5 %, such as SET, bisphosphonates).

F = AUCpo/AUCiv

(the same drug, same dose, same patient)

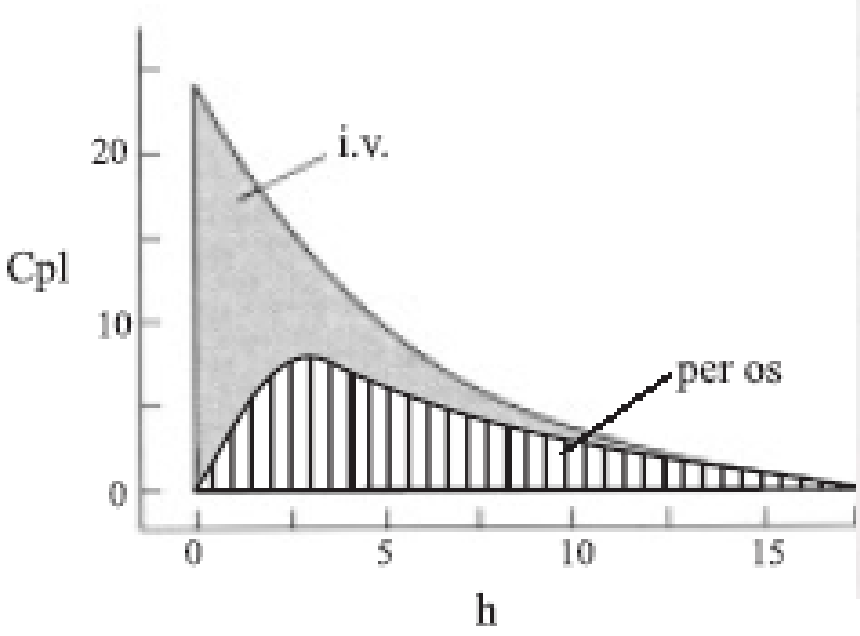
Bioavailability

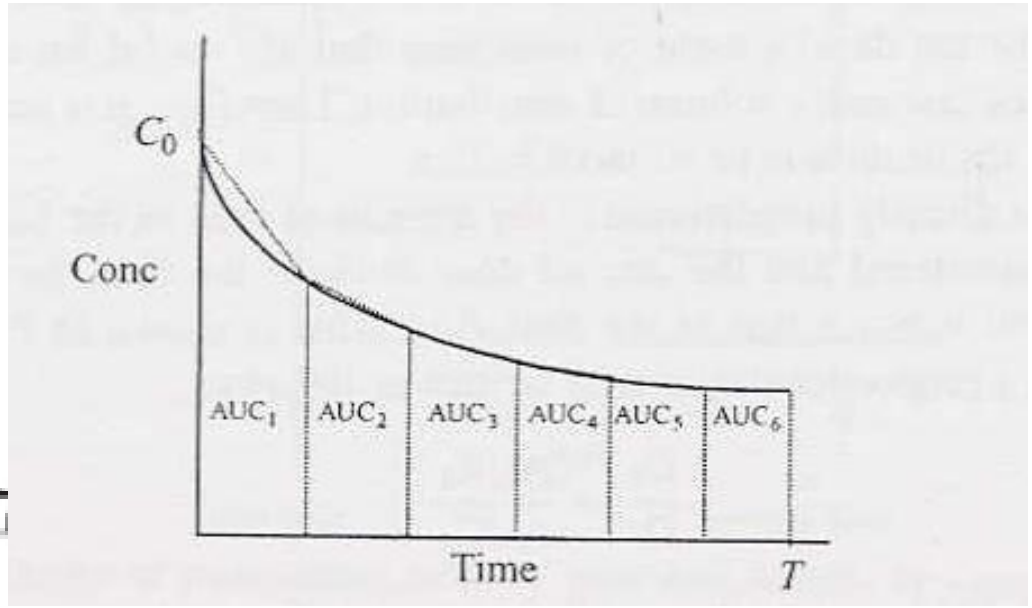
- A concept for oral (extravascular) administration
- Useful to compare two different drugs or different dosage forms of same drug
- depends, in part, on rate of dissolution (which in turn is dependent on chemical structure, pH, partition coefficient, surface area of absorbing region, etc.) Also first-pass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

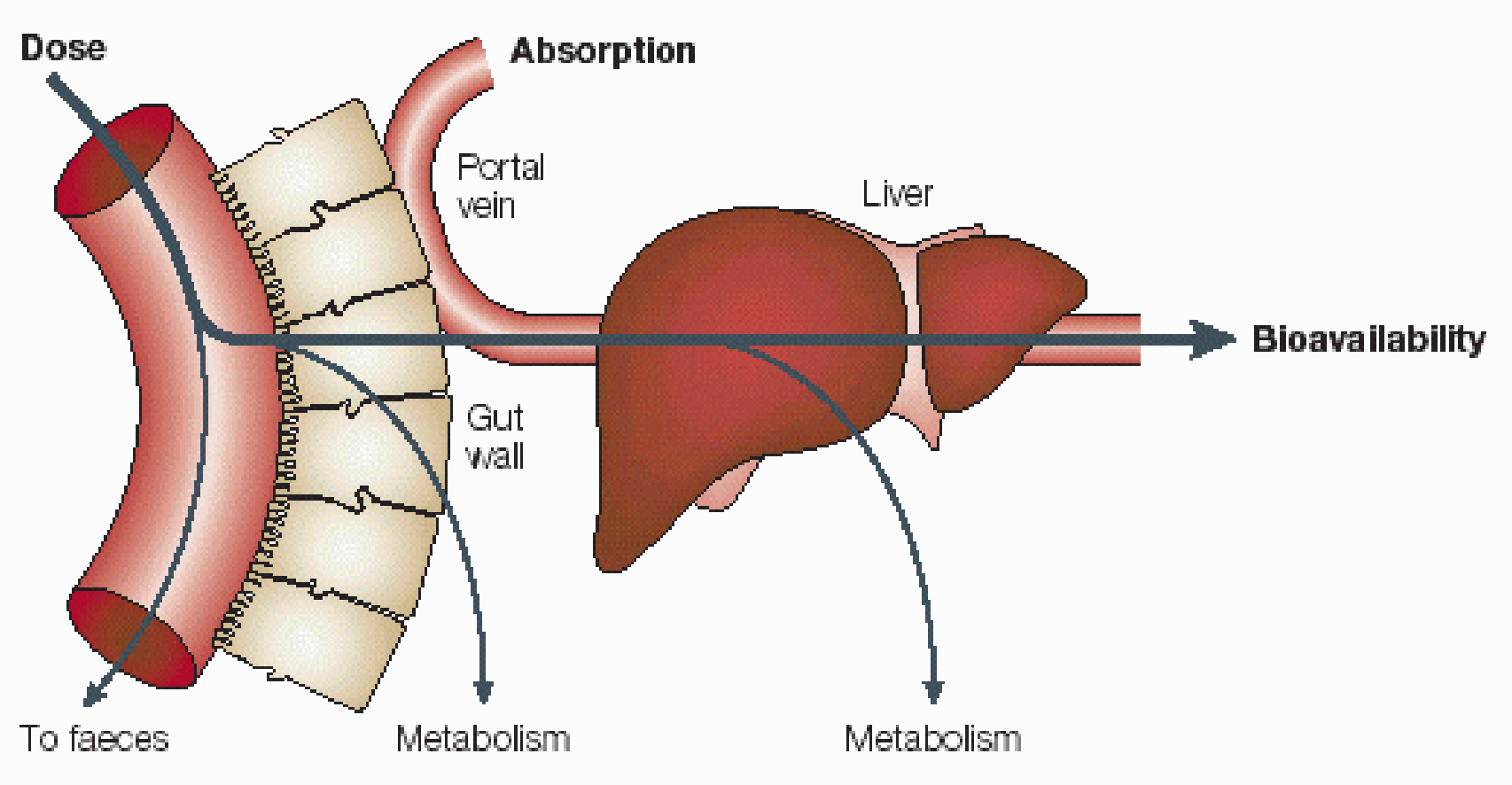
Area under curve (AUC)

- Is a measure of bioavailability





First pass effect, presysthemic elimination

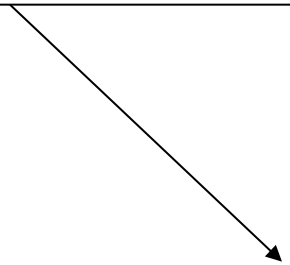


Factors influencing absorption

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

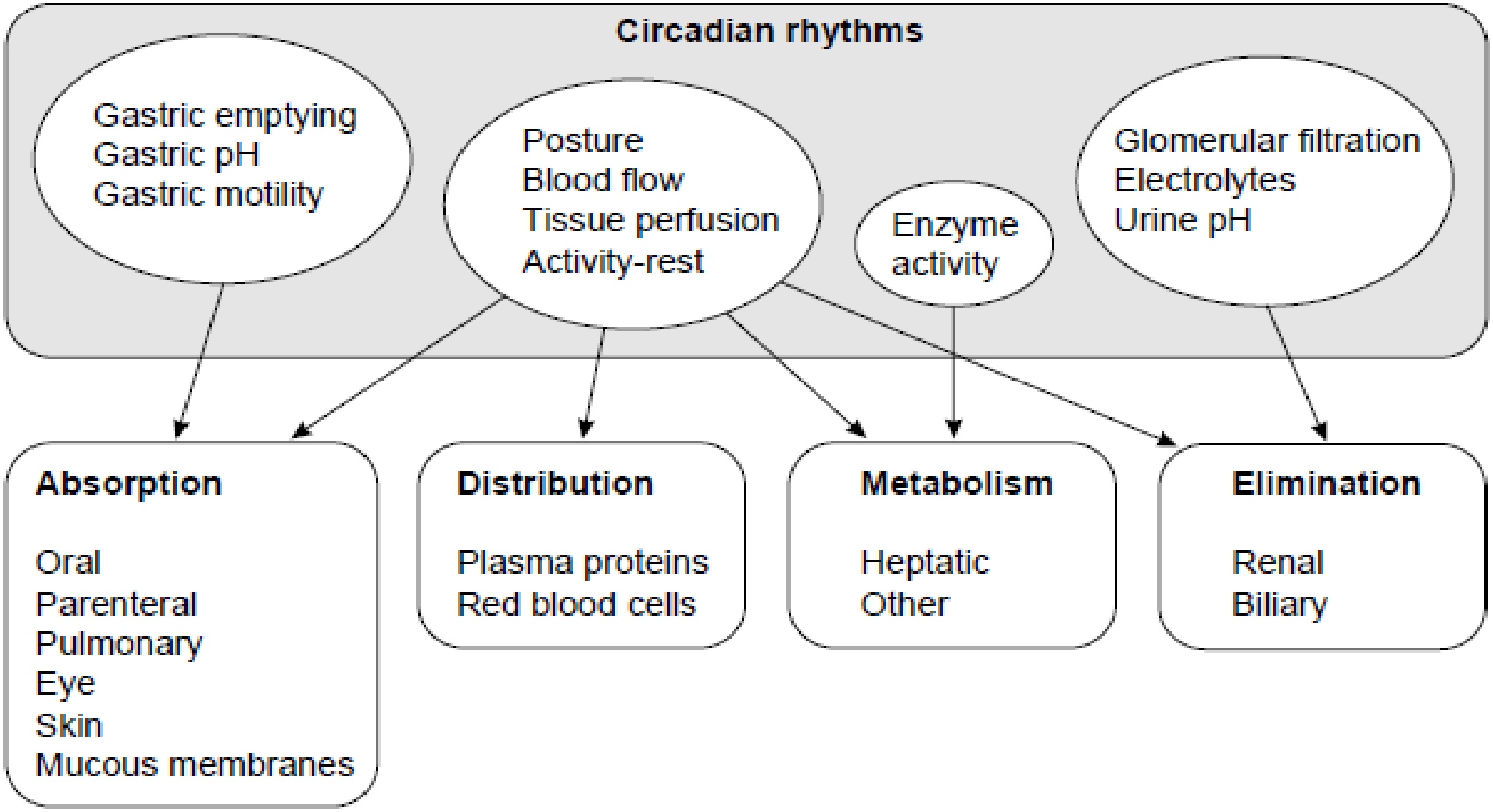
simultaneously eaten meal –

acceleration/decelaration

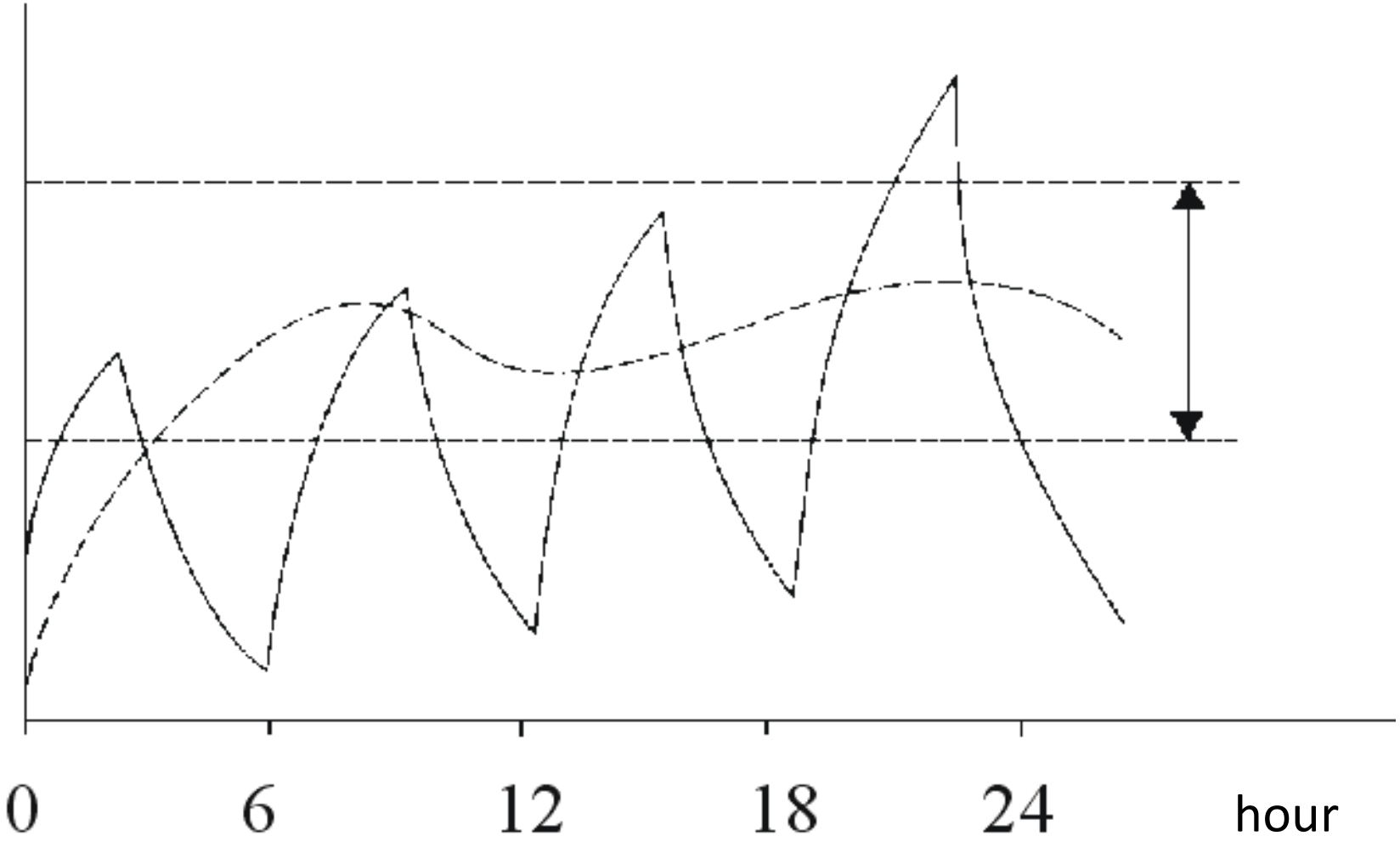
chemical incompatibilities

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

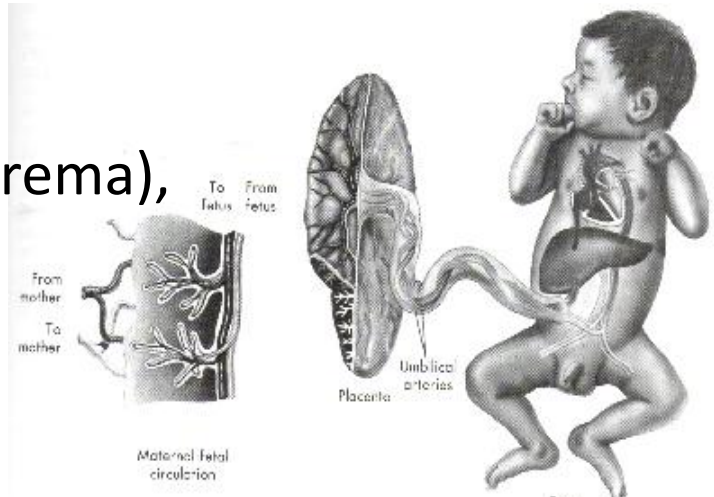
state - distribution equilibrium; the the proportion of the free (unbounded) fractions of the drug in the blood and in the tissues are the same

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

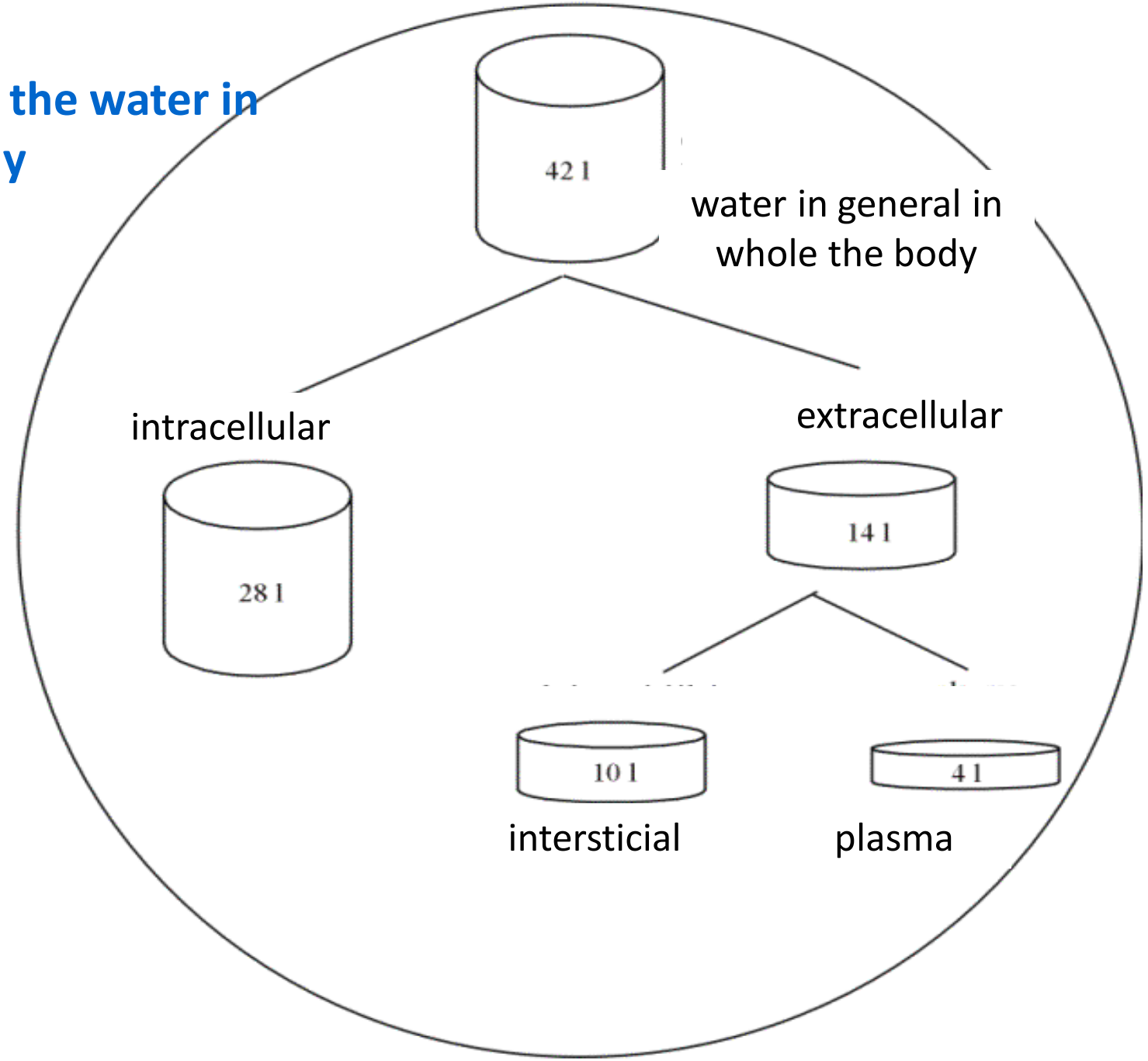
$V_d = D/C$

- 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

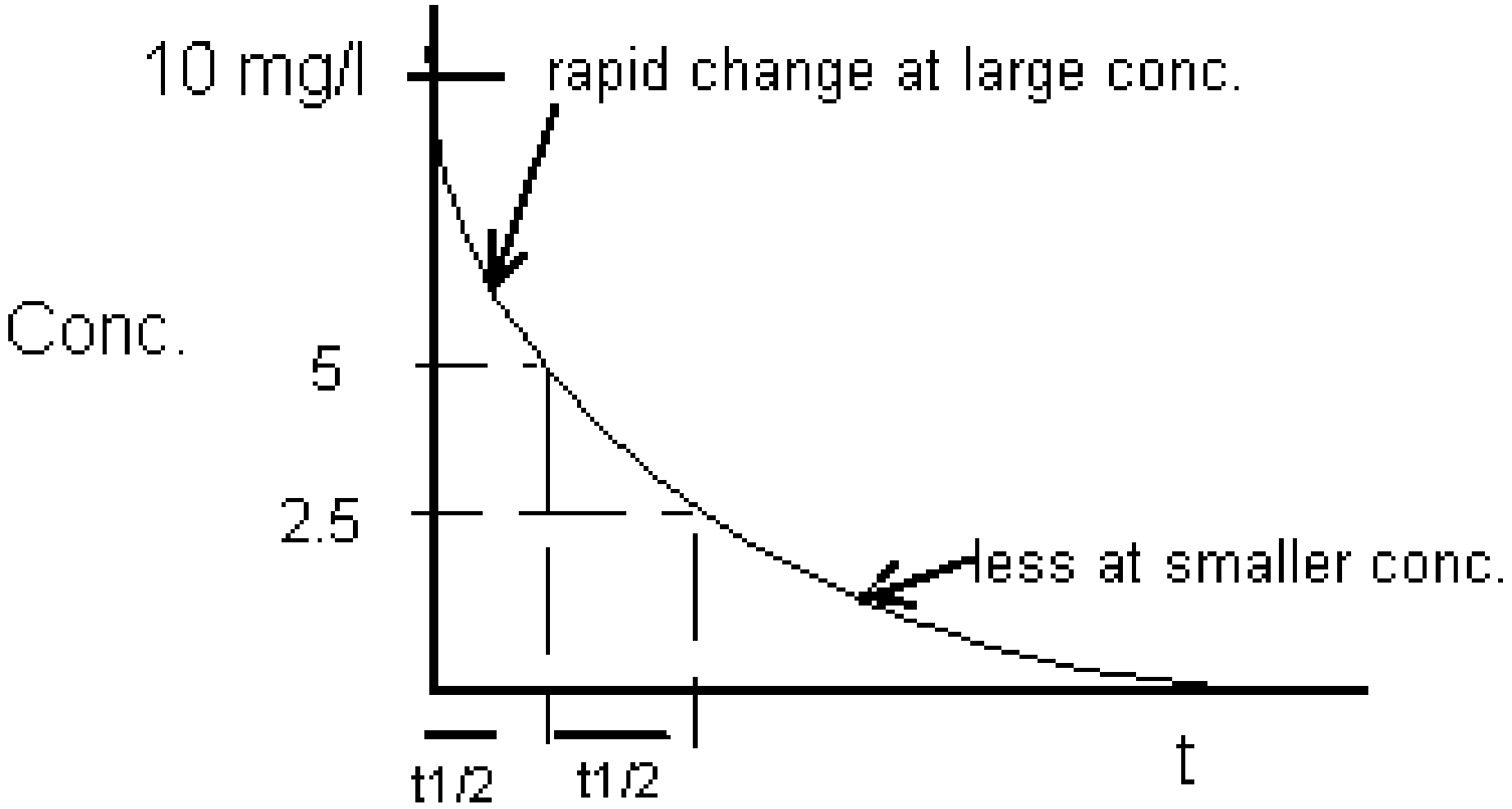
- C vs. t graph is LINEAR

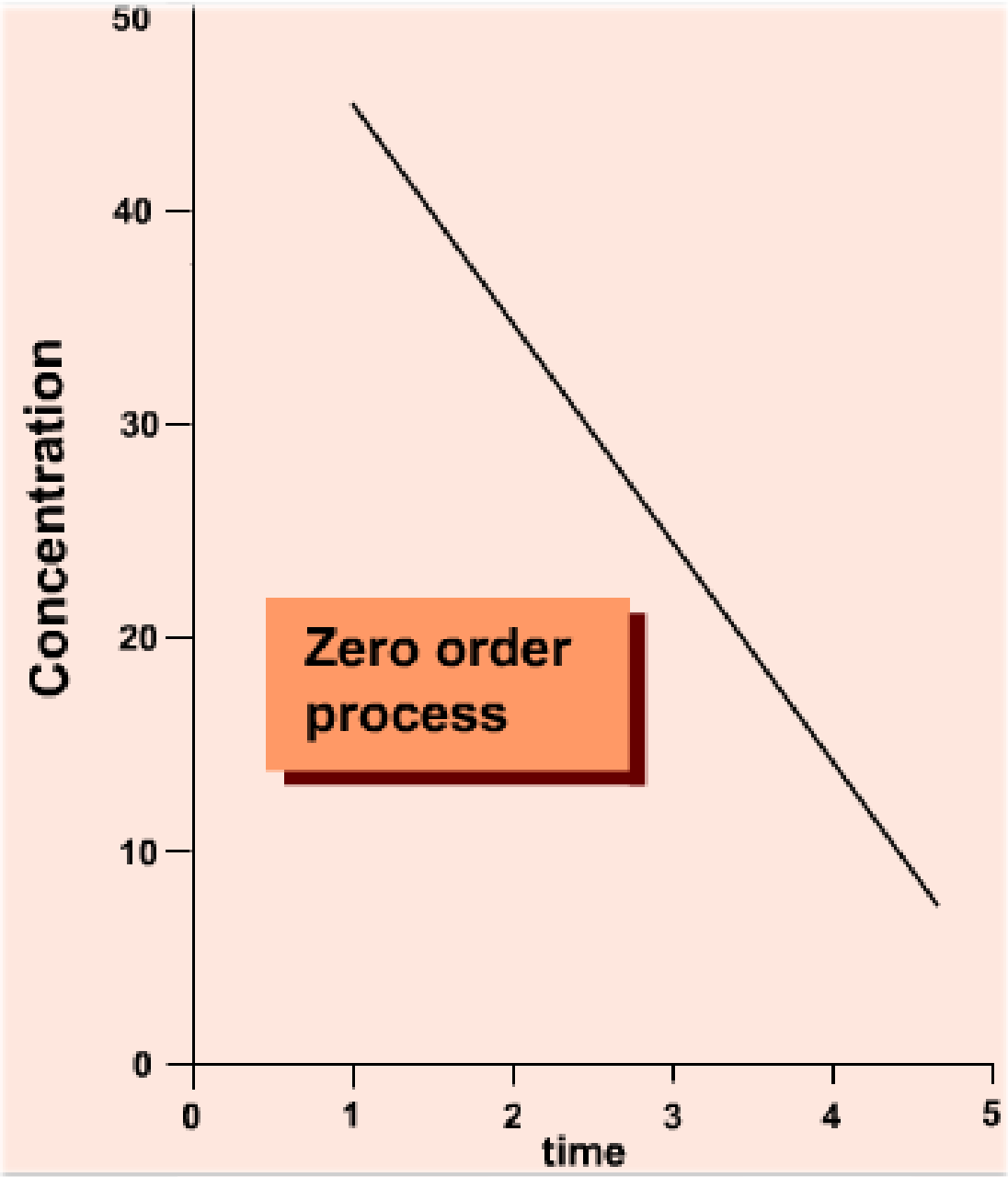
First Order Kinetics

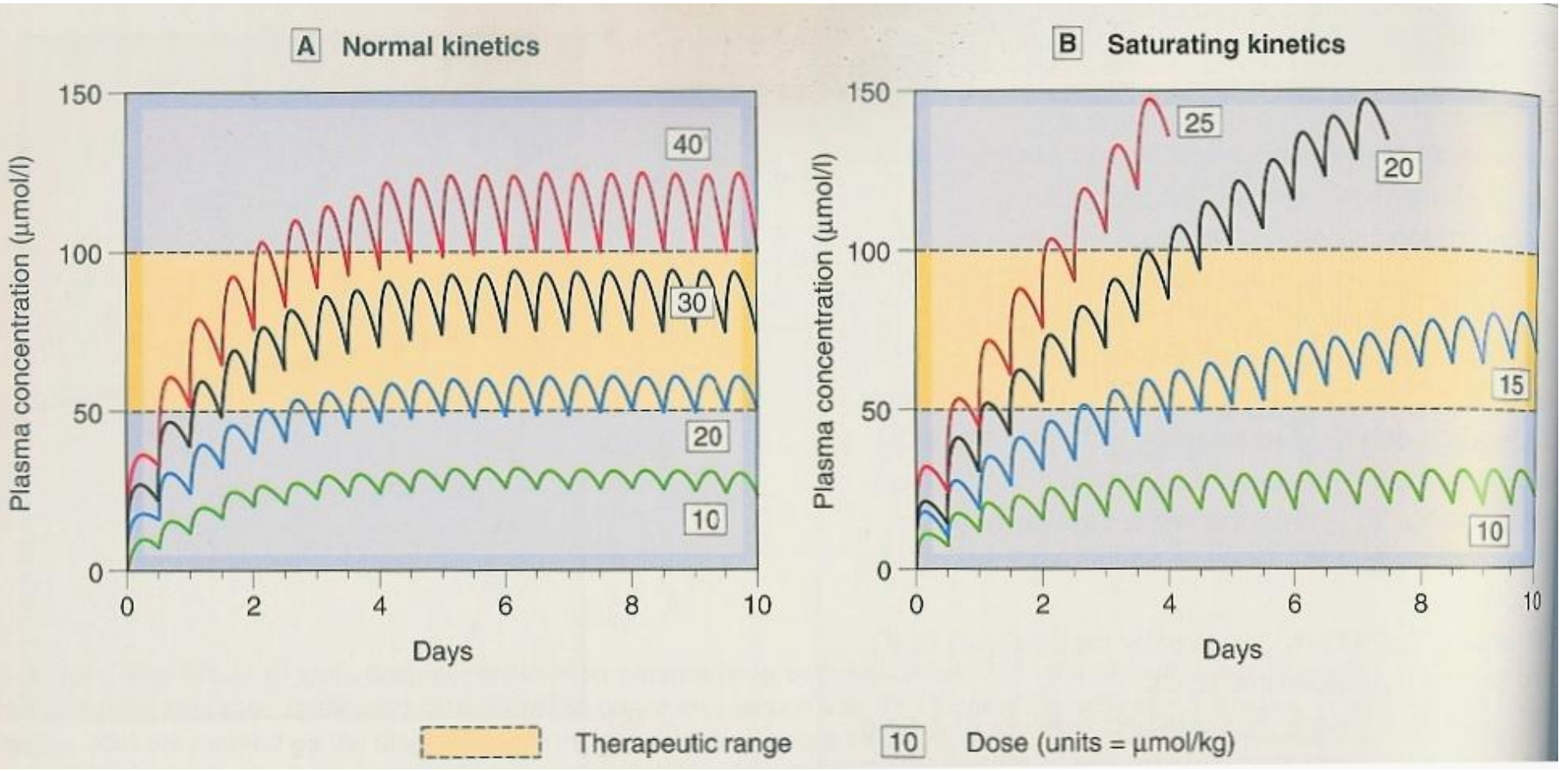
- Rate = k C
- $C = C_o e^{-kt}$

- 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

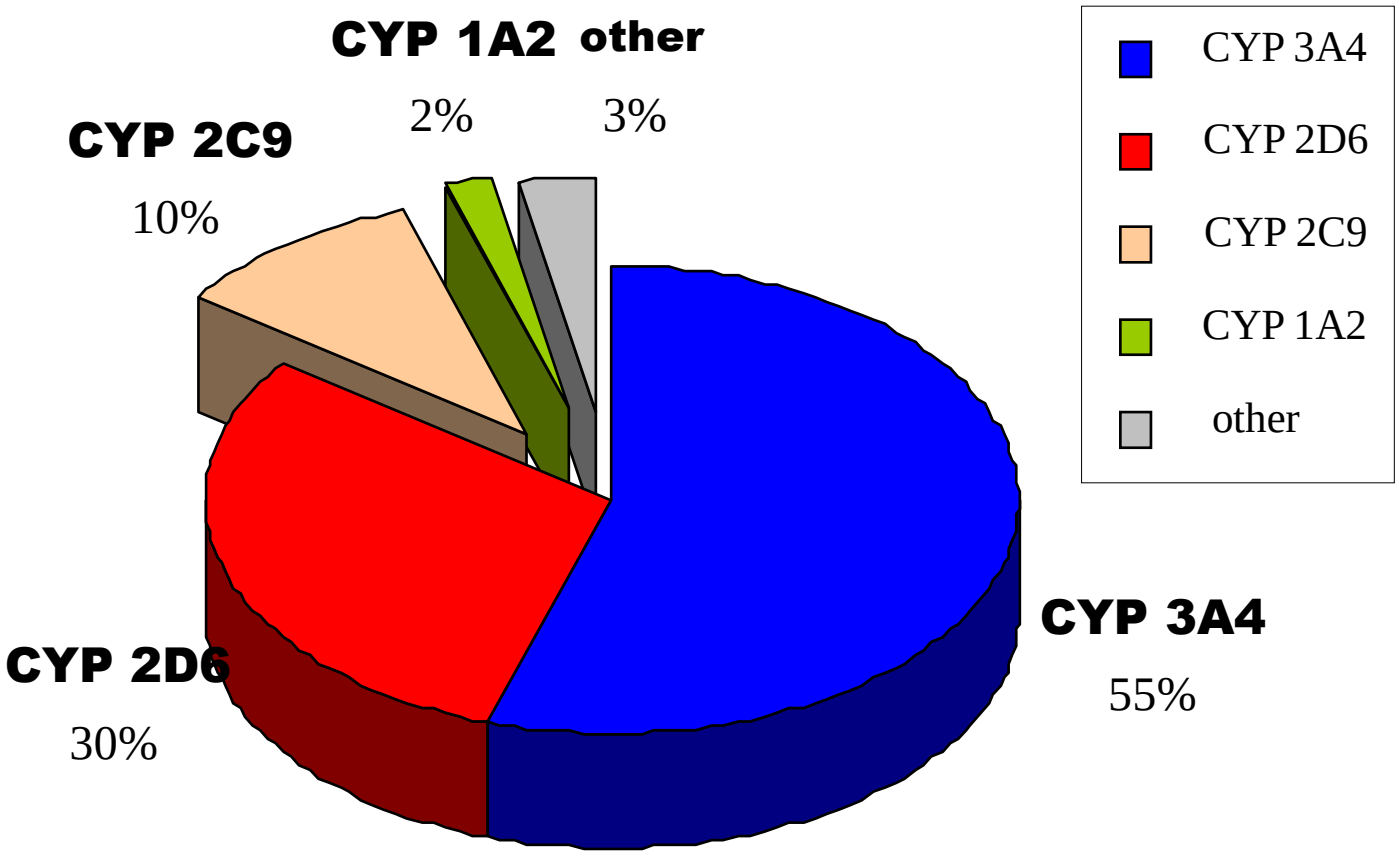
Cytochrome P450, dehydrogenases

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

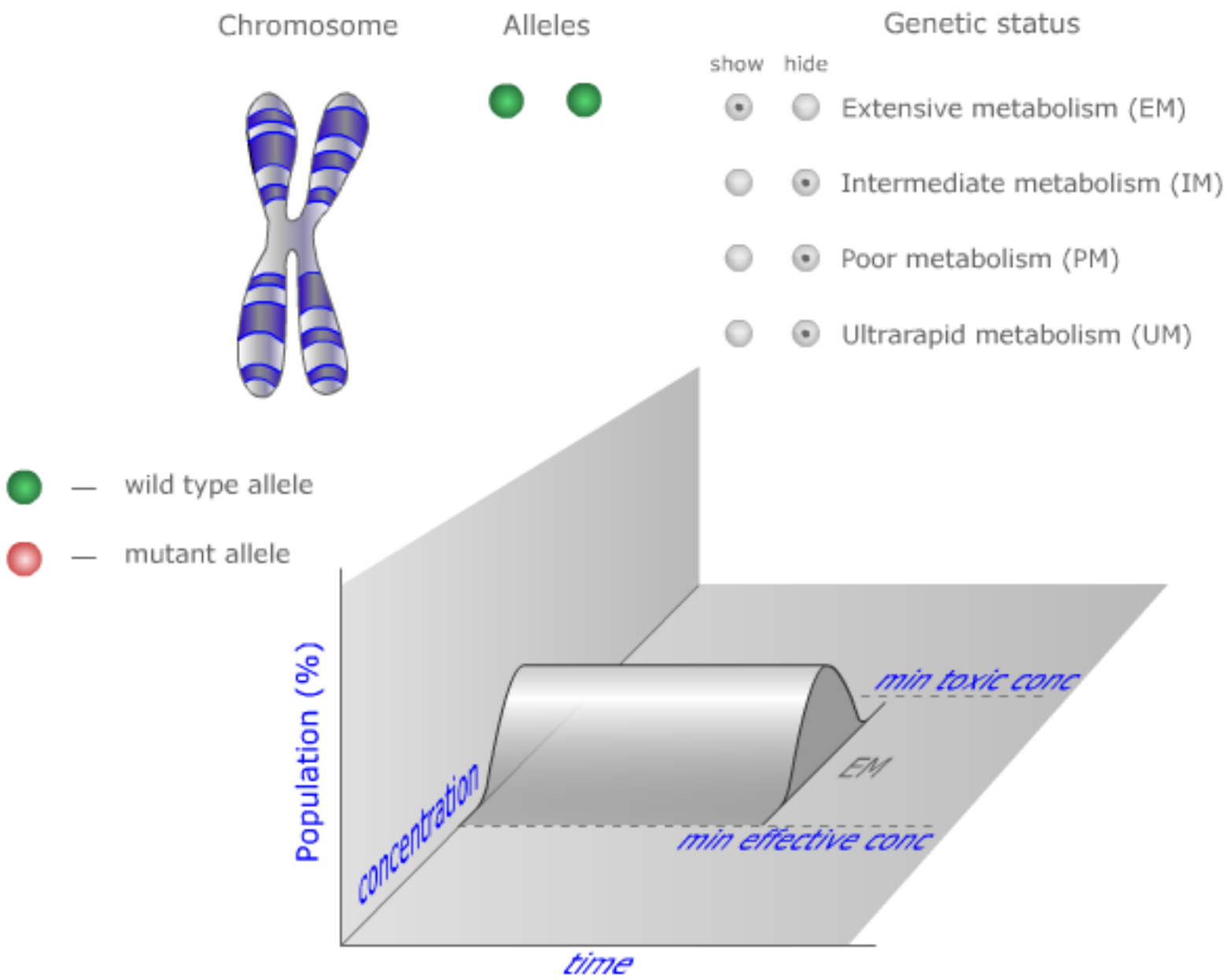
Metabolite - effective („more / less / in other way“)

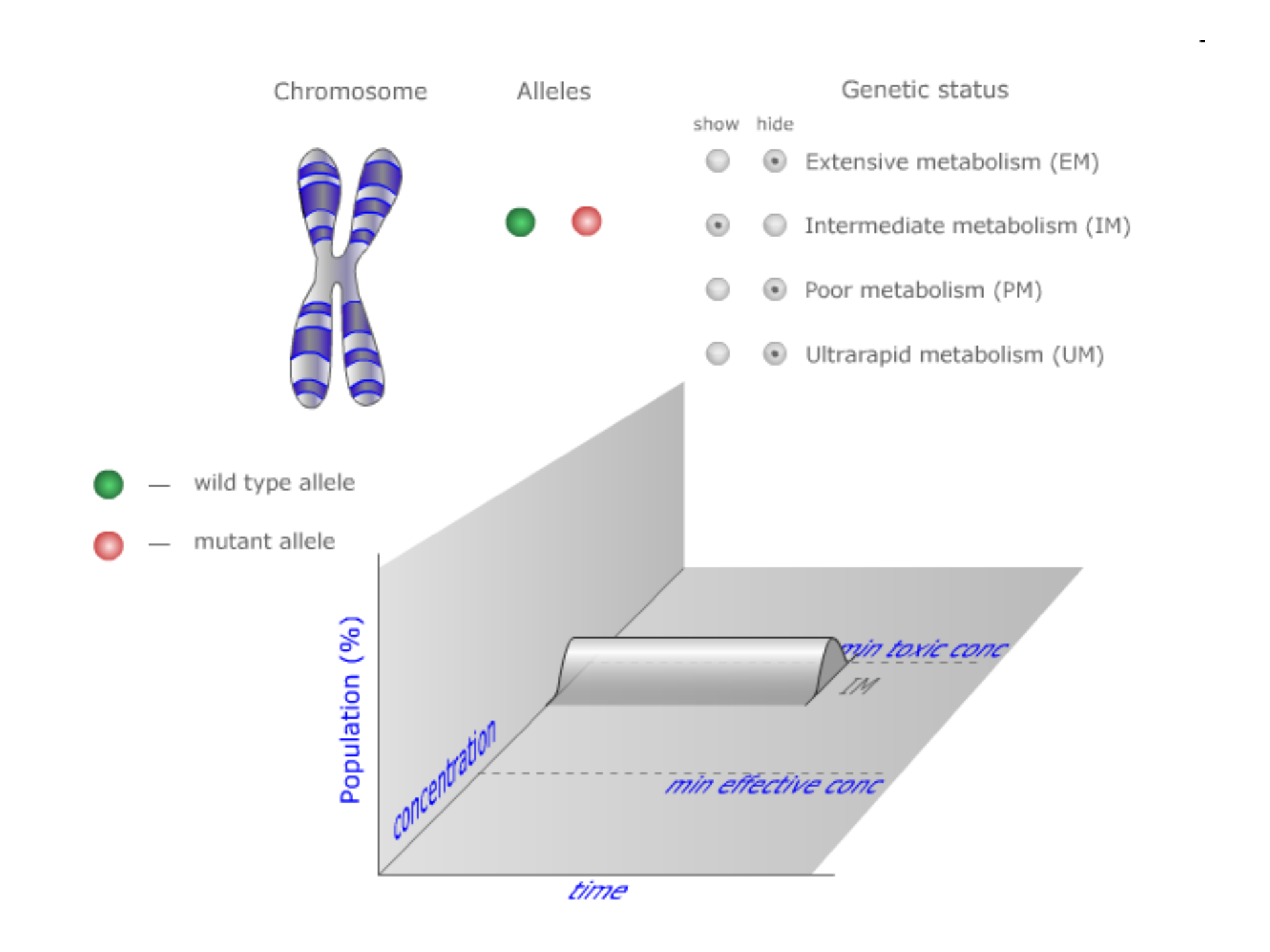
- ineffective

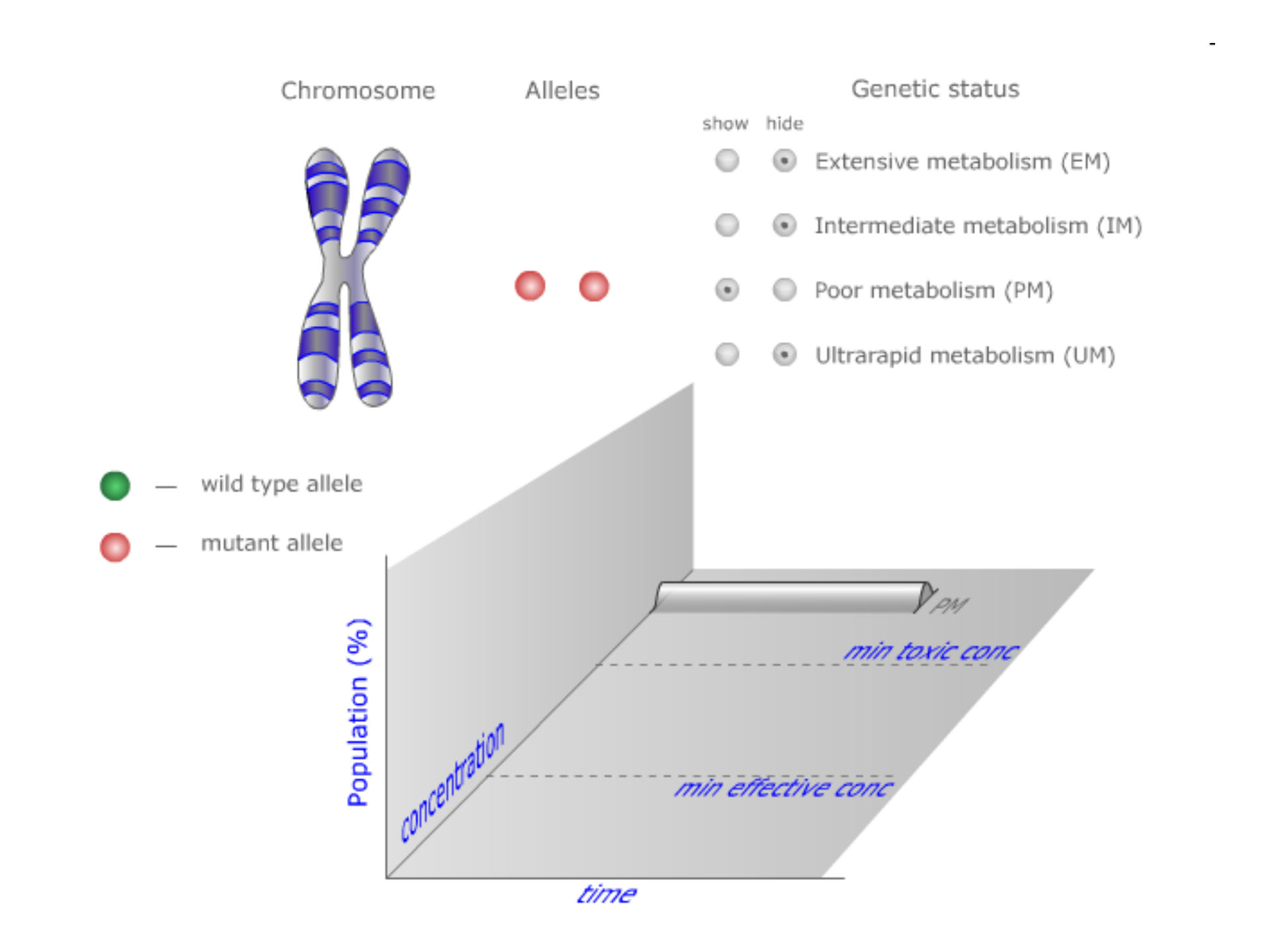
- toxic


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

Genetic polymorfism of CYP 450




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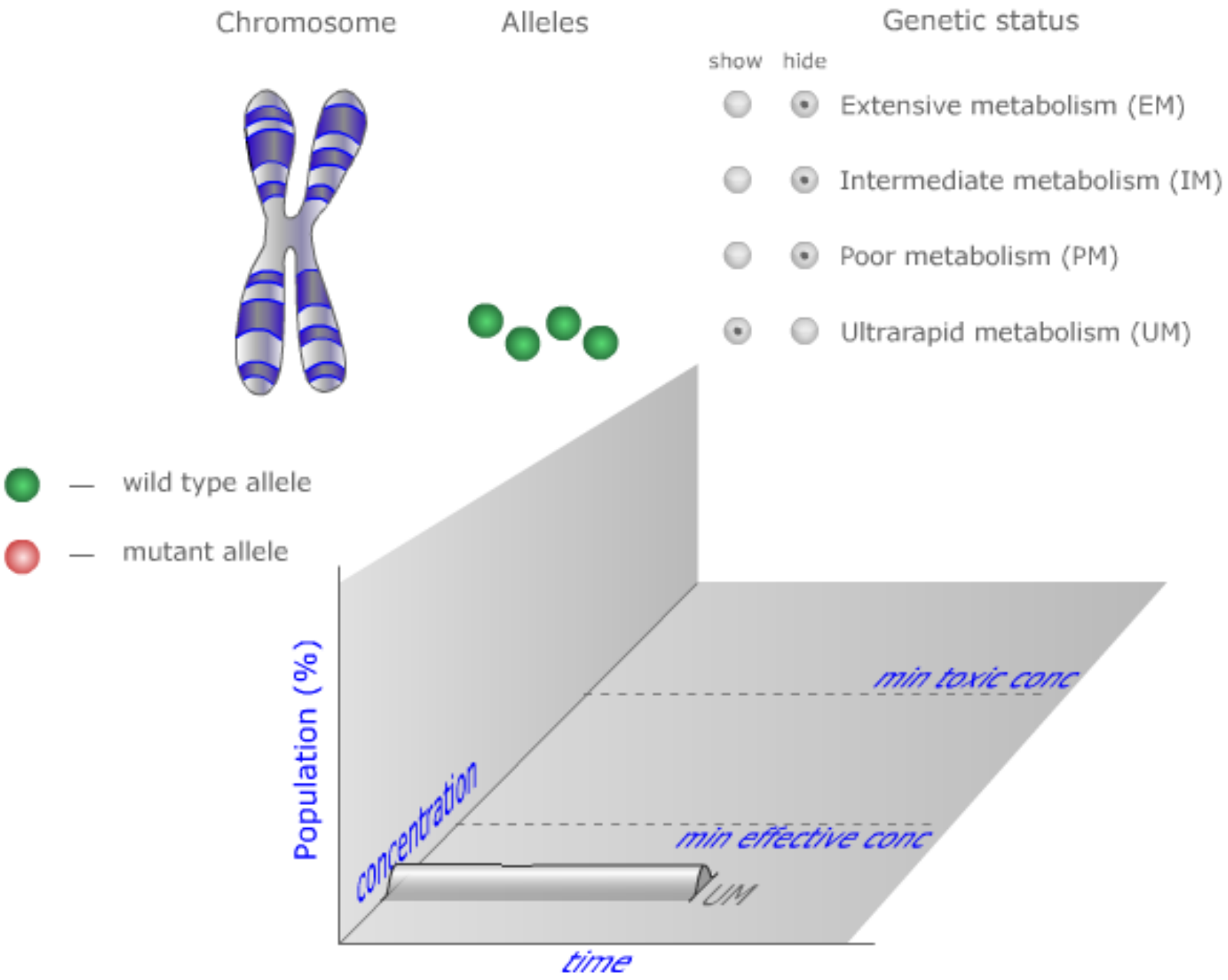
— wild type allele
— mutant allele
Population (%)
concentration
time
PM
min toxic conc
min effective conc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Population (%)
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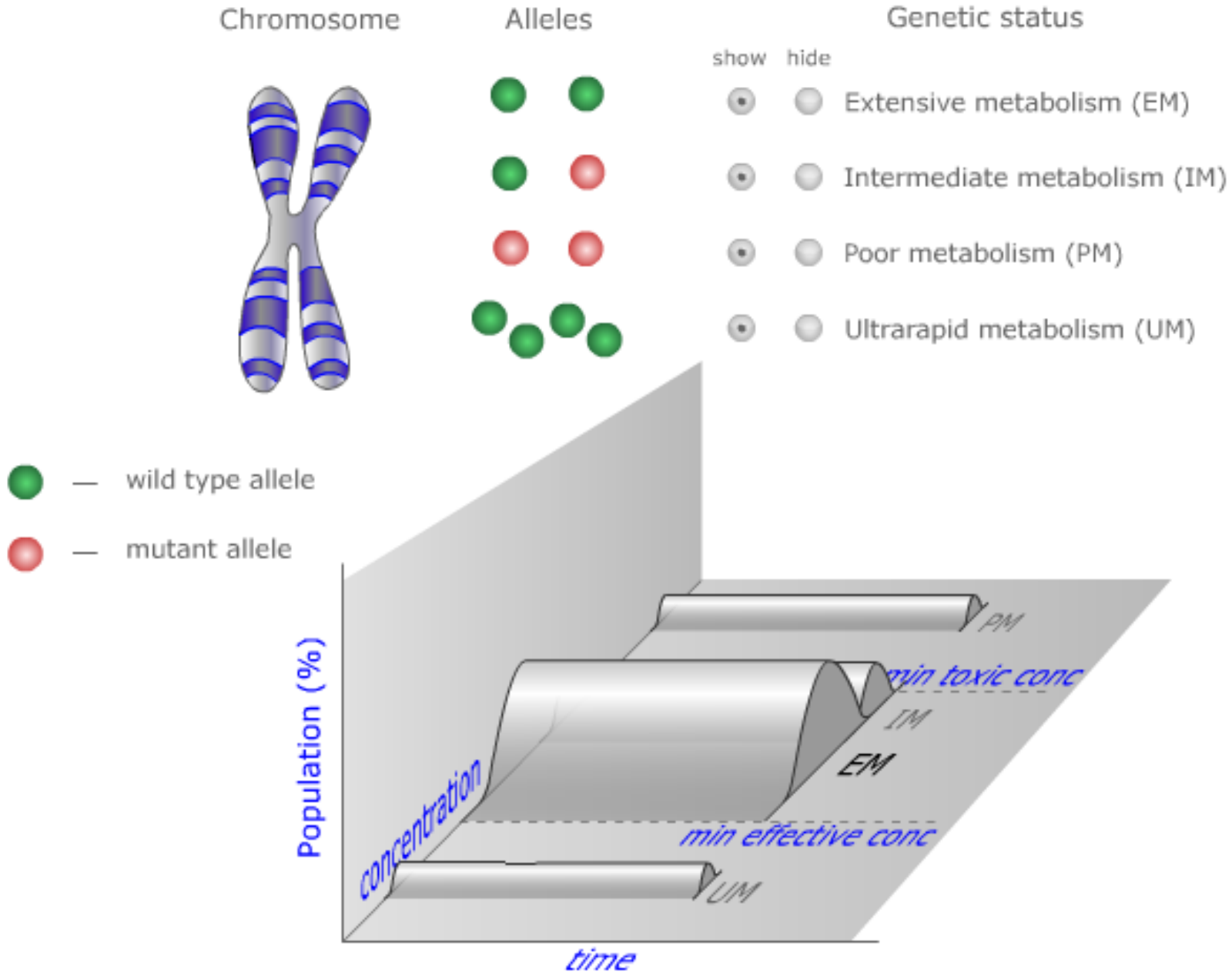
min toxic conc
min effective conc
UM
time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Intermediate metabolism (IM)
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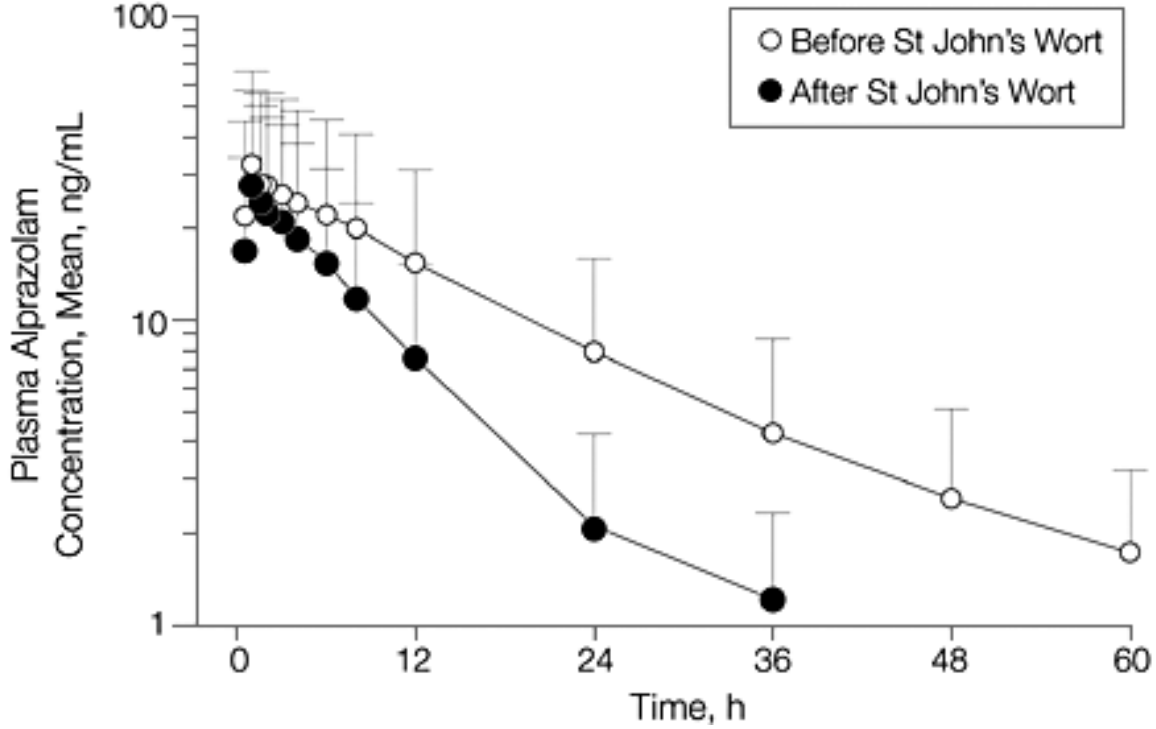
Ultrarapid metabolism (UM)
— wild type allele
— mutant allele
Population (%)
concentration
time
PM
min toxic conc
IM
EM
min effective conc
UM

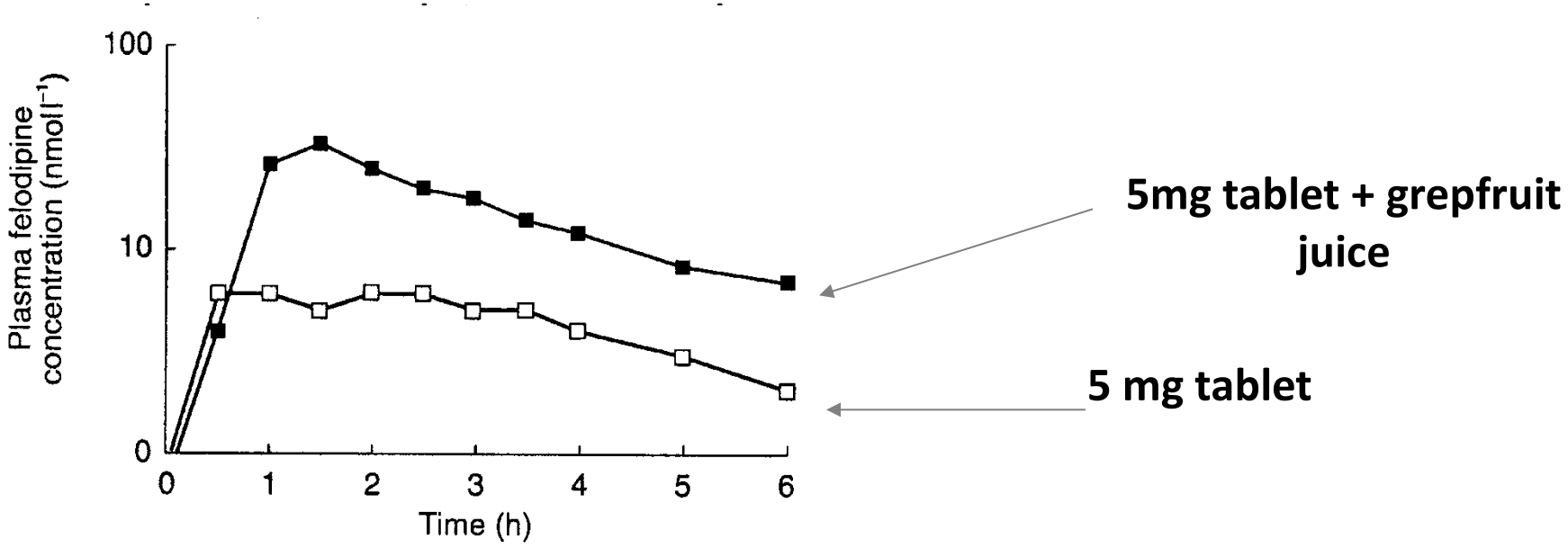
INDUCERS of CYP 450

- 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	$-CH_2CHCH_3 \rightarrow -CHCOCH_3 + NH_3$ (with 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 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

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

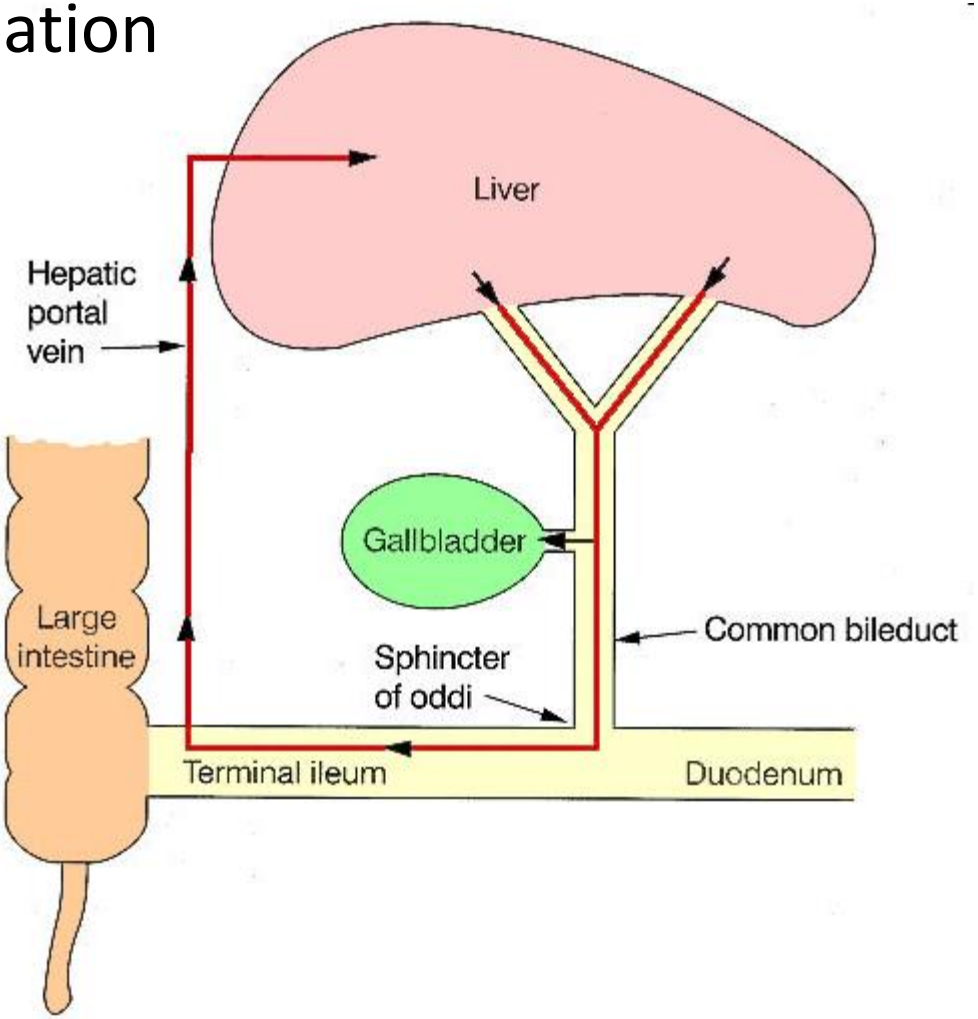
alcalization

sodium bicarbonate

Liver

Billiar excretion, clearance.

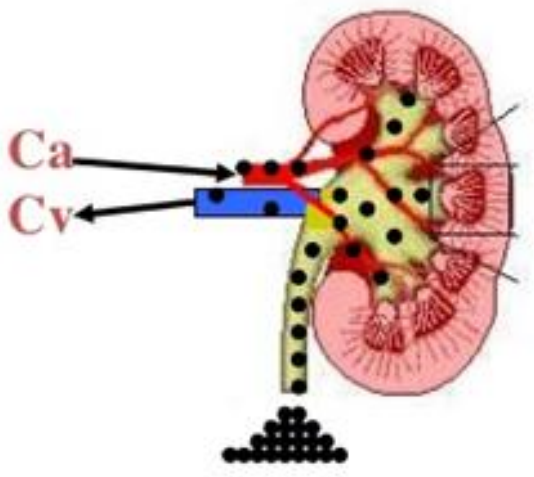
enterohepatic circulation



Extraction ratio E_R

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

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



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

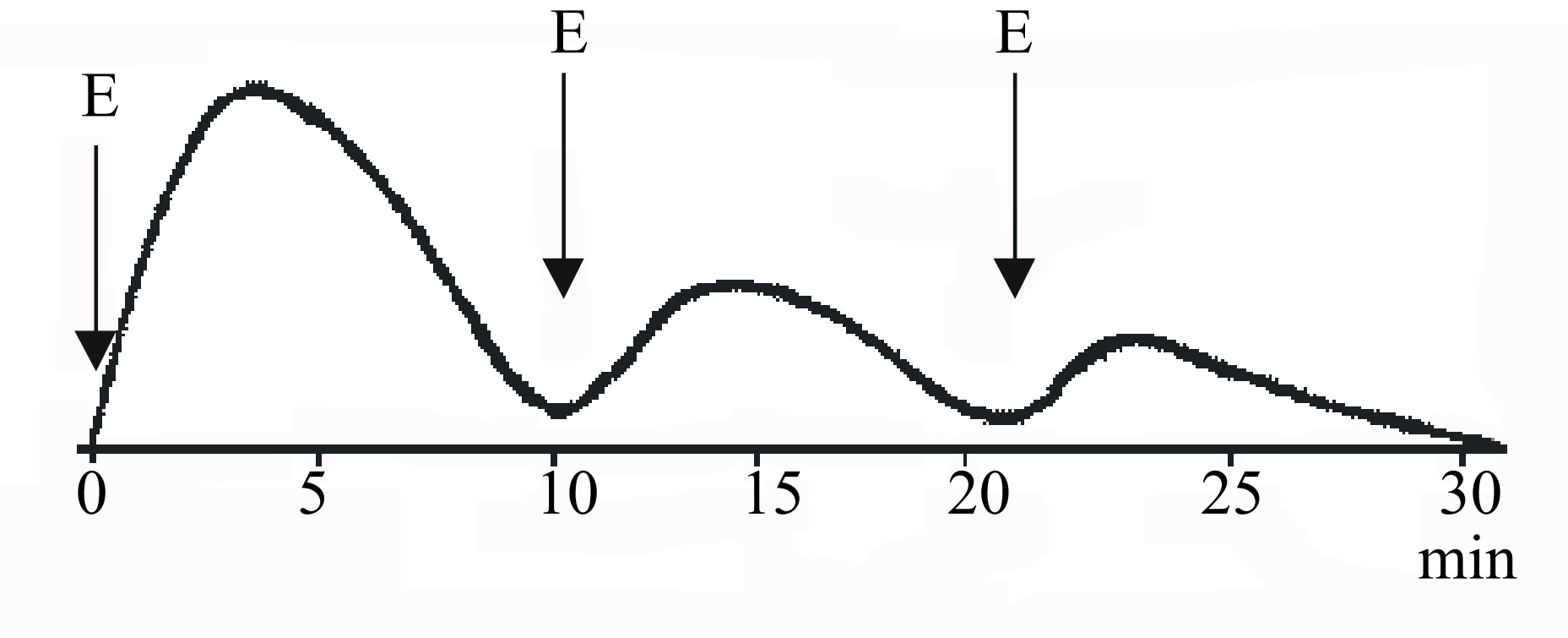
Repeated administration

- 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