Pharmacokinetics

- **General principles of the fate of the drug in the body**
- **Overview of pharmacokinetic processess: Drug absorption, distribution, metabolism and elimination**

Jan Juřica

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.

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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"

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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

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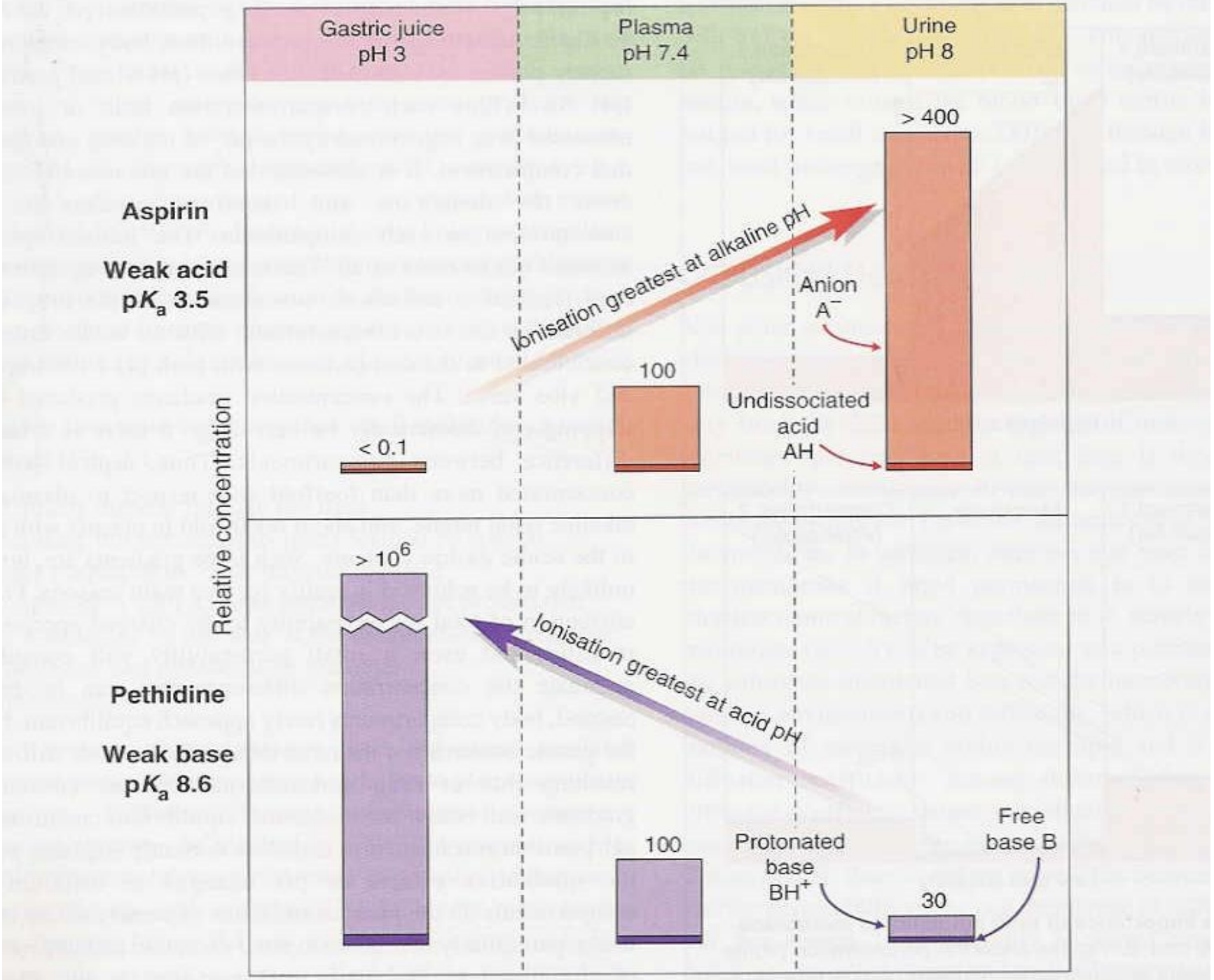
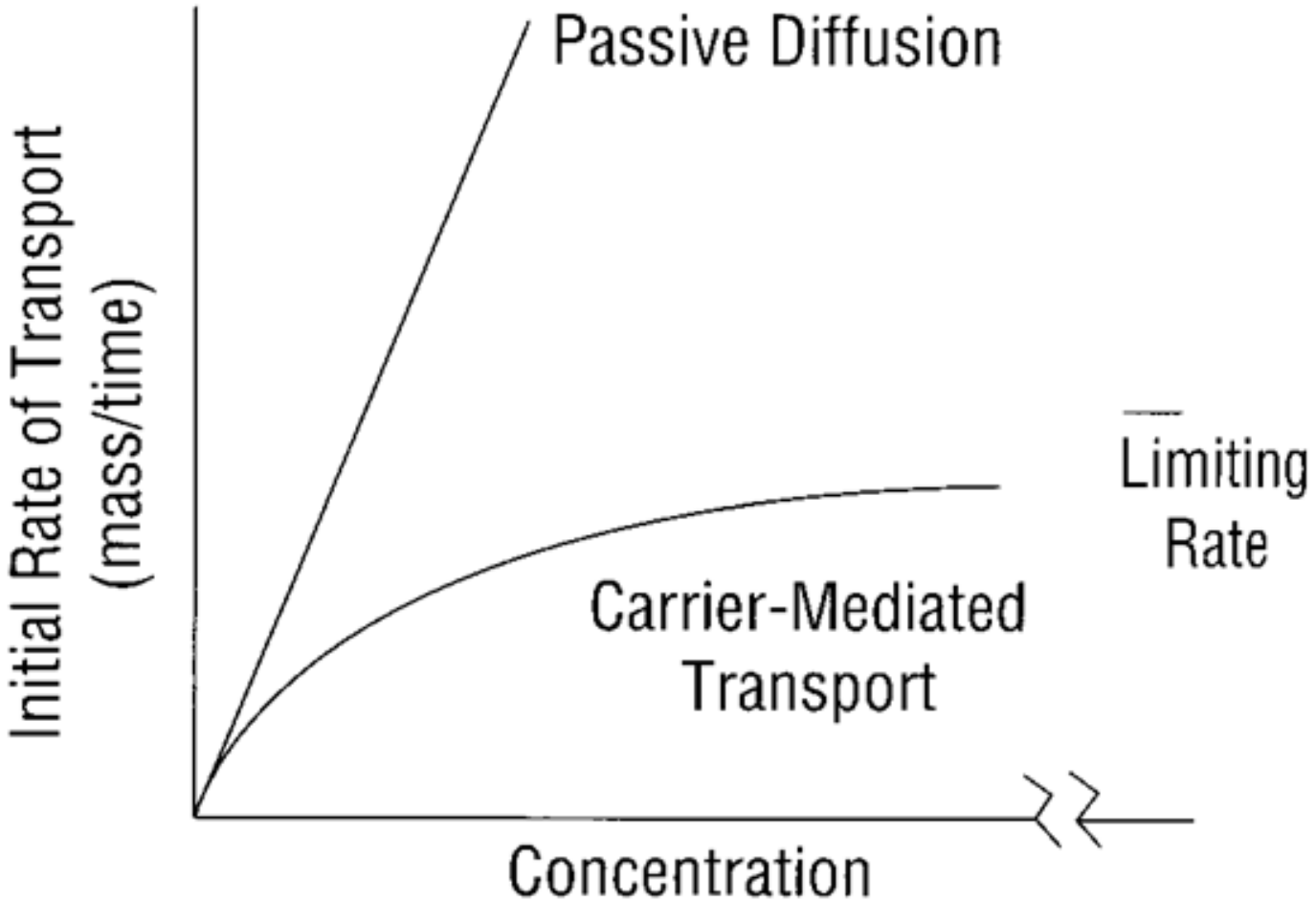

Gastric juice
pH 3
Plasma
pH 7.4
Urine
pH 8
Aspirin
Weak acid
pK_a 3.5
Relative concentration
> 400
Ionisation greatest at alkaline pH
Anion
A^-
100
Undissociated
acid
AH
< 0.1
> 10^6
Ionisation greatest at acid pH
Pethidine
Weak base
pK_a 8.6
100
Protonated
base
BH^+
Free
base B
30


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

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

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

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ABSORPTION

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

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Bioavailability

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

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

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

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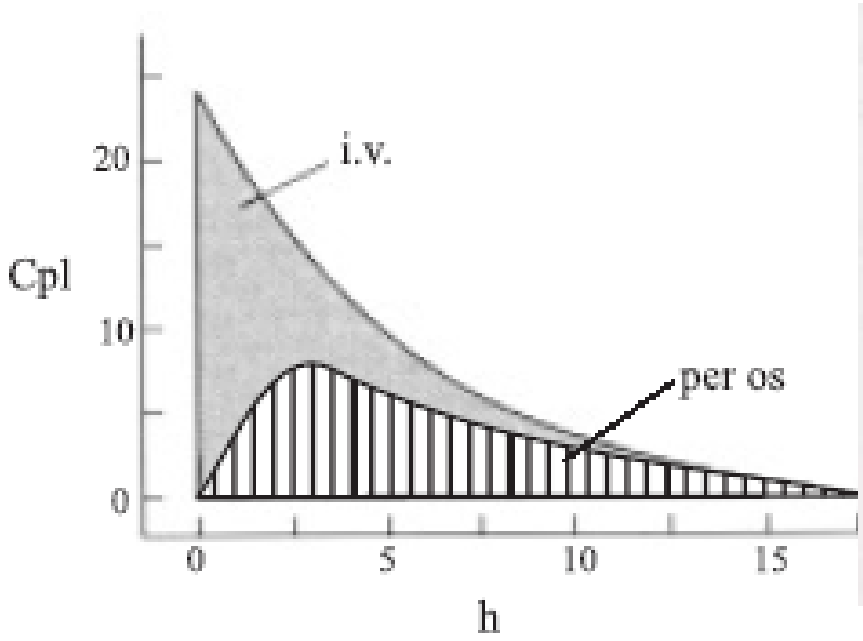
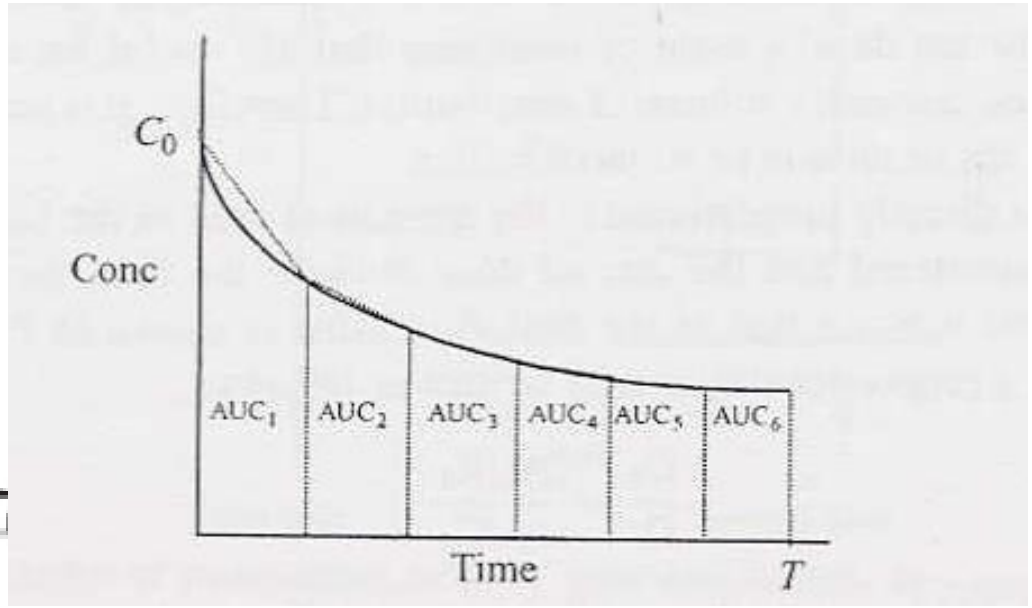
Area under curve (AUC)

Is a measure of bioavailability





$F = AUC_{p.o.} / AUC_{iv}$

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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)

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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

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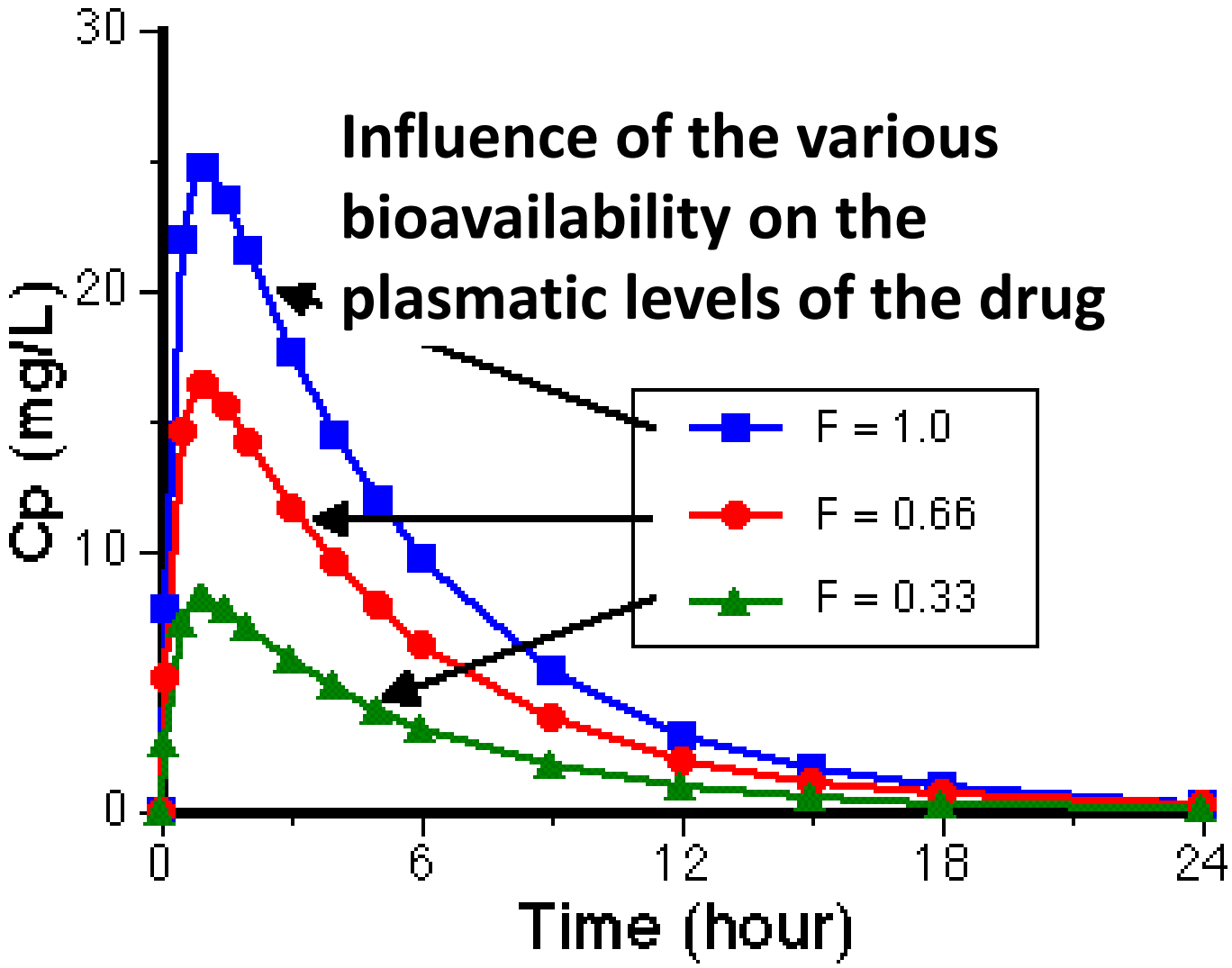
Influence of the various bioavailability on the plasmatic levels of the drug
Cp (mg/L)
30
20
10
0
0
6
12
18
24
Time (hour)
F = 1.0
F = 0.66
F = 0.33

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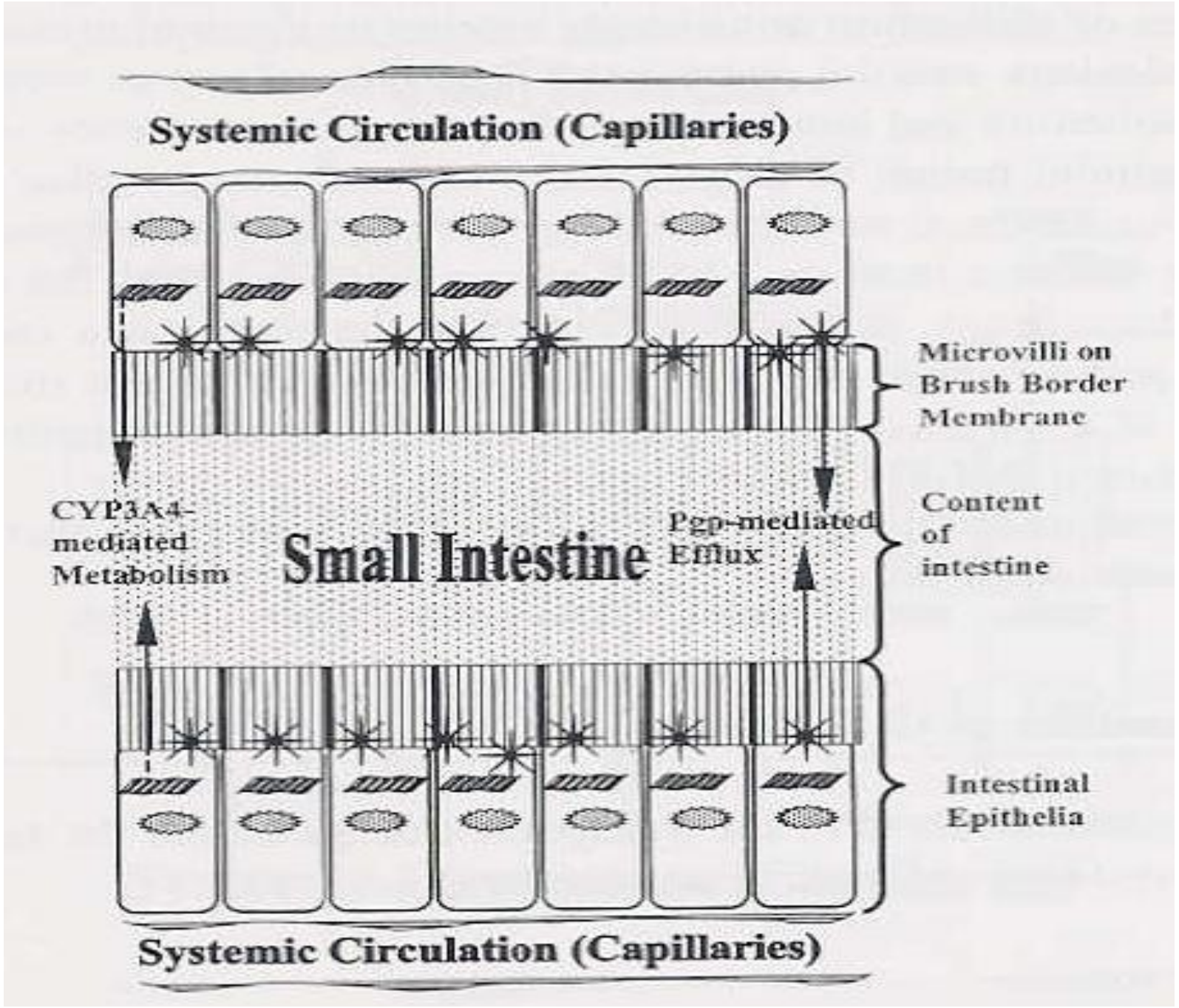
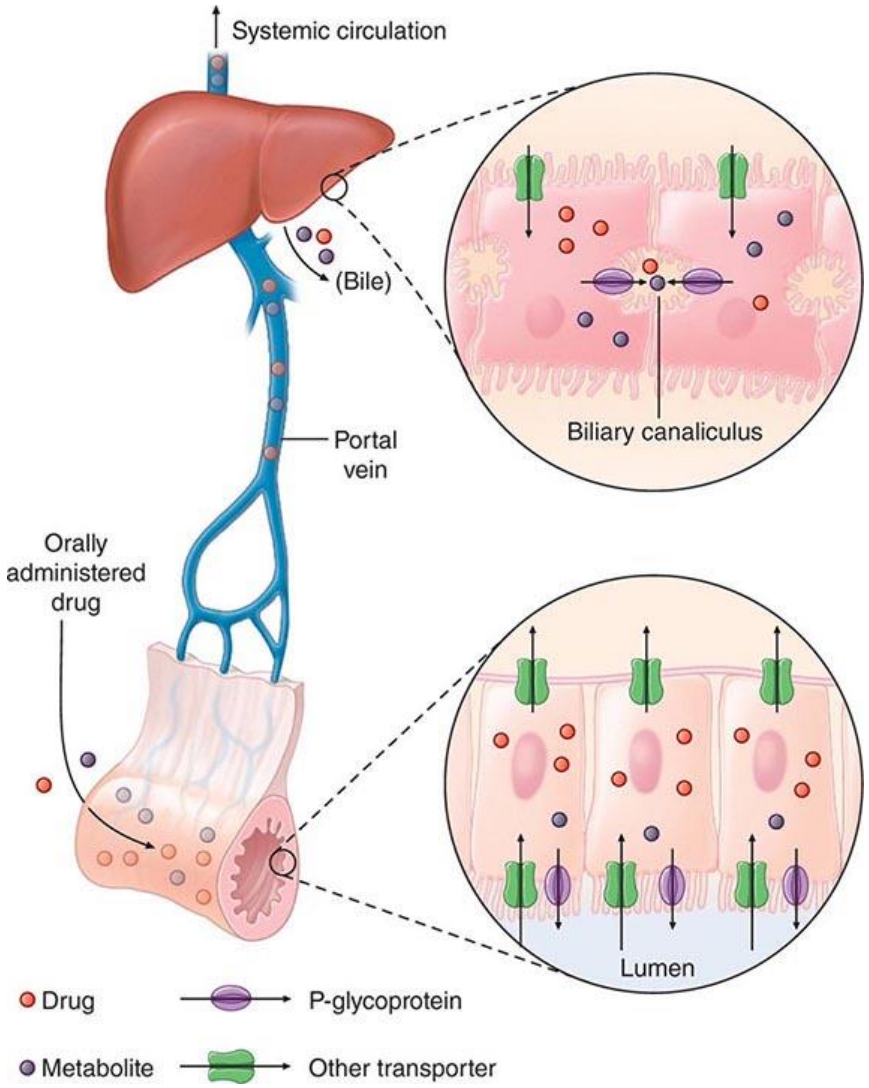
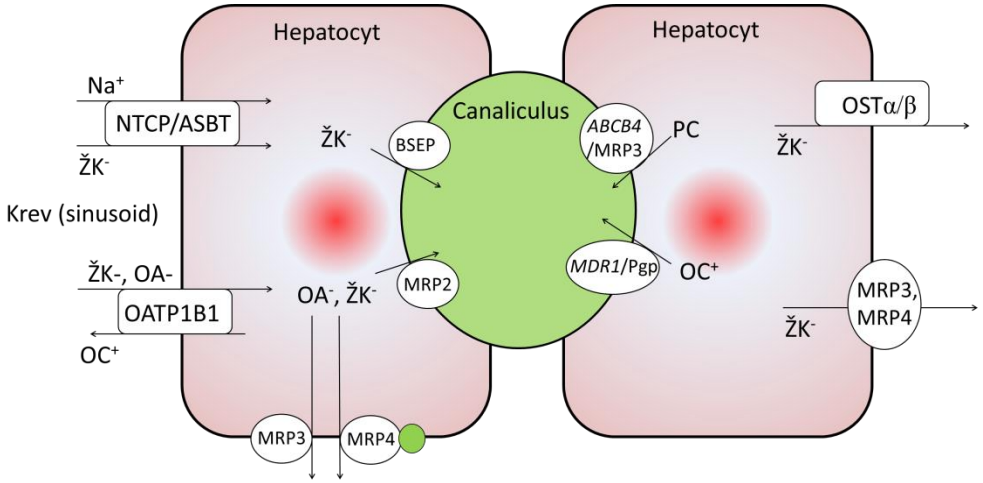

Systemic Circulation (Capillaries)
Microvilli on Brush Border Membrane
CYP3A4-mediated Metabolism
Small Intestine
Pgp-mediated Efflux
Content of intestine
Intestinal Epithelia
Systemic Circulation (Capillaries)

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

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Distribution

= permeation from the 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…

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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.

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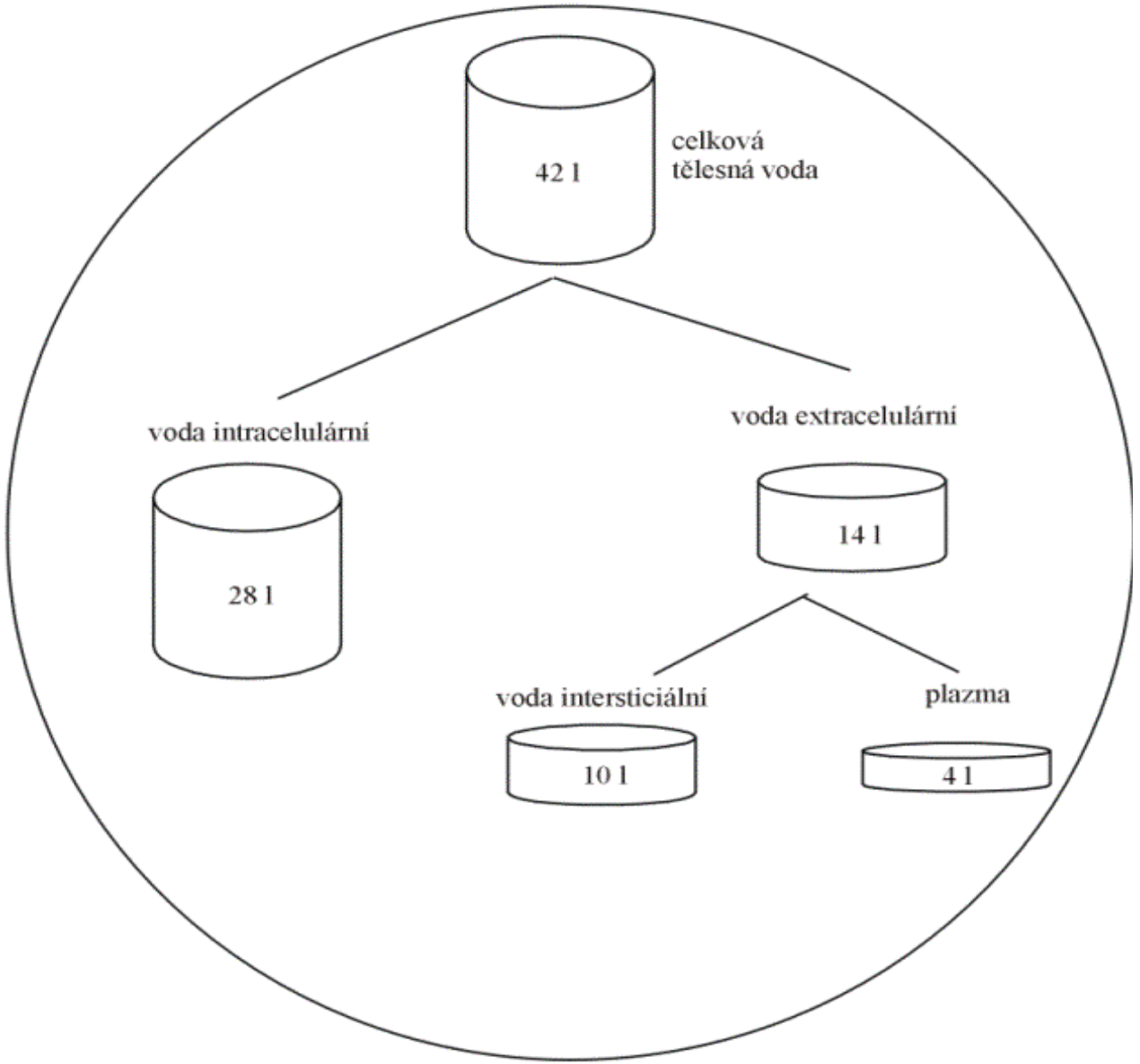
Volumes of the water in human body



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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

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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

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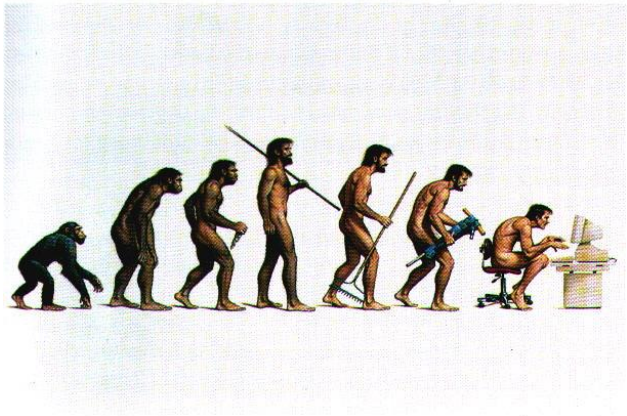


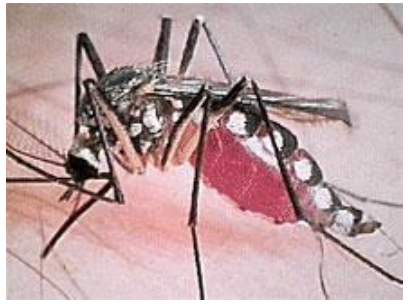
men

plants

animals

CYP 450

molluscs

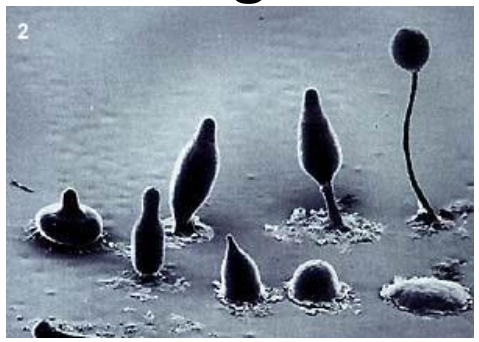


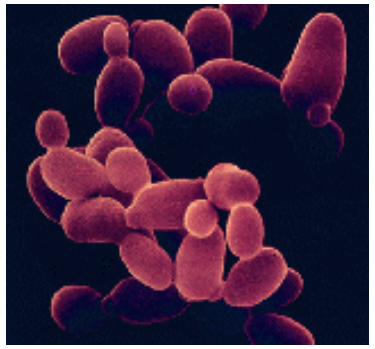
insect

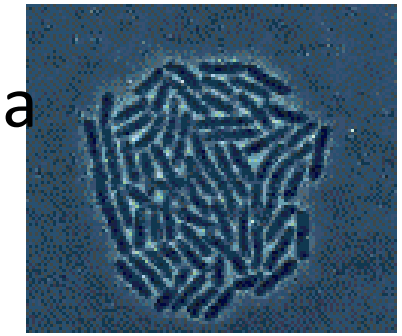
funghi

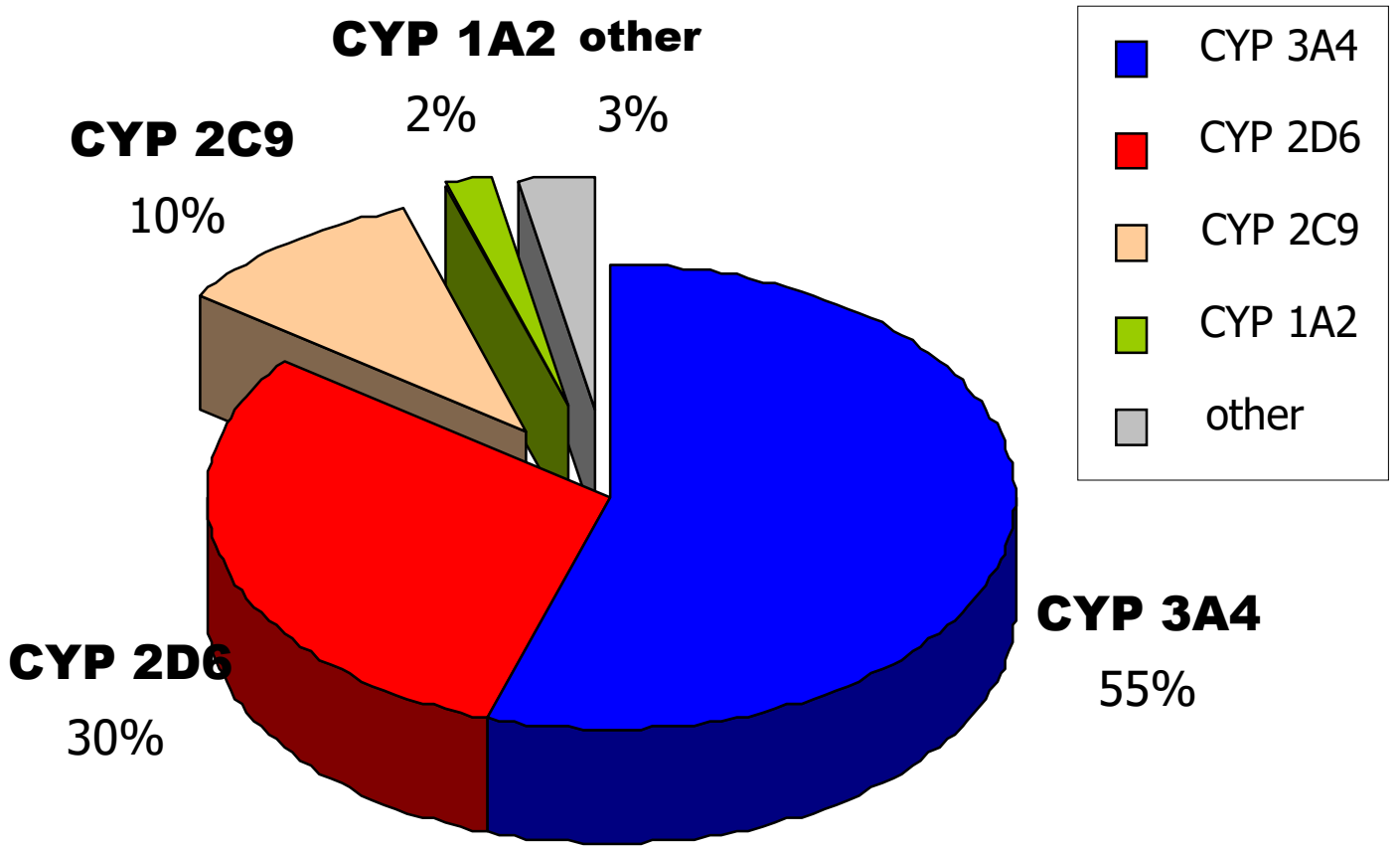
yeast

bacteria








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

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Genetic polymorphism

Genetic polymorphism = the existence of several
(At least two) alleles for the gene from which
At least part has a population frequency of at least 1 %

- Pharmacogenetics

focuses on the study of genetically conditioned variability in the response to a drug

•Pharmacogenomics examines the relationship of drug effect on the level of the whole genome, respectively transcriptome

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Genetic polymorphism of biotransformation enzymes

Polymorphism in the gene of ***N - acetyltransferase***
- Inactivation of drugs in the liver : slow x fast acetylators
- Isoniazide , procainamide, hydralazine
- Peripheral neuropathy (prevention - pyridoxine)

Polymorphism of ***thiopurine S - methyltransferase***
- the metabolism of azathioprine
- commercially available genetic test for determining the polymorphisms, prevention of serious adverse reactions

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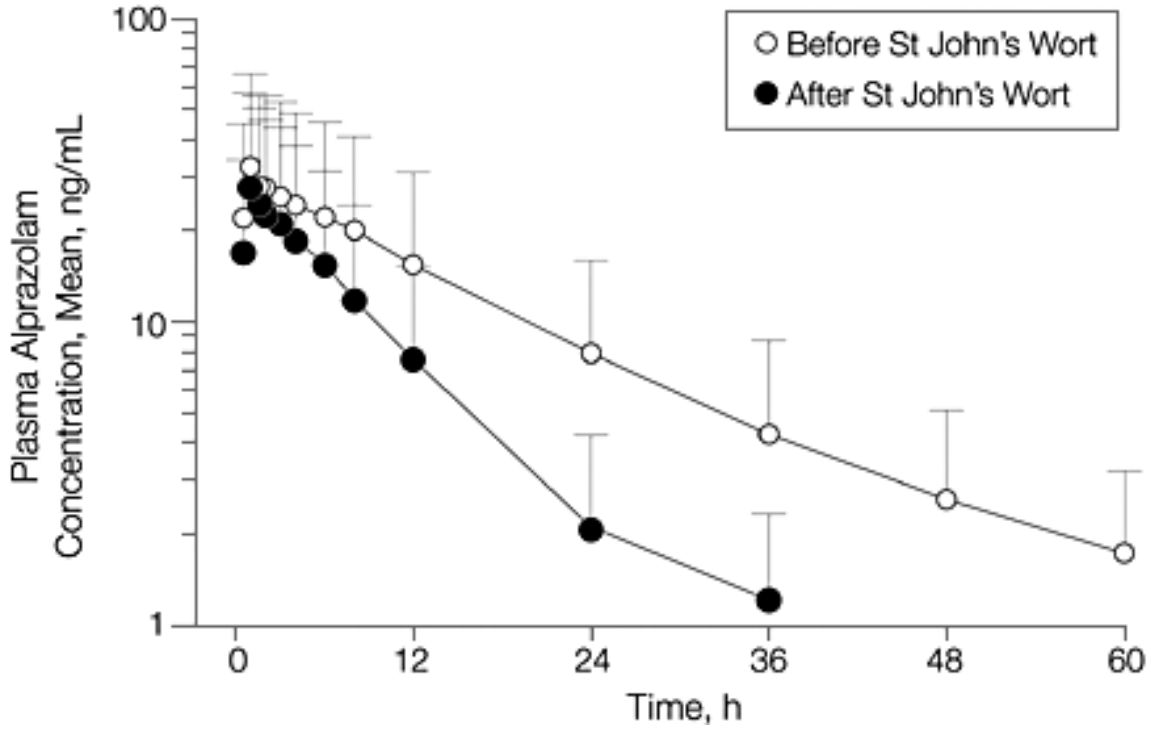
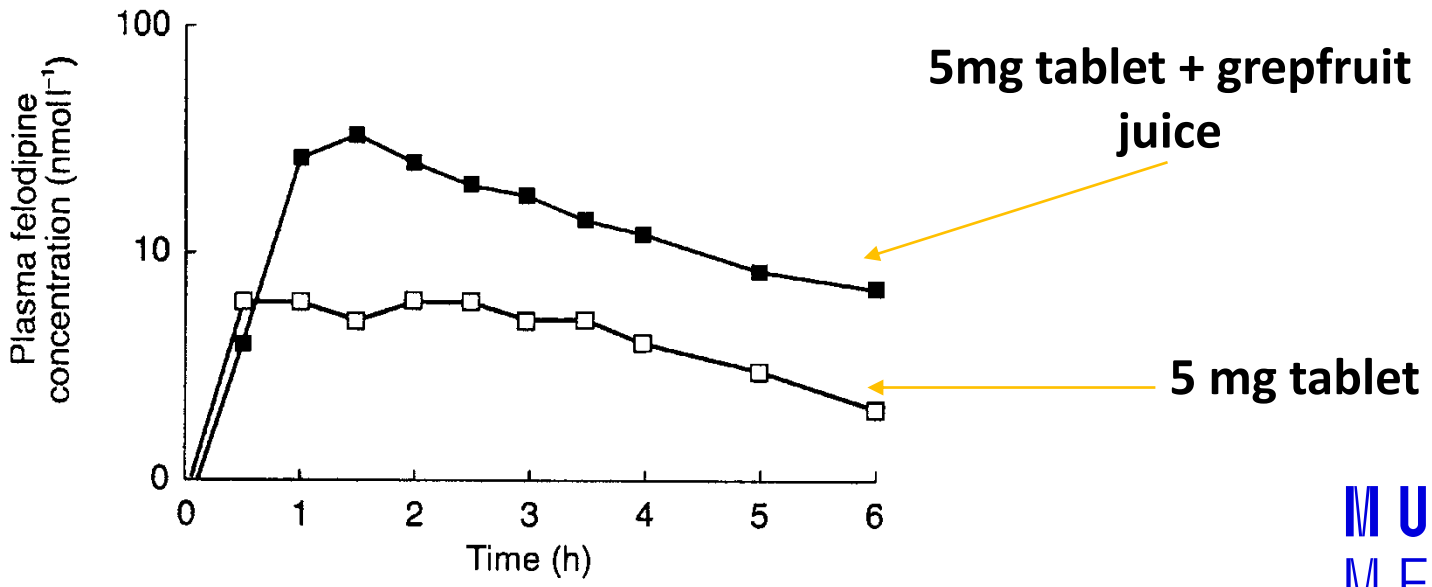
INDUCERS of CYP 450

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



INHIBITORS of CYP 450

- antidepressants (fluoxetine, fluvoxamine, paroxetine)
- quinine, quinidine
- chloramphenicol, erythromycin
- ketoconazol, itraconazol
- grapefruit juice



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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)

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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.)

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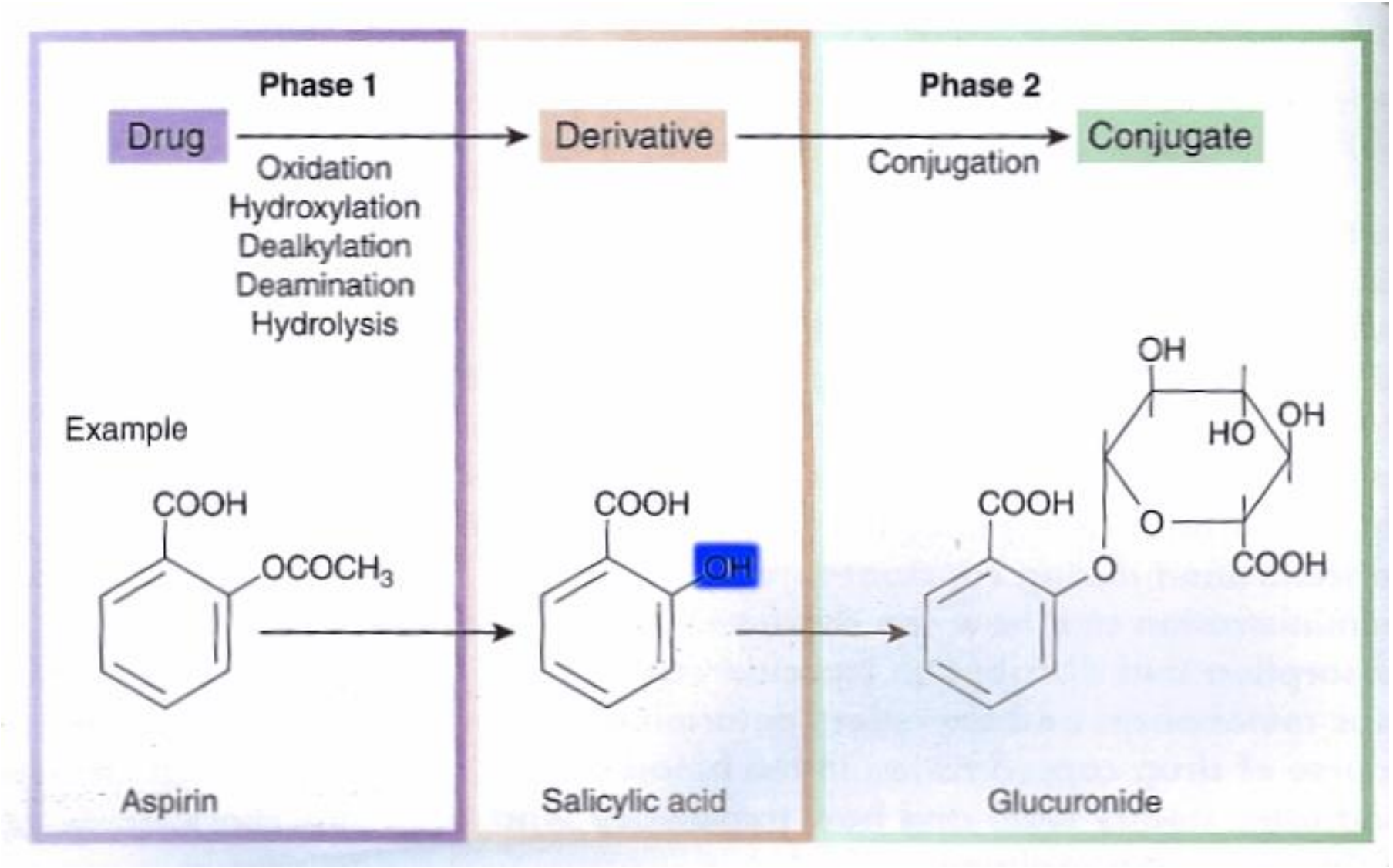
Phase 1
Drug
Oxidation
Hydroxylation
Dealkylation
Deamination
Hydrolysis
Derivative
Phase 2
Conjugation
Conjugate
Example
COOH
OCOCH3
COOH
OH
OH
HO
OH
O
COOH
O
COOH
Aspirin
Salicylic acid
Glucuronide

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

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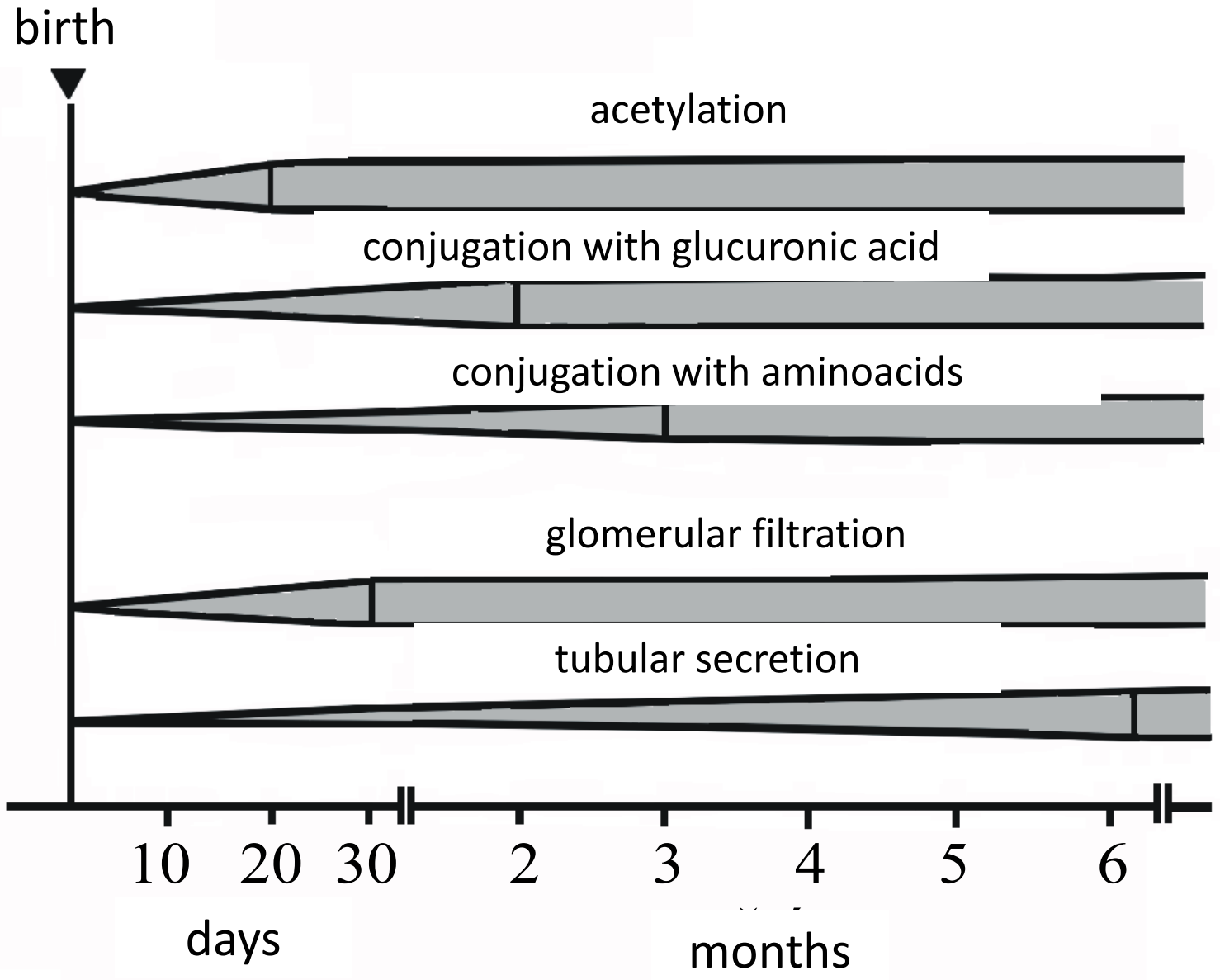
birth
acetylation
conjugation with glucuronic acid
conjugation with aminoacids
glomerular filtration
tubular secretion
10
20
30
2
3
4
5
6
days
months

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Excretion

Kidney (urine)

tubular excretion

x tubular reabsorption

liver (bile)

lungh (air)

saliva, skin, hair, breast milk...

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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

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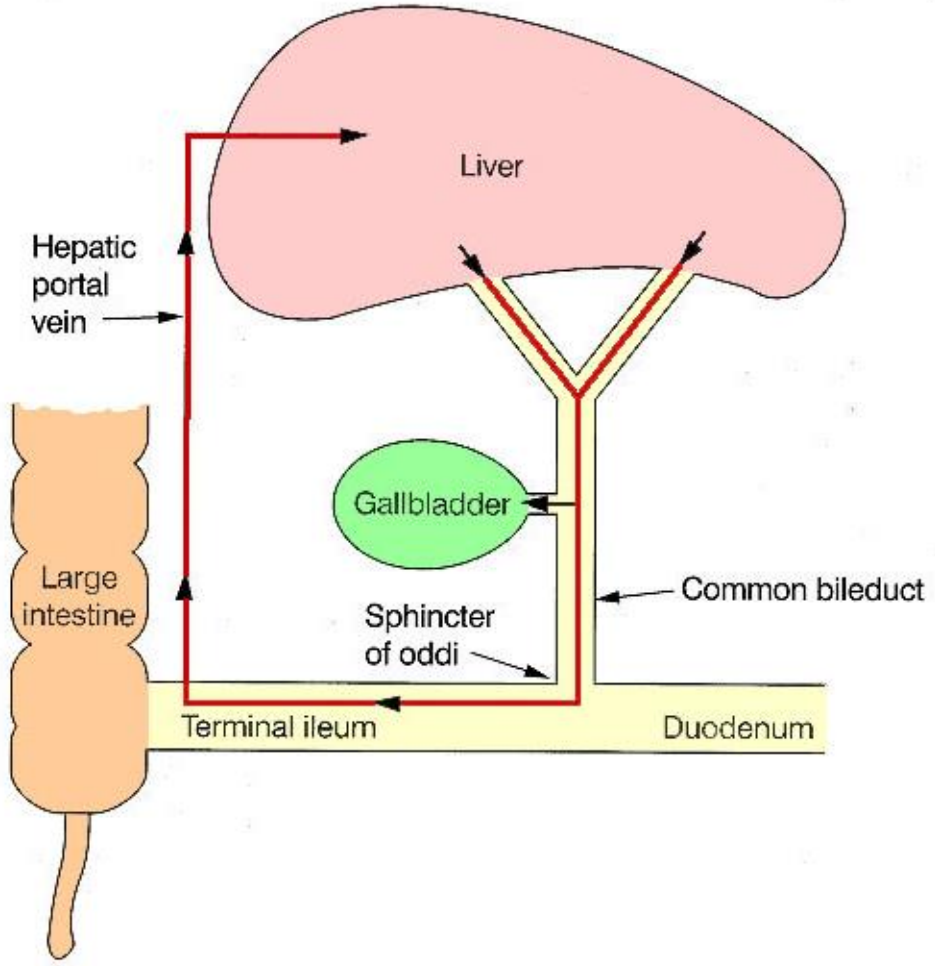
Liver

Billiar excretion, clearance.

enterohepatic circulation



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)

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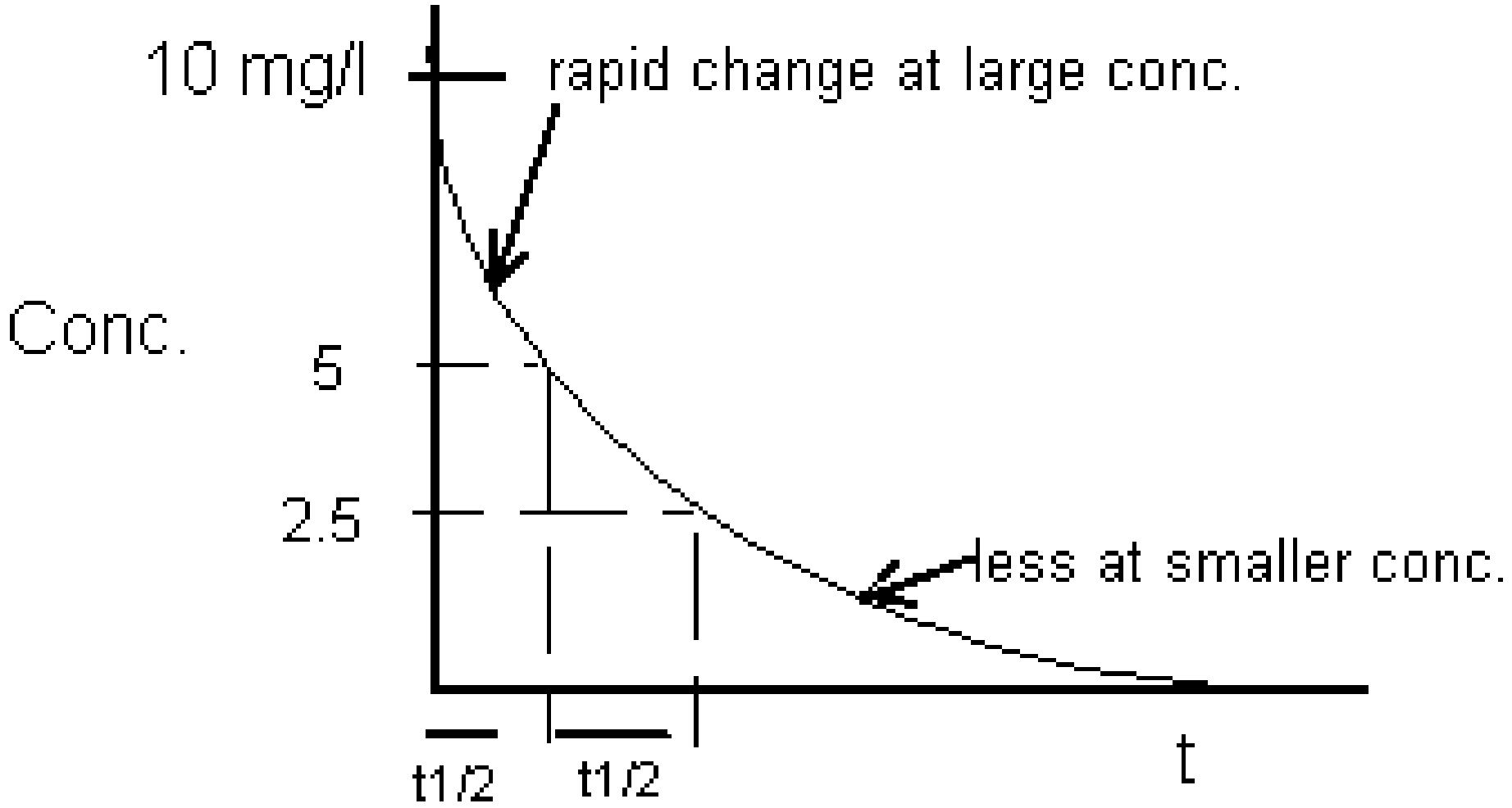
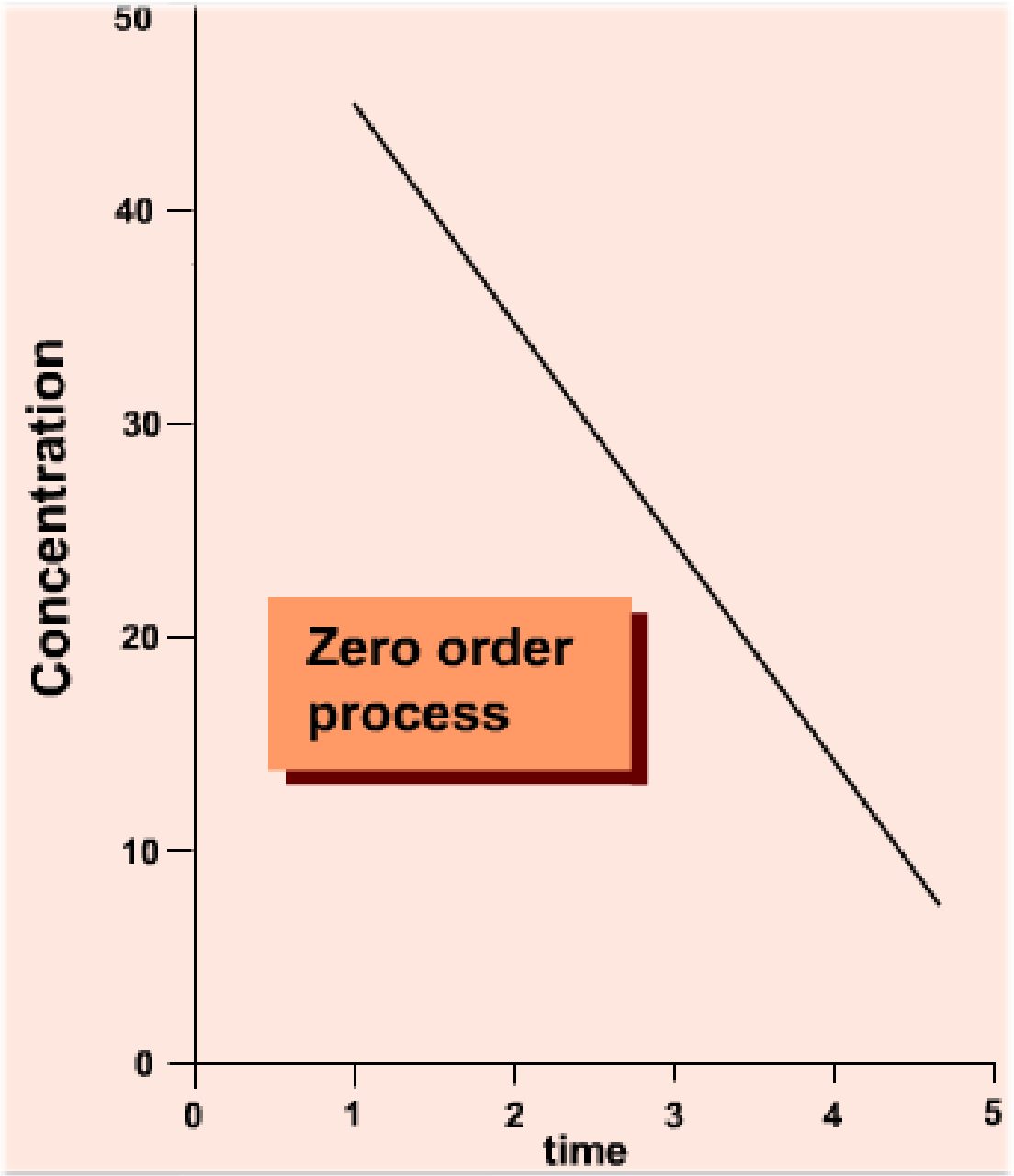
First Order Kinetics




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

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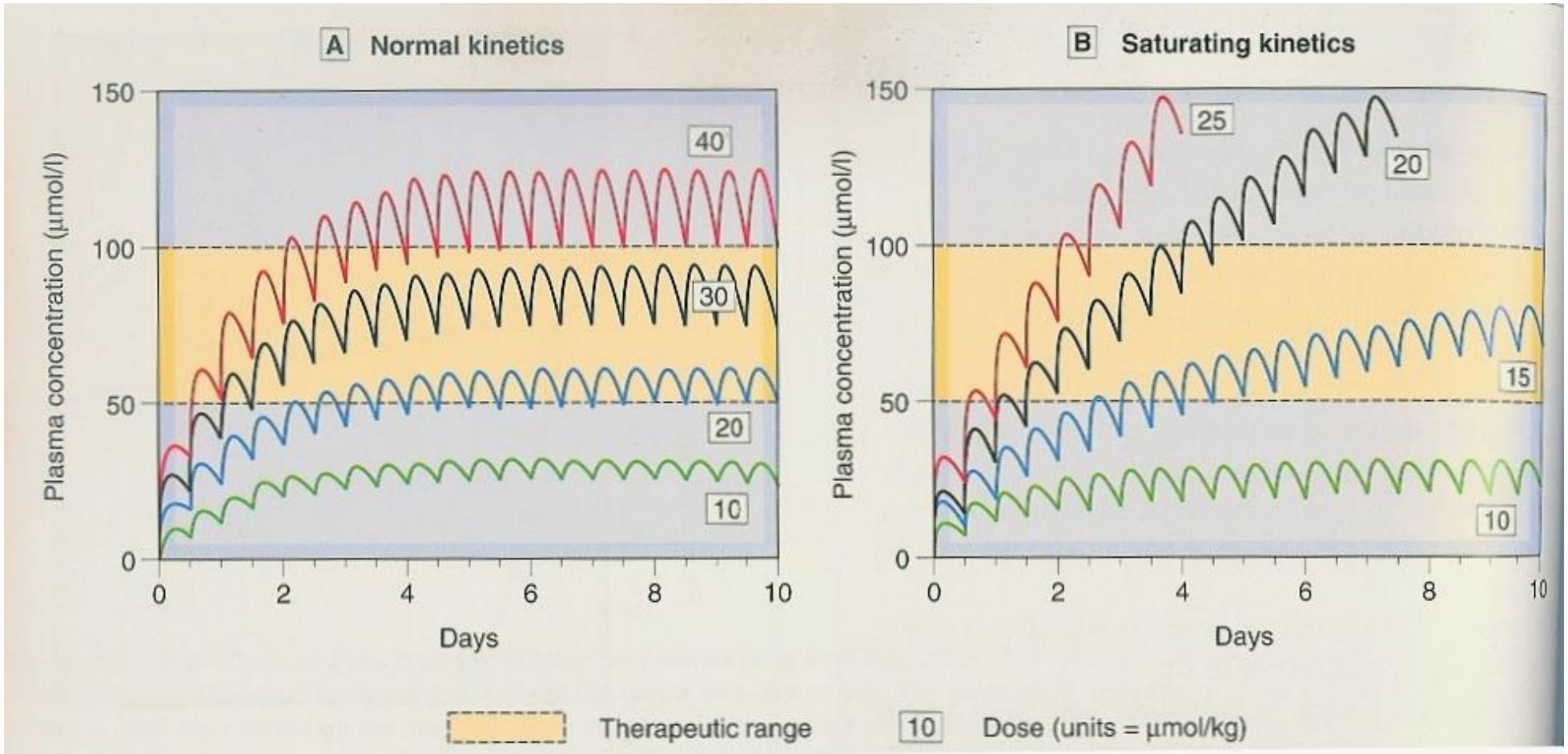
A Normal kinetics
Plasma concentration (µmol/l)
150
100
50
0
40
30
20
10
0
2
4
6
8
10
Days
B Saturating kinetics
Plasma concentration (µmol/l)
150
100
50
0
25
20
15
10
0
2
4
6
8
10
Days
Therapeutic range
10
Dose (units = µmol/kg)

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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 $t_{0,5}$

$t_{0,5} = \ln 2 / k^e = 0,7 / k_e$

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

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

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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

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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

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