Pharmacokinetics

Part 1: Drug Absorption & Distribution

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Lecture course: general pharmacology

Structure:

- Pharmacokinetics (D. Firsov, UNIL, 12h)
- Pharmacodynamics (S. Kellenberger, UNIL, 14h)

Pharmacology –

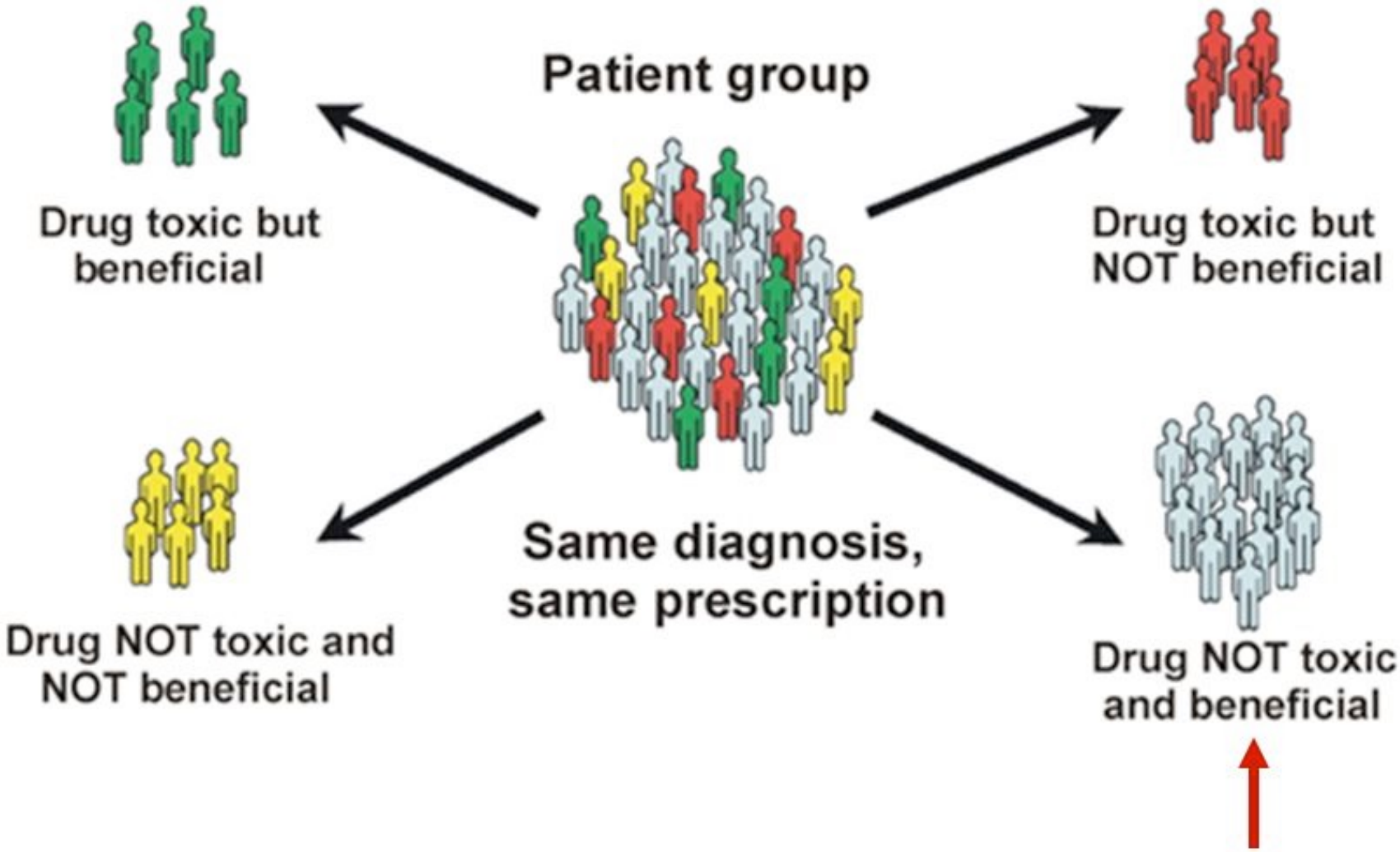
science of drug action on biological systems

originates from Greek *pharmakon* (φαρμακον) **– remedy, poison, cosmetic, perfume, intoxicant**

main domains:

- identification of biological targets
- drug development
- characterization of biological activity
- drug delivery
- drug breakdown
- drug elimination
- drug safety

Inter-individual variability in drug response



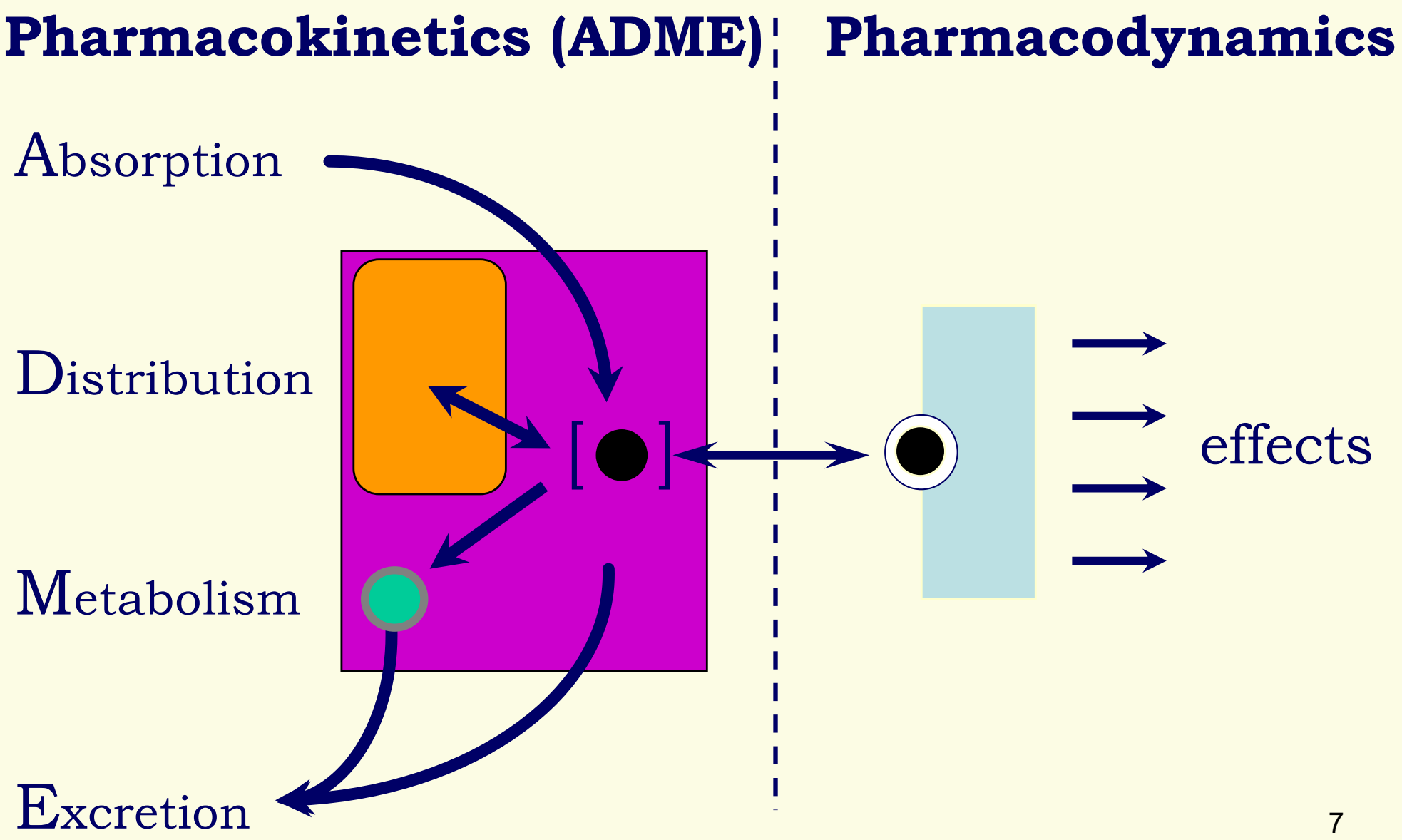
Pharmacology and public health (FDA):

- Most major drugs are effective in only 25 to 60 % of patients
- Adverse Drug Reactions (ADR: any injury caused by drugs) account for up to 7 % of hospitalization/USA
- ADR are estimated to be 5th or 6th cause of illness (2'000'000 cases/year, USA)
- ADR is the 4th leading cause of death (100'000 death/year, USA), ahead of pulmonary disease, diabetes, AIDS, automobile accidents, pneumonia,..
- Cost estimates range between 30 to 150 billion $/ year (USA)

General Pharmacology

- **Pharmacokinetics** is the study of what the **body does** to a **drug**.
- **Pharmacodynamics** is the study of what a drug **does** to the **body**.

General Pharmacology



Learning Objectives of the Pharmacokinetics Course:

- Describe mechanisms of Drug Absorption, Distribution, Metabolism and Excretion (ADME)
- Describe principal models and parameters of pharmacokinetics
- Describe the effect of circadian rhythms on drug action (chronopharmacology)
- Explain the role of genetic polymorphisms in variable drug response (pharmacogenetics)

Course content (files & handouts):

Part 1: Absorption + Distribution

Part 2: Metabolism

Part 3: Excretion

Part 4: Parameters and Models in Pharmacokinetics

Part 5: Pharmacogenetics

Pharmacokinetics: Absorption

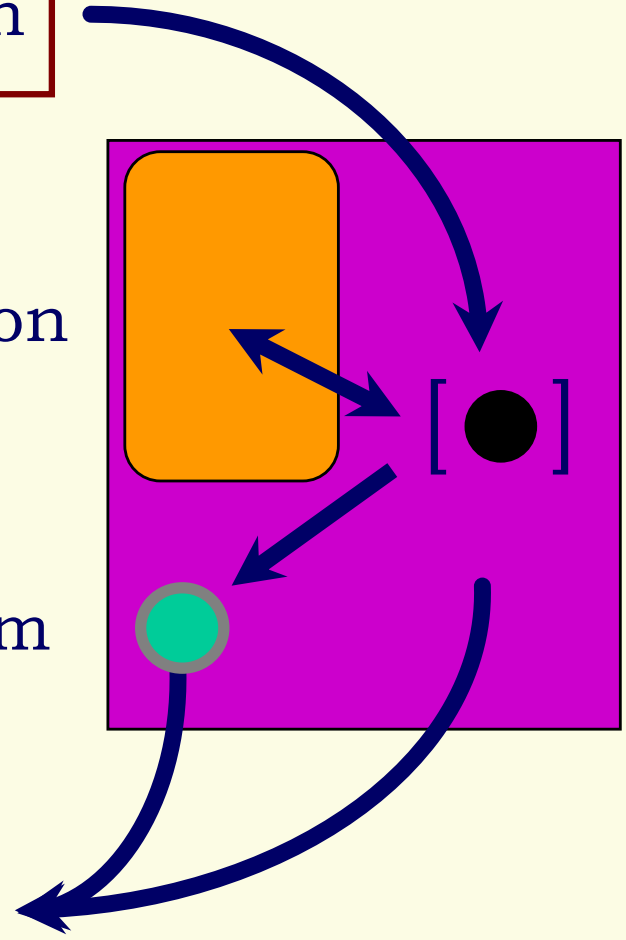
Pharmacokinetics (ADME)

Absorption

Distribution

Metabolism

Excretion



- The process by which a drug moves from the site of administration to the blood or site of action.

- Absorption?: how quickly and how much of a drug reaches its intended target (site) of action

Absorption: routes of drug administration

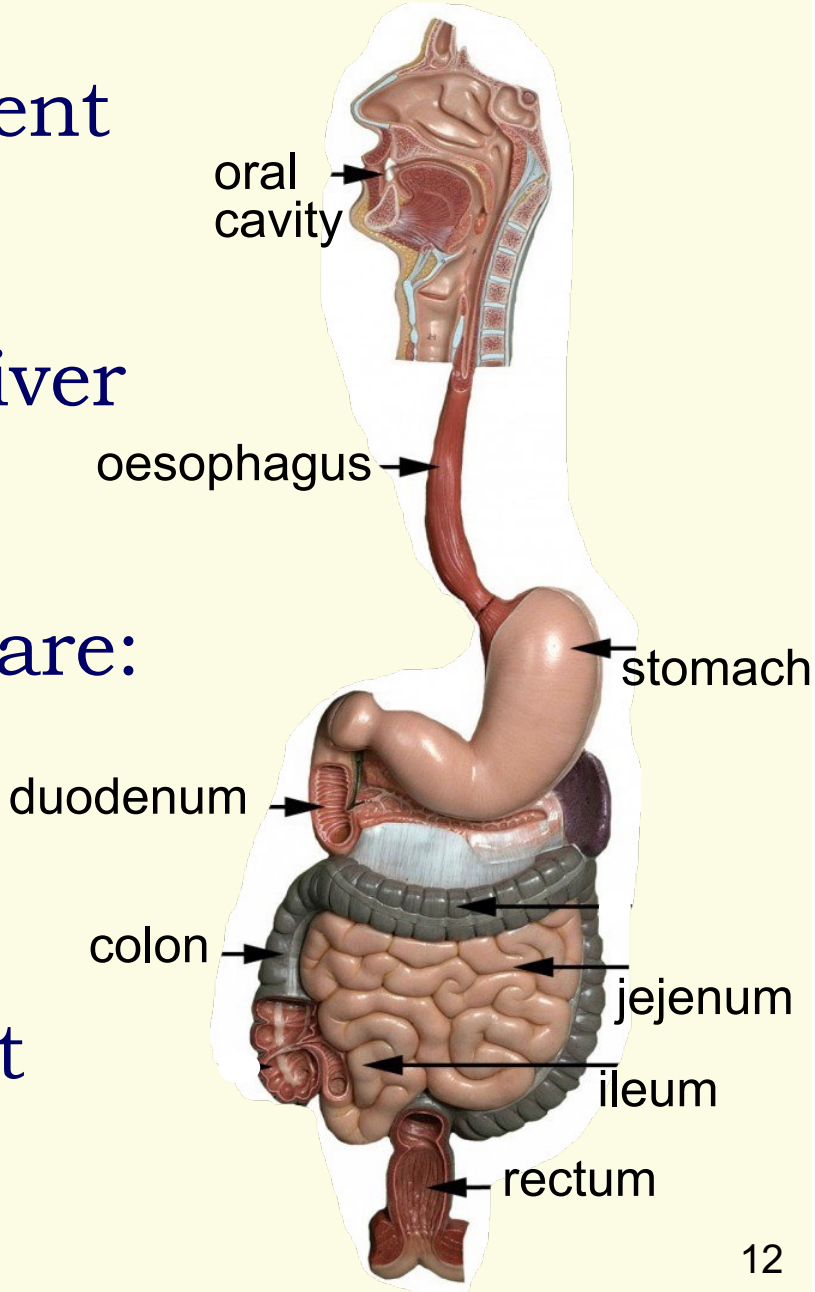
- Enteral (through any part of the gastrointestinal tract (GIT))
  - orally (tablets, capsules, drops)
  - rectally (drugs in suppository)
  - feeding tubes (gastric or duodenal)

- Parenteral
  - injection or infusion into vein, artery, muscle, intracardiac, subcutaneous, etc…

- Topical
  - transdermal, inhalation, sublingual, eye and ear drops, intranasal, vaginal, etc…

Absorption: routes of drug administration

- Enteral
  - Most common and convenient
  - Subject to first-pass effect
    - metabolism in the GIT/liver
    - reduced bioavailability
  - Not suitable for drugs that are:
    - rapidly metabolized
    - acid labile
    - intended for a local effect
  - Slow onset of action



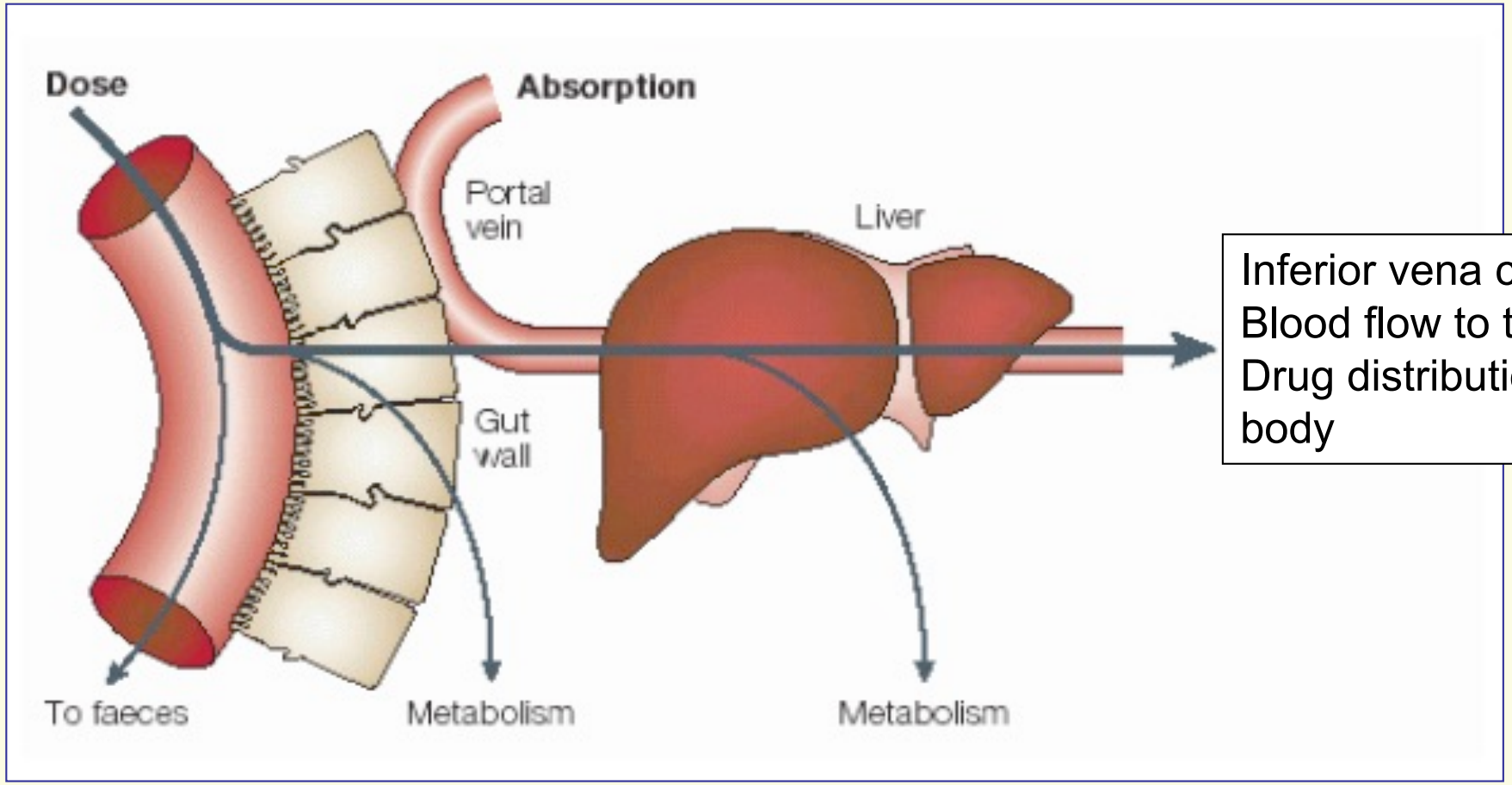
Enteral drug administration: absorption

- Mouth: usually low (surface 100-200 cm^2), but could be high for some compounds (nitroglycerin)
- Stomach: usually weak, surface S ~1 m^2, blood flow ~150 ml/min, low pH
- Small intestine: S ~200 m^2, blood flow ~1L/min
  - most of drug absorption takes place in the duodenum
- Rectal: rectum's wall is thin and its blood supply rich, drugs are readily absorbed

Enteral drug administration: absorption

absorbed	*% in stomach*	*% in small intestine*
phenobarbital	3	52
pentobarbital	4	55
promethazine	0	38
ethanol	6	64

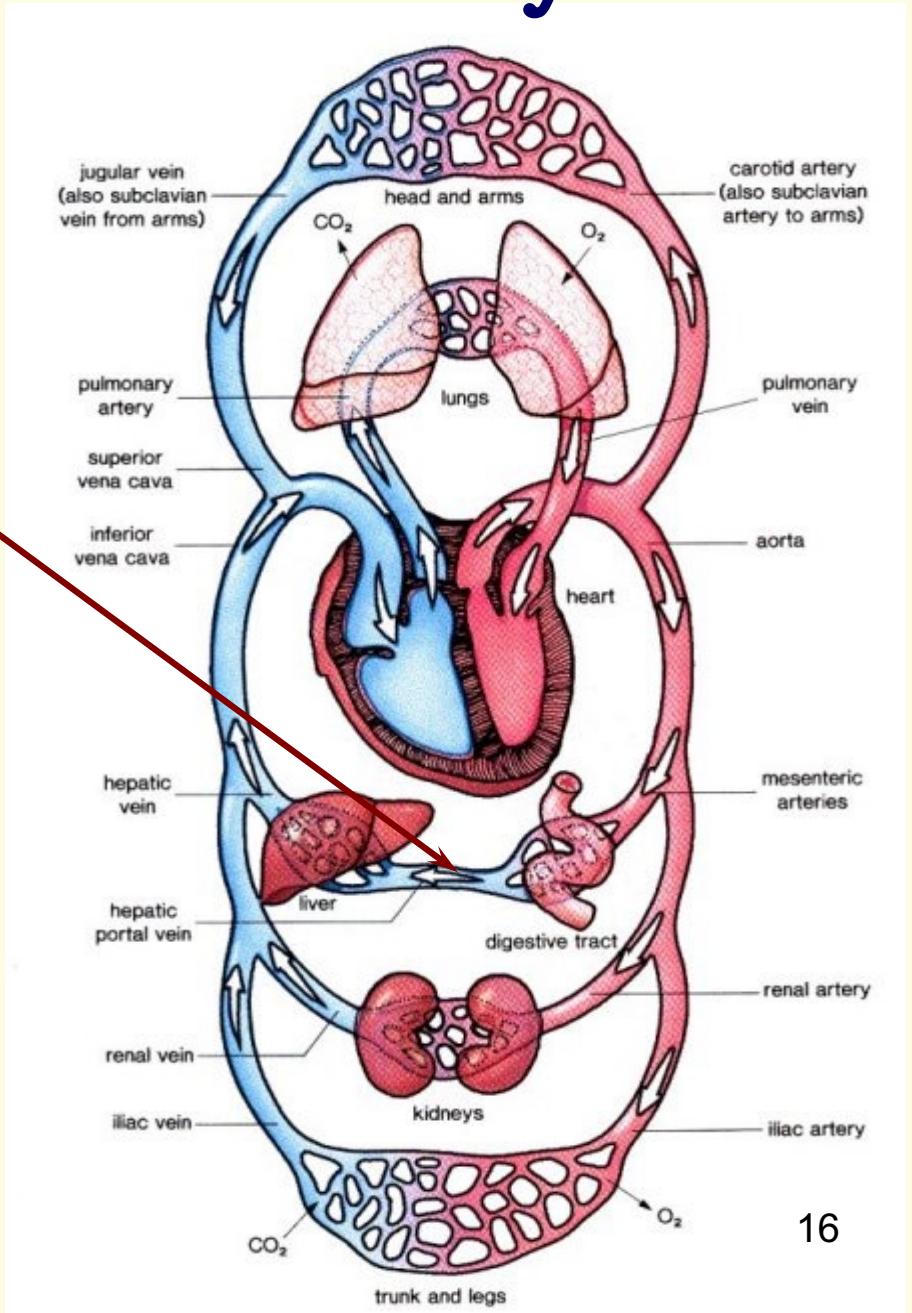
Enteral drug administration: first-pass effect / portal vein system



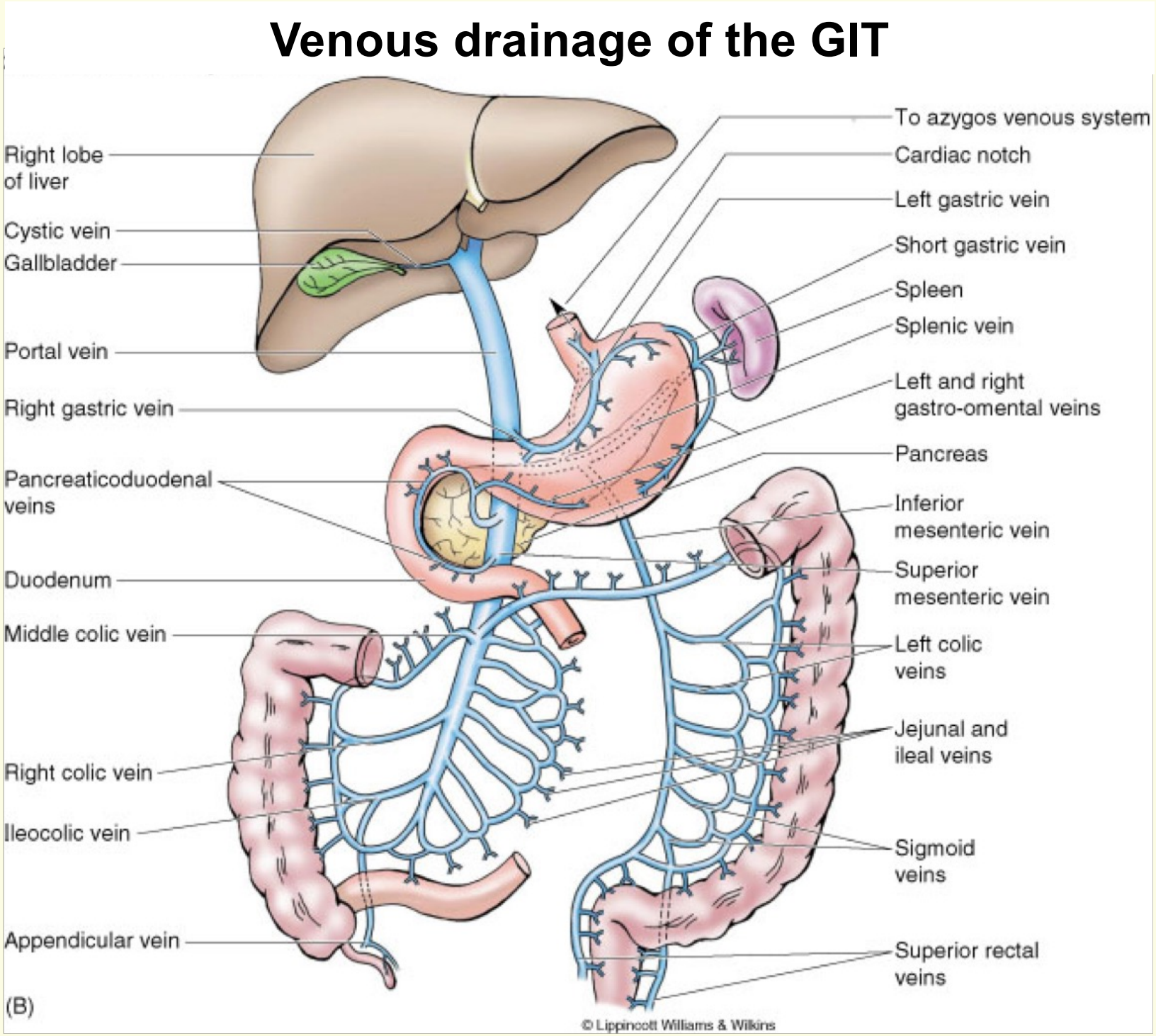
- The metabolism of enterally administered drugs by gastro-intestinal and hepatic enzymes, resulting in a significant reduction of the amount of non-metabolized drug reaching the systemic circulation.

Enteral drug administration: first-pass effect / portal vein system

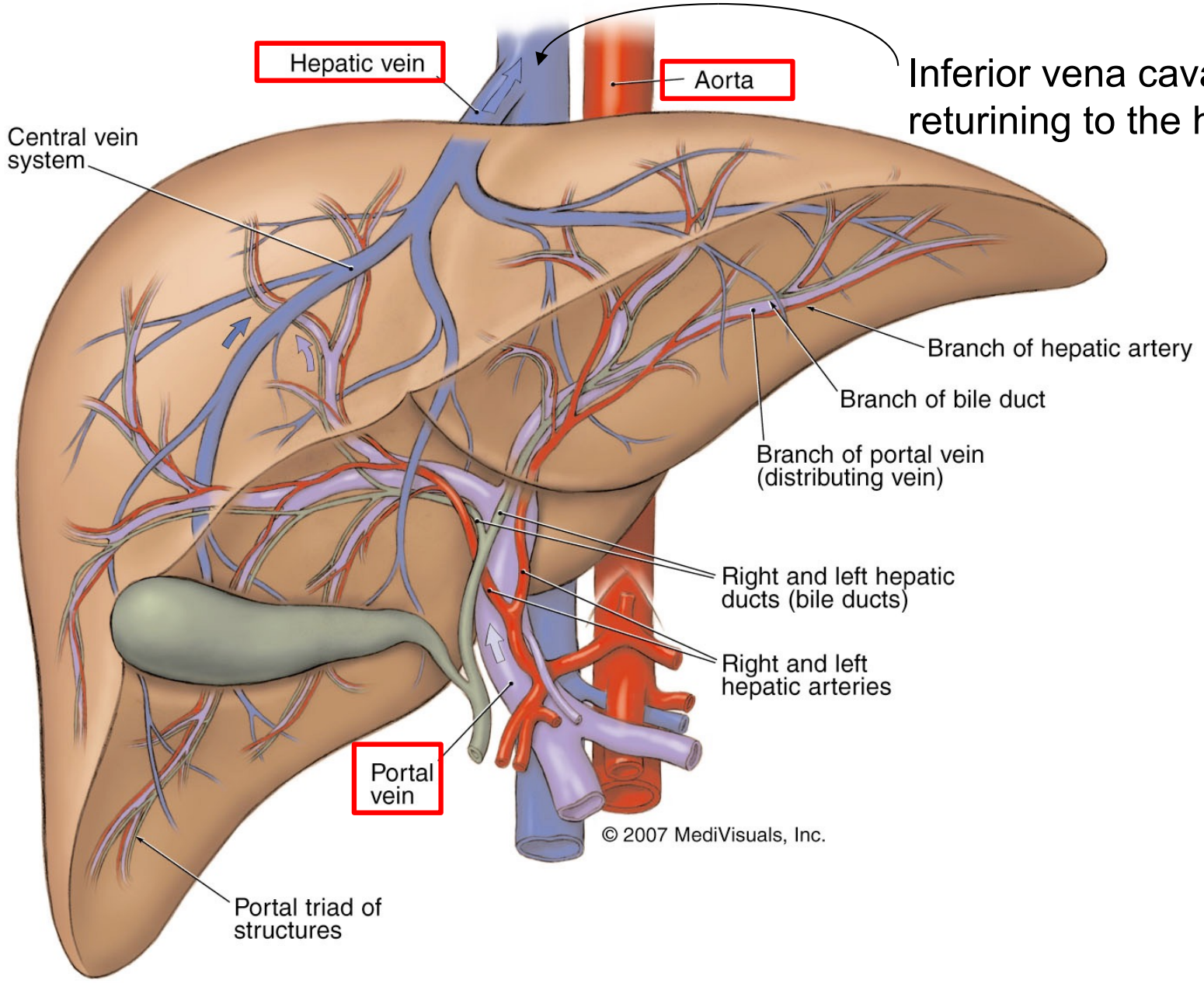
Portal vein - a large vein that carries blood from the stomach and the intestines to the liver.



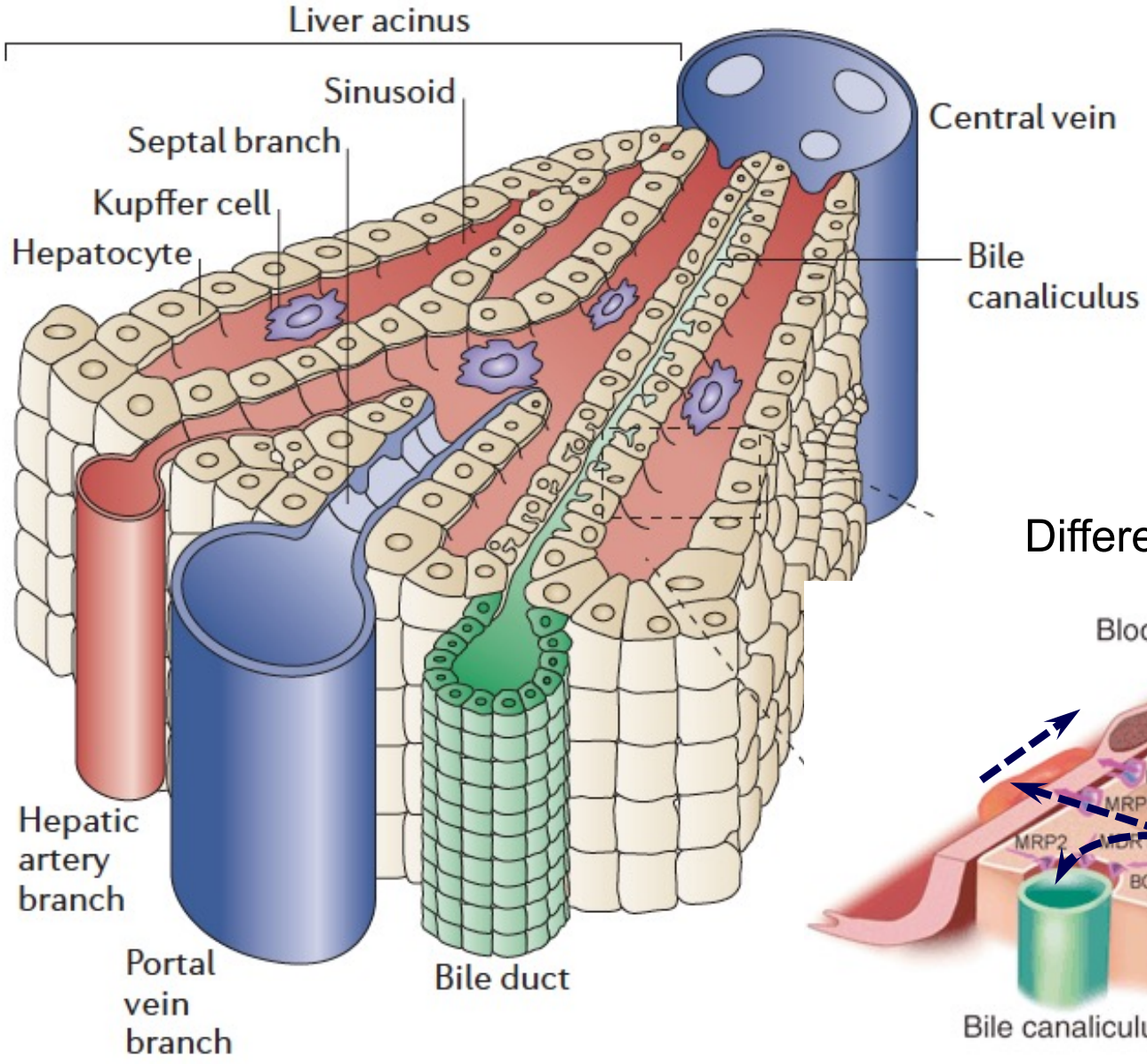
Venous drainage of the GIT



Enteral drug administration: first-pass effect – blood circulation in the liver



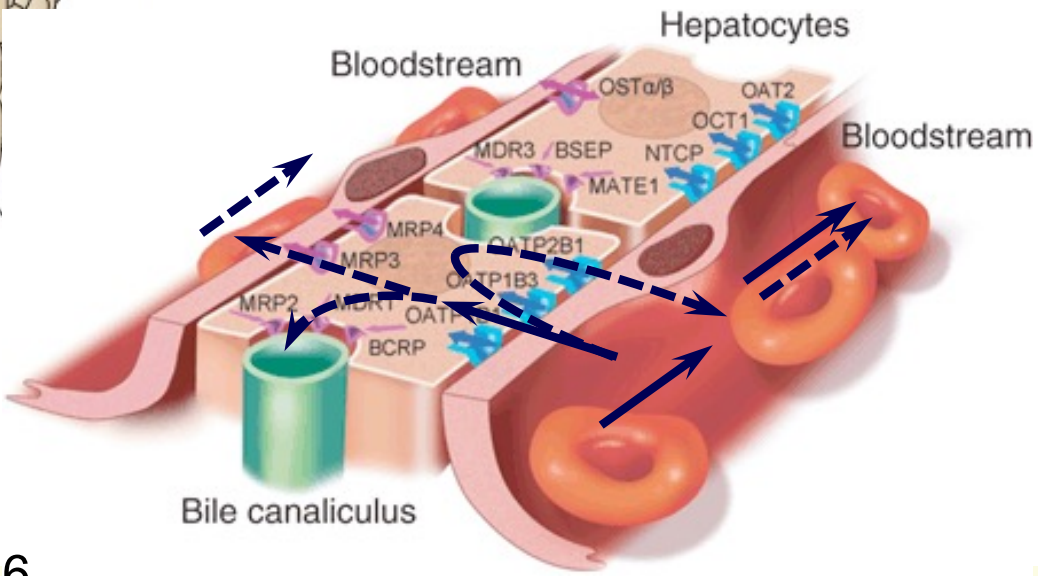
Enteral drug administration: first-pass effect – blood circulation in the liver



Parent drug

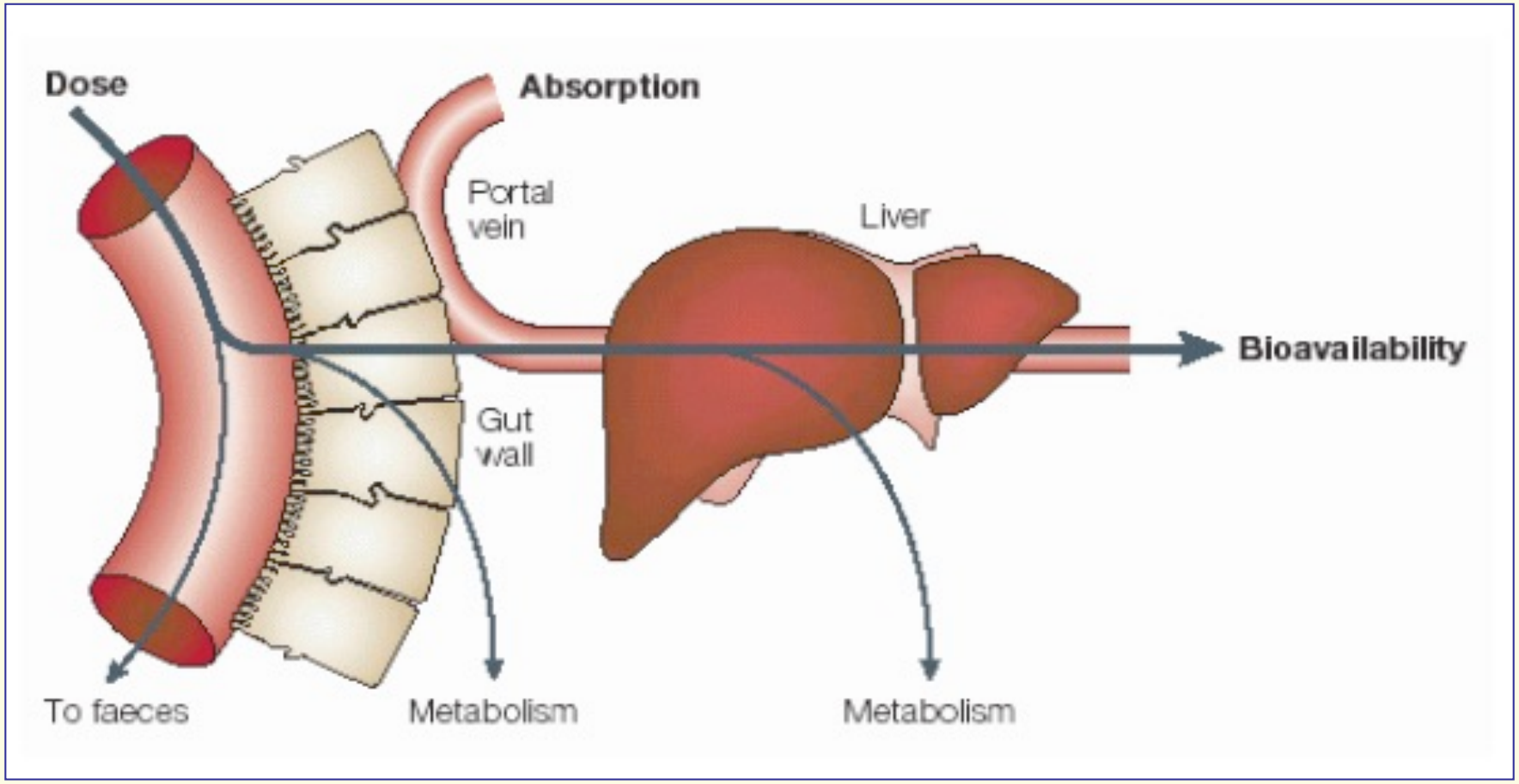
Drug metabolite

Different fates of drugs in the liver



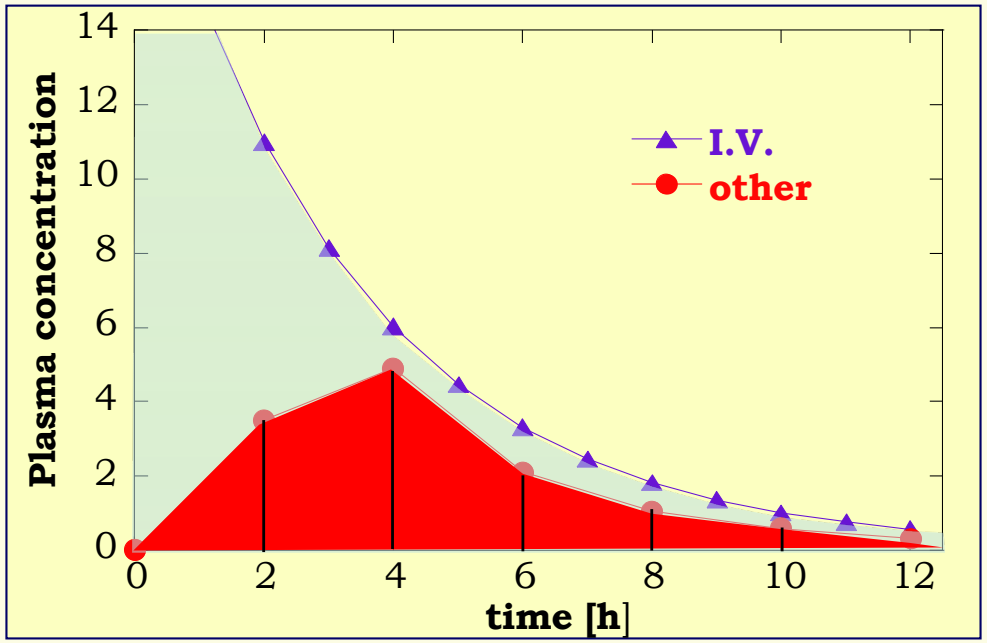
Adams & Eksteen, 2006

Enteral drug administration: Bioavailability



Bioavailability **refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action (100% when intravenously).**

Pharmacokinetics: Bioavailability



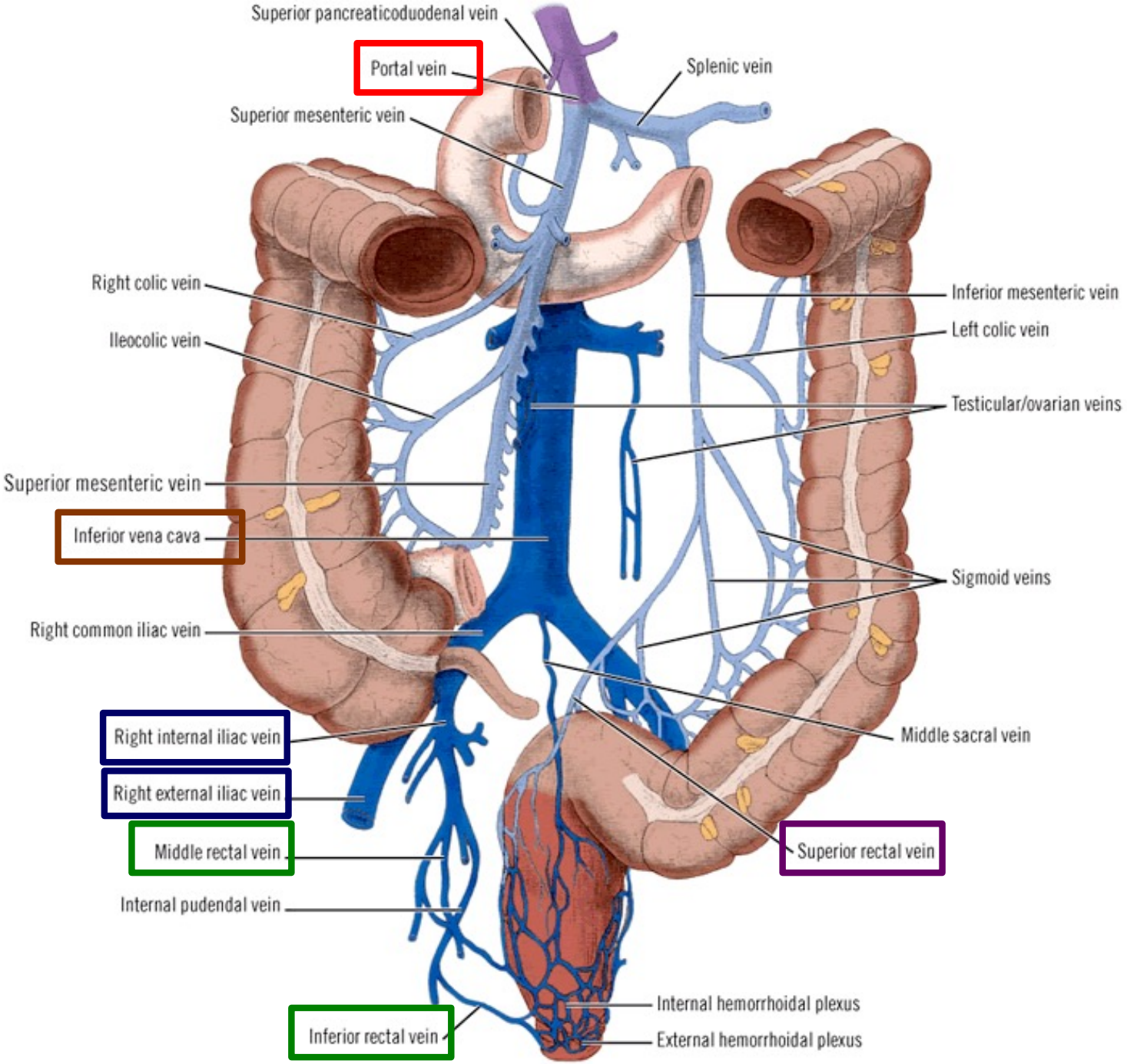
$$\text{Bioavailability} = \frac{\text{AUC}}{\text{AUC i.v.}}$$

AUC – area under the curve

i.v. - intravenously

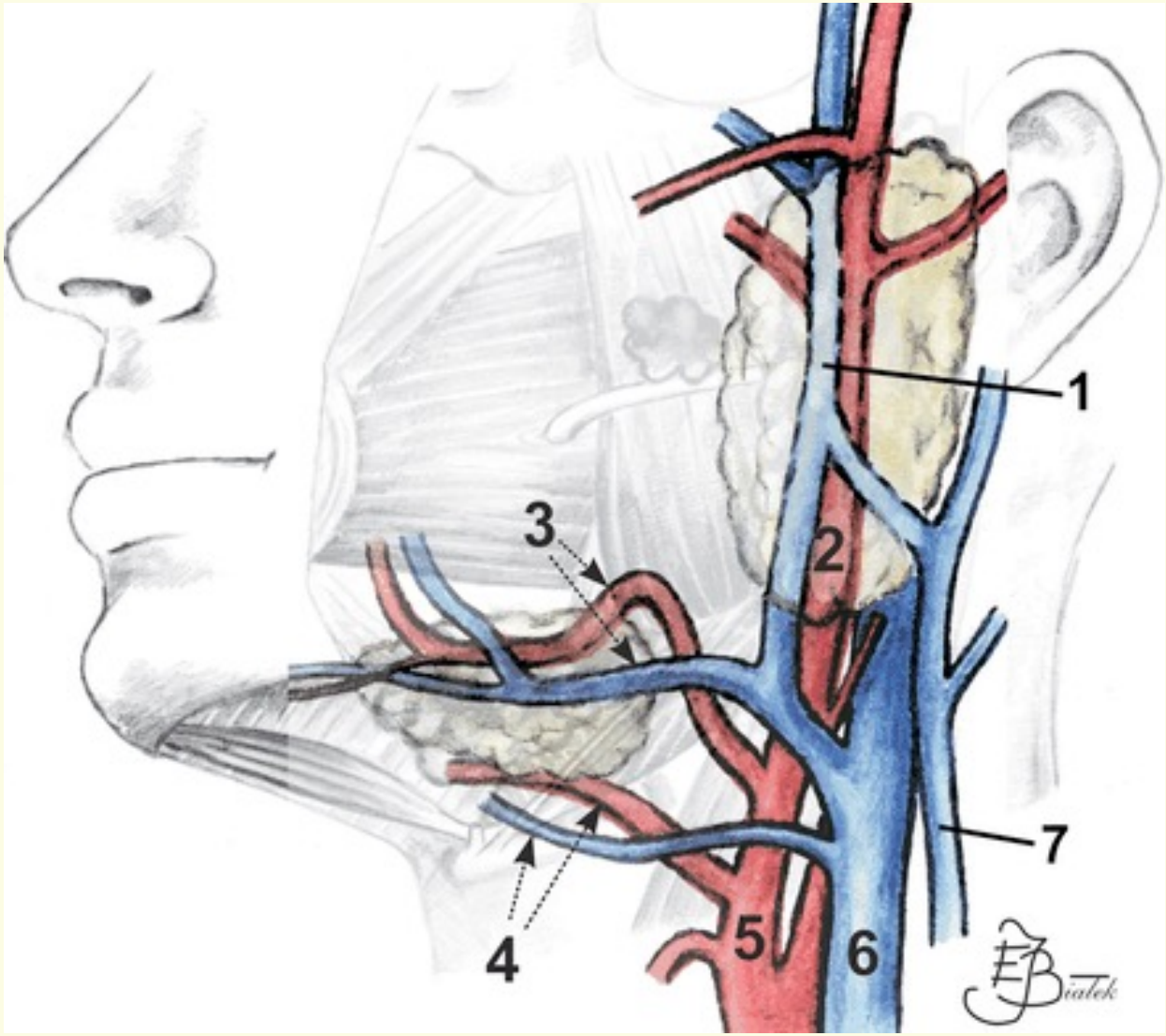
- For i.v. the bioavailability is = 1 (100% bioavailable)
- For other routes, the bioavailability is < 100 % due to:
  - incomplete absorption
  - first-pass metabolism
- Determined by comparison of AUC for a single i.v. dose and other ways of dosage.

Enteral exceptions: rectal suppositories



The upper (superior) rectal vein is connected with the portal system, while the middle and inferior rectal veins are connected via iliac veins with the inferior vena cava.

Enteral exceptions: sublingual absorption



to Superior Vena Cava

1 = retromandibular vein, 2 = external carotid artery, 3 = facial artery and vein,
4 = lingual artery and vein, 5 = external carotid artery, 6 = internal jugular vein,
7 = external jugular vein.

Factors affecting enteral drug absorption

1) Gastrointestinal motility

- decreased stomach emptying slows drug absorption
- can be decreased by food, disease, drugs.

2) Gastrointestinal blood flow

- removes drug from site of absorption (concentration gradient)
- limiting factor for highly absorbed drugs

3) Surface area

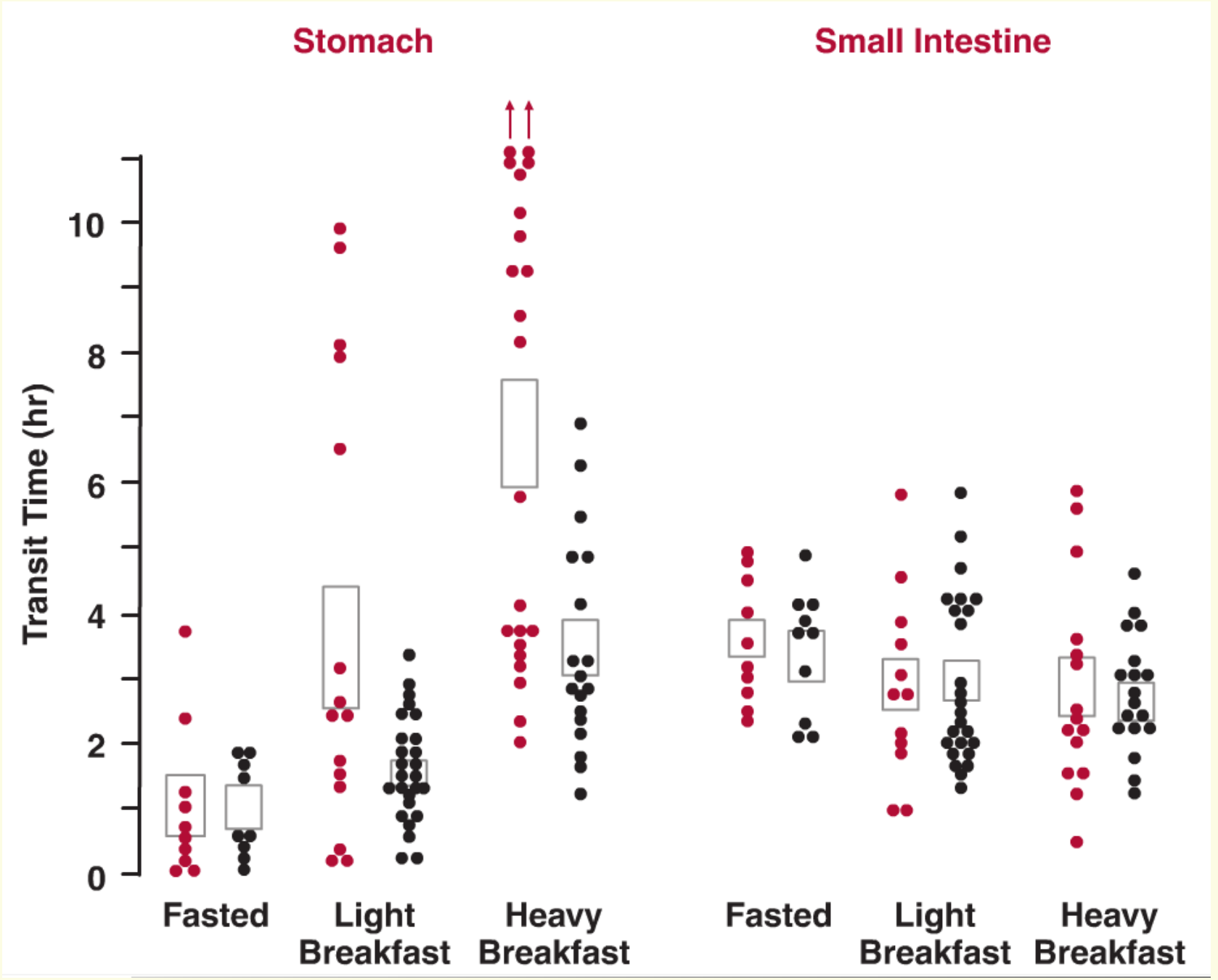
- surgery (most drug absorption occurs in the small intestine, ➔ duodenum)

4) Metabolism and efflux

- many drugs are metabolized in the intestinal wall
- many drugs are effluxed from enterocytes back to the gut lumen

5) Changes in pH of Gastrointestinal Tract

- affects polarity of drug
- can be altered by food, disease, other drugs



● small pellets ● large pellets

Absorption: routes of drug administration

- **Parenteral**

  - intravenous injection or infusion are the most rapid means for delivery of drugs to the systemic circulation
  - bypasses first-pass effect (100% bioavailability)
  - suitable for acid labile drugs

Common problems:

- may require professional administration
- costs associated with injection material and disposal
- requires sterile preparation

Absorption: routes of drug administration

- **Topical**

nasal

- local delivery of drugs (e.g. antihistamine sprays)

ocular

- local delivery of drugs e.g. pupil dilation, cataracts

vaginal

- local delivery of drugs (e.g. induction of labor)

rectal (dual classification)

- systemic delivery of potent drugs
- local delivery of drugs (e.g. analgesics)

sublingual (dual classification)

- systemic delivery of potent drugs (nitroglycerine)

Achieve rapid onset of action, bypasses first-pass effect, suitable for acid labile drugs.

Absorption: routes of drug administration

- **Topical**

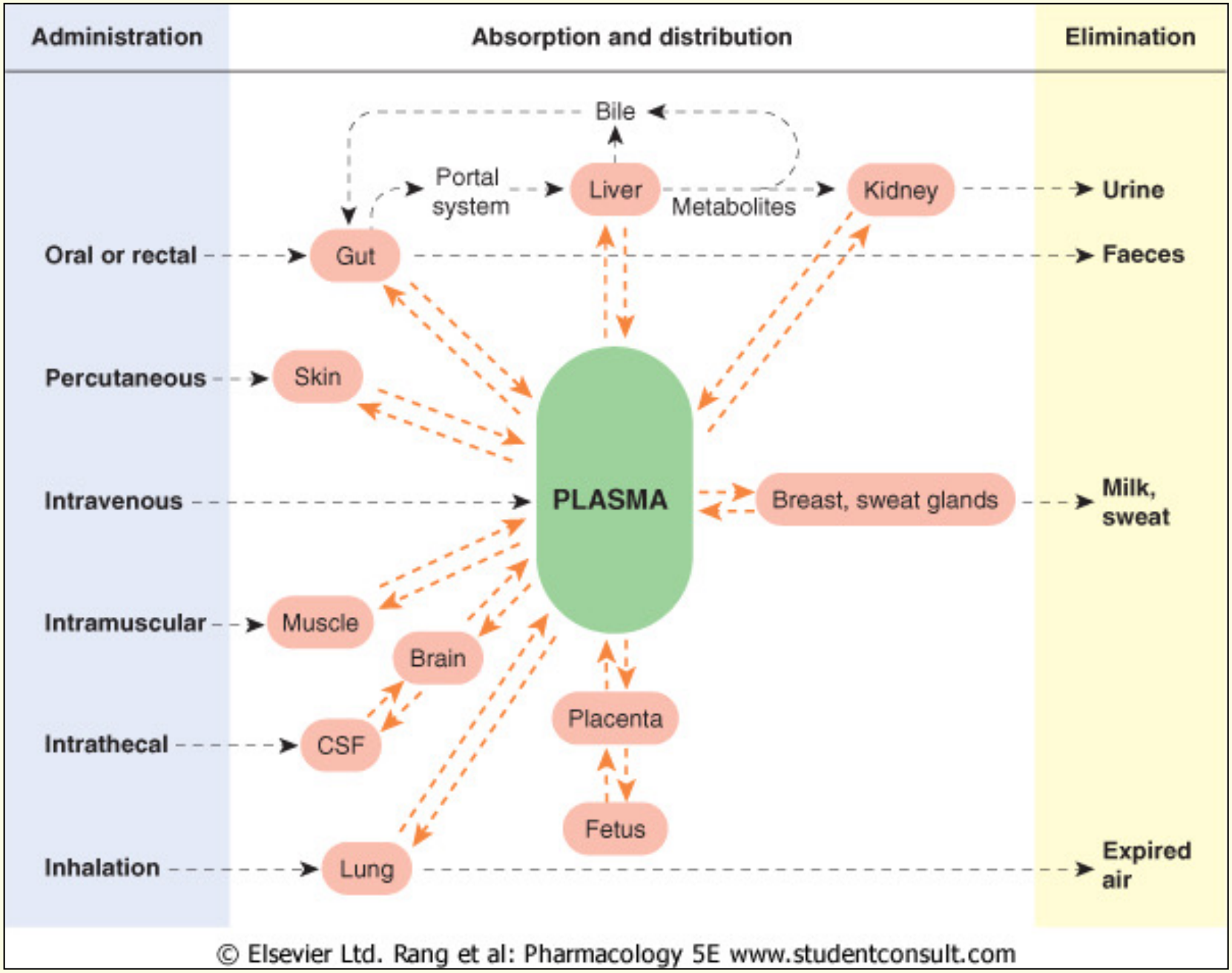
inhalation

- for systemic delivery of potent drugs (e.g. anesthetics)
- local delivery of drugs (asthma inhalers)
- bypass first-pass effect
- many drugs are lung irritants (pain, expulsion)

percutaneous (transdermal)

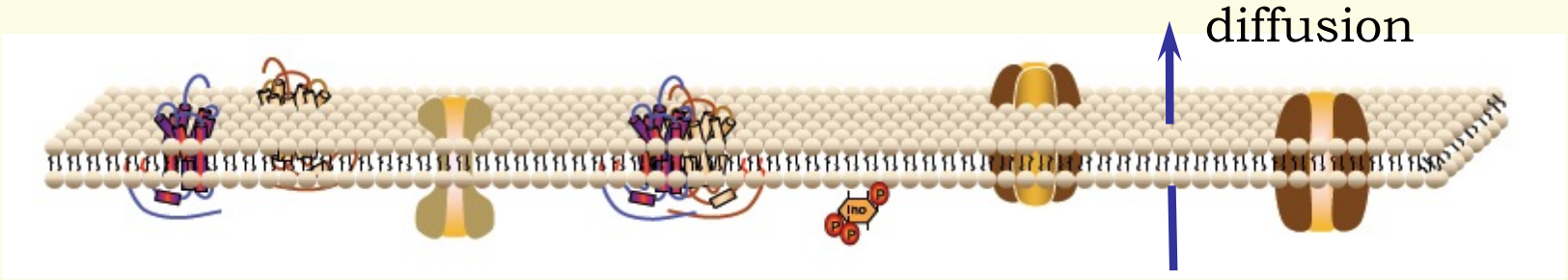
- systemic delivery of potent drugs (e.g. nicotine patch)
- local delivery of drugs (analgesic or antibiotic creams)
- bypass first-pass effect
- can achieve long-term delivery of controlled dose
- may be increased in elderly due to thinning of dermal layer, depends on the state of the skin

Roots of drug administration: Résumé



Drug Absorption

- The process by which a drug moves from the site of administration to the blood or site of action.
- Requires passage across epithelial cell layers.

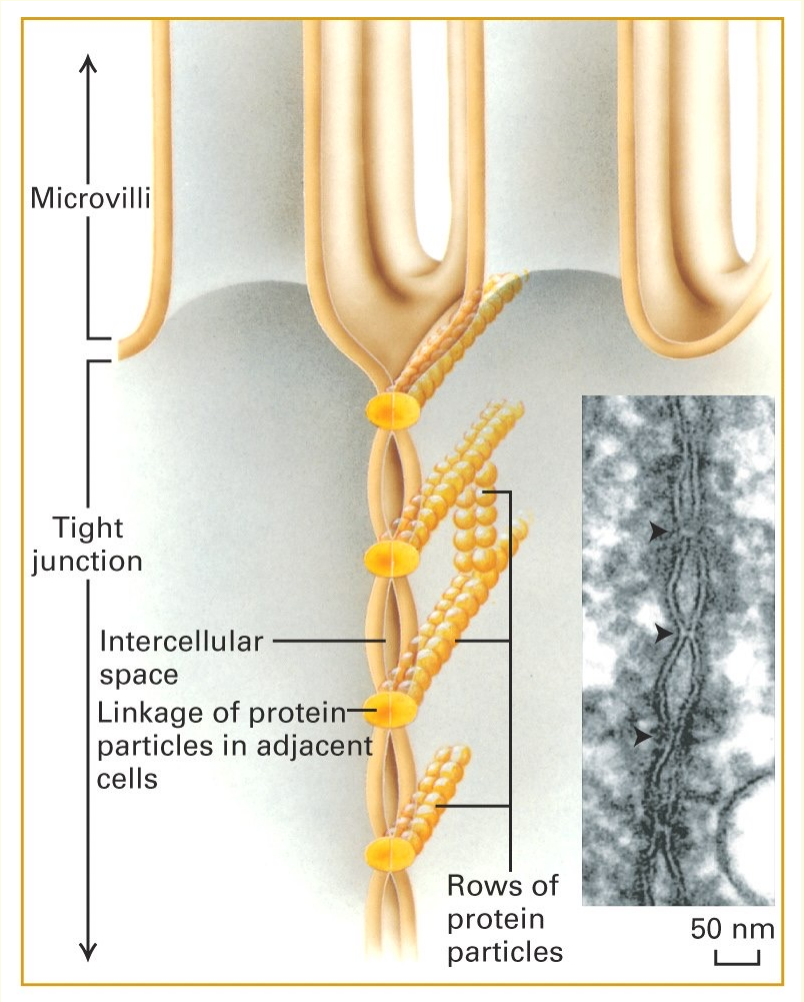


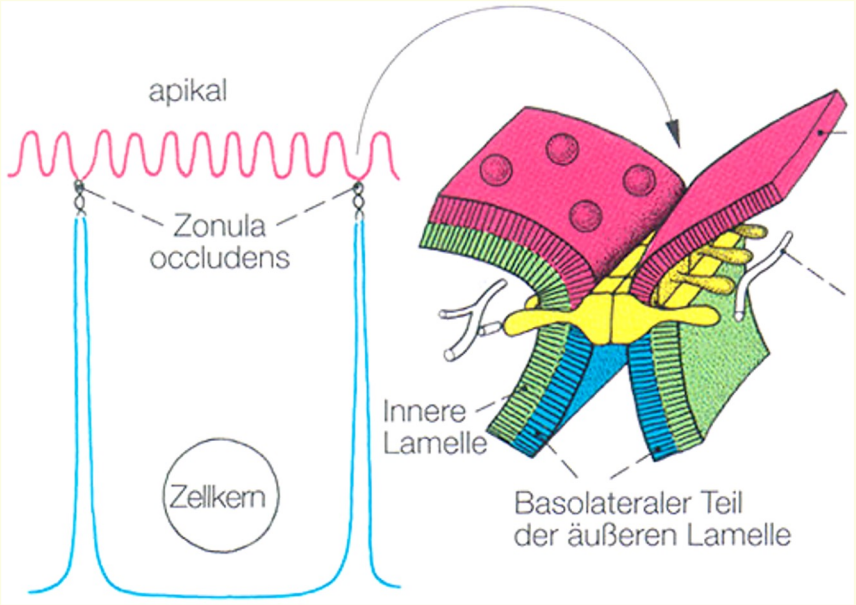
- Possible Mechanisms of Drug Absorption:
  - A. Paracellular: Diffusion
  - B. Transcellular: Carrier-mediated (facilitated) transport
  - C. Transcellular: Endocytosis
  - D. Transcellular: Transmembrane diffusion (non-facilitated)

Drug Absorption: A. Paracellular diffusion

In general, paracellular transport represents poor absorption:

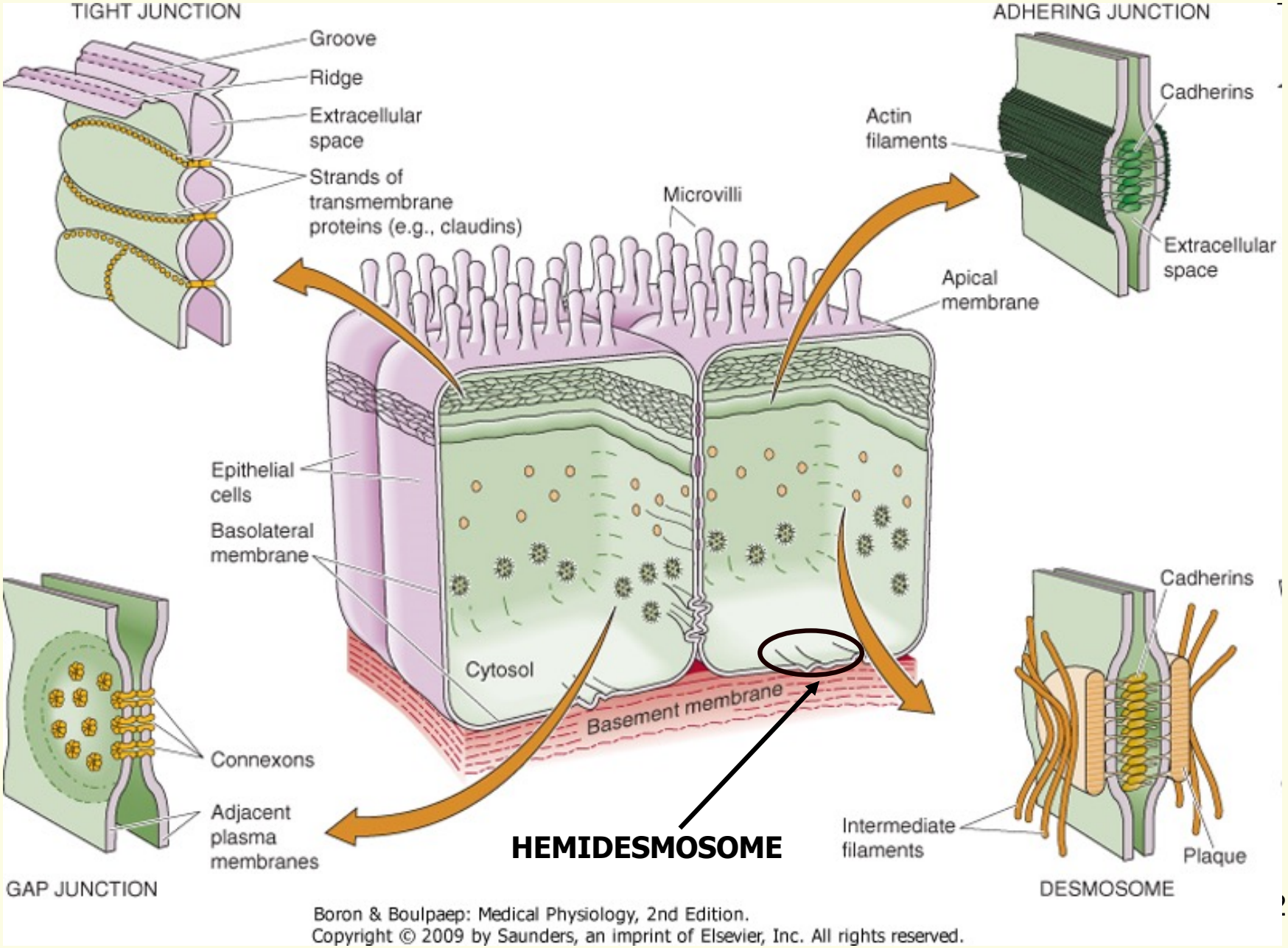
- low surface area (0.01 % of total cell surface facing central compartment)
- tight junction complex in GIT





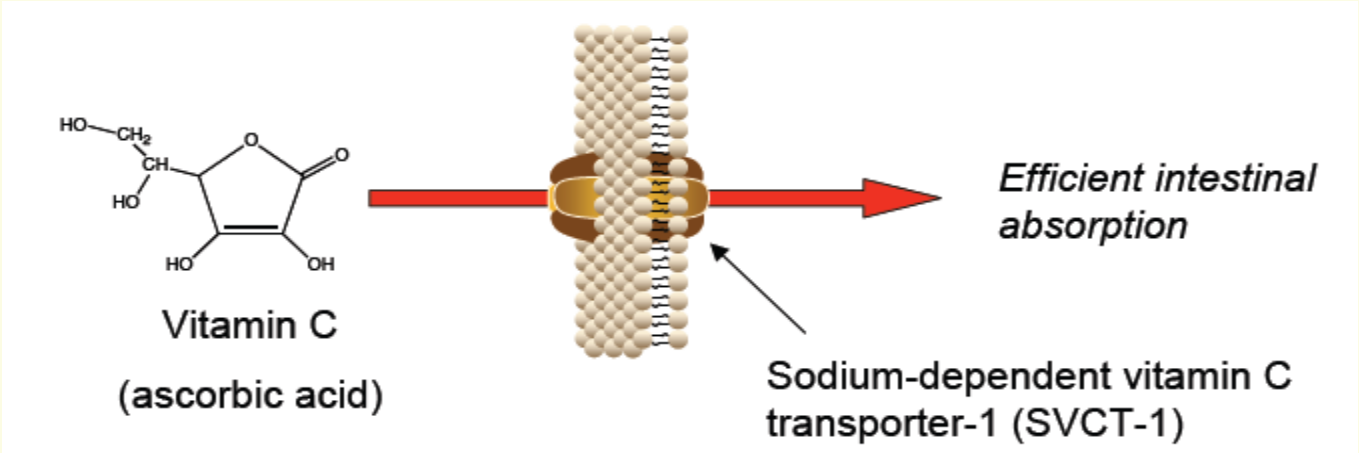
- Tight junctions demarcate the boundary between the apical and basolateral membrane domains of a cell

Tight junctions and drug absorption

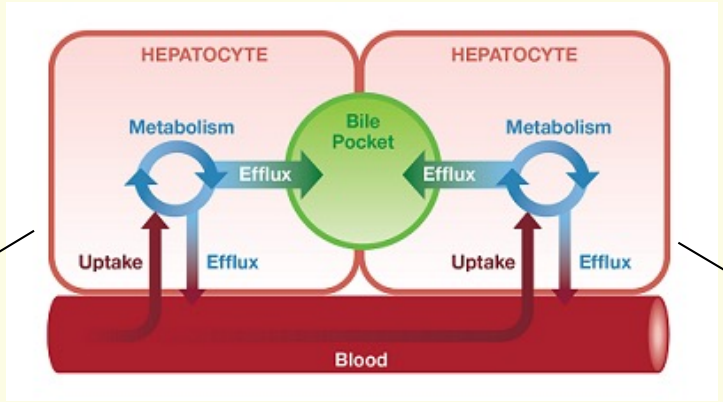


Drug Absorption: B. Carrier-mediated (facilitated) transport (transcellular)

- Compared to diffusion:
  - not common for drugs, but common for drug metabolites
  - requires specific transport proteins
  - requires energy expenditure (active)
  - saturable
  - inhibitable



Carrier-mediated transport: hepatocytes



Hepatocyte

Hepatocyte

Phase I metabolism

CYP450

UGT

NAT2

GST

Phase II metabolism

OATP1B1

OATP1B3

OATP2B1

OCT1

OCT3

OAT2

OAT7

NTCP

Basolateral/sinusoidal membrane

BSEP

ABCB1

MDR3

MRP2

Bile canaliculus

Apical/canalicular membrane

APT8B1

MATE1

ABCG5/8

ABCG2

Tight junction

MRP3

MRP4

MRP6

Basolateral/sinusoidal membrane

Carrier-mediated transport: kinetics

- **Occurs in accordance with MICHAELIS-MENTEN kinetic**

$$\textbf{Absorption rate (V)} = \frac{\textbf{Vmax} \cdot \textbf{C}}{\textbf{Km} + \textbf{C}}$$

- **If C is very small versus Km (small dose)**

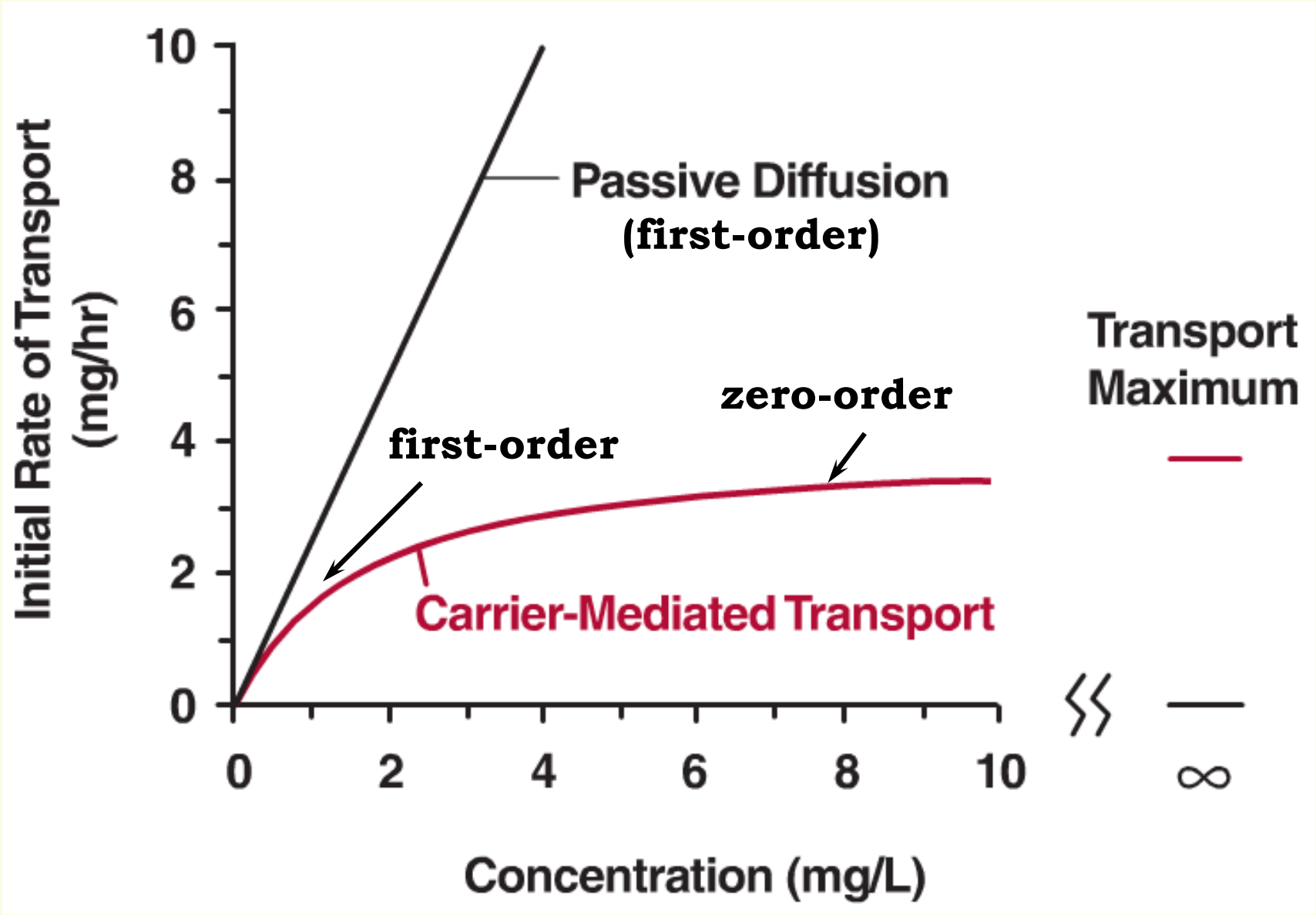
$$\textbf{V} = \frac{\textbf{Vmax} \cdot \textbf{C}}{\textbf{Km}} \qquad \textbf{first-order kinetic!}$$

- **If C is very big versus Km (high dose)**

$$\textbf{V} = \textbf{Vmax} \qquad \textbf{zero-order kinetic!}$$

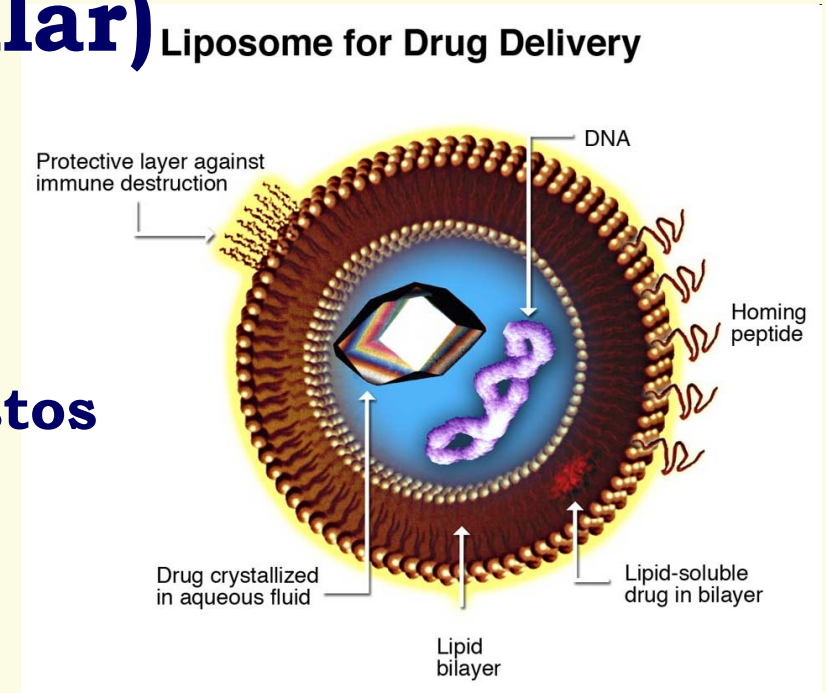
- A **zero-order reaction** has a rate that is **independent** of the concentration of the reactant.
- In a **first-order reaction** the rate is **directly proportional** to the concentration of the reactant.

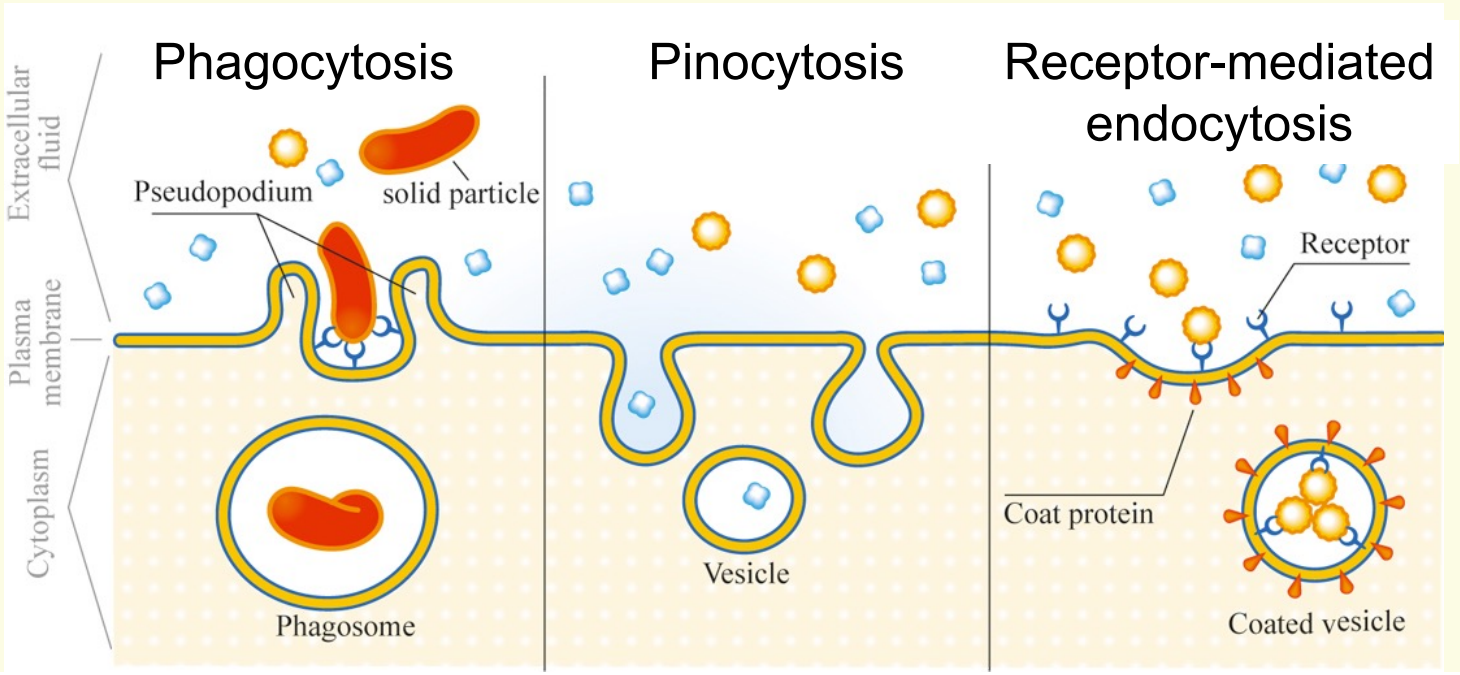
Passive diffusion vs carrier-mediated transport



Drug Absorption: C. Endocytosis (transcellular)

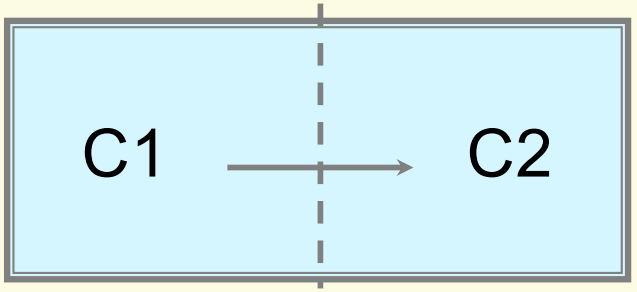
- **Compared to diffusion:**
  - **not common for drugs**
  - **absorption of some vitamins, asbestos**
  - **currently tested for drug delivery**





Drug Absorption: D. Transmembrane diffusion (non-facilitated or passive)

- **Most common mean of drug absorption**
- **Rate of passive diffusion depends on :**
  - Surface of absorption (S)
  - Drug size (usually 100-500 MW)
  - Drug ionization
    - lipid/water partition coefficient
    - coefficient of diffusion in lipids
  - Concentration gradient across the membrane (usually very large) – thus, <u>first order</u> kinetic



Passive diffusion: Fick's law

$$\frac{dQ}{dt} = \frac{DSk(C1 - C2)}{e}$$

Q - net quantity of drug transferred across the membrane

t - time

C_1 C_2 - concentrations of the drug at two sides of the membrane

e - thickness of the membrane (50 Å)

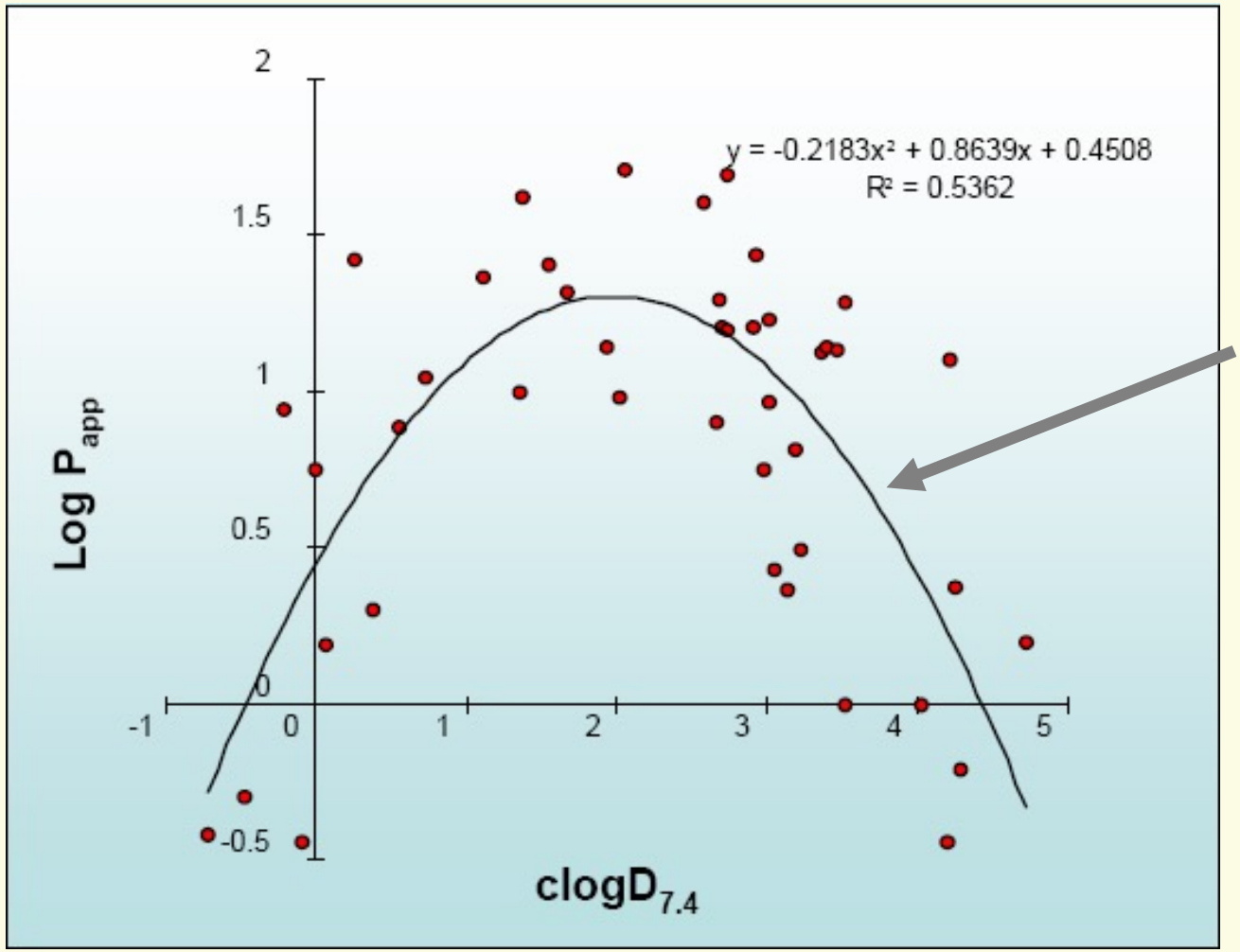
S - surface area of the membrane

D - coefficient of diffusion in lipids

k - lipid/water partition coefficient of the drug

~ drug ionization

Transmembrane diffusion: biphasic effect of lipophilicity



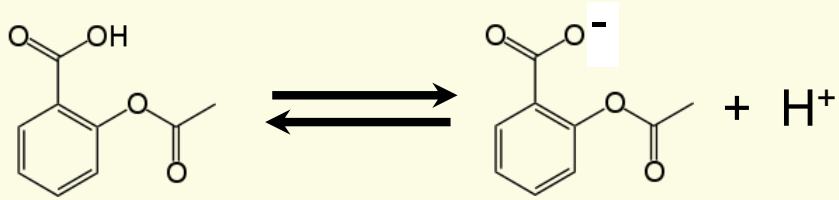
Permeability

Membrane retention

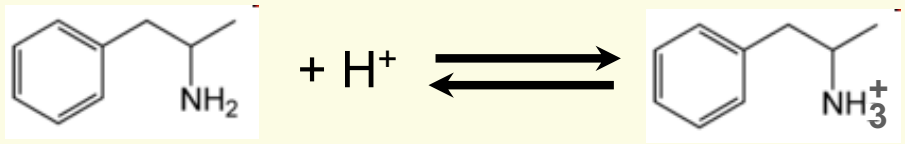
Lipophilicity

Transmembrane diffusion: drug ionization

- **most drugs are weak acids or bases that are present in solution as both unionized and ionized species**
- **a weak acid is defined as a neutral molecule that can reversibly dissociate into an anion and a proton**

neutral aspirin  + H^+ aspirin anion

- **a weak base is defined as a neutral molecule that can form a cation by combining with a proton**

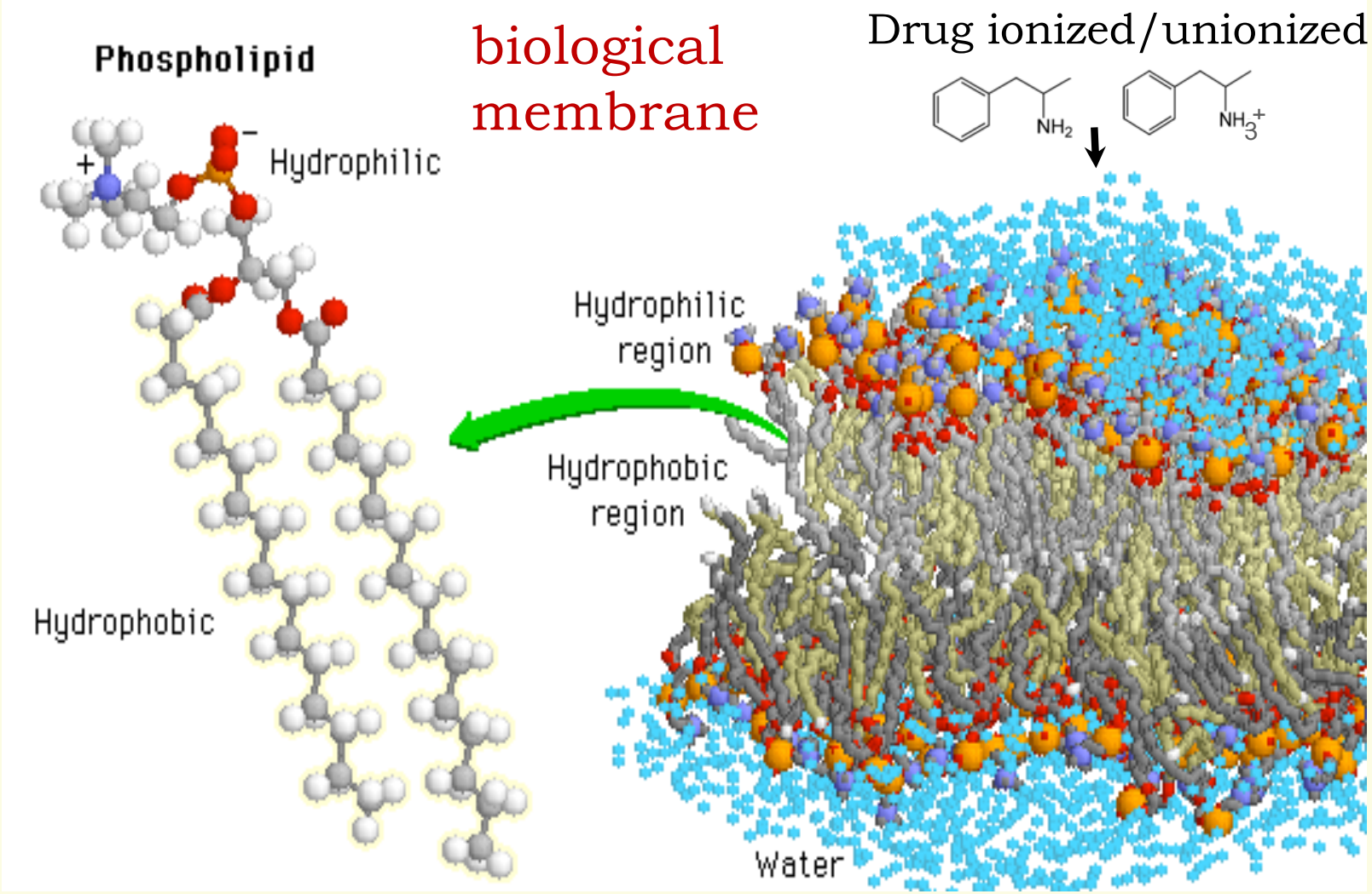
neutral amphetamin  + H^+ amphetamin cation

n.b. most drugs-weak bases are amine-containing molecules:

$$R\text{-}NH_2 \leftrightarrow R\text{-}N^+H_3$$

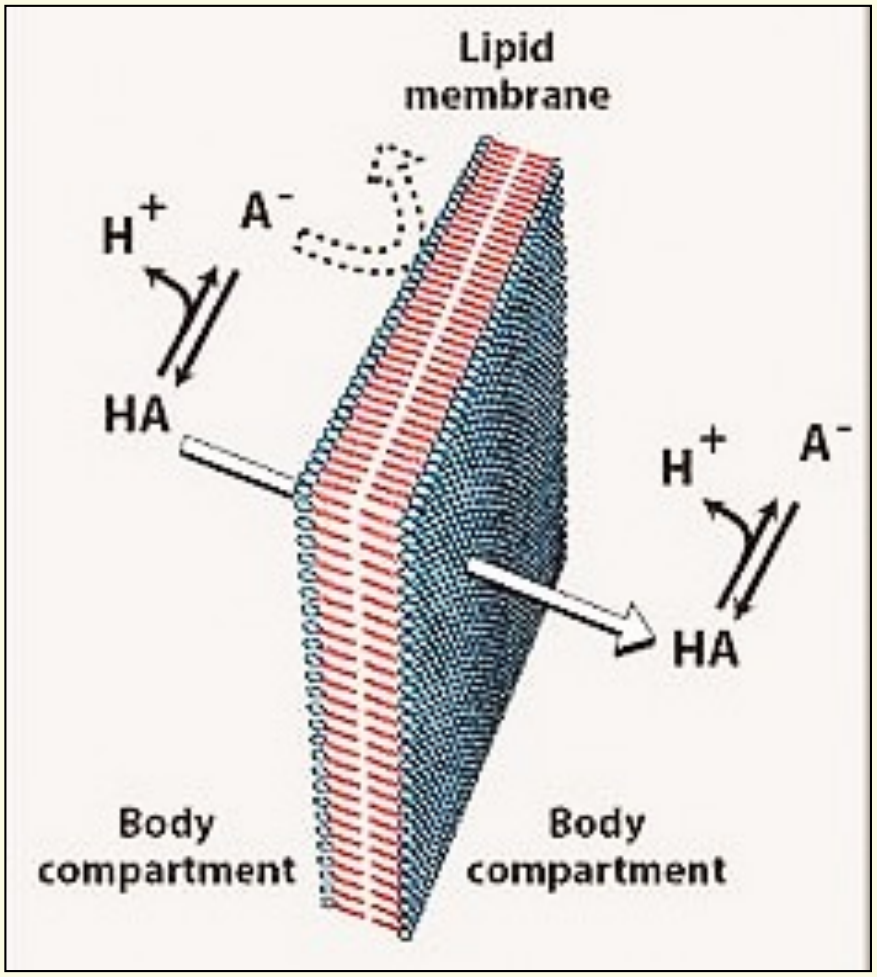
Effect of ionization on drug transmembrane diffusion

- **The central principle is that only unionized (neutral) form of drugs is capable of crossing biological membranes**

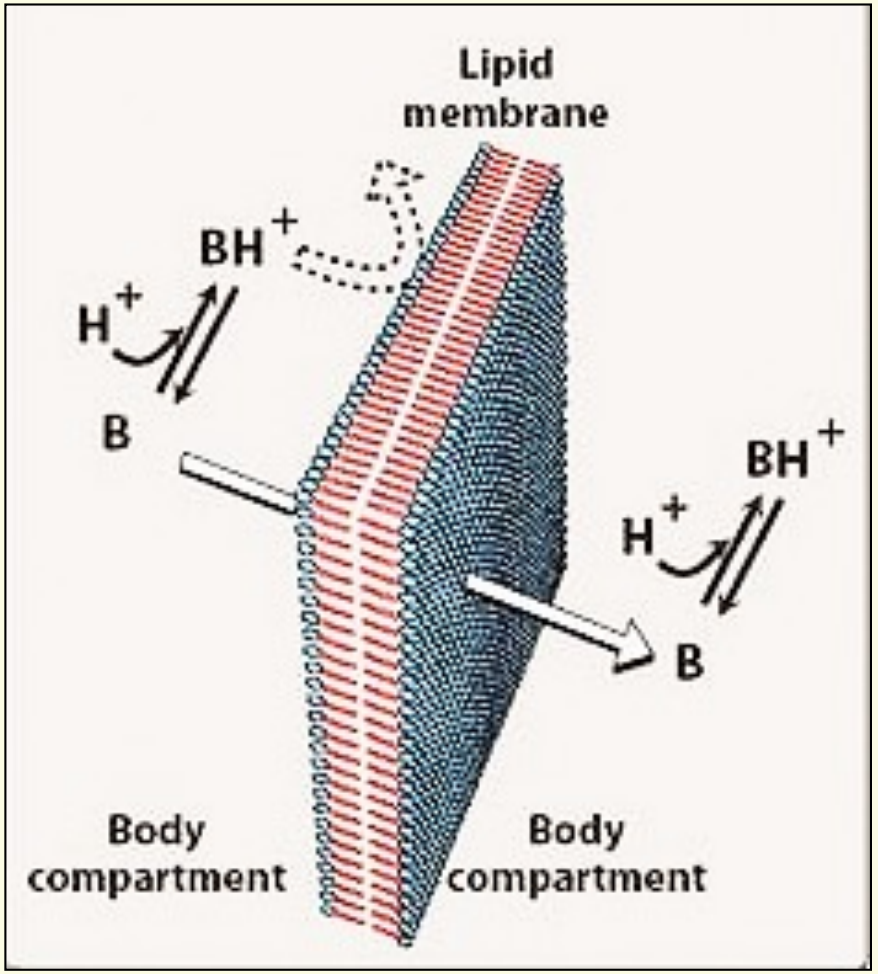


Effect of ionization on drug transmembrane diffusion

Weak acid



Weak base



Ionization of weak acids and bases: Henderson-Hasselbalch equation

For a weak acid that dissociates as follows: $HA \rightleftharpoons H^+ + A^-$

$$\text{acid ionization constant} = Ka = \frac{[H^+] \times [A^-]}{[HA]}$$

For a weak base that associates as follows: $B + H_2O \rightleftharpoons BH^+ + OH^-$

$$\text{base ionization constant} = Kb = \frac{[BH^+] \times [OH^-]}{[B]}$$

Ionization of weak acids and bases: Henderson-Hasselbalch equation

$$\log_{10}Ka = \log_{10}[H^+] + \log_{10}[A^-] - \log_{10}[HA] \rightarrow$$

$$- \log_{10}[H^+] = - \log_{10}Ka + \log_{10}[A^-] - \log_{10}[HA]$$

equation: $pH = pKa(HA) + \log_{10}\left(\frac{[A^-]}{[HA]}\right)$ ➔ pKa=pH at which the molecule is 50% ionized

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$$\log_{10}Kb = \log_{10}[BH^+] + \log_{10}[OH^-] - \log_{10}[B]$$

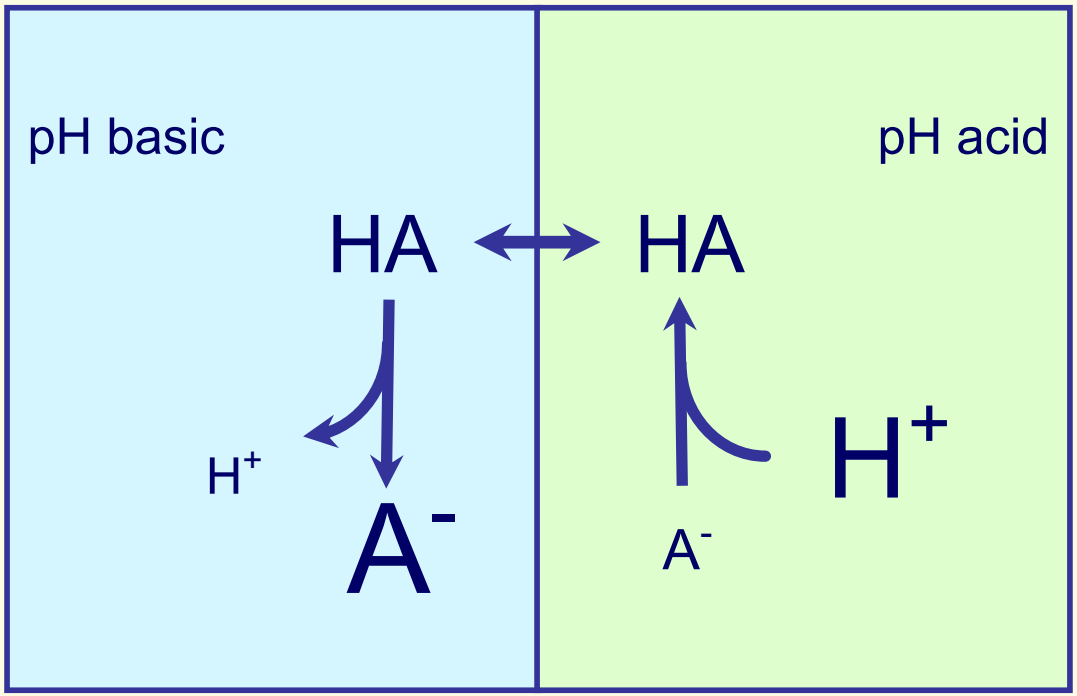
equation: $pOH = pKb + \log_{10}\left(\frac{[BH^+]}{[B]}\right)$ $pOH + pH = pKa + pKb = 14$ ➔

$14 - pH = 14 - pKa + \log_{10}\left(\frac{[BH^+]}{[B]}\right)$ ➔ equation $pH = pKa(BH^+) + \log_{10}\left(\frac{[B]}{[BH^+]}\right)$

$$\left(\frac{[HA]}{[A^-]}\right) = 10^{\,pKa - pH} \qquad \left(\frac{[BH^+]}{[B]}\right) = 10^{\,pKa - pH}$$

Non-ionic diffusion of weak acids and bases

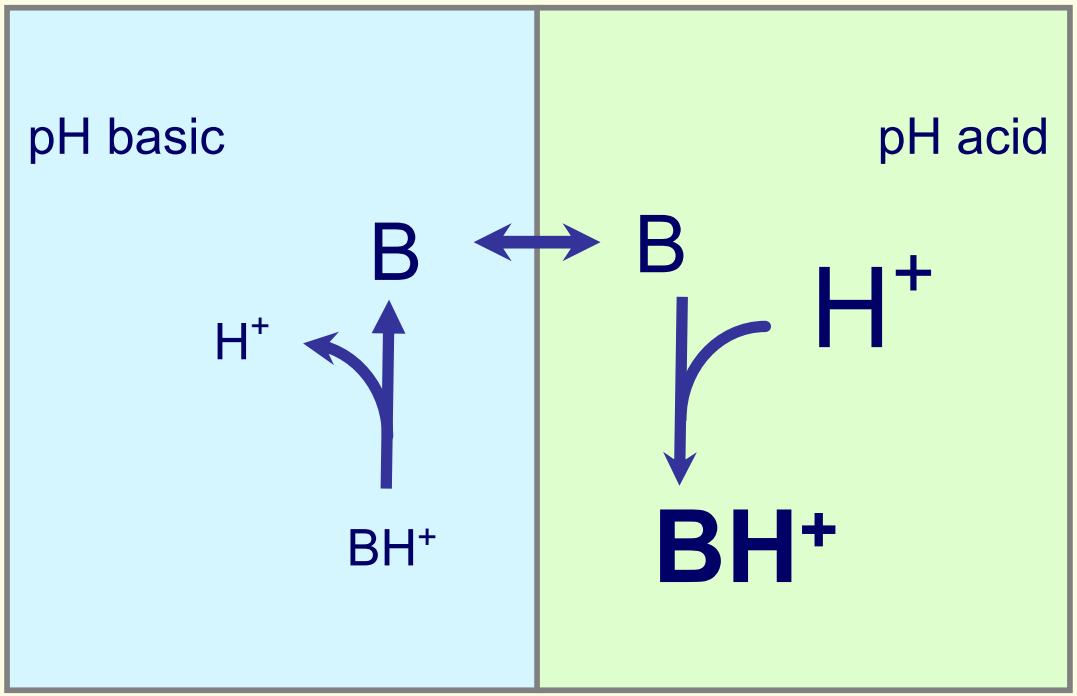
$$\left(\frac{[HA]}{[A^-]}\right) = 10^{\,pKa - pH}$$



- a weak acid is accumulated in the basic compartment

Non-ionic diffusion of weak acids and bases

$$\left(\frac{[BH^+]}{[B]}\right) = 10^{\,pKa - pH}$$



- a weak base is accumulated in the acid compartment

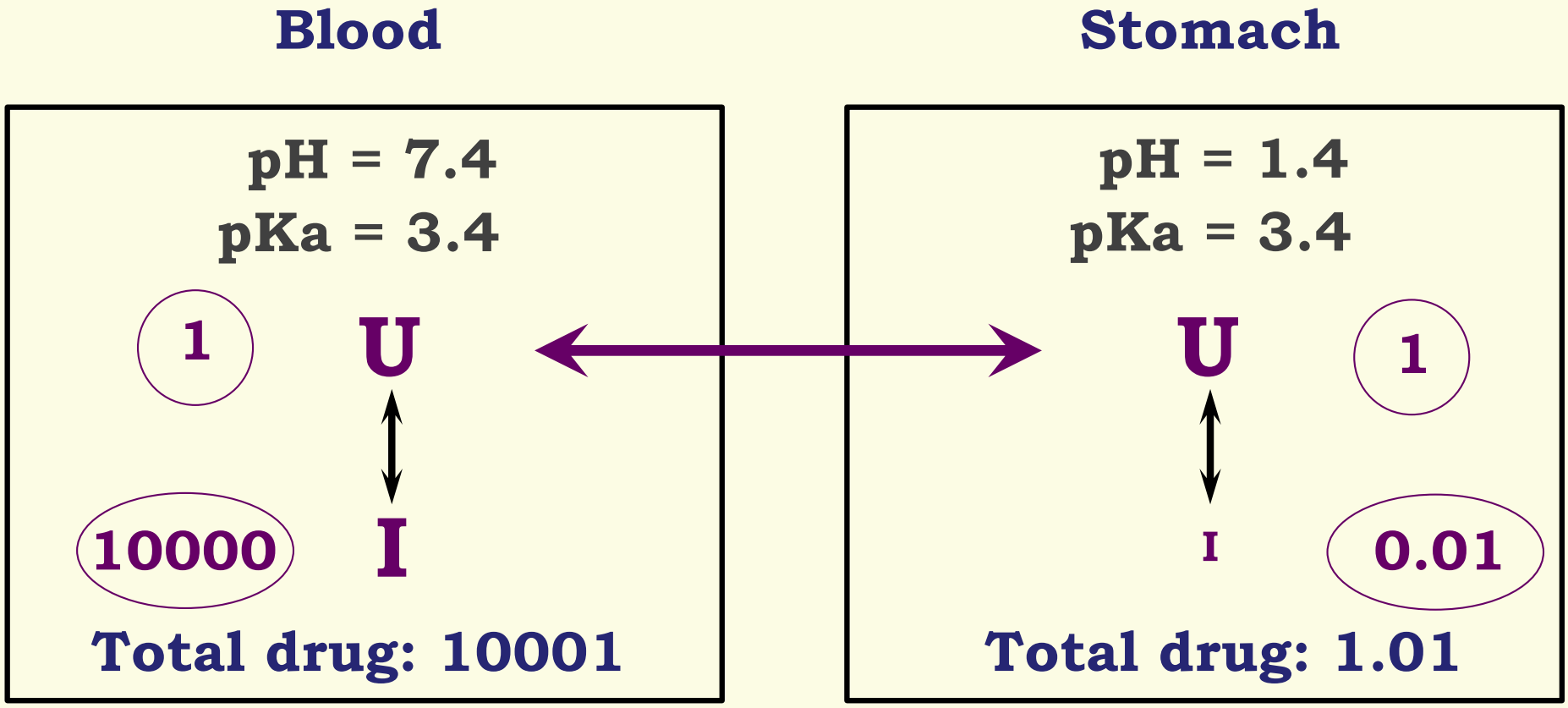
Example: absorption of aspirin from the stomach

- Aspirin is a weak acid, pKa = 3.4
- Stomach pH = 1.4 Blood pH = 7.4

$$\left(\frac{[HA]}{[A^-]}\right) = 10^{pKa - pH} = 100$$ Stomach

$$\left(\frac{[HA]}{[A^-]}\right) = 10^{pKa - pH} = 0.0001$$ Blood

Example: absorption of aspirin from the stomach



- Conclusion: aspirin will move from the stomach into the blood

U – unionized form of the drug; I – ionized form of the drug

Example: absorption of codeine from the stomach

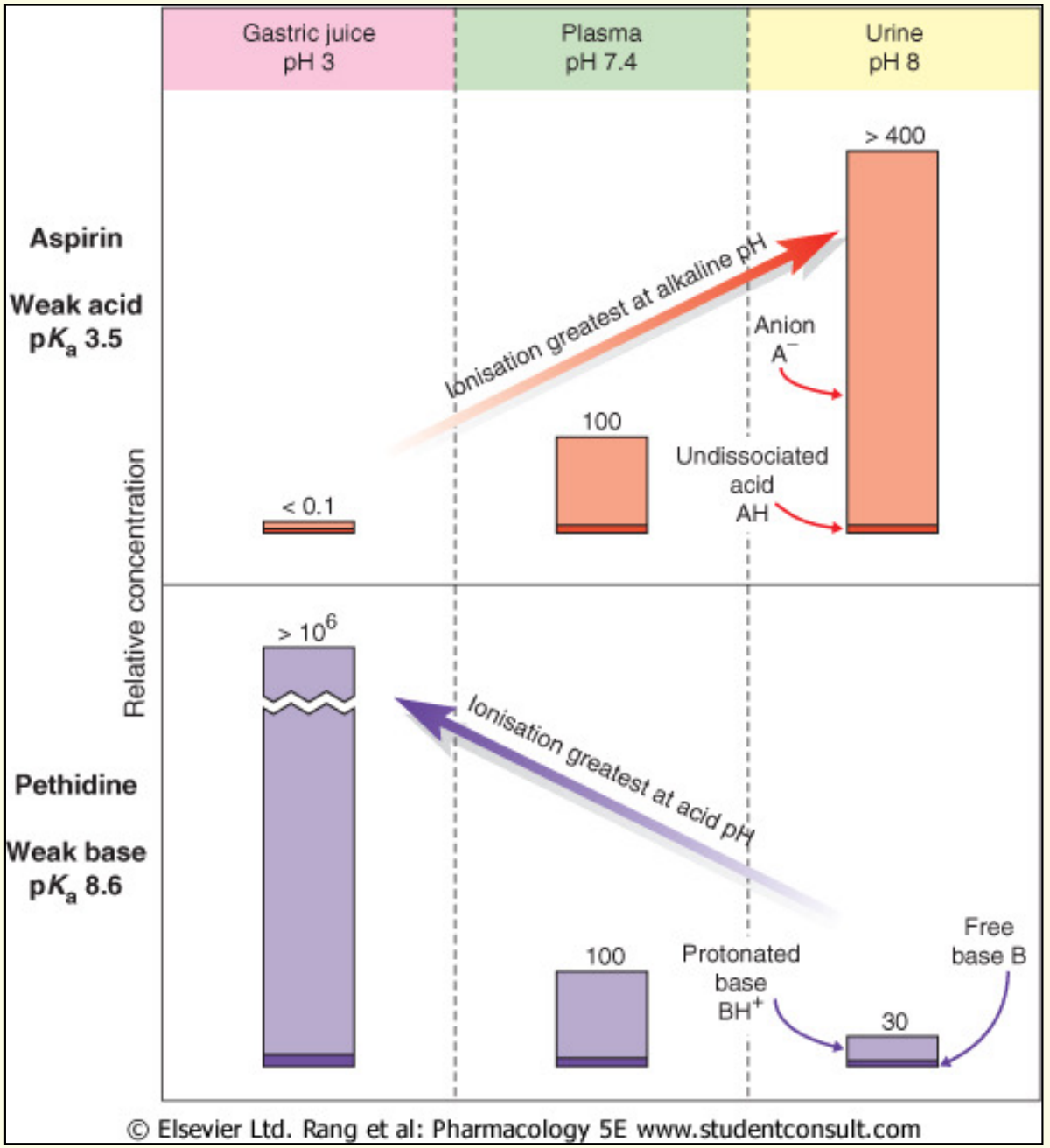
- Codeine is a weak base, pKa = 7.9
- Stomach pH = 1.9 Blood pH = 7.4

$$\left(\frac{[BH^+]}{[B]}\right) = 10^{pKa - pH} = 1000000$$ Stomach

$$\left(\frac{[BH^+]}{[B]}\right) = 10^{pKa - pH} = \sim 3$$ Blood

- Conclusion: little or no codeine will move from the stomach into the blood

Partition of aspirin (a weak acid) and pethidine (a weak base) between aqueous compartments

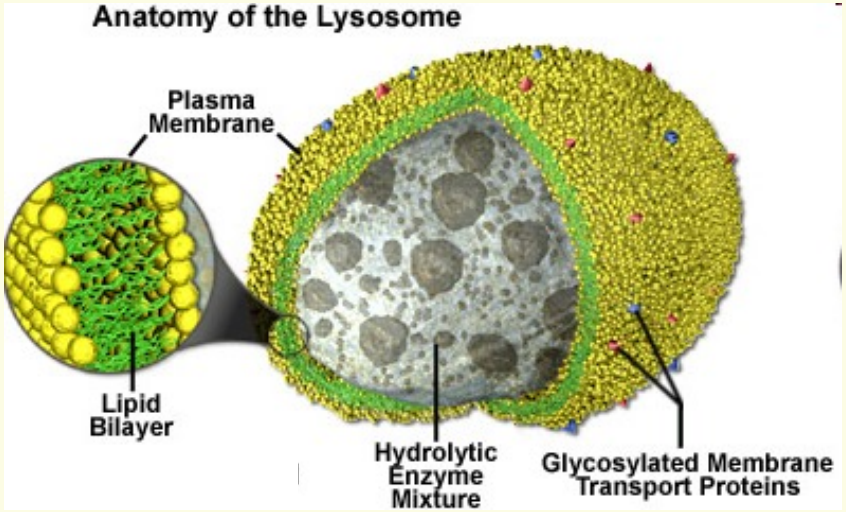


Drug ionization - exercise

- A strong acid has a high pKa (T/F)
- If you wish to enhance the renal elimination of a weak base you would acidify or alkalinize the urine (with ammonium chloride or bicarbonate?)
- If a weak base is administrated intravenously eventually a higher concentration will be found in the gastric juice than in the blood (T/F)

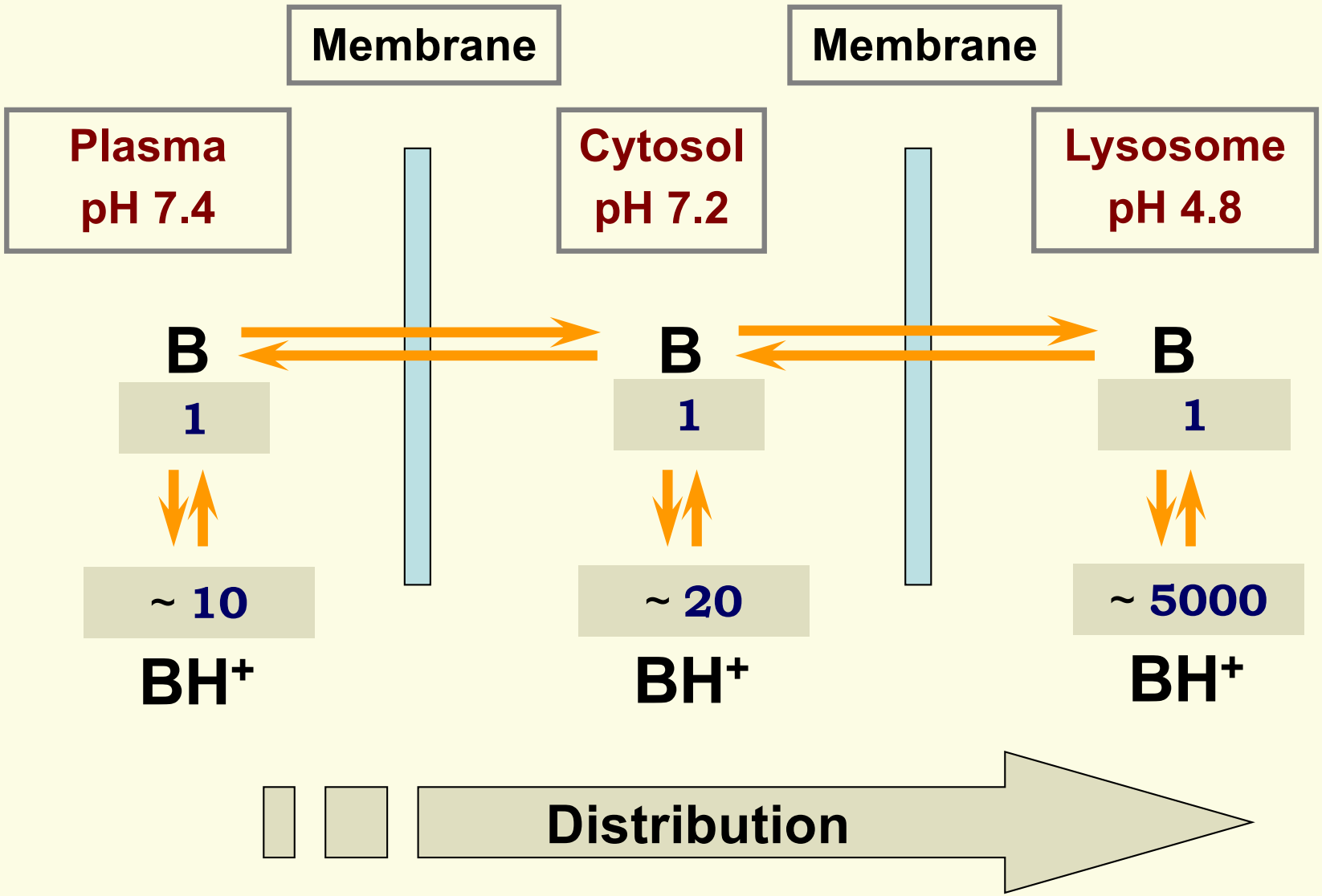
Drug trapping organelles: lysosomes

- Lysosomes are membrane-enclosed organelles
- Contain a range of hydrolytic enzymes responsible for autophagic and heterophagic digestion
- Abundant in lung, liver, kidney, spleen with smaller quantities in brain and muscle
- pH maintained at ~ 5 (4.8)



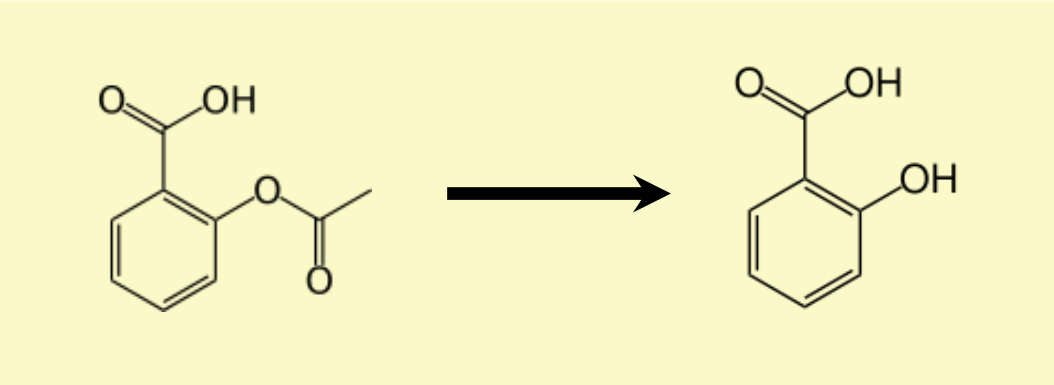
Drug trapping: lysosomes

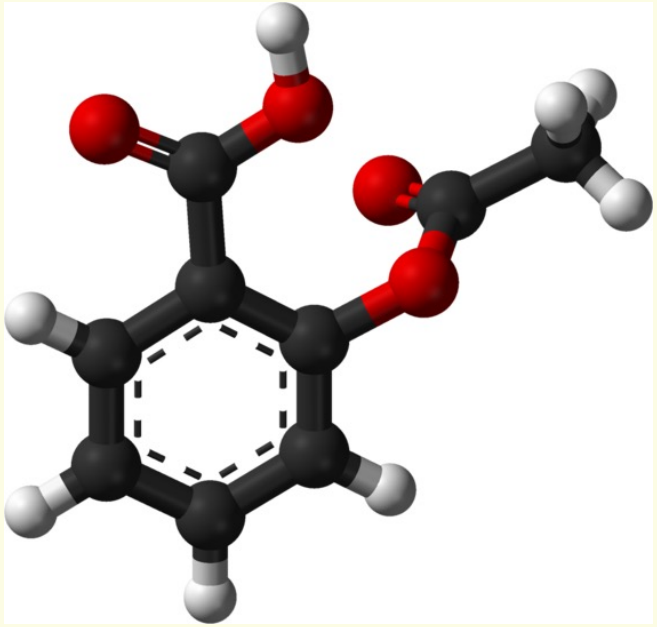
- **ion trapping of a weak base pKa ~ 8.5**



Clinical case: salicylate poisoning

- Aspirin – analgesic, antipyretic, anti-inflammatory, anti-clotting,…
- Aspirin (acetylsalicylic acid) is metabolized to an active component – salicylic acid
- Mechanism – inhibition of prostaglandin synthase
- pKa ~ 3.49





Salicylate poisoning statistics (USA)

- 10’000 tons of aspirin are consumed in the US/year
- source of both accidental and suicidal ingestion.
- 24’700 cases in 2014 (60 fatalities)
- 3’837 cases in patients younger than 8 years
- in acute overdose (2009, source - FDA)

  16% morbidity/mortality

- in chronic intoxication

  30% morbidity/mortality

Clinical case: salicylate poisoning

- Due to its acidic nature and extensive ionization, salicylate is not readily distributed into the CNS (Blood-Brain barrier)
- But, after an overdose, salicylate enters the CNS where the drug stimulates the respiratory center in the brainstem by uncoupling oxidative phosphory-lation cycle in mitochondria
- This promote reduction in blood CO_2
- The loss of blood CO_2 leads to a rise in blood pH – **respiratory alkalosis**

Timbrell, 1999

Clinical case: salicylate poisoning

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

$$Ka = \frac{H^+ \times HCO_3^-}{H_2CO_3} \qquad pH = pKa + \log \frac{HCO_3^-}{H_2CO_3}$$

$$PaCO_2 \approx 33 \times H_2CO_3 \qquad pH = pKa + \log \frac{HCO_3^-}{0.03 \times PaCO_2}$$

- **alkalosis:**

  mild poisoning causes nausea, vomiting, tinnitus, lethargy or dizziness.

  more severe poisoning causes dehydration, restlessness, sweating, warm extremities with bounding pulses, increased respiratory rate, hyperventilation and deafness.

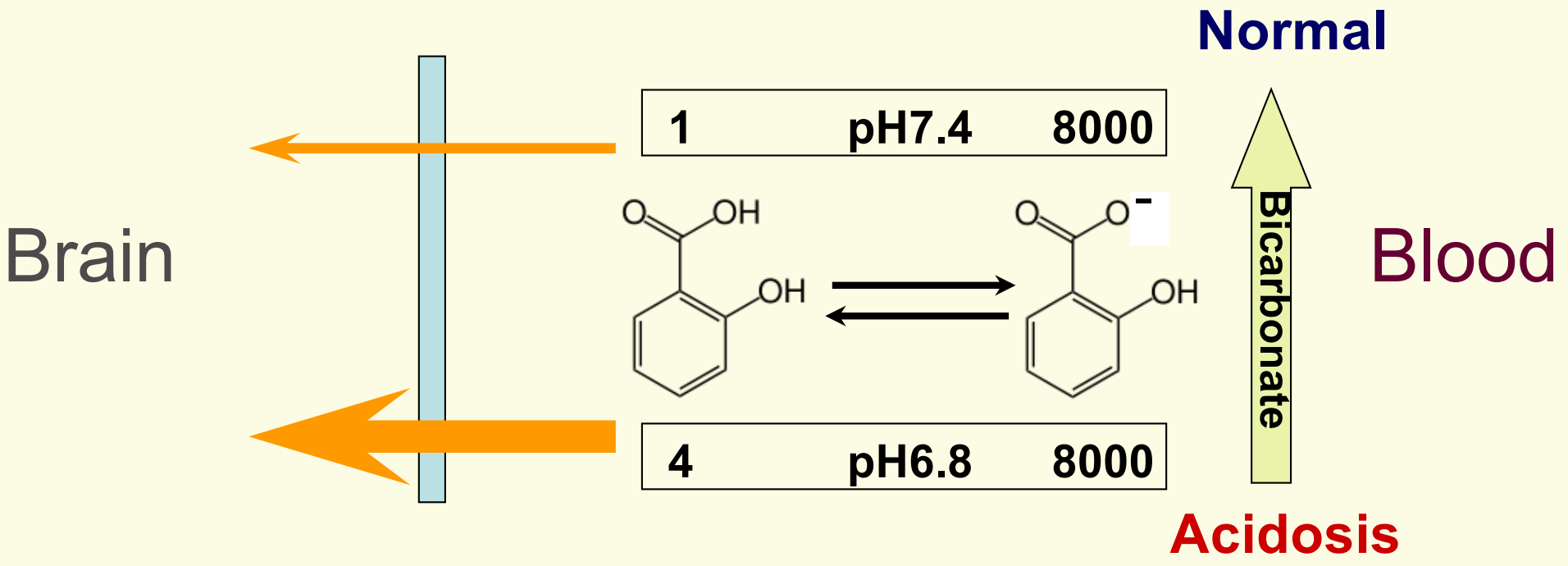
Clinical case: salicylate poisoning

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

$$pH = pKa + \log \frac{HCO_3^-}{0.03 \times PaCO_2}$$

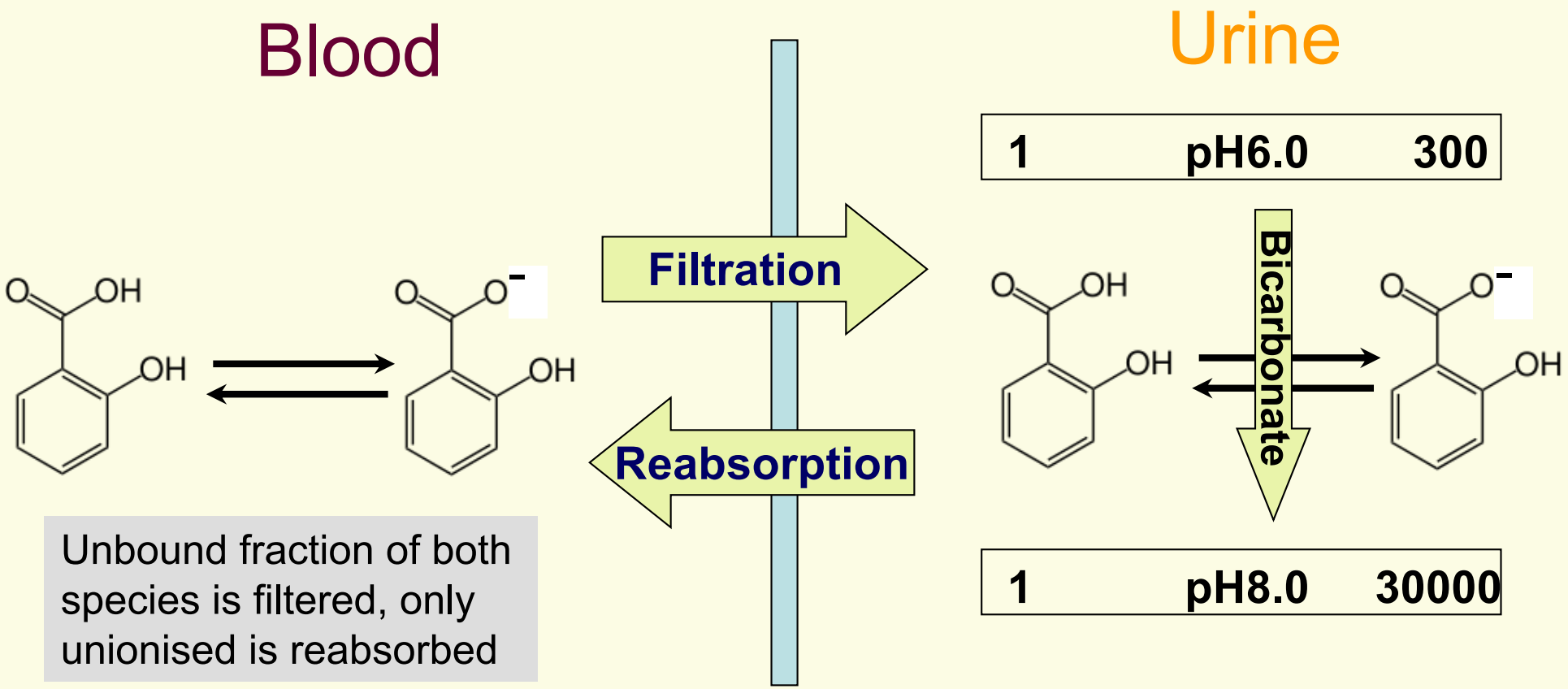
- The body responds to the alkalosis by excreting bicarbonate to reduce blood pH back to normal
- In mild cases blood pH returns to normal. However, in severe cases (in children) blood pH can drop too far leading to **metabolic acidosis**
- This will further increase salicylate diffusion into the CNS

Salicylate poisoning



- Acidosis leads to increase in unionized salicylate in the blood, promoting distribution into brain resulting in CNS toxicity
- This is treated with bicarbonate which increases blood pH and promoted redistribution out of the CNS

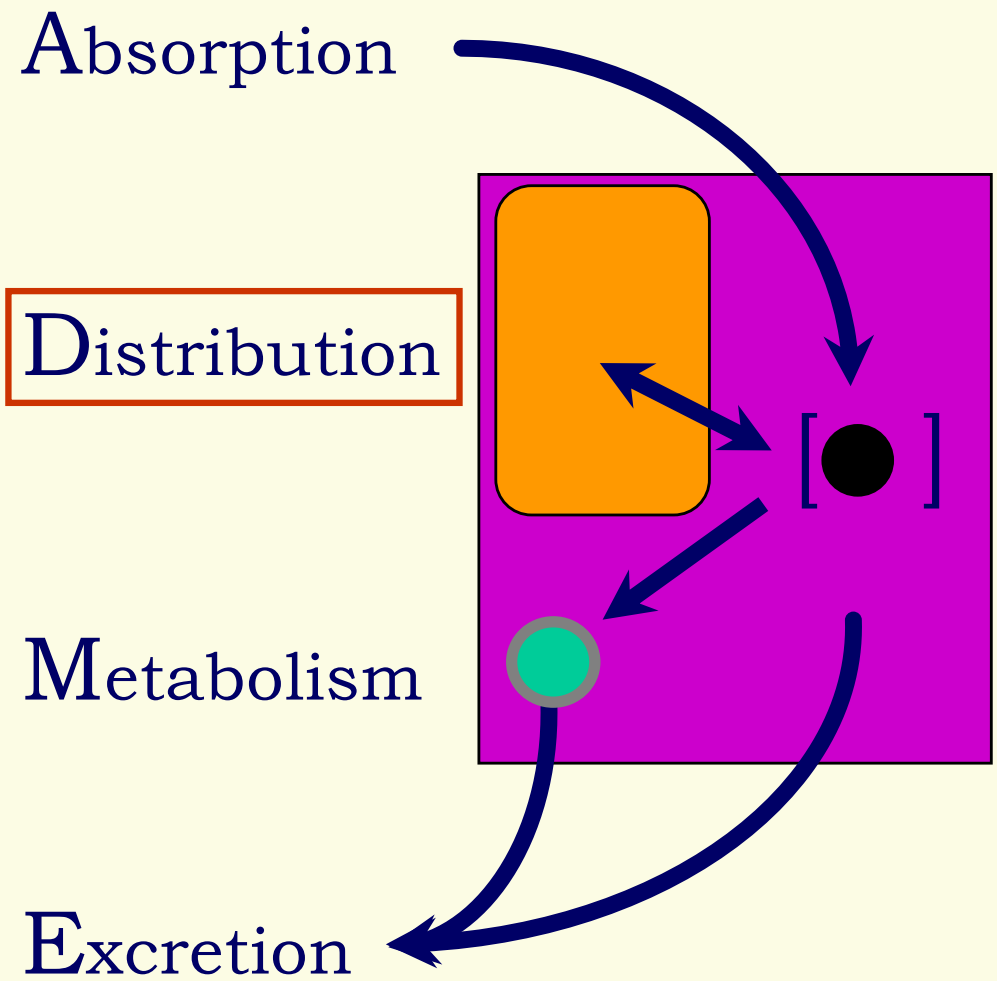
Salicylate poisoning



- Bicarbonate increases urine pH leading to significantly decreased reabsorption and hence increased excretion

Pharmacokinetics: Distribution

Pharmacokinetics (ADME)

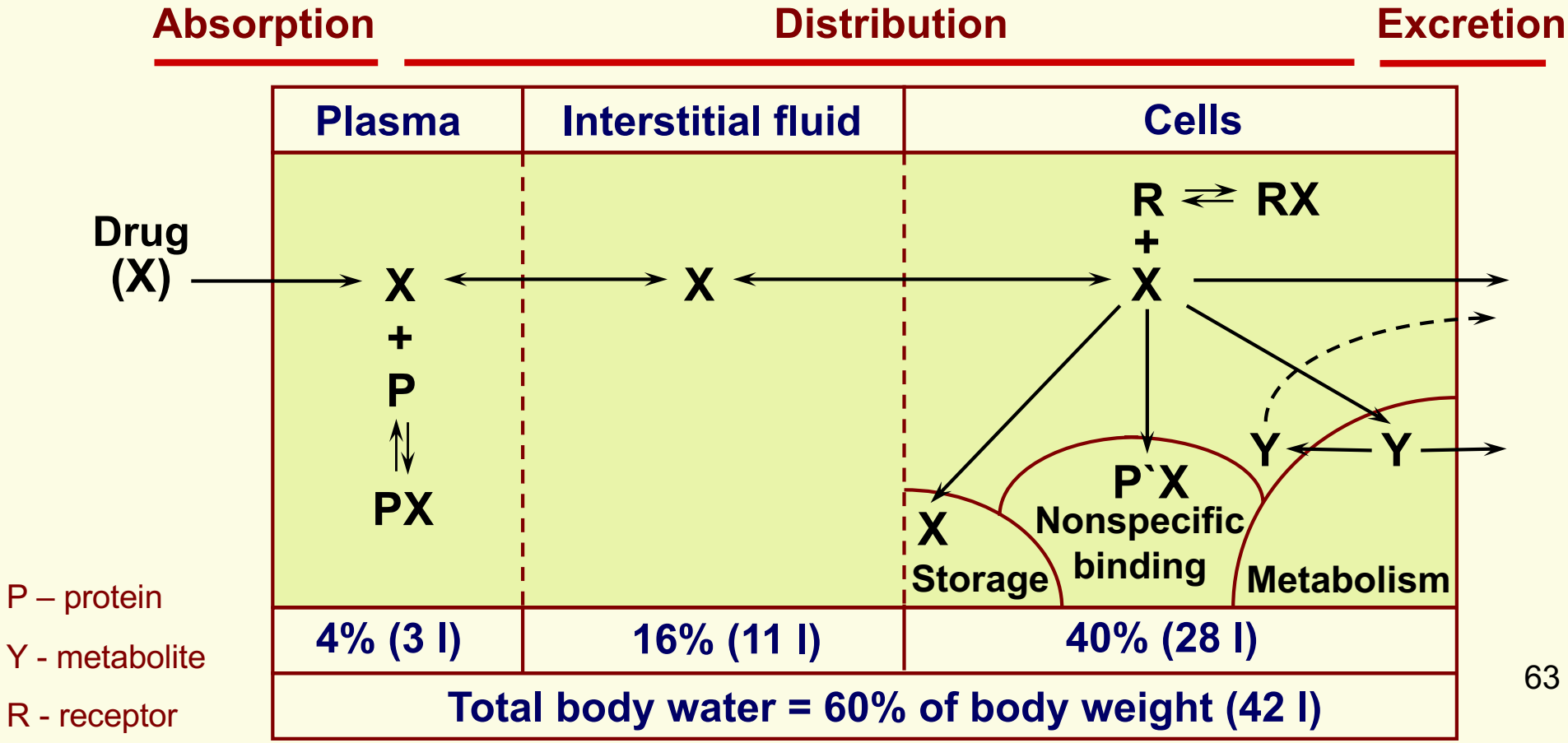


- The movement of a drug between different compartments in the body, affected by
  - lipophilicity
  - binding to plasma proteins

Pharmacokinetics: Distribution

The body water may be regarded as partitioned into several compartments that are functionally distinct:

- vascular fluid
- interstitial fluid
- intracellular fluid



Apparent volume of distribution - Vd

- Vd is the fluid volume in which a drug seems to be dissolved
- Vd is determined as following:

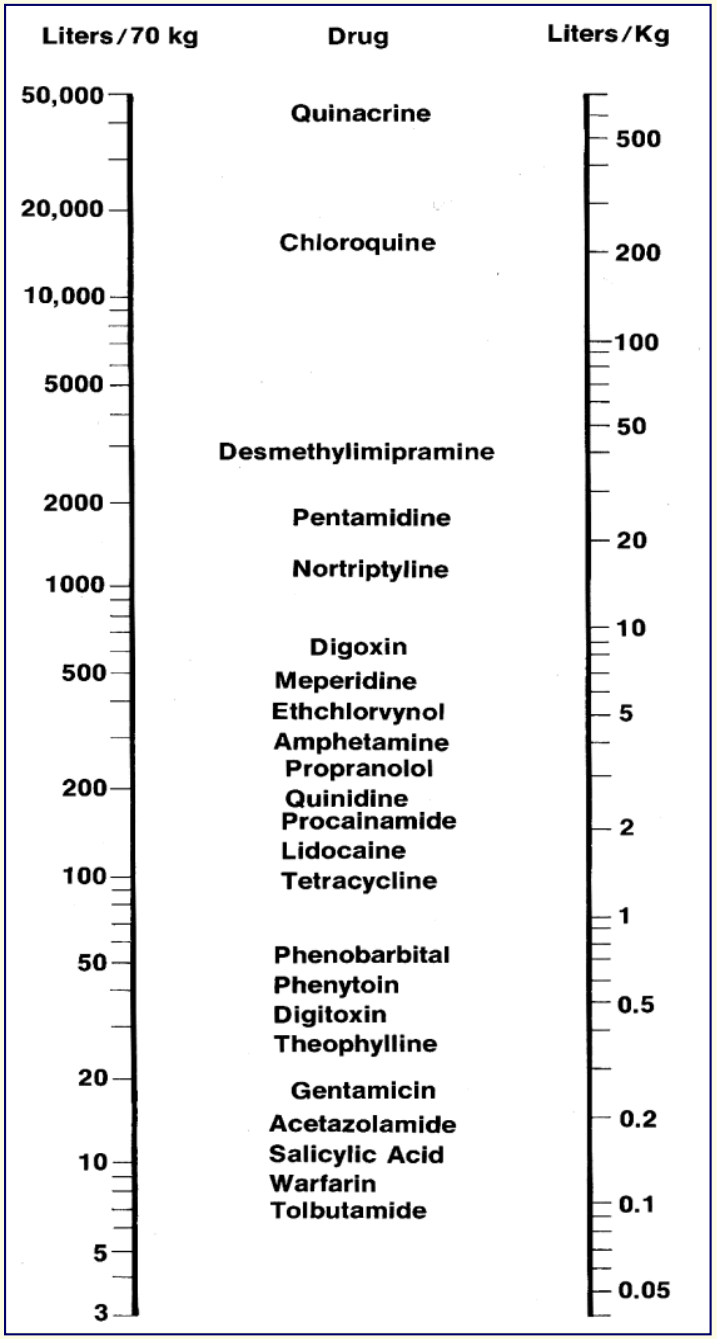
$$Vd = Q / C_0$$

where Q – dose of applied drug

C_0 – plasma drug concentration (T_0)

Apparent - because an even distribution in the body is assumed in its calculation

- The Vd could be significantly bigger than the blood volume due to the distribution of drug to the peripheral compartments
  - a small Vd infers retention within plasma
  - a large Vd infers retention in volumes outside of plasma

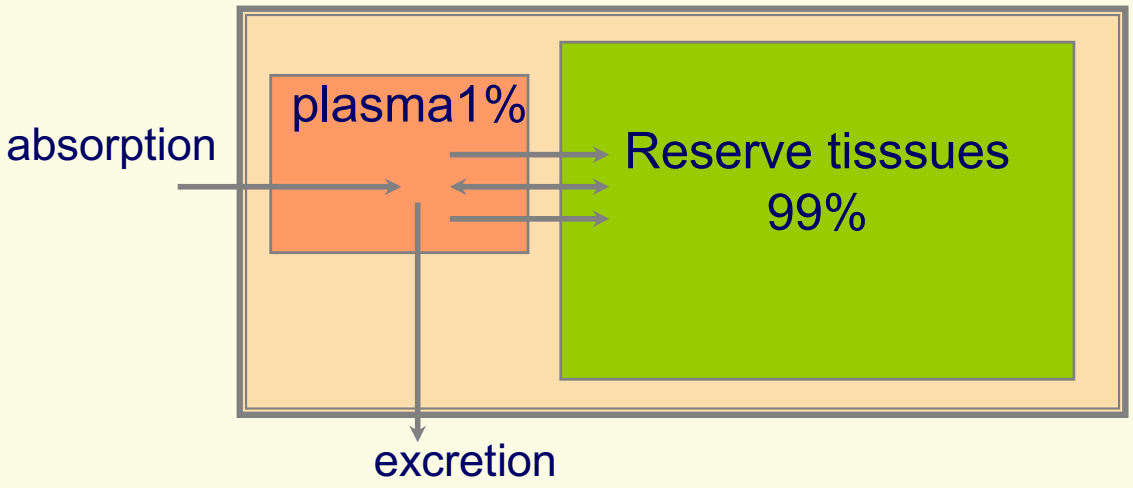


Reserve tissues

- adipose tissue-can accumulate large amount of lipid-soluble drugs
- bone - drugs with high affinity to calcium (tetracycline)
- specific tissues - e.g. iodine-containing drugs accumulation in thyroid

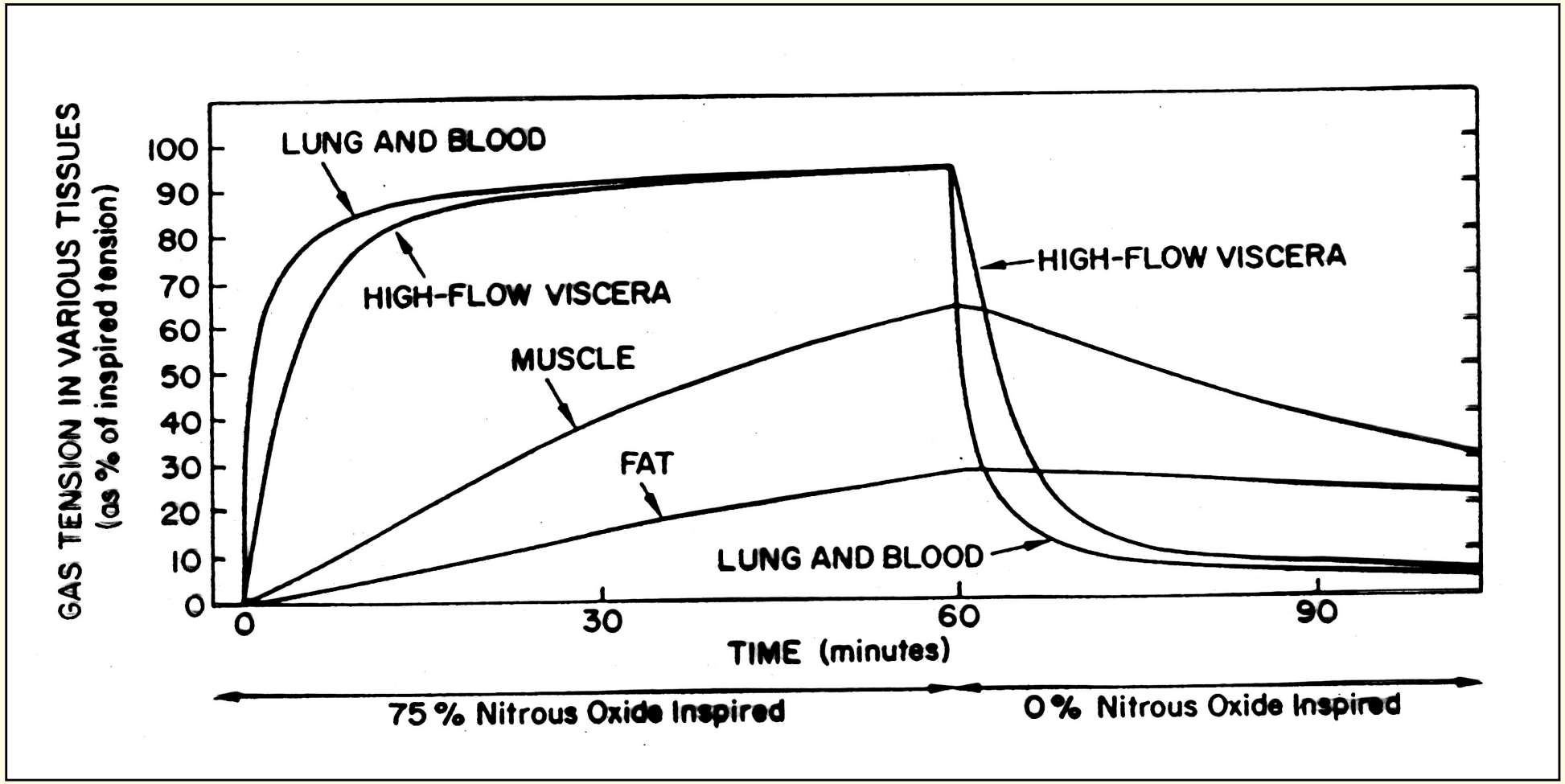
Effect of reserve tissues on drug dosage:

- as Vd increases, the dose (Q) of drug required to achieve a particular plasma concentration (C) also increases



Kinetic of distribution in different compartments: effect of tissue vascularization

Example: anesthesia with N_20

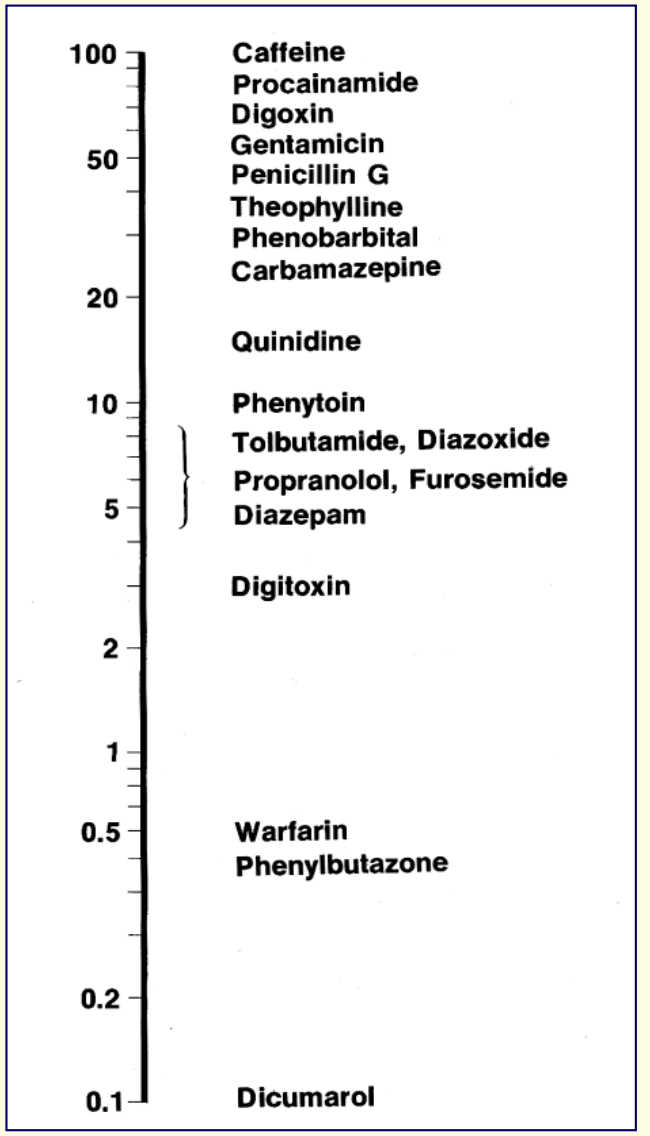


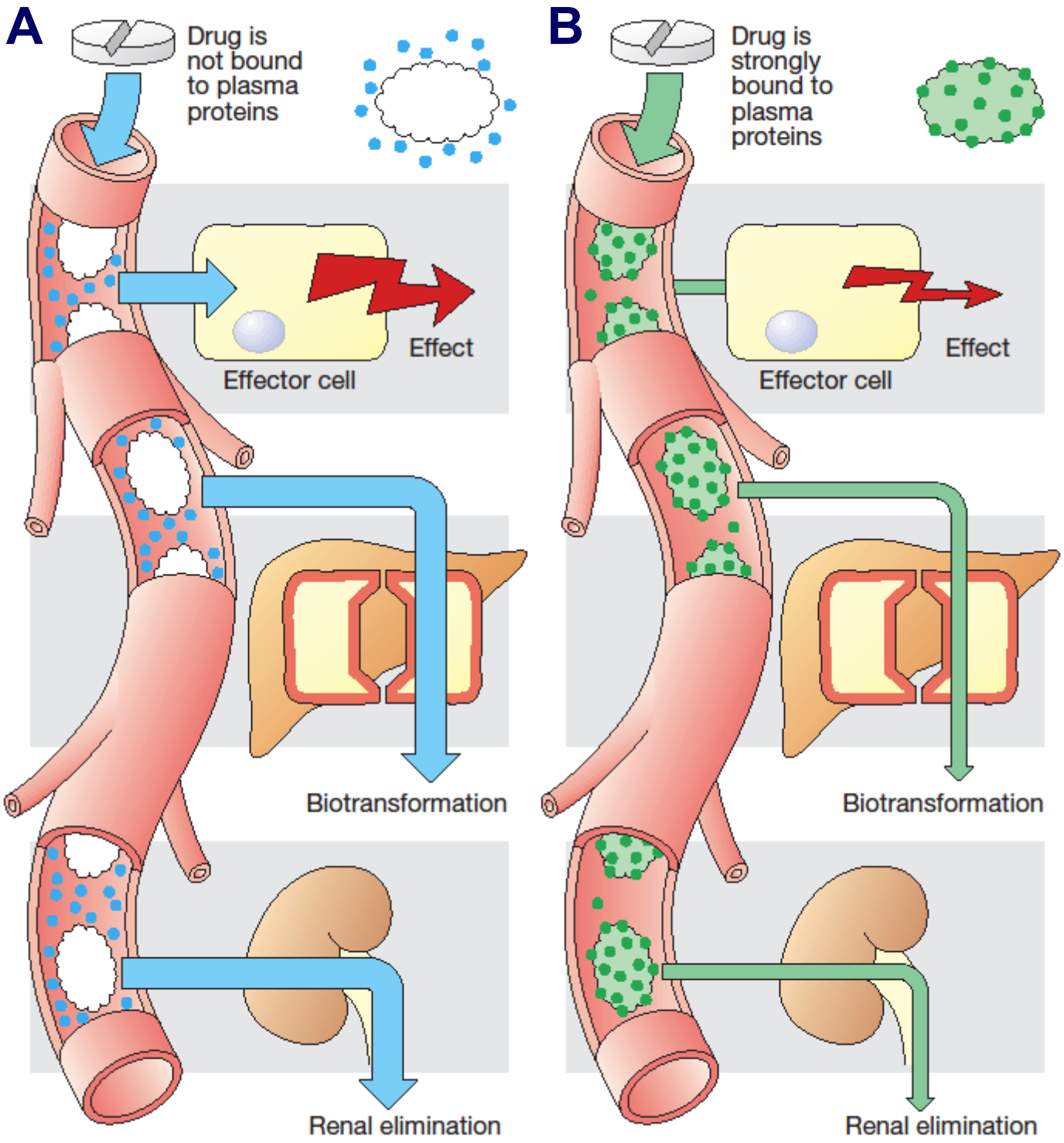
Distribution – Plasma Protein Binding

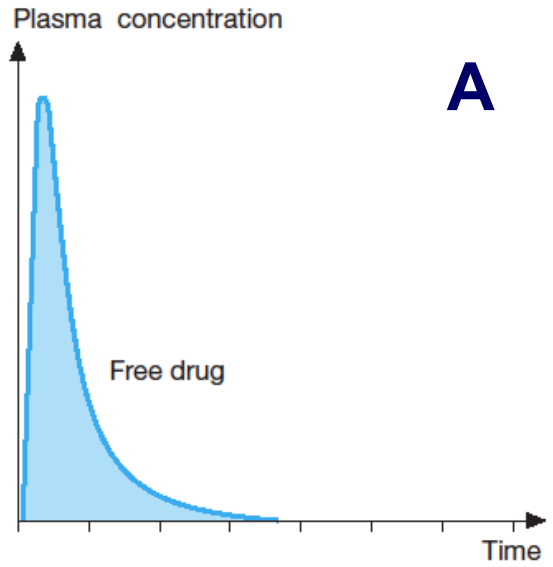
- many drugs bind reversibly with proteins in blood and other tissues
- binding to serum proteins in the blood is a common occurrence for drugs (especially lipophilic drugs)

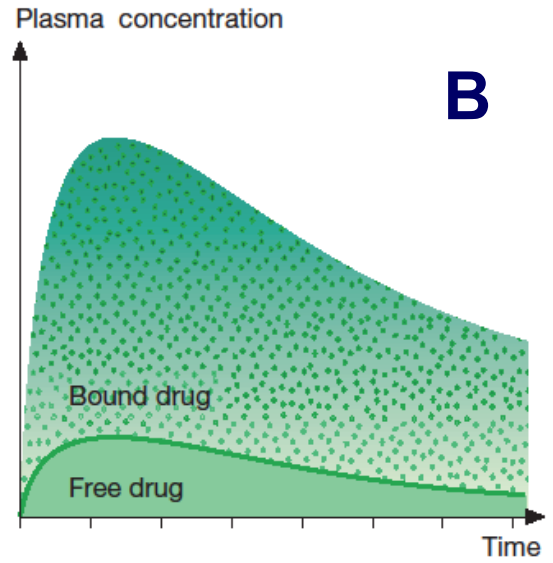
Drug + Protein = Drug ● Protein

- drug bound to serum proteins can act as a reservoir of drug
- <u>drug bound to serum proteins is not available to reach therapeutic target</u>
- amount of free drug can be increased by:
  - displacement by another drug
  - reduction of serum albumin level in disease




A
Drug is not bound to plasma proteins
Effector cell
Effect
Biotransformation
Renal elimination
B
Drug is strongly bound to plasma proteins
Effector cell
Effect
Biotransformation
Renal elimination


Plasma concentration
A
Free drug
Time


Plasma concentration
B
Bound drug
Free drug
Time