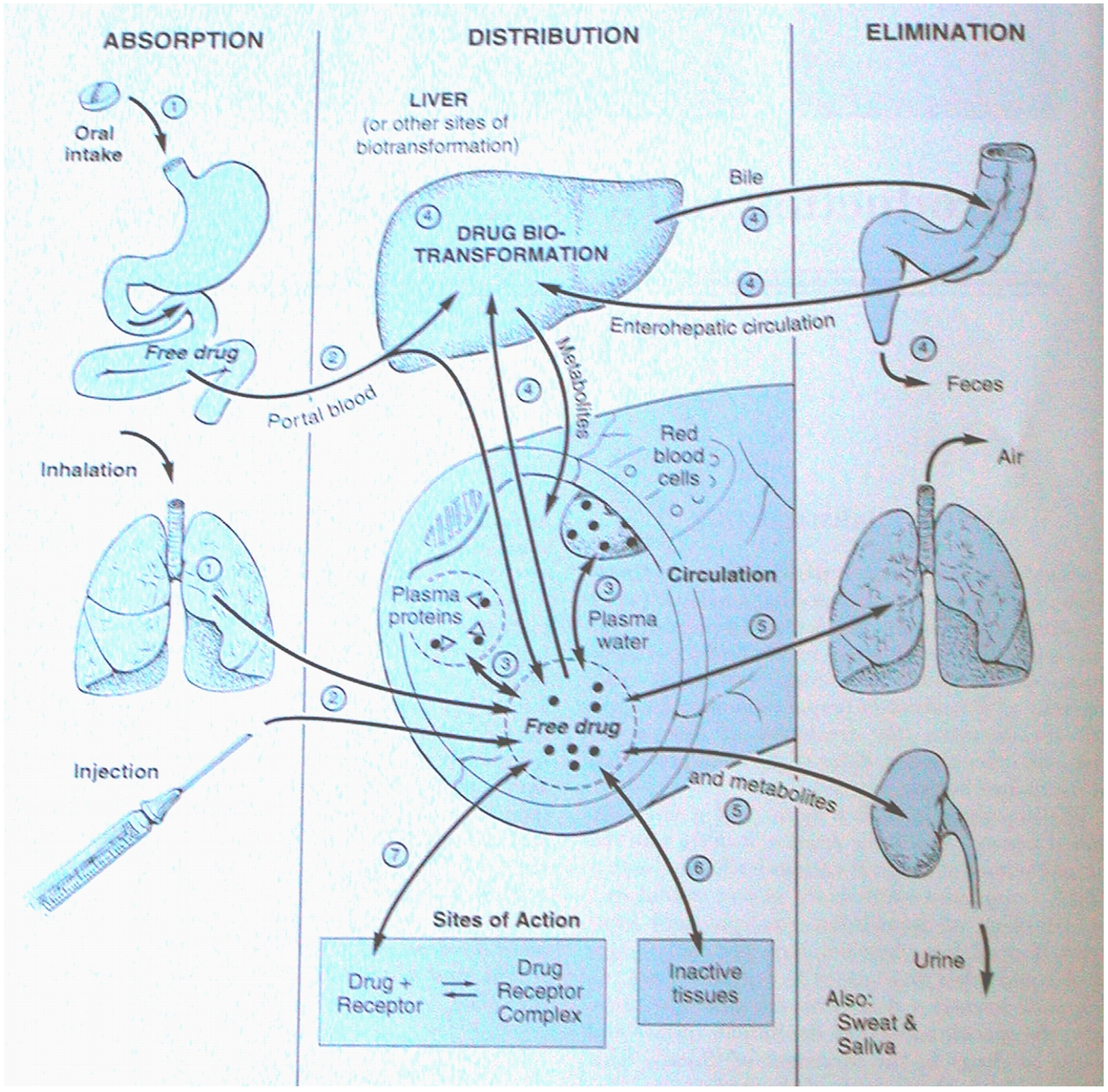
ADME: Distribution



Delivery of the drug from the blood to the tissues

It depends on:

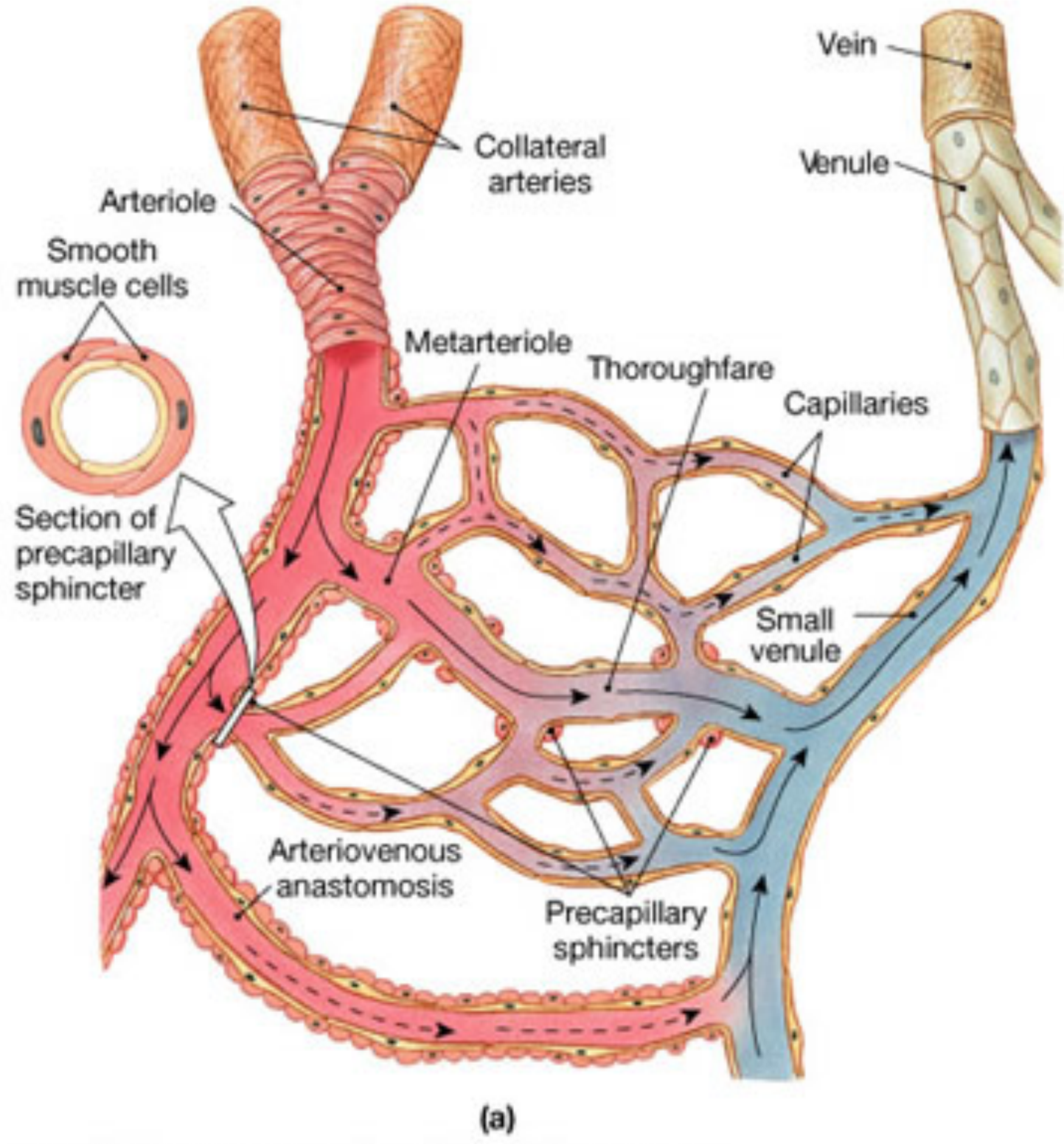
1. Tissue perfusion rate and type of capillaries

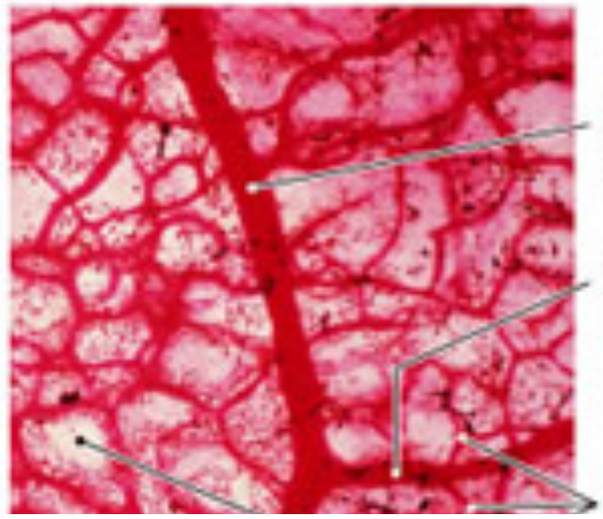
2. Plasma protein (albumin) binding

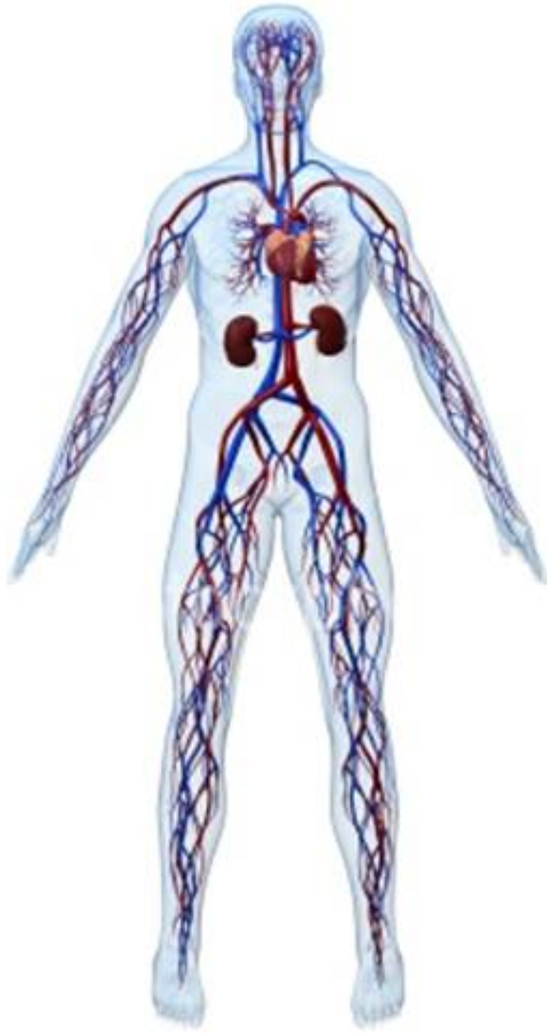
3. Accumulation in tissues

4. Presence of barriers

1. Rate of perfusion



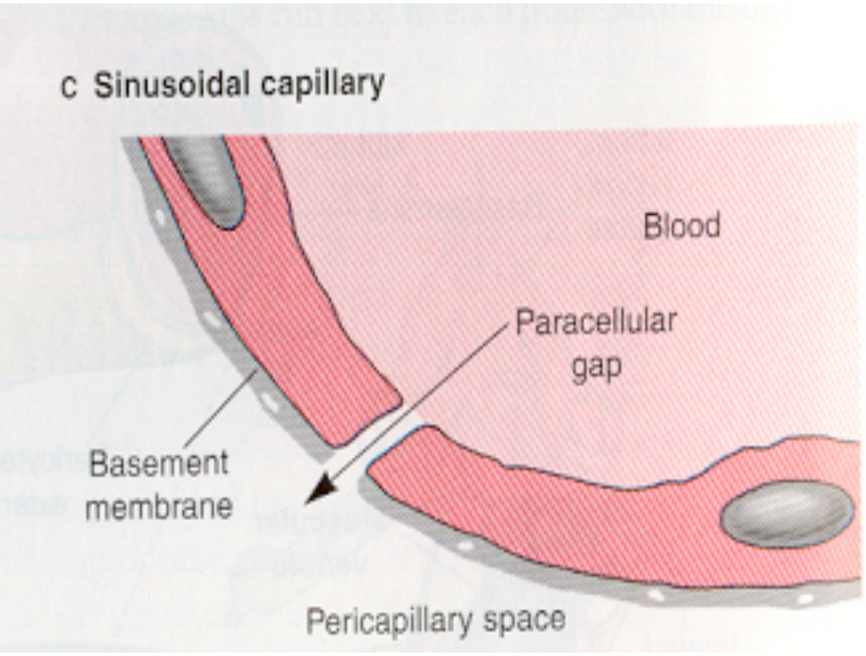


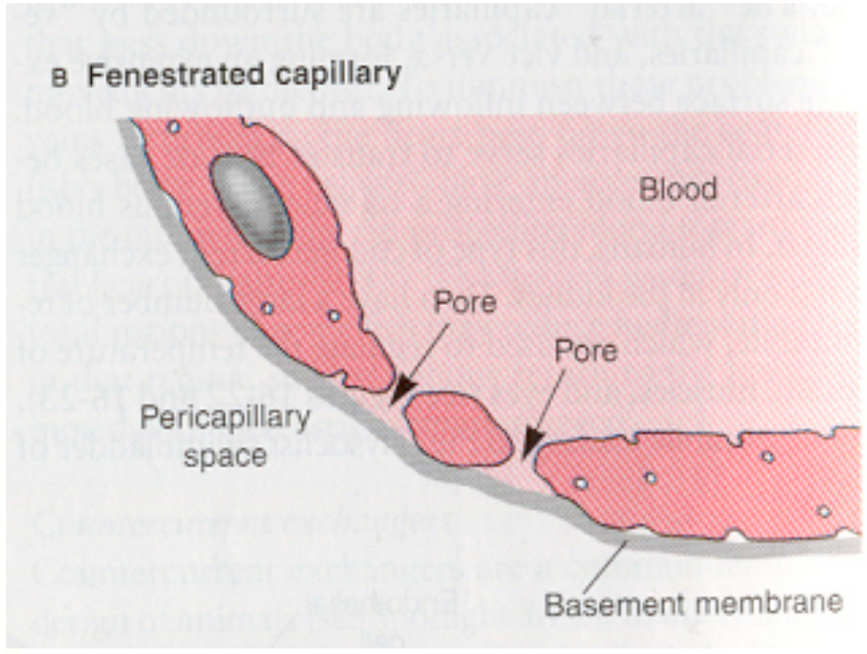


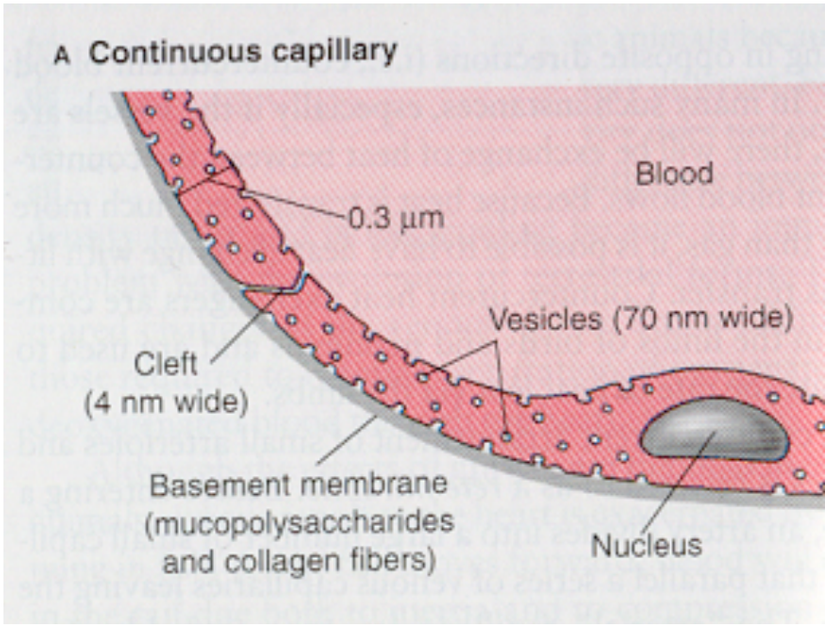
1. Rate of perfusion

ORGAN	PERFUSION RATE (ml/min)	% of cardiac output
Liver	**1350**	**27**
Kidneys	**1100**	**22**
Muscle	**750**	**15**
Brain	**700**	**14**
Skin	**300**	**6**
Heart	**300**	**6**
Bone	**250**	**5**
Fat	**200**	**4**

Different types of capillaries





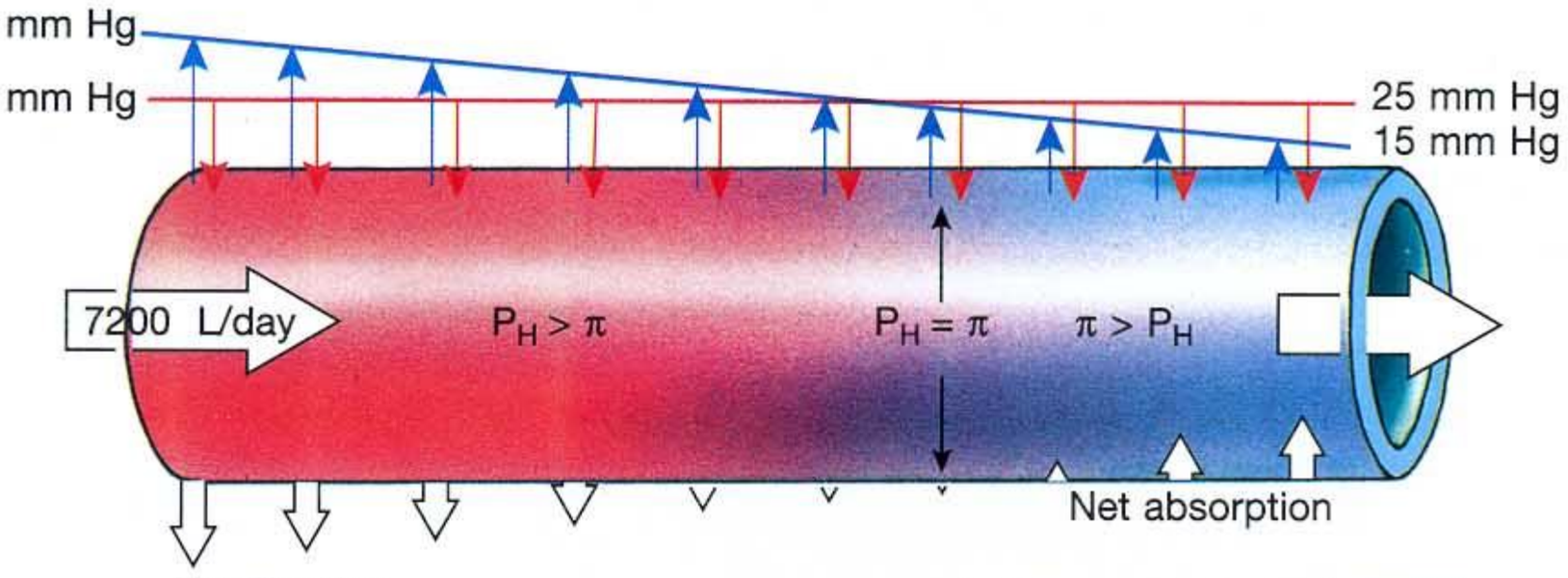


Sinusoids: **endothelium and basal membrane presents intercellular cleft**	***Fenestrated:*** **endothelium presents intercellular cleft, basal membrane is continous**	***Continous*****: endothelium and basal membran presents no intercellular cleft**
Localization**:**		
liver **spleen** **Bone marrow** **limphonodes**	**Gastro-intestinal mucosa** **kidney** **Endocrin glands**	**Skeletal and cardiac muscle** **Smooth muscle** **lung**
Permeability for hydrofilic molecules		
excellent	**good**	**scarce**

1. Rate of perfusion

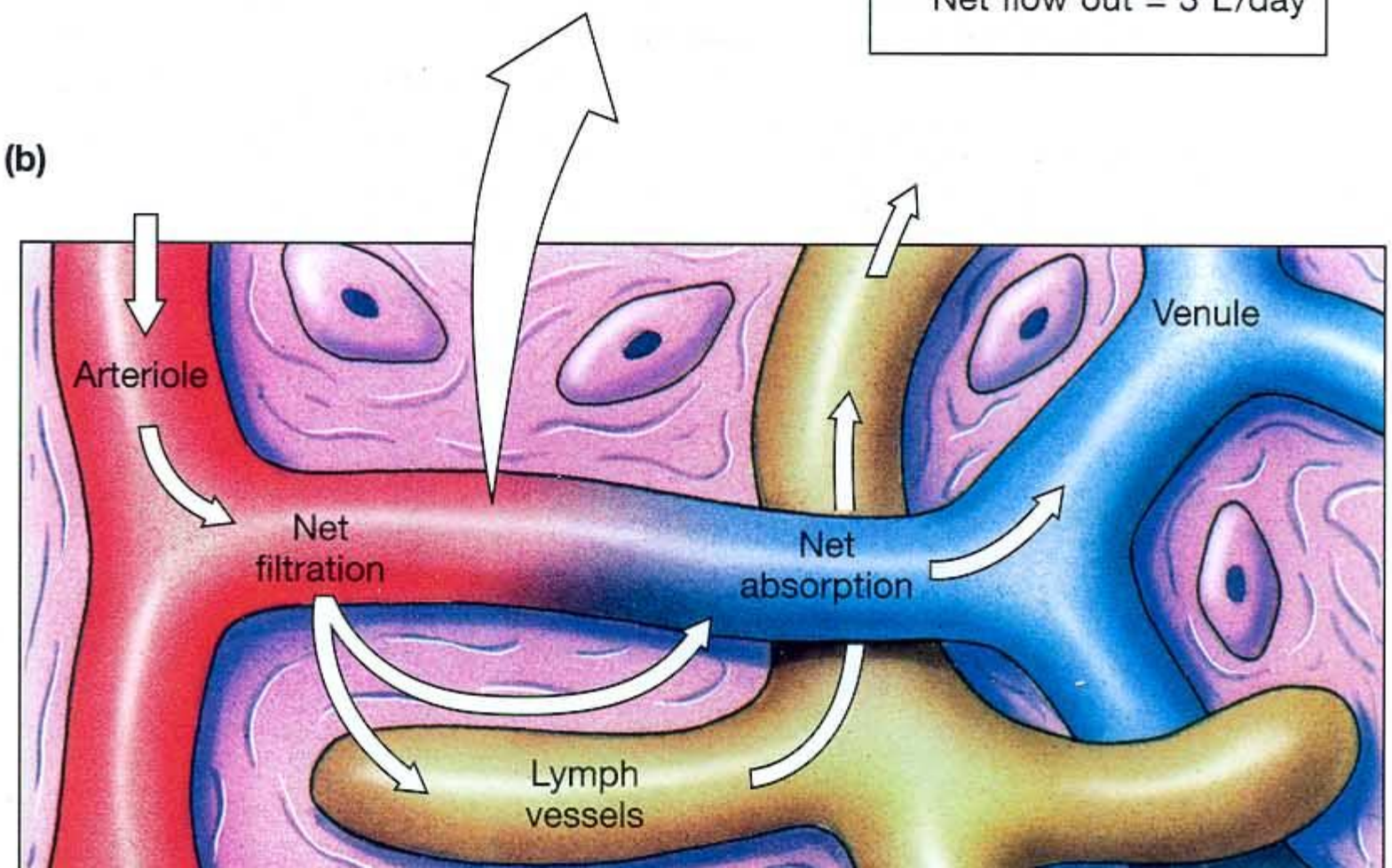
,π = Colloid osmotic pressure

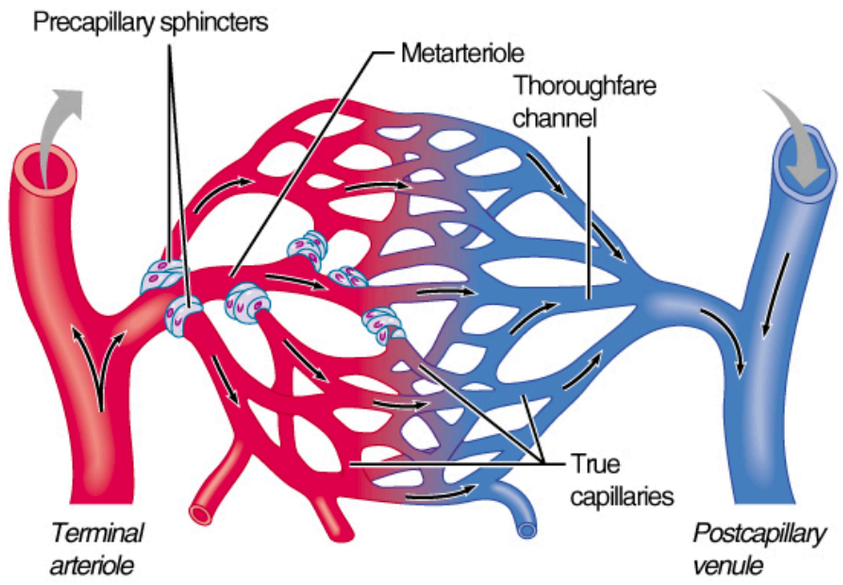
,P = Capillary hydraulic pressure



Net filtration

Net flow out = 3 L/day



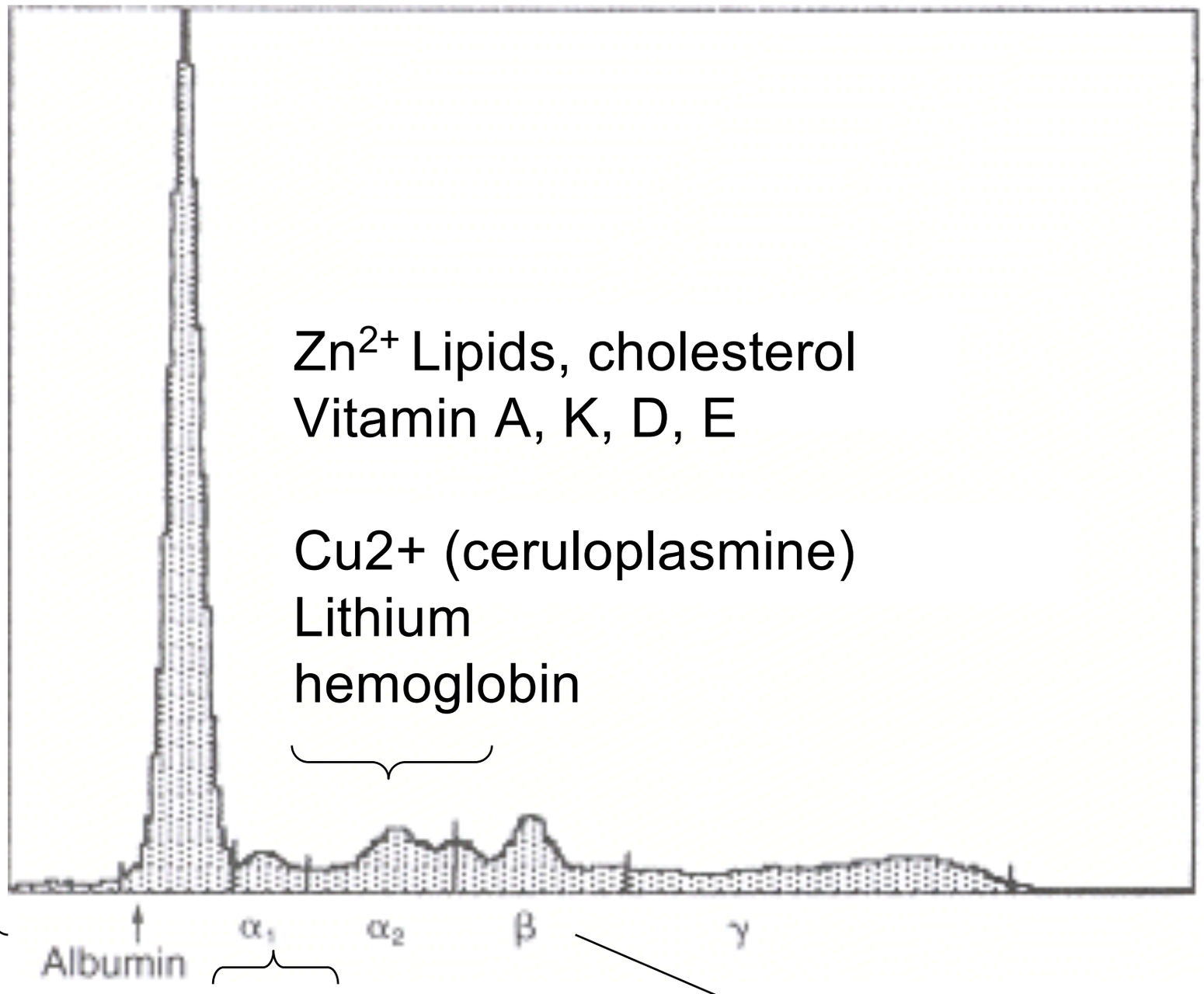


(a) Sphincters open

2. Plasma proteins binding

Bilirubin
Uric acid
Vitamin C
Adenosine
Tetracycline
Fatty Acids
Penicillin

Salicilates
Streptomicine
Histamine
Barbiturates
Ca^{2+}
Cu^{2+}
Zn^{2+}



Zn^{2+} Lipids, cholesterol
Vitamin A, K, D, E

Cu2+ (ceruloplasmine)
Lithium
hemoglobin

steroid hormones
(transcortine)
Vitamin B12
tiroxine

Fe^{2+}
(Transferrine)

2. Plasma proteins binding

drug-protein complex

Binding to plasma proteins is reversible

K_1 K_2

inert, non-diffusible, not available for metabolism and excretion. It acts as a reservoir for drug

Free drug + protein

Sites of action of the drug:

Capillaries wall
Cell membranes
Intracellular sites

Sites of drug elimination:

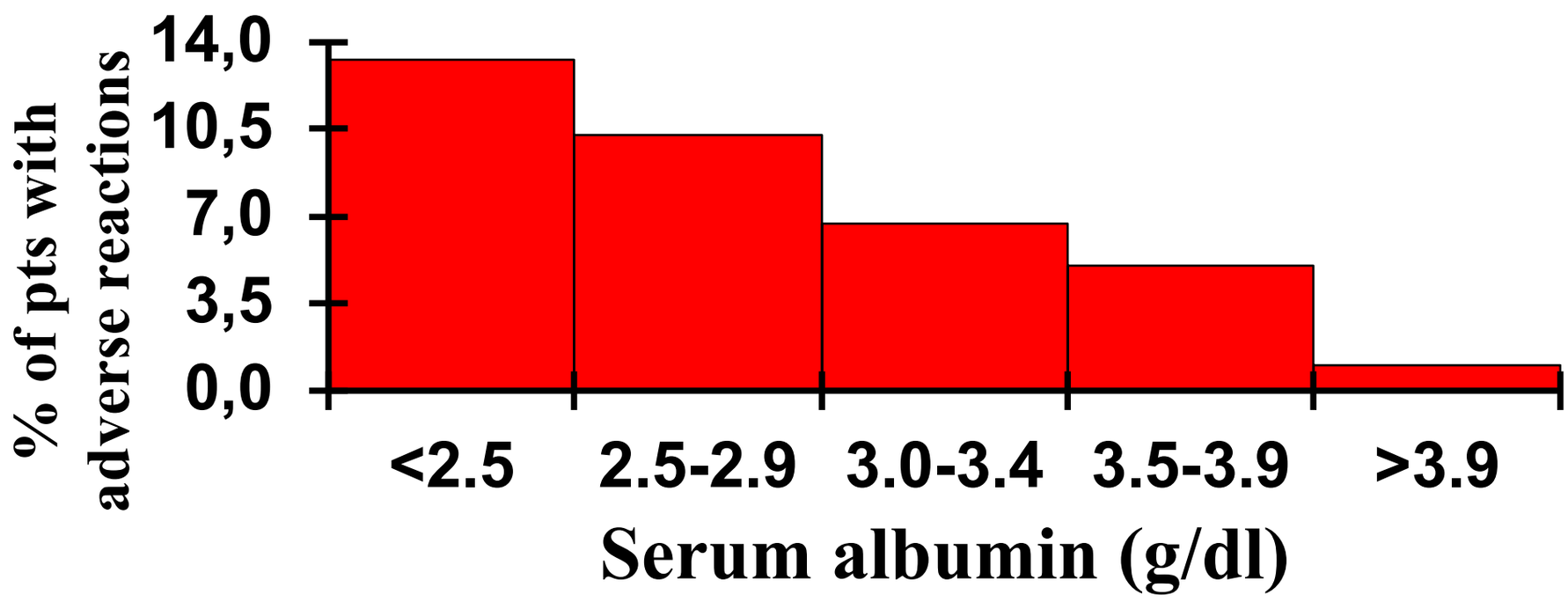
glomerular filtration
tubular secretion
biotrasformations
biliar secretion

2. Plasma proteins binding

The formation of drug-protein complex depends on:

- physiochemical properties of the drug
- drug concentration
- drug-protein affinity
- total proteins

Adverse Reactions to Phenytoin as a Function of Serum Albumin Concentration



2. Plasma proteins binding

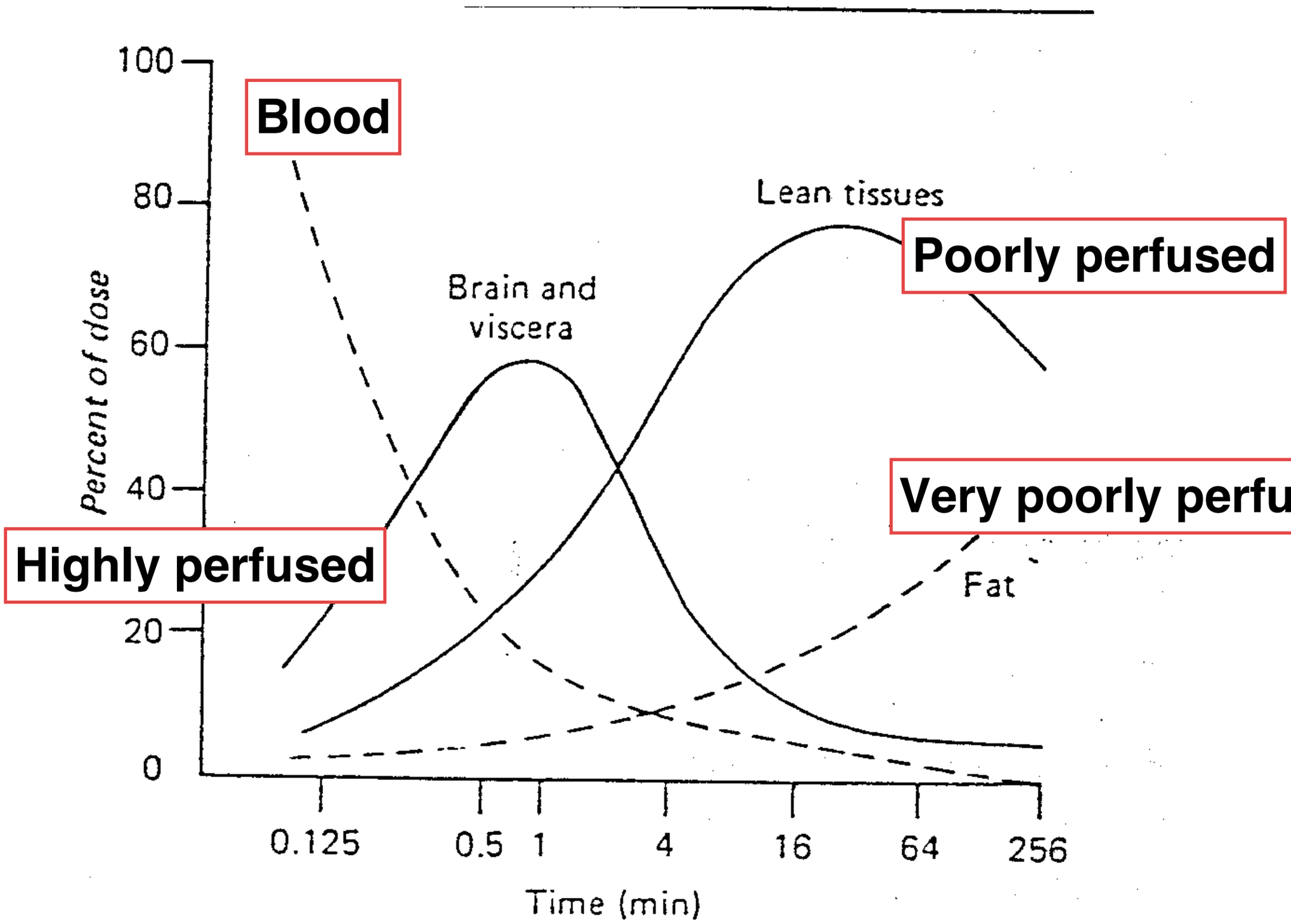
- **Drugs highly bound to plasma proteins generally persist in body longer than those less bound, have lower therapeutic activity and less efficient distribution**

- **Two drugs with affinity for plasma proteins compete with each other leading to displacement <u>drug interactions</u>**

Effect of the displacement of drugs highly bound to plasma protein

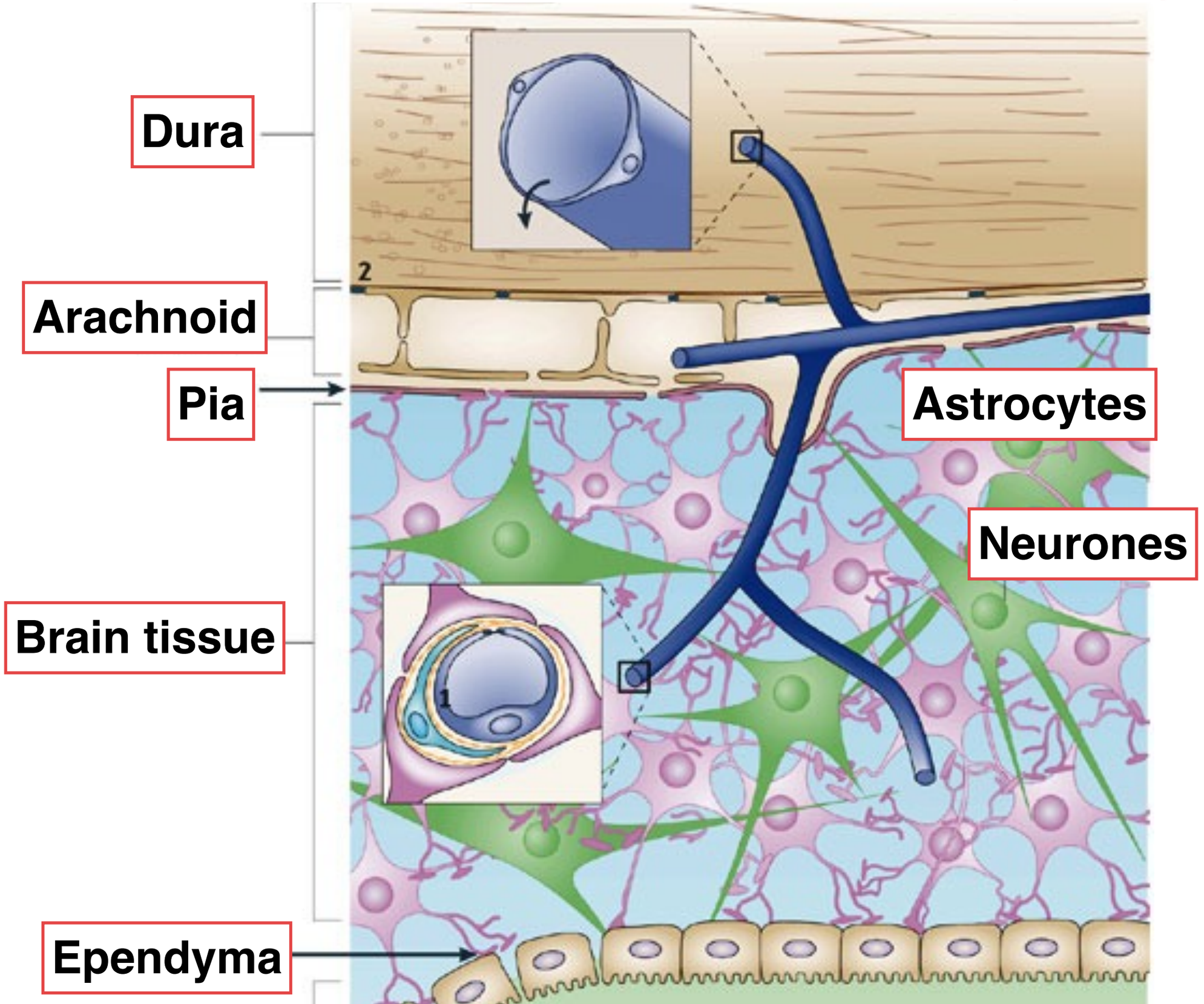
	% BEFORE DISPLACEMENT	% AFTER DISPLACEMENT	% INCREASE OF FREE DRUG
DRUG A			
% bound drug	95	90	
% free drug	5	10	+ 100
DRUG B			
% bound drud	50	45	
% free drug	50	55	+ 10

3. Accumulation in tissues

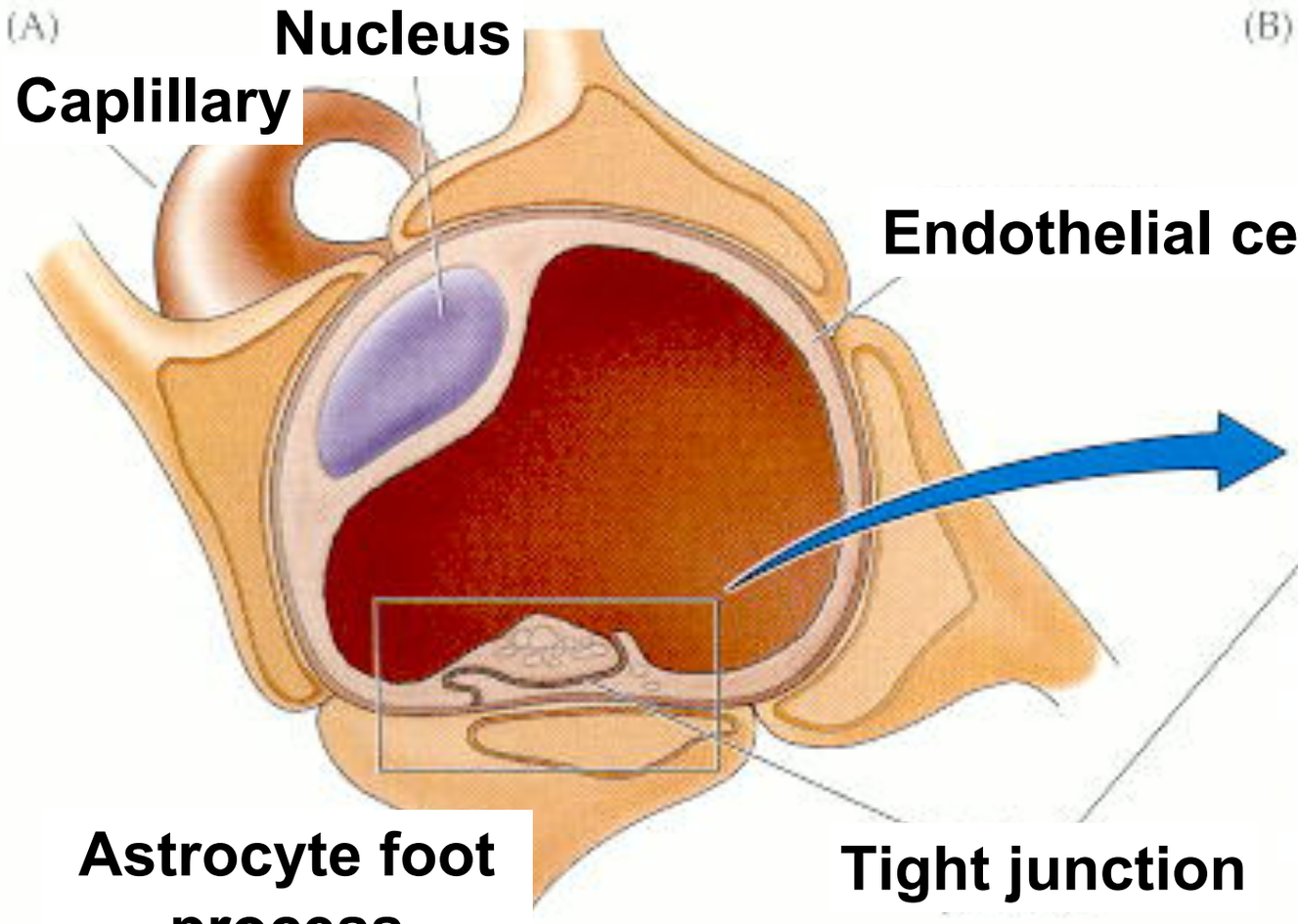


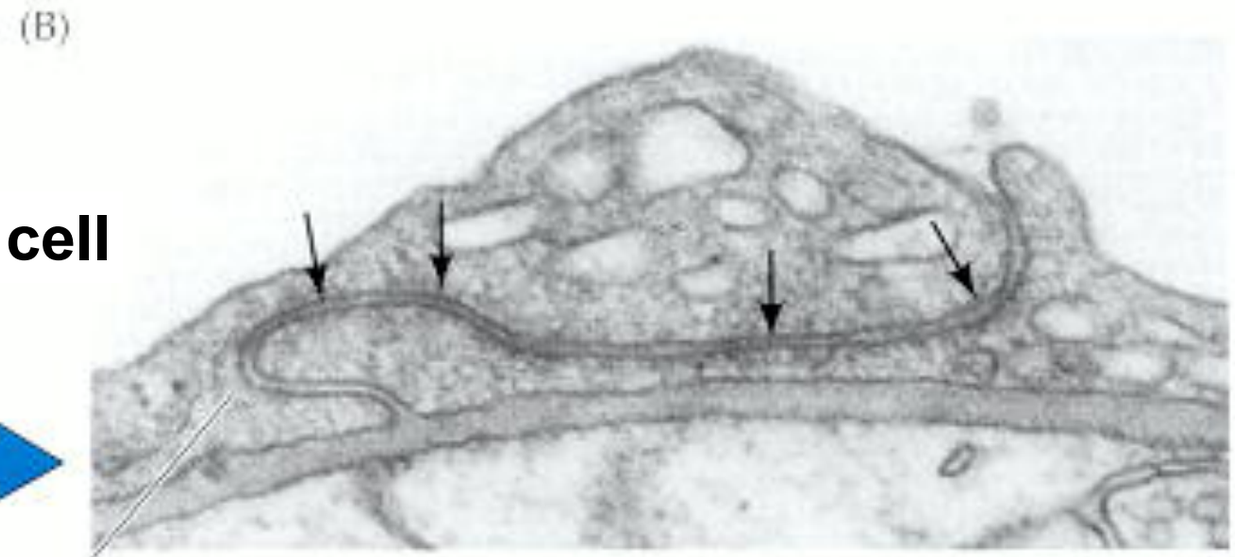
Time course of thiopental in blood and tissues after intravenous administration

4. Ability to cross barriers: the blood-brain barrier (BBB)



Blood Brain Barrier characteristics

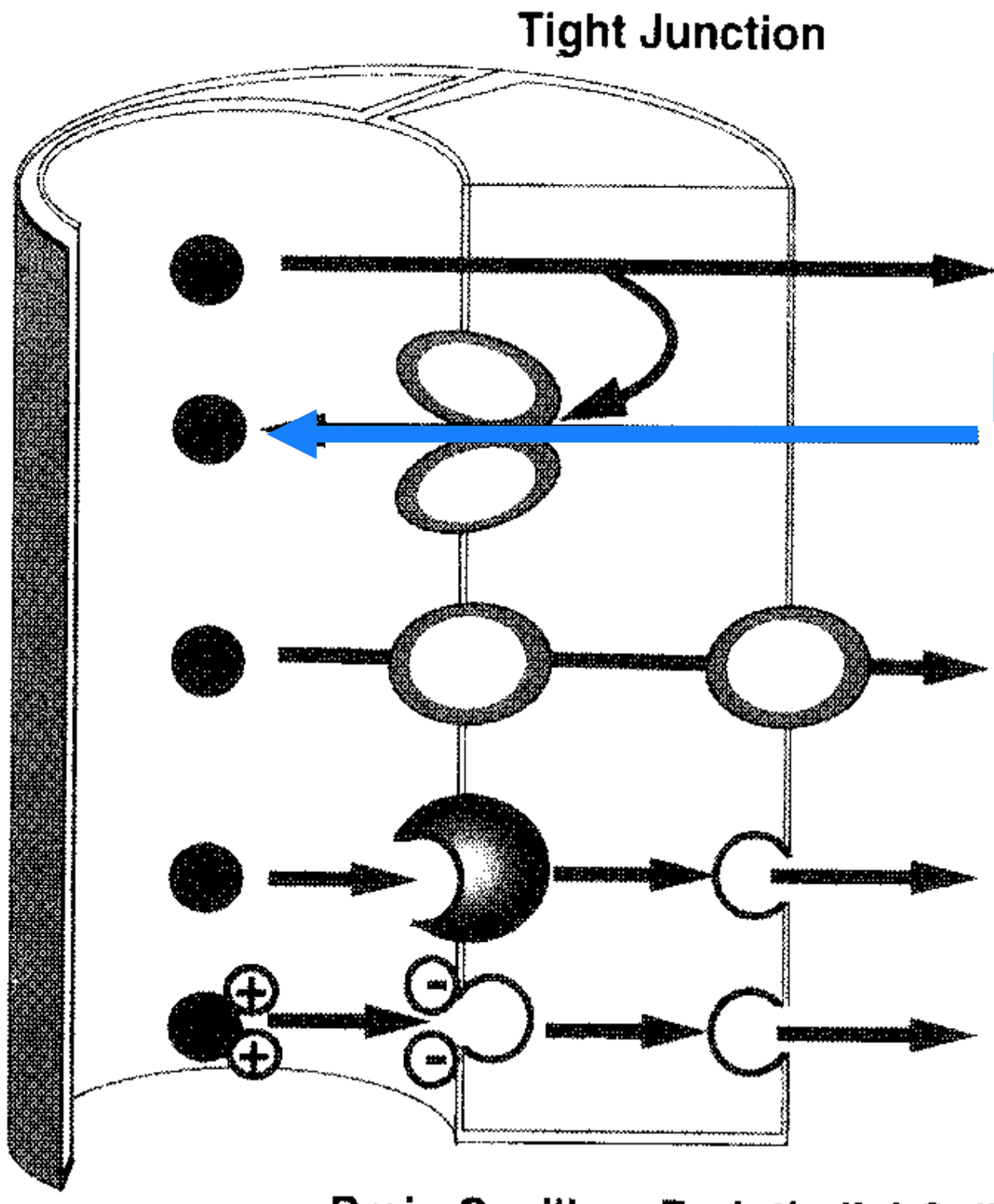




The cellular basis of the blood-brain barrier. (A) Diagram of a brain capillary in cross section and reconstructed views, showing endothelial tight junctions and the investment of the capillary by astrocytic end feet. (B) Electron micrograph of boxed area in (A), showing the appearance of tight junctions between neighboring endothelial cells (arrows). (A after Goldstein, Goldstein and Betz, 1986; B from Peters et al., 1991.)

1. No pores in endothelial membrane
2. Glial cells surround endothelial cells
3. Transporter in endothelial cells
4. Less protein concentration in interstitial fluid

Mechanisms of Blood-Brain Barrier Biotransport



Passive Diffusion

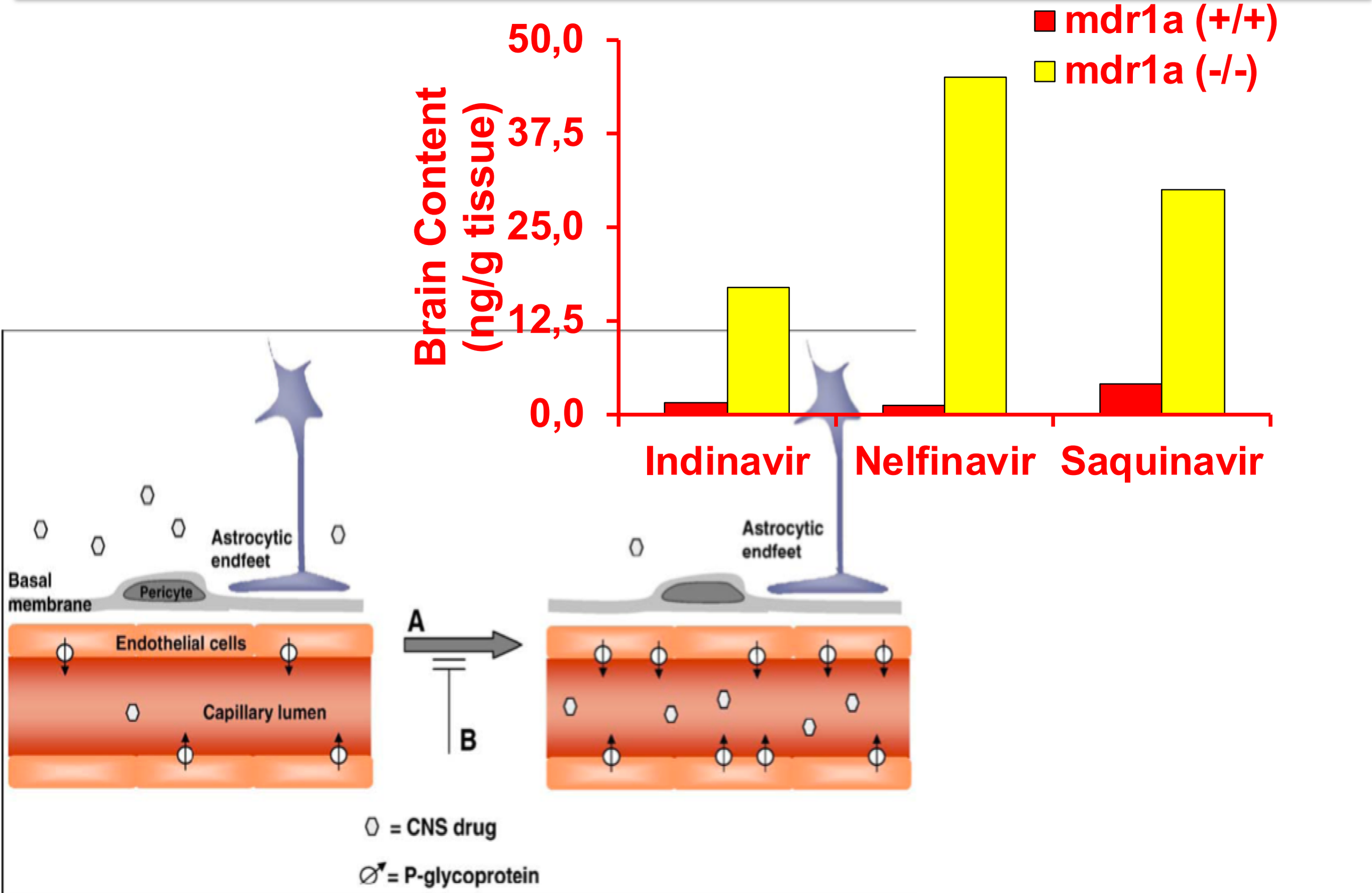
Carrier-Mediated Efflux Transport
ABC transporter (P-gp, MRP)
Transporters for organic anions,
CRH, anionic cyclic peptides,
cationic cyclic peptides, etc.

Carrier-Mediated Influx Transport
Transporters for monocarboxylates,
valproic acid, amines, amino acids,
hexose, nucleosides, glutathione,
small peptides, etc.

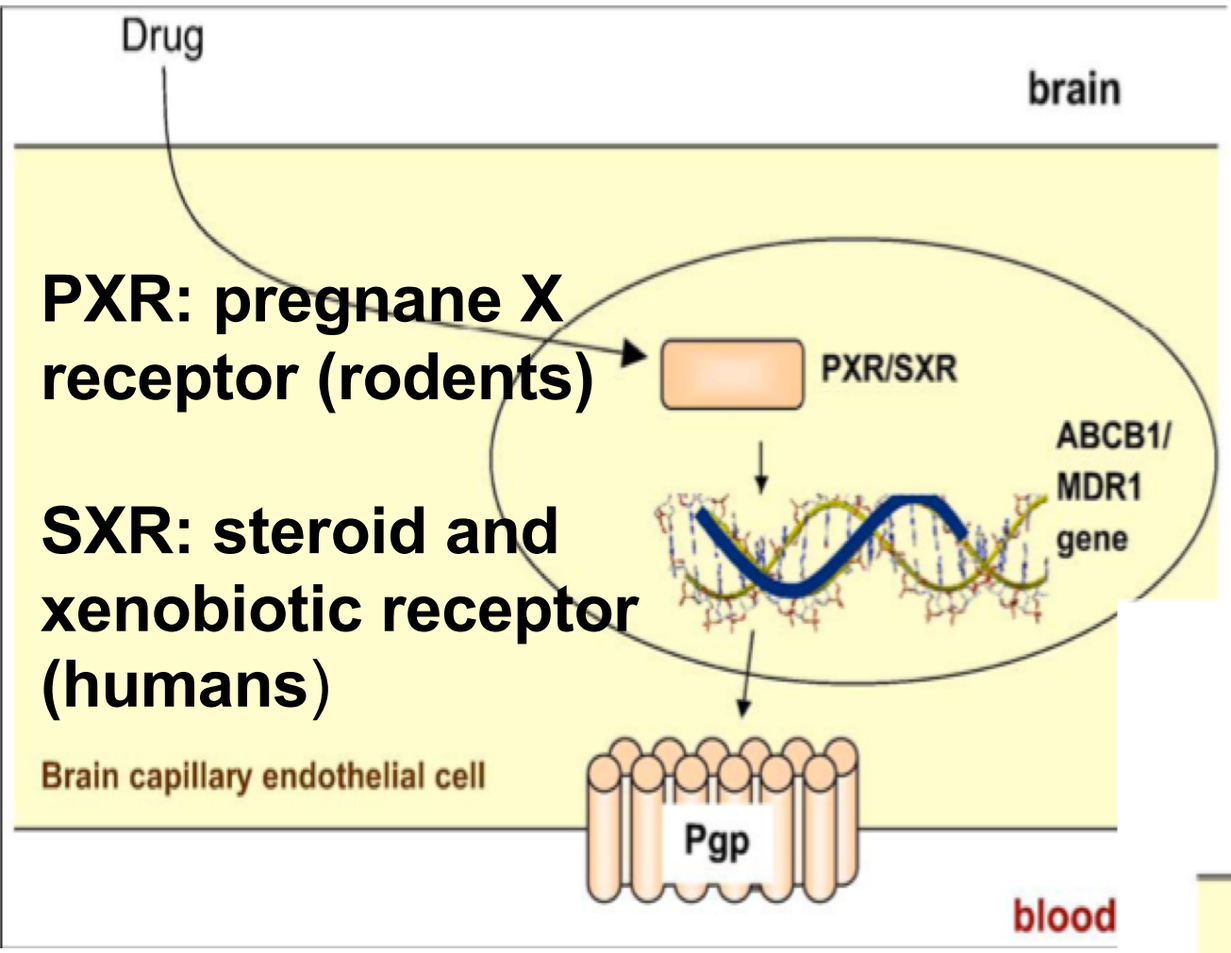
Receptor-Mediated Transcytosis
Transferrin, insulin

Adsorptive-Mediated Transcytosis
Histone, avidin, cationized albumin,
ebiratide, E-2078, cationic peptides

Role of P-glycoprotein determining brain content of protease inhibitors. Data from: Kim et al. *J Clin Invest* 101:289-294, 1998.



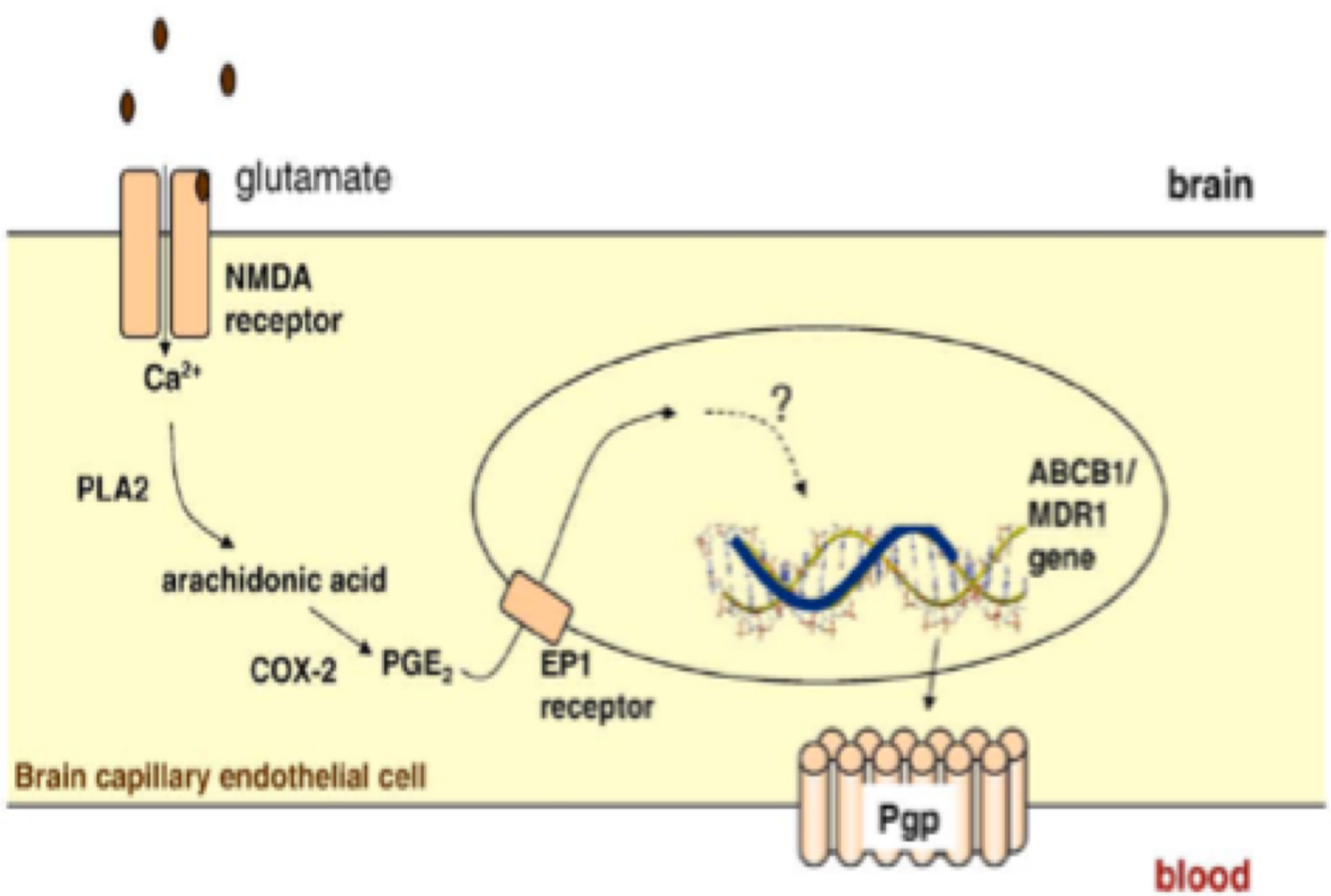
Role of drugs in the expression of P-glycoprotein at brain capillary endothelial cells



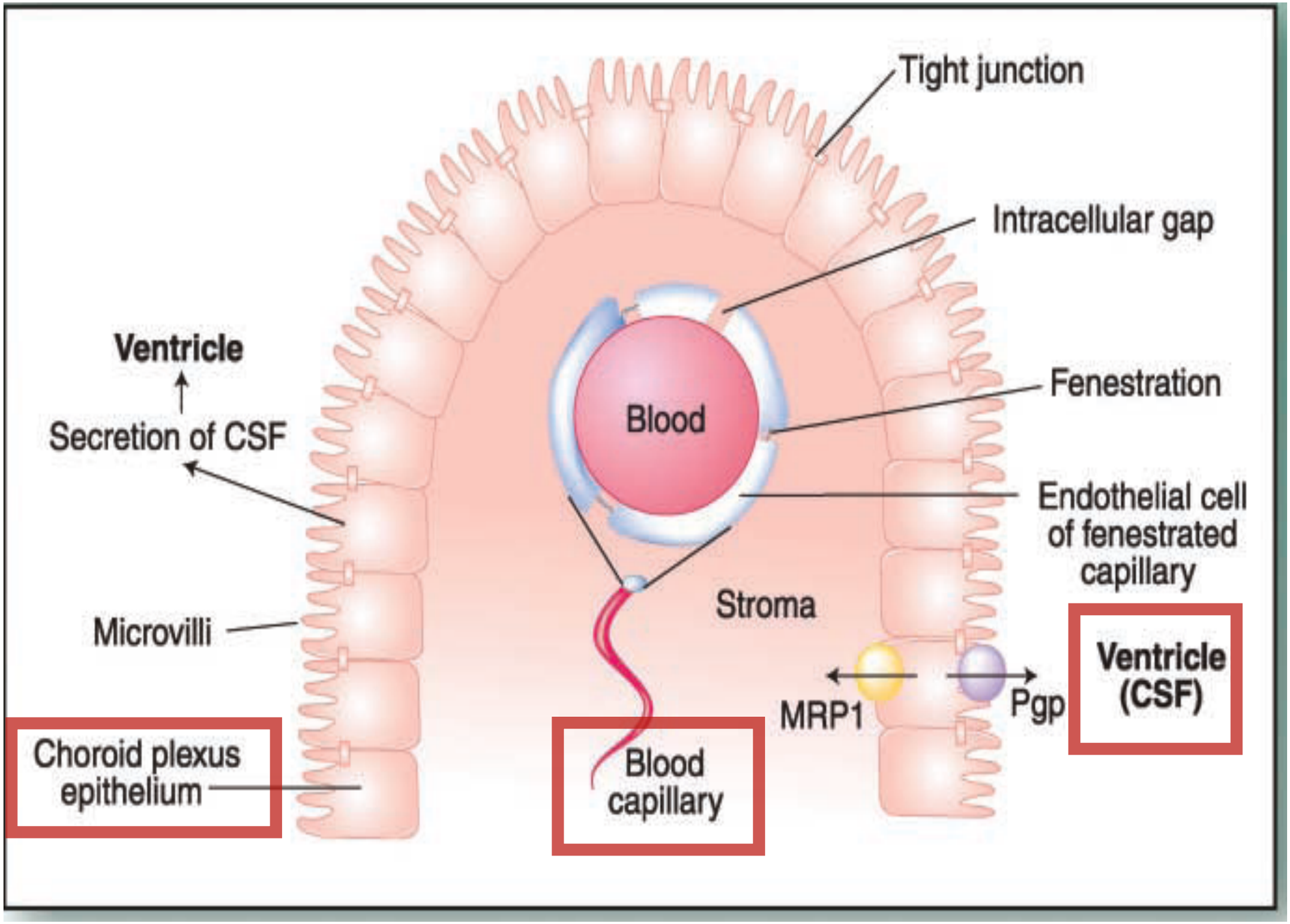
PXR: pregnane X receptor (rodents)

SXR: steroid and xenobiotic receptor (humans)

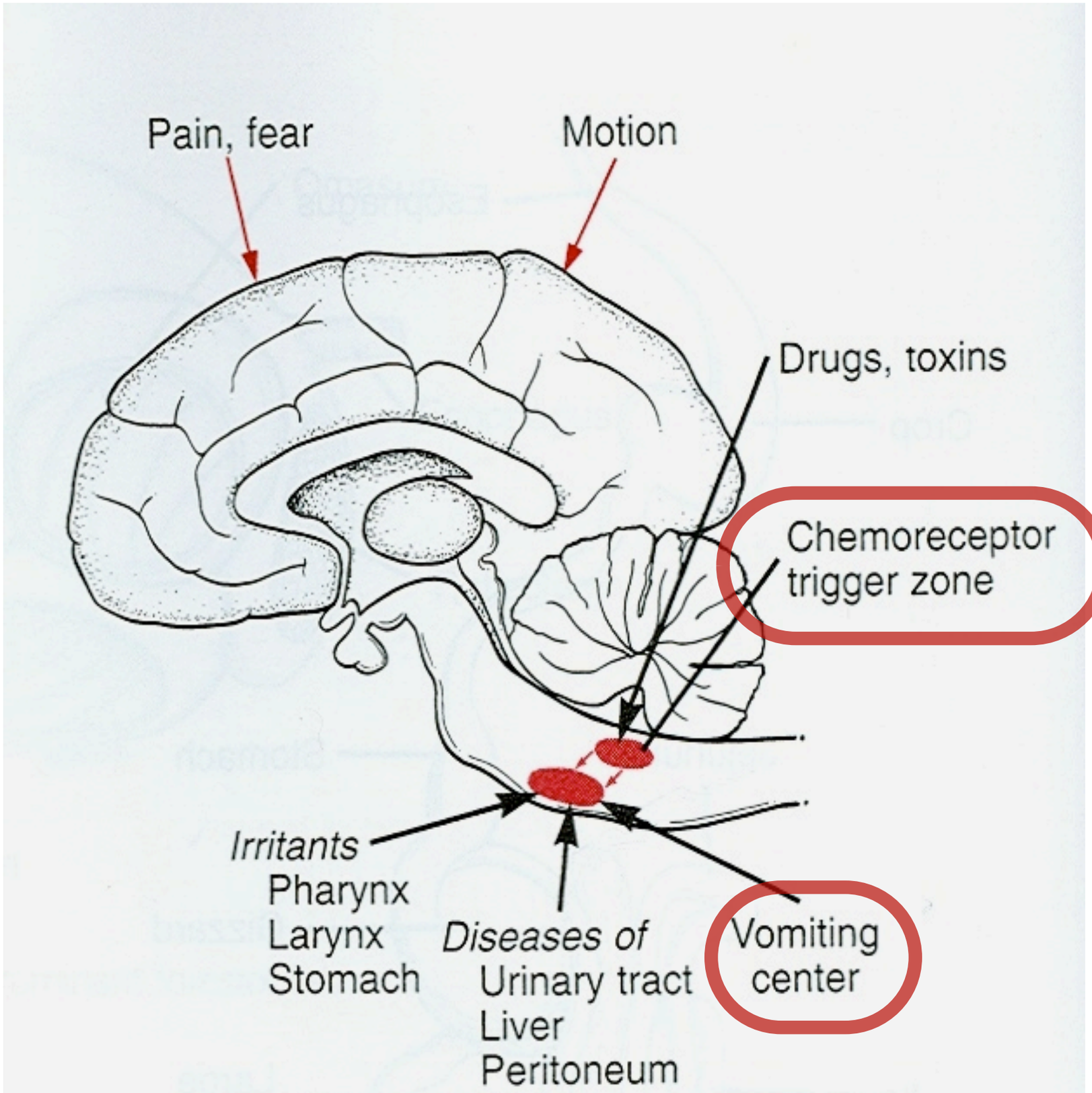
Epileptic seizure activity represents a strong trigger of transcriptional activation of P-glycoprotein



4. Ability to cross barriers: the blood-cerebrospinal barrier



The Chemoreceptor Trigger Zone (CTZ or Area Postrema)



The CTZ lies outside the BBB

Contains receptors for dopamine, serotonin, opioids, acetylcholine and substance P

Stimulation of these receptors activates the Vomiting center, leading to nausea and vomiting

Drug distribution

Four types of patterns:

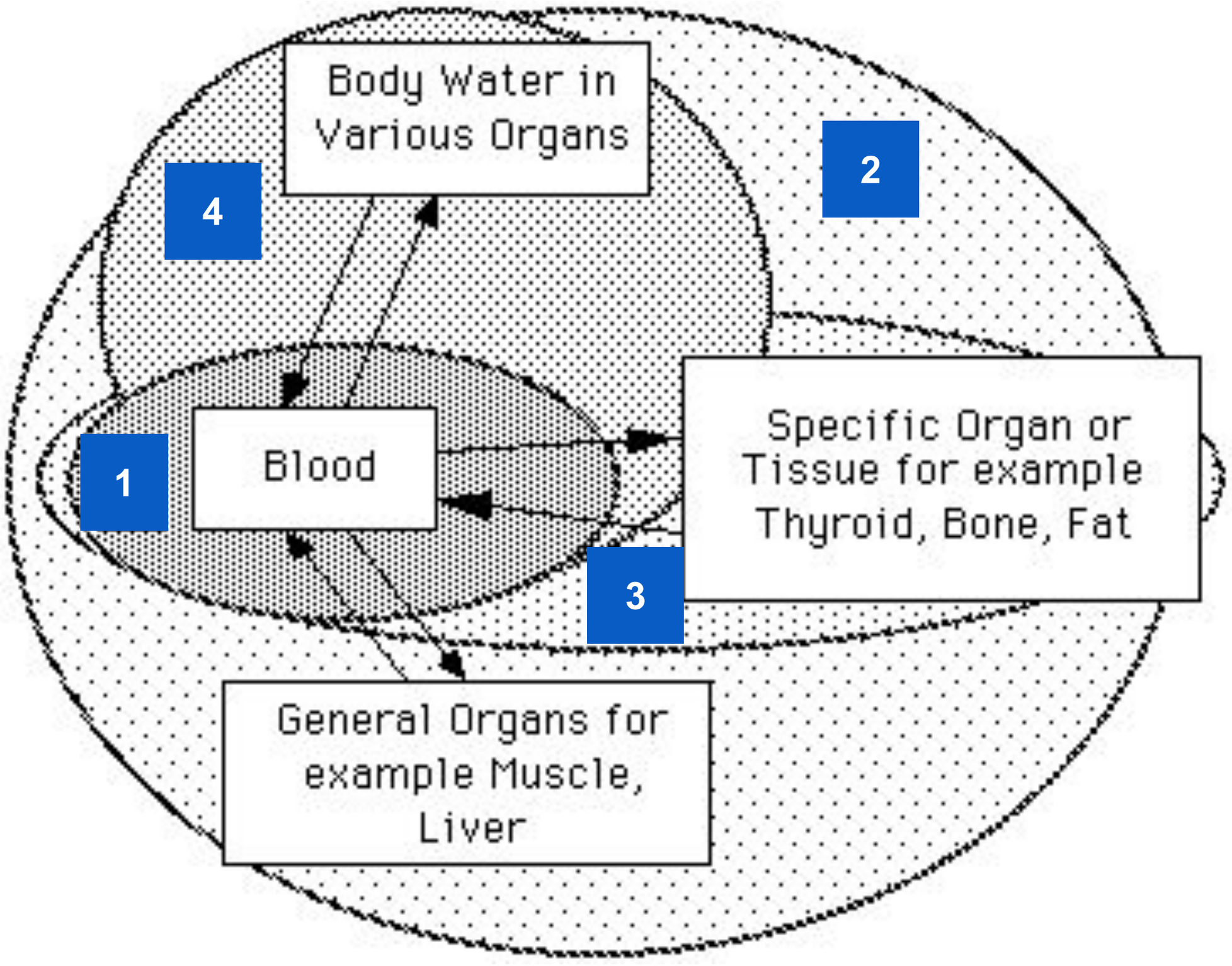
1) Some drugs may remain largely within the vascular system (eparin, drugs strongly bound to plasma protein)

2) Low molecular weight water soluble compounds (ethanol and a few sulfonamides) are uniformly distributed throughout the body water

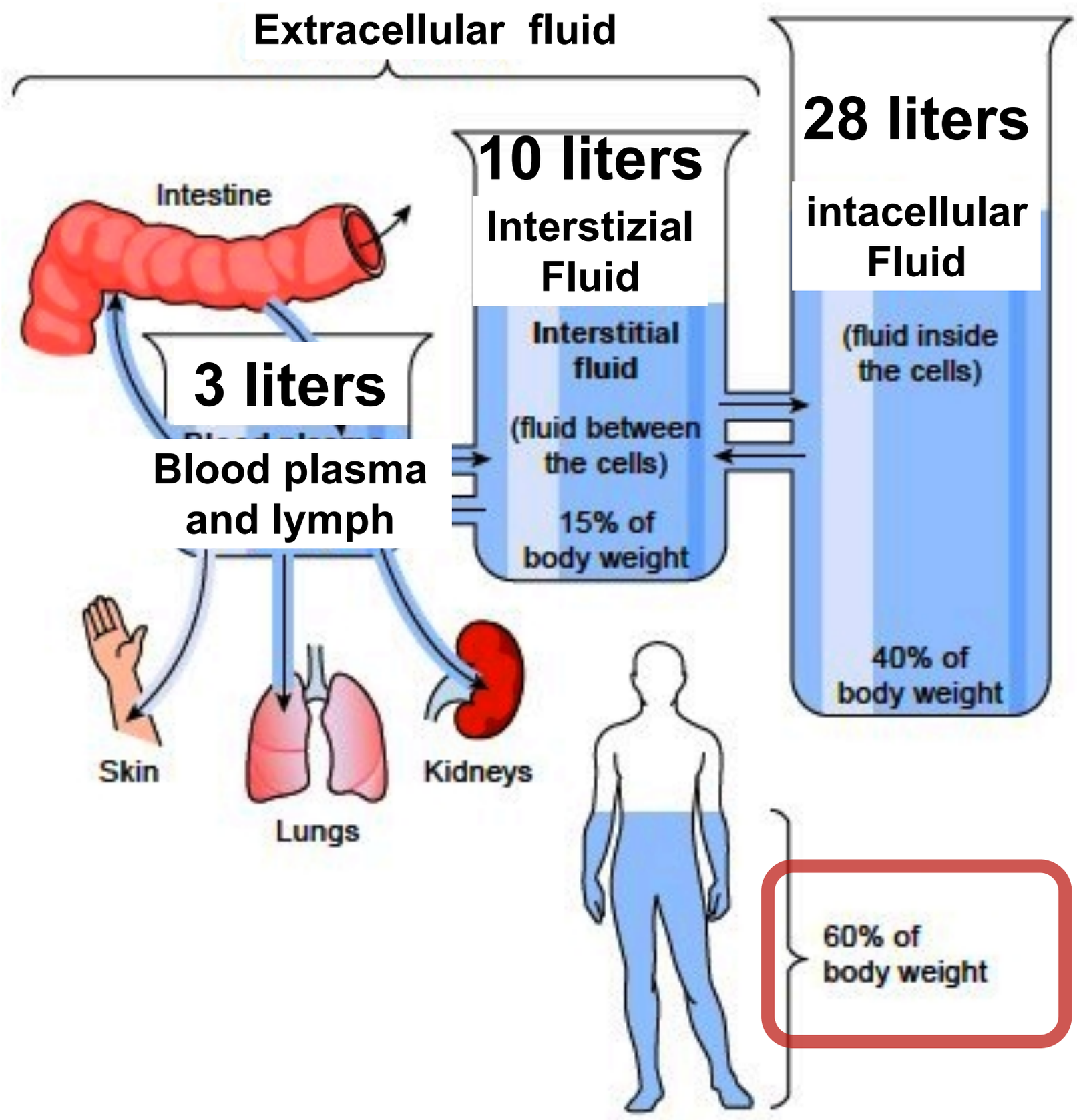
3) A few drugs are concentrated specifically in one or more tissues (iodine in the thyroid gland, chloroquine in the liver, tetracycline in bon and developing teeth, highly lipid soluble compounds in fat tissue)

4) **Most drugs exhibit a non-uniform distribution with variations that are largely determined by the ability to pass through membranes and their lipid/water solubility**

Drug distribution



Water compartments in the body



The Apparent Distribution Volume (Vd)

The Vd is an useful indicator of the type of the distribution pattern that characterizes a drug

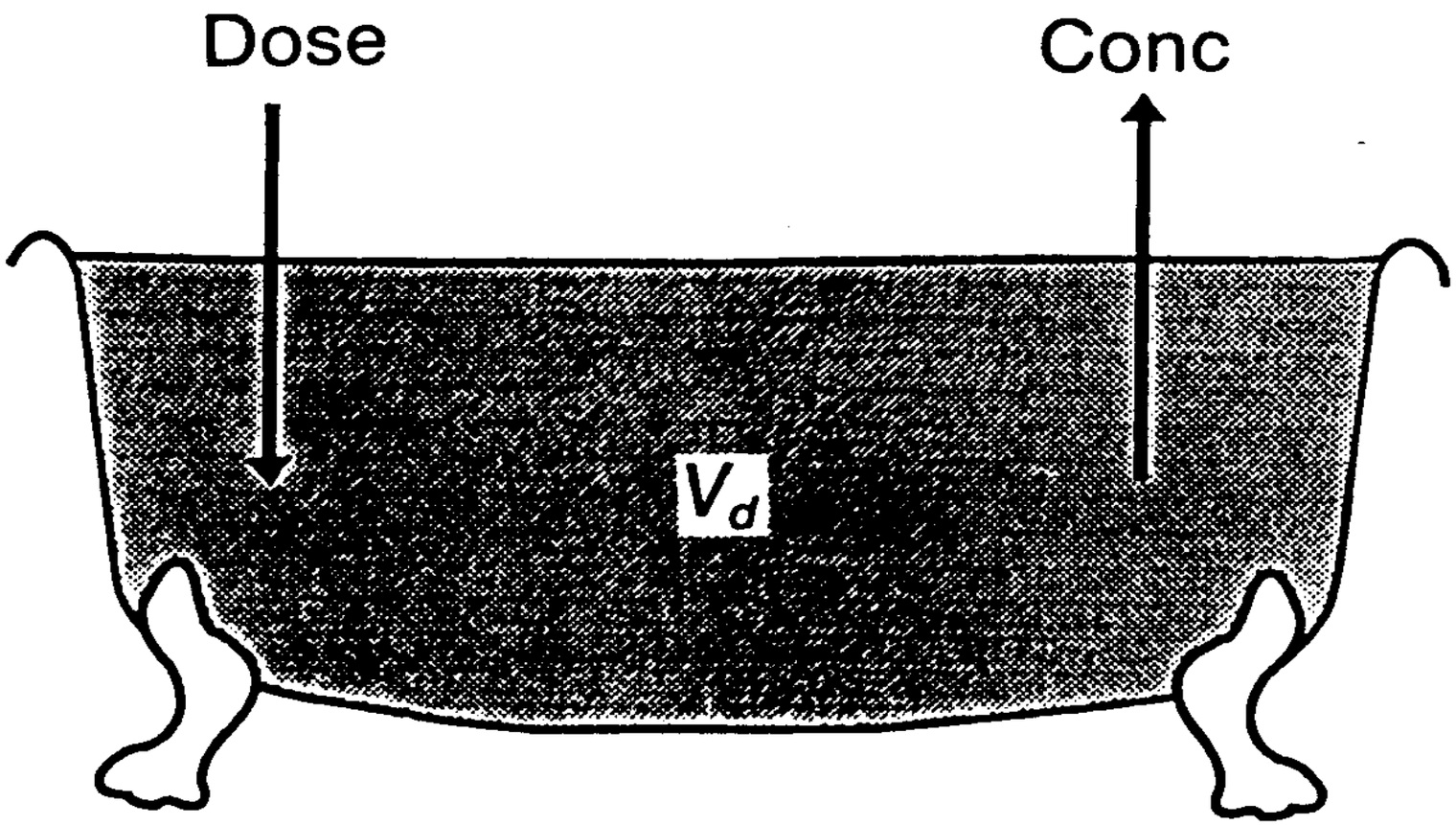
Vd describes the relationship between the concentration of the drug in the blood and the amount of the drug in the body

$$Vd = \frac{\text{Amount of drug administered (mg)}}{\text{Drug concentration in plasma (mg/L)}}$$

By definition, Vd is the volume into which a drug *apparently* distributes to achieve a concentration equal to its (measurable) plasma concentration

The Apparent Distribution Volume (Vd)

The bathtube model

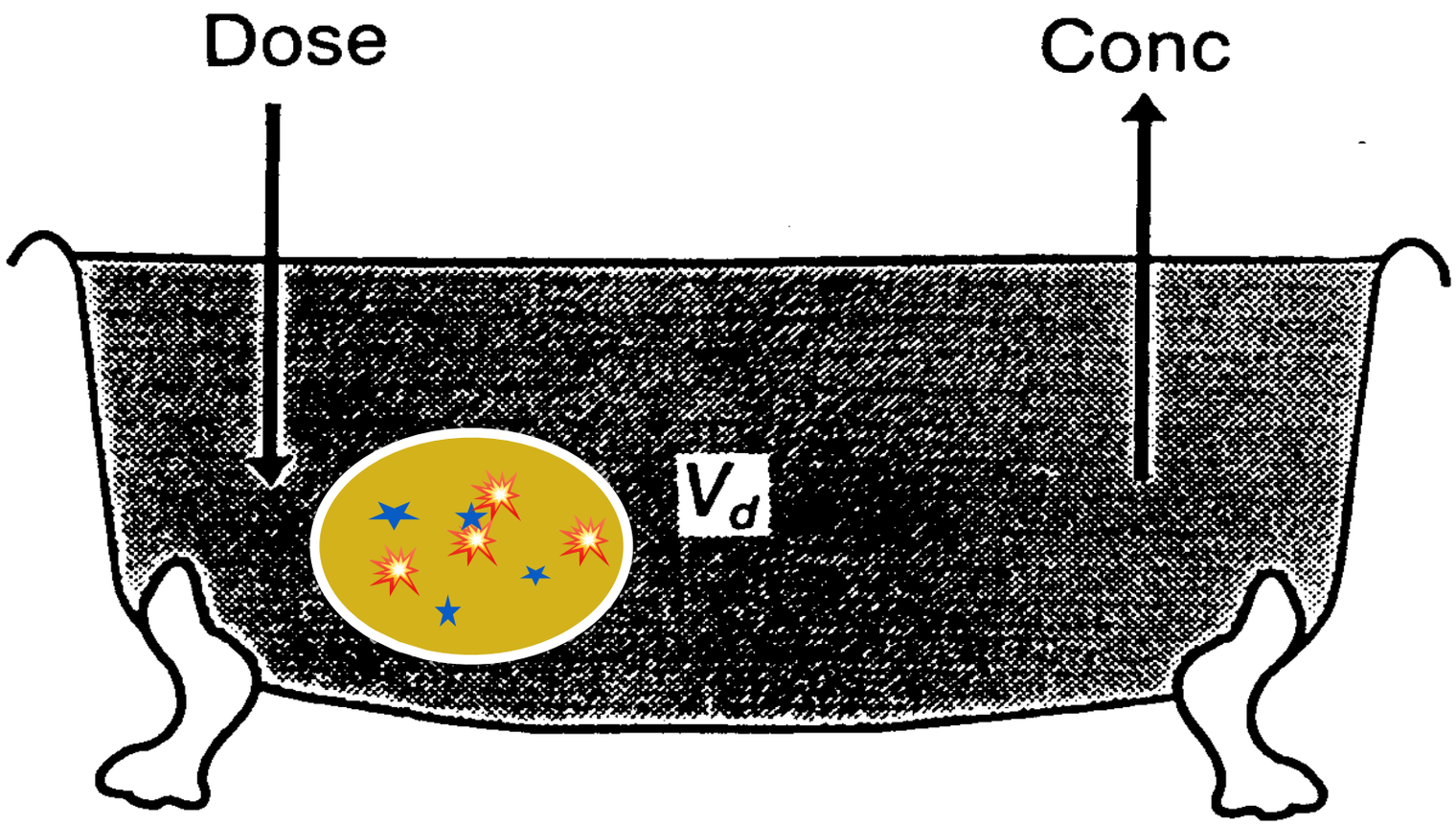


$$Vd = \frac{\text{amount of drug administered}}{\text{drug concentration in plasma}}$$

$$50\ L = \frac{500\ mg}{10\ mg/L}$$

The Apparent Distribution Volume (Vd)

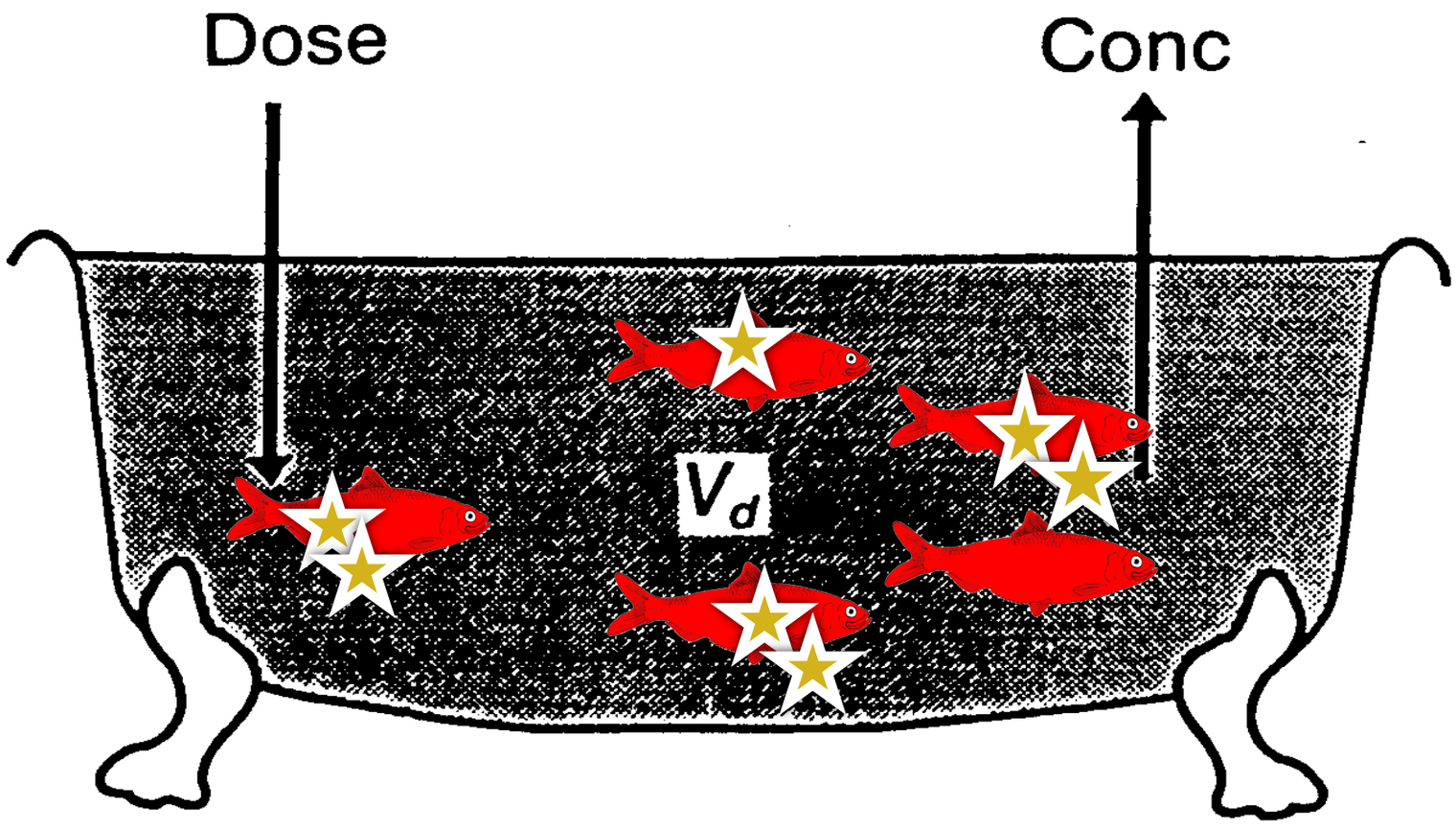
Tissue accumulation: the sponge model



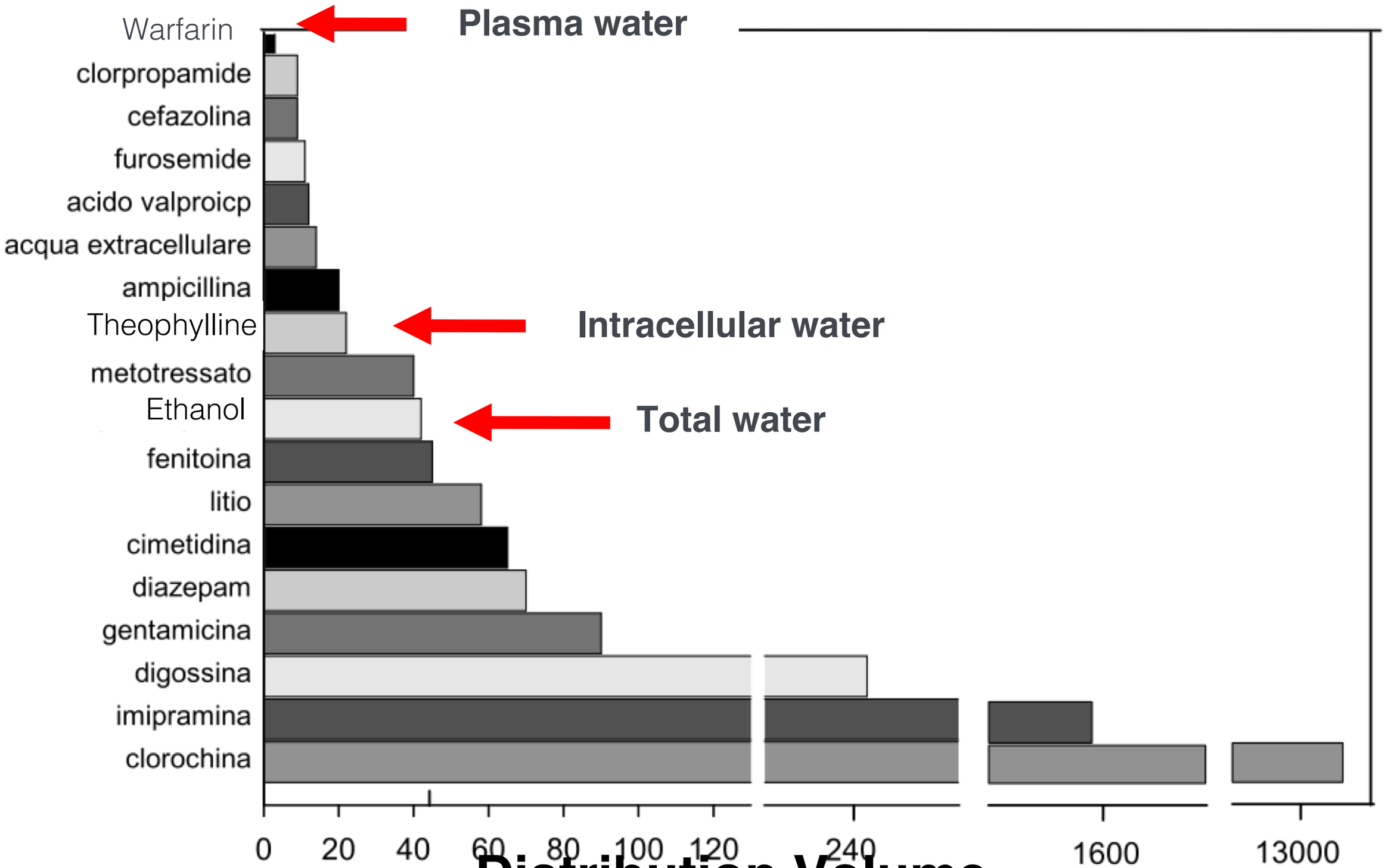
$$Vd = \frac{\text{amount of drug administered}}{\text{drug concentration in plasma}} \qquad 500\ L = \frac{500\ mg}{1\ mg/L}$$

The Apparent Distribution Volume (Vd)

Binding to plasma proteins: the red herring model



$$Vd = \frac{\text{amount of drug administered}}{\text{drug concentration in plasma}} \qquad 5\ L = \frac{500\ mg}{100\ mg/L}$$


Warfarin
clorpropamide
cefazolina
furosemide
acido valproicp
acqua extracellulare
ampicillina
Theophylline
metotressato
Ethanol
fenitoina
litio
cimetidina
diazepam
gentamicina
digossina
imipramina
clorochina
Plasma water
Intracellular water
Total water
0
20
40
60
80
100
120
240
1600
13000
Distribution Volume
(L)