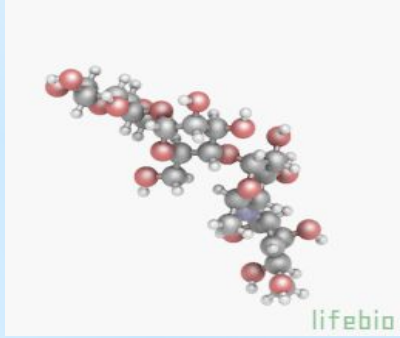
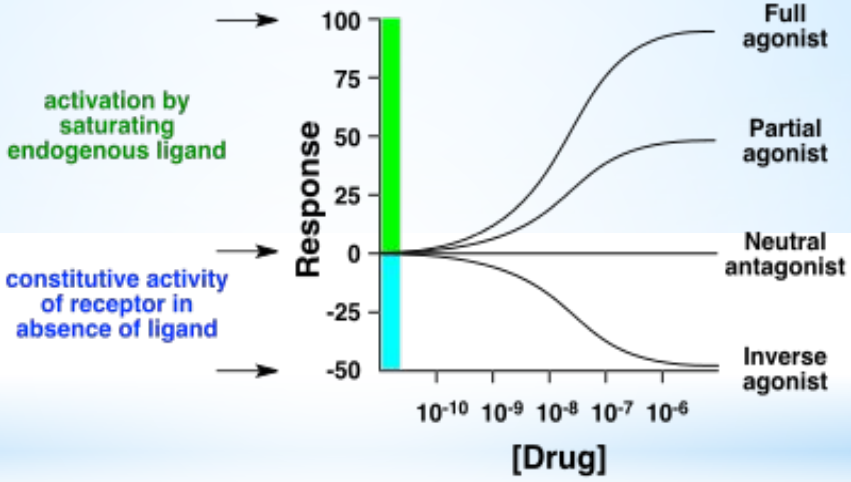
Zaporizhzhia State Medical University
Pharmacology Department



Lecture №1

General Pharmacology



Lecturer: Assoc. Prof. **Irene Borisovna Samura**

«All is a poison, all is a medicine; either depends on the dose»

Paracelsus
(1493-1541)

Pharmacology (In Greek: pharmacon - drug, remedy; logos - science) is the science which studies interaction between a drug and an organism:

Pharmacodynemics - studies physiological and biochemical effects of drugs and their mechanisms of action at molecular, subcellular, and organ system levels.

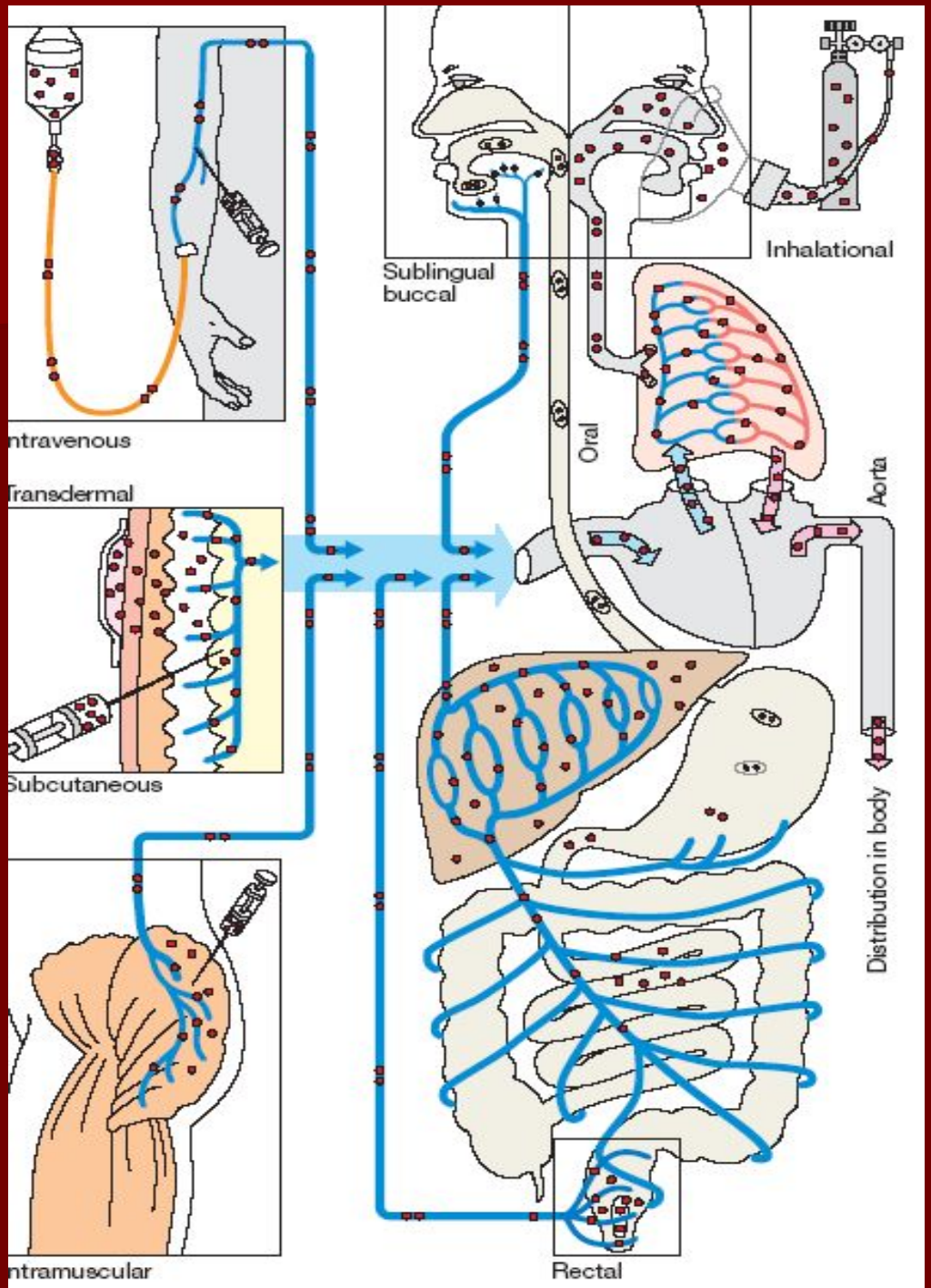
- What does the Drug do to the Body?

Pharnacokinetics - refers to movement of the drug in and alteration of the drug in the body.

- What does the Body do to the Drug?

Pharmacokinetics studies the processes of:

- **absorption** of the drugs from external inviroment into the blood;
- **distribution** of the drugs from the blood to tissues;
- **biotransformation** of the drugs in the human organism to another active or inactive substances;
- **excretion** of unchanged drugs or products of their metabolism from the organism.


Inhalational
Sublingual
buccal
Oral
Aorta
Distribution in body
Rectal

1. Bioavaliability is:

- the ratio of the portion of a drug which was absorbed to the blood to the total introduced dose.
- After intravenous introduction bioavaliability of drug is always 100%, but in other routes - less.

2. Bioequivalency is:

- bioavaliability of the same drug in different drug forms (tablets, powder, solution etc.).

For most majority of drugs

BIOAVAILABILITY **is equal to**

40-70% **- Average level**

If *Bioavailability*

< 40% - Low level

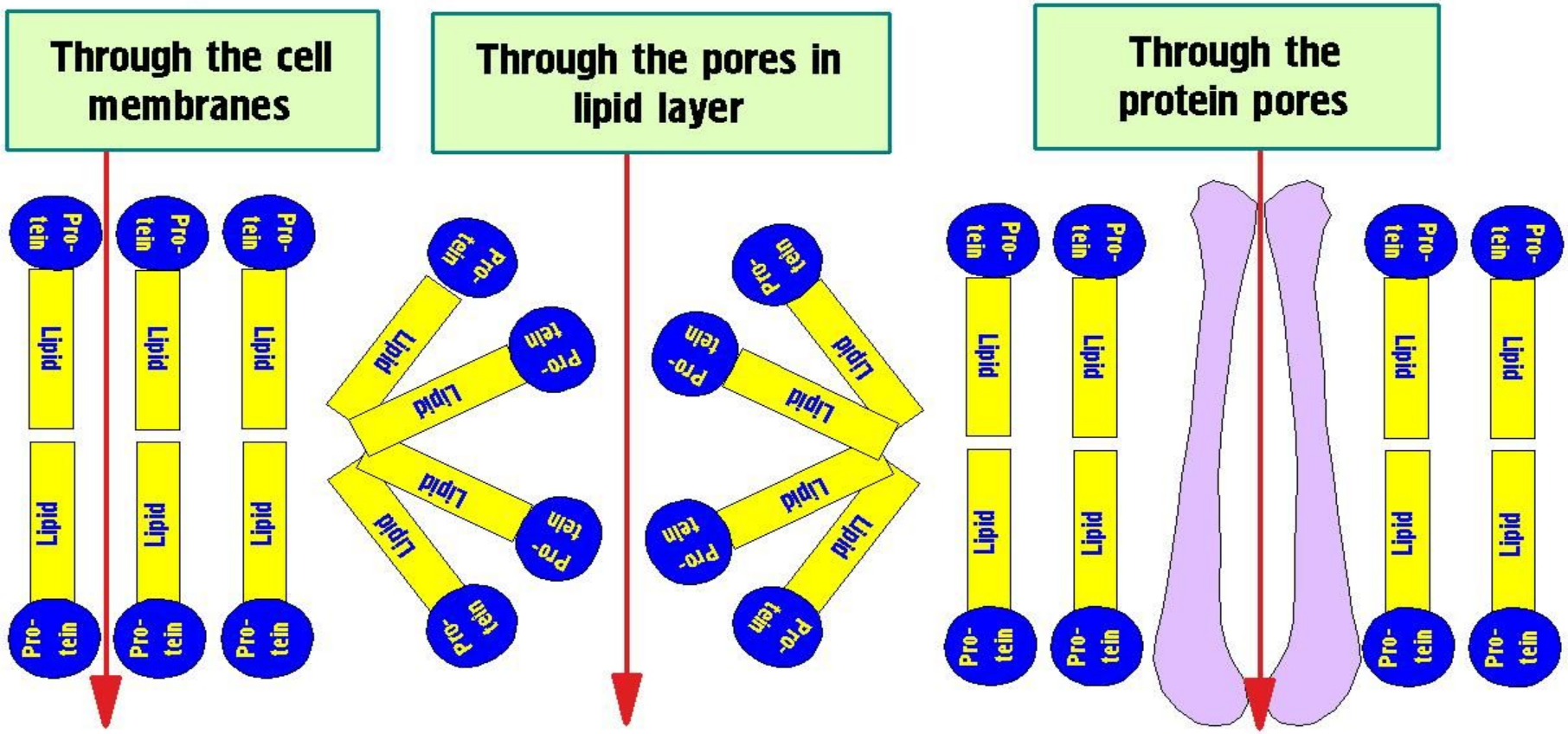
< 70% - High level

MECHANISMS OF DRUG ABSORPTION

1. Passive diffusion

- is realized according to the concentration gradient without energy consumption;

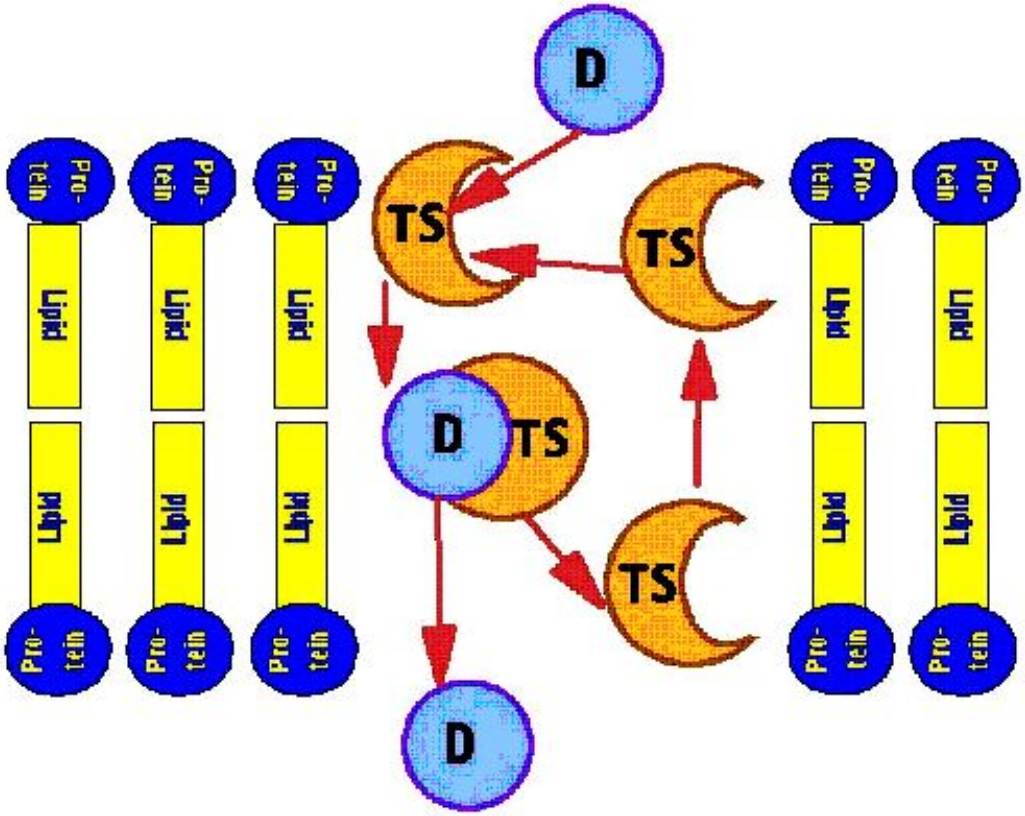
Lioposoluble non-polar compounds are absorbed:

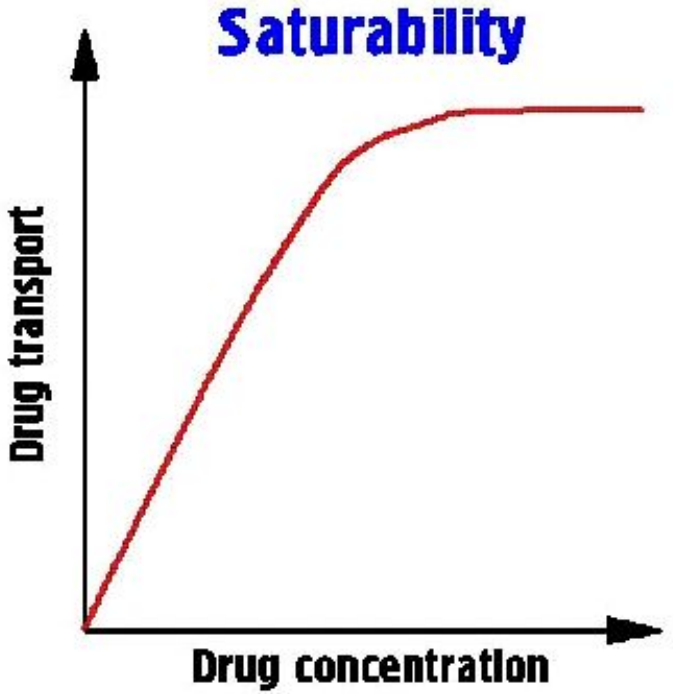


2. Simplified diffusion

- Is realized according to the concentration gradient without energy consumption, but with the help of special transport protein systems (TS);

Liposoluble Non-Polar Compounds are absorbed:

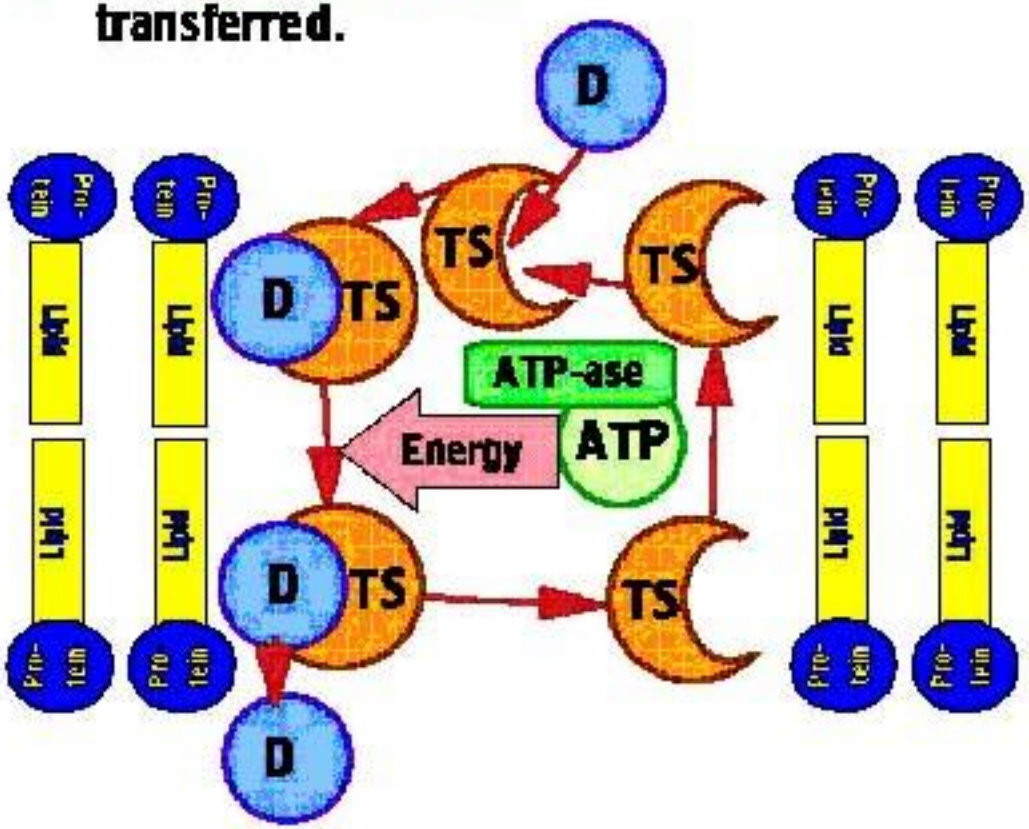


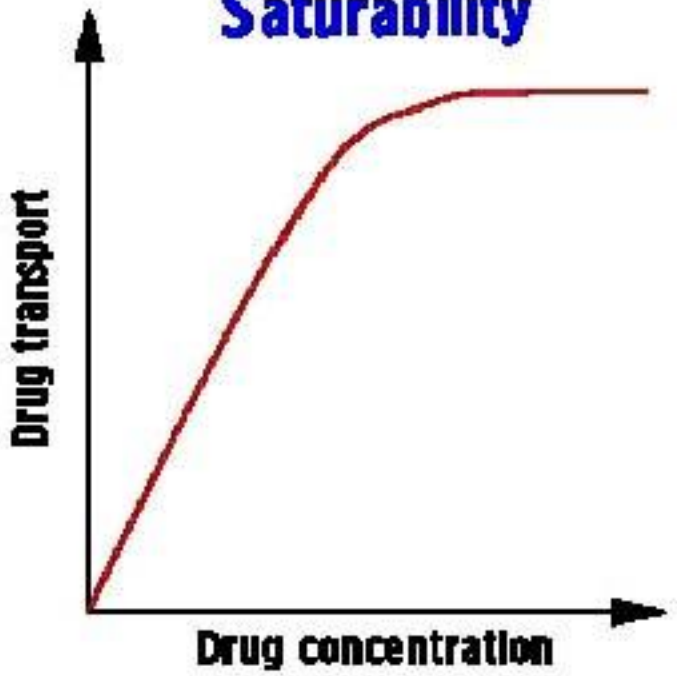


3. Active transport

- Is realized against the concentration gradient with energy consumption

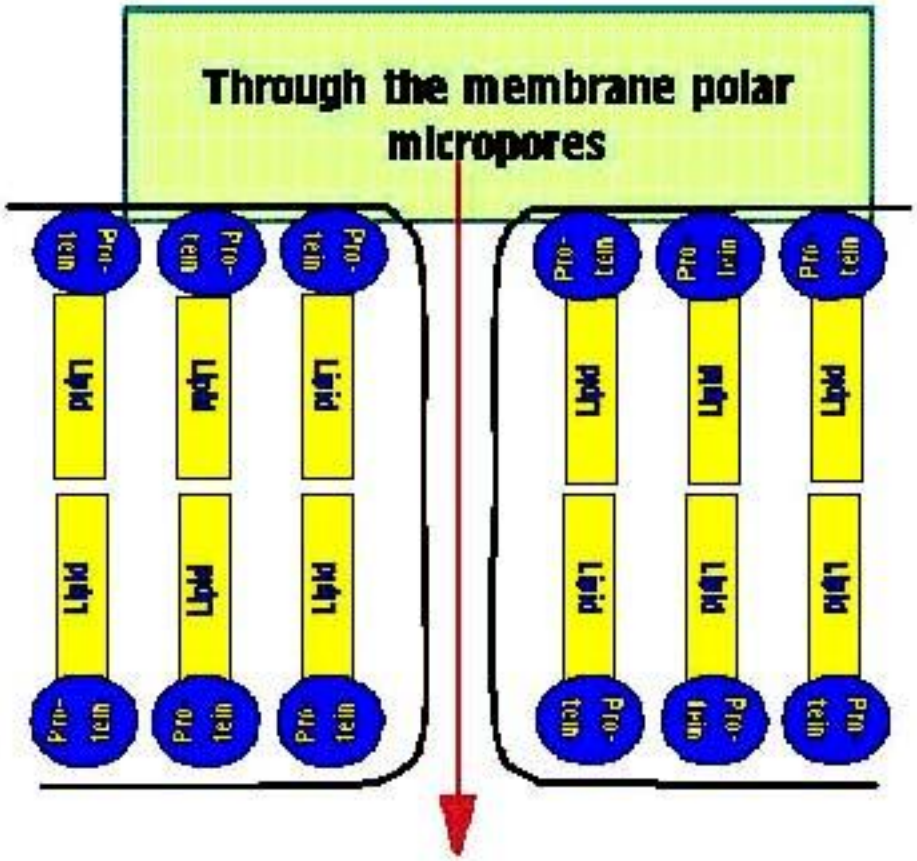
- the hydrophylic polar substances: sugars, ions, aminoacids, pyrimidines are transferred.

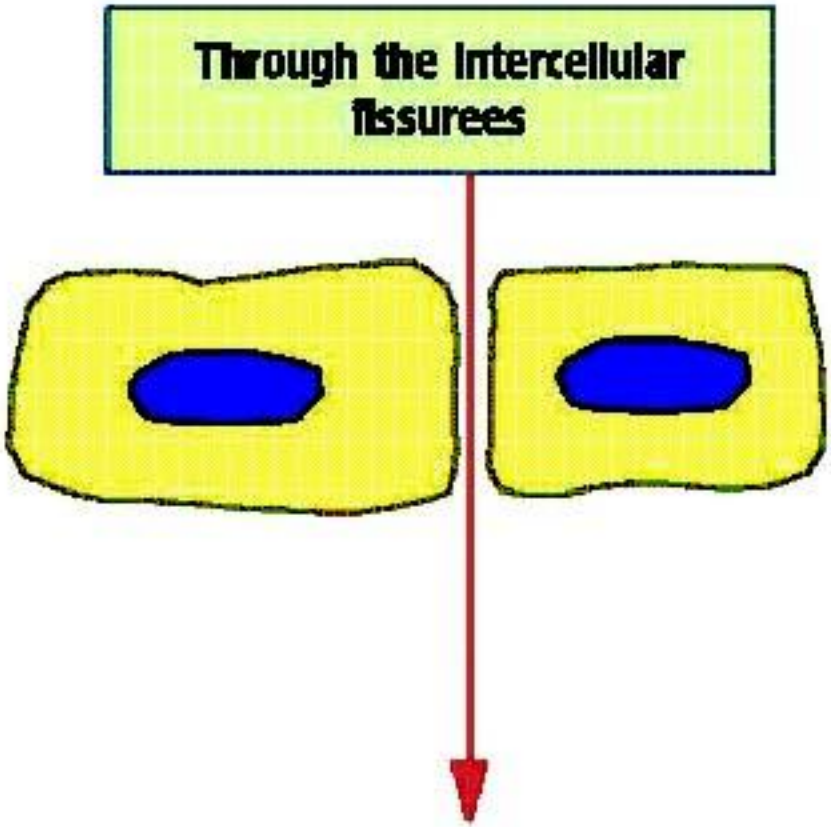




4. Filtration

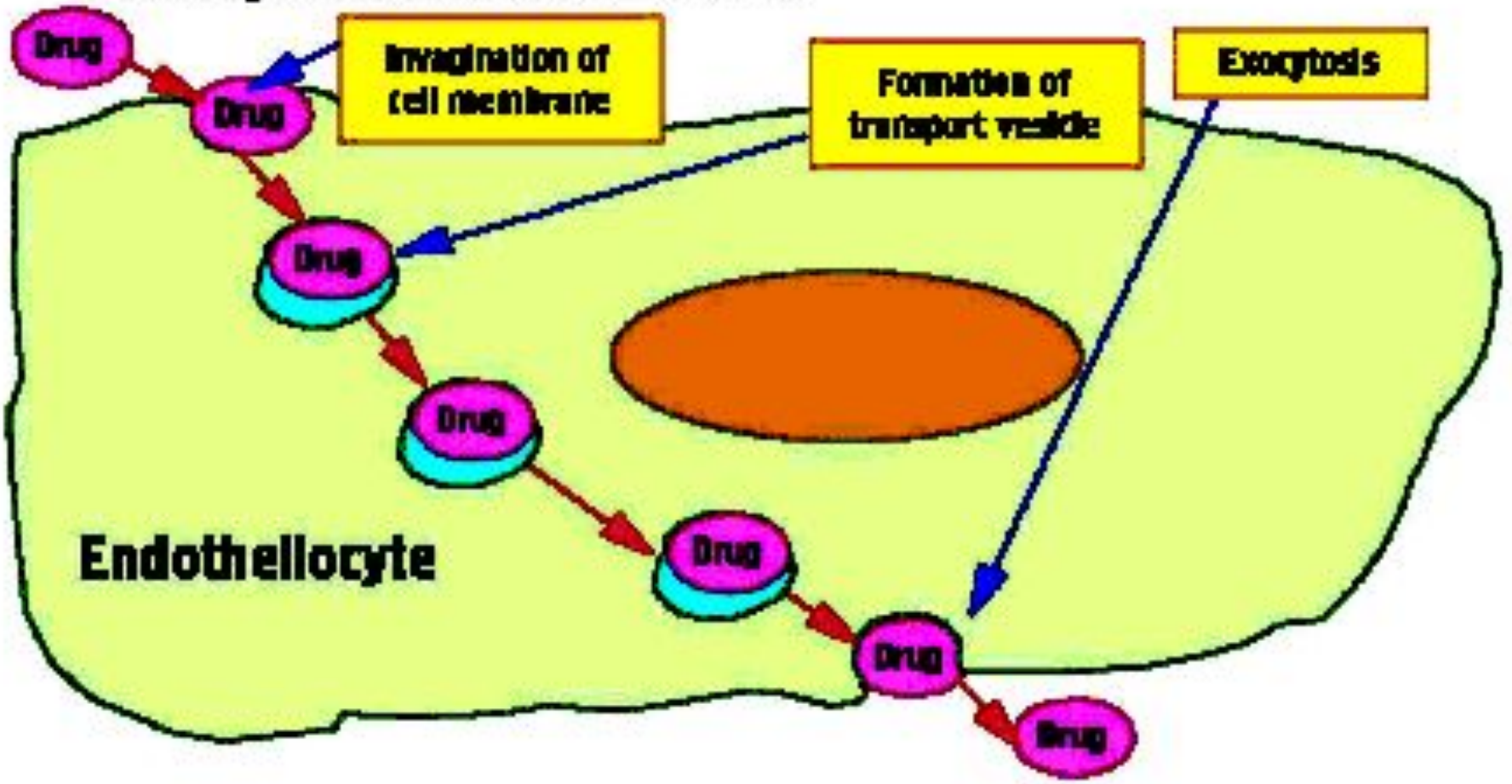
- Is realized according to the hydrostatic pressure gradient **without energy consumption**, through the membrane micropores or intercell fissurees;
- the small **hydrophylic polar** molecules and some ions are transferred.





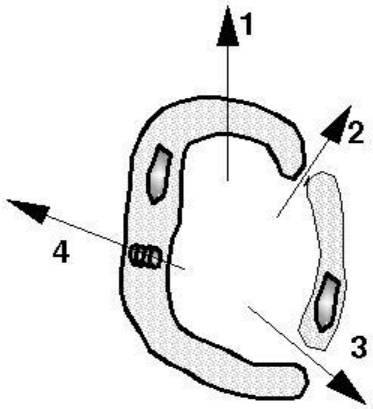
5. Pinocytosis

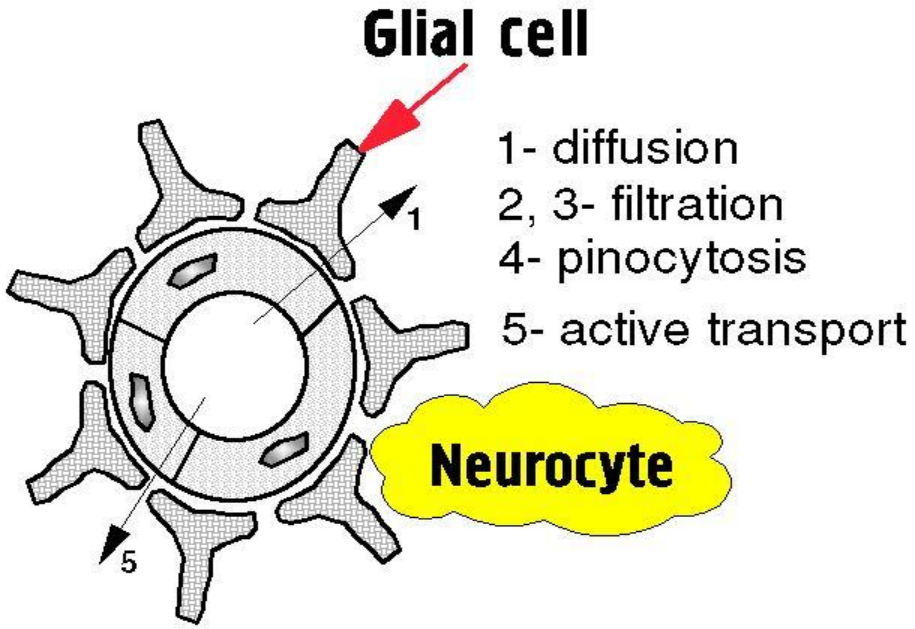
- is realized by formation of vacuole and it's transport through the endothelial cell;
- the large molecules are transferred.



Distribution of the drugs in the tissues and organs depends on:

1. the level of vascularisation of tissue
2. affinity of the drug molecule to the tissue proteins
3. the structure of histo-hematic barier
   - hemato-encephalic
   - placental
   - hemato-testicular



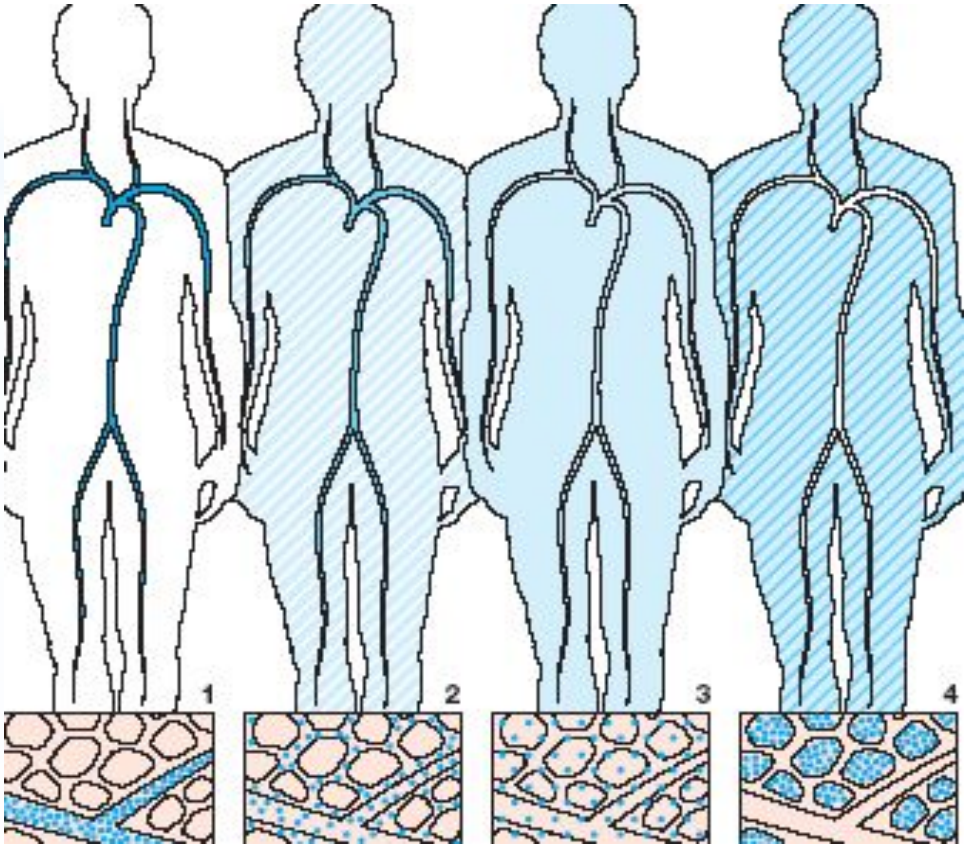


Volume of destruburion (Vd) –

is a hypothetical volume of fluid into which the drug is dissemineted

Water compartments in the body:

1. **Extracellular Volume** - ***14 L***
   - **plasma Volume** - ***4 L***
   - **interstitial Volume** - ***10 L***
2. **Intracellular Volume** - ***28 L***



V_d is the ratio of

the total amount of drug in the body to

the concentration of drug in plasma:

$$V_d = D/C \text{ or } C = D/V_d$$

D – total amount of drug in the body

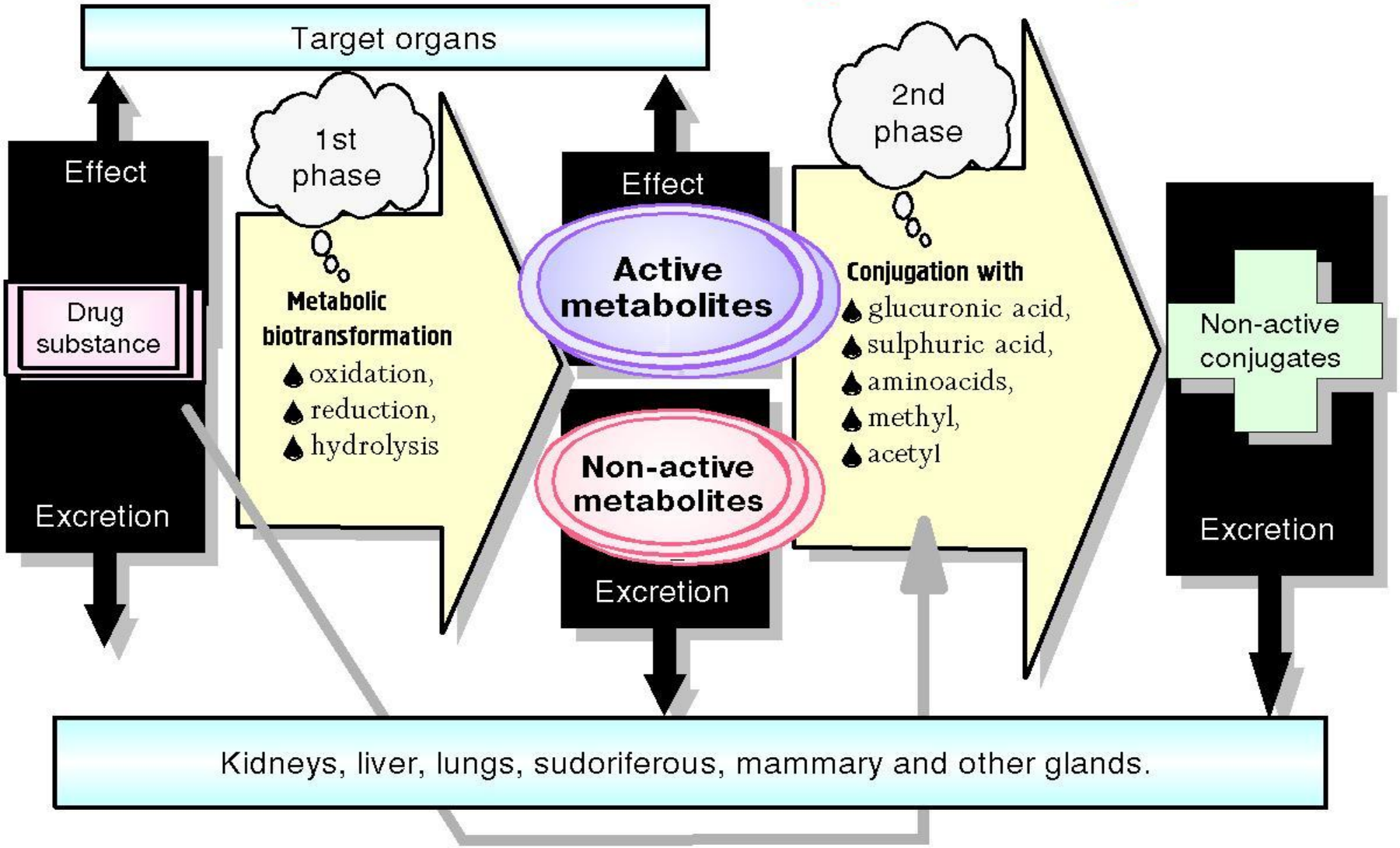
C – plasma concentration of drug

V_d = 100 mg / 25 mg/L = 4 L

V_d = 100 mg / 7 mg/L = 14 L

V_d = 100 mg/0.25 mg/L = 400 L

Biotransformation of drugs in an organism



Phase I – Metabilic Biotransformation

Lipophilic molecules => *Polar Molecules* by introducing or unmasking a polar functional group, such as **–OH** or **–NH_2**

a) Utilizing the Cytochrome P-450

b) Not involving the Cytochrome P-450

- ► **Oxidation**
- ► **Reduction**
- ► **Hydrolysis**

Phase II – **Conjugation Reactions** with *an* **Endogenous substrate:**

- Glucuronic acid
- Sulfuric acid
- Acetic acid
- Amino acid

=> Polar Water-Soluble compounds that are most often therapeutically inactive

Enzyme Induction - the ability of some drugs to **induce CYP-450** by:

- the rate of its **synthesis** or
- its rate of **degradation**:

Phenobarbital

Isoniazid

Glucocorticoides

Anticonvulsants

Macrolid antibiotics

Chronic ethanol administration

Steroids

Enzyme Inhibition - the ability of drugs **to inhibit CYP-450** by:

- the rate of its **synthesis** or
- its rate of **degradation**.

Cimetidine and ***Ketoconazol*** bind to the *heme iron* of CYP-450 and

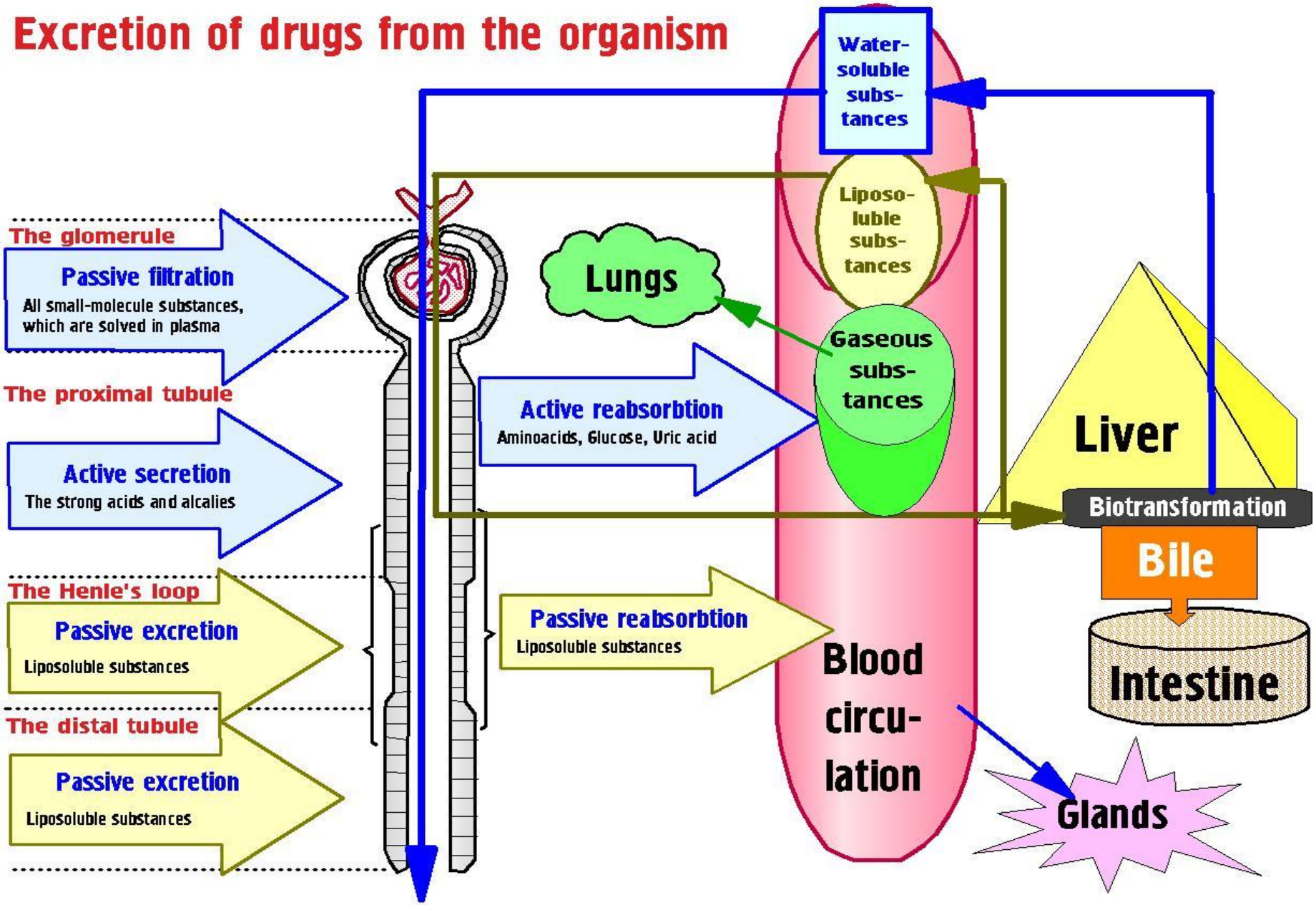
- **Metabolism** of *Endogenous Substrates* and other coadministered drugs.

Ethinylestradiol

Spironolacton

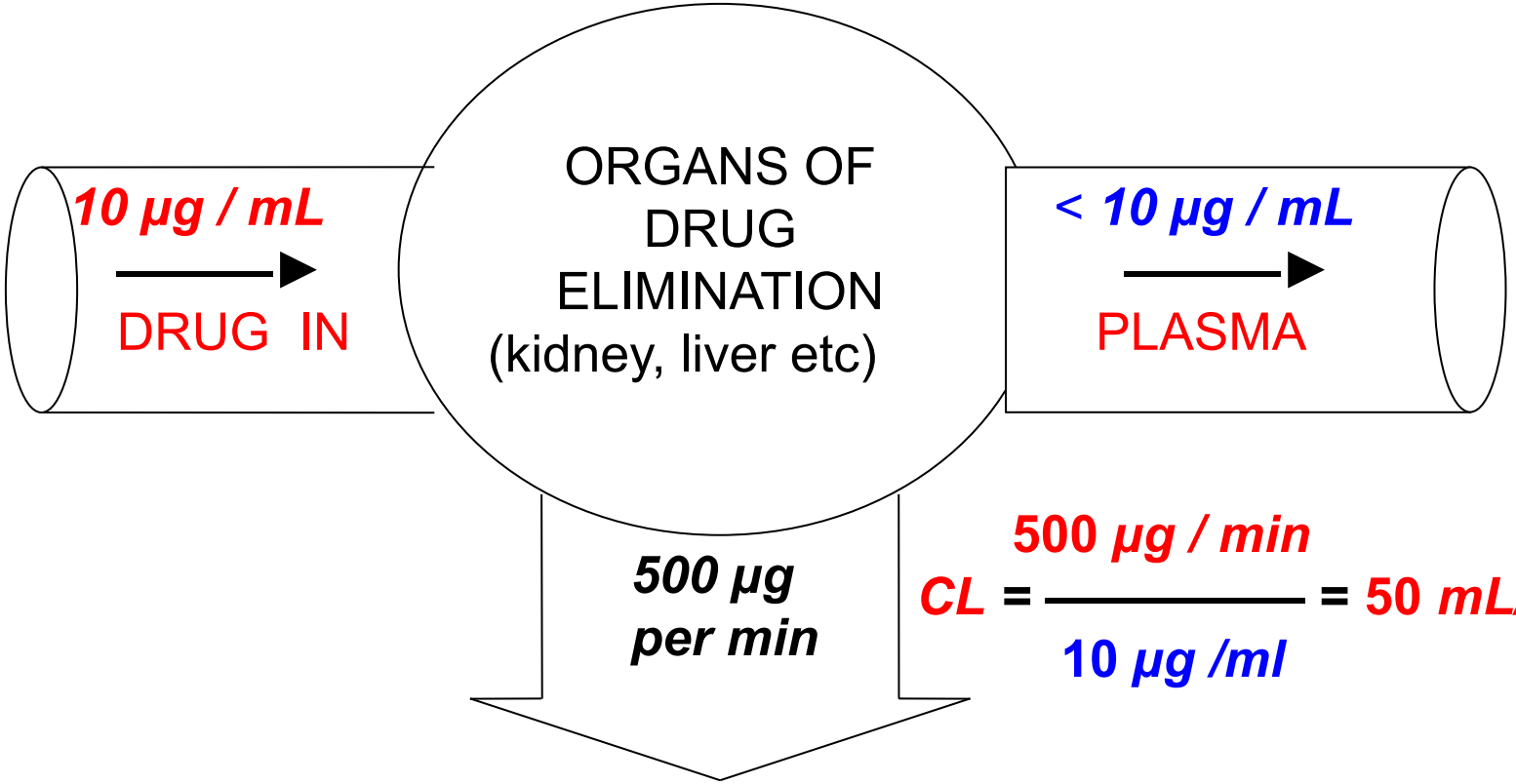
Allobarbital

Excretion of drugs from the organism



Clearance of a Drug

Cl = Rate of Elimination / C



$$CL = \frac{500\ \mu g / min}{10\ \mu g / ml} = 50\ mL / min$$

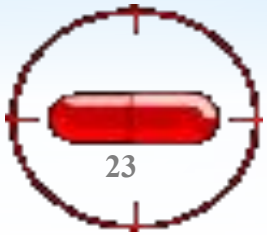
First-order (*exponential*) kinetics

Rate of Elimination = ***Cl*** x **C**

Steady State Plasma Concentration (Css)

$$Css = \frac{Dose}{Cl} \quad \text{or} \quad Dose = Css \times Cl$$

!! Doubling the **Dose** rate would Double the C_{ss}



For drugs with ***Michaelis-Menten*** kinetics, elimination changes from **1st Order** to **Zero Order** kinetics over the therapeutic range

$$\text{Rate of Elimination} = \frac{V_{max} \times C}{K_M + C}$$

V_{max} - the maximum rate of drug elimination

K_m - the drug concentration at which the rate of elimination is 50% of V_{max}

For drugs with **1st order** kinetics:

$$\text{Rate of Elimination} = \frac{V_{max} \times C}{K_M + C}$$

For drugs with **Zero Order** kinetics over the therapeutic range:

$$\text{Rate of Elimination} = \frac{V_{max} \times C}{C} = V_{max}$$

The parameters of elemination speed

1. The Half-life period ($t_{\frac{1}{2}}$):

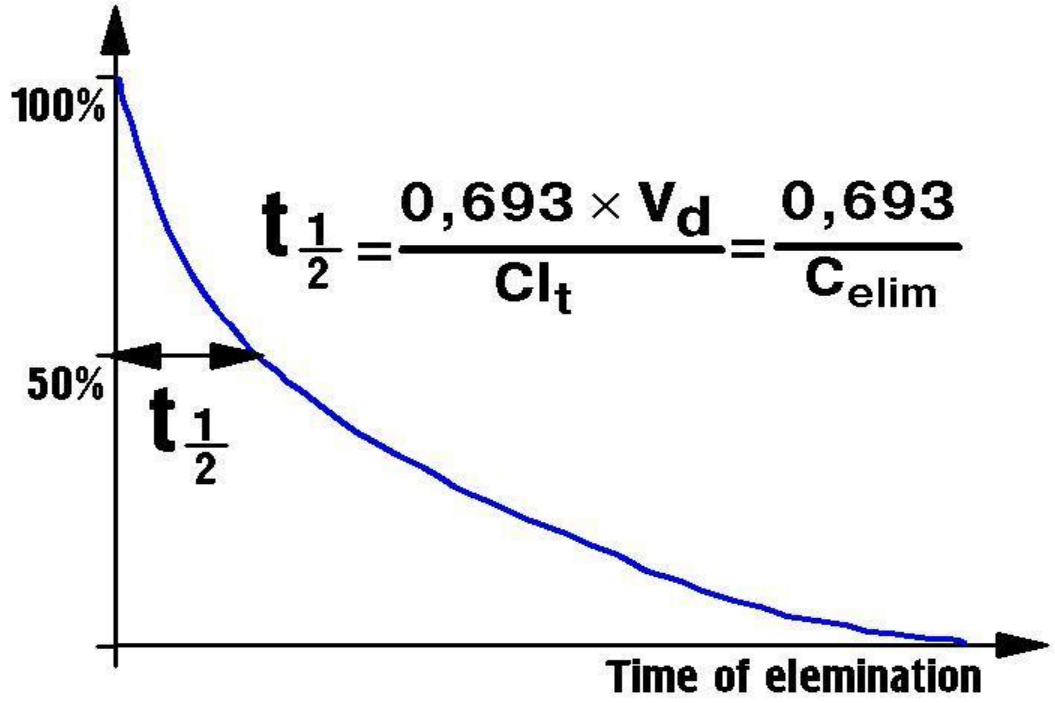
- it is time during which concentration of a drug in an organism is reduced by 50%
- **Where:**

$0,693 = Ln(2)$

C_{elim} – Constsnt of elimination

Cl_t – Clearance

V_d – Apparent volume of distribution



The parameters of elemination speed

2. The Constant of elimination (C_{elim}):

- it is the drug part (put into % from the introduced dose) which is excreted from the organism during 24 hours.
- **Where:**

$0,693 = Ln(2)$

$t_{\frac{1}{2}}$ – Half-life period

$$c_{elim} = \frac{0,693}{t_{\frac{1}{2}}}$$

The parameters of elemination speed

3. The clearance (Cl_t):

- it is product of the constant of elimination and apparent volume of distribution.
- **Where:**

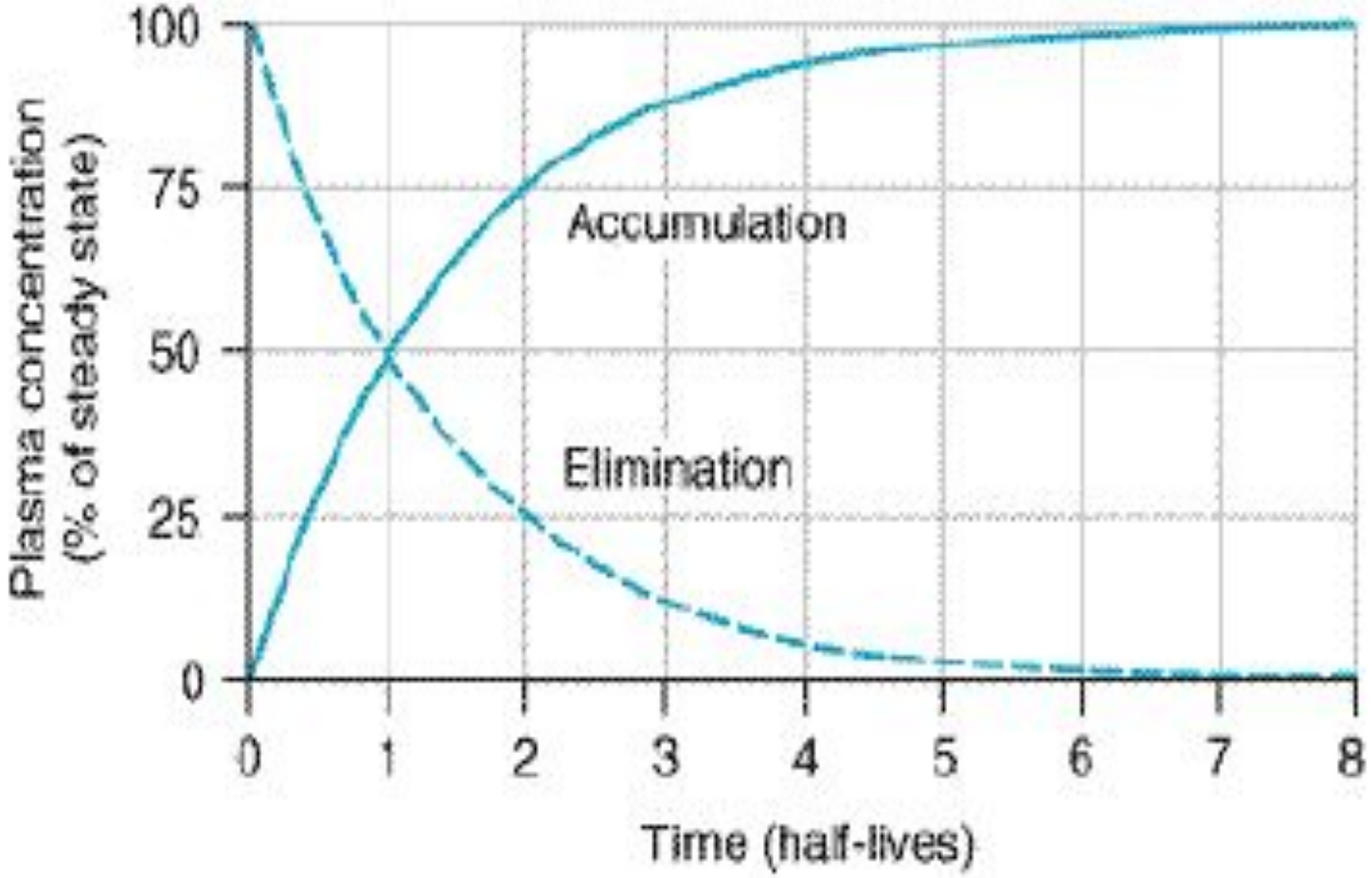
$0,693 = Ln(2)$

$t_{\frac{1}{2}}$ – Half-life period

C_{elim} – Constant of elimination

V_d – Apparent volume of distribution

$$Cl_t = C_{elim} \times V_d = \frac{V_d \times 0,693}{t_{\frac{1}{2}}}$$



50 % of the drug is lost after one $T_{1/2}$

75% - after 2 $T_{1/2}$

> 90% - after 4 $T_{1/2}$

The types of actions of the drugs

1. By prevalence:

- resorbtive, or general, which develops after absorption of the drug into the blood;
- local (topical) action of the drug - in the place of it's application;

2. By the method of contact with target organs:

- direct - change of function of organ on which a drug acts directly;
- indirect - change of function of organ on which a drug doesn't act directly;
- reflex - as a result of irritation of various receptors and further changes of inner organ functions due to impulse transmission through the CNS (via the reflex arch).

Principal mechanisms of action of drugs

- interaction with receptors;
- change of activity of enzymes;
- influence on conductivity of ionic channels;
- influence on transport systems;
- antimetabolitic;
- influence on molecules of DNA.

The main concepts of receptor's theory:

1. Receptor - active part of protein macromolecule built in the cell membrane or been in cytoplasm:

- specific - which ensures manifestation of the drug action;
- nonspecific - binding to which doesn't cause special effects (blood plasma proteins, mucopolysaccharides et c.).

Drugs' interaction by the direction:

- **Synergism - strengthening of action of interacting drugs:**
  - **sensitisation** - the action of a drug is increased by indifferent substance;
  - **additive synergism** - mutual result is less than arithmetical sum of both drugs' effects;
  - **summation** - mutual result is equal to the arithmetical sum of both drugs' effects;
  - **potentiation** - is augmentation of effects, the mutual result is more than the arithmetical sum of both drugs' effects.

The changes of pharmacological effects of the drugs after repeated introduction

- **Cumulation - which leads to manifestation of toxic effects:**
  - **Material cumulation** is the increase of drug concentration in the organism. The level of free fraction is increased synchronously to saturation of bound fraction;
  - **Functional cumulation** is the accumulation of drug's effect in spite of elimination of a drug.

The changes of pharmacological effects of the drugs after repeated introduction

- **Drug tolerance** is weakening of drug's effect after repeated introduction in some days. It may be caused by lowering of drug's absorption, or by speeding up of it's biotransformation and excretion as well as by decrease of receptor sensebility. To overcome drug tolerance the drug dose should be increased that may lead to intoxication.
- **Tachyphylaxis** is weakening of drug's effect in rapid repeated introduction (after 10-30 min.)

The changes of pharmacological effects of the drugs after repeated introduction

- **Drug dependence** is the constant desire to take the drug:
  - **Psychical dependence** is the constant overmastering craving for taking of drug, that is accompained by various disorders of behavioural reactions;
  - **Physical dependence** includes the psychical one and in addition is accompanied by hard somatic disorders, moustly - during the phase of abstinence. The cessation of use of drug in this case may cause death.

The complications of pharmacological therapy

- **Complications associated with toxic properties of drugs during their prolonged taking (1):**
  - **Disturbances of functions of organs and systems:** neurotoxic, hepatotoxic, nephrotoxic, hematotoxic, ulcerogenic effects.
  - **Depression of organisms immunoprotective properties:** immunodepressive.
  - **Unfavorable effect on foetus:**
    - **Disorders of functions only:** embriotoxic (to 12 weeks), foetotoxic (after 12 weeks);
    - **Anatomic deformities:** teratogenic.

Dose: by size:

- **Minimal (threshold) dose** is the minimal quantity of drug causing the medical curative effect;
- **The highest (maximum) dose** is the maximum quantity of drug causing the medical curative effect without toxic one;
- **Medium therapeutic dose** is the dose which is in between minimal and highest and used in ordinary cases;
- **Stroke dose** is the dose which is close to the highest dose and used for short period of time with the aim of quick increase of the drug concentration;
- **Toxic dose** is the quantity of drug causing the toxic action;
- **Lethal dose** is the dose which causes death of a patient;

Placebo is an inert substance which is given in the garb of a medicine.

Placebo causes some effects up to **20-40%** of cases.

It can be:

1) Positive - **84%**
2) Negative **5-7%**
3) Mix placebo effect - **9-12%**

Thank You for Attention!