



THE NATIONAL UNIVERSITY OF PHARMACY

Pharmacology department

Lecture topic:

“GENERAL PHARMACOLOGY II”



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Objectives

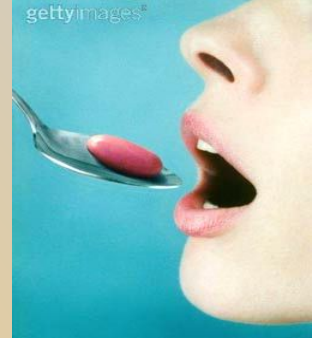
I. Pharmacokinetics

- ✓ Absorption
- ✓ Bioavailability
- ✓ Distribution
- ✓ Drug metabolism
- ✓ Excretion

II. Combined action of drugs



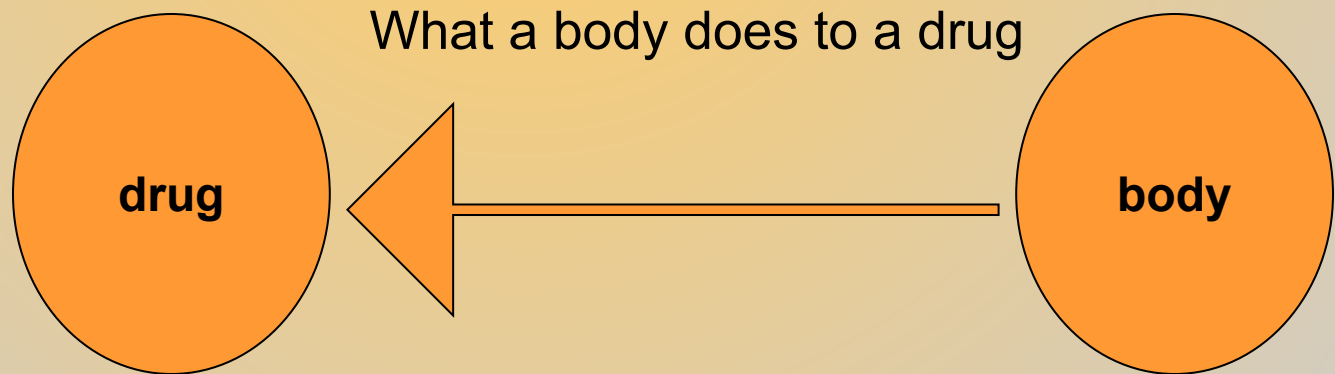
Pharmacokinetics



Pharmacokinetics

(from Greek *pharmakon* - medicine,
kineo - move)

Pharmacokinetics is the part of pharmacology that deals with compound absorption, distribution in the body, storage, metabolism and excretion.





Pharmacokinetics



Based on the hypothesis that **the action of a drug requires presence of a certain concentration in the fluid surrounding the target tissue.**



In other words, the magnitude of response (desirable or undesirable) depends on the concentration of the drug at the site of action



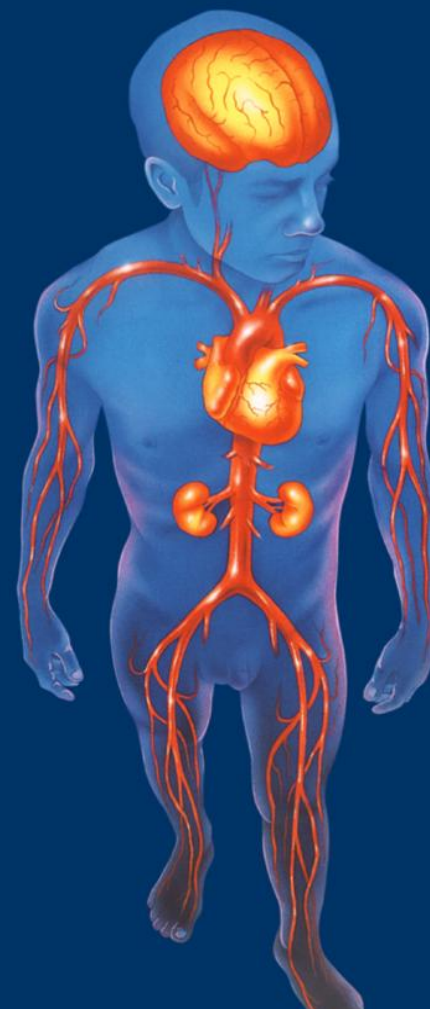


Pharmacokinetics

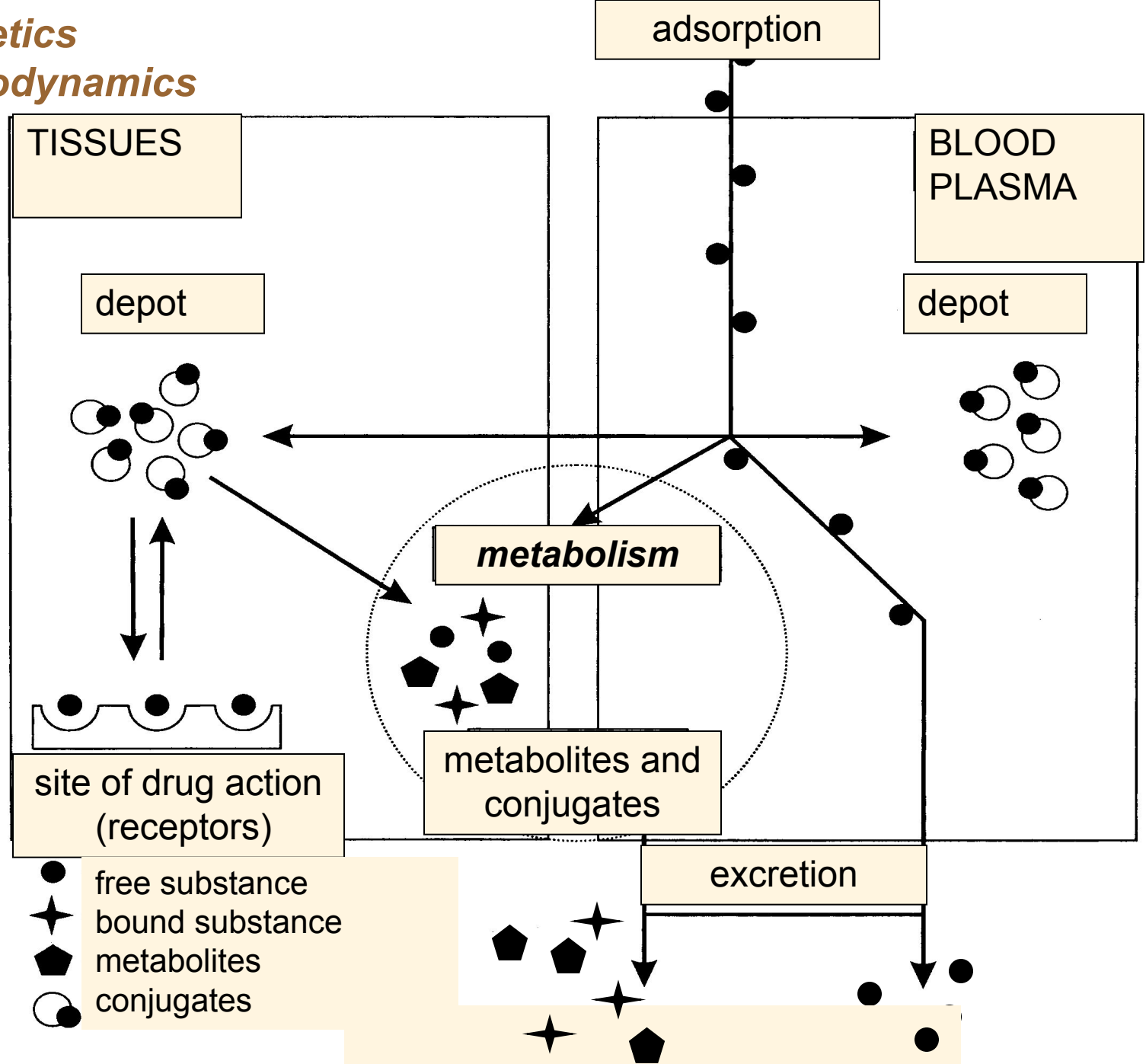
Drug Movement in the Body

ADME
profile

- Absorption
- Distribution
- Metabolism
- Excretion



Pharmacokinetics and Pharmacodynamics





Absorption

Step 1 in ADME profile



The usage of drugs starts with their administration into the organism or application onto body surface



The route of administration defines the speed of onset of effect, its intensity and duration and, in certain cases, the drug activity



There are several known absorption mechanisms

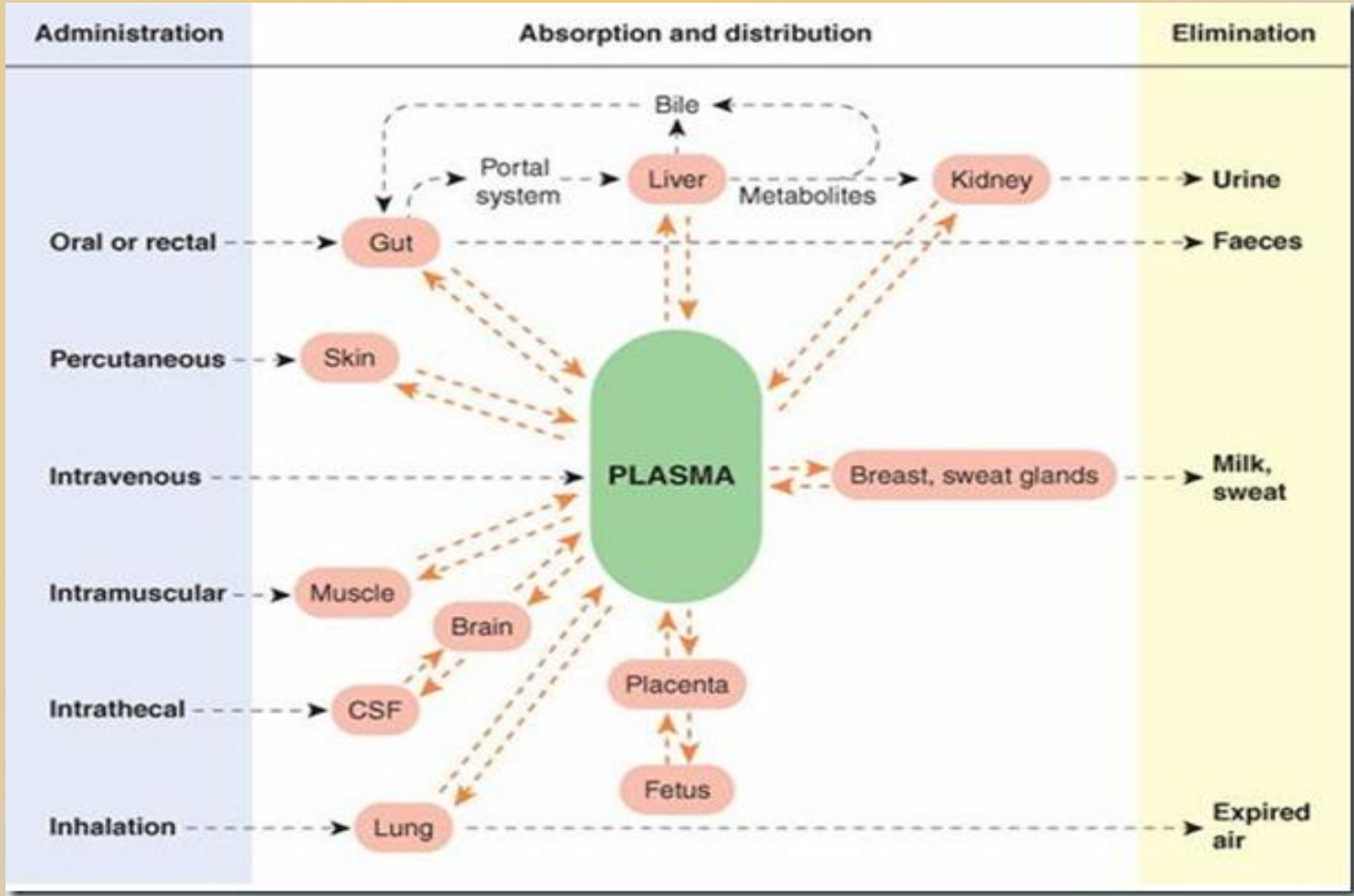


Absorption





Absorption

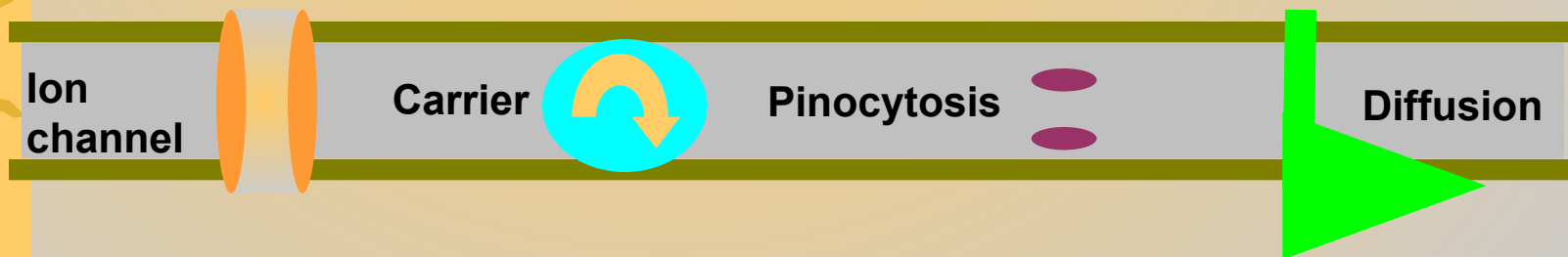


Absorption

Absorption of drugs from the gastrointestinal tract through the skin, respiratory and vascular walls is connected with several known mechanisms.

Types of transport:

- **passive** transport
(simple diffusion, facilitated diffusion, ultrafiltration)
- **active** transport
- **pinocytosis**





Absorption



Passive diffusion: substances move from the area with high concentration to the area with low concentration
(*small neutral molecules, oxygen*)



Facilitated diffusion: involves transport systems (specific carriers) functioning without energy consumption, along the concentration gradient (*adenilyc nucleotides*)



Active transport: can occur against the concentration gradient and with energy consumption. Involves transport systems that are selective to certain compounds and saturable
(*Na⁺ and K⁺ ions, sugars, aminoacids*)

Pinocytosis: involves formation of a vesicle filled with fluid and large molecules of transported substances. The vesicle migrates via the cytoplasm to the opposite side of the cell where the vesicle content is expelled from the cell



Absorption

<i>Mechanism</i>	<i>Direction</i>	<i>Energy required</i>	<i>Carrier</i>	<i>Saturability</i>
Passive diffusion	Along the gradient	No	No	No
Facilitated diffusion	Along the gradient	No	Yes	Yes
Active transport	Against the gradient	Yes	Yes	Yes



Passive transport





Membranes and Absorption



Small,
uncharged

Hydrophilic
Heads

H_2O , urea,
 CO_2 , O_2 , N_2

Lipid Bilayer

Hydrophobic
Tails

Swoosh!



Large,
uncharged

Glucose
Sucrose

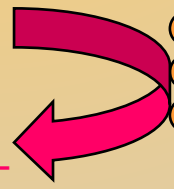
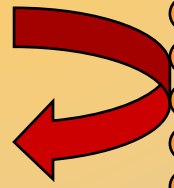
DENIED!



Small
charged
ions

H^+ , Na^+ ,
 K^+ , Ca^{2+} ,
 Cl^- , HCO_3^-

DENIED!





Facilitated transport





Active transport



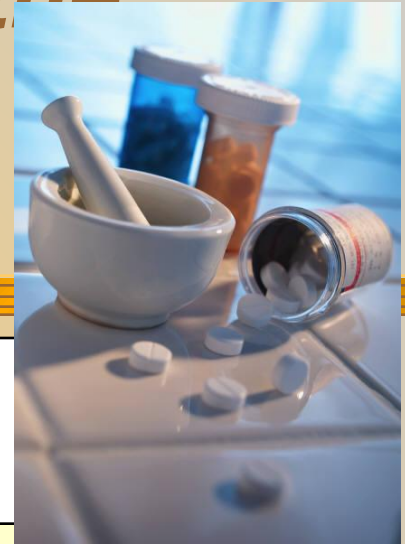


Pinocytosis





Factors that influence the absorption



Physical properties

- Physical state
- Solubility

Medicinal forms

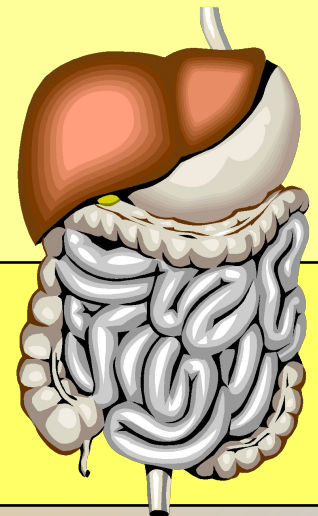
- Type of a medicinal form
- Size of drug particles
- Disintegration time

Physiological factors

- pH of GI fluids
- Ionization
- GI transit time

Diseased state

- Gastric disorders
- Liver disorders



Bioavailability

Systemic effect of a substance develops only after its entrance into the bloodstream from which it moves to tissues

bioavailability is the proportion of the initial drug dosage that reaches blood plasma (systemic circulation) without changes

after i.v injection - 100% bioavailability

In bioavailability assessment, the area under the curve (AUC) is usually measured

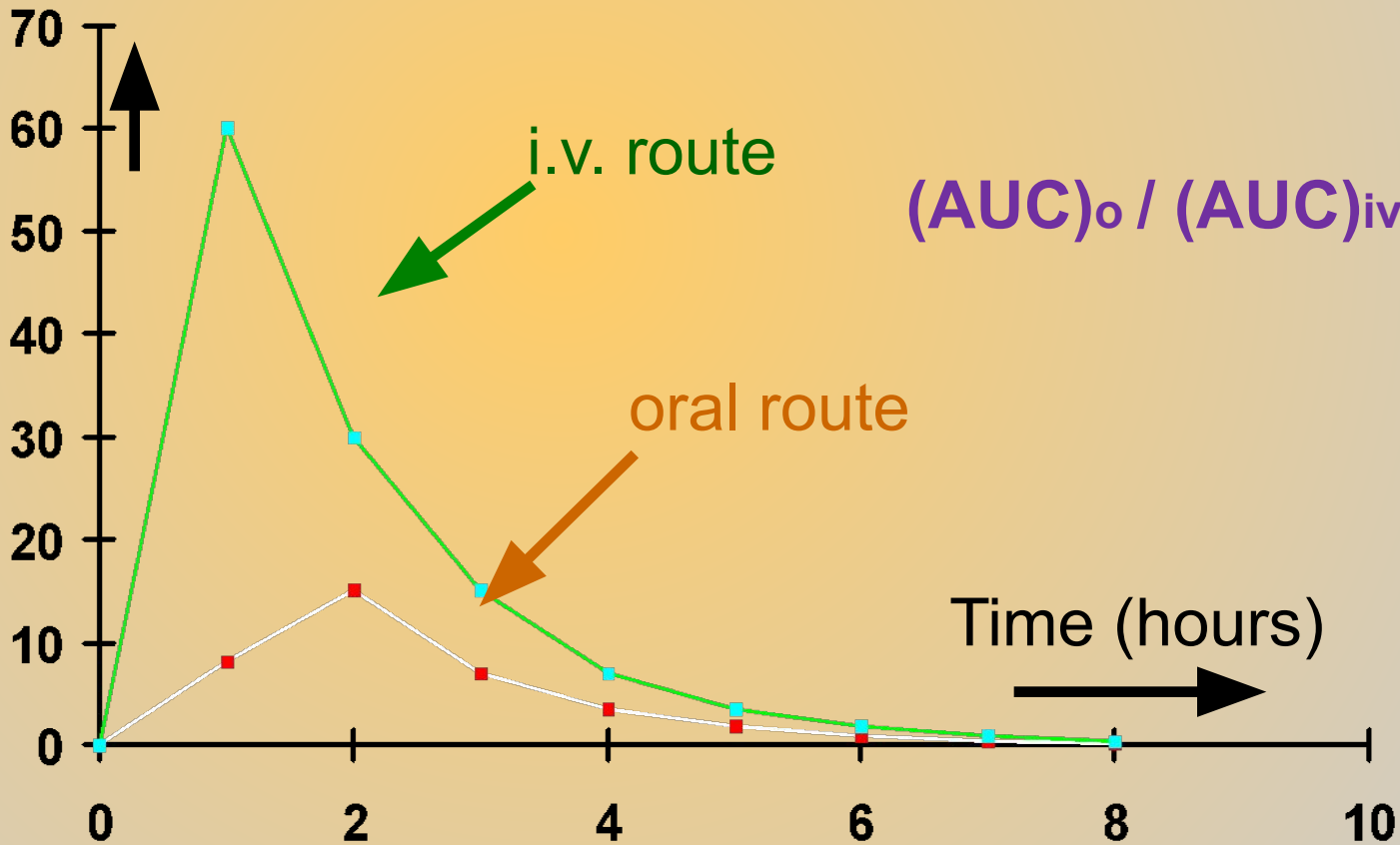
Says nothing about effectiveness



Bioavailability

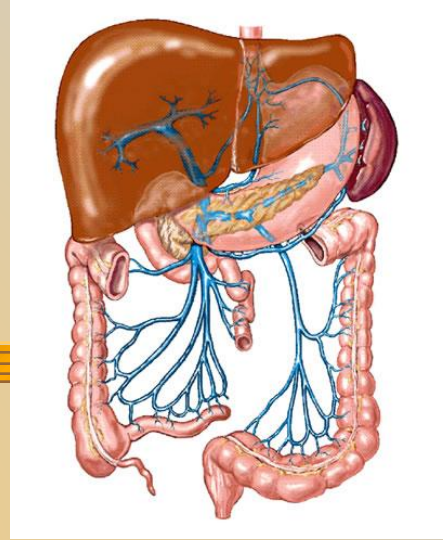


Plasma concentration





Bioavailability



Destroyed
in gut

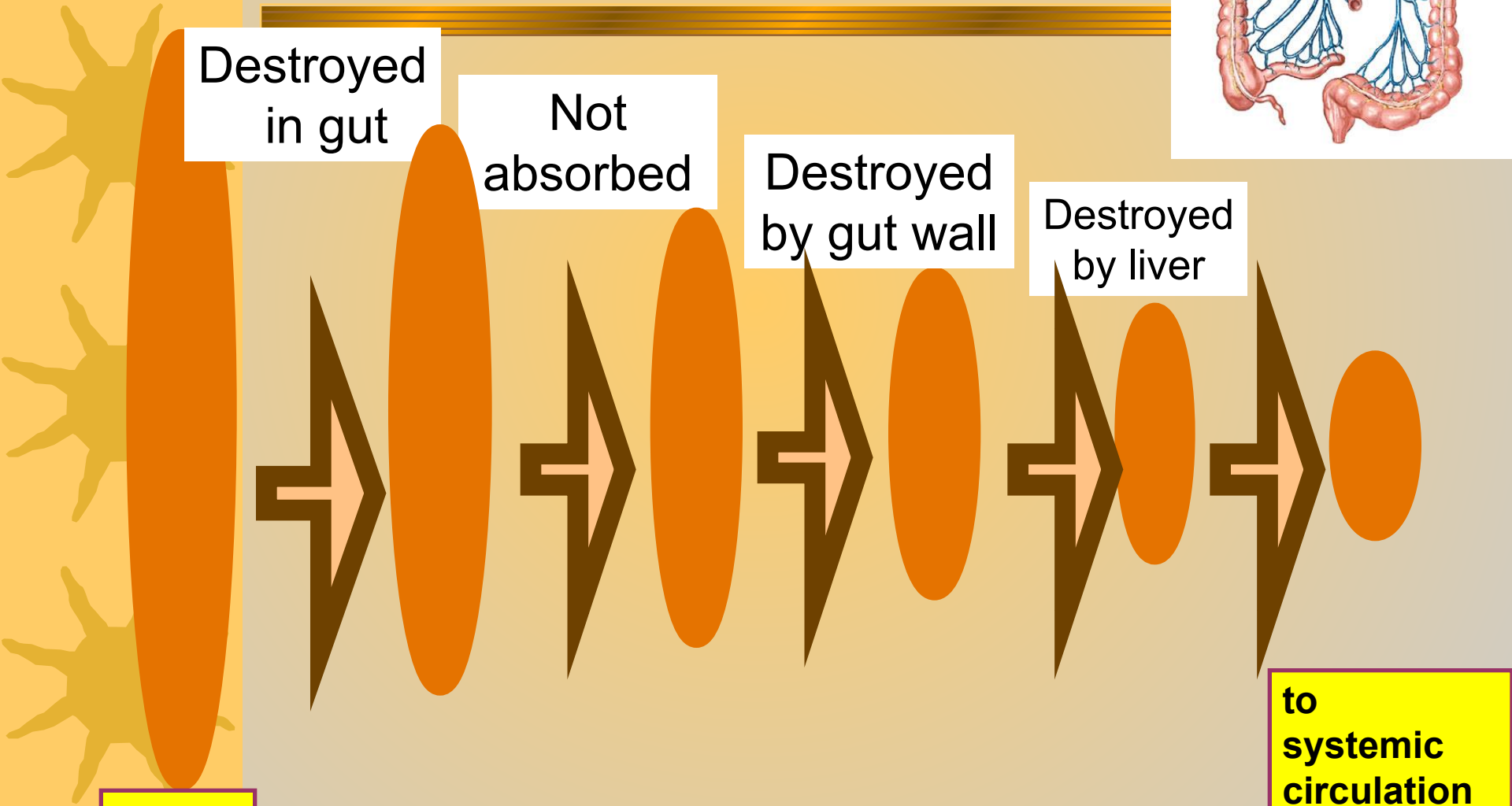
Not
absorbed

Destroyed
by gut wall

Destroyed
by liver

to
systemic
circulation

Dose





Distribution

Step 2 in ADME profile

After absorption, drug enters the blood, than different organs and tissues

The majority of drugs are distributed unevenly

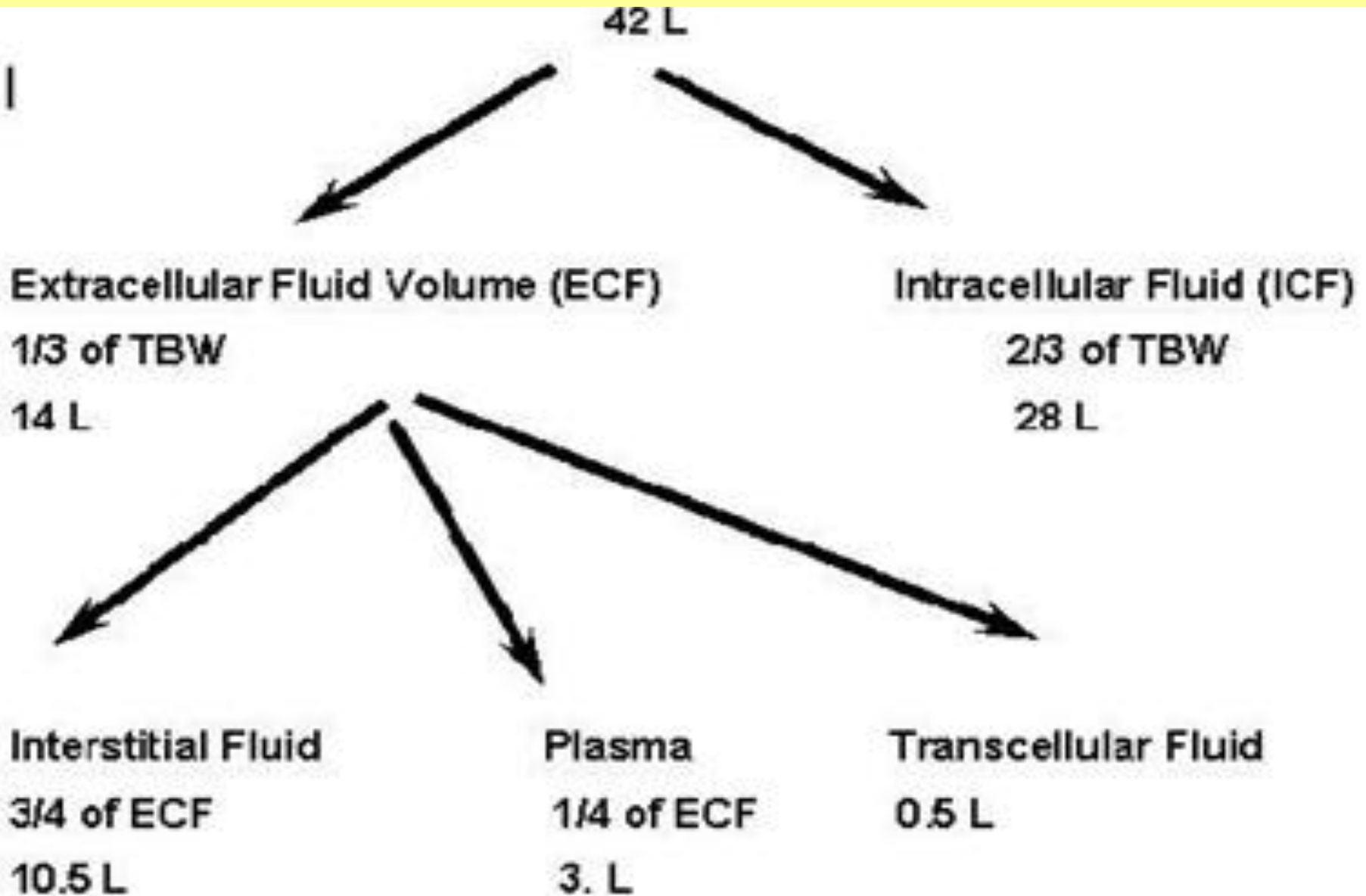
Drugs more easily penetrate into most organs with intensive blood circulation (heart, liver, kidneys)

Distribution into the body compartments

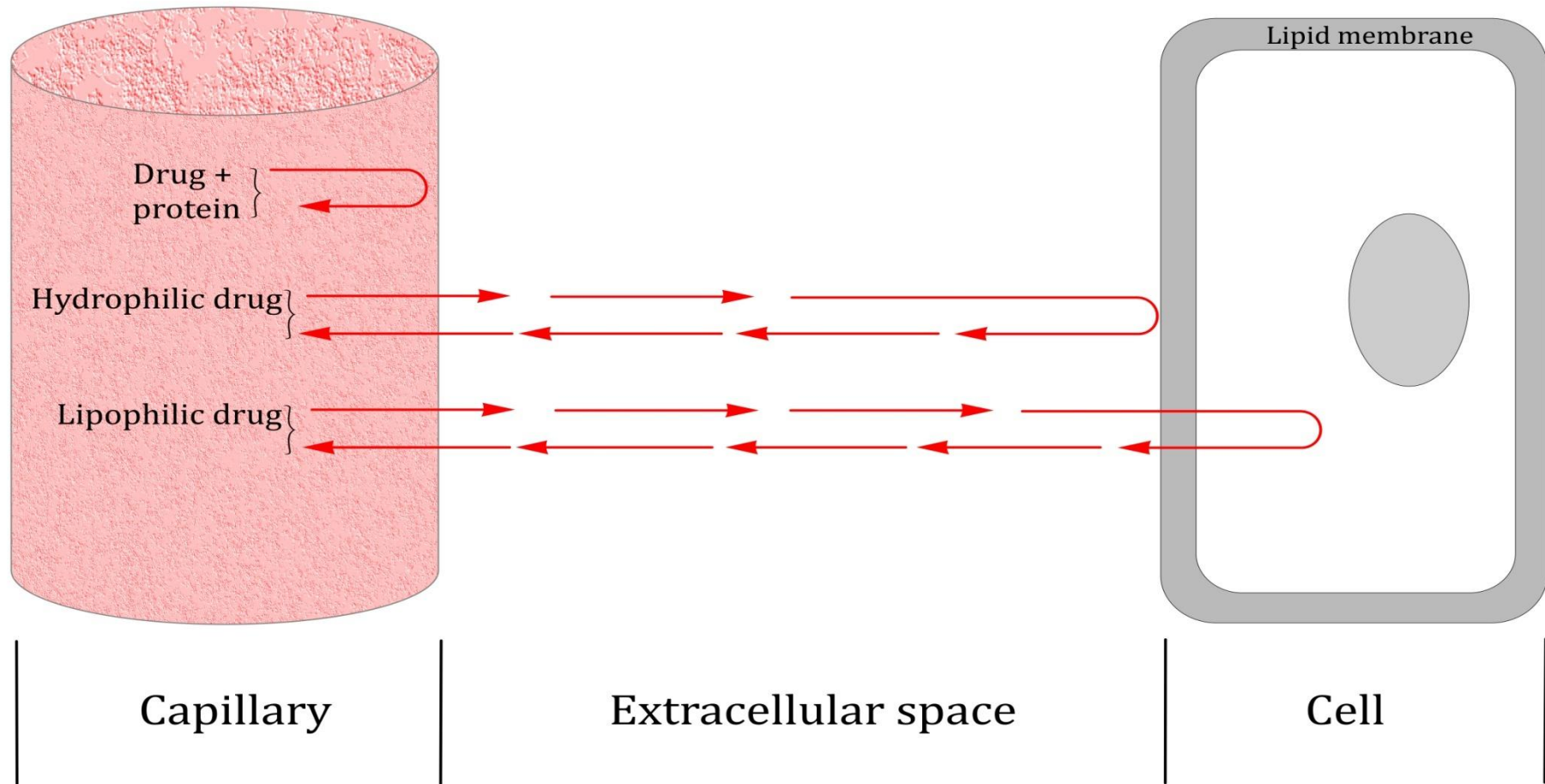
- ★ **Plasma 3.5 litres** (*heparin, plasma expanders*)
- ★ **Extracellular fluid 14 litres**, (*tubocurarine, charged polar compounds*)
- ★ **Total body water 40 litres** (*ethanol*)



THE BODY COMPARTMENTS



Factors influencing drug distribution





Distribution of drugs in the body



In the body drugs partially bind to other molecules and form extracellular and cellular depots

Plasma proteins (especially albumins) are the most important extracellular depots

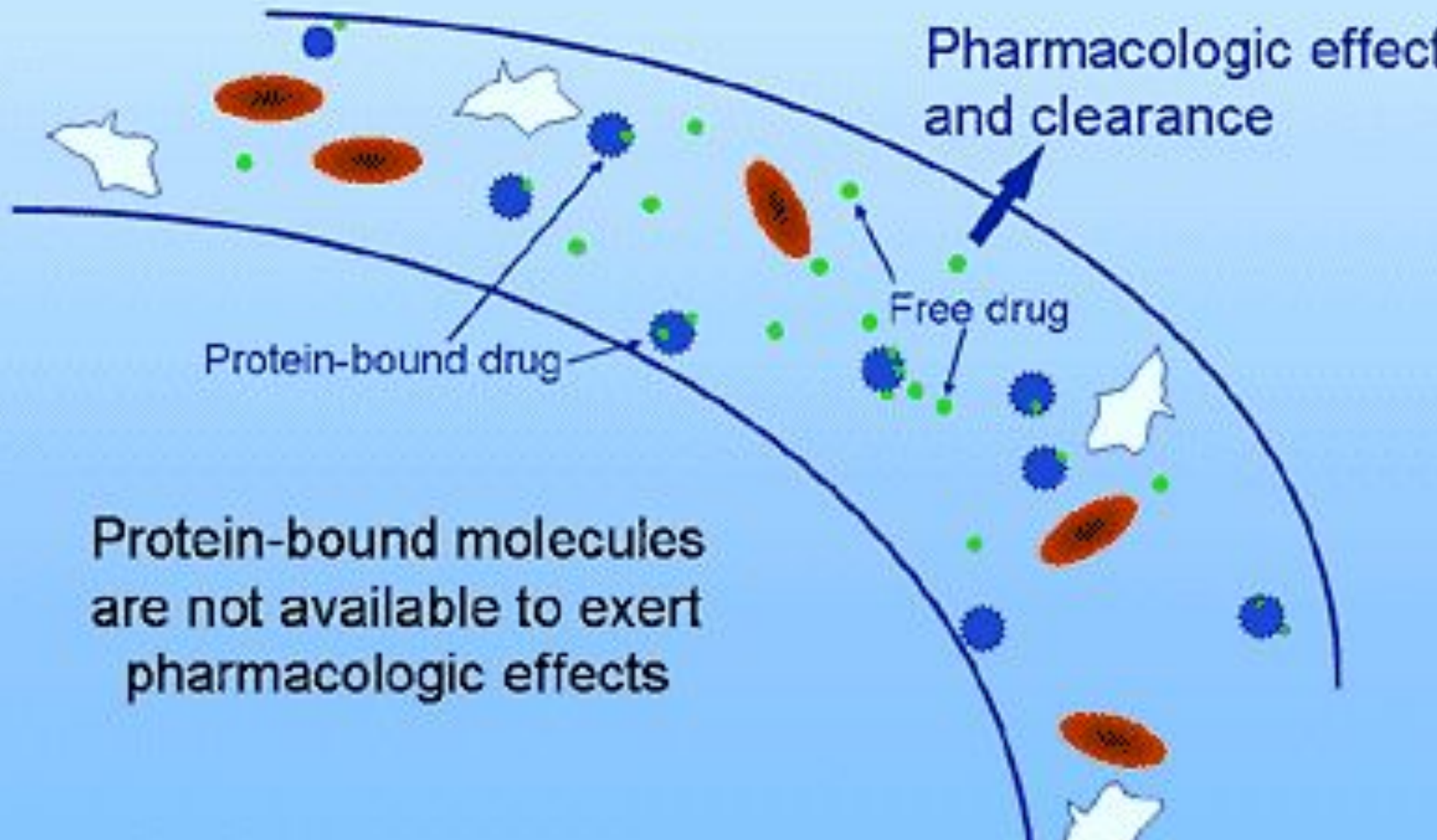


Only free drug fraction can move through the membrane, render a pharmacological effect, undergo biotransformation and excretion



Binding of drugs to proteins may be reduced in liver and kidney diseases, sepsis, burns, gastritis, enteritis, protein deficiency, and due to the drug interaction (if two drugs get bound with the same proteins)

Schematic Representation of Protein Binding



Protein-bound molecules are not available to exert pharmacologic effects



Distribution





Distribution

The apparent volume of distribution



Important for clinical pharmacology

It is the presumed volume of liquid in which a drug can be distributed (assuming that drug concentrations in plasma and other liquid media of the body is equal)

$$V_d = \frac{\text{Total amount of drug in the body}}{\text{Drug concentration in plasma}}$$

Lipophilic compounds with wide distribution have high value of V_d

Drugs that only circulate in blood have low value of V_d

Plasma 3.5 litres

Extracellular fluid 14 litres

Total body water 40 litres

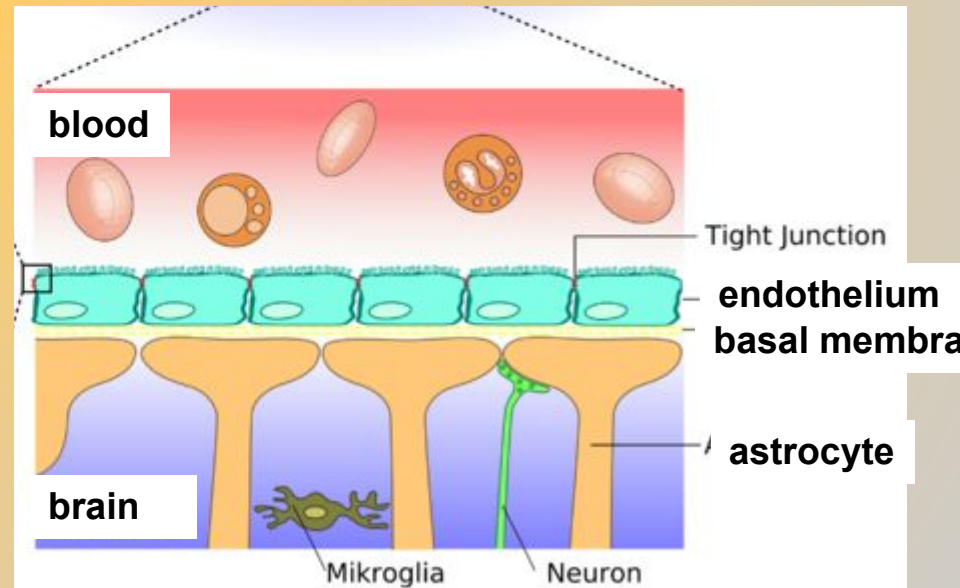
Distribution

Biological barriers

substantially influence drug distribution

There are such biological barriers:

- capillary wall
- cell membranes
- blood-brain barrier
- placental barrier



blood-brain barrier

Metabolism

Step 2 in ADME profile

Most drugs undergo biotransformation in the body

Biotransformation of drugs (drug metabolism)

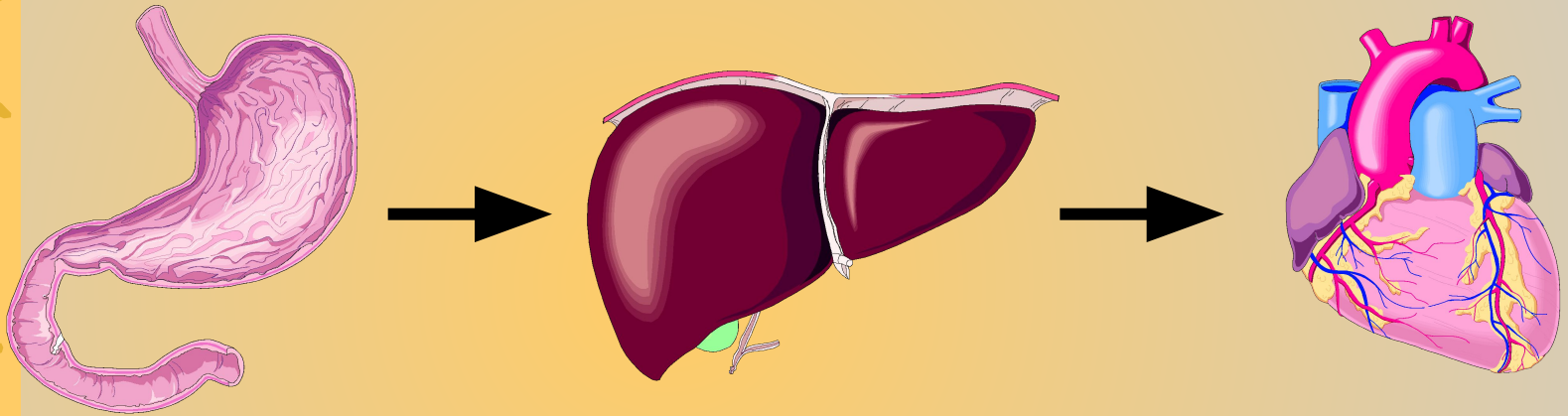
is the process of drugs (xenobiotics) conversion into metabolites that are easily dissolved in water and can be excreted by the kidneys.

Many enzymes participate in drug biotransformation, the most important among them are **microsomal enzymes of the liver**, they do not have substrate specificity

Non-microsomal enzymes are localized in the liver and in the intestines, lungs, kidneys, blood, placenta and others.

Drug metabolism determines drug dosage regimen.

METABOLISM



Lipid soluble drug → Water soluble drug

or

Active drug → Inactive metabolite

or

Prodrug → Active drug



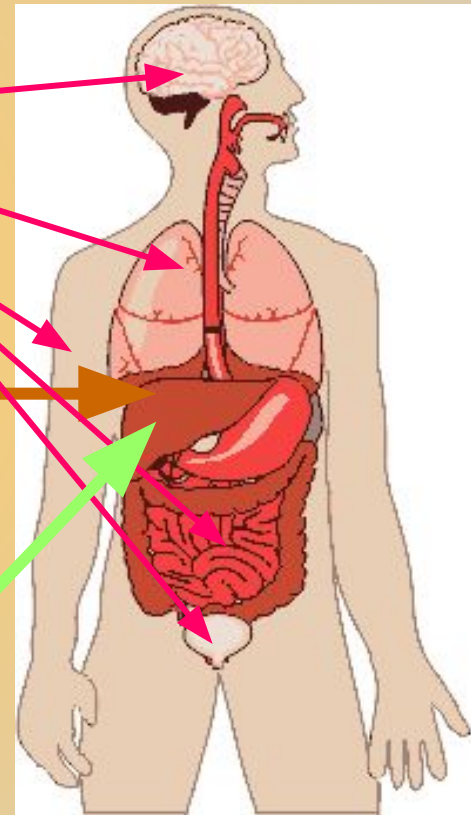
Drug Metabolism



**Extrahepatic microsomal enzymes
(oxidation, conjugation)**

**Hepatic microsomal enzymes
(oxidation, conjugation)**

**Hepatic non-microsomal
enzymes
(acetylation, sulfation, GSH,
alcohol/aldehyde
dehydrogenase,
hydrolysis, ox/red)**



Metabolism

Step 3 in ADME profile

There are two main types of drugs biotransformation

1. *Metabolic transformation*

occurs through oxidation, reduction, hydrolysis

In these reactions groups with active hydrogen atoms (oxy-, aminogroups) are formed

2. *Conjugation*

Functional groups of a drug get bound with endogenous compounds such as glucuronic residues, sulfur and amino acids. Also methylation and acetylation can take place.

Nb! *Biotransformation can increase drug activity or toxicity*

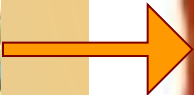
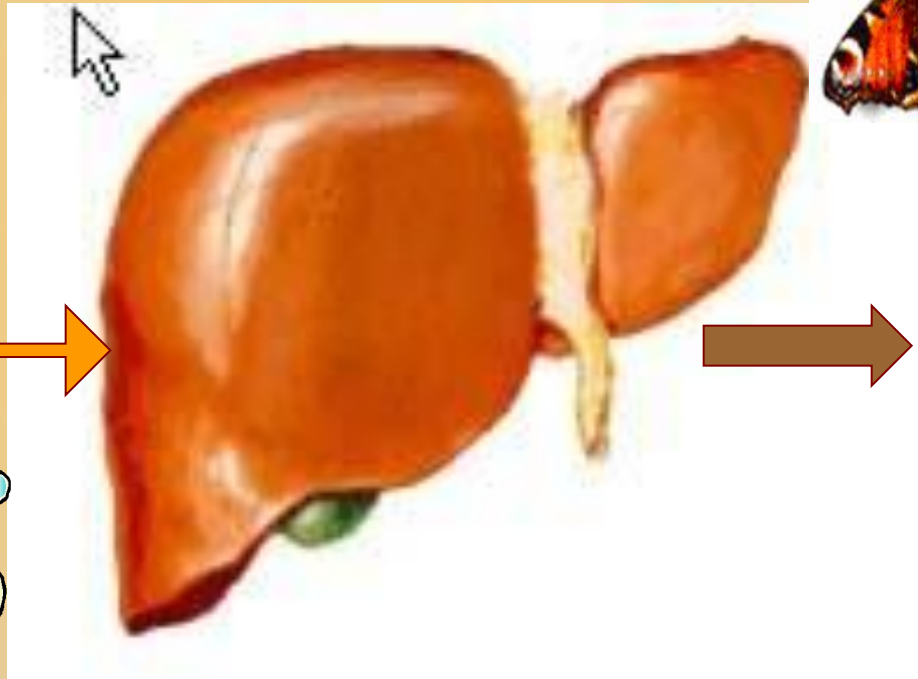
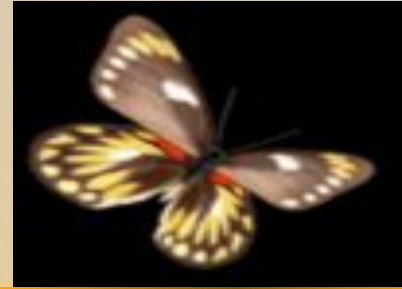
Prodrugs – active molecule is formed in the body

(sulphenamide is an active metabolite of omeprazole)

“**Lethal synthesis**” – if the toxic metabolites are formed

(acetaldehyde is the toxic metabolite of ethanol)

METABOLISM





Metabolism

Metabolic rate depends on genetic factors.

Induction and inhibition of metabolism enzymes influences the rate of metabolism of drugs.

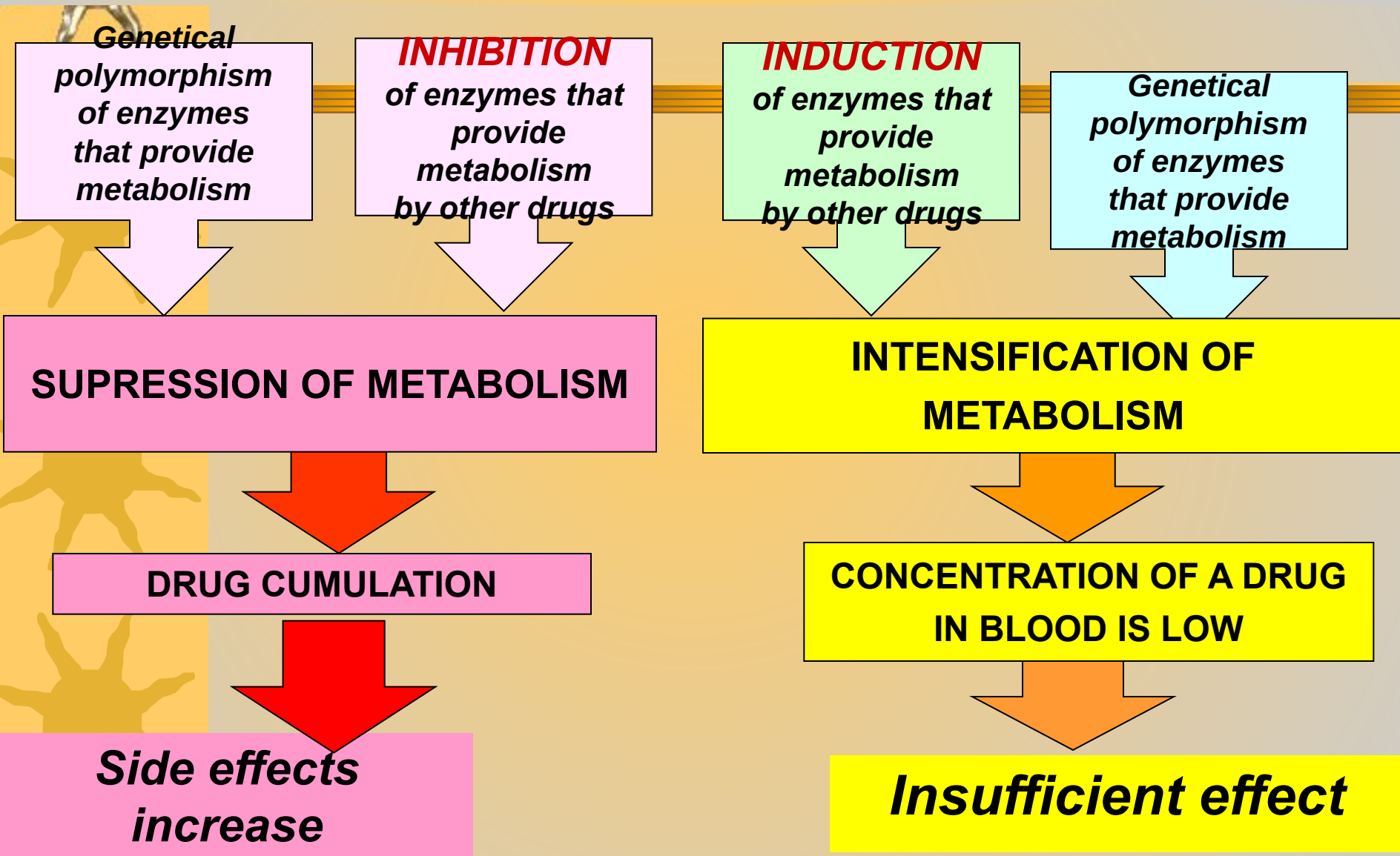
***Induction of metabolism enzymes* – increase of their activity – acceleration of the drug metabolism**

***Inhibition of metabolism enzymes* – decrease of their activity – retarding of the drug metabolism**

While the use of drugs with inductors or inhibitors drug doses should be adjusted.

Concentration of a drug in blood is variable

because of the changes in biotransformation processes



Excretion

Step 4 in ADME profile



Drugs and their metabolites are mainly eliminated with urine and bile

and sometimes with expiratory air, by salivary glands, sweat glands, gastric and intestinal glands, lacrimal glands, mammary glands
(*caution is needed when administering drugs to a nursing mother!*)

Ways of excretion	Drugs
1. With urine	Most drugs in the free state
2. With bile	Penicillin, tetracycline, streptomycin, strychnine, quaternary ammonium derivatives
3. Through intestine	Doxycycline, ionized organic acids
4. By lungs	Inhalation anesthetics, iodides, camphor, ethanol, essential oils
5. With sweat	Sulfonamides, thiamine
6. With saliva	Penicillin sulfanilamides, salicylates, thiamine, benzodiazepines, ethanol
7. With milk	Anticoagulants, antibiotics, thyrostatics, carbamazepine



Excretion


$t_{1/2}$

The elimination half-life or «half-life»




Important for clinical pharmacology

It shows **the time necessary to decrease drug concentration in blood plasma by 50%**



It is used to adjust doses of drugs and intervals between the times of their administration in order to achieve stable drug concentration



90% of the drug is eliminated during the period that equals $4 t_{1/2}$

$t_{1/2}$ is defined not only by the drug elimination from the body, but also by its biotransformation and storage

EXCRETION





Drug interactions



★ **Based on the change in drugs pharmacokinetics**



★ **Based on the change in drugs pharmacodynamics**



★ **Pharmaceutical interaction**



Drug interactions based on the change in drugs pharmacodynamics



★ Synergism

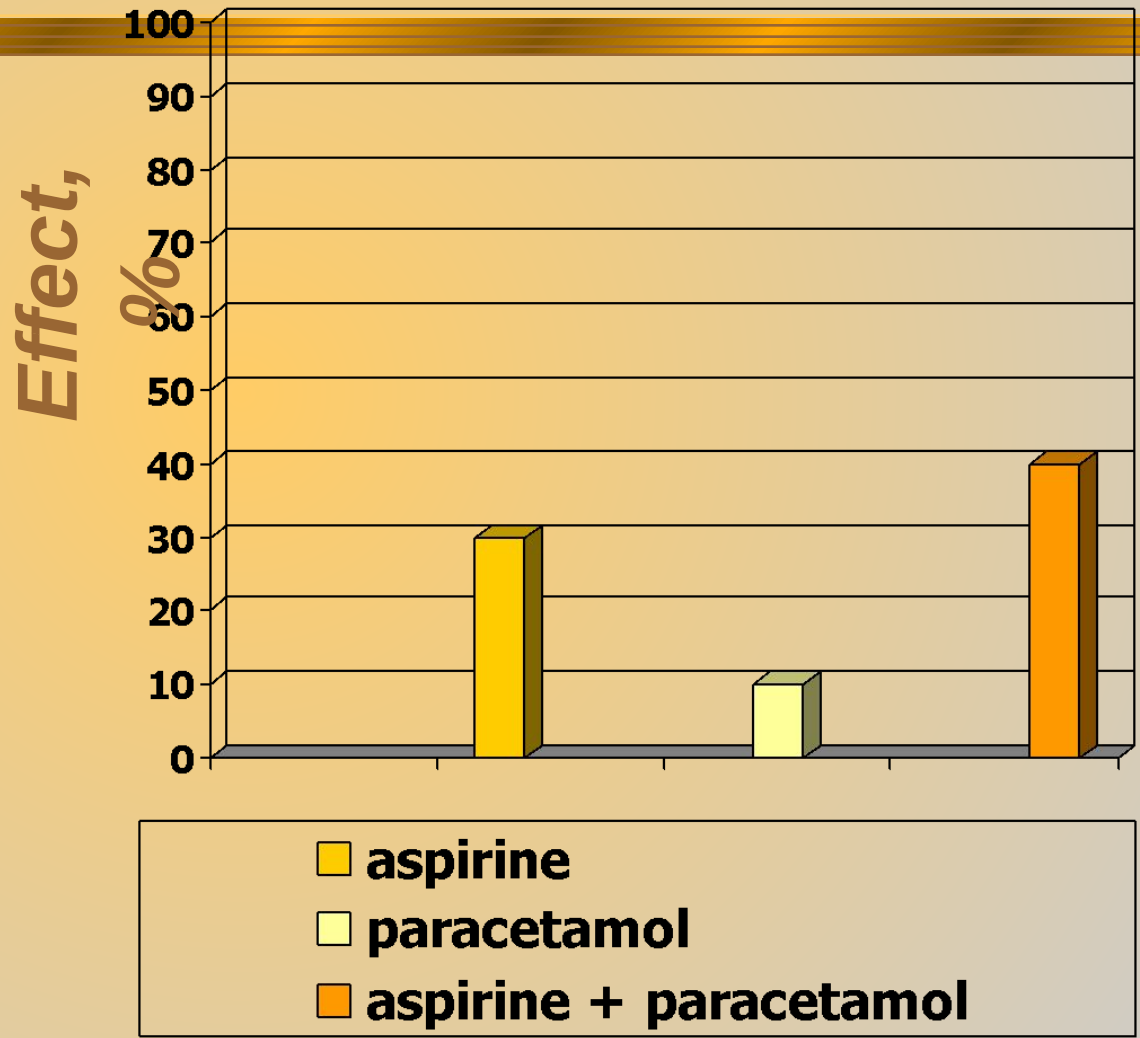
(from Greek *syn* – together, *ergos* – work)
**increase in effect of drugs used at
the same time** (*unidirectional effects*)

Two types of drug synergism

- **Summing up or additive effects**
- **Potentialiation**

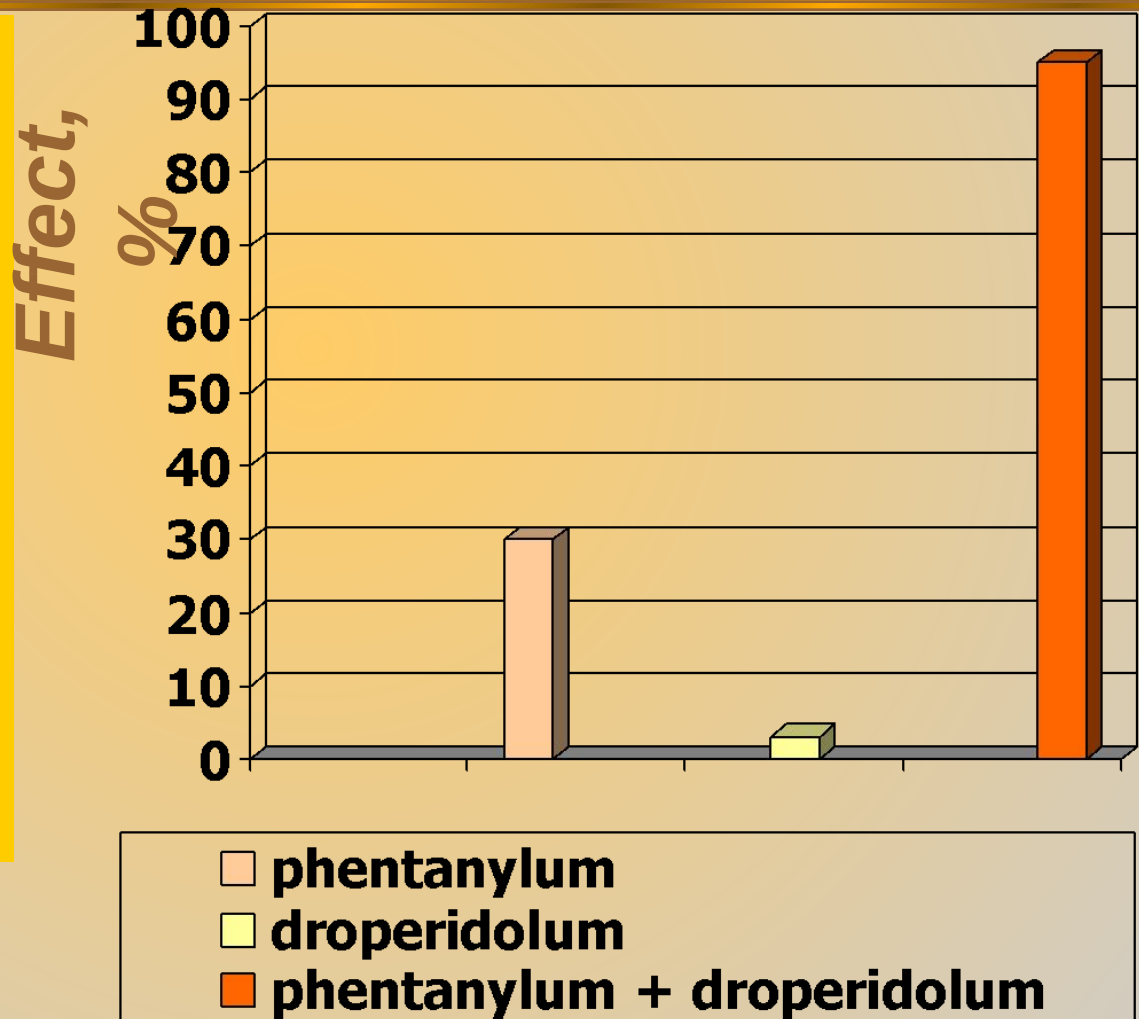
Summing up or additive effects (combination of analgesics)

- * The mechanisms of actions of both drugs are similar
- * Summed effect represents the actual sum of effects of the individual drugs



Potentialiation (neuroleptanalgesia)

- ★ The drugs differ in mechanisms of action
- ★ The total effect exceeds the sum of effects of the individual drugs




Drug interactions based on the change in drugs pharmacodynamics

Antagonism

(from Greek *antagōnisma* – *struggle, conflict*)

**the ability of drug to decrease the effect
of the other one**

Types of antagonism

 **direct (competitive)**

the same target but the opposite effect

(contraction or relaxation of the same muscle)

- indirect (noncompetitive)

different targets and the opposite effect

Drug interactions based on the change in drugs pharmacodynamics

★ Antagonism

Types of antagonism

- two-way and one-way antagonism

A blocker reliably eliminates the effects of a mimetic (activator)

but a mimetic (activator) usually is ineffective against a background of a blocker

Synergoantagonism

Occurs when some effects of the combined drugs are intensified, and others are weakened

Drug incompatibility

Incompatibility is the weakening, full loss or change in the pharmacotherapeutic effect, intensification of side or toxic effects

– **Pharmacological incompatibility** – in the body

Antagonistic combinations of drugs (*activator + blocker*) or drugs with food (*nialamide + chocolate, iron compounds + milk and others*)

Dangerous combinations of drugs (*astemisole + itraconazole; cardiac glycosides + calcium salts and others*), or drugs with food (*niphedipine + grapefruit and others*) or drugs with herbal preparations (*drugs decreasing blood coagulation + ginkgo or garlic*)

★ **Pharmaceutical incompatibility** – during the production process, storage or mixing of the drugs in one syringe

physical

chemical

physico-chemical



Thank you!
