POLTAVA STATE MEDICAL UNIVERSITY
Department of Pharmacology, Clinical Pharmacology and Pharmacy

Lecture:

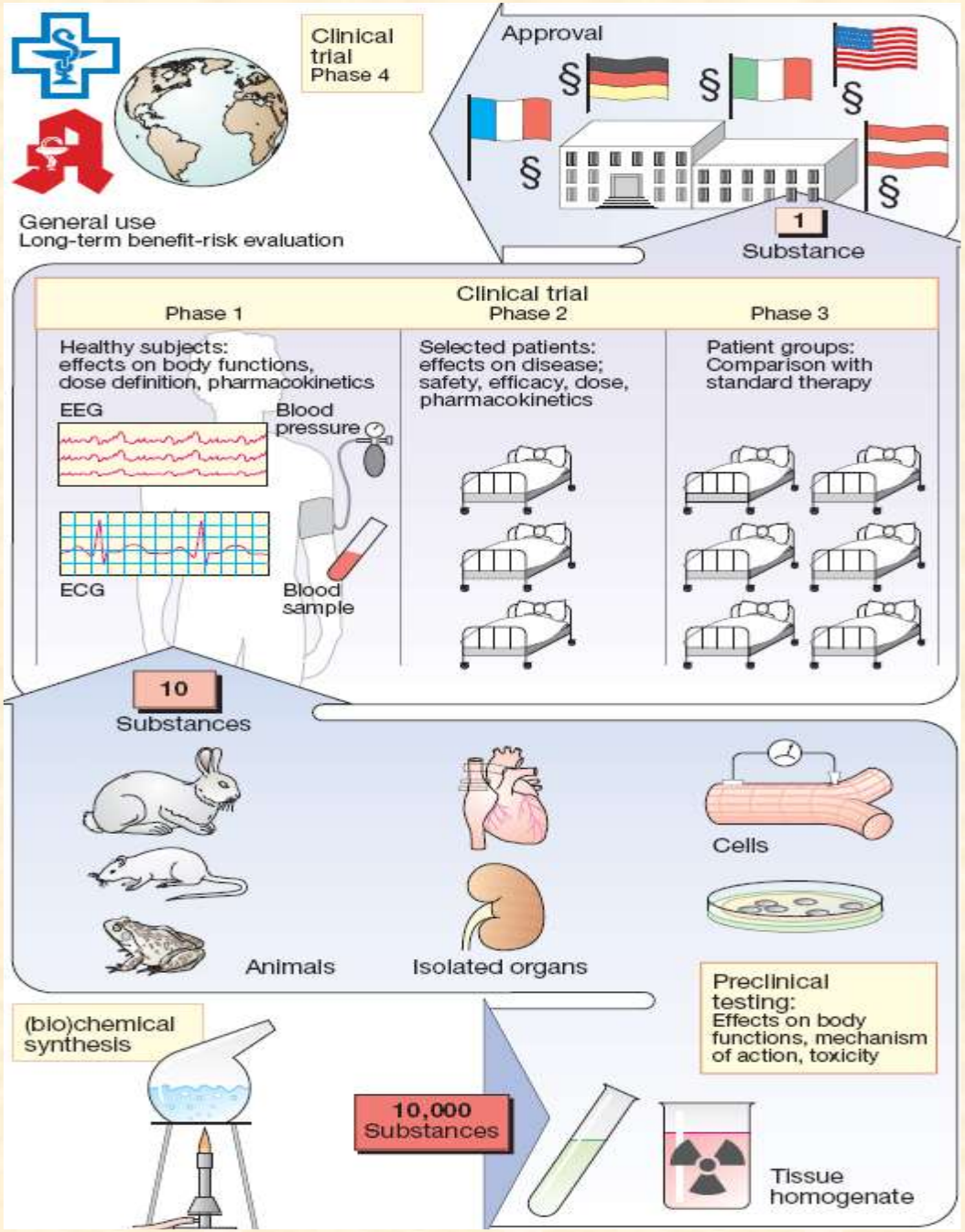
GENERAL PHARMACOLOGY. PHARMACOKINETICS

PHARMACOLOGY: DEFINITION AND MAIN TASKS

- ***Pharmacology*** is the science about drugs. It studies their properties and use.
- Main task of pharmacology is to create new more effective medicinal drugs for treatment and prophylaxis of diseases.
- ***Medicinal drug*** is a medicinal remedy in the shape of medicinal form.
- ***Medicinal remedy*** is medicinal substance approved for use in a clinic by the special committee of the country.
- ***Medicinal substance*** is a chemical substance or biological active substance which can prevent or lessen pathological processes and to do a medical action.
- ***Medicinal form*** **is** a distinctive size, shape and external appearance of medicinal substance convenient for use.

DRUG DEVELOPMENT

- ***Drug development*** includes many stages. It is very difficult and expansive.
- The process starts with the **synthesis of novel chemical compounds or obtaining of medicinal substances from various sources** (plants, animal tissues, microbial cultures, human cells).
- Next stage of drug development is **preclinical testing** with biochemical-pharmacological investigations, toxicological investigations, study of pharmacokinetics and pharmaceutical technology (methods of drug formulation).
- **Clinical testing** starts with **Phase I**. During this Phase the future drug is studied on healthy subjects and seeks to determine whether effects observed in animal experiments also occur in humans. In **Phase II** the potential drug is studied on large groups of patients to determine its clinical efficacy. In **Phase III** the drug is compared with standard therapy.


Clinical trial
Phase 4
General use
Long-term benefit-risk evaluation
Approval
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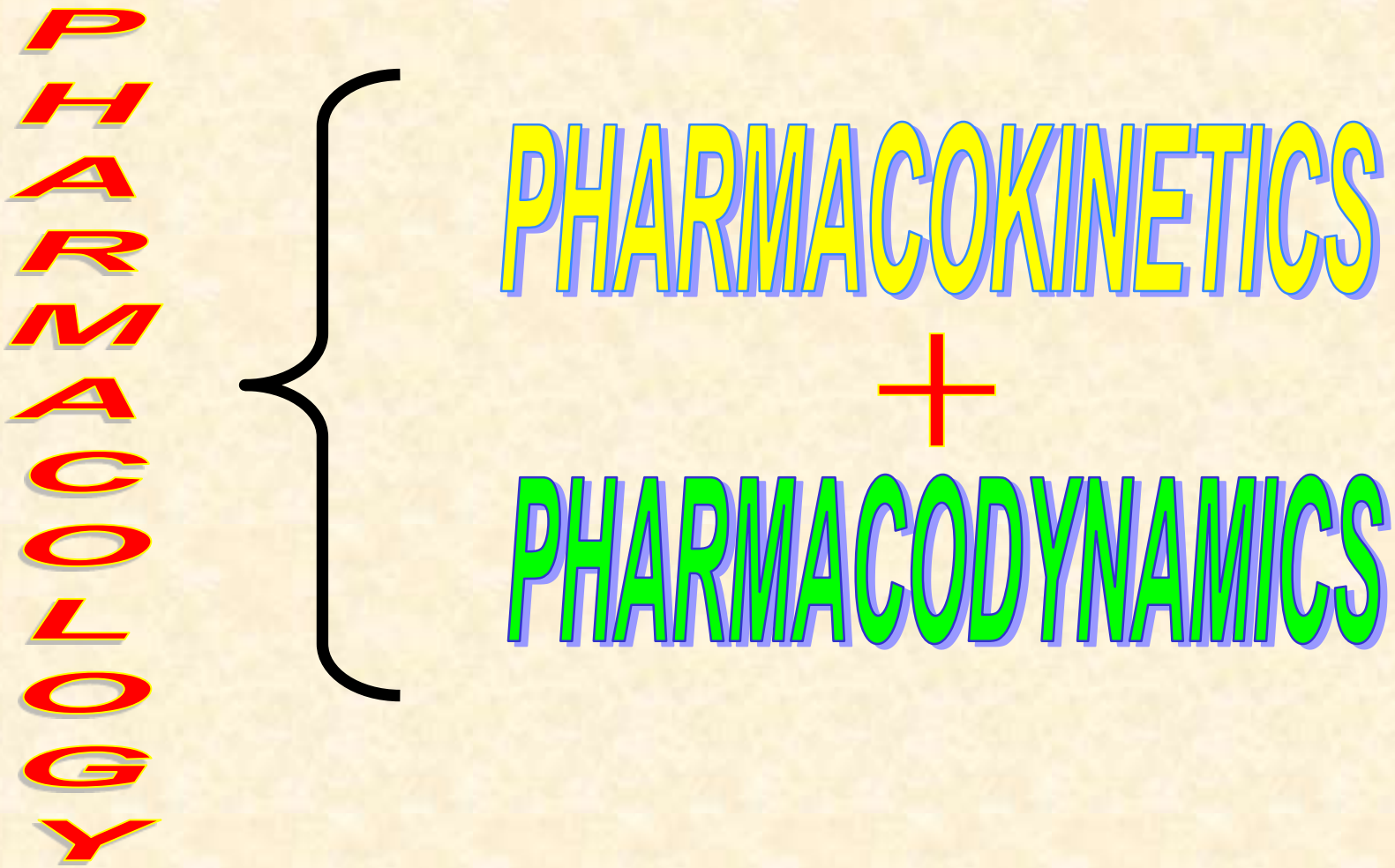
1
Substance
Clinical trial
Phase 1
Phase 2
Phase 3
Healthy subjects:
effects on body functions,
dose definition, pharmacokinetics
EEG
Blood pressure
ECG
Blood sample
Selected patients:
effects on disease;
safety, efficacy, dose,
pharmacokinetics
Patient groups:
Comparison with
standard therapy
10
Substances
Animals
Isolated organs
Cells
Preclinical testing:
Effects on body functions, mechanism of action, toxicity
(bio)chemical synthesis
10,000
Substances
Tissue homogenate

GENERAL PHARMACOLOGY

(general concepts of pharmacology)



PHARMACOKINETICS

Pharmacokinetics is the section of pharmacology that studies how the body acts on the drug.

Pharmacokinetics studies:

- Routes of administration
- Absorption
- Distribution
- Biotransformation
- Elimination
- Excretion.

ROUTES OF DRUG ADMINISTRATION

Enteral (through the gut)

1. Sublingual (under the tongue)
2. Oral (by mouth, per os)
3. Rectal (in rectum)

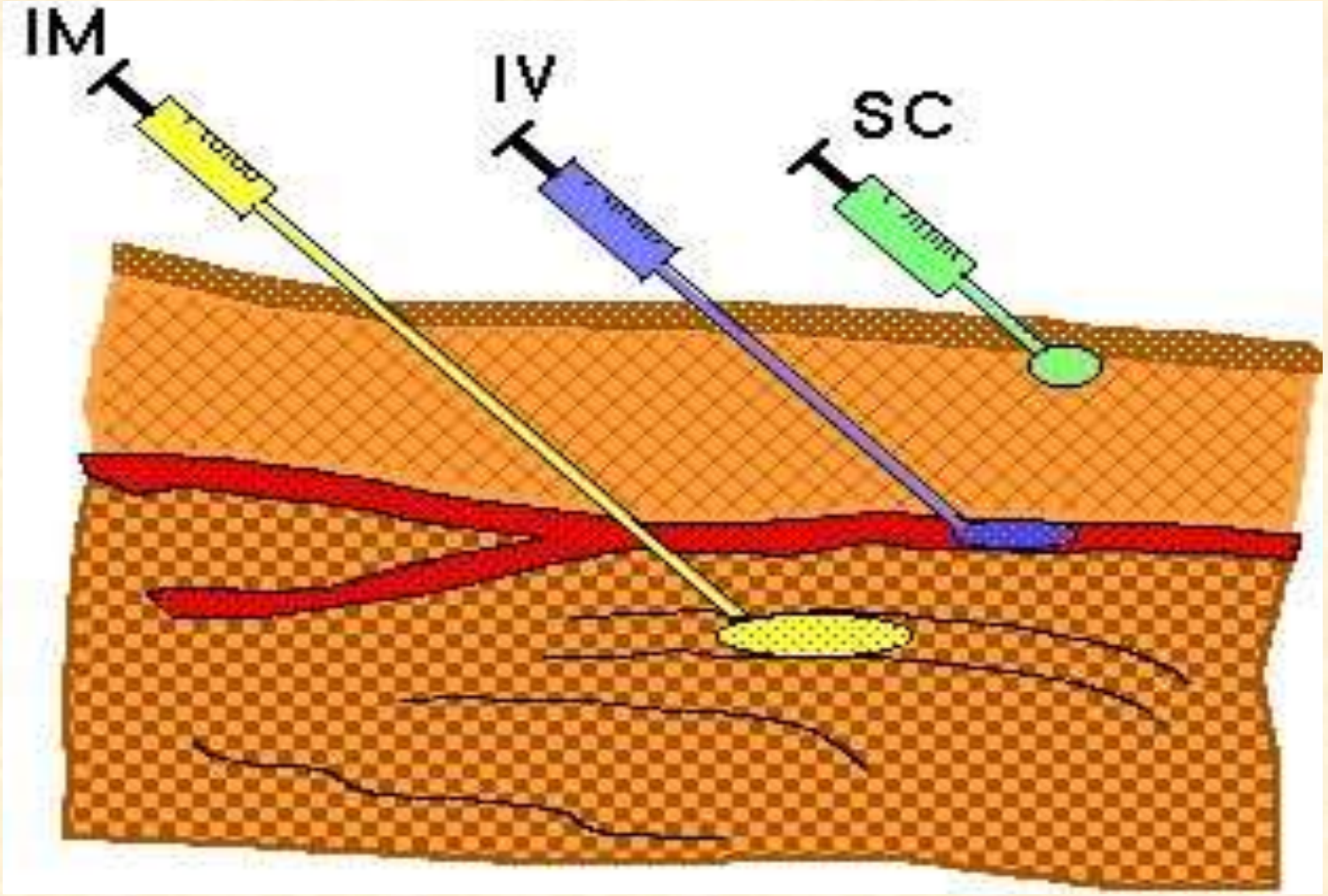
Parenteral (not through the gut)

1. Injections
2. Inhalations (through the respiratory pathways)
3. Intranasal
4. Transcutaneous

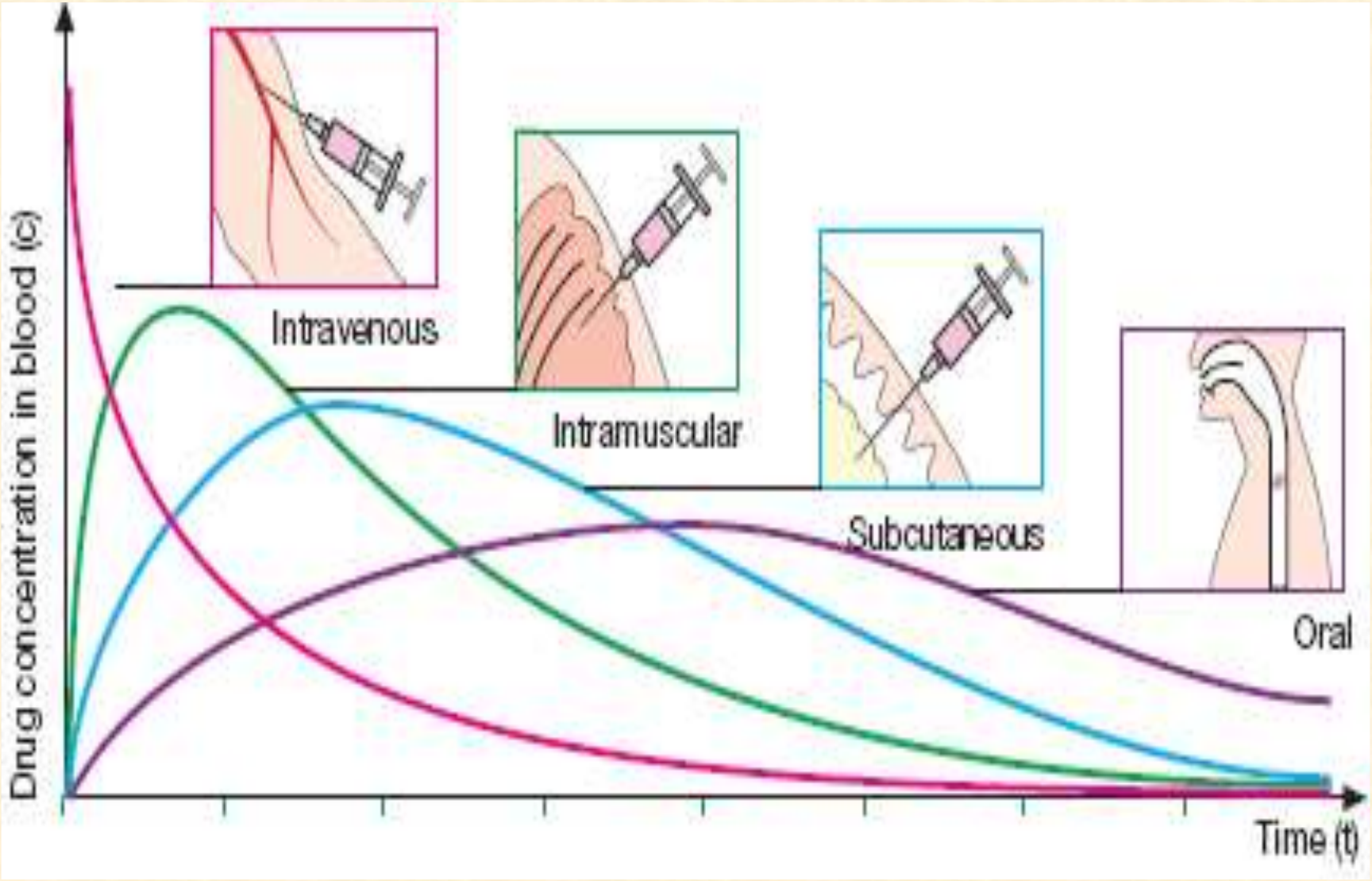
Topical application (for local action)

1. On the surface of skin
2. On the surface of mucous membrane

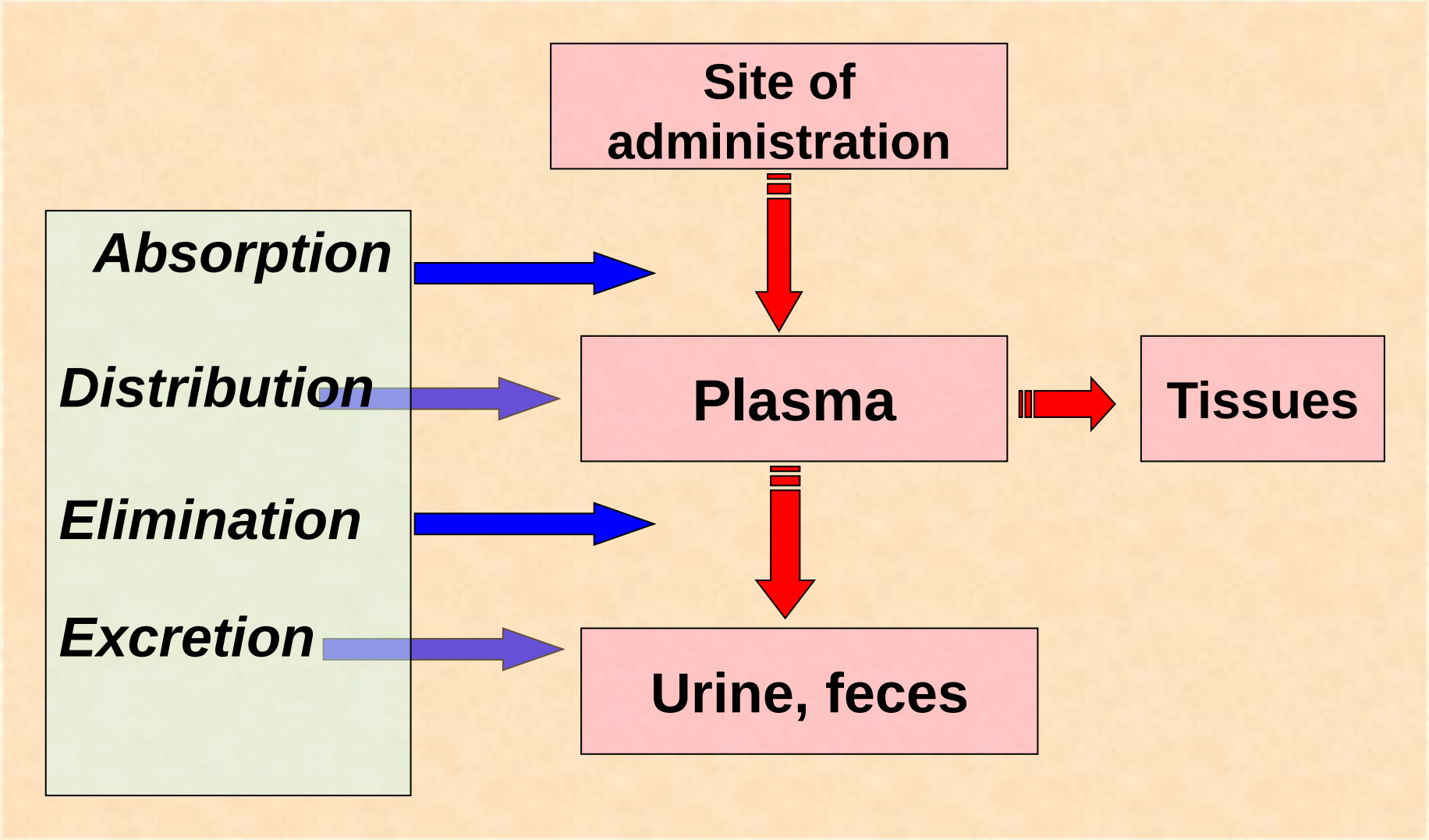
INJECTIONS:
IV (intravenous),
IM (intramuscular), SC (subcutaneous)



THE COMPARISON OF DRUG CONCENTRATION IN BLOOD IN DIFFERENT ROUTES OF ADMINISTRATION



SCHEMATIC REPRESENTATION OF DRUG ABSORPTION, DISTRIBUTION AND ELIMINATION

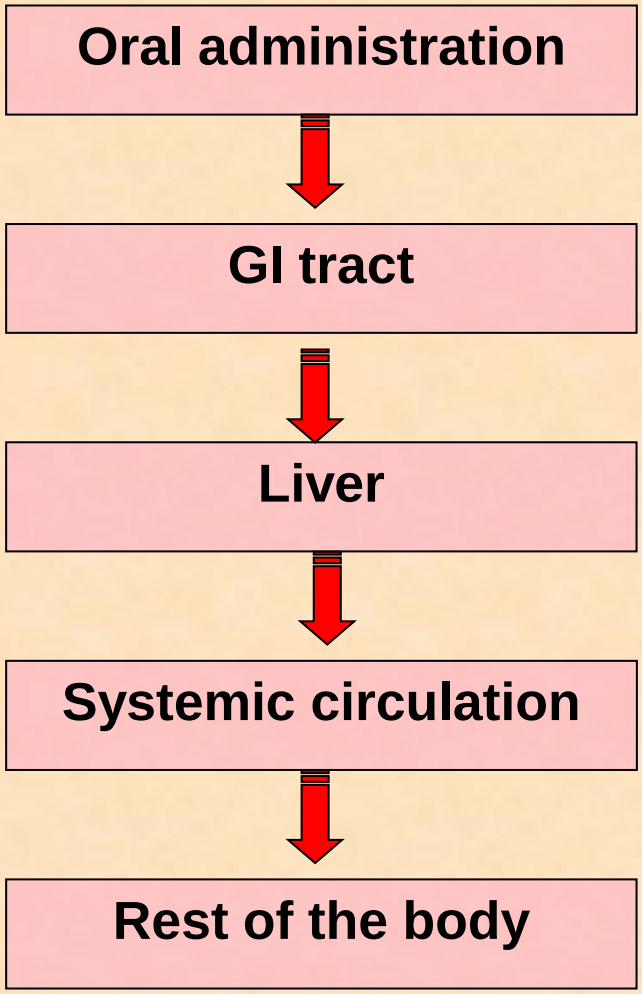


ABSORPTION

- ***Absorption*** is the enter of the drug into blood from the site of administration.

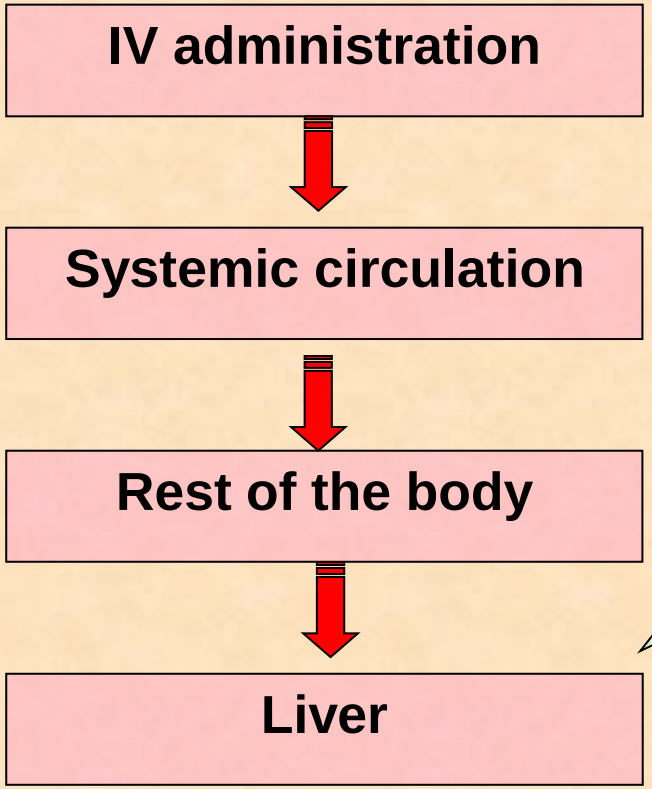
- ***First-pass metabolism*** is the metabolism of the drug in the liver before its action. First-pass metabolism can occur with orally administered drugs.

FIRST-PASS METABOLISM CAN OCCUR WITH ORALLY ADMINISTERED DRUGS



Drugs administered orally are fist exposed to the liver and may be extensively metabolized before reaching the rest of body

IV AND SUBLINGUAL ADMINISTRATIONS ARE WITHOUT FIRST-PASS METABOLISM



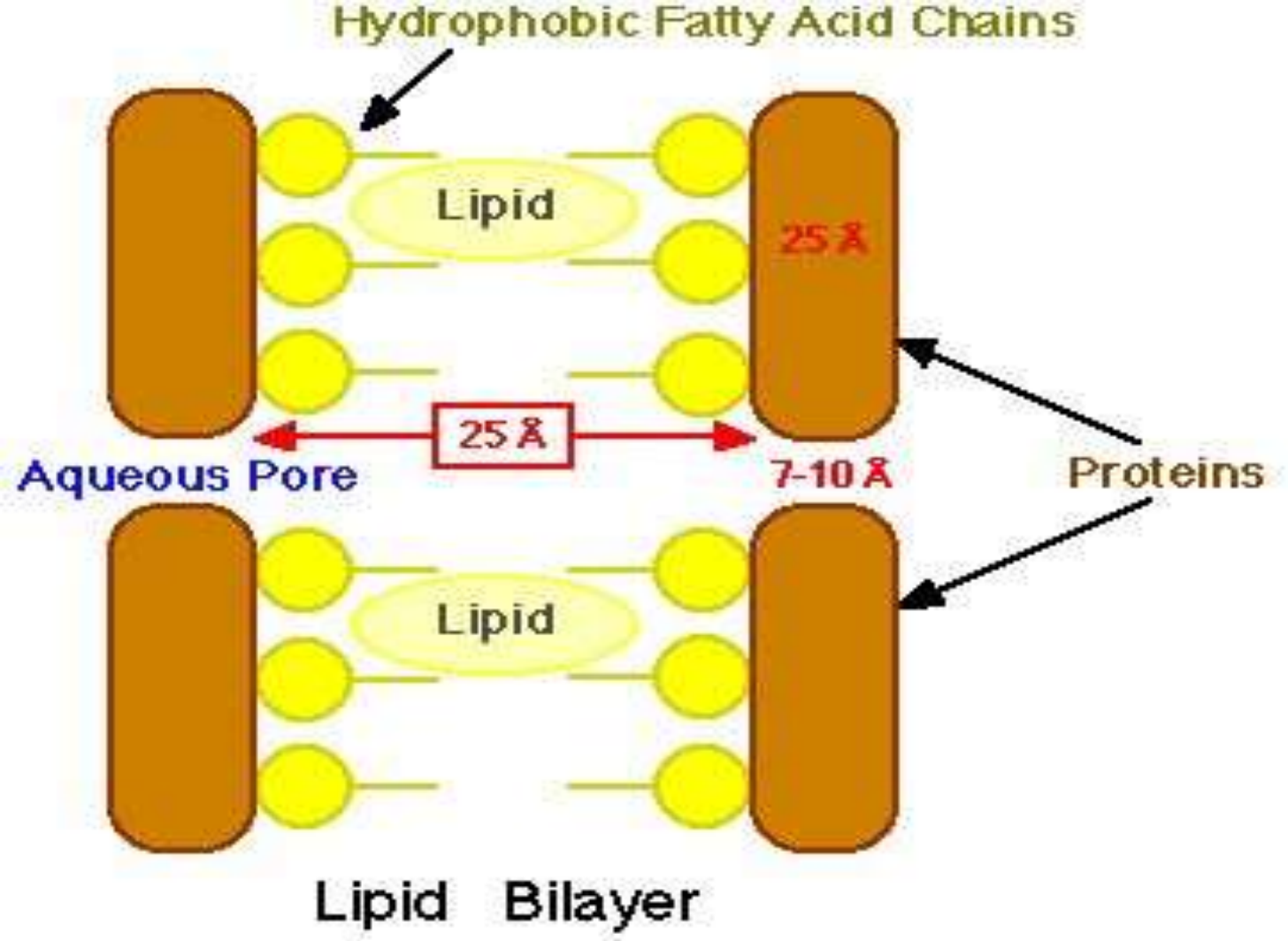
Drugs administered IV enter directly into the systemic circulation and have direct access to the rest of body

DRUS CROSSING THROUGH CELL MEMBRANES

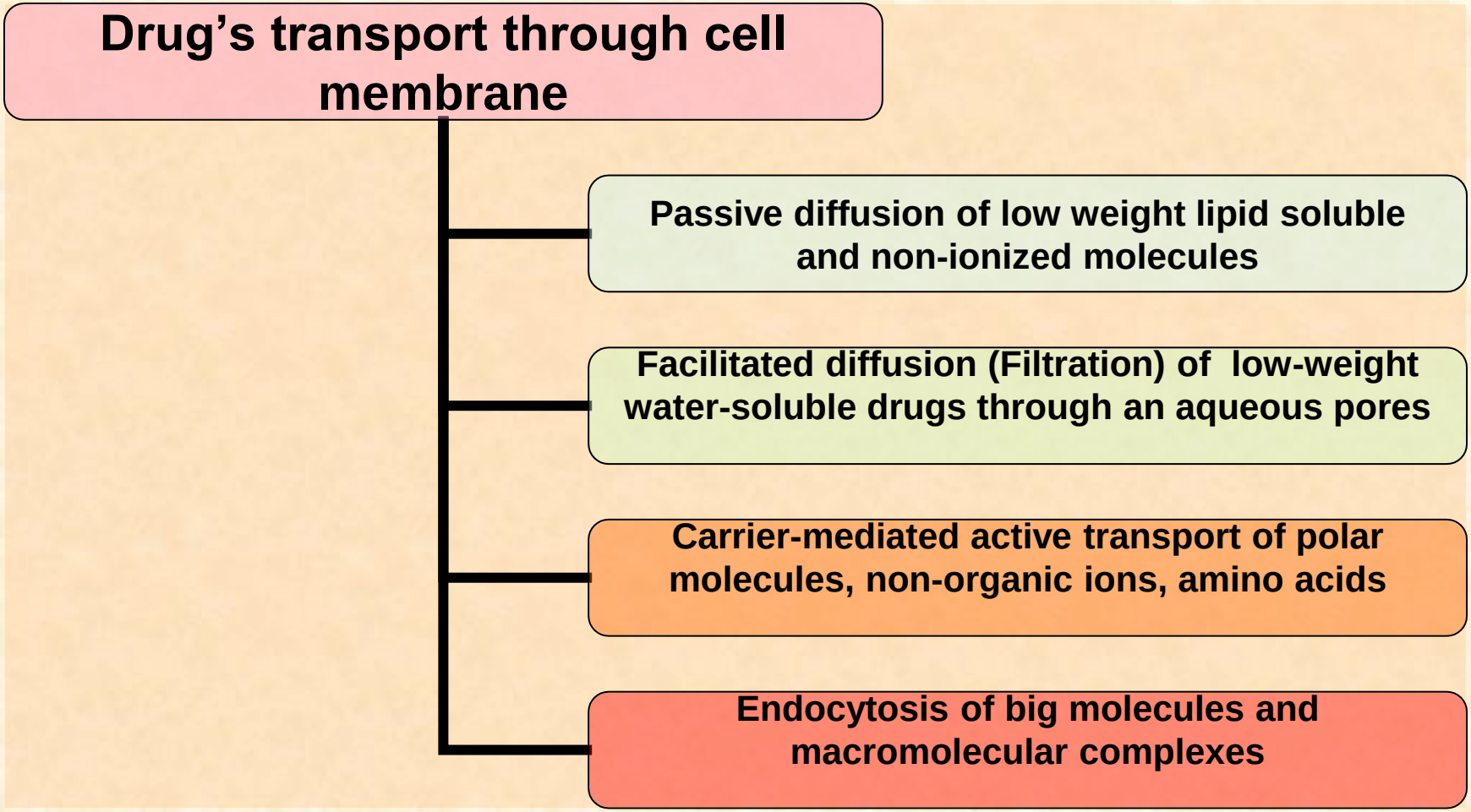
During the absorption the drug crosses cell membranes. There are such kinds of this crossing:

- ***passive diffusion***
- ***facilitated diffusion (filtration)***
- ***active transport***
- ***endocytosis.***

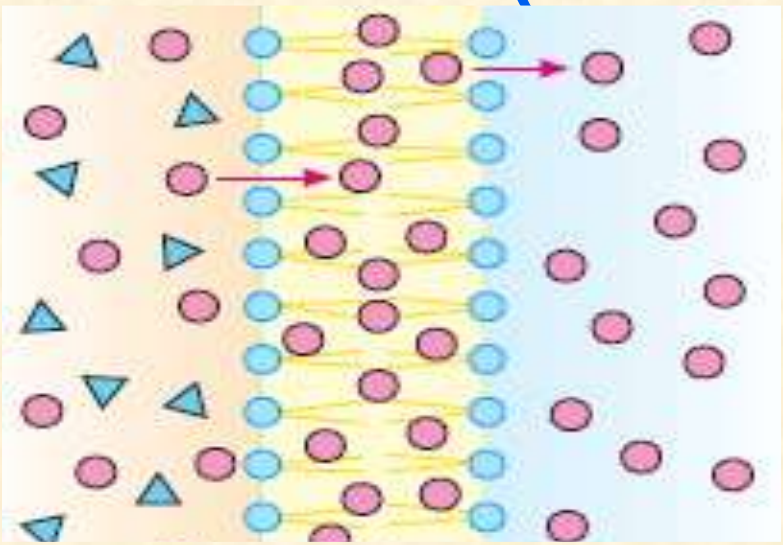
STRUCTURE OF CELL MEMBRANE



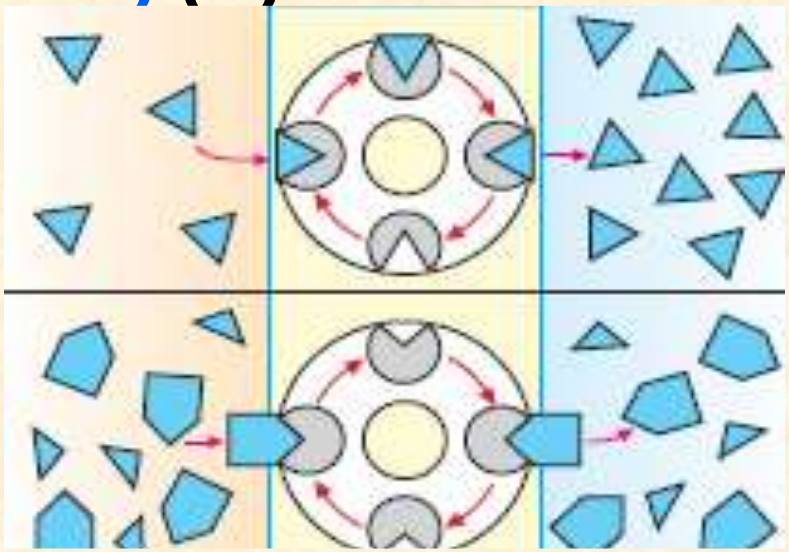
MEMBRANE PERMEATION FOR THE DRUGS



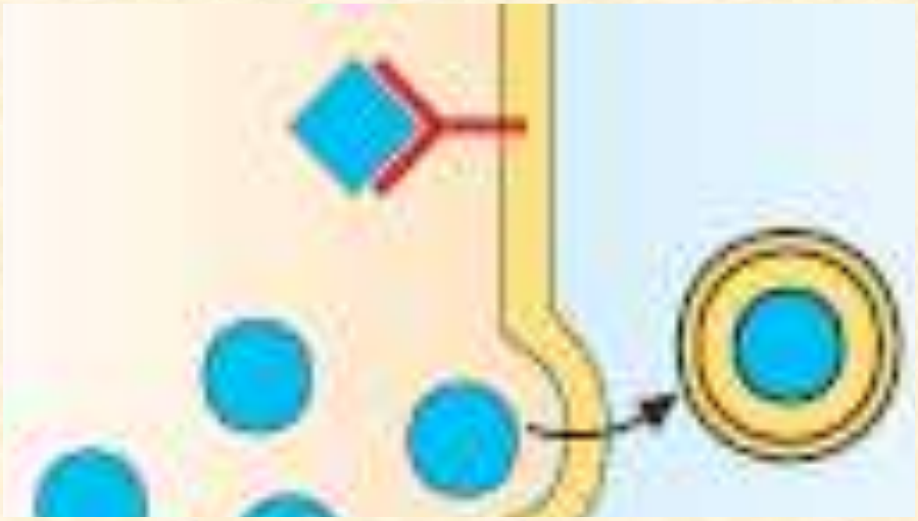
PASSIVE DIFFUSION (A), ACTIVE TRANSPORT (B), AND VESICULAR TRANSPORT (ENDOCYTOSIS) (C)



A



B

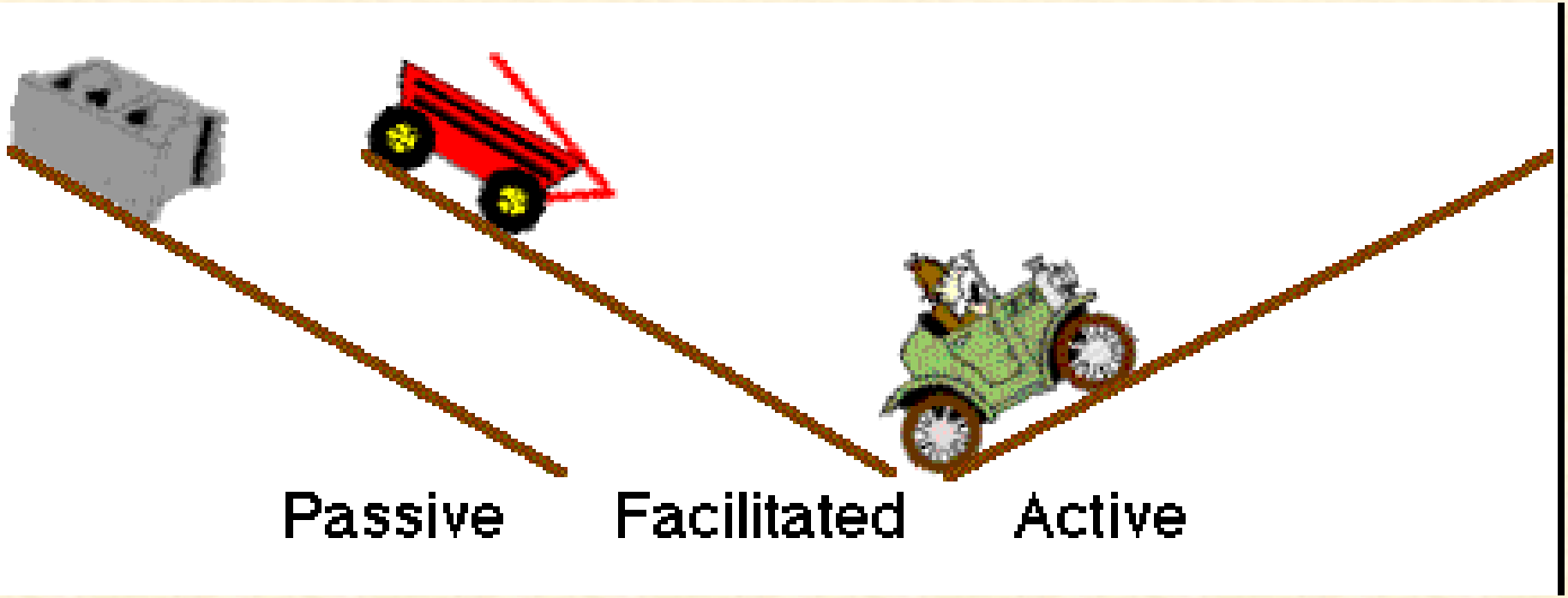


C

ENERGY-DEPENDENCE IN MEMBRANE PERMEATION FOR THE DRUGS:

passive diffusion, facilitated diffusion (filtration) are energy-independent;

active transport is energy-dependent



MODES OF DRUG TRANSPORT ACROSS MEMBRANE: the summary

Mechanism	Direction	Energy Required	Carrier	Saturable
Passive diffusion	Down gradient	No	No	No
Facilitated diffusion	Down gradient	No	Yes	Yes
Active transport	Against gradient (concentration/ electrical)	Yes	Yes	Yes

FACTORS INFLUENCING ABSORPTION

Factors influencing absorption are:

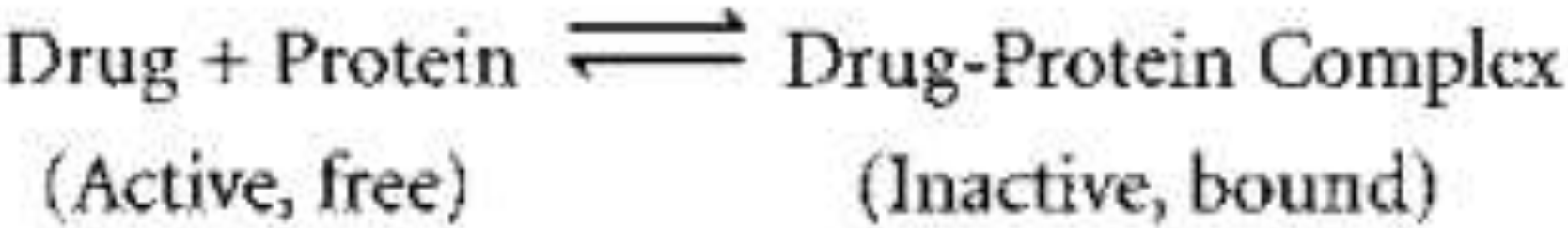
- chemical structure
- water- or lipid-solubility
- ionization
- medicinal form
- route of administration
- state of tissues in the site of administration.

TRANSPORT IN THE ORGANISM

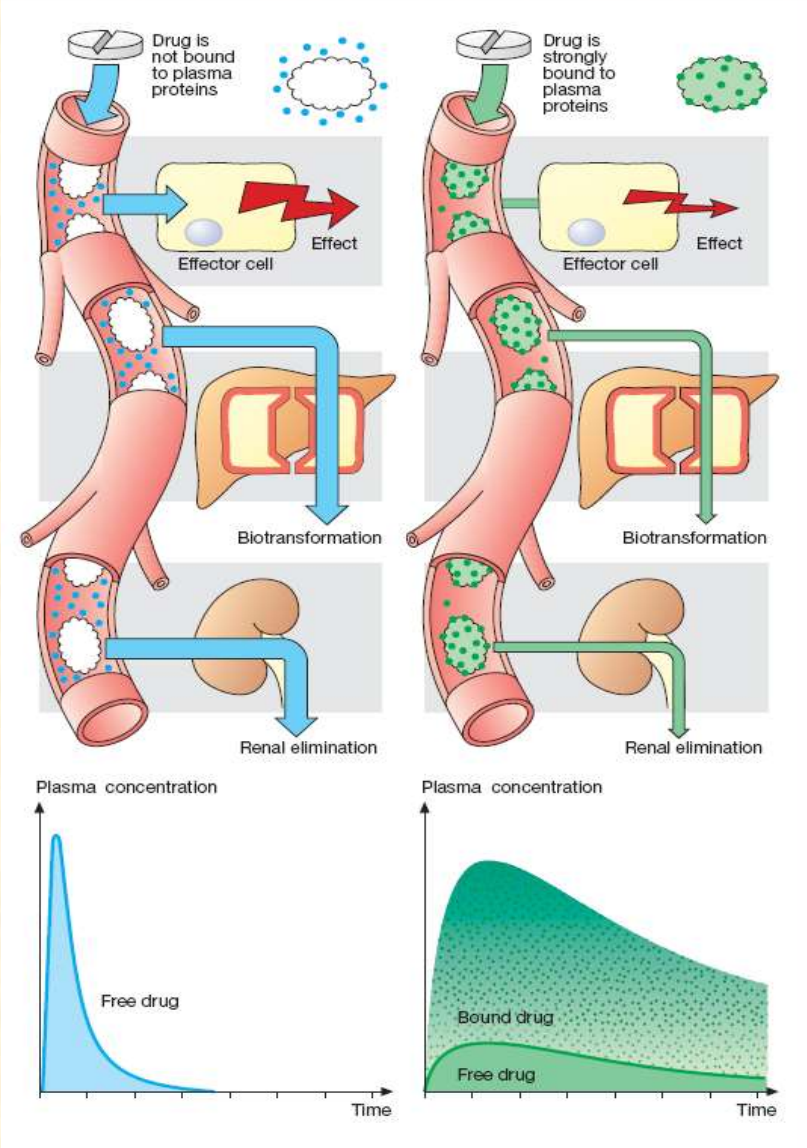
Drugs transport in the body is realized:

- by proteins of plasma (e.g.: aspirin, sulfa drugs, hormonal preparations, iron)
- by lipoproteins of plasma (e.g.: vitamin A, vitamin D)
- by blood cells (some antibiotics)
- by water fraction of plasma (ions of sodium and potassium, glucose)

FREE DRUG AS ACTIVE FRACTION



IMPORTANCE OF PROTEIN BINDING FOR INTENCITY AND DURATION OF DRUG'S ACTION



DRUG DISTRIBUTION

Distribution is the process by which a drug leaves the blood stream and enters the interstitium (extracellular fluid or the cells of tissues)

Distribution depends on:

- drug structure
- binding of drugs to plasma proteins
- blood flow
- capillary permeability (blood-tissue barriers).

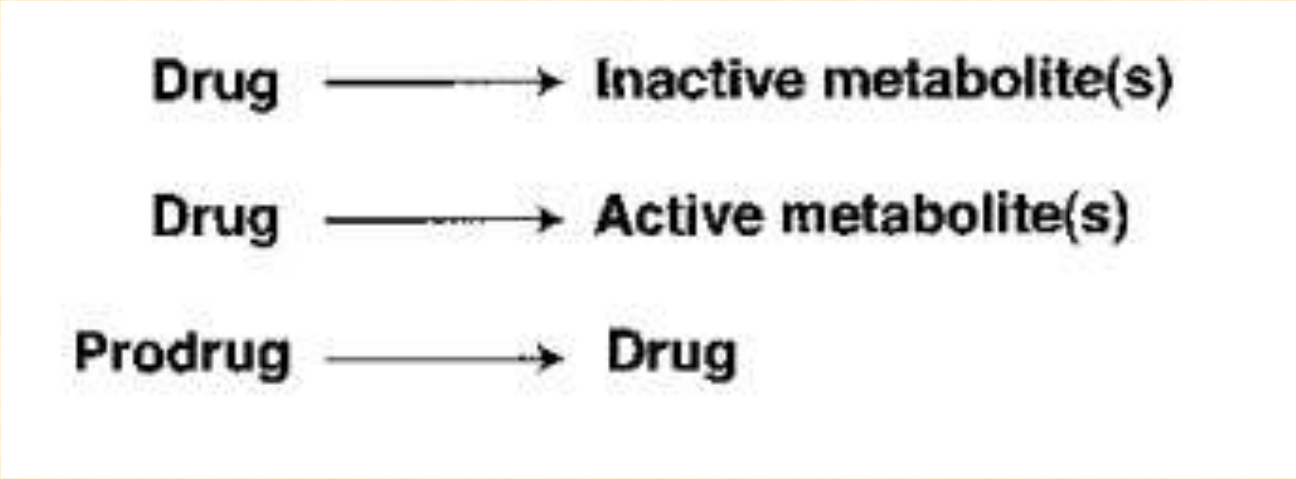
BARRIERS TO DISTRIBUTION

Placental—most small molecular weight drugs cross the placental barrier, although fetal blood levels are usually lower than maternal. Example: propylthiouracil (PTU) versus methimazole

Blood–brain—permeable only to lipid-soluble drugs or those of very low molecular weight. Example: levodopa versus dopamine

BIOTRANSFORMATION OF DRUGS

The biotransformation is the metabolism of drugs in the body.



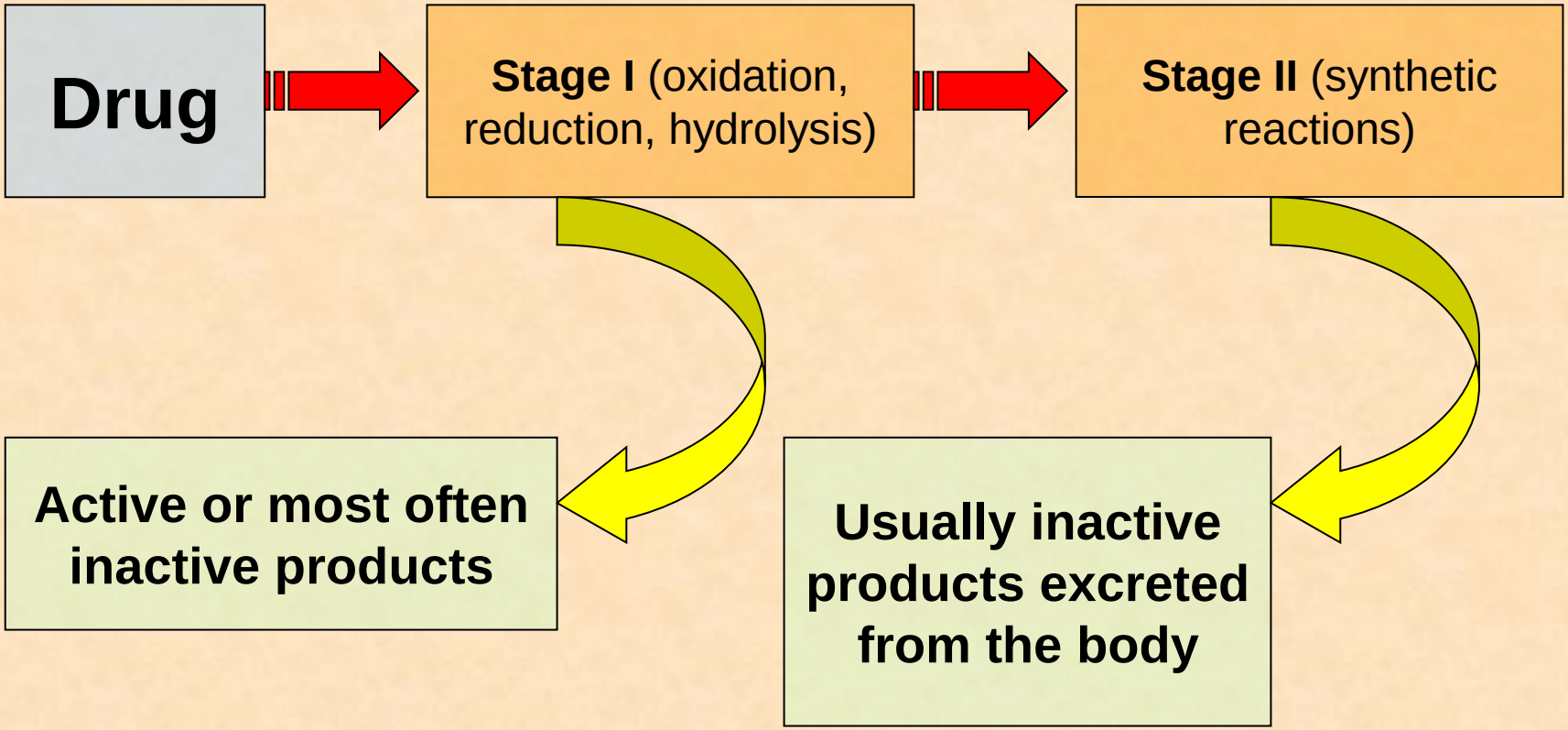
THE BIOTRANSFORMATION OF DRUGS

The liver is the main organ for drugs metabolism.

Biotransformation in the liver is realized in two stages:

- ***stage I*** (non-synthetic reactions with formation of active and inactive metabolites)
- ***stage II*** (synthetic reactions with formation of non-active metabolites)

STAGES OF BIOTRASNSFORMATION



INDUCTORS AND INHIBITORS OF MICROSOMAL OXIDATION

- Drugs which increase the activity of microsomal enzymes in the liver, are named the ***inductors of microsomal oxidation*** *(e.g.: phenobarbital, chlorpromazine).*
- Drugs which decrease the activity of microsomal enzymes in the liver, are named the ***inhibitors of microsomal oxidation*** *(e.g.: metronidazole).*

INDUCTION OF MICROSOMAL OXIDATION

Drug

↓

Enzyme induction:

P-450

P-450

P-450

↓

The intensification of drugs metabolism,
a decrease in efficacy of co-administered drugs

INHIBITION OF MICROSOMAL OXIDATION

Drug

↓

Enzyme inhibition:

P-450

P-450

P-450

↓

The inhibition of drugs metabolism,
an increase in toxicity of co-administered drugs

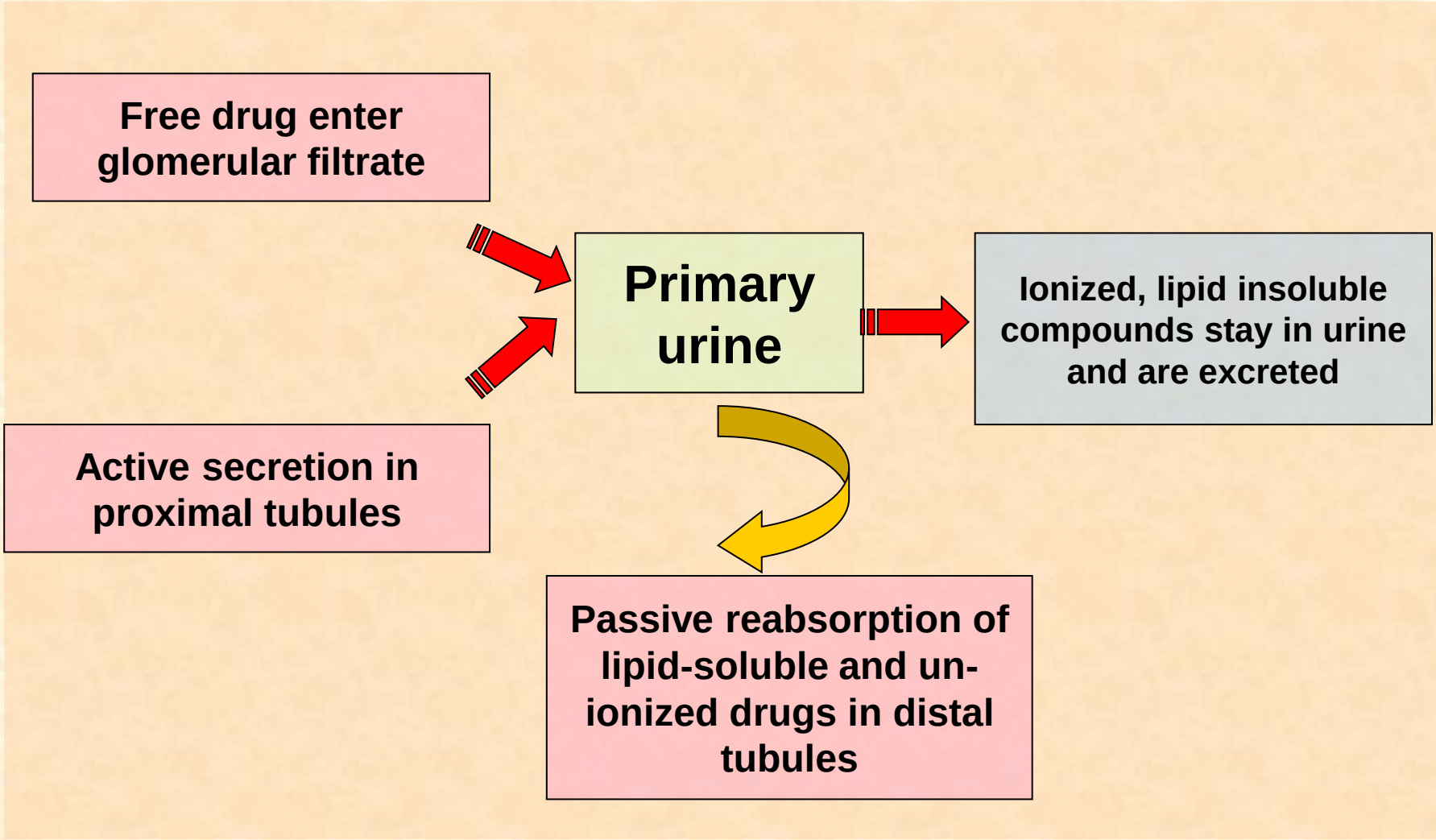
DRUGS EXCRETION

Excretion is the process by which drug leaves the body.

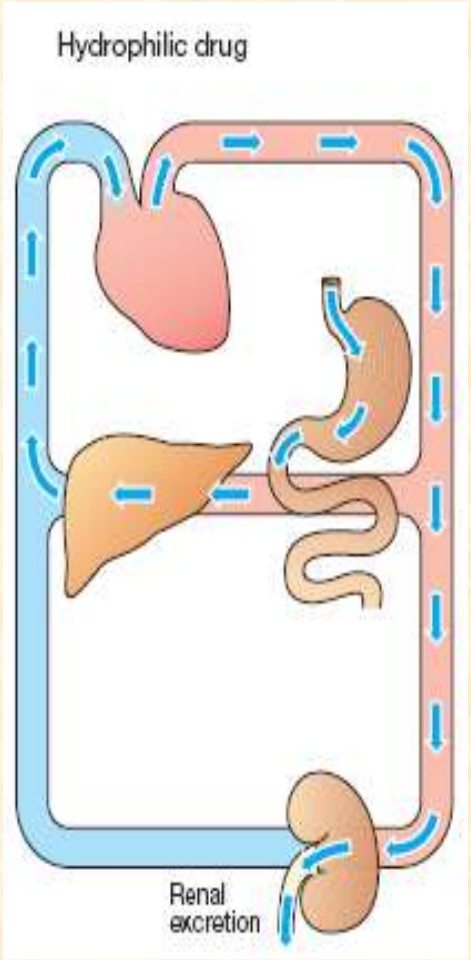
Drugs are excreted:

- with urine *(e.g.: sulfa drugs, hypnotics and majority of other drugs)*
- with bile *(e.g.: antibiotic tetracycline)*
- with mother's milk *(e.g.: hypnotics, antibiotics, antihistamines)*
- with saliva *(e.g.: bismuth preparations)*
- with sweat *(e.g.: bromides, chlorides)*
- with air *(ether for narcosis).*

DRUGS ELIMINATION IN THE KIDNEY



RENAL EXCRETION OF HYDROPHILIC (A) AND LIPOPHILIC DRUGS (B)



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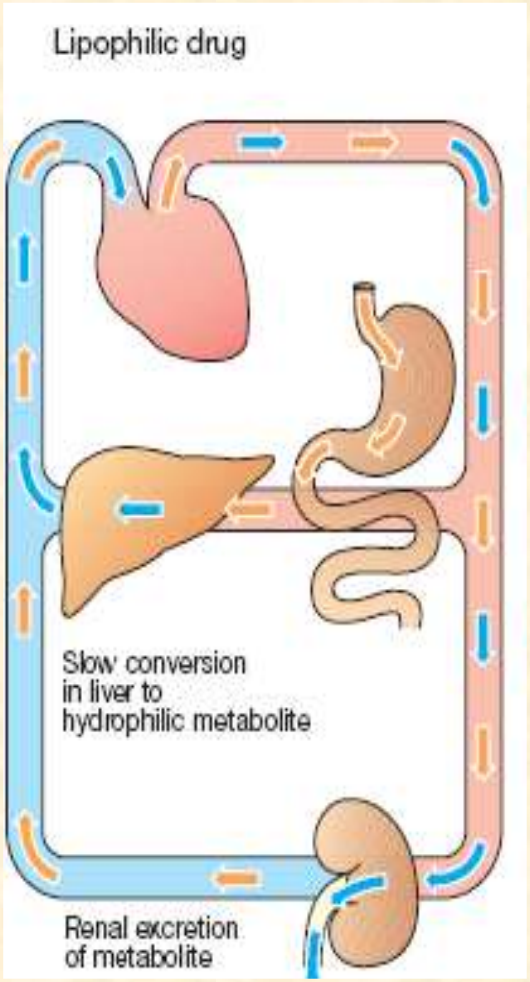
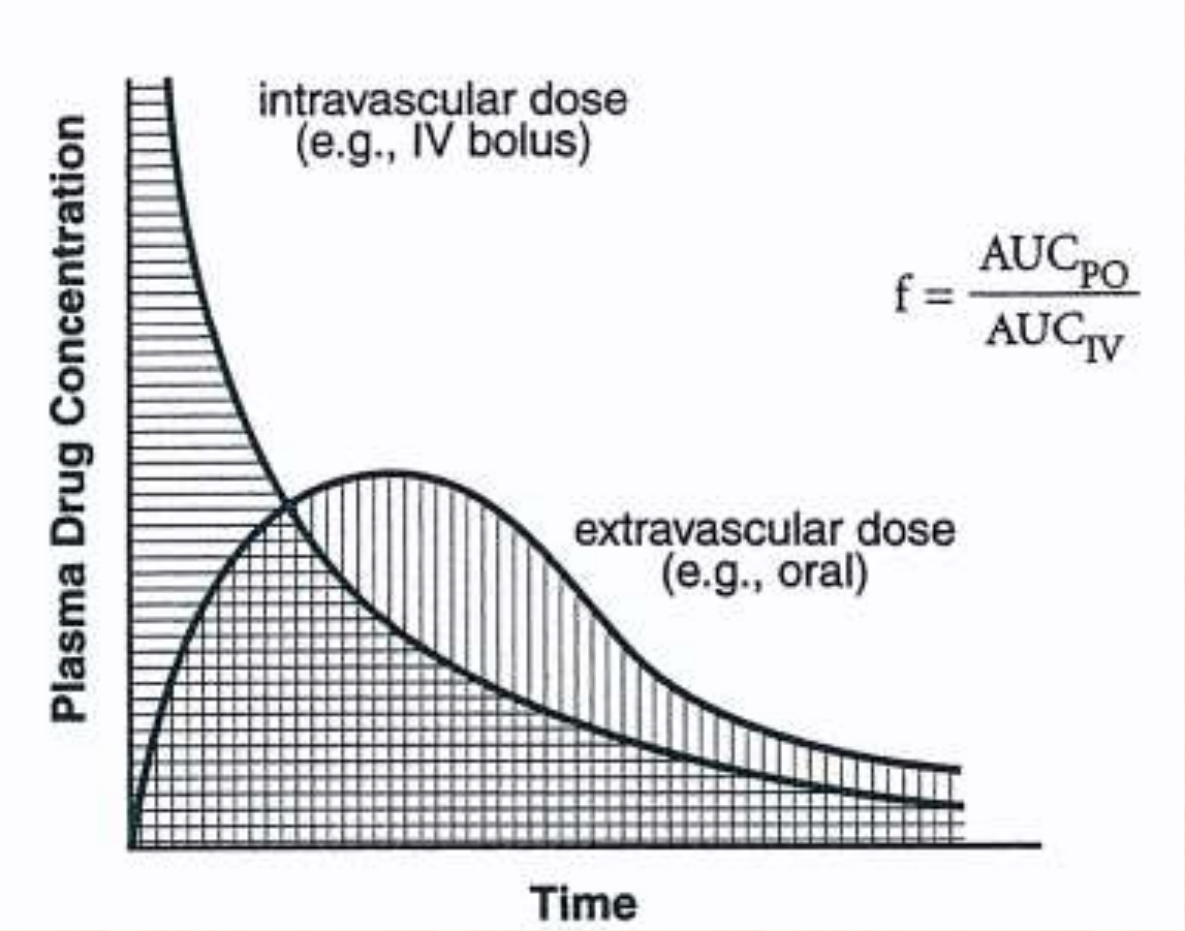


B

PHARMACOKINETIC FACTORS: bioavailability



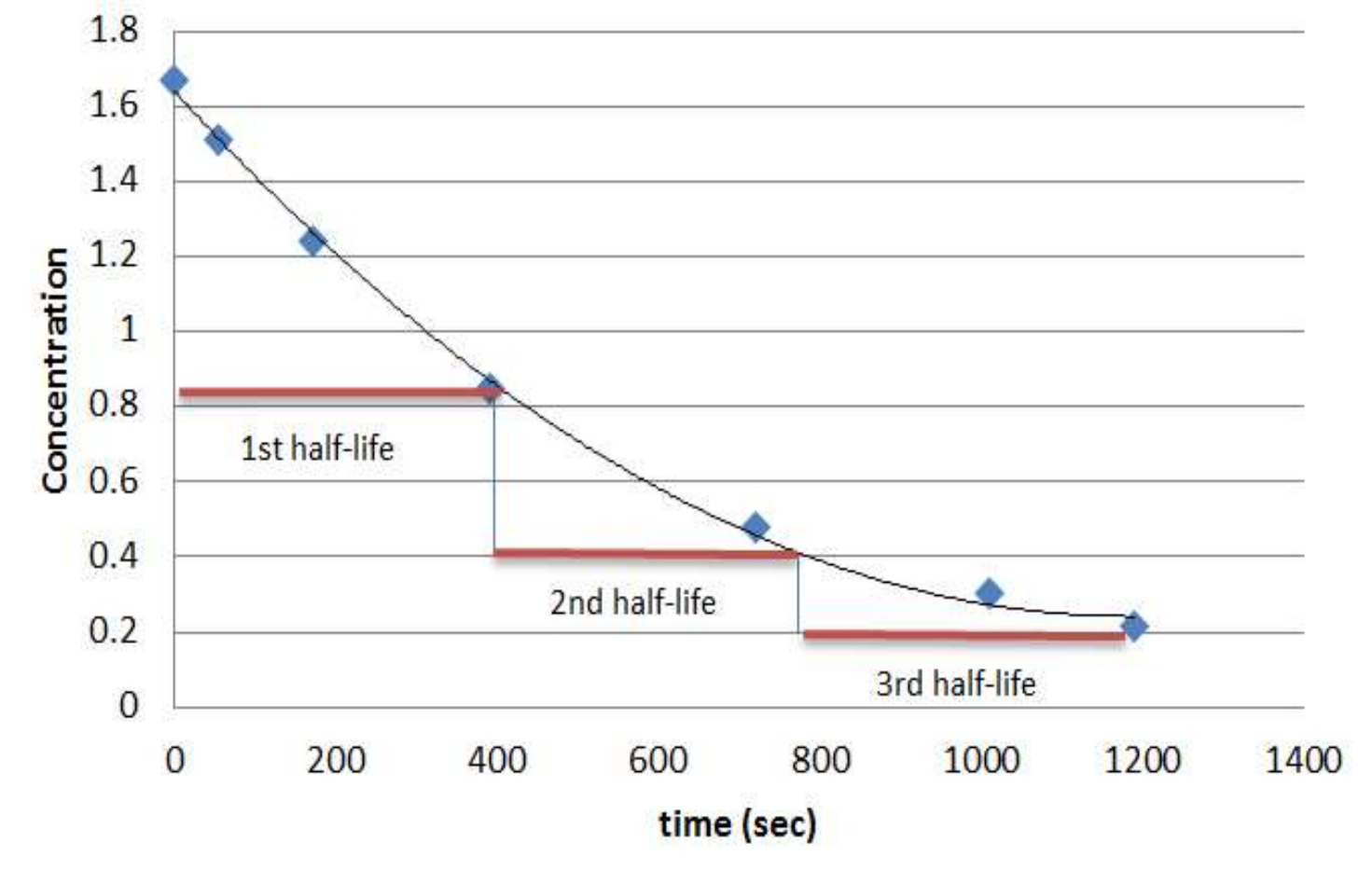
PHARMACOKINETIC FACTORS:
volume of distribution

A kinetic parameter of a drug that correlates dose with plasma level at zero time.

$$V_d = \frac{\text{Dose}}{C^0}$$ where C^0 = [plasma] at zero time

PHARMACOKINETIC FACTORS:

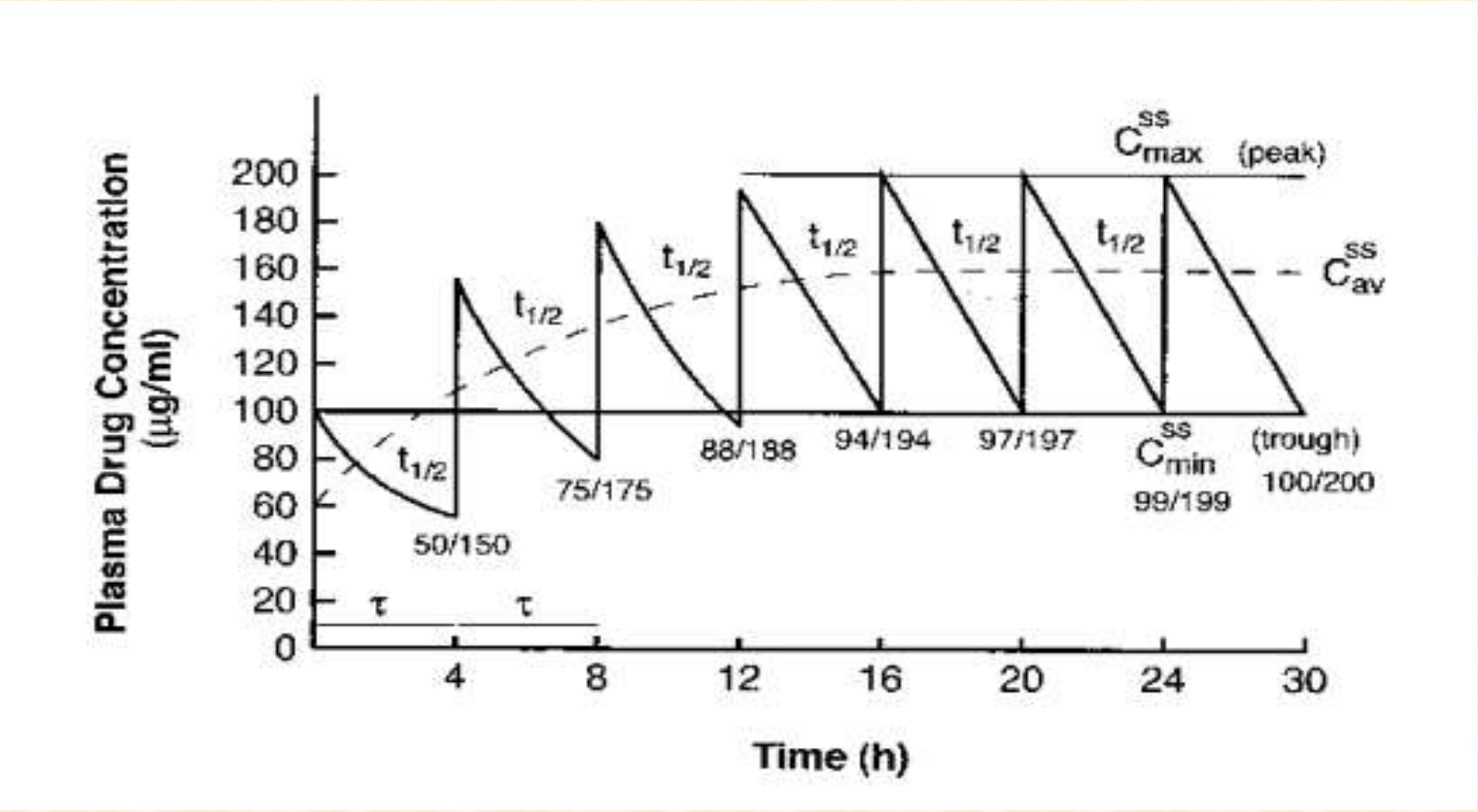
half-life



PHARMACOKINETIC FACTORS:

steady state

Steady state is reached either when **rate in** = **rate out** or when values associated with a dosing interval are the same as those in the succeeding interval.



PHARMACOKINETIC FACTORS:

clearance

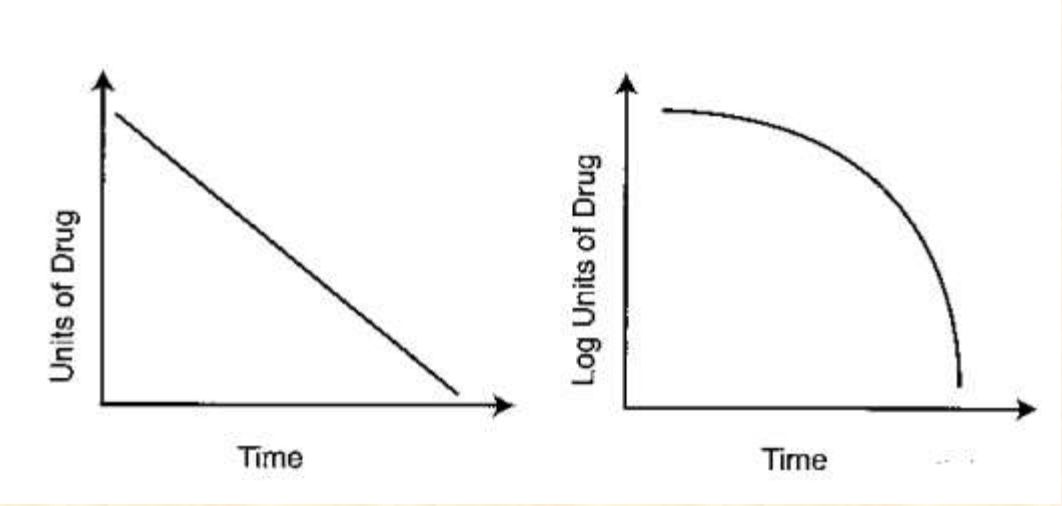
Clearance is the volume of plasma which is cleaned from the drug during 1 minute. Total body clearance is the sum of the clearances from the drug metabolizing and drug-eliminated organs.

RATE OF ELIMINATION

Zero-Order Elimination Rate

- A constant amount of drug is eliminated per unit time; for example, if 80 mg is administered and 10 mg is eliminated every 4 h, the time course of drug elimination is:

	4 h		4 h		4 h		4 h	
80 mg	→	70 mg	→	60 mg	→	50 mg	→	40 mg

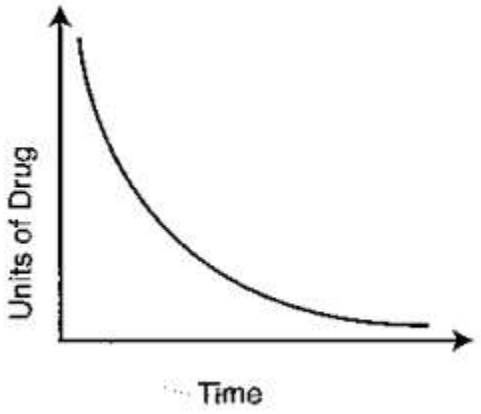


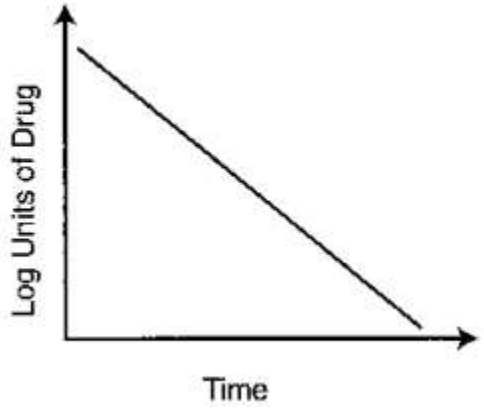
RATE OF ELIMINATION

First-Order Elimination Rate

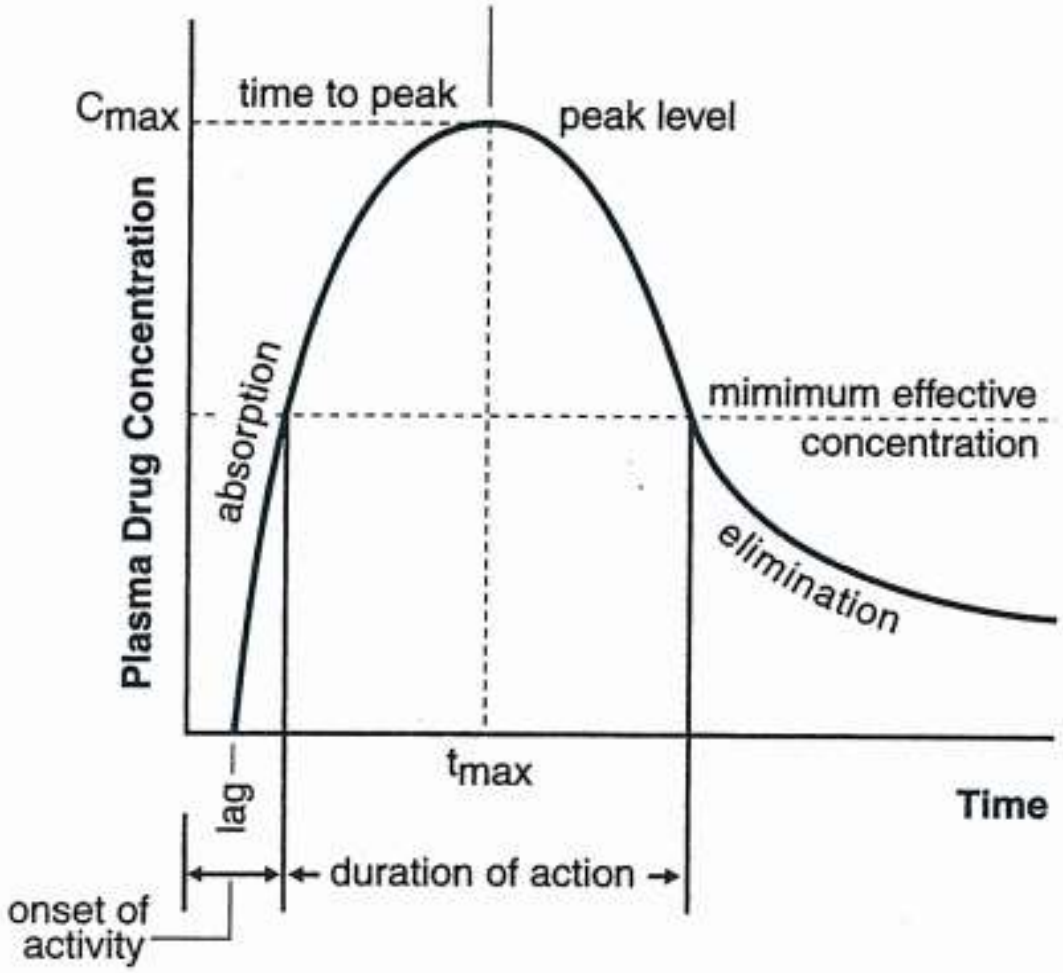
- A constant fraction of the drug is eliminated per unit time ($t_{1/2}$ is a constant). Graphically, first-order elimination follows an exponential decay versus time.
- For example, if 80 mg of a drug is administered and its elimination half-life = 4 h, the time course of its elimination is:

	4 h		4 h		4 h		4 h	
80 mg	→	40 mg	→	20 mg	→	10 mg	→	5 mg





PLOT OF PLASMA CONCENTRATION VERSUS TIME



C_{max} = maximal drug level obtained with the dose.
t_{max} = time at which C_{max} occurs.
Lag time = time from administration to appearance in blood.
Onset of activity = time from administration to blood level reaching minimal effective concentration (MEC).
Duration of action = time plasma concentration remains greater than MEC.
Time to peak = time from administration to C_{max}.