NEUROPHARMACOLOGY

The course is composed of 3 parts

PART 1 (Prof. Chiara Florio)
PHARMACOKINETIC (drug absorption, distribution, metabolism and excretion) - PHARMACODYNAMIC - THE AUTONOMIC NERVOUS SYSTEM - THE OPIOID SYSTEM

PART 2 (Prof. Gabriele Stocco)
DRUGS OF THE CENTRAL NERVOUS SYSTEM: ANTIDEPRESSANT DRUGS - ANTIPSYCHOTIC DRUGS - ANXIOLYTIC DRUGS - ANTI-EPILEPTIC DRUGS

PART 3 (Prof. Gabriele Stocco): PHARMACOGENOMICS

AIM of the course is to provide the basic notions for the comprehension of the pharmacokinetic and pharmacodynamics properties of drugs and of their mechanism of action, with particular reference to drugs acting at the central nervous system in order to allow the students to:

1) to discuss clearly and with appropriate scientific terms pharmacological concepts
2) continue to enlarge autonomously and critically their knowledges
3) use the knowledges acquired for a proper use of drugs in experimental set-ups
4) apply knowledges for a critical consideration of experimental results

Students are provided by the slides used during the frontal lessons thought **Moodle (**Access code: 779SM)

Recommended text book:
Rang, Ritter, Flower, Henderson “Rang & Dale’s Pharmacology” Eighth Edition, Elsevier 2016

For further information, students are invited to contact dott. Florio by mail (florioc@units.it) using their institutional E-mail address

FINAL EXAMINATION

At the end of the course, students are required to take a final oral examination of 20-40 min consisting on three different topics covering the course program (1. Basic Pharmacology (pharmacokinetic and pharmacodynamics) or Autonomous nervous system, 2. Pharmacogenomics and 3. Drugs acting at the Central Nervous System)

The student should demonstrate to be able to link together different topics of the program and to communicate the acquired knowledges in a precise and efficacious manner.
The mark/30 must be equal or higher than 18.
The final mark/30 is the arithmetic mean of Neuroanatomy and Neuropharmacology

Phar·ma·col·o·gy

Etymology: Gk, pharmakon, drug + logos, science

The science that deals with the origin, nature, chemistry, effects, and uses of drugs; it includes pharmacognosy, pharmacokinetics, pharmacodynamics, pharmacotherapeutics, and toxicology (Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health)

pharmacokinetic

pharmacodynamic

Pharmacokinetic

How the drug comes and goes

Drugs need to achieve an adequate concentration in their target tissues to give the requested pharmacologic effect (pharmacodynamic)

The fundamental processes that determine the concentration of the drug at any moment and in any region of the body are:

1) Absorption from the site of administration

2) Distribution within the body

3) Biotransformation (drug metabolism)

4) Excretion

"ADME"

Pharmacokinetic

A: absorption

From its site of administration, drugs cross various barriers (membranes, capillaries, cell wall….) and reach the bloodstream (or lymphatic or cerebrospinal fluids)

D: distribution

The drug moves from the bloodstream (or lymphatic or cerebrospinal fluids) to its site of action (eg, the brain), again crossing various barriers

Distribution affects drug concentration at site of action (pharmacodynamic effect), drug site of excretion and biotransformation

Pharmacokinetic

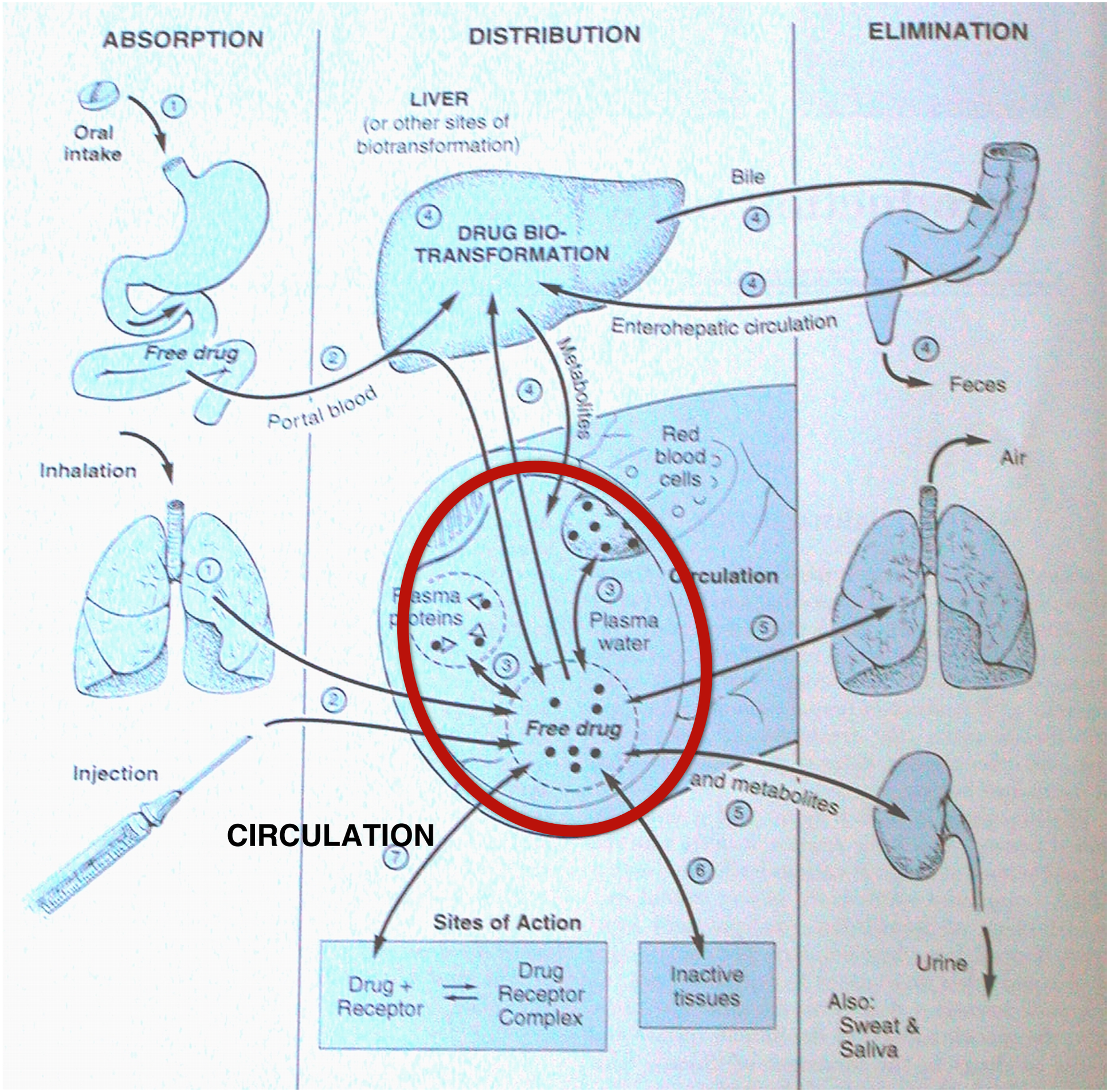
M:metabolism

Drugs are biotransformed into several different compounds by enzymes evolved to cope with natural compounds

Biotransformation may increase, decrease or change drug actions

E: excretion

Drugs are eliminated by excretion from the body through different pathways, e.g. renal


ABSORPTION
DISTRIBUTION
ELIMINATION
Oral intake
LIVER
(or other sites of biotransformation)
DRUG BIO-TRANSFORMATION
Bile
Enterohepatic circulation
Feces
Free drug
Portal blood
Metabolites
Red blood cells
Inhalation
Air
Plasma proteins
Plasma water
Free drug
Injection
and metabolites
CIRCULATION
Sites of Action
Drug + Receptor
Drug Receptor Complex
Inactive tissues
Urine
Also: Sweat & Saliva

Drug Administration Routes

PARENTERAL: occurs elsewhere in the body than the mouth and intestine

ENTERAL: involves the passage through the intestine

Administration Routes: PARENTERAL

	ADVANTAGES	DISADVANTAGES
INTRAVENOUS	**Rapid attainment of concentration; precise delivery of dosage; easy to titrate dose**	**High initial concentration (toxicity risk); risk of infection; requires skill**
SUBCUTANEOUS **INTRAMUSCULAR**	**Prompt absorption from aqueous medium; little training needed; avoid gastrointestinal environment**	**Cannot be used for large volume; potential pain or tissue damage; variable absorption**

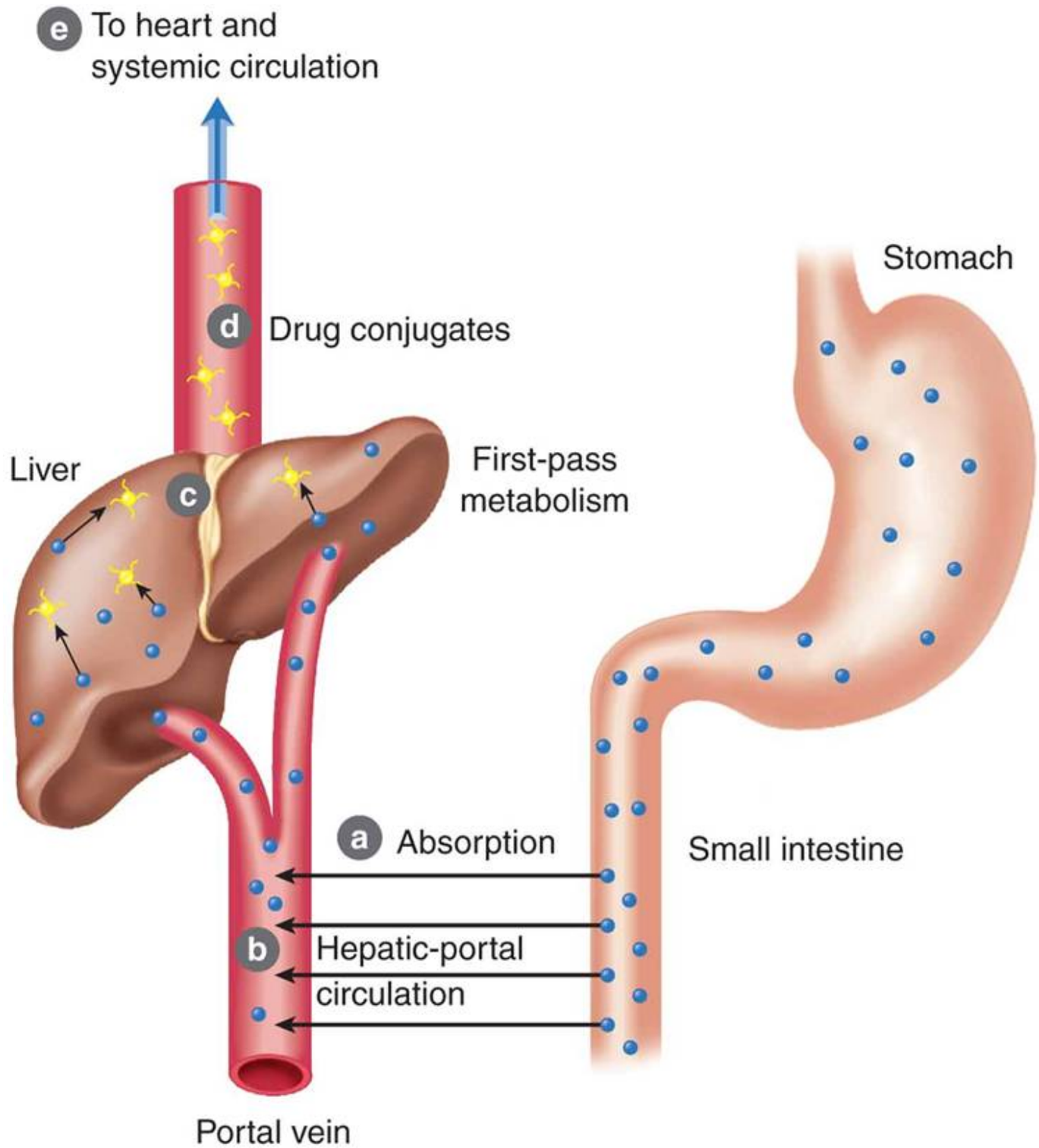
Administration Routes: PARENTERAL

	ADVANTAGES	DISADVANTAGES
PULMONARY	**Easy to titrate dose Rapid onset local effect Minimize toxic effects**	**Variable delivery Requires coordination lung disease limits**
TOPICAL	**Minimize side effects Avoid first pass metabolism**	**Erratic absorption**

Administration Routes: ENTERAL

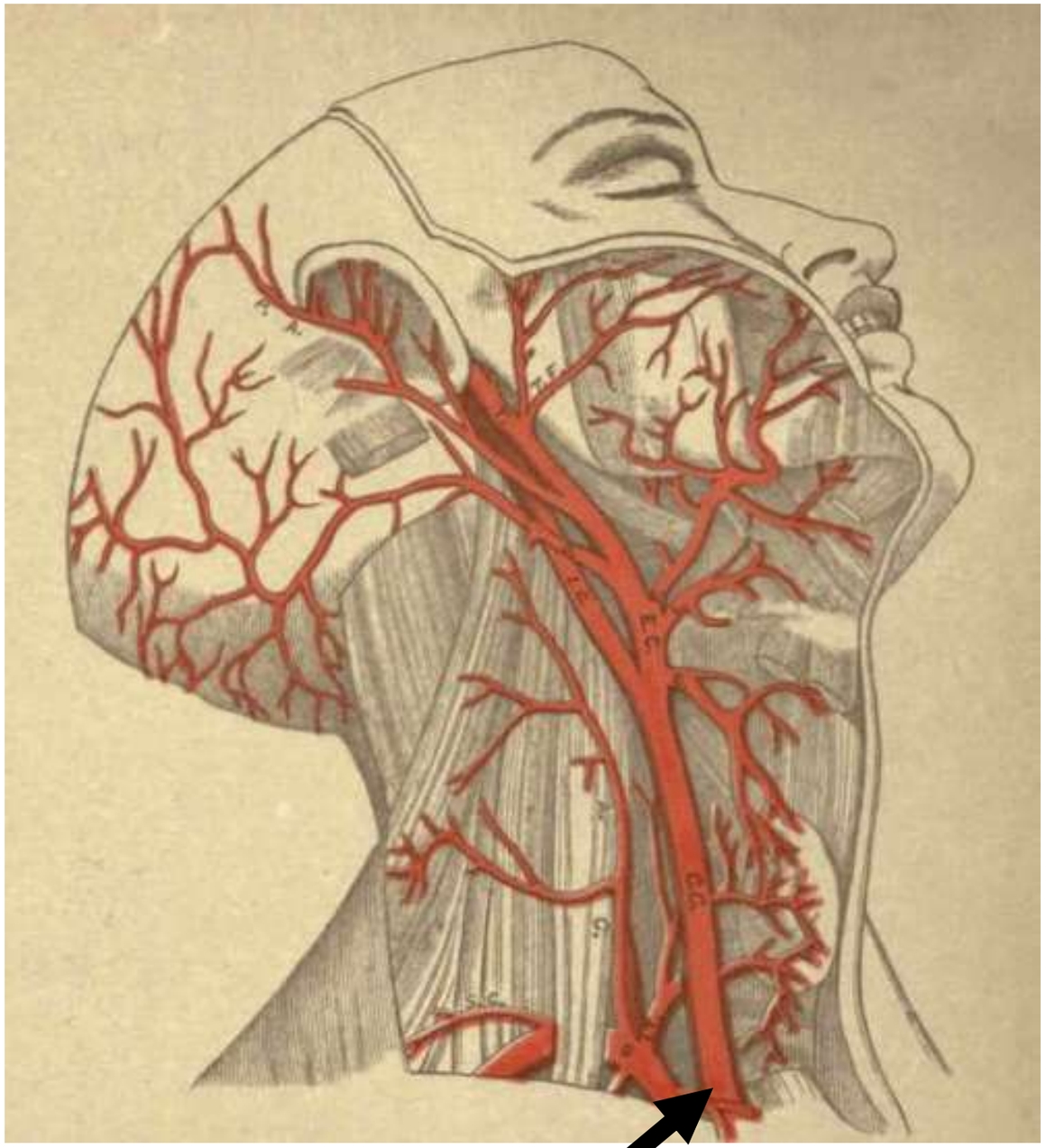
	ADVANTAGES	DISADVANTAGES
ORAL	**Convenient (storage, portability)** **Economical** **Non invasive** **Safe** **Requires no training**	**Delivery can be erratic or incomplete** **Depends on patient compliance** **First passage metabolism**
SUBLINGUAL	**Rapid onset** **Avoid first passage metabolism**	**Few drugs adequately absorbed** **Patient must avoid swallowing** **Difficult compliance**

First Pass Metabolism



First Pass Metabolism reduces the bioavailability of drugs

Sublingual or Buccal



Though the superior cava vein to the heart

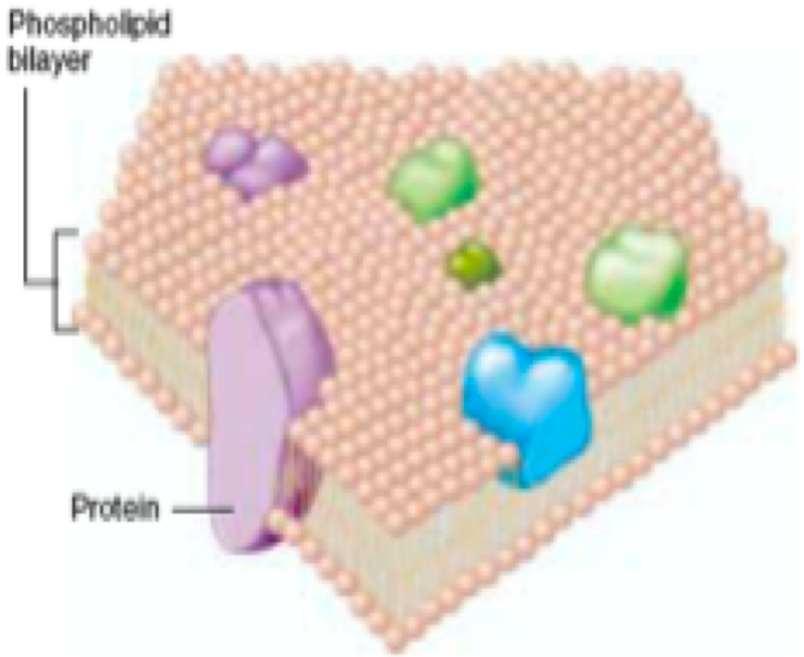
ADME: Absorption

Absorption is the process by which a drug moves from its site of application and enters the bloodstream **crossing cell barriers**

The movement of drug molecules across cell barriers

Cell membranes form barriers between aqueous compartments in the body

The most universal function of cell membrane is to act as a selective barrier to the passage of molecules, allowing some molecules to cross while excluding others



Lipid Bilayer

Hydrophilic Heads

Hydrophobic Tails

Small, uncharged

H_2O, urea, CO_2, O_2, N_2

Large, hydrophilic

Glucose
Sucrose

DENIED!

Small charged ions

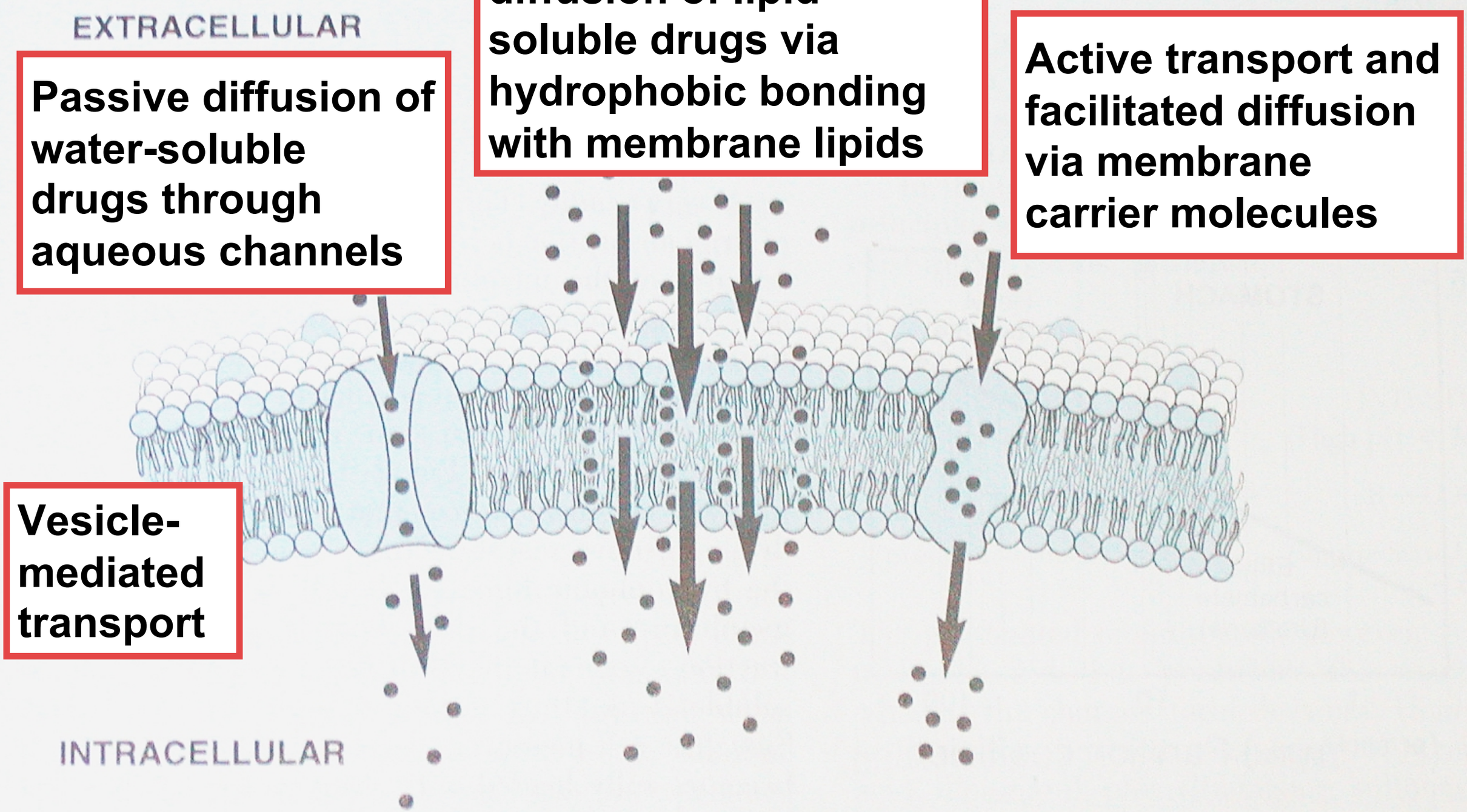
H^+, Na^+, K^+, Ca^{2+}, Cl^-, HCO_3^-

DENIED!

Mechanisms of Absorption

Passive (or simple) diffusion of lipid-soluble drugs via hydrophobic bonding with membrane lipids

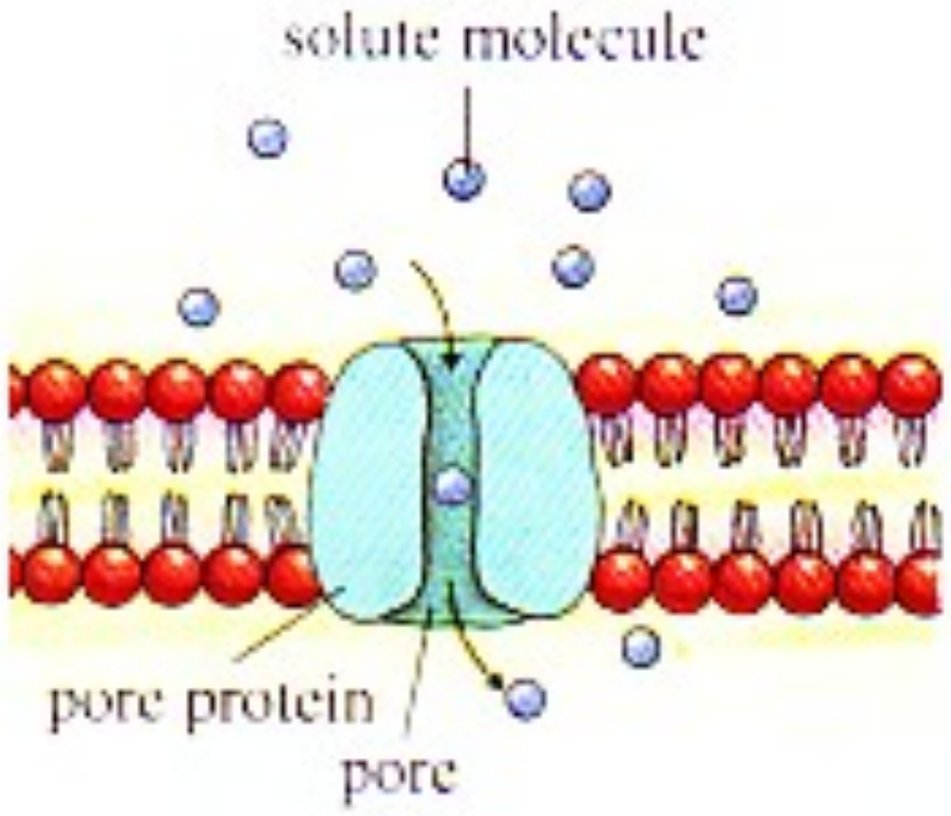
Active transport and facilitated diffusion via membrane carrier molecules



Passive diffusion of water-soluble drugs through aqueous channels

Vesicle-mediated transport

Passive (or simple) diffusion of hydrophilic molecules trough acqueuos channels



Drug	Molecular weigth	Ripartition Coefficient
Caffein	194	0.17
Ascorbic acid	176	0.02
Ephedrin	165	1.6

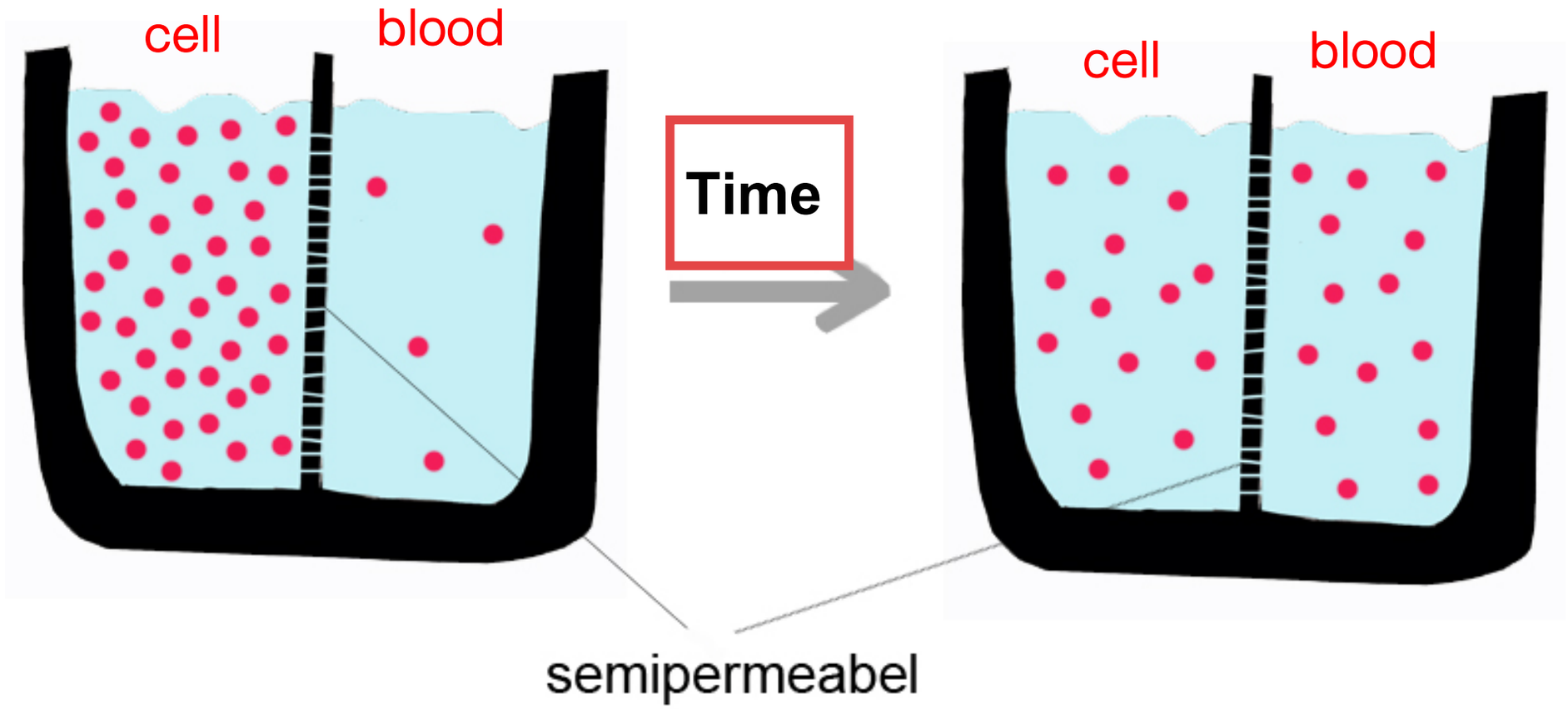
Passive (or simple) Diffusion

The vast majority of drugs move through the body by passive diffusion

Passive diffusion depends on drug-dependent and drug-independent factors:

1. **Drug concentration gradient**
2. **Drug lipid solubility**
3. **Drug degree of ionization**
4. **Thickness of membrane**
5. **Surface area**

Passive (or simple) Diffusion

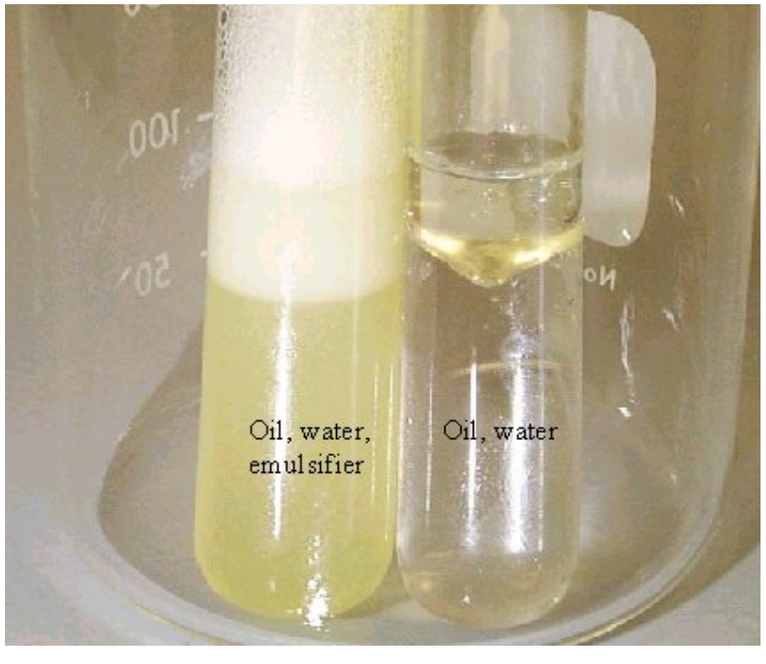


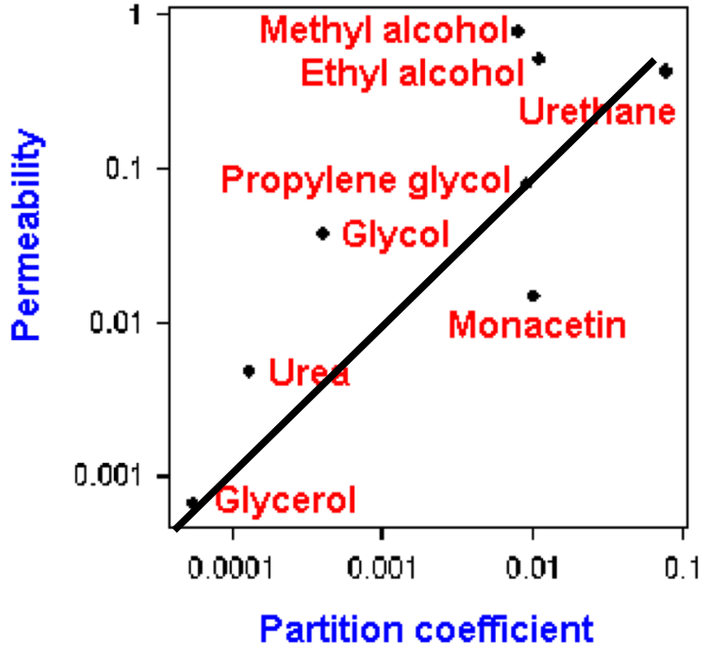
1) In an open system, the drug concentration gradient is maintained by removal of the drug due to the blood flow

Passive (or simple) Diffusion

2) Lipid solubility depends on the physiochemical properties of the drug

Is measured by the lipid/water partition coefficient (ratio of drug concentration in lipid phase and water phase when shaken in one immiscible lipid/water system)





Passive (or simple) Diffusion

3) **Degree of ionization** **(for week acidic or basic drugs)**

Acids **Release/Donate H^+**

$$HA \rightleftharpoons H^+ + A^-$$

Ionized form

Bases **Bind/Accept H^+**

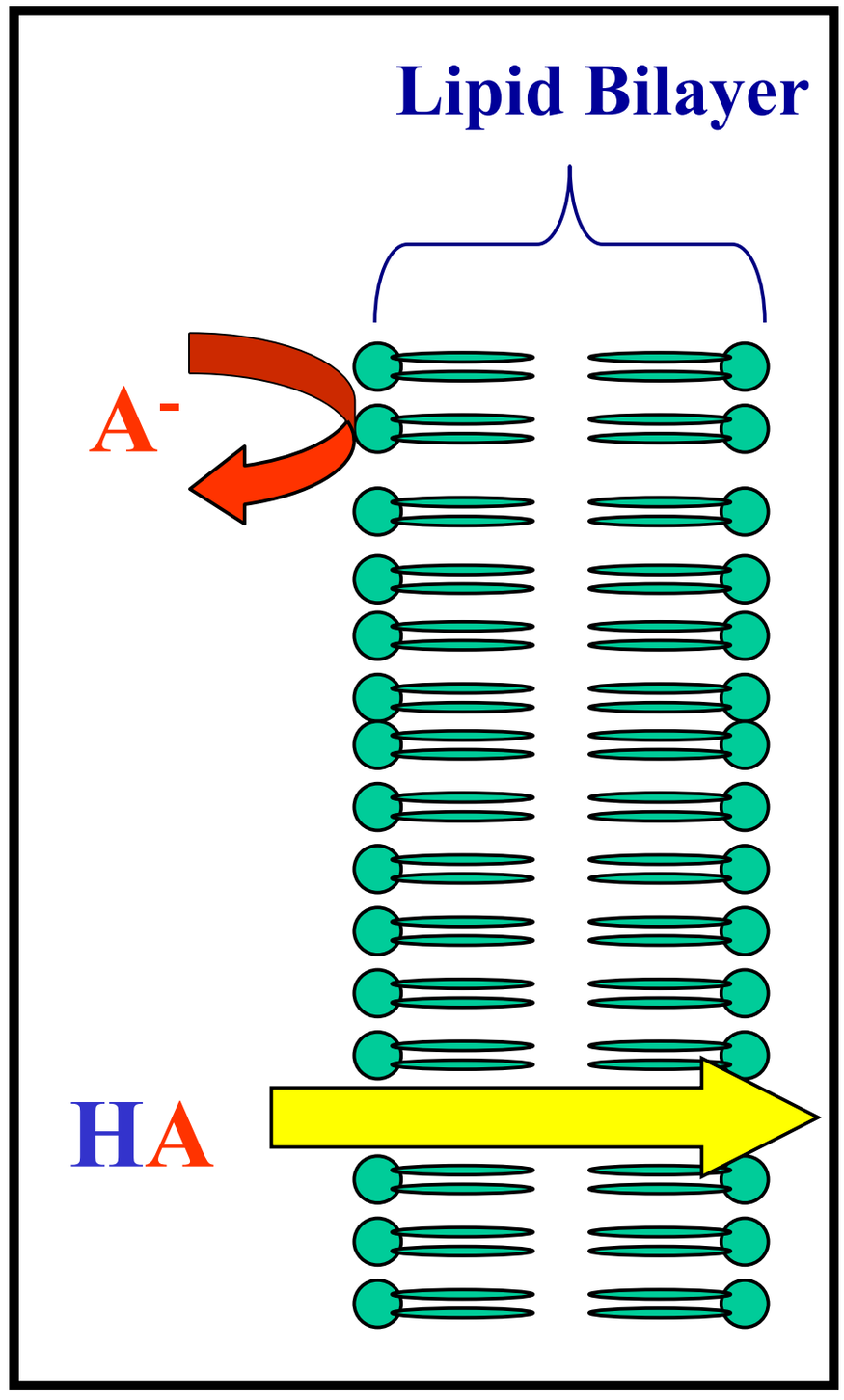
$$H^+ + B^- \rightleftharpoons HB$$

Non-ionized form

Environmental pH and Ionization

For an acidic drug, in an environment with low pH the non-ionized form will predominate

whereas in an environment with high pH the ionized form will predominate



As a consequence:

Acidic drugs are best absorbed from acidic environments
Basic drugs are best adsorbed from basic environments

And...

To increase absorption of an acidic drug acidify the environment
To reduce the absorption (or increase the elimination) of an acidic drug alkalinize the environment

The relative amount of charged and uncharged species for any drug molecule depends on the pH of the medium and on the molecule's pKa

pKa

pH value at which the drug is 50% in the ionized form and 50% in the non-ionized form

pH	Acidic drug	% non ionized form	Basic drug	% non ionized form
1		99.9		0.1
2		99		1
3	HA	90	BH^+	10
4		***50***		***50***
5	A^-	10	B	90
6		1		99
7		0.1		99.9

pKa

Passive (or simple) Diffusion

The vast majority of drugs move through the body by this mechanism

Passive diffusion depends on:

1. **concentration gradient**
2. **lipid solubility**
3. **degree of ionization**
4. **thickness of membrane (e.g. capillaries vs big vessels)**
5. **surface area (e.g. stomach vs intestine)**

Passive (or simple) Diffusion

Fick's Law

$$\frac{dQ}{dt} = \frac{PA}{h}(Cp - Ct)$$

dQ/dt = diffusion rate

P = oil/water partition coefficient

A = surface area

Ct = drug concentration in the tissue

Cp = drug concentration in the plasma

} **concentration gradient**

h = thickness of the membrane

Passive (or simple) Diffusion

- **Diffusion rate depends on the drug concentration gradient**
- **No energy or carrier is required**
- **It is not saturable**