Pharmacokinetics I
Drug administration and absorption

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By the end of this lecture, the student should be able to

- **Know the meaning of pharmacology and its branches.**
- **Discuss the different routes of drug administration**
- **Identify the advantages and disadvantages of various routes of drug administration**
- **Know the various mechanisms of drug absorption**
- **List different factors affecting drug absorption**
- **Define bioavailability and factors affecting it.**

Recommended books

- **Lippincott's illustrated reviews (Pharmacology) *by Howland and Mycek***

- **Basic and Clinical Pharmacology *by Katzung***

What is Pharmacology?

- From the Greek pharmakon (drug),

and legein (to speak or discuss)

- Broadly defined as the study of how chemical agents affect living processes.
- e.g Hormones, Neurotransmitters and drugs

What is Pharmacology

- Pharmacology studies the effects of drugs and how they exert their effects.
- Acetylsalicylic acid (ASA) or Aspirin can reduce
- inflammation, , pain and fever
- It inhibit the action of a human cell membrane enzyme known as cyclooxygenase
- Penicillin cures certain bacterial infections disrupt the synthesis of cell walls in susceptible
- bacterial strains by inhibiting a key enzyme.

Pharmacology is the science that deals with the drugs regarding clasification, pharmacokinetics, pharmacodynamics, side effects and therapeutic uses.

Pharmacokinetics

are studies of the absorption, distribution, metabolism & excretion of drugs.(ADME)

(what the body does to a drug?)

Pharmacodynamics

Are studies of

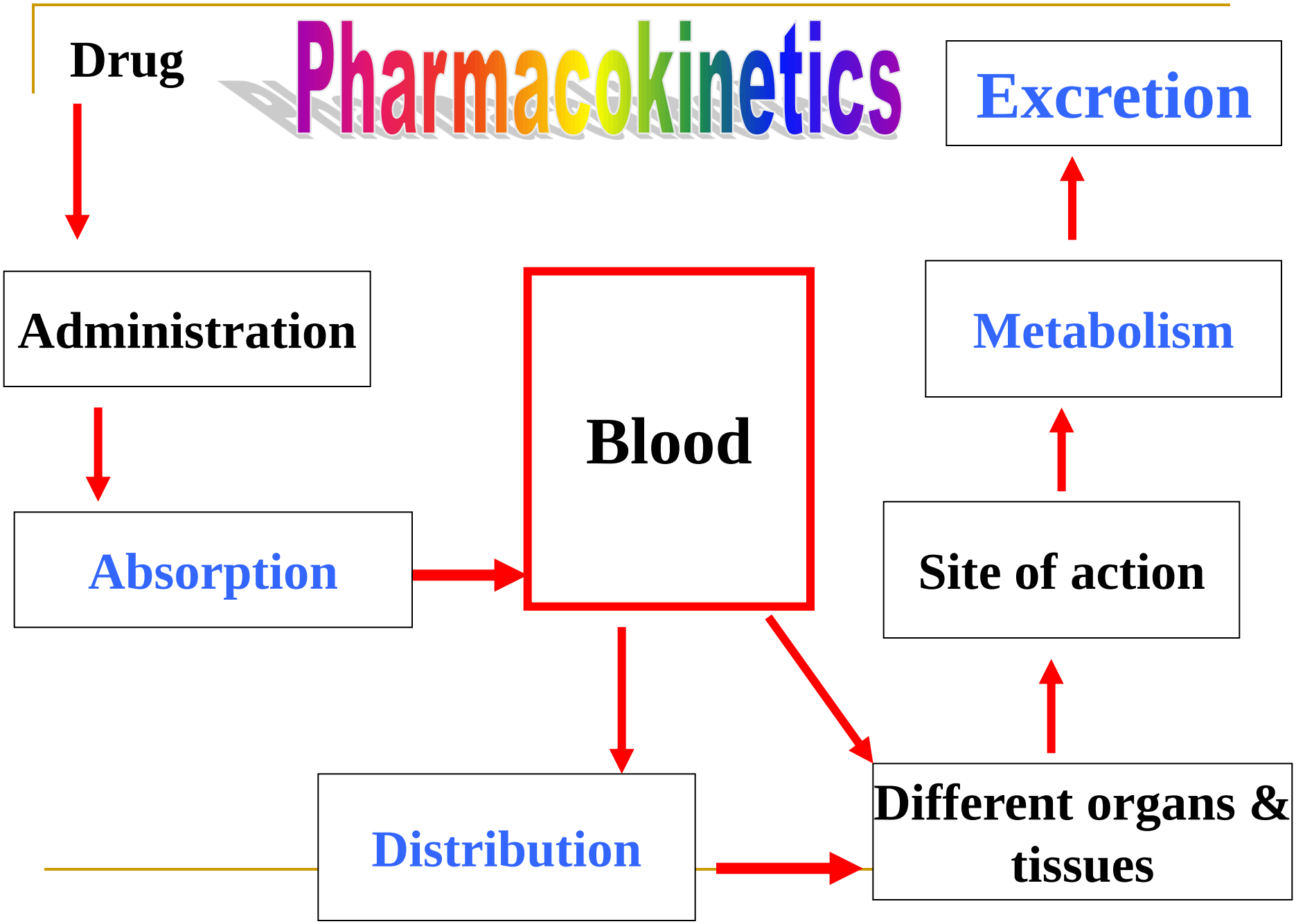
- **Mechanisms of drug action.**
- **Pharmacological effects of drugs.**

(what the drug does to the body?)

Pharmacokinetics of drugs

Are studies of drugs regarding ADME

- **Absorption**
- **Distribution**
- **Metabolism**
- **Excretion**


Drug
Pharmacokinetics
Excretion
Administration
Metabolism
Blood
Absorption
Site of action
Distribution
Different organs & tissues

Routes of drug administration

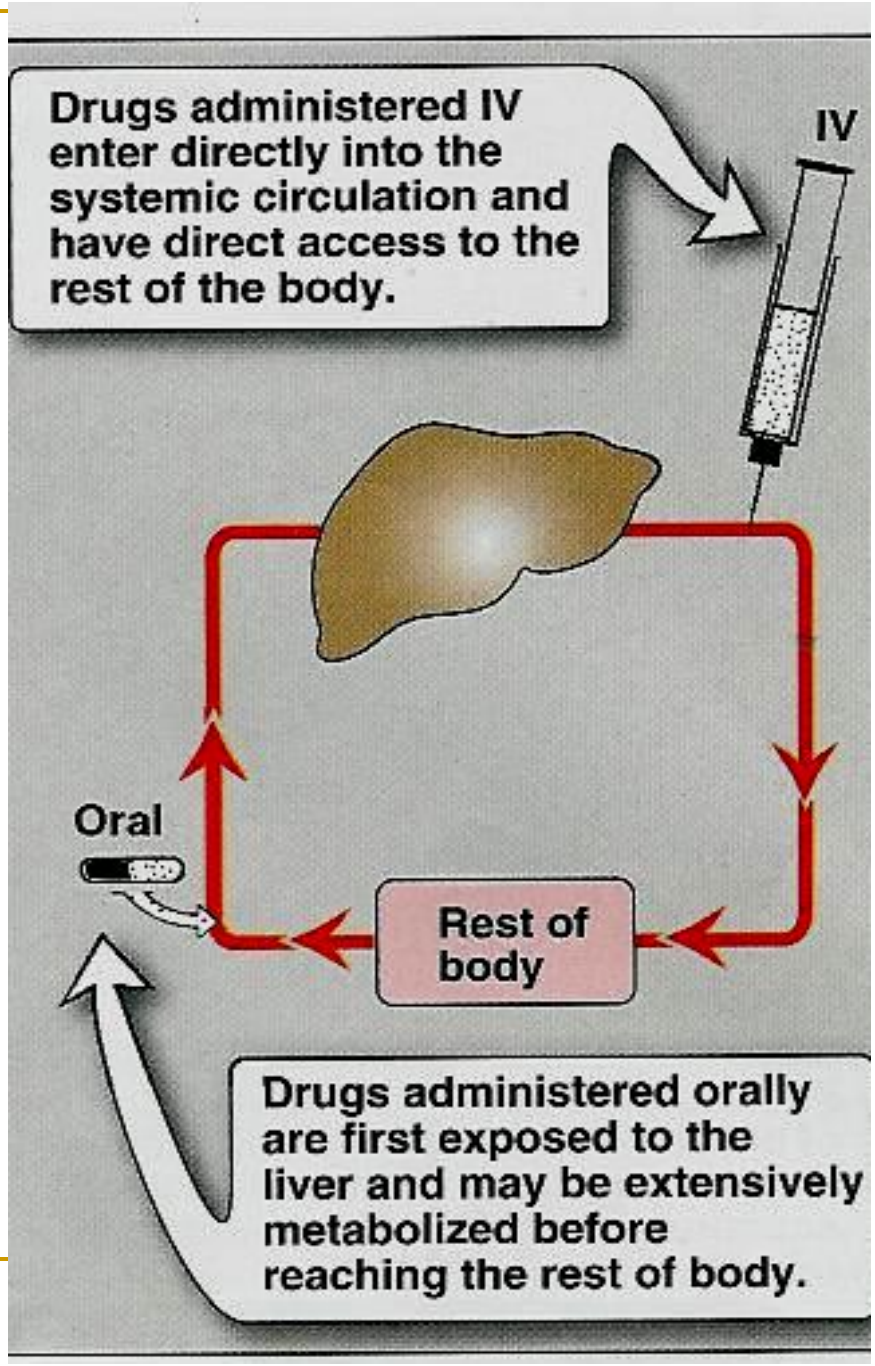
- **Enteral via gastrointestinal tract (GIT).**
  - ***Oral***
  - ***Sublingual***
  - ***Rectal***
- **Parenteral administration = injections.**
- **Topical application**
- **Inhalation**

Oral administration

Advantages	Disadvantages
- Common - Easy - Self use -convenient - cheap - No need for sterilization	- Slow effect, GIT irritation - Destruction by pH & enzymes - Food - drug interactions - Drug-drug interactions - First pass effect - No complete absorption - Low bioavailability *Not suitable* for ❑vomiting & unconscious patient ❑ emergency & bad taste drugs

First pass effect

- **Drugs given orally are first taken to the liver (via portal circulation), where they are metabolized before reaching to the blood to be distributed to all other body compartments.**



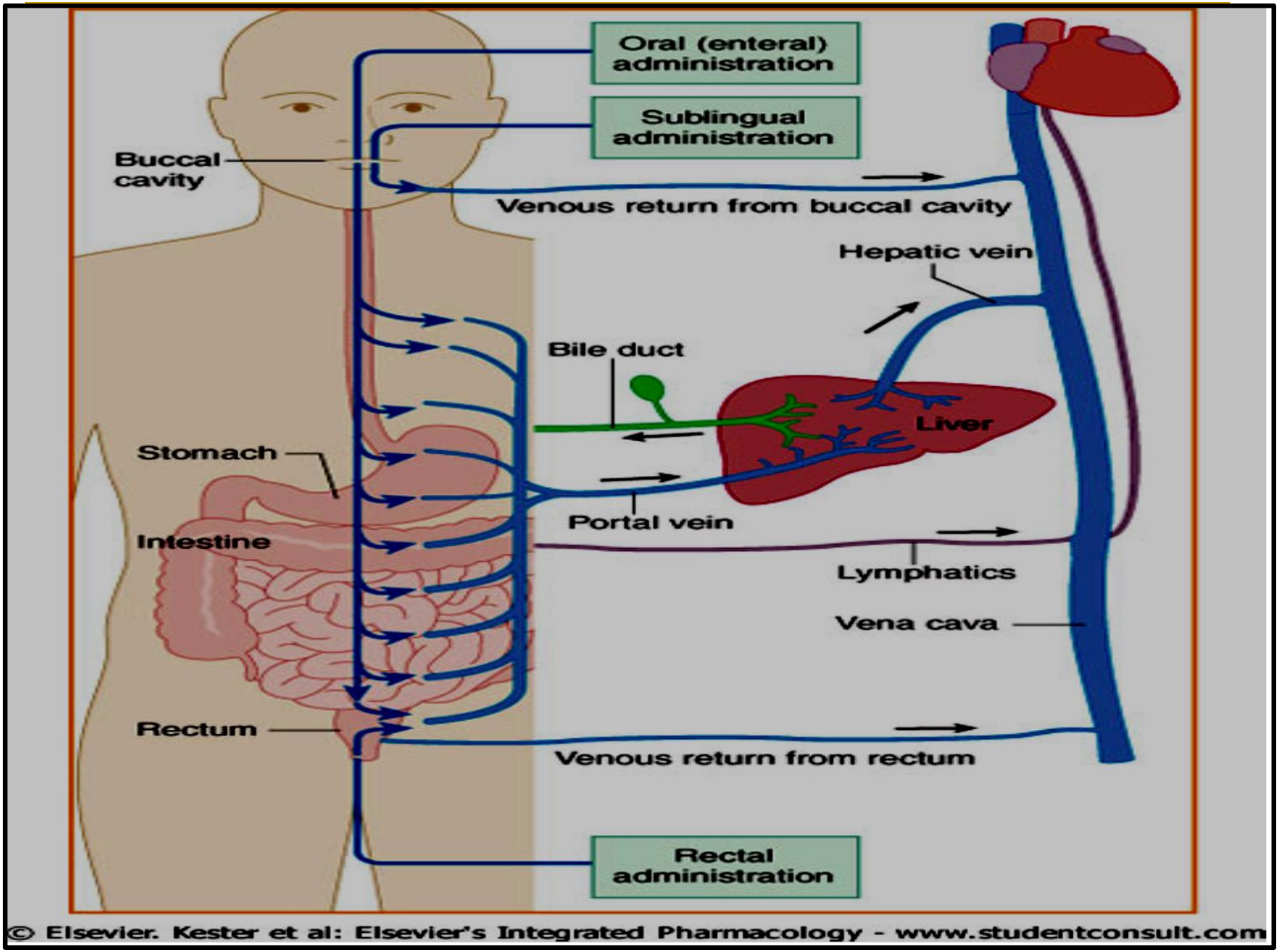
First pass Metabolism

Where does it occur?

- **Liver**
- **GIT wall**
- **GIT lumen**

First pass metabolism results in:

- **Low bioavailability** (low conc. of drug in blood).
- **Short duration of action (t ½).**
- drugs with high first pass effect should not be given orally but parenterally.



Oral Dosage Forms (oral formulations)

- **Tablets**
  - **Coated tablets: sugar-coated to mask bad taste**
  - **Enteric coated tablets: dissolve only in intestine**
- **Capsules**
  - **Hard gelatin capsules: (contain powder)**
  - **Soft gelatin capsules: (contain liquid)**
- **Syrup (e.g. Cough syrups)**
- **Suspension (mixture of solid in liquids e.g. antibiotics).**

Tablets

Spansule

Hard- gelatin capsule

Soft- gelatin capsule

Sublingual

Advantages	Disadvantages
❑ Rapid effect ❑ can be used in emergency ❑ High bioavailability ❑ No first pass effect. ❑ No GIT irritation ❑ No food drug – interaction ❑ *Dosage form:* friable tablet (easily breaks and dissolves)	*not suitable for* Irritant drugs Frequent use

Rectal administration

Advantages	Disadvantages
Suitable for ▫ children, vomiting, unconscious patients ▫ Irritant & bad taste drugs ▫ less first pass metabolism (50%) ▫ *Dosage form:* suppository or enema	▫ Irritation of rectal mucosa ▫ Irregular absorption & bioavailability

Parenteral administration

Intradermal (I.D.) (into skin)

Subcutaneous (S.C.) (under skin)

Intramuscular (I.M.) (into muscles)

Intravenous (I.V.) (into veins)

Intra-arterial (I.A.) (into arteries)

Intrathecal (I.T.) (cerebrospinal fluids)

Intraperitoneal (I.P.) (peritoneal cavity)

Intra - articular (Synovial fluids)

Parenteral administration

Advantages of injections

- No gastric irritation
- No food-drug interaction
- No drug-drug interaction
- No first pass metabolism
- higher availability than oral

Disadvantages

- Need skill
- Pain, tissue necrosis or abscess (I.M.)
- Anaphylactic reaction (I.V.)

Intradermal administration

- **Minute volume of drug (0.1 ml)**
- **suitable for vaccinations**
- **sensitivity test**

not suitable **for large volumes**

Subcutaneous administration

- **larger volume (0.1 ml – 1 ml)**
- **used for sustained release effect**
- **suitable for <u>poorly soluble suspensions</u> e.g. insulin zinc preparation**

Not suitable **for large volumes**

Intramuscular administration

- **moderate volumes (3-5 ml)**
- **prolonged duration of action**
- **oily preparations or poorly soluble substances can be used**

Not suitable for

- **irritant drugs**
- **pain, abscess, tissue necrosis may happen**

Intravenous administration

Advantages	Disadvantages
❑ Large volume (500ml can be given by infusion) ❑ Rapid action (emergency) ❑ High bioavailability ❑ No food-drug interaction ❑ No first pass metabolism ❑ No gastric irritation *Suitable for* ❑ Vomiting &unconscious ❑ Irritant & bad taste drugs.	❑ used only for water soluble drugs ❑ Infection ❑ Anaphylaxis ❑ Sterilization ❑ Expensive *Not suitable* for oily solutions or poorly soluble substance

Ampoule

Single use

Vial

Repeated use

Injection	Advantages	Disadvantages
I.D.	minute volume (0.1 ml) suitable for vaccinations & sensitivity test	not suitable for large volumes
S.C.	Volume (0.1 ml – 1 ml) suitable for poorly soluble suspensions and for instillation of slow-release implants e.g. insulin zinc preparation	not suitable for large volumes
I.M.	Suitable for moderate volumes 3-5 ml, for oily solutions or poorly soluble substances	not suitable for irritant drugs Abscess- necrosis may happen
I.V.	suitable for large volumes and for irritating substances (500 ml can be given by infusion).	not suitable for oily solutions or poorly soluble substances Must inject solutions slowly as a rule

Topical application

- **Drugs are mainly applied topically to produce local effects. They are applied to**
- **Skin (percutaneous) e.g. allergy test, topical antibacterial and steroids and local anesthetics.**
- **Mucous membrane of respiratory tract (Inhalation) e.g. asthma**
- **Eye drops e.g. conjunctivitis**
- **Ear drops e.g. otitis externa**
- **Intranasal e.g. decongestant nasal spray**

Inhalation

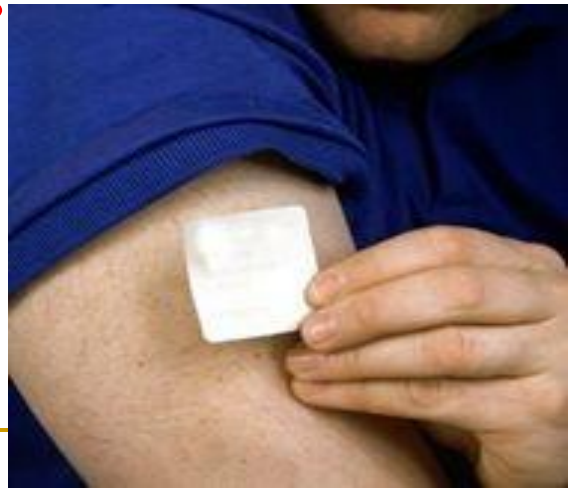
Advantages	Disadvantages
❑ rapid absorption *(due to large surface area)* ❑ suitable for emergency ❑ provide local action ❑ limited systemic effect ❑ less side effects ❑ no first pass effect ***Dosage form:*** ❑ volatile gases e.g. anesthetics ❑ liquids given by aerosol, nebulizer/inhaler for asthma treatment	Not suitable for irritant drugs Only few drugs can be used

Transdermal patch

are medicated adhesive patch applied to skin to provide systemic effect (prolonged drug action).

e.g. the nicotine patches (quit smoking).

e.g. Scopolamine (vestibular depressant, antiemetic for motion sickness).

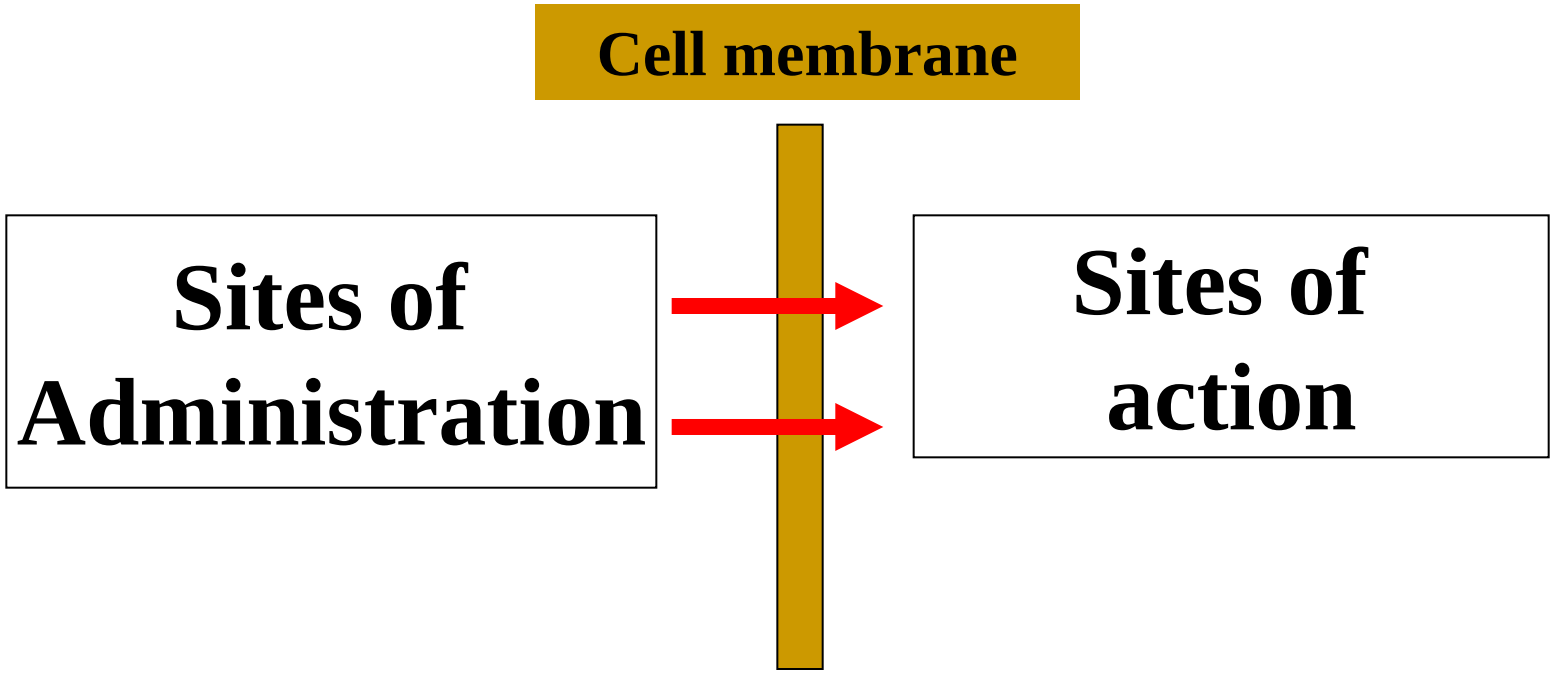


Nebulizer

Atomizer

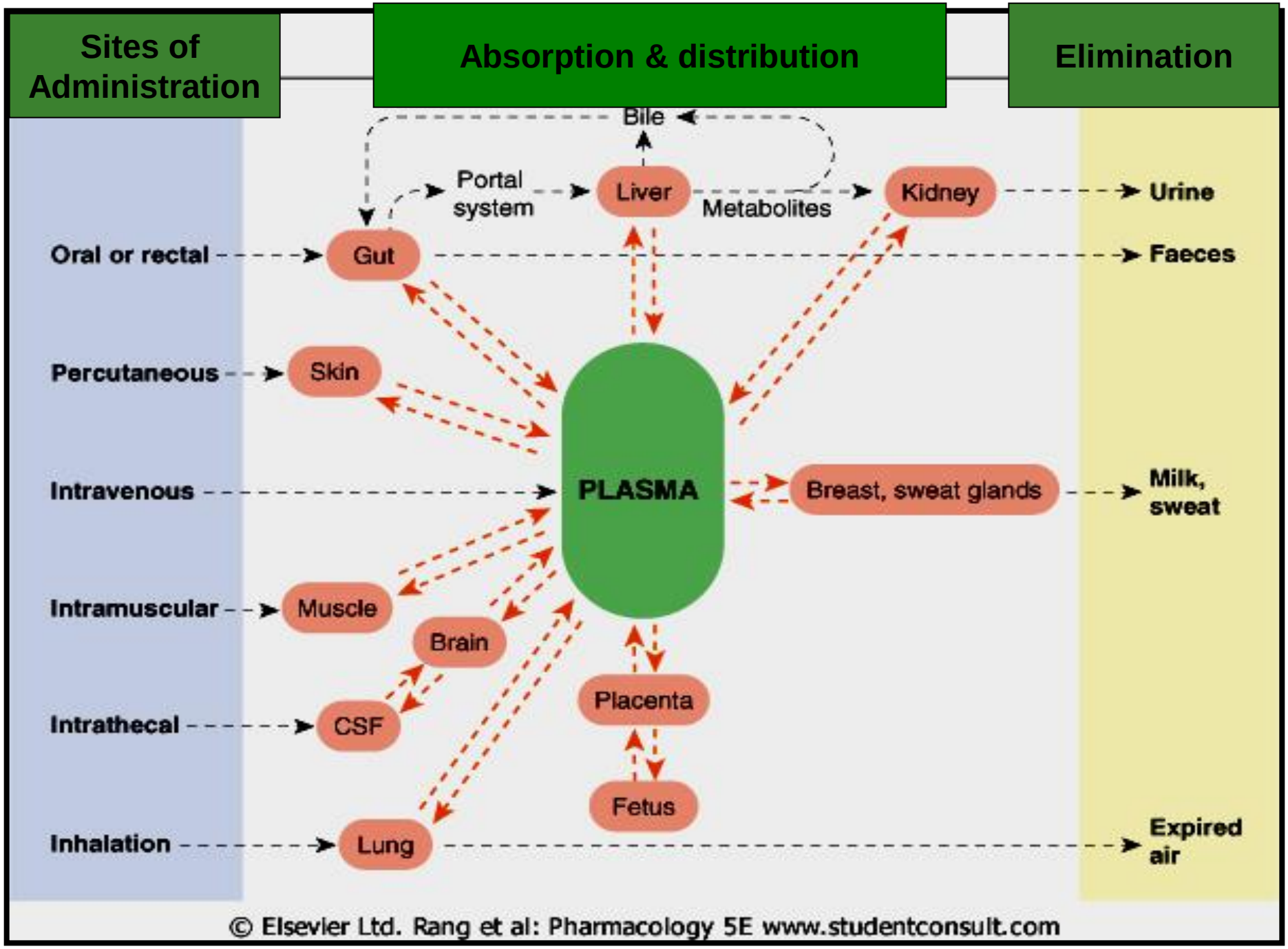
Drug absorption

Is the passage of drug from its site of administration to site of action across cell membranes.



Drug absorption

- Except for intravenous administration, all routes of drug administration require that the drug be absorbed from the site of administration into the systemic circulation (blood).
- **I.V. administration requires no absorption**


Sites of Administration
Absorption & distribution
Elimination
Bile
Portal system
Liver
Kidney
Urine
Metabolites
Oral or rectal
Gut
Faeces
Percutaneous
Skin
PLASMA
Intravenous
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Placenta
Intrathecal
CSF
Fetus
Inhalation
Lung
Expired air
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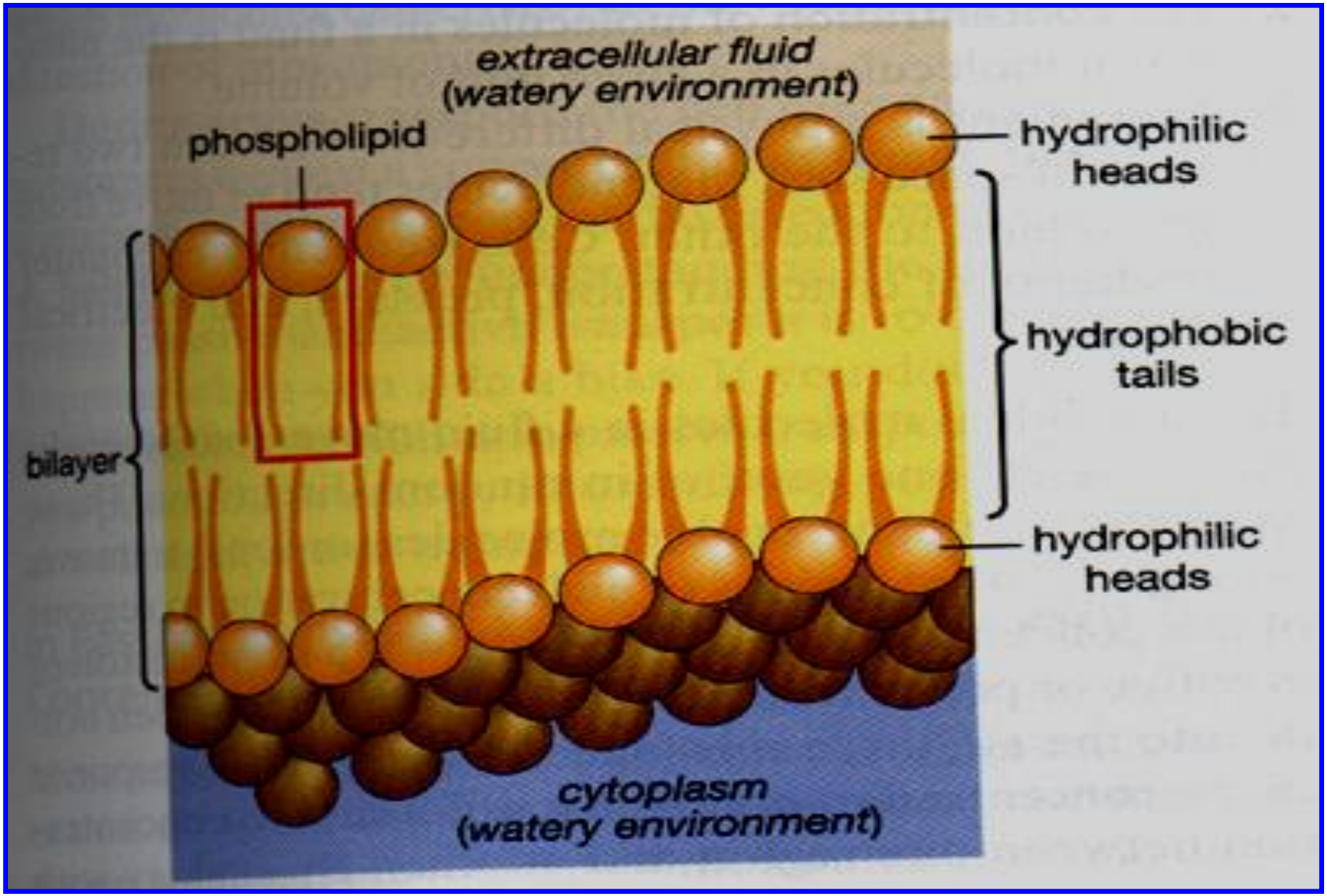
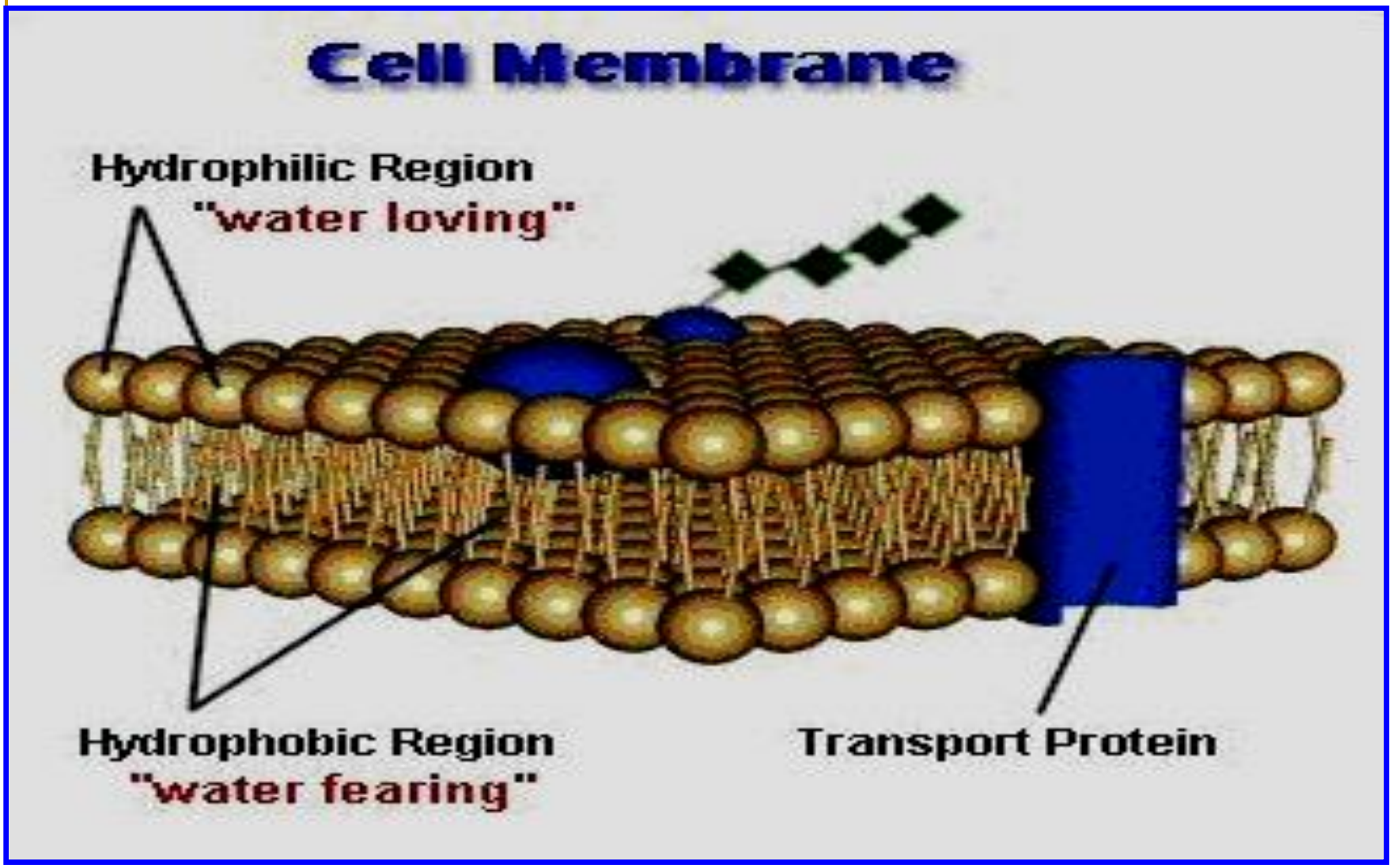
Mechanisms of drug absorption

- The transport of drugs across cell membrane occurs through one or more of the following processes:

1. **Simple diffusion = passive diffusion.**
2. **Active transport.**
3. **Facilitated diffusion.**
4. **Pinocytosis (Endocytosis).**

Cell membrane

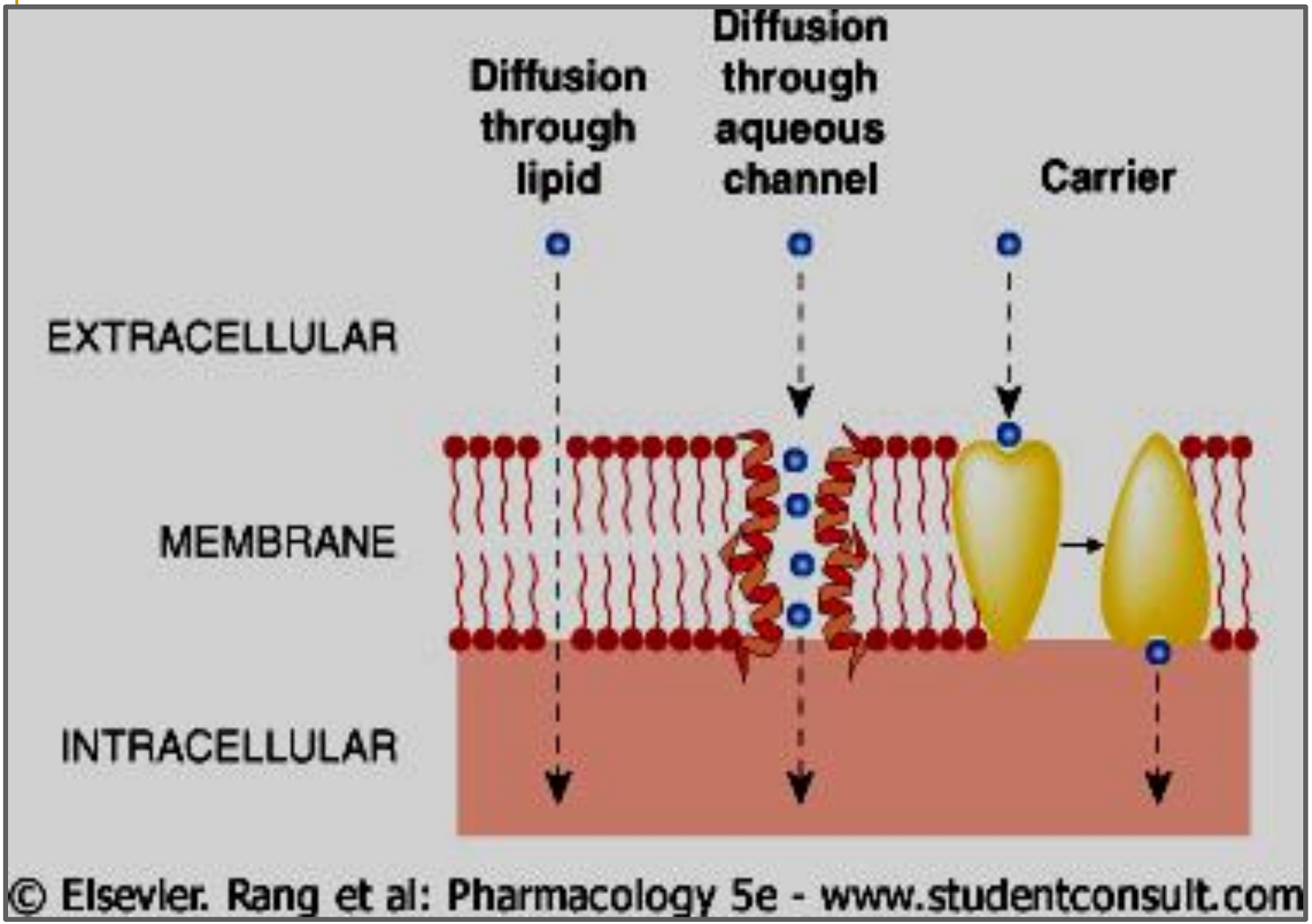


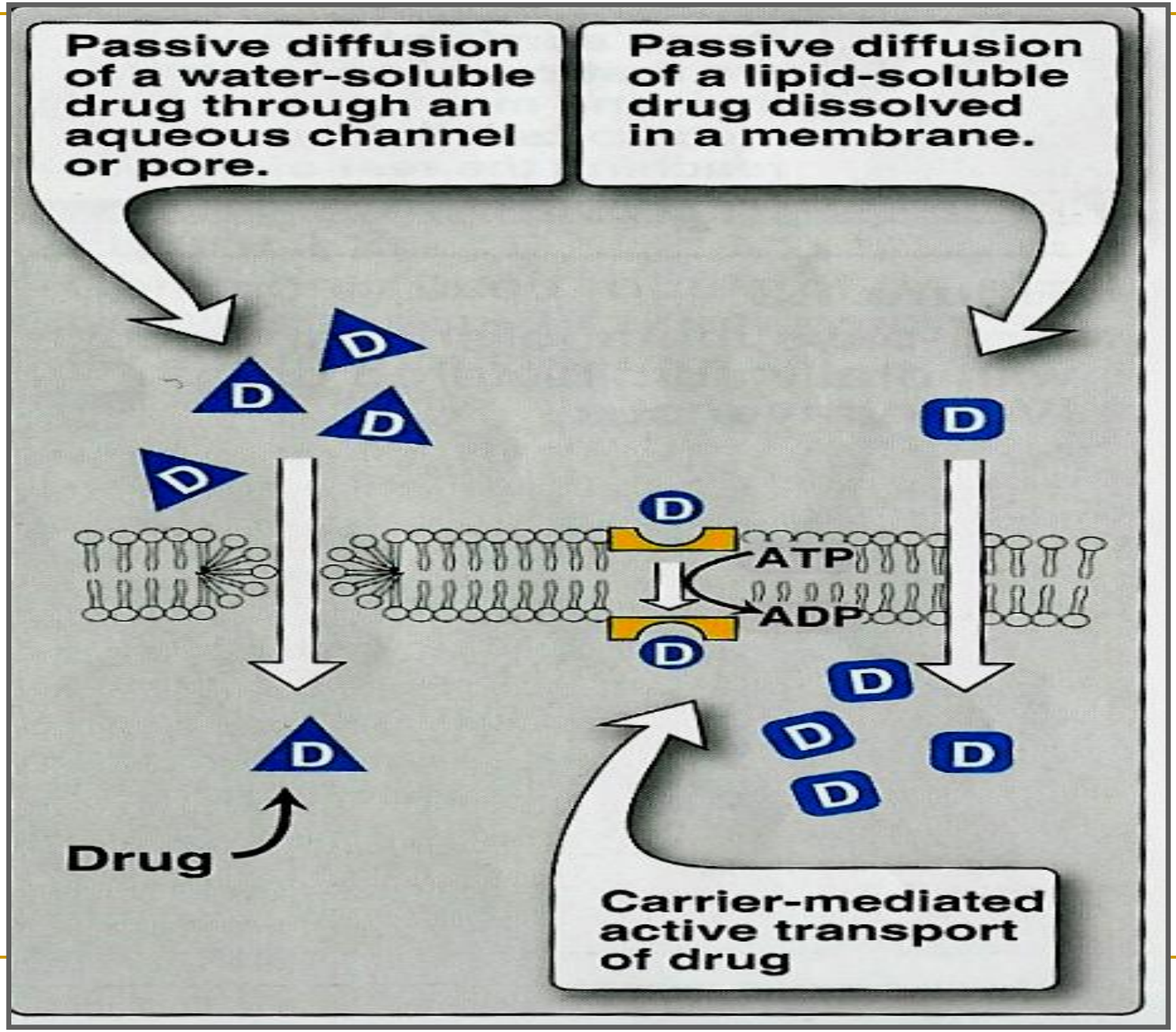

Cell Membrane
Hydrophilic Region
"water loving"
Hydrophobic Region
"water fearing"
Transport Protein

Types of passive diffusion

- **Aqueous diffusion:** low molecular weight and water soluble drugs can diffuse through aqueous channels or pores in cell membrane **(filtration).**
- **Lipid diffusion:** low molecular weight and lipid soluble drugs are absorbed via diffusion through lipid cell membrane itself.

Simple diffusion



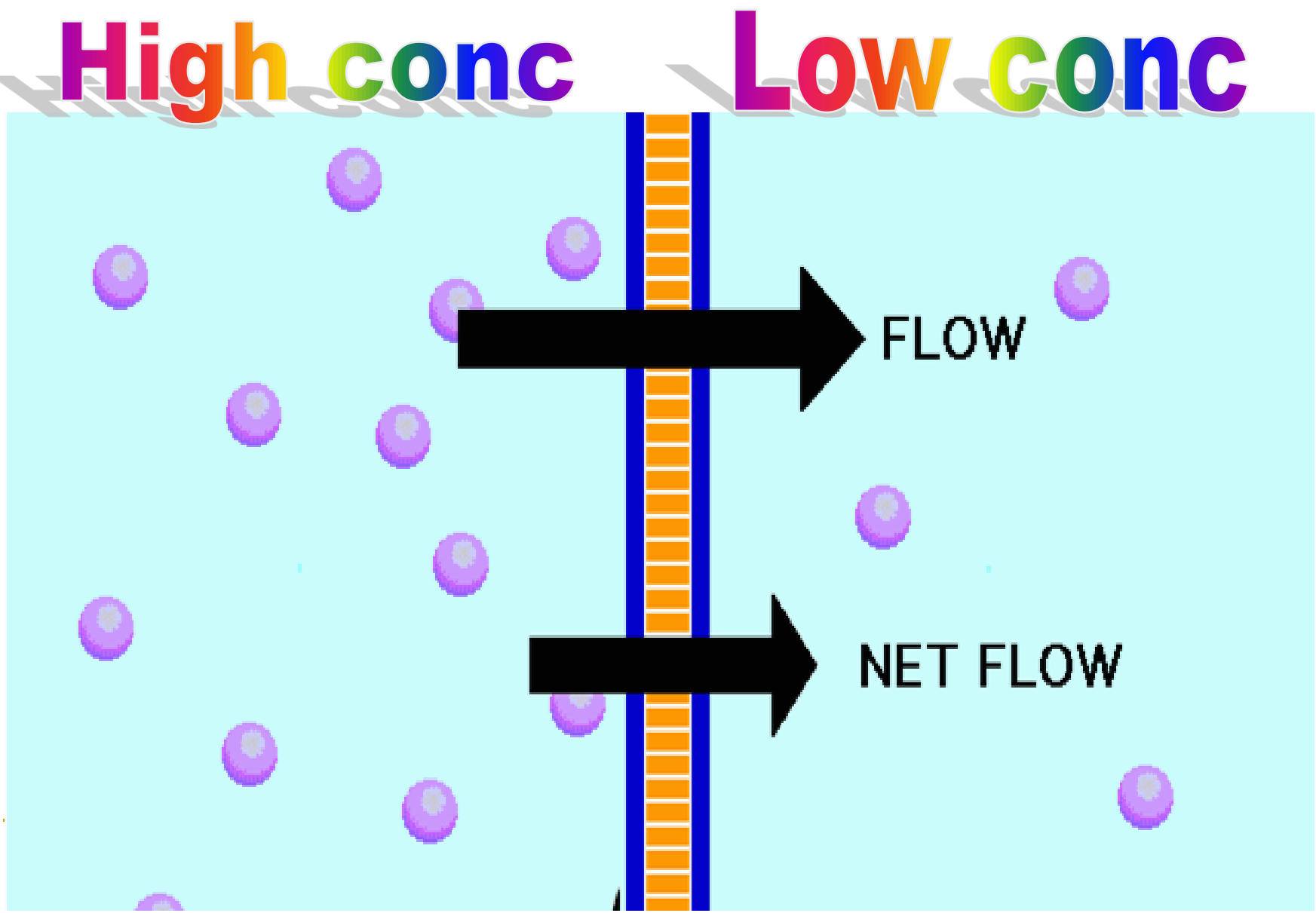

Passive diffusion of a water-soluble drug through an aqueous channel or pore.
Passive diffusion of a lipid-soluble drug dissolved in a membrane.
D
ATP
ADP
Drug
Carrier-mediated active transport of drug

Simple diffusion

Characters

- Common.
- Occurs with or along concentration gradient.
- No energy
- No carrier
- Non selective
- Not saturable
- depends on lipid solubility.
- depends on pka of drug - pH of the environment (it can be fluid of the cell body, blood, urine).

Simple diffusion



pH Effect

- **Most drugs are weak acids or weak bases.**
- **Drugs can exist in two forms ionized (water soluble) & unionized forms (lipid soluble) in equilibrium.**
- **Only unionized form is absorbable.**
- **Ionization of drugs reduce passage of drugs across cell membranes.**
- **The degree of ionization of drugs is determined by their pKa and pH of the surrounding.**

Remember

- **Water soluble drugs = ionized = polar = charged are difficult to permeate cell membranes.**

- **Lipid soluble drugs = unionized = non polar = uncharged are easy to permeate cell membranes**

pH Effect

Affects degree of ionization of drugs.

- **Weak acidic drugs** → best absorbed in stomach (in acidic medium of stomach, drug exists in unionized form that is lipid soluble and easily absorbed).

- **Weak basic drugs →** best absorbed in intestine**.**

(in basic medium of intestine, drug exists in unionized form that is lipid soluble and easily absorbed).

PKa of the drug

(Dissociation or ionization constant): pH at which half of the substance is ionized & half is unionized.

- The lower the pKa value (pKa < 6) of the acidic drug, the stronger the acid e.g aspirin (Pka= 3.0).

- The higher the pKa value (pKa >8) of a basic drug, the stronger the base e.g propranolol (pKa= 9.4)

Which one of the following drugs will be best absorbed in stomach (pH=1-2)?

Aspirin pka=3.0

Propranolol pka= 9.4

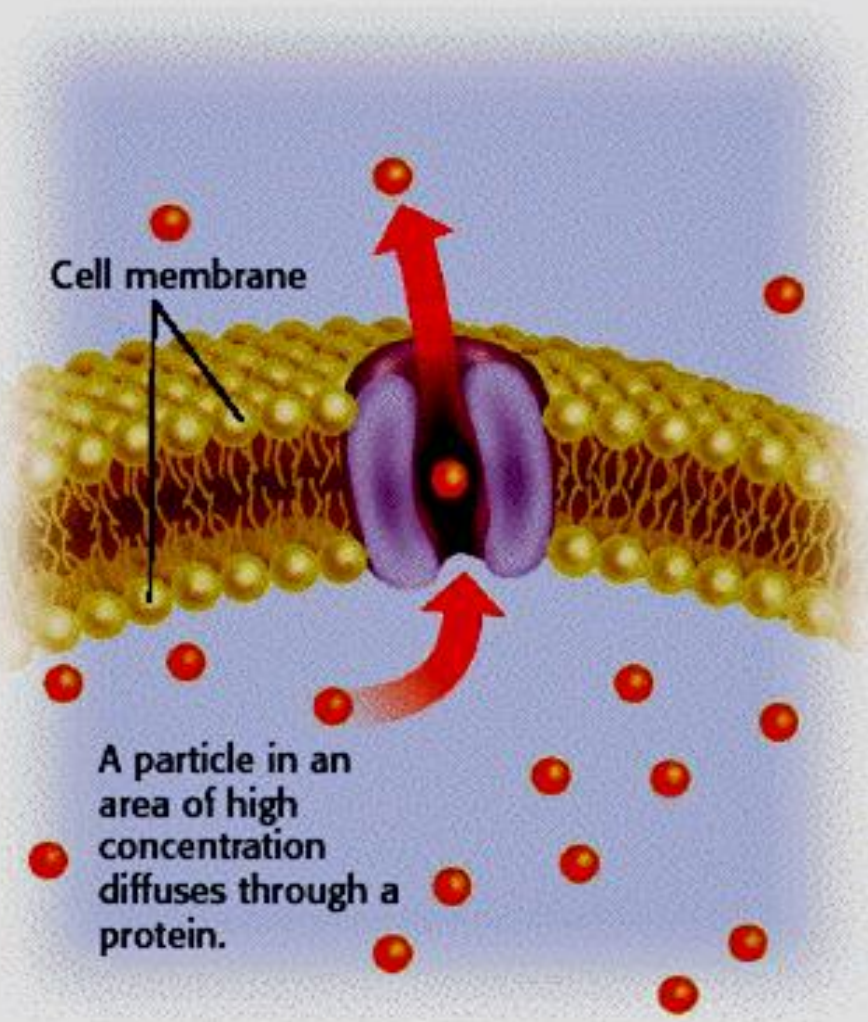
Active Transport

- relatively uncommon.
- occurs against concentration gradient.
- requires carrier and energy.
- specific or selective
- saturable

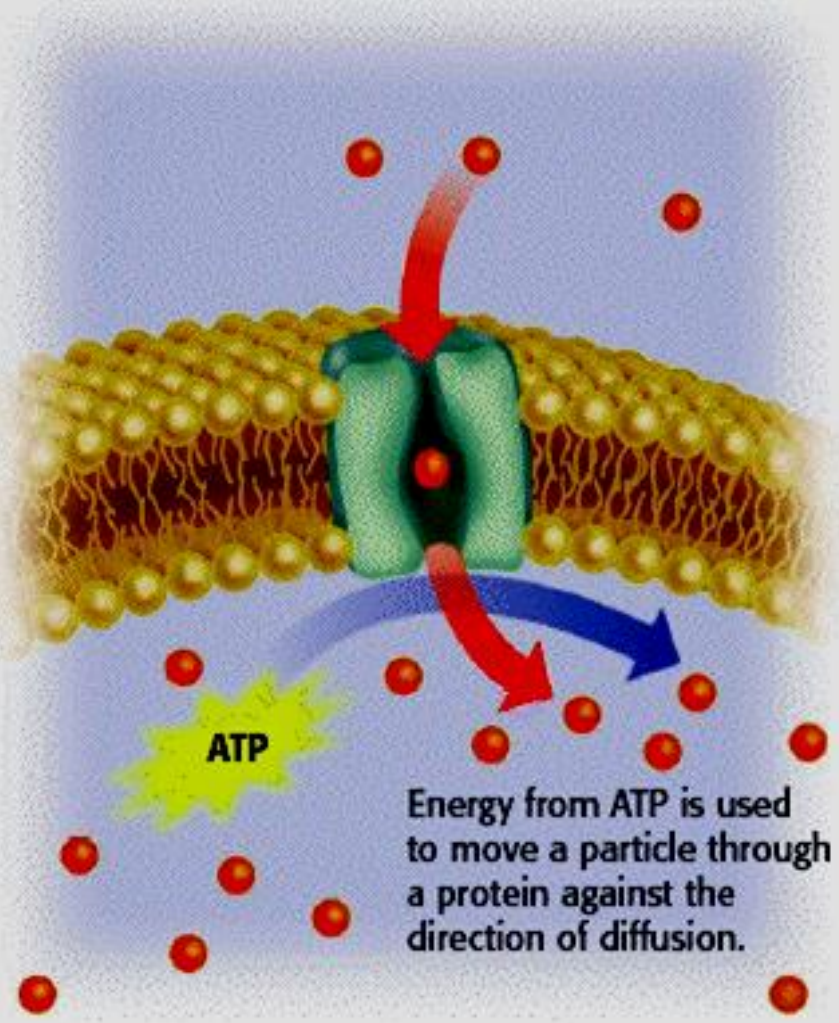
e.g.

- absorption of sugar, amino acids.
- uptake of levodopa by brain.
- Levodopa is used in treatment of parkinsonism

PASSIVE TRANSPORT



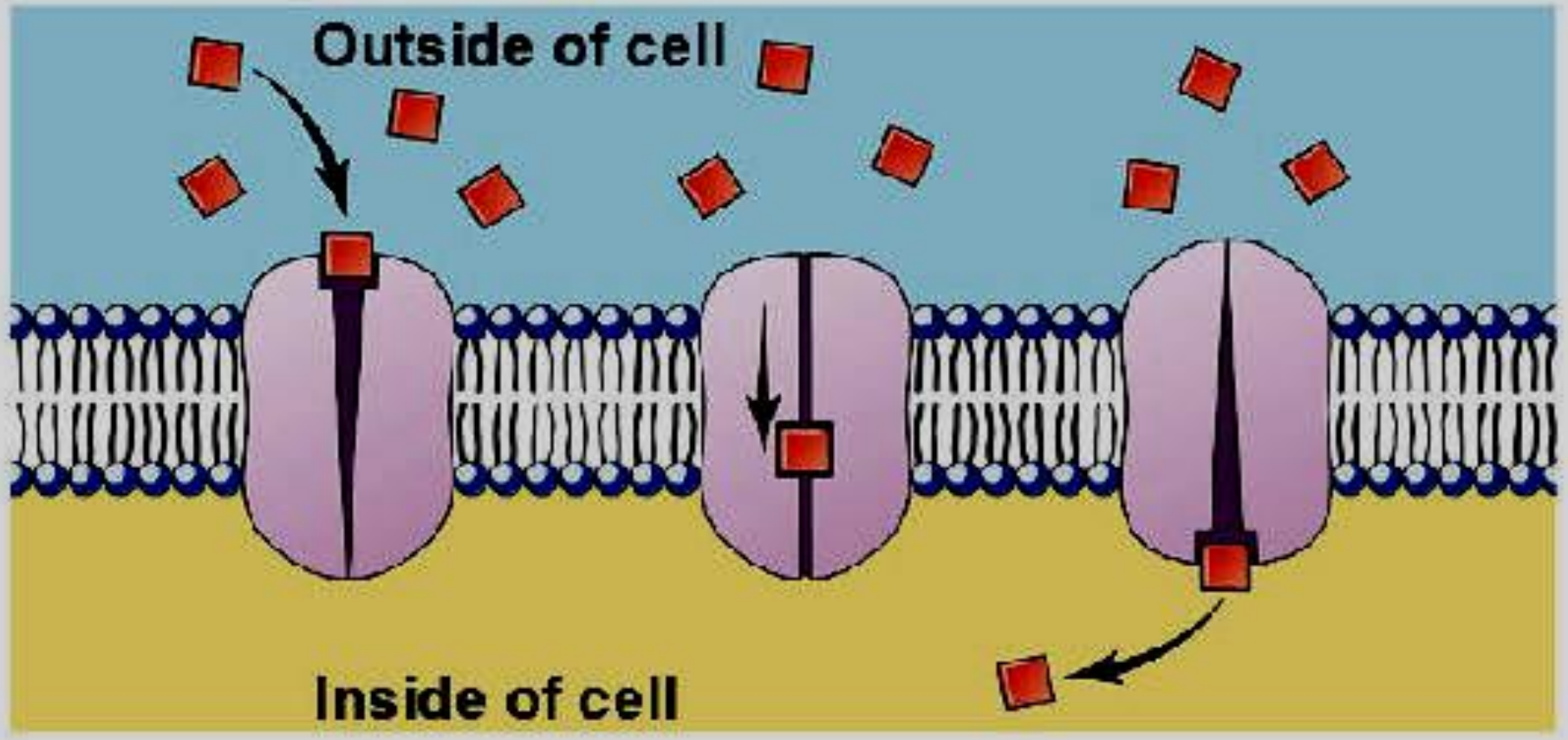
ACTIVE TRANSPORT



Carrier-mediated Facilitated Diffusion

- occurs along concentration gradient
- No energy is required
- requires carriers
- selective
- Saturable
- Similar to entry of glucose into muscle.

Facilitated Diffusion



Phagocytosis (Endocytosis & Exocytosis)

Endocytosis:

uptake of membrane-bound particles.

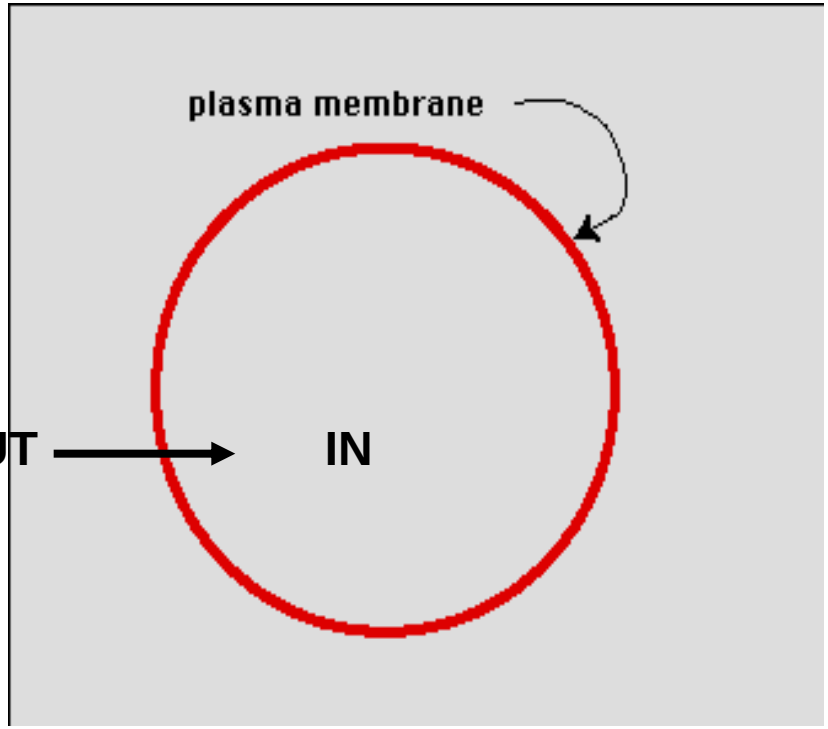
Exocytosis:

expulsion of membrane-bound particles

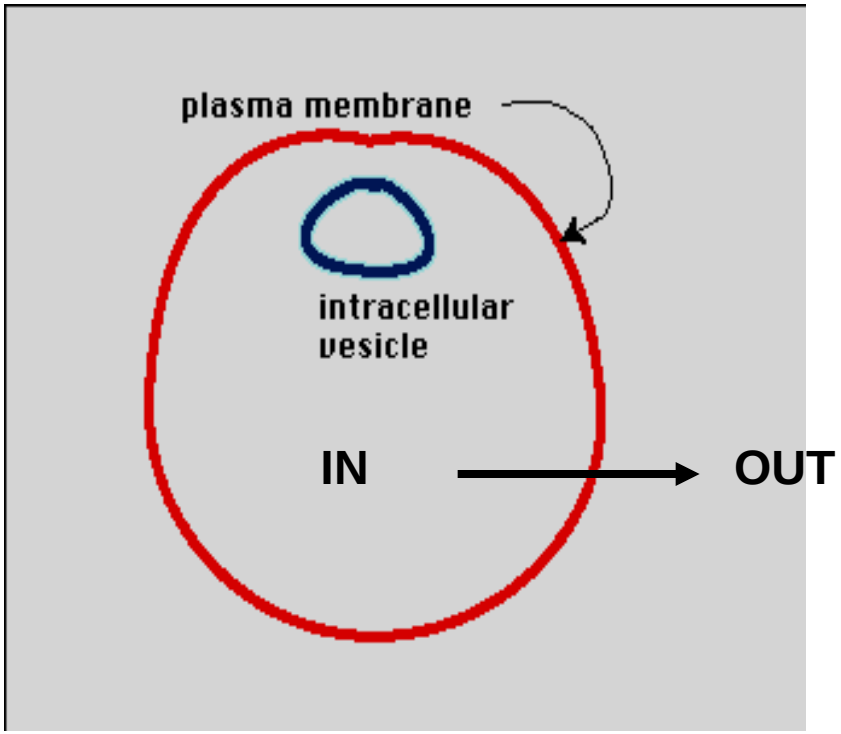
Endocytosis occurs

- for high molecular weight drugs
  - large molecules such as **peptides**
- high polar substances, such as vitamin B12 & iron
  - vitamin B12 combines with intrinsic factor.
  - iron combines with transferrin.

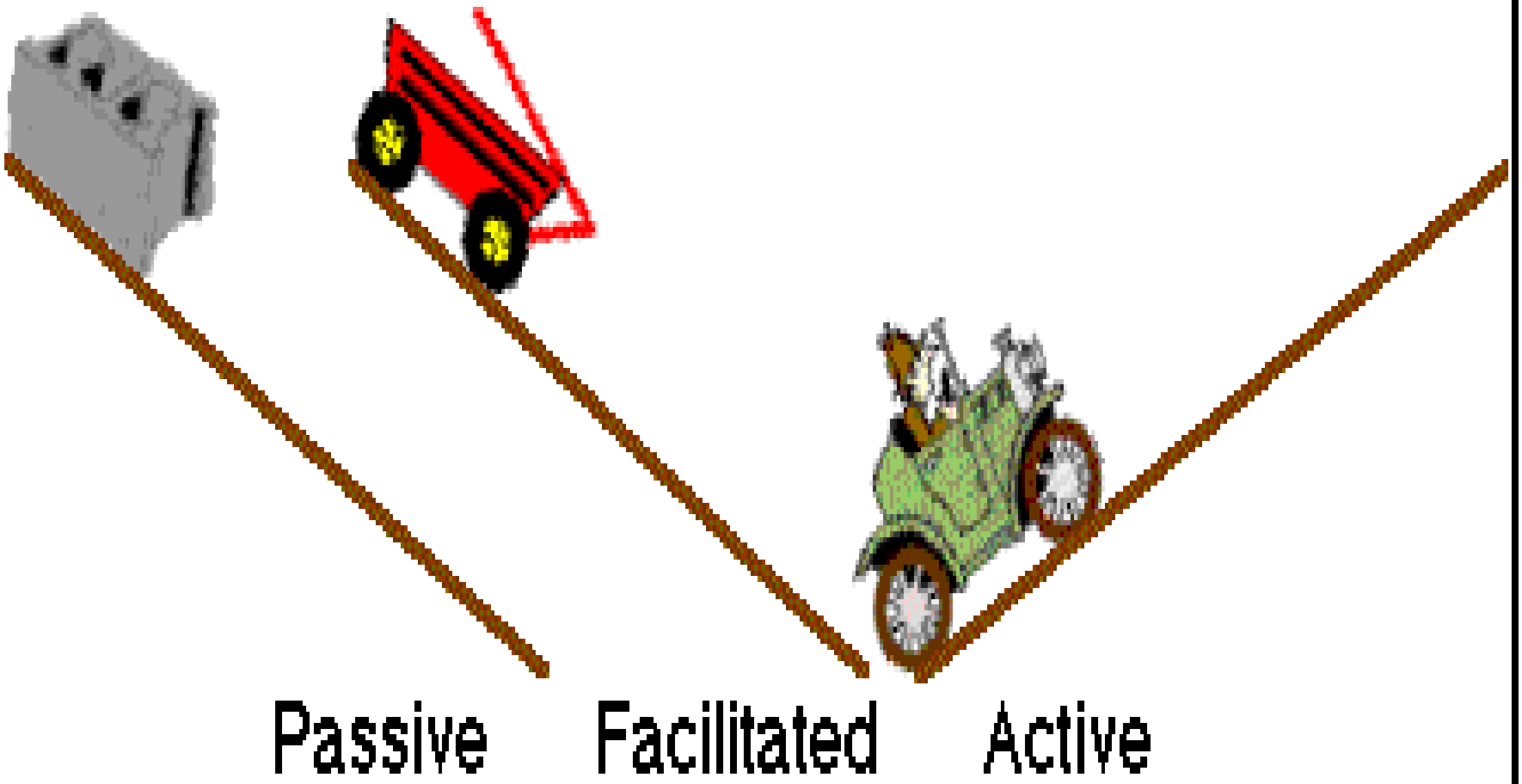
(Endocytosis)



(Exocytosis)



Mechanisms of drug absorption



Factors affecting absorption :

- Route of administration.
- Dosage forms (depending on particle size and disintegration, ease of dissolution).

  (solution > suspension > capsule > tablet)

- Molecular weight of drug.
- Lipid solubility
- Degree of ionization
- Drug solubility (aqueous preparation better than oily, suspension preparations)
- Chemical instability in gastric pH

(Penicillin & insulin)

Factors affecting absorption :

- **Surface area available for absorption.**
  - small intestine has large surface area than stomach due to intestinal microvilli.
- **Blood flow to absorptive site**
  - **greater** blood flow increases bioavailability
  - Intestine has greater blood flow than stomach
- **Intestinal motility (transit time)**
  - Diarrhea reduce absorption

- **Gastric emptying**
  - drugs that increase gastric emptying enhances absorption (metoclopramide).
- **Drug interactions**
- **Food**
  - **slow** gastric emptying
  - generally slow absorption
  - Tetracycline, aspirin, penicillin V
  - **A fatty meal** increase the absorption of fat soluble antifungal drug (e.g. griseofulvin)

Summary

- **Different routes of administration are available**
- **Parenteral administration is the suitable route to provide rapid effect.**
- **I.V. is used in emergency and provide high availability**
- **Oral administration is best avoided during emergency or when severe first pass metabolism may occur**
- **Drugs may cross any cell membrane by simple diffusion, active transport, facilitated diffusion, and pinocytosis.**

Active transport	Carrier-mediated facilitated diffusion
Against concentration gradient (From low to high)	along concentration gradient (From high to low)
Needs carriers	Needs carriers
saturable	Saturable
Selective	Selective
Energy is required	No energy is required

Questions?