بسم الله وبه نستعين

كلية الطب البيطري – جامعة تكريت

ماجستير أدوية

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2024-2025 \ First Term 1

Advanced Pharmacology

INTRODUCTION

Basic Principles

PHARMACOKINETICS & PHARMACODYNAMICS

BASIC & APPLICATIONS

What is pharmacology

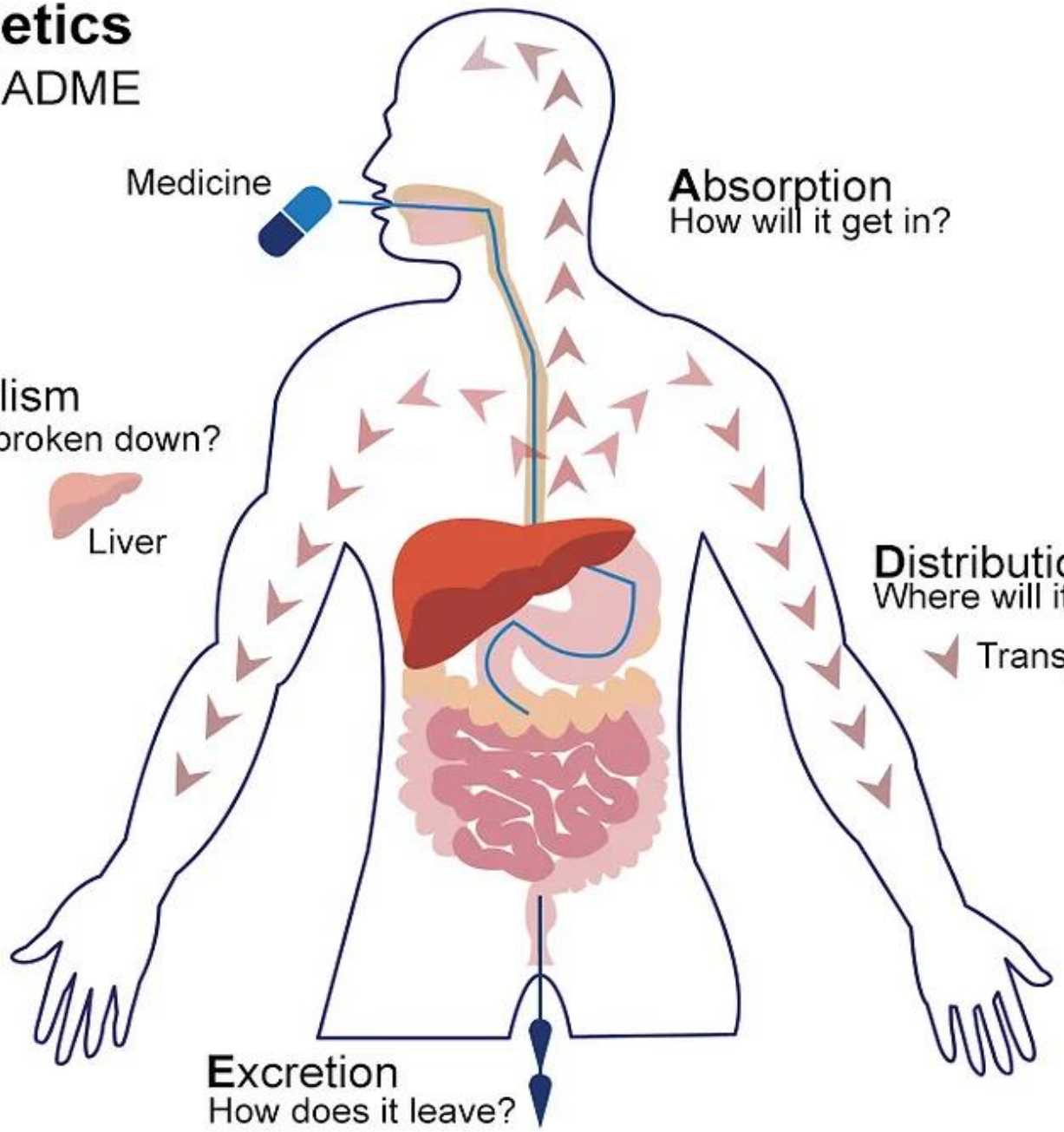
- **Pharmacology**: the study of substances (drugs) that interact with living systems through chemical processes. It is the science that deals with the mechanism of action, uses, adverse effects of drugs.
- **A drug**: a chemical substance of known structure, other than a nutrient, when administered to a living organism, produces a biological effect. It can be natural, synthetic, or genetic engineering product.

- **Toxicology:** study of harmful effects of drugs
- The interaction between drugs & the body can be divided into:

1. **Pharmacodynamics**: is the action of the drug on the body. It includes drug-receptor interaction, mechanism of action & dose response phenomena.
2. **Pharmacokinetics**: The action of the body on the drug. It includes Absorption, Distribution, Metabolism & Excretion (ADME)

Pharmacokinetics

The principles of ADME



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European Patients' Academy
on Therapeutic Innovation
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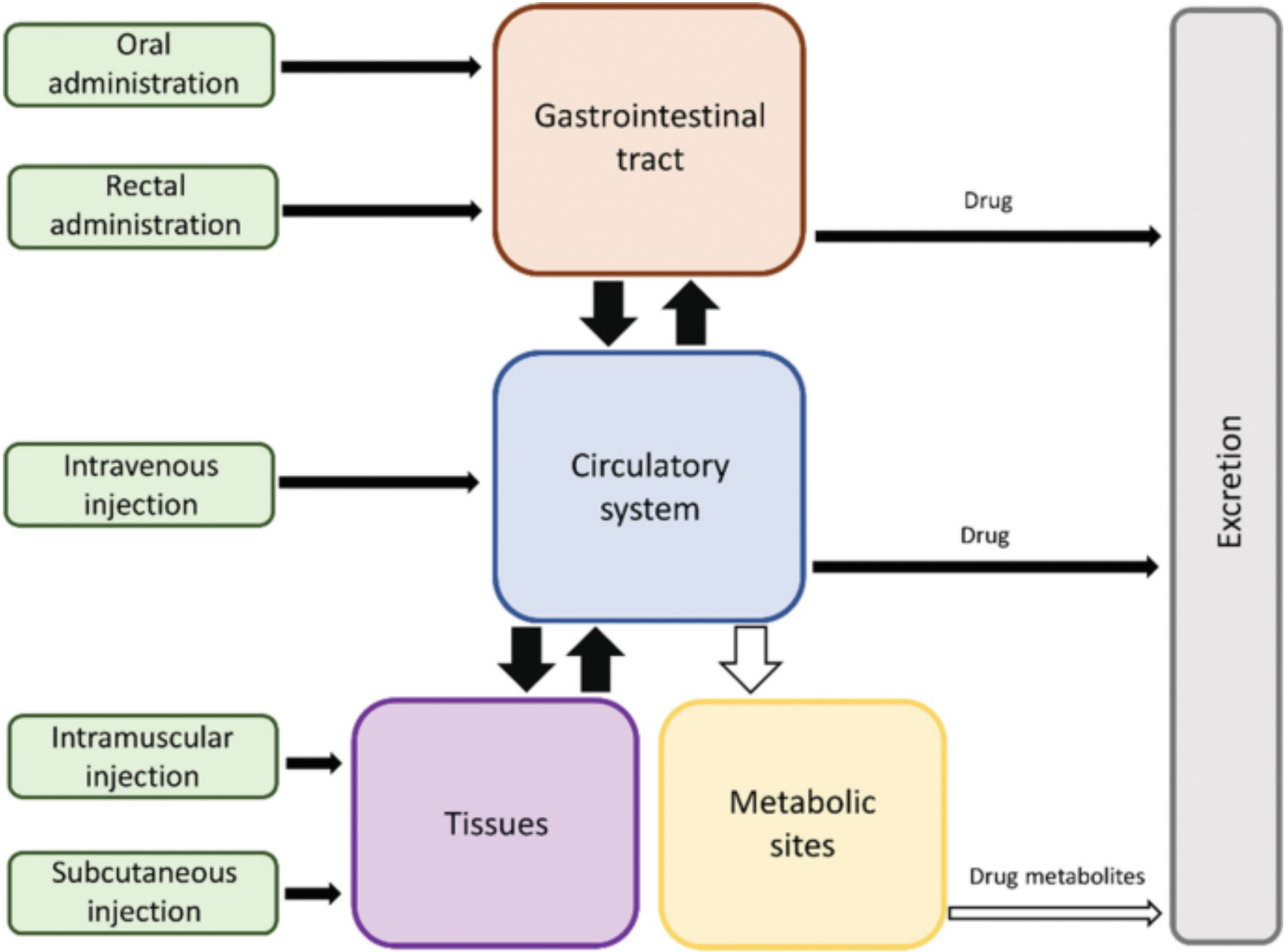
PHARMACOKINETICS

Absorption

- It is a passage of the drug from its site of administration to the plasma or systemic circulation.
- **Routes of drug administration:**

- Enteral routes (oral, sublingual, & rectal)
- Parenteral routes by injection.
- Inhalation
- Topical application


Oral administration
Rectal administration
Gastrointestinal tract
Drug
Excretion
Intravenous injection
Circulatory system
Drug
Intramuscular injection
Subcutaneous injection
Tissues
Metabolic sites
Drug metabolites

1. ***<u>Oral route (P.O.):</u>***

- **Advantages:**
- Safe, most convenient & economical.
- May provide local effect in the gut (vancomycin)
- **Disadvantages:**
- Can not be used in emergency and for patient with vomiting and diarrhea.
- Requires patient co-operation.
- May cause GIT mucosal irritation.
- Poorly soluble, gastric pH unstable drugs and drugs interact with food components → incomplete absorption.

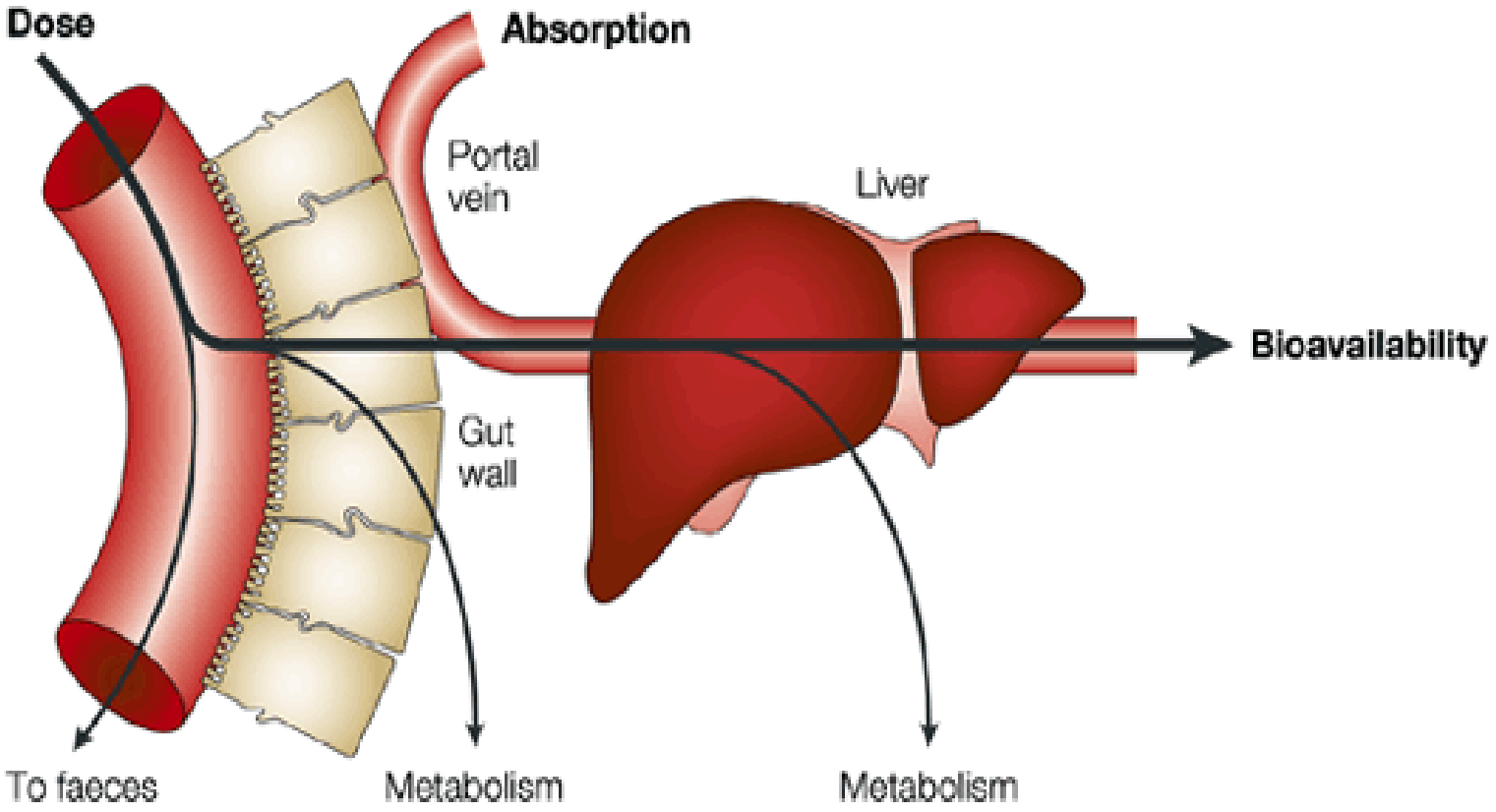
- May be subjected to **first pass metabolism**:

  The drug may be subjected to extensive metabolism in the GIT or the liver during their first passage through the liver before reaching the systemic circulation (↓amount reaches the systemic circulation) e.g glyceryl trinitrate, propranolol, levodopa & aspirin

2. ***Sublingual*** *(under the tongue)* ***& buccal*** *(inside the cheek) route:*

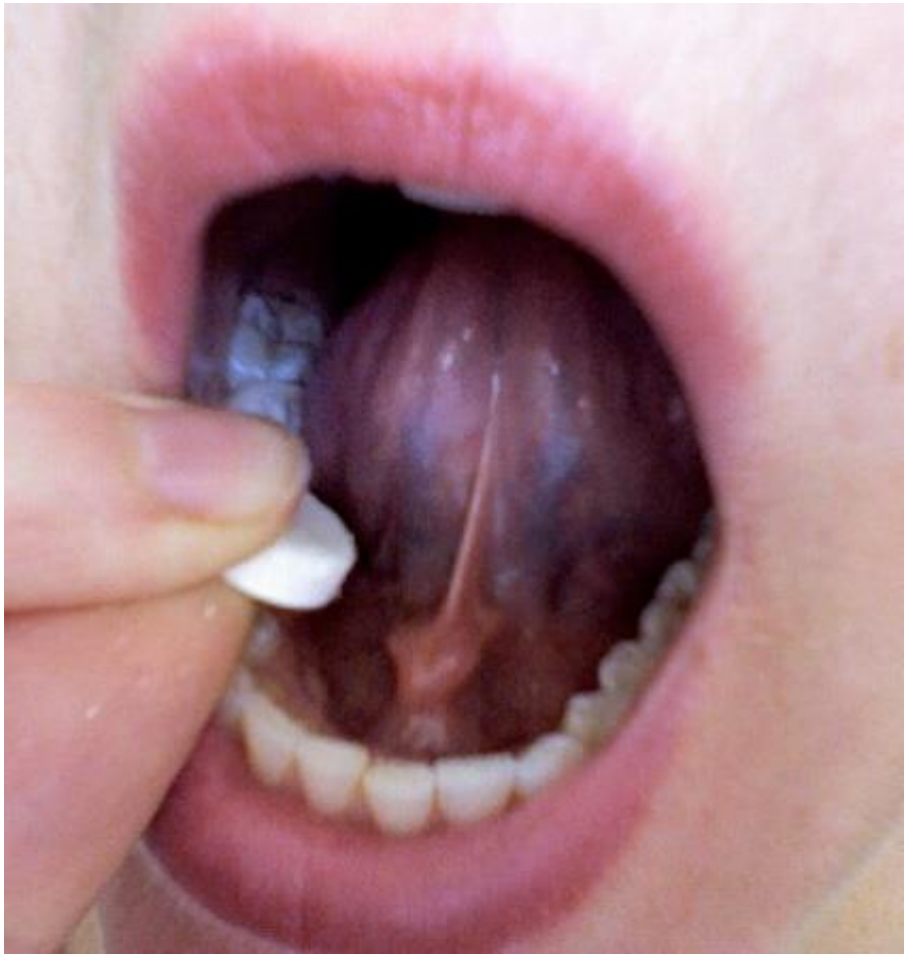
- **Advantages:**
- Produces quick response
- Escape first pass metabolism & GIT hydrolysis e.g. nitoglycerin
- **Disadvantages:**
- Not suitable for comatose patient

First pass effect (metabolism)



Nature Reviews | Drug Discovery

Inconvenient, stimulate salivation (promote swallowing) and may cause mucus membrane irritation



3. ***Rectal route:***

- Suppositories or enema
- Produces systemic or local effect e.g paracetamol, artesunate & corticosteriod.

Advantages:

- Escape 1st pass metabolism (local effect)
- Fast absorption due to large vascularity of the rectum.
- Useful for patient with vomiting & comatose patient.
- Useful for drugs that are irritant to the GIT mucosa (indomethacin).

- **Disadvantages:**
- Not suitable for patient with diarrhea
- Inconvenient & may cause irritation to rectal mucosa (highly irritating drugs are contraindicated)
- Irregular & incomplete absorption.

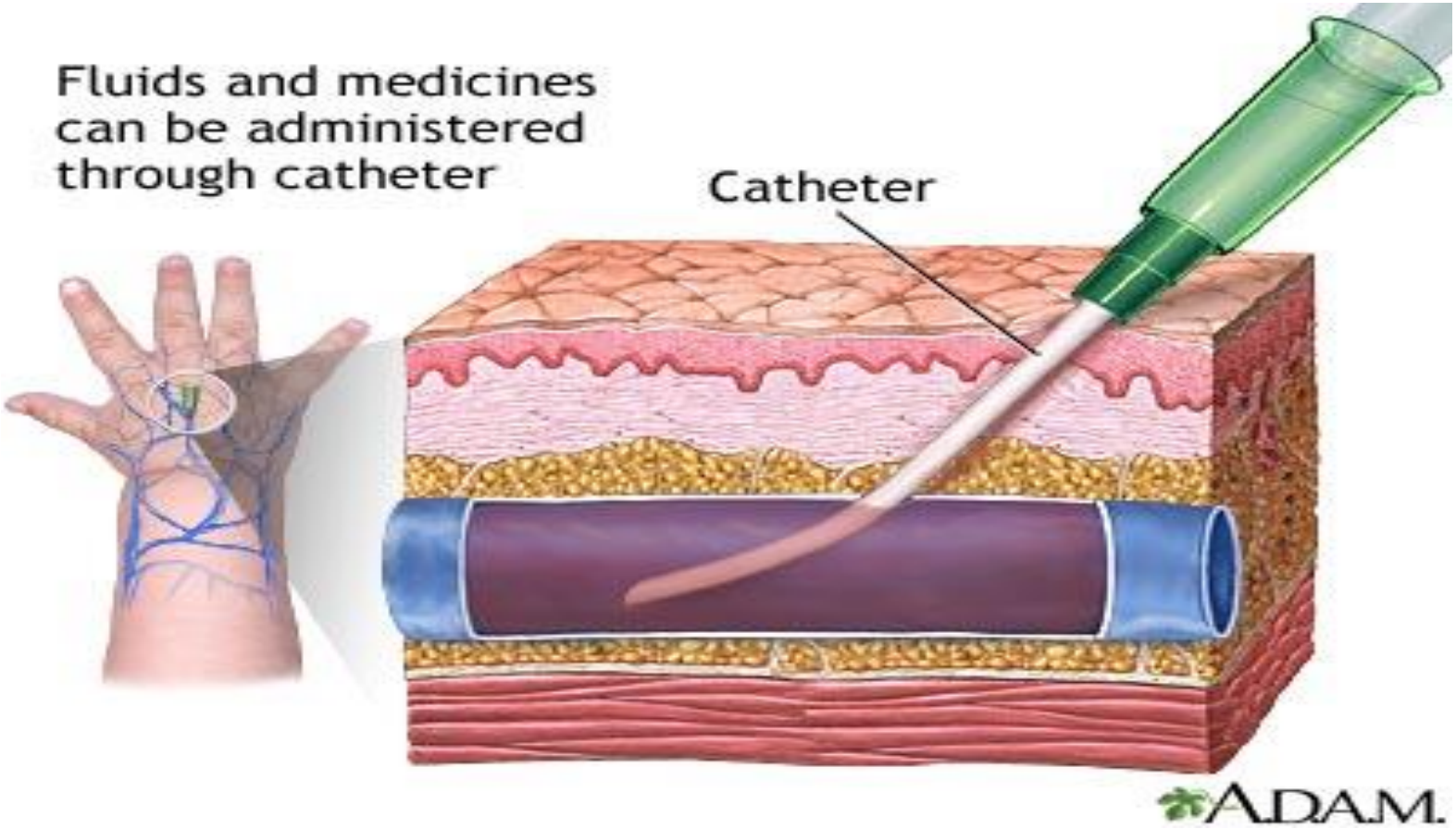
4. ***Parenteral routes by injection:***

a. Intravenous route (I.V):

Advantages:

- 100% bioavailable & escape 1st pass metabolism
- Useful in emergency, in comatose patient & patient with vomiting &/or diarrhea
- Suitable for large volumes & produces steady state concentration by continuous I.V. infusion.

- **Disadvantages:**
- Increases the risk of adverse effects (↑concentrated drugs → cardiac & respiratory complications)
- Not suitable for oily solutions or insoluble substances.
- Causes pain, irritation, necrosis & thrombosis at the site of injection.
- No retreatment once the drug is injected.
- Risk of infection.
- Need skills and not economical.


Fluids and medicines
can be administered
through catheter
Catheter
A.D.A.M.

b. Intramuscular (I.M.):

Advantages:

- Faster than the oral route and escape 1st pass metabolism
- Suitable for moderate volumes and oily solutions.
- Useful in comatose & patient with vomiting &/or diarrhea
- Suitable for irritant drugs and depot preparations (benzathine penicillin)

- **Disadvantages:**
- Painful, may cause local inflammation or abscess

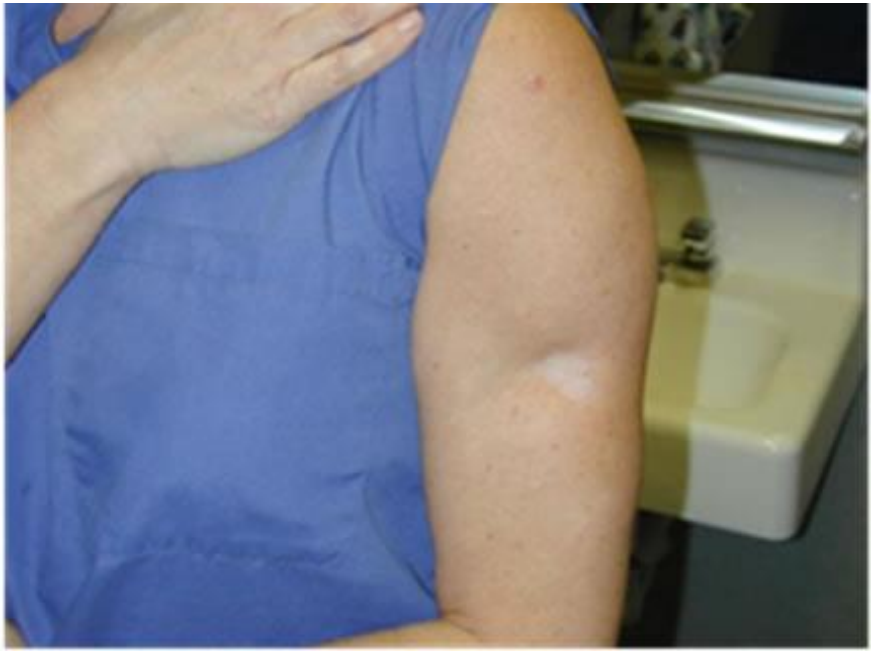
c. Subcutaneous (S.C) and local tissue infilteration:

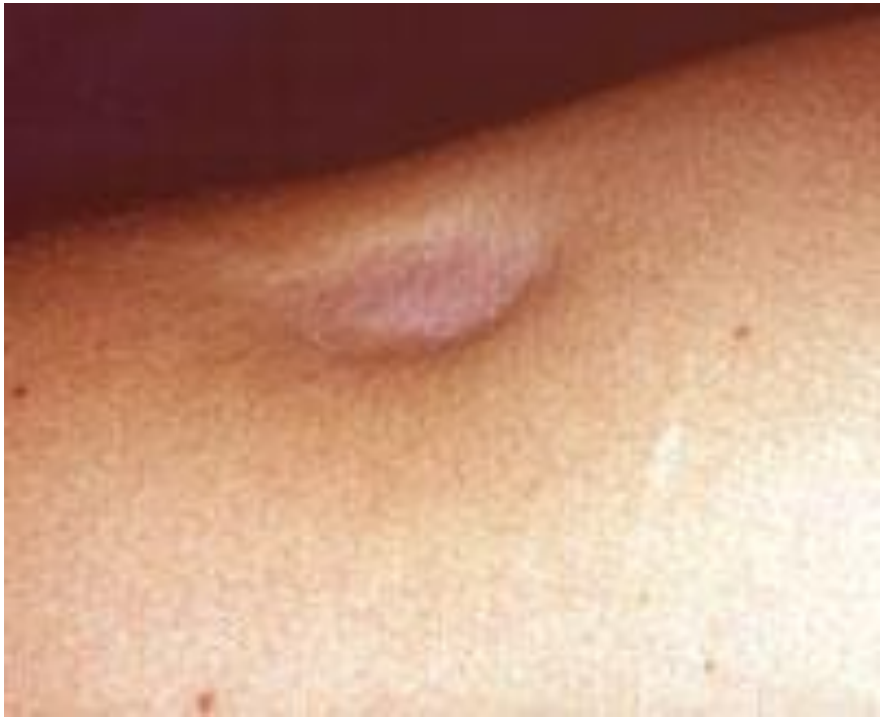
Advantages:

- Faster than the oral.
- Suitable for insoluble suspension (insulin) & implantation of solid pellets (estradiol contraceptive).
- Reliable and is acceptable for self-administration.

- **Disadvantages;**
- Not suitable for large volumes & irritant drugs
- May cause pain & necrosis at the site of injection.
- Repeated injections at one site can cause lipotrophy, resulting in irregular absorption (insulin).
- Drug absorption from the site of injection is increased by increasing local blood flow & rubbing.
- Drug absorption from the site of injection is reduced by:

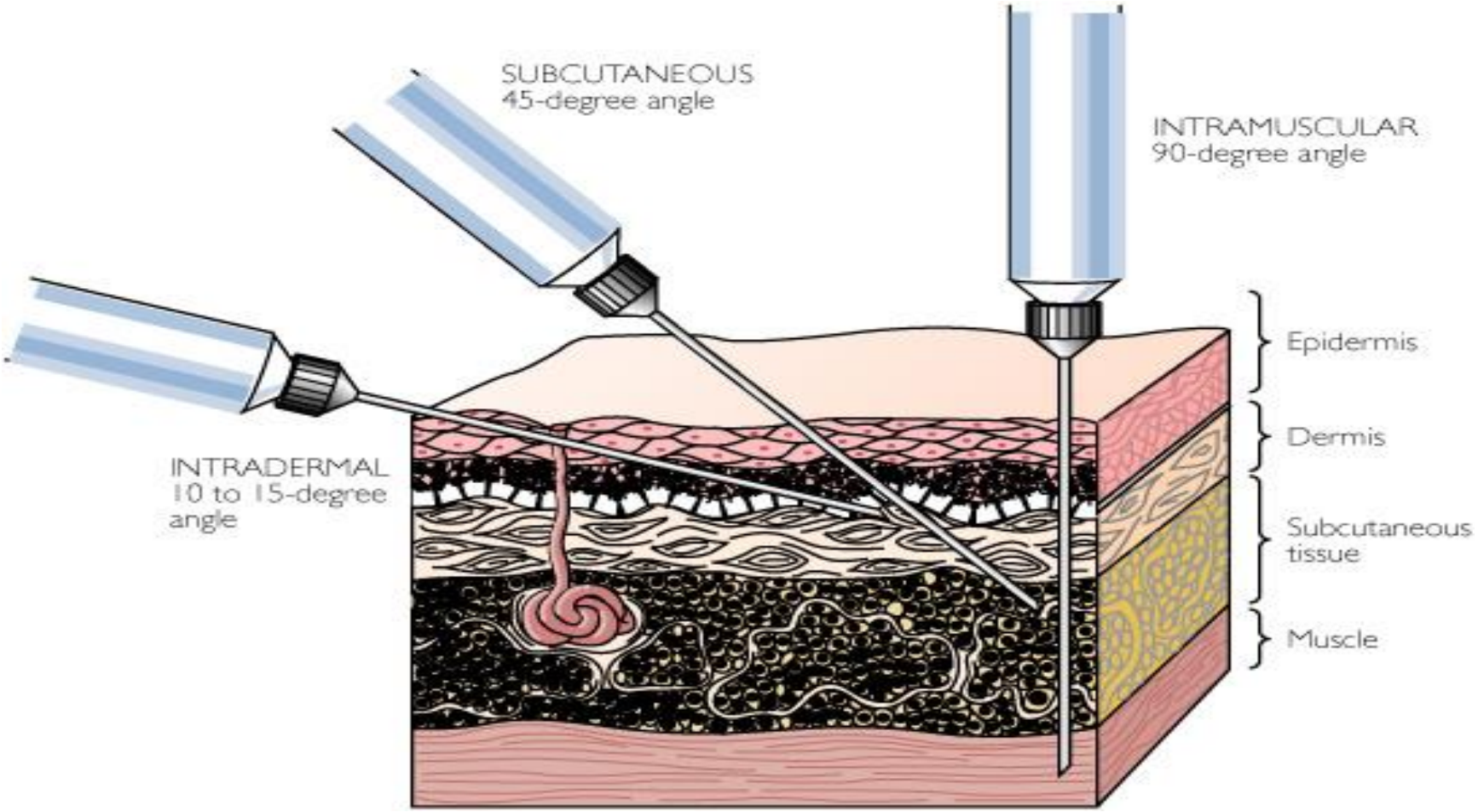
1. Decreasing local blood flow (addition of vasoconstrictors; adrenaline + local anesthetic).
2. Implantation of solid pellets.
3. The use of poorly soluble salts & oily solution. "slow-release" e.g. Procaine and benzathine penicillins, medroxy progesterone acetate.





d. Intradermal:

- Into the skin itself.
- Used for some allergen and also for mantoux test.


SUBCUTANEOUS
45-degree angle
INTRAMUSCULAR
90-degree angle
INTRADERMAL
10 to 15-degree
angle
Epidermis
Dermis
Subcutaneous
tissue
Muscle

e. Intrathecal:

(into the spinal canal) ,produces local & rapid effect on the meninges & cerebrospinal axis, most commonly used for spinal anesthesia (bupivacaine) and chemotherapy e.g methotrexate (leukemia), aminoglycoside (resistant CNS infection)

- Advantages:

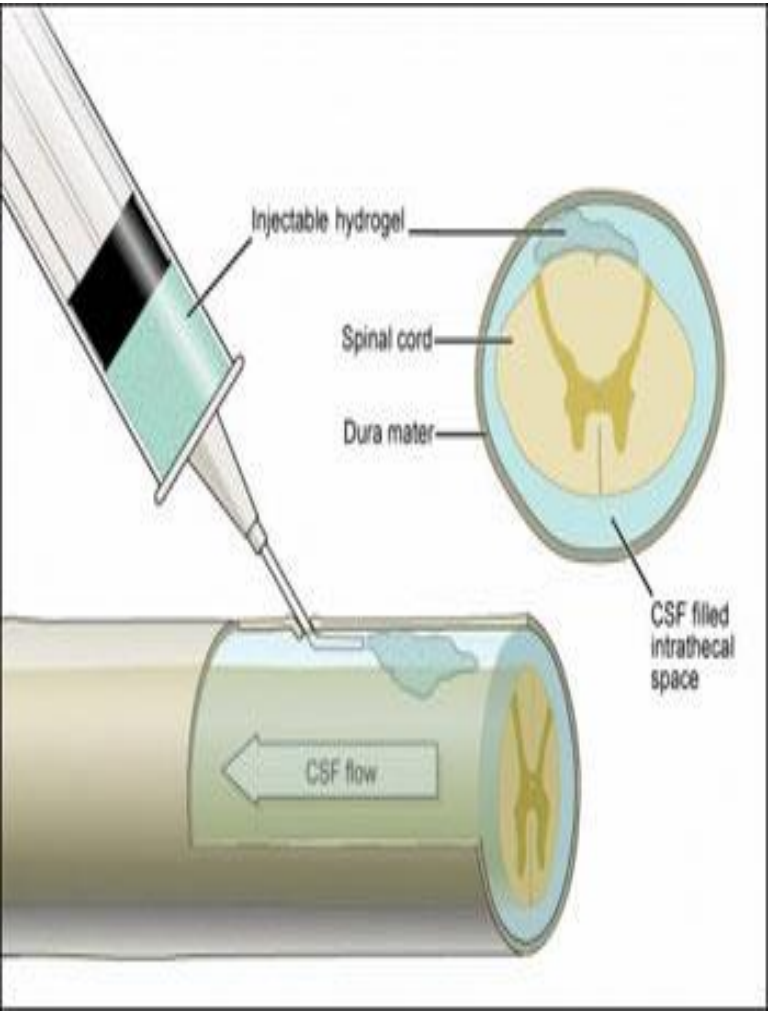
Rapid & localized effect.

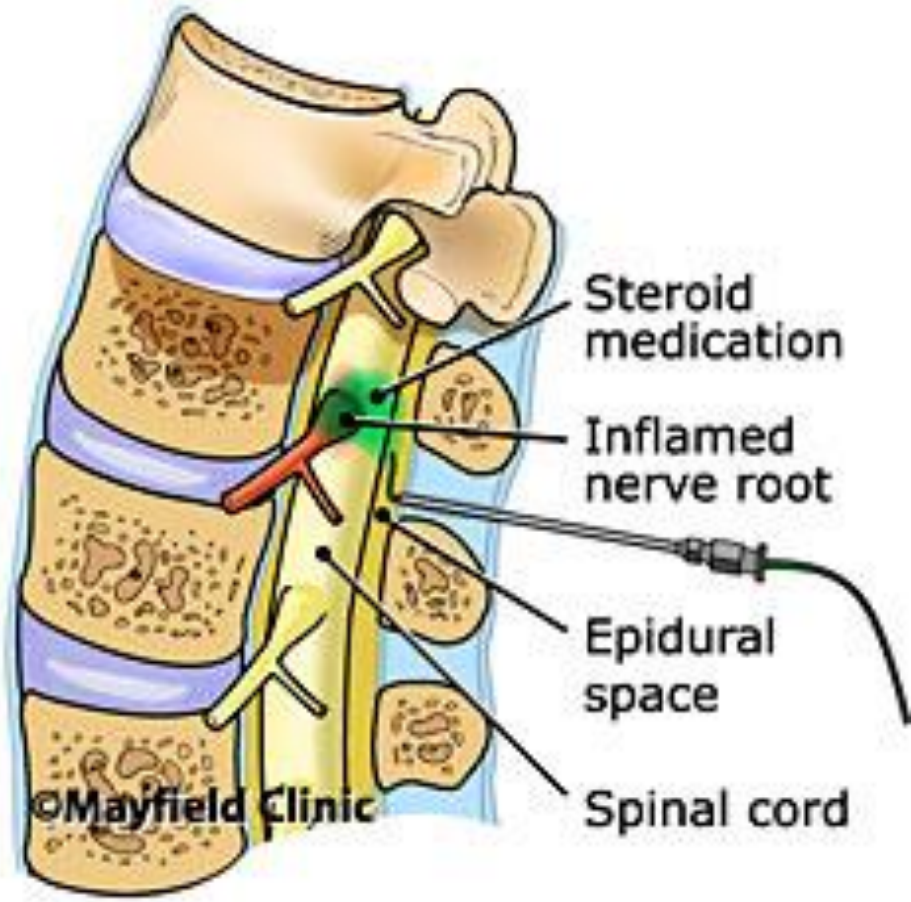
- Disadvantages:

- Needs high skills & carries some degree of risk.
- Not economical.

f. Intraperitoneal:

- into the peritoneum. Seldom to use clinically , but it is a common laboratory practice use to administer drugs to experimental animals. Advantages:
- Rapid absorption due to large surface area
- Disadvantages:
- High risk of infection, painful & may cause necrosis


Injectable hydrogel
Spinal cord
Dura mater
CSF filled intrathecal space
CSF flow


Steroid medication
Inflamed nerve root
Epidural space
Spinal cord
©Mayfield Clinic

g. Intra-arterial:

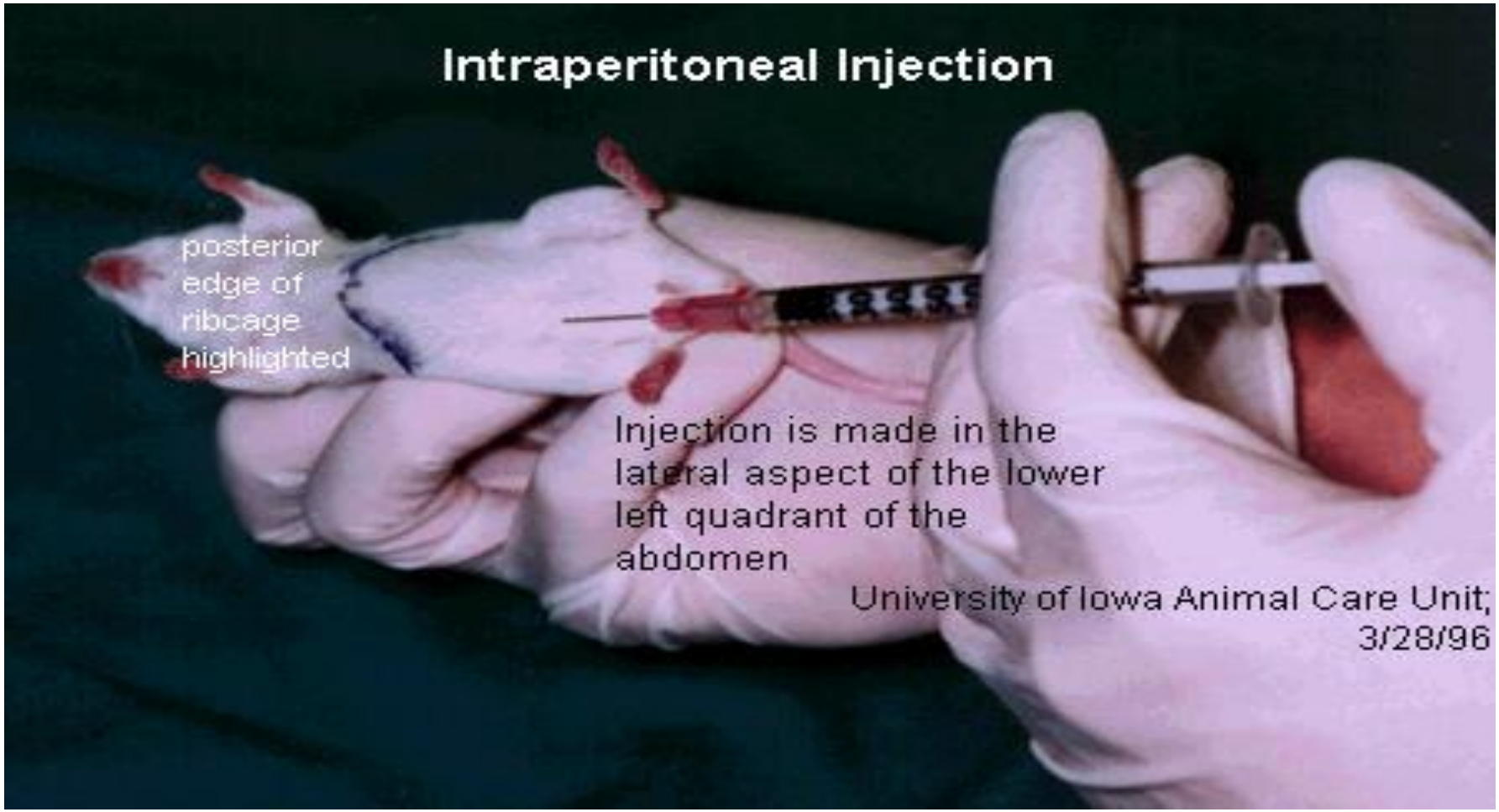
(into an artery), e.g. vasodilator drugs in the treatment of vasospasm.

- If needles are shared, there is risk of HIV and other infectious diseases

5. Inhalation:

Suitable for gases or volatile compounds (halothane), aerosol & nebulized solution (beclomethasone & salbutamol), powder (Na^+cromoglycate).

- Advantages:
- Rapid absorption due to large surface area Local application of the drug at the desired site of action (↓side effects)
- Avoid 1st pass metabolism.
- Disadvantages:
- Can cause side effects due to systemic absorption.
- May cause pulmonary irritation
- Poor ability to regulate the dose (inhaler).


Intraperitoneal Injection
posterior edge of ribcage highlighted
Injection is made in the lateral aspect of the lower left quadrant of the abdomen
University of Iowa Animal Care Unit; 3/28/96

6. ***Topical application:***

a. Cutaneous application:

- For local effect (low lipid soluble drugs in the form of creams & ointments) e.g. betamethasone. For sustained systemic effect (lipid soluble drugs in the form of transdermal patches)

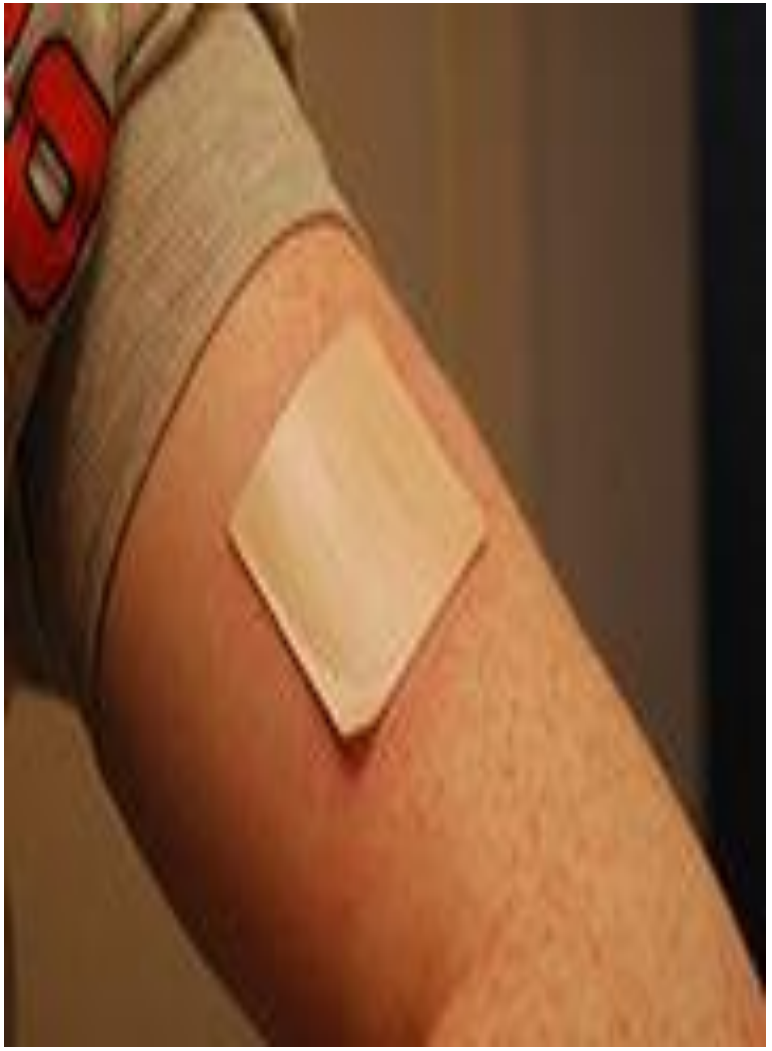
e. g. fentanyl skin patches, nicotine patches & estrogen skin patches

b. Application to the nasal mucosa e.g. Nasal decongestant → local effect. ADH (escape 1st pass effect & avoid destruction by gastric juice →systemic effect.

c. Application to the vaginal mucosa (pessaries).

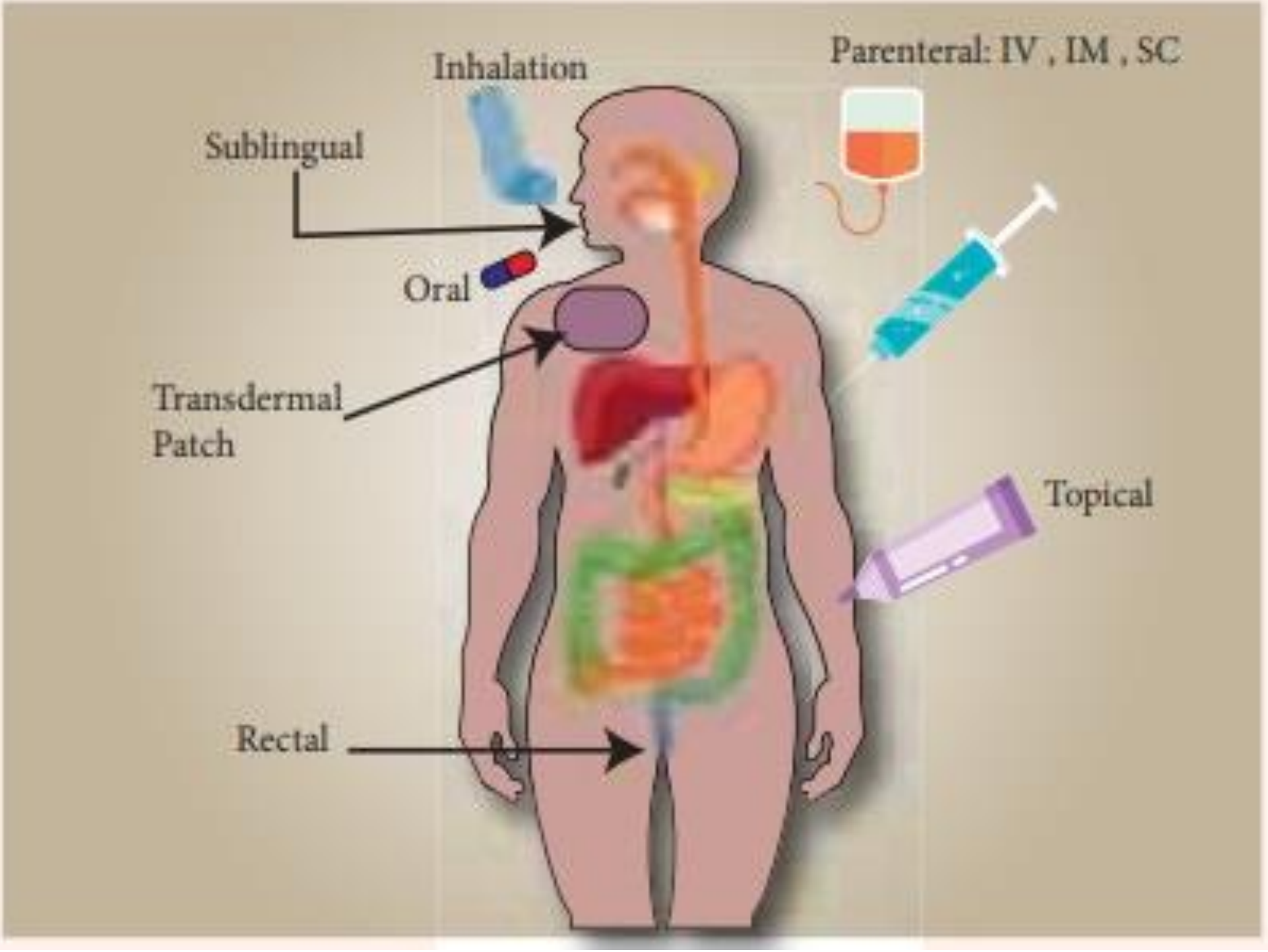
d. Application to the eye:

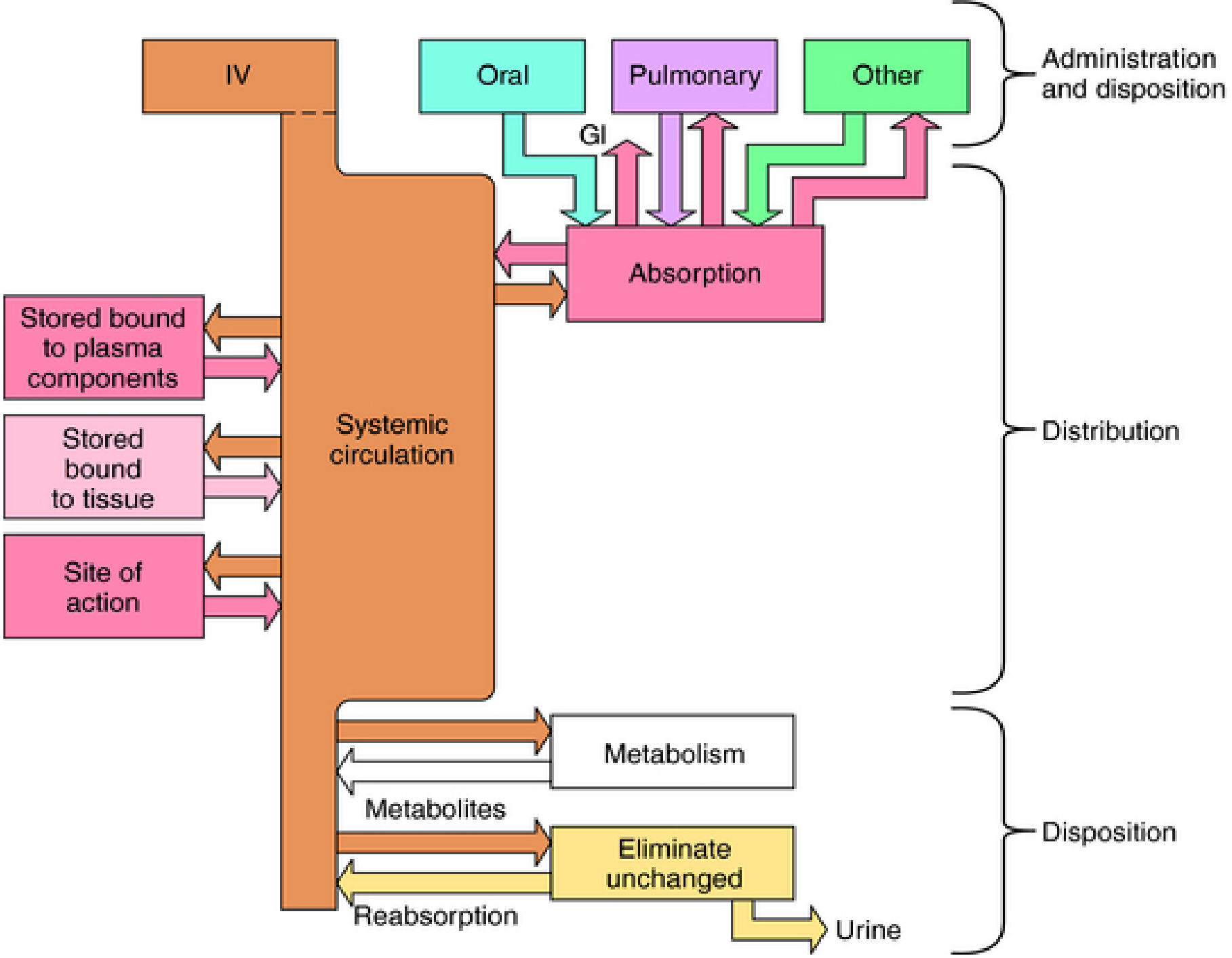
Gentamicin & timolol eye drops

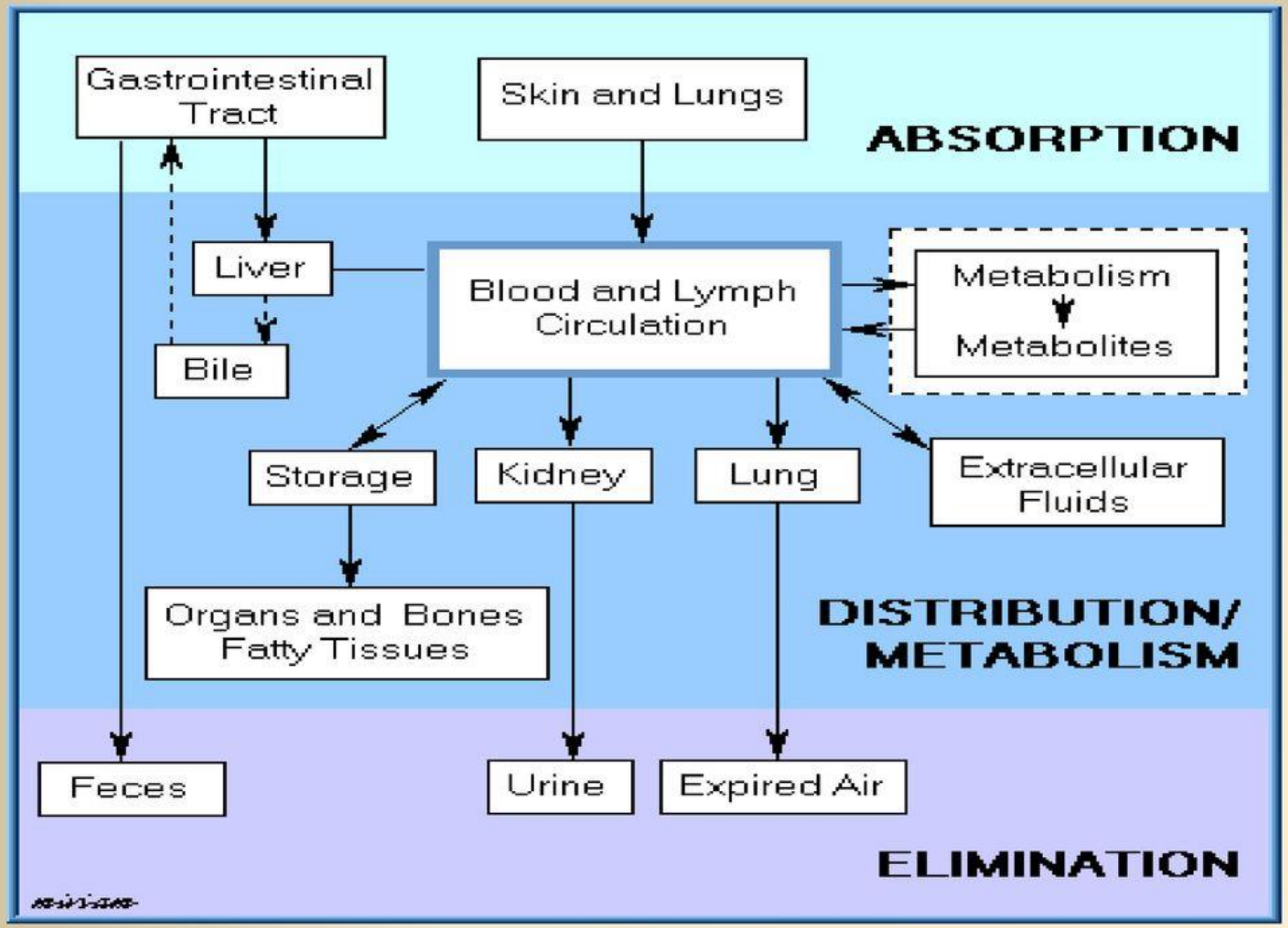


Route for administration
-Time until effect-

- *intravenous 30-60 seconds*
- *inhalation 2-3 minutes*
- *sublingual 3-5 minutes*
- *intramuscular 10-20 minutes*
- *subcutaneous 15-30 minutes*
- *rectal 5-30 minutes*
- *oral 30-90 minutes*
- *transdermal (topical) variable (minutes to hours)*


Inhalation
Parenteral: IV , IM , SC
Sublingual
Oral
Transdermal
Patch
Topical
Rectal


IV
Oral
Pulmonary
Other
Administration and disposition
GI
Absorption
Stored bound to plasma components
Stored bound to tissue
Site of action
Systemic circulation
Distribution
Metabolism
Metabolites
Eliminate unchanged
Reabsorption
Urine
Disposition


Gastrointestinal Tract
Skin and Lungs
ABSORPTION
Liver
Bile
Blood and Lymph Circulation
Metabolism
Metabolites
Storage
Kidney
Lung
Extracellular Fluids
Organs and Bones
Fatty Tissues
DISTRIBUTION/
METABOLISM
Feces
Urine
Expired Air
ELIMINATION

PHARMACODYNAMICS

- ***How Drugs Act Targets for drug Action***

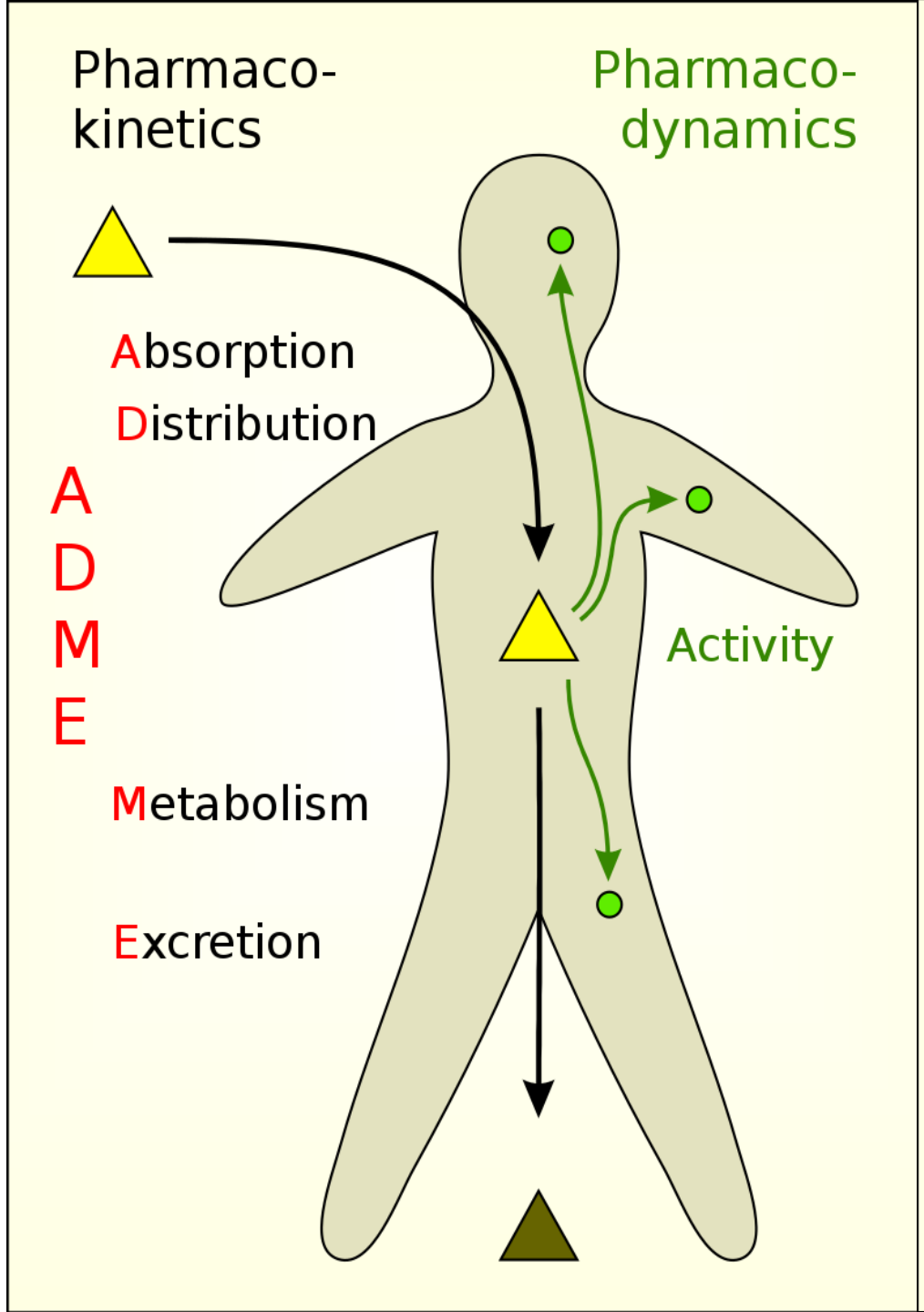
❑ Protein Targets For Drug Binding:

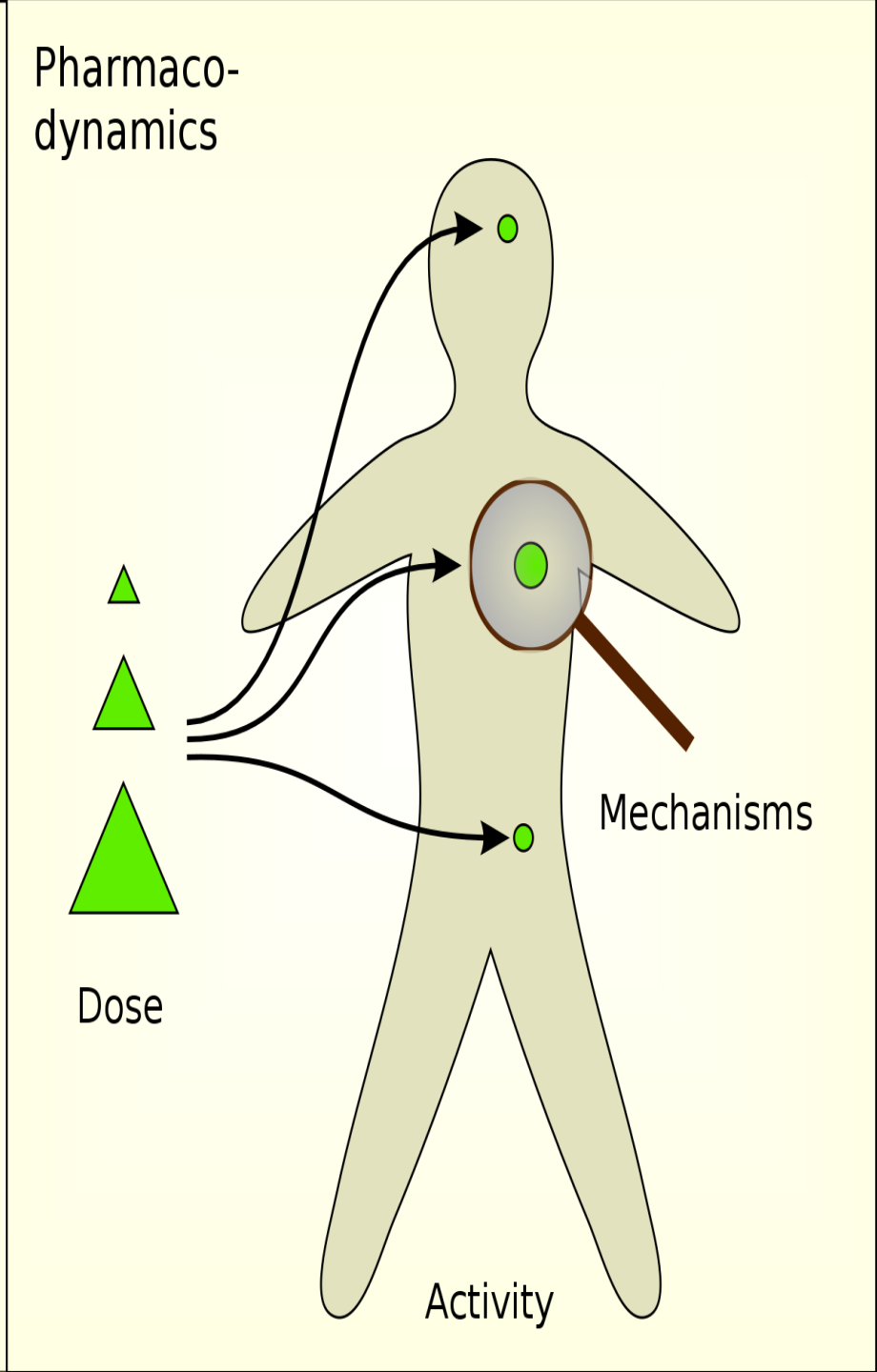
1. ***Regulatory Proteins***
2. ***Structural Proteins***

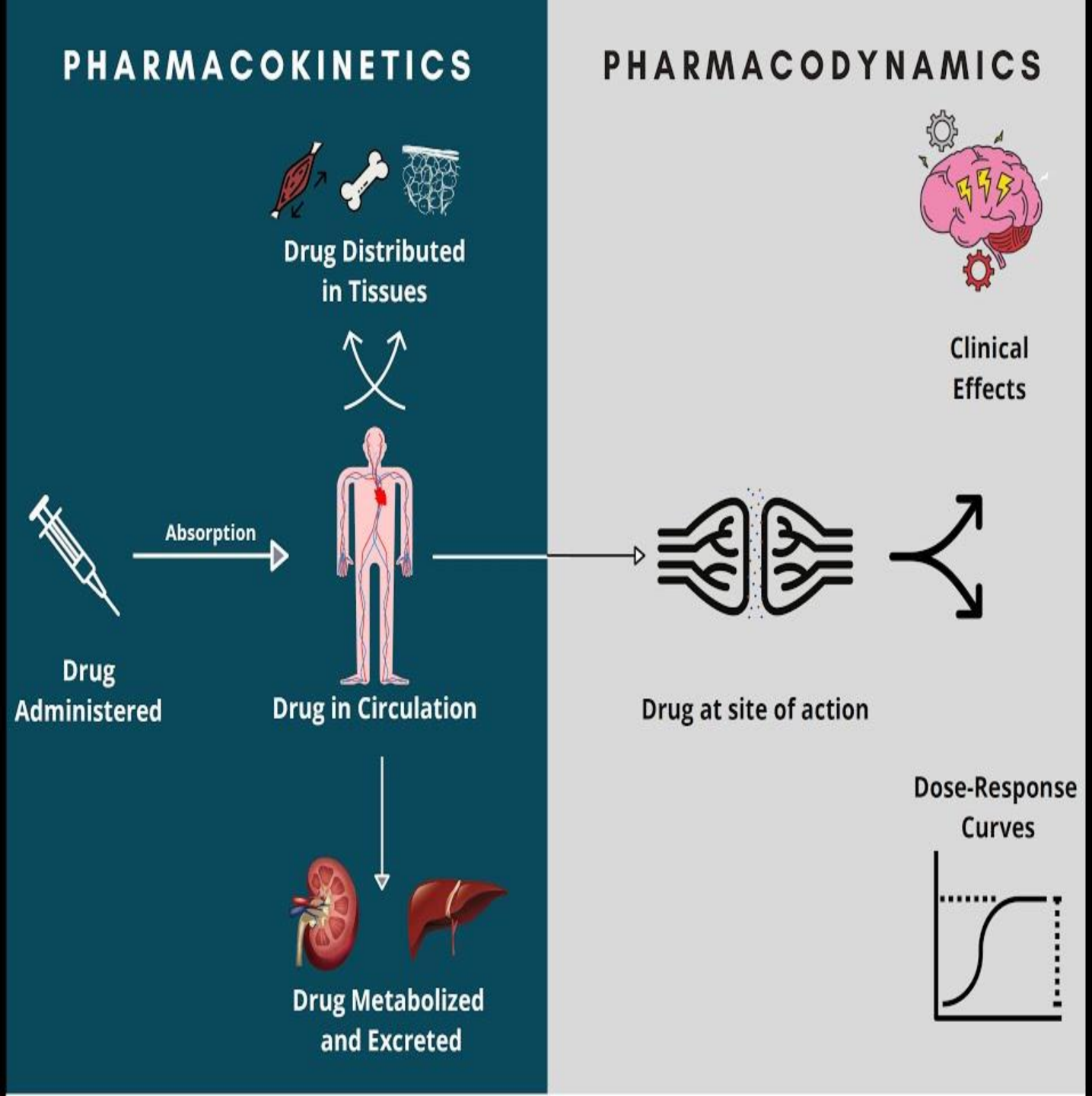
❑ *Regulatory Proteins:*

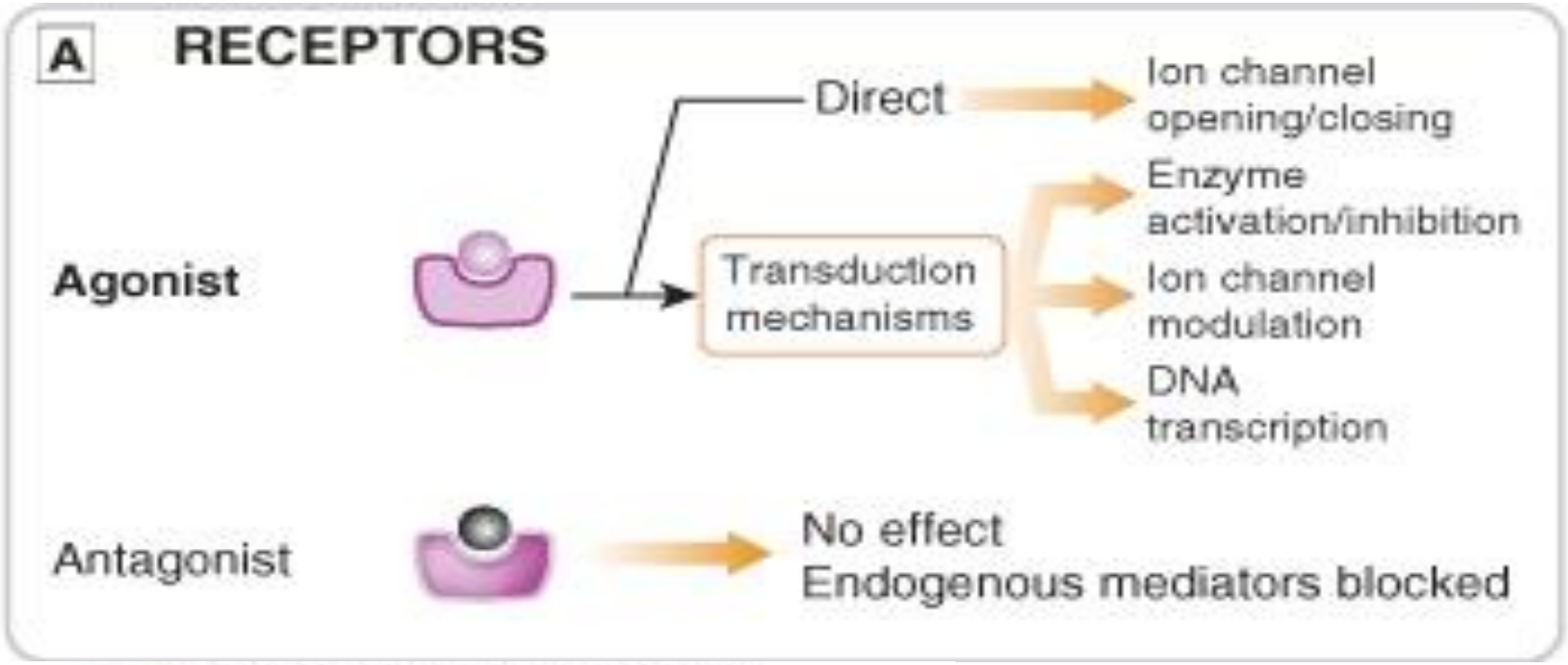
A. Receptors:

Are macromolecular proteins act as recognition sites for drugs (agonist or antagonist). They are functionally silent in the absence of the drug.


Pharmaco-
kinetics
Pharmaco-
dynamics
Absorption
Distribution
A
D
M
E
Metabolism
Excretion
Activity


Pharmaco-
dynamics
Mechanisms
Dose
Activity


PHARMACOKINETICS
PHARMACODYNAMICS
Drug Distributed in Tissues
Clinical Effects
Absorption
Drug Administered
Drug in Circulation
Drug at site of action
Dose-Response Curves
Drug Metabolized and Excreted



Elsevier Ltd. Rang et al: Pharmacology

B. Enzymes:

1. Competitive inhibitor:

a. Reversible: neostigmine inhibits acetylcholinesterase, carbidopa inhibits dopa decarboxylase

b. Irreversible: aspirin inhibits COX

2. False substrate → abnormal product

(fluorouracil)

3. Prodrug: A parent compound lacks activity & needs enzymatic degradation to convert into the active form (cortisone & enalapril).

C. Carriers:

Transport of ions & organic molecules across cell membrane requires carriers.

- Loop diuretics block Na/K/2Cl co-transporter
- TCA & cocaine block N.A carrier (uptake1)
- cardiac glycosides block Na+ / K+ pump
- Omeprazole blocks proton pump.

D. Ion channels:

1. Ligand gated ion channel: gating is controlled by ligand binding
2. Voltage-gated ion channel: controlled by membrane potential.

- **Drug-channel binding**:

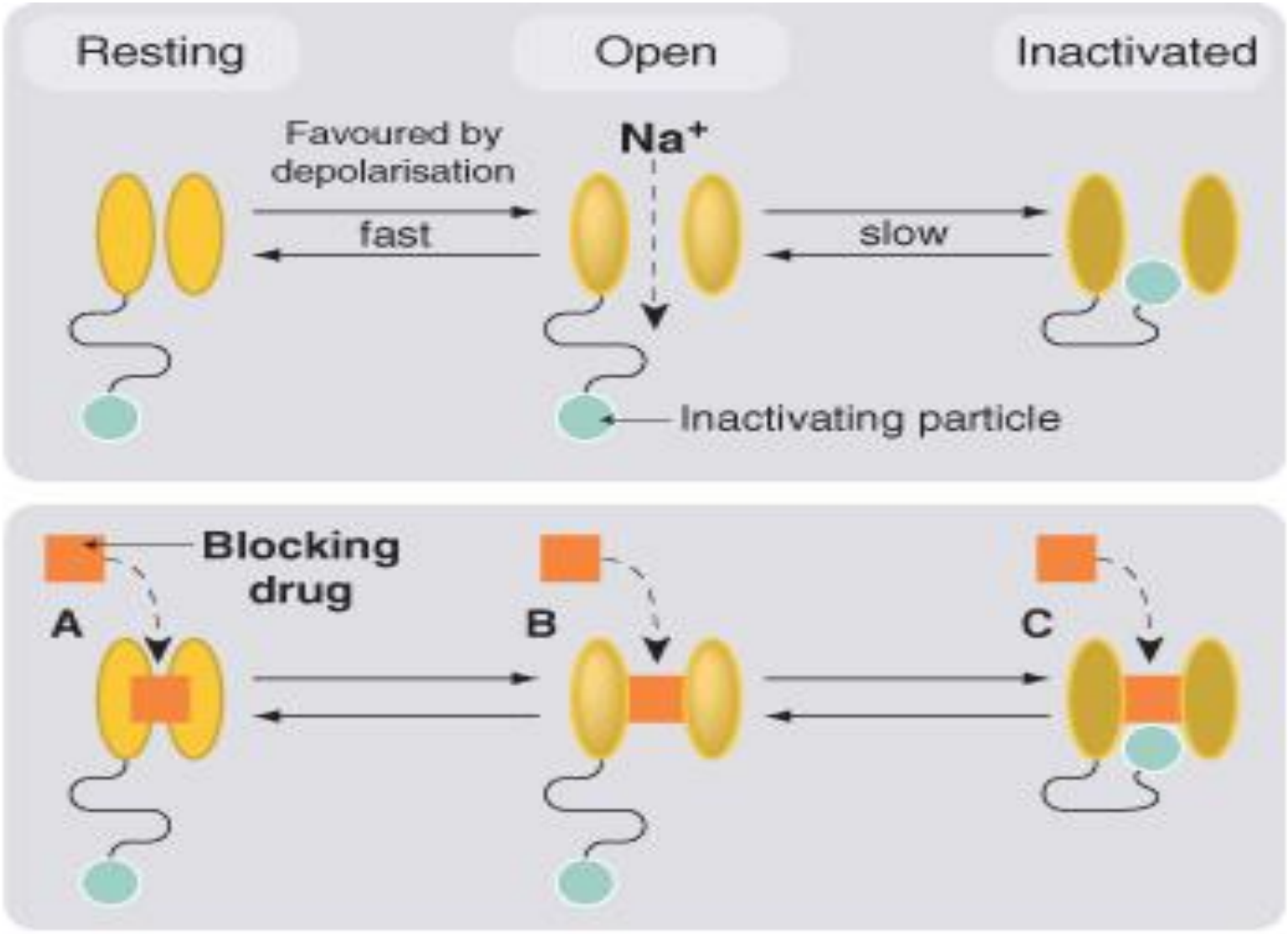
a. Direct: either Blockers (e.g local anesthetics block voltage-gated Na+ channel) or Modulators where the drug binds to an accessory site of the channel affecting gating (e.g. Ca^{2+} channel blockers inhibit opening of Ca^{2+} channel)

b. Indirect: involving G-protein

- Voltage gated ion channel exists in 3 states:

1. Resting state: closed, but opened upon stimulation.
2. Activated: open
3. Inactivated: closed, not opened upon stimulation

- Some drugs show preference for one of these states. e.g. Nifedipine (Ca^{2+} channel blocker) prefers to block the activated & inactivated state of Ca^{2+} channel (use-dependent channel block).



2. ***Structural proteins***:

- Colchicine interacts with tubulin.
- Ciclosporin acts on immunophilins.
- Therapeutic antibodies act against cytokines ,e.g. infliximab (anti-TNF-α antibody)

❑ ***Exceptions:***

- Chemotherapeutic drugs:

  antimicrobial agents

  anticancers (interact directly with DNA).
- Some drugs produce their effect without binding to any cellular components, e.g. antacids, chelating drugs, osmotic diuretics & bulk laxatives.