

Introduction to Pharmacology

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MSc. In Pharmacology)

Learning Objectives



- Define various terminologies used in Pharmacology
- Know about nature and sources of drugs.
- Understand pharmacokinetics like absorption, distribution, metabolism and excretion (ADME)
- Pharmacodynamics like mechanism of drug action, dose relationship and
  drugs.
- Understand drug safety and effectiveness like factors affecting drug action and adverse drug reactions.
- Understand new drug development and evaluation

Introduction



- Define the following terms:
- **Pharmacology**

  is the study of drugs and their interaction with living systems.
- **Drugs**

  are chemicals that alter functions of living organisms given for the diagnosis, prevention, control or cure of disease.
- **Pharmacy**: It is the science of identification, selection, preservation, standardization, compounding and dispensing of medical substance

- **Clinical pharmacology**

  the study of drugs in **humans** study of drugs in patients as well as in healthy volunteers

- **Experimental pharmacology**

involves testing of pharmacologically unknown substance and pharmaceutical products in human and animal

- **Pharmacotherapeutics**

  the use of drugs to diagnose, prevent or treat diseases or to prevent pregnancy

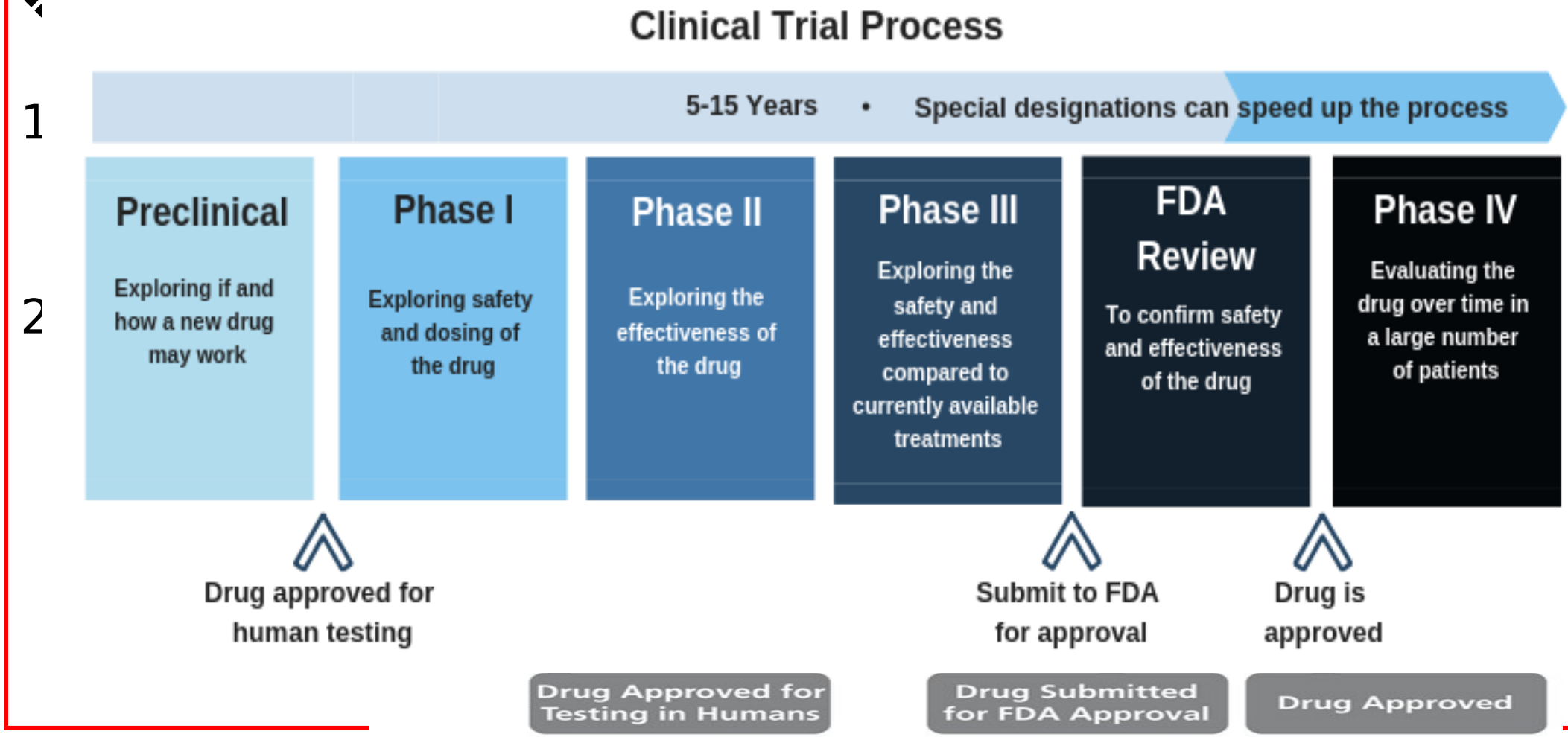
- **Toxicology**

  the study of the undesirable effects of chemical agents on living systems.





Stages of New Drug Development



Drug Names and Sources of Drugs

- Any drug can have three types of names:
- ***Chemical Name***

  A description of that drug using the nomenclature of chemistry.
- ***Generic name***

  Proposed by the company that first developed the drug and approved by international body.
- ***Trade name or brand name***

  Are the names under which a drug is marketed.
- We employ drug names in two ways;
  - ✓ for written and verbal communications about drugs
  - ✓ to put labels to identify the medications present in containers.

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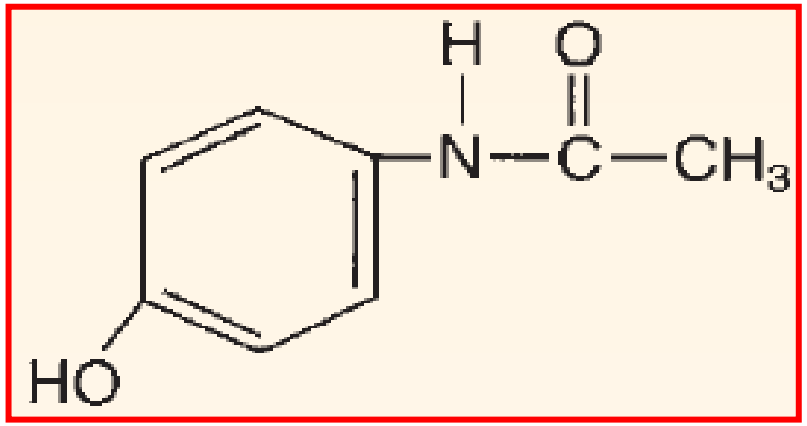



Type of drug name	Examples
Chemical name	N-acetyl-para-aminophenol
Generic name	Paracetamol/ actaminophen
Trade (brand) name	Panado, Tylenol, Dapa, Valadol,

Sources of Drugs



Drugs are obtained from:

- ***Minerals*** *e.g. Liquid* paraffin, magnesium sulfate
- ***Animals*** *e.g.* Insulin, thyroid extract, heparin
- ***Plants*** *e.g.* Morphine. digoxin, atropine, castor oil, etc.
- ***Synthetic source*** *e.g.* Aspirin, sulphonamides, paracetamol, etc.
- ***Microorganisms*** *e.g.* Penicillin, streptomycin and many other antibiotics.
- ***Genetic engineering*** *e.g.* Human insulin, human growth hormone

Basic Principles of pharmacology

- ***Pharmacodynamic***
- ***Pharmacokinetics***

From two words

- pharmakon---------- drugs or poison
- kinesis---------- motion

- The four major pharmacokinetic processes are:

✓ **Drug absorption**

the movement of drugs from the site of administration into the blood.

✓ **Drug distribution**

drug movement from the blood to the interstitial space of tissues and from there into cells.

✓ **Drug metabolism**

enzymatically mediated alteration in drug structure.

✓ **Drug excretion**

movement of drugs (and their metabolites) out of the body.

Passage of drugs across membranes

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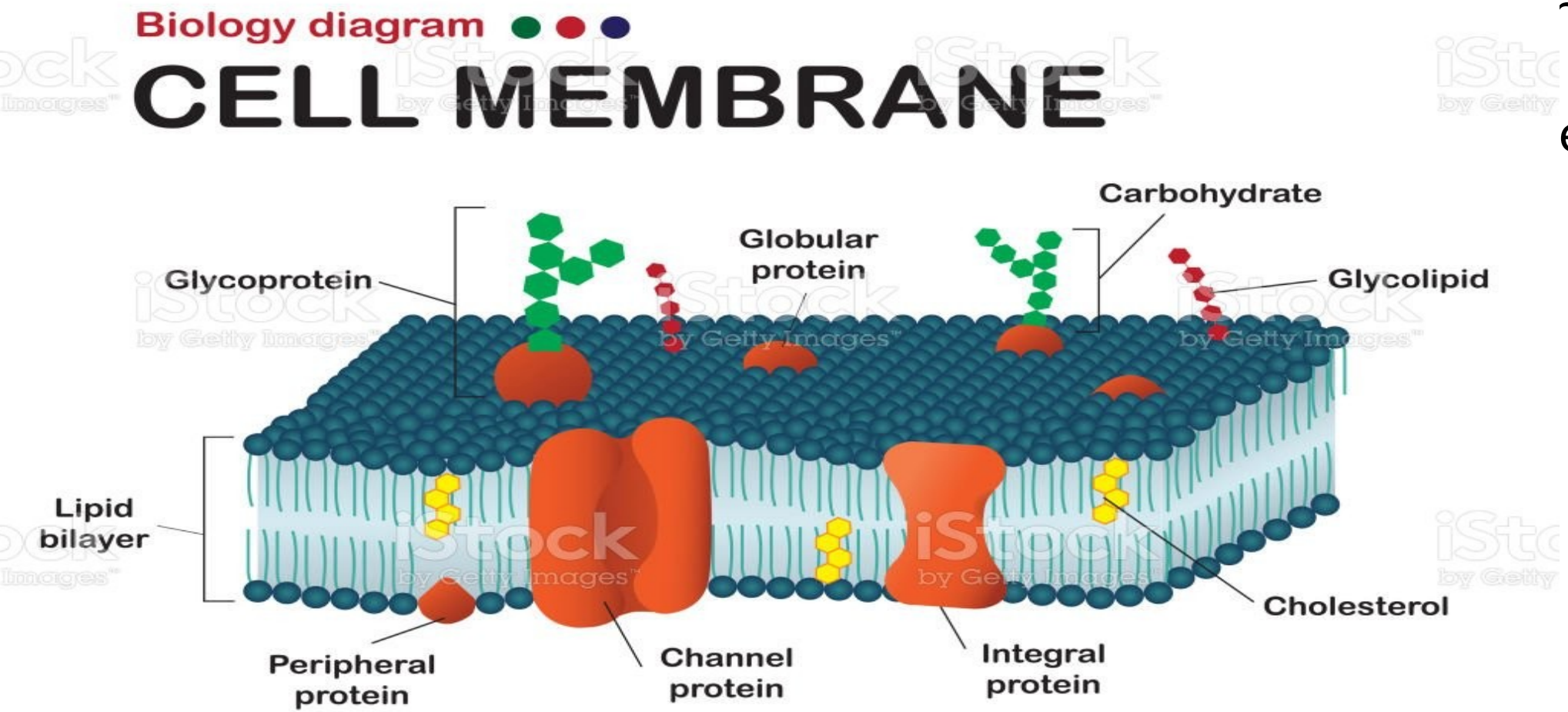


Drugs can cross cellular membranes by:

(A). **Passive transfer**

(1). Simple passive diffusion

(2). Filtration

(B). **Specialized transport**

(1). Facilitated diffusion

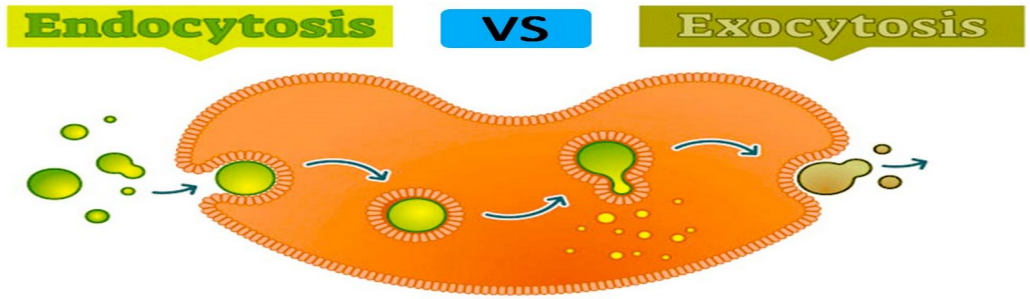
(2). Active transport

(3). Endocytosis and Exocytosis

i)Simple diffusion: Movement of a solute through a biological barrier from the phase of higher concentration to phase of lower concentration. No need of energy e.g. **highly lipid soluble drugs**

ii) Filtration: Is the process by which water soluble drug of relatively low molecular weight crosses the plasma membrane through pores as a result of hydrodynamic pressure gradient across the membrane e.g. **urea and ethylene glycol.**

- ***Facilitated diffusion***: It means the passage of drug across the biological membrane along the concentration gradient by the protein carrier mediated system also called as **carrier mediated** diffusion. It depends on number of carrier e.g. **tetracycline, pyrimidine**.
- ***Active transport:*** The process by which drugs pass across the biological membrane most often against their concentration gradient with the help of carriers along with the expenditure of energy e.g. **alpha methyl dopa, levodopa**
- ***Endocytosis:*** It is the process by which the large molecules are engulfed by the cell membrane and releases them intracellularly e.g. **protein, toxins (botulinum, diphtheria)**
- **Exocytosis** is a form of active transport through which large molecules are moved from the interior to the exterior of the cell. **(Neurotransmitters release)**

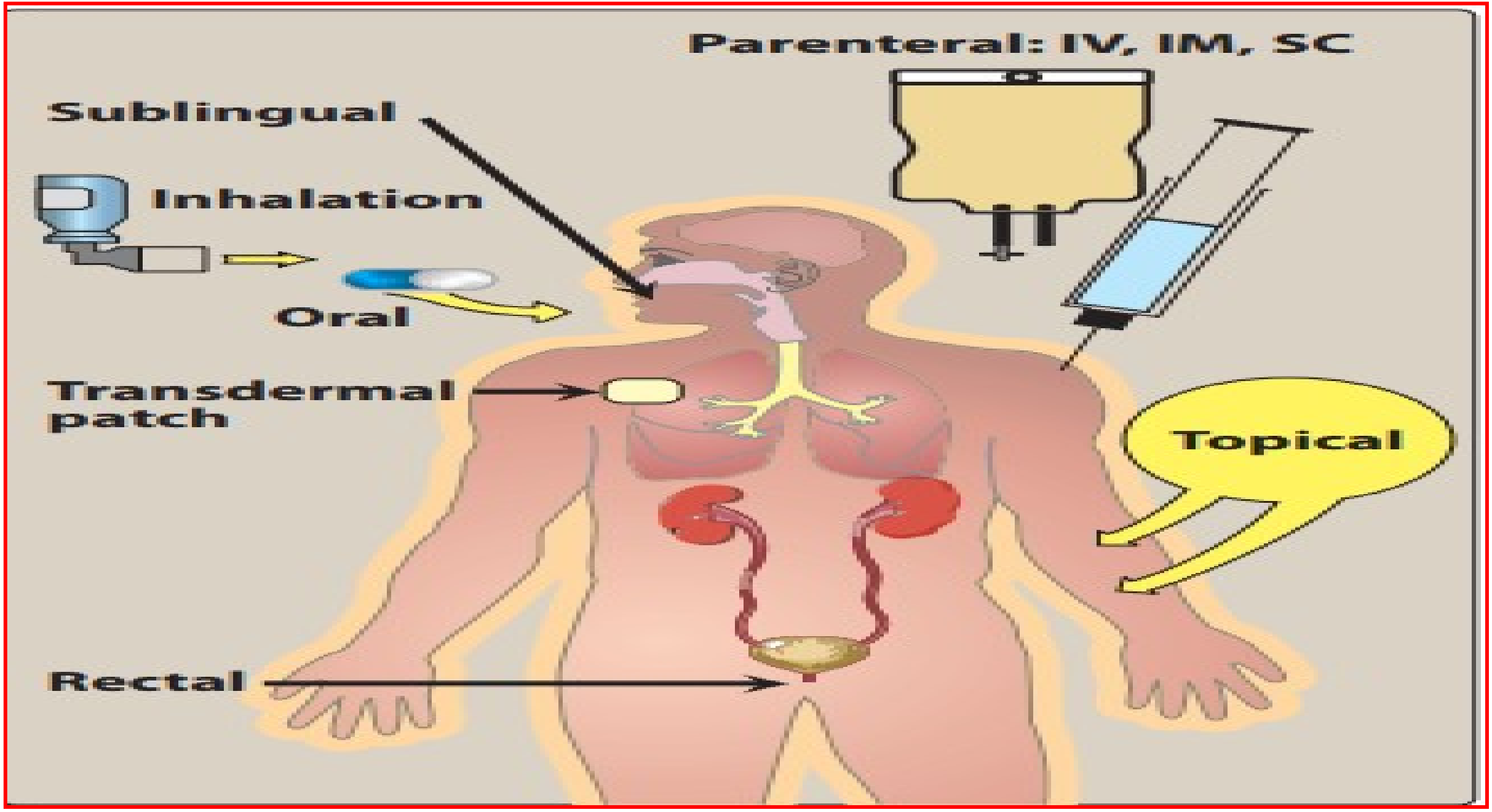


Classification of Routes of Administration

Routes of administration can be:

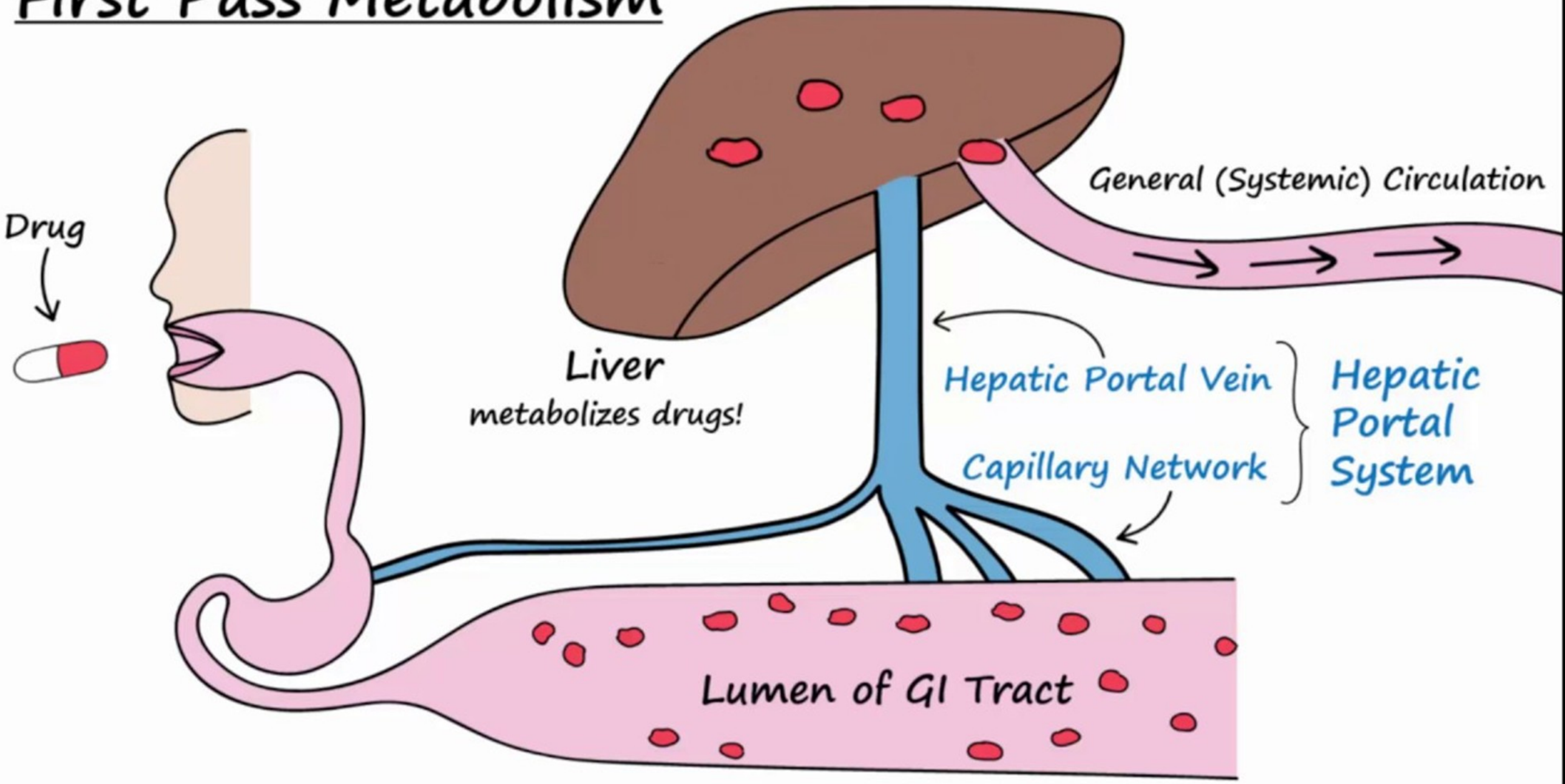
- **Enteral routes**: administration through the alimentary tract (oral, sublingual, and rectal route).
- **Parenteral routes**: administration through other sites, non alimentary (injections) E.g. subcutaneous (SC/SQ), intraperitoneal (IP), intravenous (IV), intradermal (ID), and intramuscular (IM)
- **Topical route**: local application of drugs on the skin and mucus membrane.

E.g. eye drops, ear drops, and lotions


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

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high-molecular-weight proteins and peptide drugs	• Unsuitable for oily or poorly absorbed substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)

First Pass Metabolism



Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic, thus requiring prolonged administration • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route.
Inhalation	• Systemic absorption may occur. This is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs: lower doses used compared to that with oral or parental administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed

Absorption

- The movement of drugs from the site of administration into the blood.
- the total dose of drug administered reaches the systemic circulation (100% bioavailability). **IV**
- Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability

Bioavailability(F)

- Bioavailability is the amount of drug which enters the plasma
- For an IV infusion, all the drug administered appears in the plasma, and so bioavailability = 100%
- Bioavailability is often expressed as fractional bioavailability, F, where

$$F = \frac{AUC_{oral}}{AUC_{iv}}$$

$$= \frac{\text{amount of drug in the plasma of an oral dose}}{\text{amount of drug in the plasma after IV dose}}$$

$$= \frac{\text{amount of drug in the plasma of an oral dose}}{\text{actual dose given}}$$

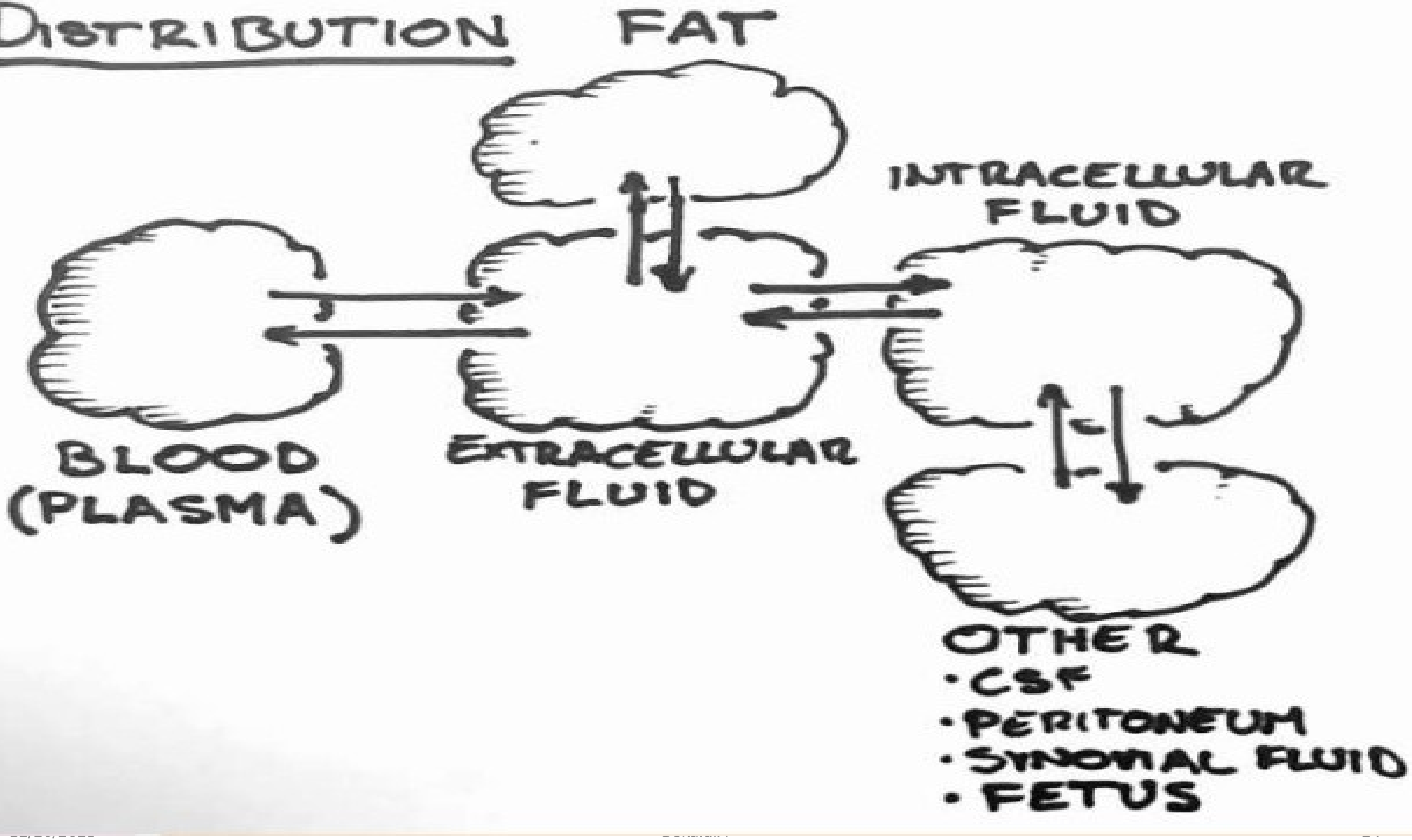
Factors affecting drug absorption

1. ***Rate of dissolution***
2. ***Surface area of absorption***
3. ***Blood flow***
4. ***Lipid solubility***

Distribution

- Drug movement from the blood to the interstitial space of tissues and from there into cells.
- The distribution of any given drug is determined by
  - ✓Permeability or The Blood brain barrier
  - ✓Placental barrier
  - ✓Plasma protein binding
  - ✓Lipid solubility
  - ✓Molecular size
  - ✓**Plasma Protein binding**
    - refers to the degree to which medications attach to proteins within the blood. A drug's efficiency may be affected by the degree to which it binds. The less bound a drug is, the more efficiently it can traverse cell membranes or diffuse

DISTRIBUTION



Plasma Protein Binding

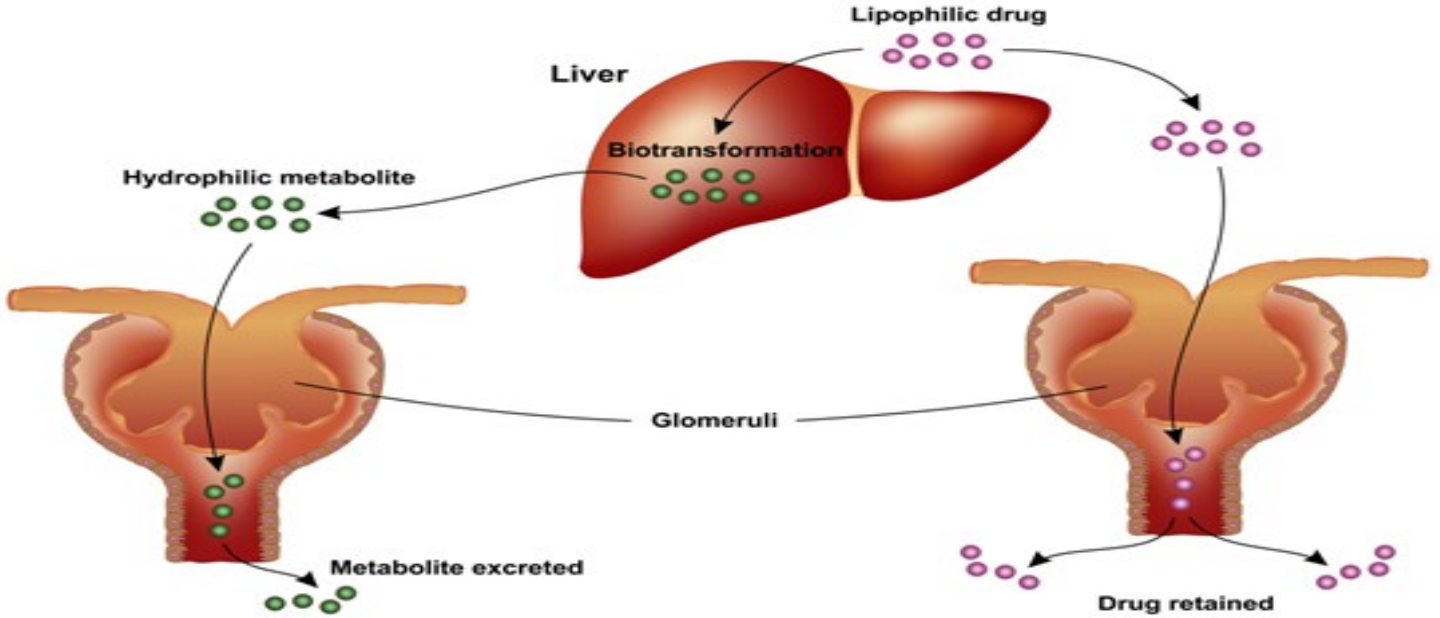
- Albumin has various binding sites for anionic drugs, (Acidic drugs)
- Alpha 1-acid glycoprotein possesses a single binding site for cationic drugs (B

Drugs highly bound to plasma protein

To albumin	*To α_1-acid glycoprotein*
Barbiturates	β-blockers
Benzodiazepines	Bupivacaine
NSAIDs	Lidocaine
Valproic acid	Disopyramide
Phenytoin	Imipramine
Penicillins	Methadone
Sulfonamides	Prazosin
Tetracyclines	Quinidine
Tolbutamide	Verapamil
Warfarin	

Metabolism (Biotransformation)

- Enzymatically mediated alteration of drug structure.
- Liver is the major organ for biotransformation of



Enzymes responsible for metabolism of drugs

Microsomal enzymes. Present in the smooth endoplasmic reticulum of the liver, kidney and GIT

e.g.

- ✓ glucuronyl transferase,
- ✓ dehydrogenase , hydroxylase and
- ✓ **cytochrome P450**

Types of biotransformation

- Classified as **phase-I** and **phase – II**
- In phase-I reaction the drug is converted to more **polar** metabolite.
- Some metabolites may not be excreted and further metabolized by phase –II reactions.
- ***Phase-I:*** Oxidation, reduction and hydrolysis.

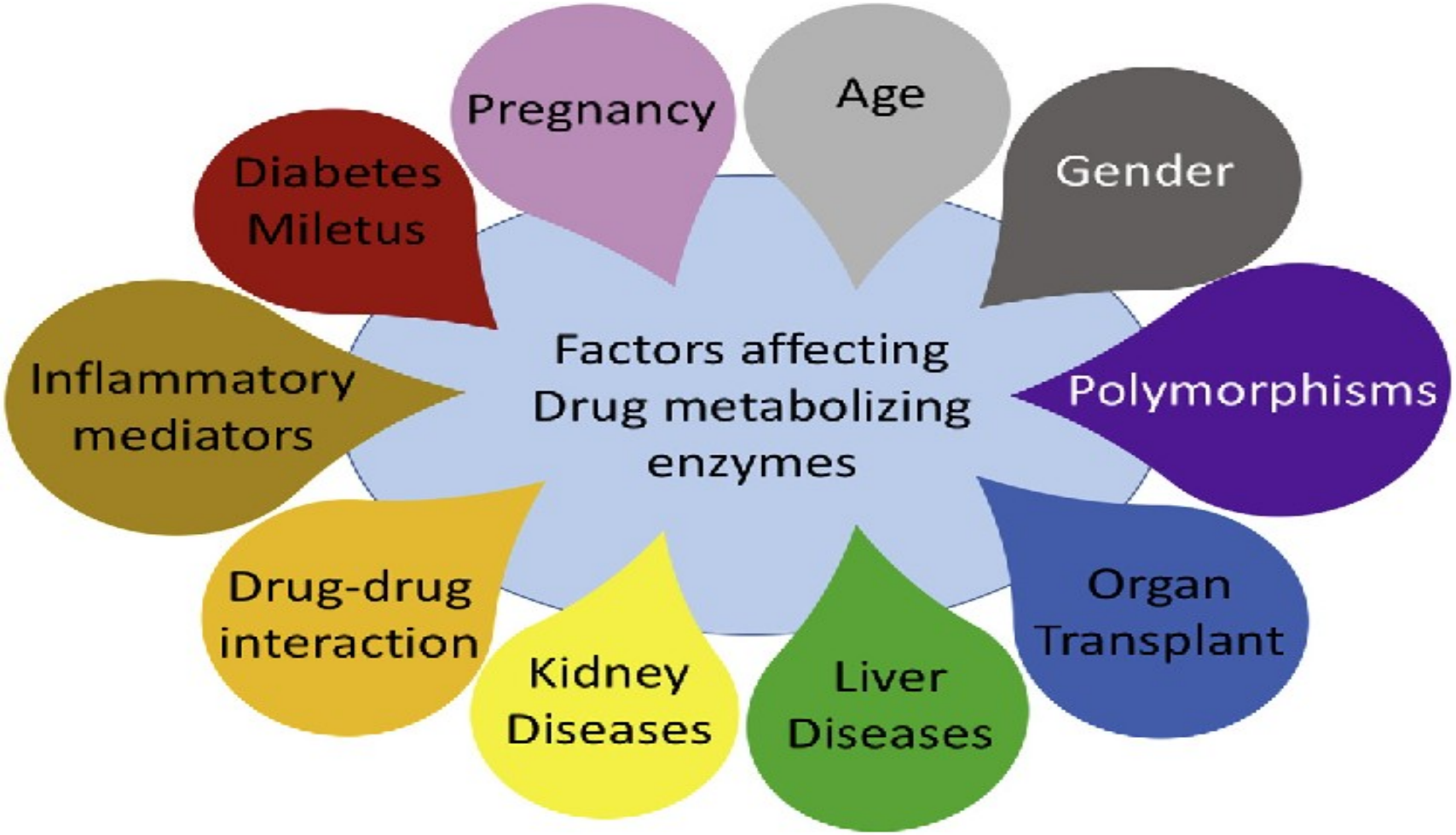
e.g *Aspirin,sulphonamide and atropine*

- ***Phase-II:*** Glucuronidation, acetylation,conjugation and methylation
- E.g *Phenobarbital, Isoniazid,*

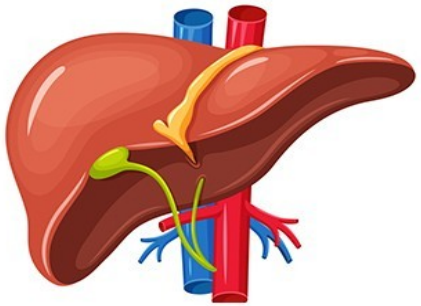
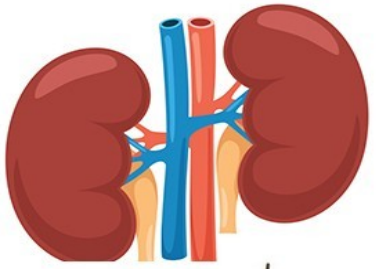
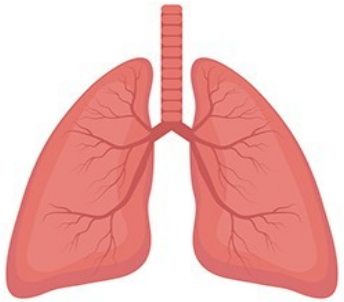
Therapeutic Consequences of Drug Metabolism

1) Promotion of renal excretion,
2) Reduction of therapeutic action,
3) Activation of a prodrug, E.g **Enalapril, Diazepam**
4) Enhancement of therapeutic action and
5) Alteration of toxicity

Factors affecting drug metabolism



Excretion


- Removal of drugs from the body
- The major processes of excretion includ
  - ✓ renal excretion,
  - ✓ hepatobiliary excretion and
  - ✓ pulmonary excretion.
- The minor routes of excretion are saliva, sweat, tears, breast milk, vaginal fluid, nails and hair.
- **First-order elimination kinetics**: The rate of elimination is proportional to the amount of drug in the body. The majority of drugs are eliminated in this way
- **Zero-order kinetics** undergo constant elimination regardless of the plasma concentration E.g Ethanol, Phenytoin, Salicylates

Time Course of Drug Responses

A. Plasma Drug Levels

Clinical significance of plasma drug levels—there is usually direct correlation between therapeutic and toxic responses and plasma drug levels.

Two plasma drug levels defined

- **Minimum effective concentration (MEC)** –

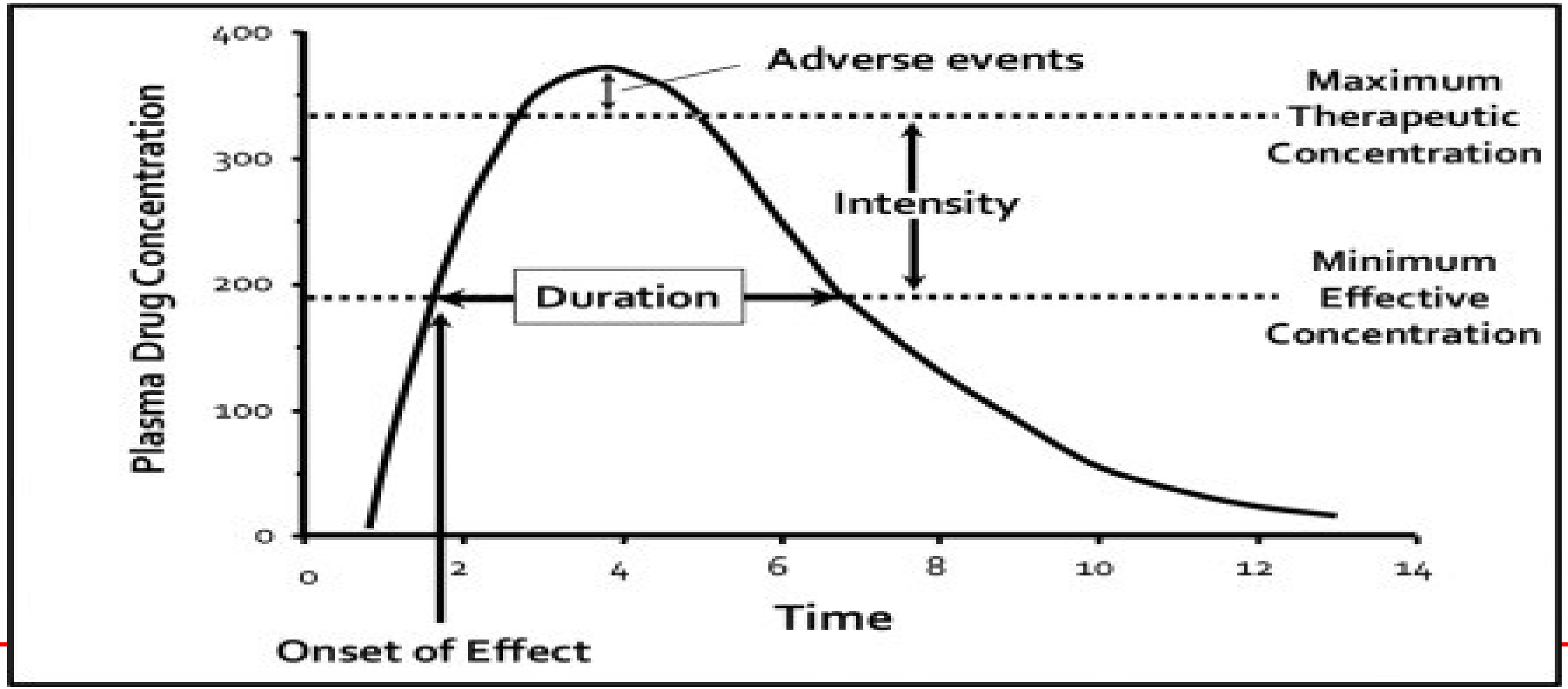
  is defined as the plasma drug level below which therapeutic effect will not occur.

- **Toxic concentration** – the plasma drug level at which toxic effects begin.

- **Maximum effective concentration- or** minimum toxic concentration (MTC) is the concentration at which a drug produces unwanted side effects

Therapeutic range—Objective of drug dosing (between MEC and toxic levels)

B. Single-Dose Time Course



How do drugs act?

- Drugs exert their effect either by binding to *biological molecules* or *through non-specific physicochemical mechanisms.*
  - The biological molecules include:
- **Receptors**: Cimetidine + Histamine receptor
- **Enzymes**: Aspirin + Cyclooxygenase
- **Transporters (carriers)**: Cardiac glycosides + Na^+/K^+ ATPase,
- **Structural proteins**: Colchicine + tubuline (subunits of microtubules)

Pharmacodynamics

- the study of the biochemical an physiological effects of drugs and
- the molecular mechanisms by which these effects are produced.

- Is the study of what drugs do to the body and how they do it.



Receptor interactions

- A **receptor** is macromolecule typically made of proteins that interacts with either an endogenous ligand or a drug to mediate a pharmacological or physiological effect
- Functions of receptor:
  - ✓ Ligand binding
  - ✓ Activation of an effector system
- Drugs binds to the receptors through the following bonds
  - ✓ Covalent is strongest bond, Electrostatics, Hydrogen bond

- A macromolecule transduce drug-receptor interaction in to cellular effects

There are four type of drug receptors:

✓Ligand gated ion channels (ionotropic receptors)

✓Kinase receptors

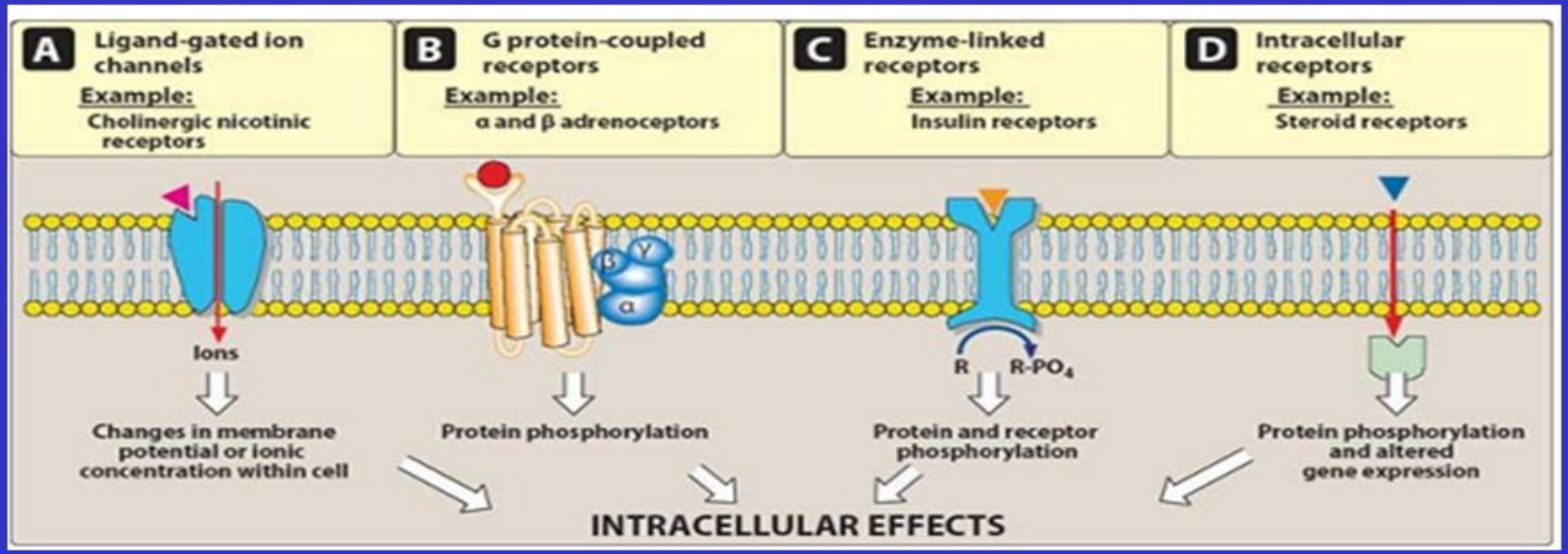
✓G-protein coupled receptors(metabotropic receptors)

✓Intracellular receptors

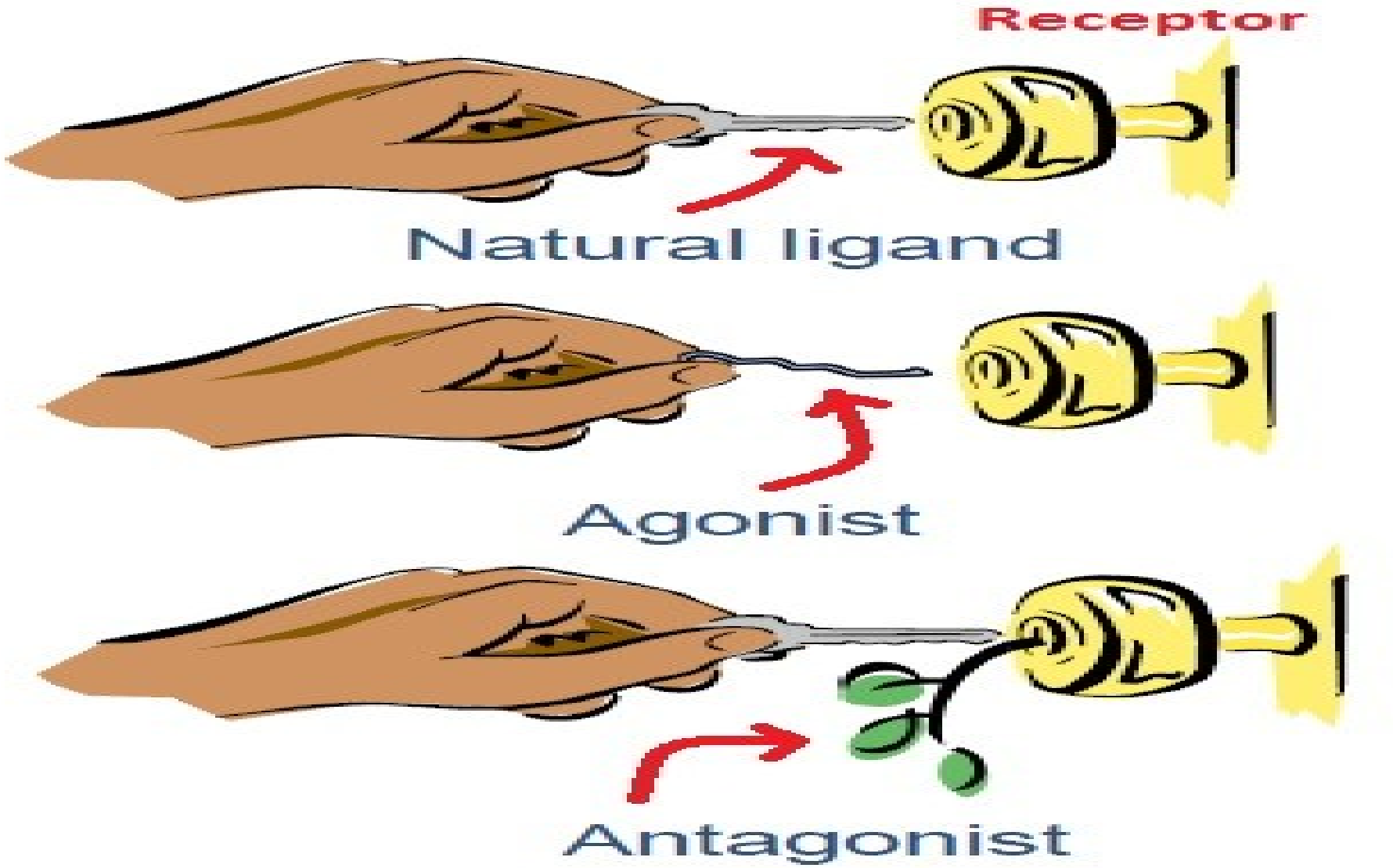
..\..\PHARMACOLOGY\Video\Types of Drug Receptors (video-converter.com).mp4

Mechanism of Drug action cont.

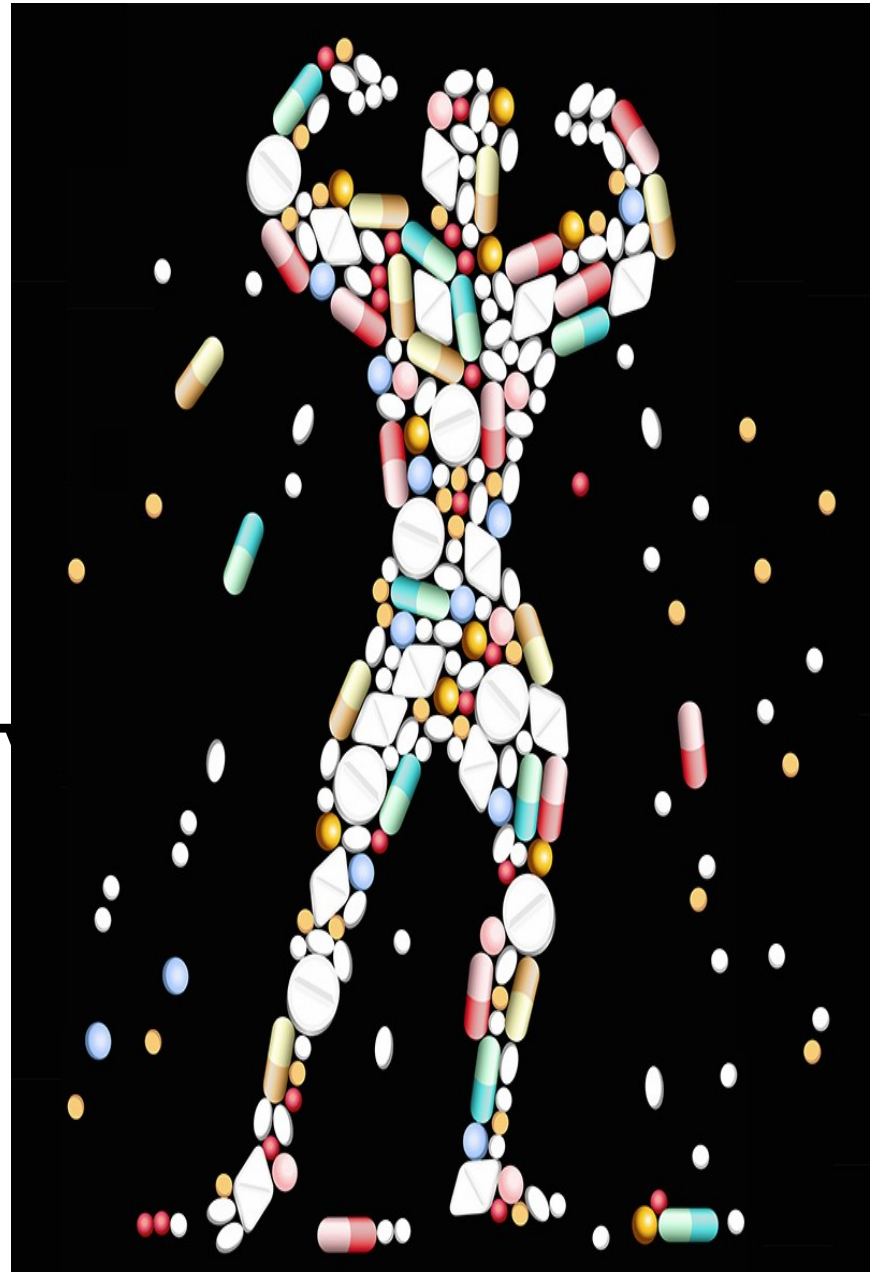
Types of receptors



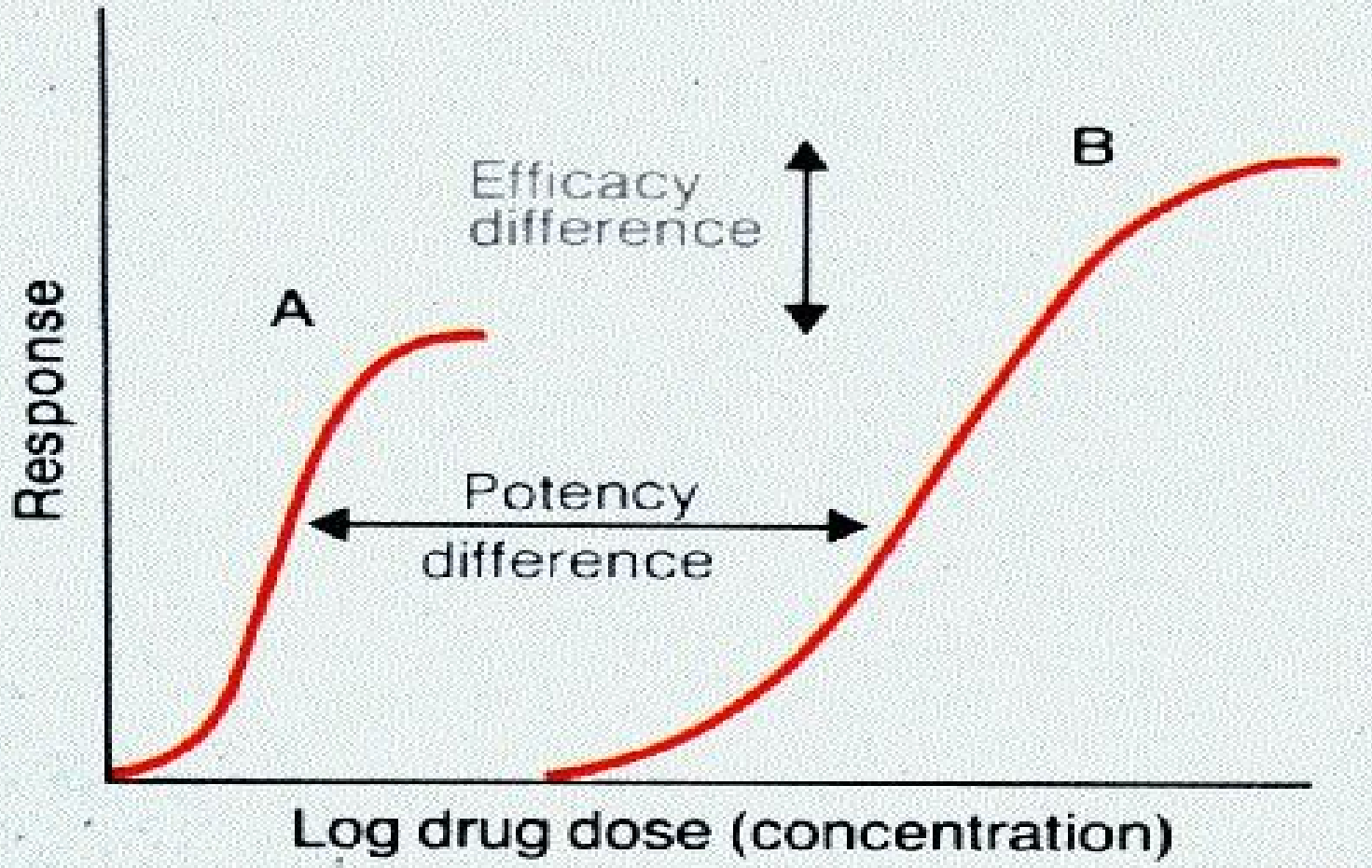
- R … s of m… and di… lls.
- ***A…***
- ***I…*** …d to ca… upon ***bi…***
- **P…** …given ef…
- In…
  - …A=1,
  - …tivity
  - ***Partial agonist/antagonist:*** have affinity but with submaximal intrinsic activity (A=1, 0<IA<1)

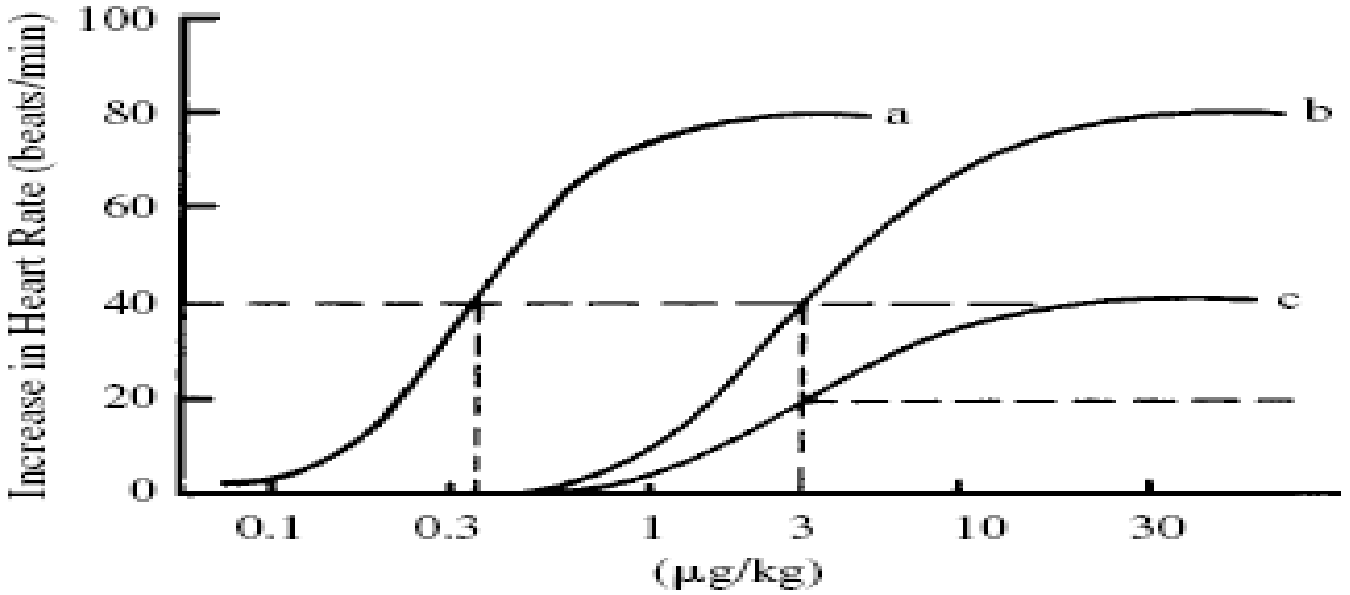


Potency
&
Intrinsic Acti



The difference between 'potency' (affinity) and 'efficacy' (activity)





- Potency
  - Drug “a” is more potent than drug “b”
  - Drugs “b” and “c” are of equal potency
  - Configuration of curve with respect to the x-axis is indication of potency

- Intrinsic activity (IA)
  - Related to the attainment of maximum response
  - Drugs “a” and “b” have equal IA while “c” has less IA
  - Configuration of curve with respect to the Y-axis gives indication of IA

Types of Drug Interaction



- **Synergism**: the combined effect of two drugs action is greater than the sum of the effect of each drug (1+1>2).
  - E.g. penicillin + aminoglycoside antibacterial
- **Additive**: combined effect of two drugs having the same action is equal to the sum of effect of each drug (1+1=2).
  - **E.g. sulbutamol + theophyline**
- **Potentiation**: the effect of one drug is increased by the other which does not have the same action. (1+0>1)
  - E.g. penicillin + probenicid

- Antagonism: action of one drug inhibits the action of anc



1. **Physical antagonism**: charcoal adsorbs water and to
2. **Chemical antagonism**: NaHCO3 and gastric HCl
3. **Physiological/functional**:
   - Both agents act on different receptors on the same organ and give antagonistic effect/opposite effect. E.g. histamine and adrenaline on bronchial smooth muscle and blood pressure.
4. **Pharmacokinetic antagonism**

- Certain agents or drugs may interfere with drugs or antagonize them at the level of absorption, distribution, biotransformation or excretion by preventing absorption, interfere with PPB, enhancement of biotransformation and excretion. E.g **Phenobarbital-induced enzyme induction increases the metabolism of the anticoagulant coumadin**

5. **Pharmacological /receptor antagonism:**

- ✓ Antagonism takes place at the receptor site which could be of two types: competitive and non-competitive.

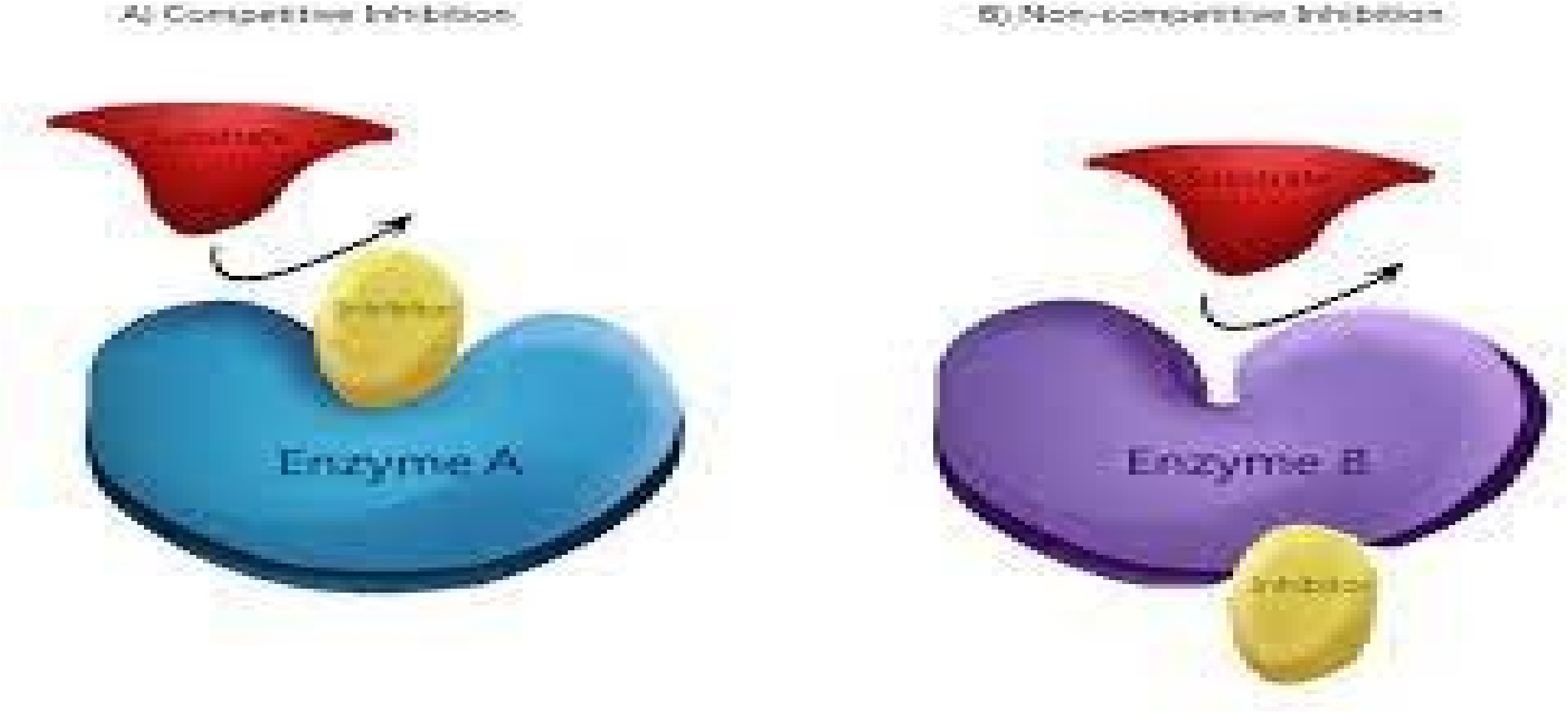
➢ **Competitive antagonism**

- Same binding site for agonist and antagonist
- The inhibition can be overcome by increasing the concentration of the agonist. E.g **Naloxone is a competitive antagonists at all opioid receptors** and.

➢ **Non-competitive antagonism**

- Binding site of the agonist and antagonist is different

E.g ketamine is a non-competitive antagonist at the NMDA-glutamate receptor


A) Competitive Inhibition
Enzyme A
B) Non-competitive Inhibition
Enzyme B

- The **ED50** (median effective dose) is the dose of a medication that produces a specific effect in 50% of the population that takes that dose
- **TD50** is a toxicology term that relates to the median toxic dose of a substance in which toxicity occurs in 50% of a species
- **Therapeutic Index (TI)** is a quantitative measurement of the relative safety of a drug
- Comparisons between ED50 and TD50 values permit evaluation of the relative safety of a drug (the therapeutic index), as would comparison between ED50 and the lethal median dose (LD $TI = \frac{TD50}{ED50}$ or $\frac{LD50}{ED50}$ known;





Pregnancy Category

Category	Risk	
	Animals	Humans
A	−	−
B	+/−	−/o
C	+/o	o
D	+	+
X	+	+

− = Studies have proven absense of teratogenicity;
o = no studies available;
+ = studies have proven teratogenicity