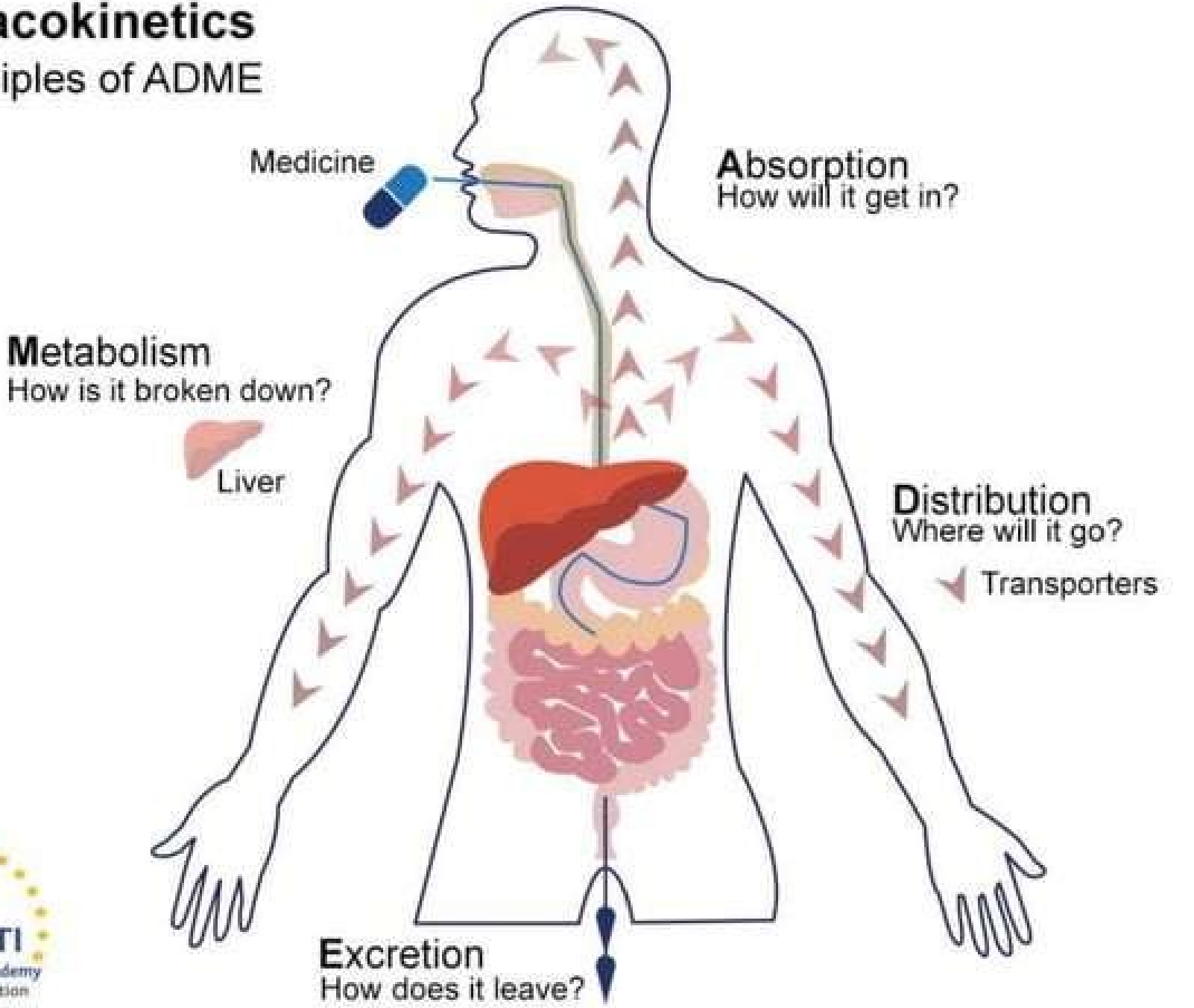
PHARMACOKINETICS

- Pharmacokinetics is the quantitative study of drug movement in, through & out of the body.
- It is the study of process by which a drug is absorbed, distributed, metabolized & eliminated by the body.
- The absorption, distribution, metabolism, and excretion of a drug all involve its passage across cell membranes.
- Pharmacokinetic properties are affected by the route of administration and the dose of administered drug.

Pharmacokinetics

The principles of ADME



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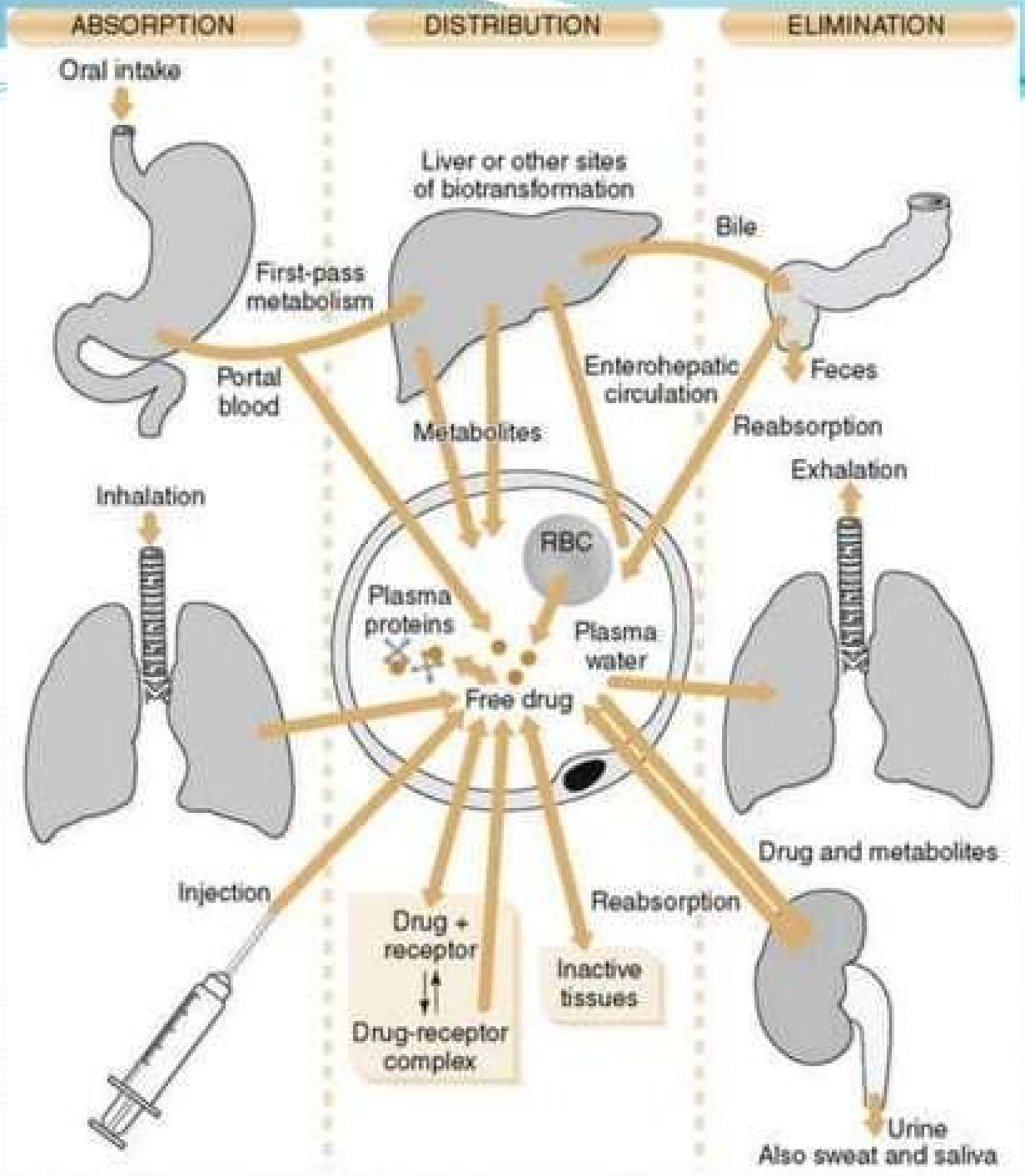
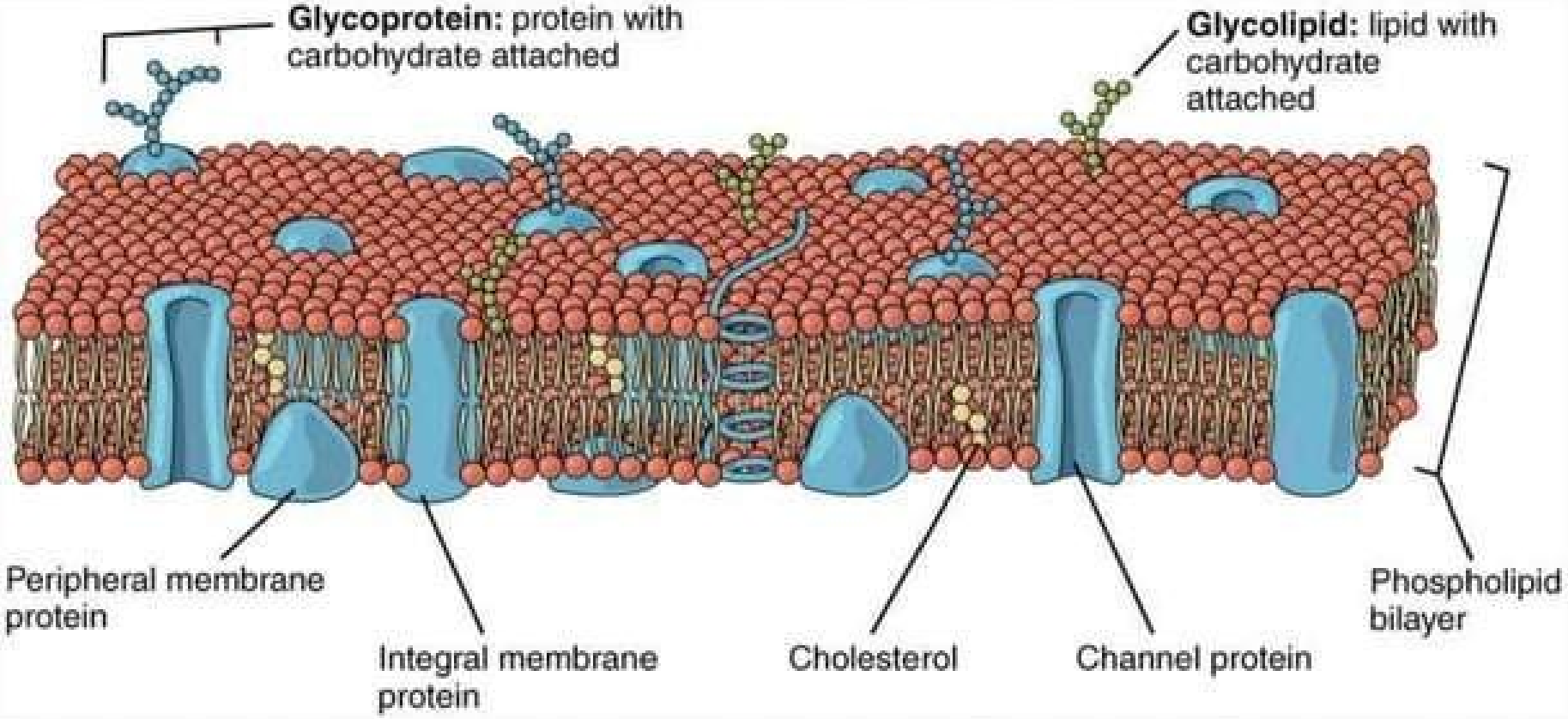

ABSORPTION
DISTRIBUTION
ELIMINATION
Oral intake
Liver or other sites of biotransformation
Bile
First-pass metabolism
Portal blood
Metabolites
Enterohepatic circulation
Feces
Reabsorption
Exhalation
Inhalation
RBC
Plasma proteins
Plasma water
Free drug
Drug and metabolites
Injection
Reabsorption
Drug + receptor
Drug-receptor complex
Inactive tissues
Urine
Also sweat and saliva

ABSORPTION

- **Absorption** is the process by which drugs enters systemic circulation. The rate of absorption of a drug is determined by the properties of drugs & biological membranes of the body.
- It takes place from different routes of administration and it is affected by the permeability of the drug at the absorption site.
- **Bioavailability** is the fraction of administered drug that reaches the systemic circulation in an unchanged form.

Biological membrane are the outermost layer of the cell consisting of phospholipid bilayer along with membrane proteins & sugar molecules embedded within it. It maintains the integrity of the cell and allows transport of ions & molecules across it.

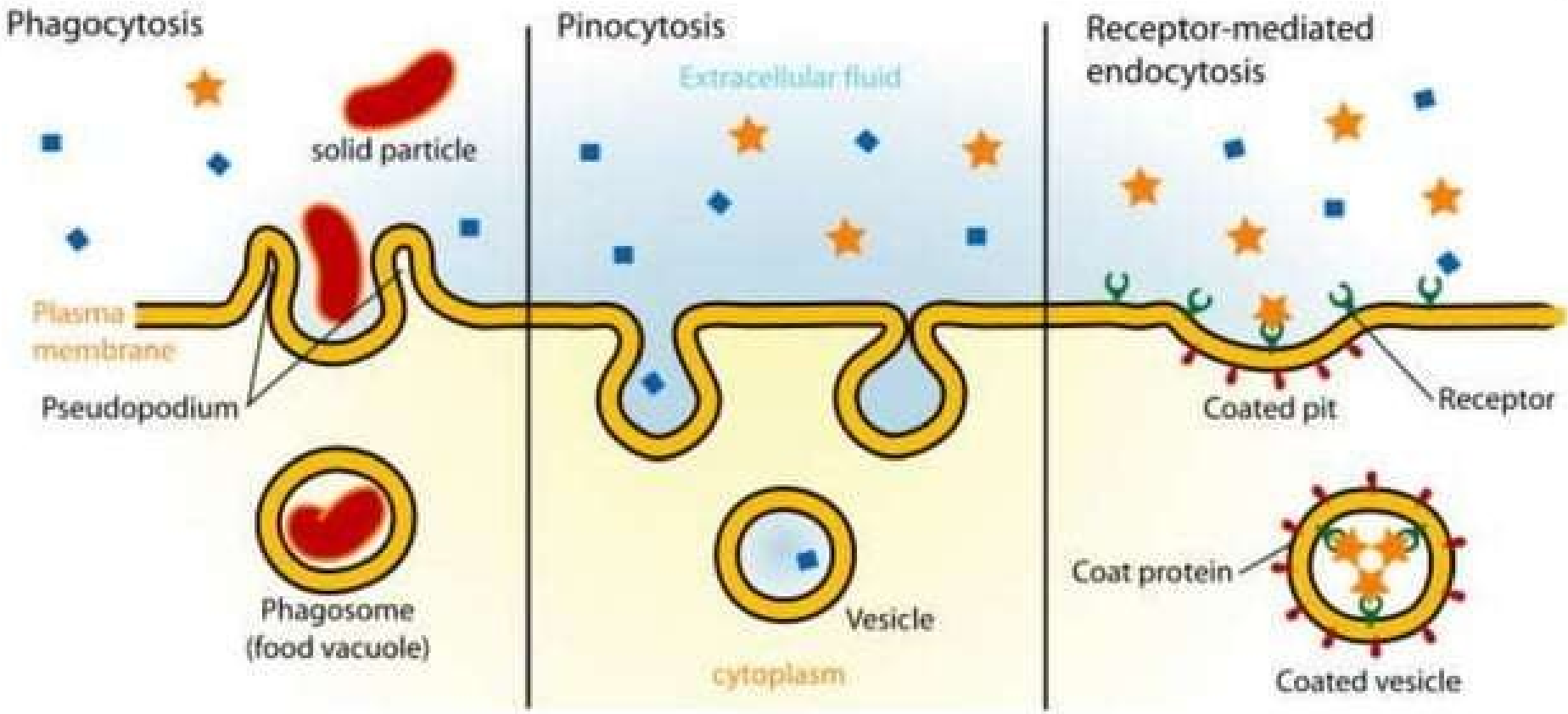


Transport across the cell membrane/biological membrane

- **Passive Transport**
- It does not require energy
- **Passive Diffusion**
- The process in which drug molecules are transported by diffusion process along a concentration gradient across the lipid bilayer is known as passive diffusion. This type of transport does not require energy.
- It is directly proportional to the concentration gradient across the membrane, the lipid-water partition coefficient of the drug and the membrane surface area exposed to the drug. The greater the partition coefficient, the higher is the concentration of drug in the membrane, and the faster is its diffusion.
- **Facilitated Diffusion**
- The process in which drug molecules are transported across the biological membrane through concentration gradient with the help of carrier protein is known as Facilitated Diffusion.

- **Active transport**
- The transport of molecules across a membrane against a concentration gradient that requires energy is known as active transport.
- This energy can be obtained from ATP hydrolysis (primary active transport) or from an electrochemical gradient of an ion such as Na^+ or H^+ (secondary active transport).
- **Primary active transport**: the membrane transport that directly couples with ATP hydrolysis is called *primary active transport*. ABC transporters are examples of primary active transporters.
- **Secondary active transport**: it requires an ion electrochemical gradient to drive the uphill transport of another solute. The downhill movement of one species drives the uphill movement of the other.
- This can be symport (in which both types of molecule or ion travel across the membrane in the same direction) or antiport (in which the two species travel in opposite directions)
- **Endocytosis:** It is a form of active transport in which a cell transports molecules into the cell by engulfing them using energy. Endocytosis includes pinocytosis(cell drinking) and phagocytosis (cell eating).

Endocytosis



DISTRIBUTION

- Distribution is followed by absorption. The drug passes through several body fluid compartments depending upon its physicochemical properties. Different fluid compartments are:
- Plasma
- Interstitial fluid
- Transcellular Fluid
- Intercellular fluid

- $V_d = \frac{\text{total amount of drug absorbed}}{\text{plasma concentration}}$

- Factors affecting volume of distribution

1. Lipid-water partition coefficient of drug
2. Pka value of the drug
3. Degree of plasma protein binding
4. Affinity to different tissues
5. Fat lean body mass ratio
6. Diseases

- **Blood Brain Barrier**
- Penetration of drug into brain & CSF require crossing of blood brain barrier and blood CSF barrier. The blood brain barrier is made up of capillary endothelial cells tightly joined together lacking paracellular spaces. BBB are lipophilic so they do not allow the movement of non-lipid drugs. They also contain enzymes that prevent entry of catecholamines in active forms. They are very selective to the entry of drugs.

- **Placental Barrier**
- Placental membranes are lipoidal so they allow the entry of lipophilic drugs & restrict the entry of hydrophilic drugs. Placental barrier limits foetal exposure of maternally administered drugs. Placenta is also a site for metabolism of drugs. However high concentration drugs taken for long periods may gain access to placenta.

- **Plasma Protein Binding**
- Most of the drugs have physicochemical affinity for the plasma proteins and get reversibly bound to it. Acidic drugs bind to plasma albumin & basic drugs bind to α_1 acid glycoprotein. Protein bound drugs generally have longer duration of action as they remain in body for long time.
- Binding of some benzodiazepines:

  Flurazepam 10% Alprazolam 70 % Diazepam 99%

- **Tissue Storage**
- Drug may accumulate in specific organs by active transport or get bound to specific tissue components. Drugs stored in tissues are unequally distributed & have large volume of distribution & longer duration of action. Some may also cause local toxicity. e.g: sequestration of tetracycline in bone & teeth causes discoloration of teeth

METABOLISM

- Metabolism(Biotransformation) means chemical alteration of a drug into body to less toxic form. The elimination of xenobiotics depends upon its conversion into water soluble compounds catalyzed by enzymes. The primary site of drug metabolism is liver. Metabolism also occurs in lungs, kidney, plasma & blood.

PHASE I METABOLISM

- Phase I reaction introduces a functional group(-OH,-NH_2,-SH) and usually result in increase of hydrophilicity of drug molecules.

1.OXIDATION

It is the most important drug metabolizing reaction. Oxidation involves addition of oxygen or negatively charged radicals. It is mostly carried out by monoxygenases enzymes in liver.eg: cytochrome P450, NADPH, etc.

2.REDUCTION

It is the reverse of oxidation. Reduction is the removal of oxygen or addition of hydrogen. Drugs like alchohol, aldehydes & quinines are reduced. Cytochrome P450 enymes act on opposite direction in reduction process.

- **3.HYDROLYSIS**: it is the cleavage of drug molecules by addition of water. Different enzymes catalyze hydrolytic reactions are carboxyesterases, peptidases, epoxide hydrolases, etc. It occurs in liver, intestines, plasma & other tissues.

- **4.CYCLIZATION**: It is the formation of ring structure from straight chain compound. e.g: Proguanil

- **5.DECYCLIZATION**: it is the opening of ring structure from cyclic compounds. e.g: barbiturates

PHASE II METABOLISM

- **1.GLUCURONIDE CONJUGATION**: It is the conjugation reaction carried out by Uridine Di-Phospho-Glucuronic Acid (UDP-GA). Drugs with hydroxyl & carboxylic acid are easily conjugated by glucuronic acid. E.g: chloraphenicol, aspirin, paracetamol, diazepam, morphine, metronidazole, etc.

- **2.SULFATE CONJUGATION**: It is the conjugation reaction carried out by sulfotransferases (SULTs). e.g: methyldopa, steroids, etc

- **3.GLUTATHIONE CONJUGATION**: It is the conjugation reaction carried out by Glutathione-S-Transferase (GST). It is responsible for inactivation of highly reactive quinine or epoxide intermediates formed during metabolism. e.g: paracetamol

- **4.AMINO ACID CONJUGATION**: It is the conjugation reaction carried out by glycine, taurine or glutamine. e.g: salicylates

- **5.ACETYLATION:** it is carried out by Acetyl Coenzyme-A. Drugs having amino or hydrazine residues are conjugated by acetylation. e.g: sulphonamides, isoniazid, dapsone, clonazepam, etc

- **6.METHYLATION:** It is carried out by methyltransferases. Drugs having amine & phenols can be methylated by methyltransferases. e.g: adrenaline, histamine, captopril, etc

General Pathways of Xenobiotic Biotransformation and Their Major Subcellular Location

REACTION	ENZYME OR SPECIFIC REACTION	LOCALIZATION
Hydrolysis	Carboxylesterase	Microsomes, cytosol, lysosomes, blood
	Alkaline phosphatase	Plasma membrane
	Peptidase	Blood, lysosomes
	Epoxide hydrolase	Microsomes, cytosol
Reduction	Azo- and nitro-reduction	Microflora
	Carbonyl (aldo-keto) reduction	Cytosol, microsomes, blood
	Disulfide reduction	Cytosol
	Sulfoxide reduction	Cytosol
	Quinone reduction	Cytosol, microsomes
	Dihydropyrimidine dehydrogenase	Cytosol
	Reductive dehalogenation	Microsomes
	Dehydroxylation (cytochrome b_5)	Microsomes
	Dehydroxylation (aldehyde oxidase)	Cytosol
Oxidation	Alcohol dehydrogenase	Cytosol
	Aldehyde dehydrogenase	Mitochondria, cytosol
	Aldehyde oxidase	Cytosol
	Xanthine oxidase	Cytosol
	Monoamine oxidase	Mitochondria
	Diamine oxidase	Cytosol
	Peroxidase	Microsomes, lysosomes, saliva
	Flavin-monooxygenases	Microsomes
	Cytochrome P450	Microsomes
Conjugation	UDP-Glucuronosyltransferase	Microsomes
	Sulfotransferase	Cytosol
	Glutathione transferase	Cytosol, microsomes, mitochondria
	Amino acid transferase	Mitochondria, microsomes
	N-Acetytransferase	Mitochondria, cytosol
	Methytransferase	Cytosol, microsomes, blood

FIRST PASS METABOLISM

- It is the metabolism of drugs during its passage from site of absorption to systemic circulation.
- All orally administered drugs are exposed to drug metabolizing enzymes in intestinal wall & liver where they first reach through portal vein.

ELIMINATION

- Excretion is the process of removal of drug & its metabolites through different body parts.
- Kidney
- Lungs
- Biles
- Intestines
- Skin
- Saliva & milk

Route of Elimination	Drugs
Kidney	Majority of drugs
Lungs	Alchohol, General Anaesthetics
Intestines	Ampicillin, Erythromycin, Tetracyclines
Saliva & sweat	Lithium, Potassium Iodide, Rifampin
Milk	Lipid soluble drugs

- **Clearence** of a drug is the theoretical volume of plasma from which drug is completely removed in unit time.

$$CL = \frac{\text{Rate of elimination}}{\text{Plasma concentration}}$$

- **Plasma half life** ($t^{1/2}$) of a drug is the time taken for reduction of plasma concentration of drug to half of its original value.