ABSORPTION OF DRUGS

CONTENTS

- Introduction of absorption.
- Structure of the Cell Membrane.
- Gastro intestinal absorption of drugs.
- Mechanism of Drug absorption.
- Factors affecting drug absorption
- Absorption of drugs from non-per oral routes
- Methods of determining absorption
- References.

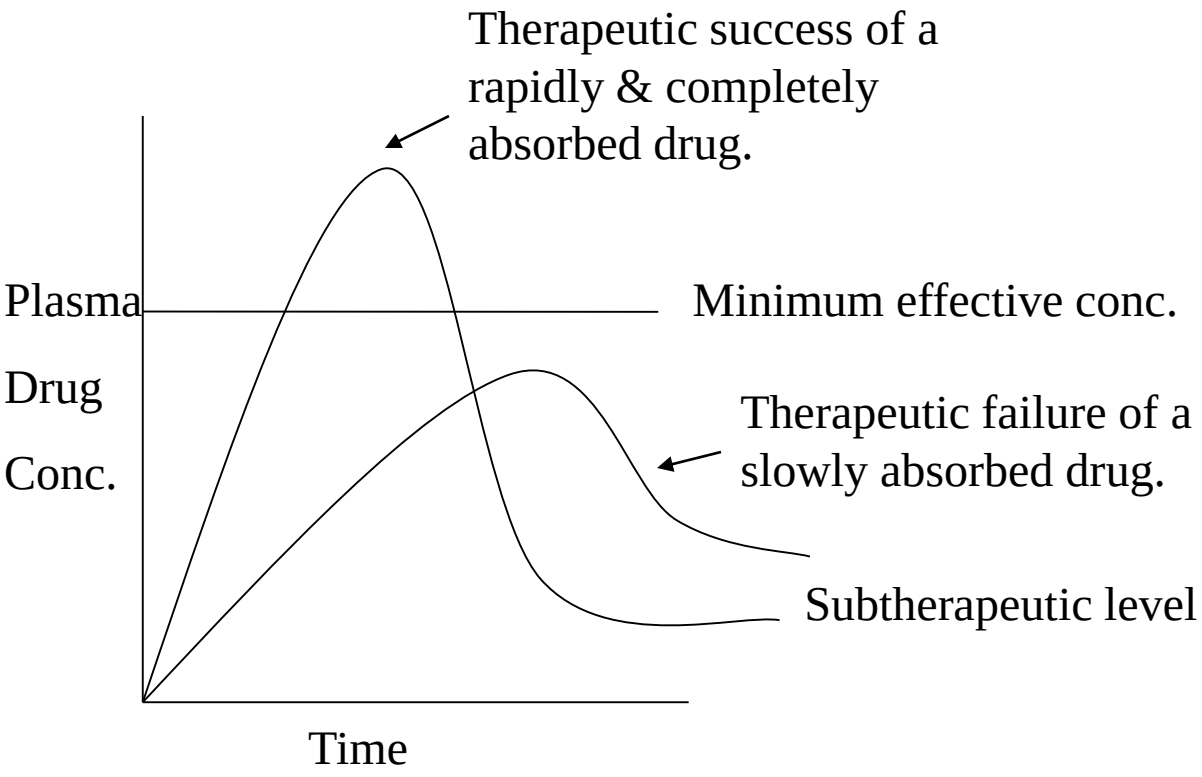
Introduction of Absorption

- Definition :

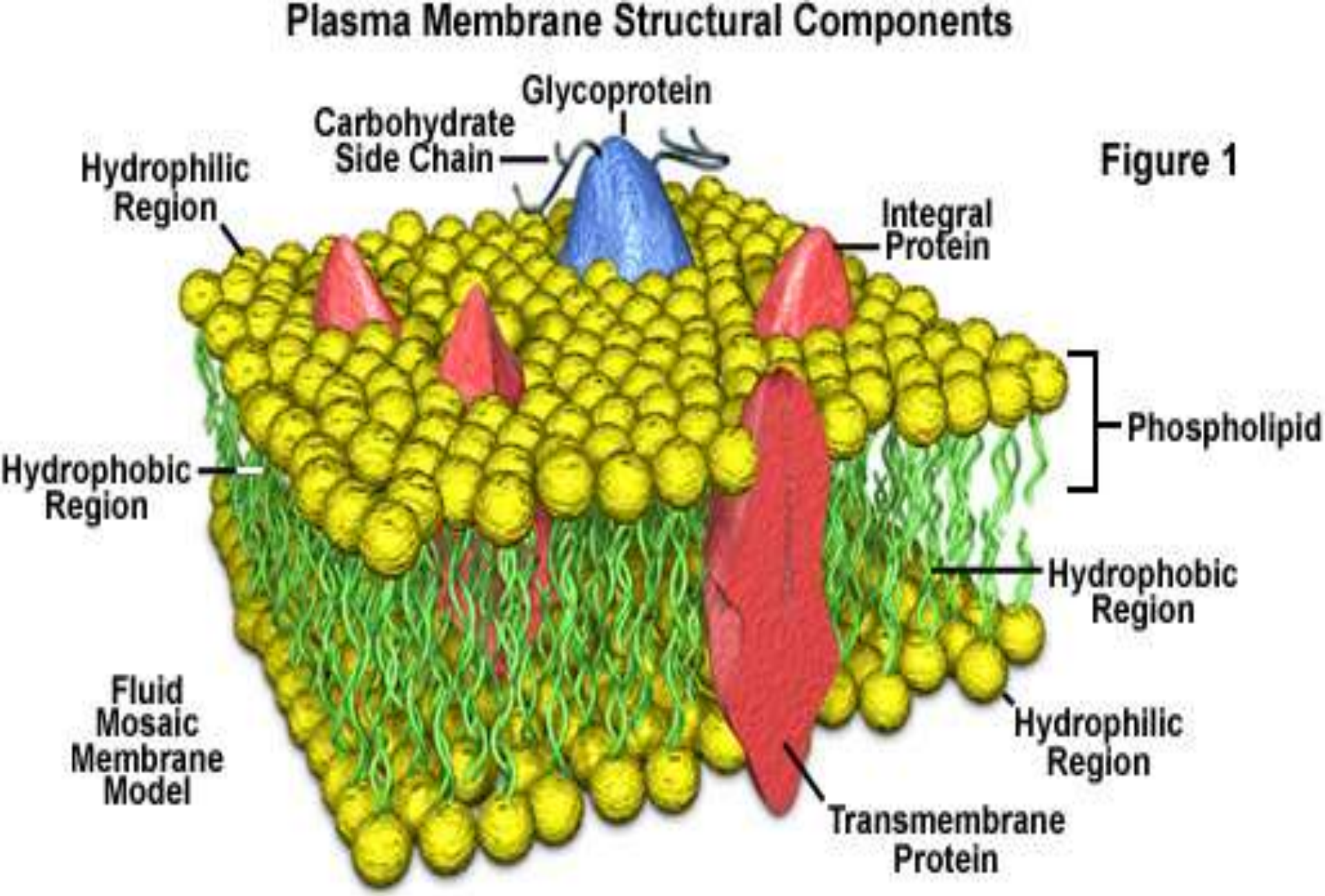
  The process of movement of unchanged drug from the site of administration to systemic circulation.

- There always exist a correlation between the plasma concentration of a drug & the therapeutic response & thus, absorption can also be defined as the process of movement of unchanged drug from the site of administration to the site of measurement.

  i.e., plasma.



→Not only the magnitude of drug that comes into the systemic circulation but also the rate at which it is absorbed is important this is clear from the figure.


Plasma Membrane Structural Components
Glycoprotein
Carbohydrate Side Chain
Hydrophilic Region
Figure 1
Integral Protein
Phospholipid
Hydrophobic Region
Hydrophobic Region
Fluid Mosaic Membrane Model
Hydrophilic Region
Transmembrane Protein

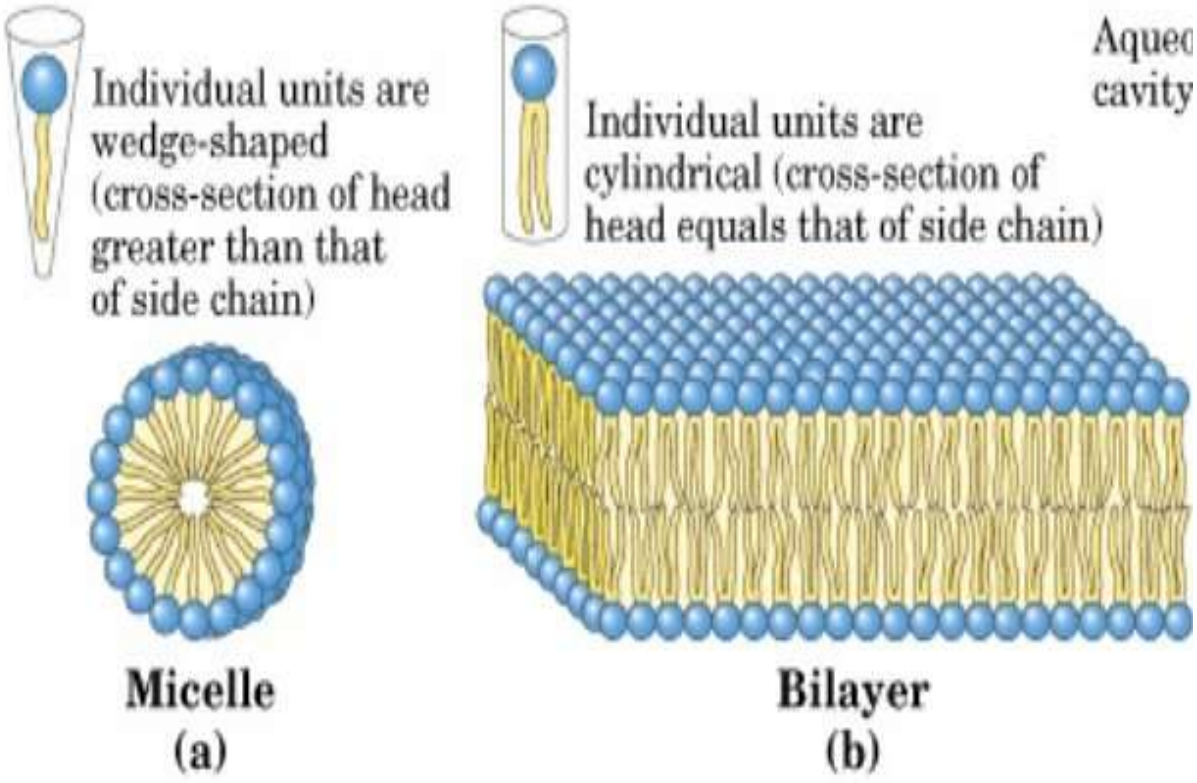
CELL MEMBRANE

- Also called the plasma membrane, plasmalemma or phospholipid bilayer.
- The plasma membrane is a flexible yet sturdy barrier that surrounds & contains the cytoplasm of a cell.

- Cell membrane mainly consists of:

1. Lipid bilayer-
   - -phospholipid
   - -Cholesterol
   - -Glycolipids.
2. Proitens-
   - -Integral membrane proteins
   - -Lipid anchored proteins
   - -Peripheral Proteins

Lipid Bilayers

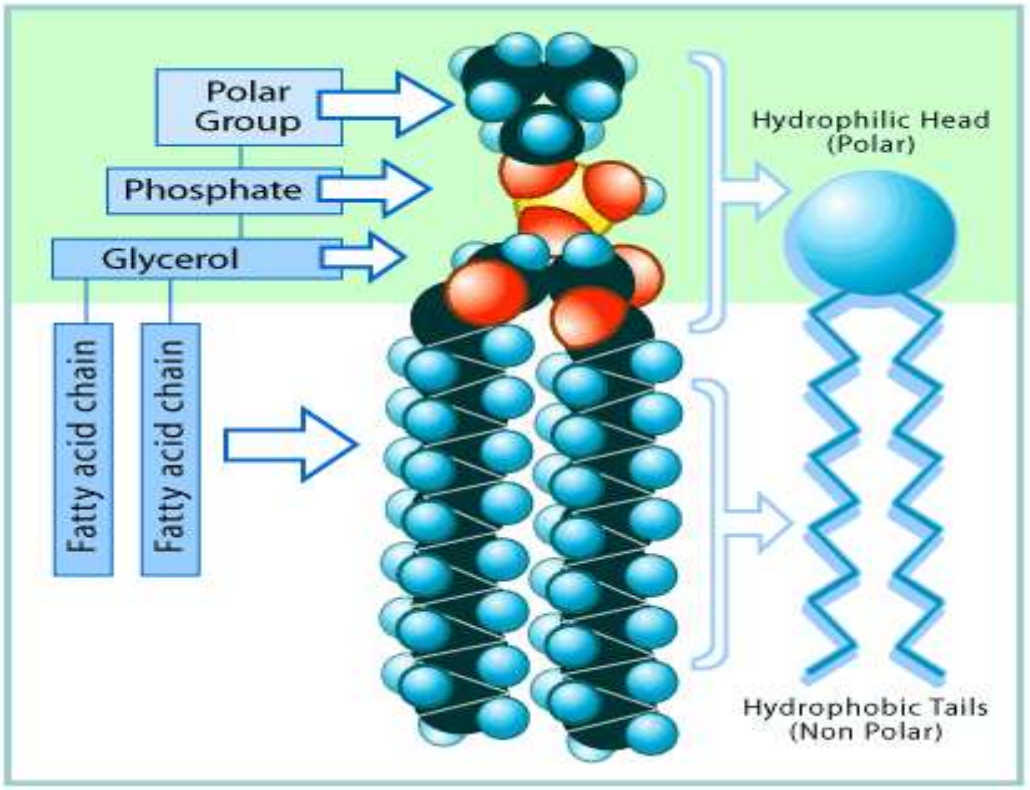


LIPID BILAYER

- The basic structural framework of the plasma membrane is the lipid bilayer.
- Consists primarily of a thin layer of amphipathic phospholipids which spontaneously arrange so that the hydrophobic “tail” regions are shielded from the surrounding polar fluid, causing the more hydrophilic “head” regions to associate with the cytosolic & extracellular faces of the resulting bilayer.
- This forms a continuous, spherical lipid bilayer app. 7nm thick.

It consists of two back to back layers made up of three types: Phospholipid, Cholesterol, Glycolipids.

1) Phospholipids :



→Principal type of lipid in membrane about 75 %.
Contains polar and non polar region.
→Polar region is *hydrophilic* and non polar region is *hydrophobic*.
Non polar head contain two fatty acid chain.
→One chain is straight fatty acid chain.(Saturated)
Another tail have cis double bond and have kink in tail.
(Unsaturated)

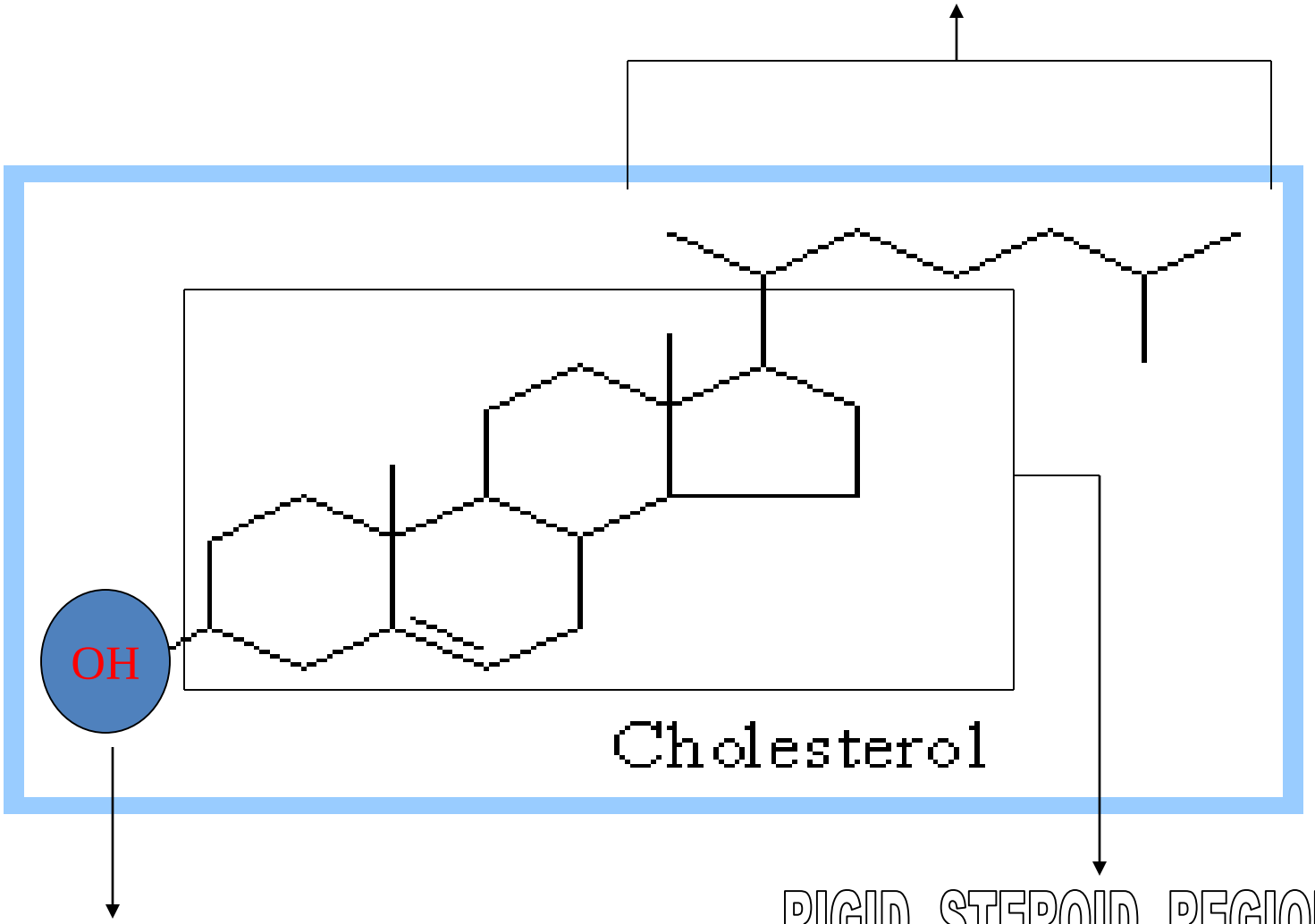
CHOLESTEROL

- Amount in membrane is 20 %.
- Insert in membrane with same orientation as phospholipids molecules.
- Polar head of cholesterol is aligned with polar head of phospholipids.

→<u>FUNCTION:</u>

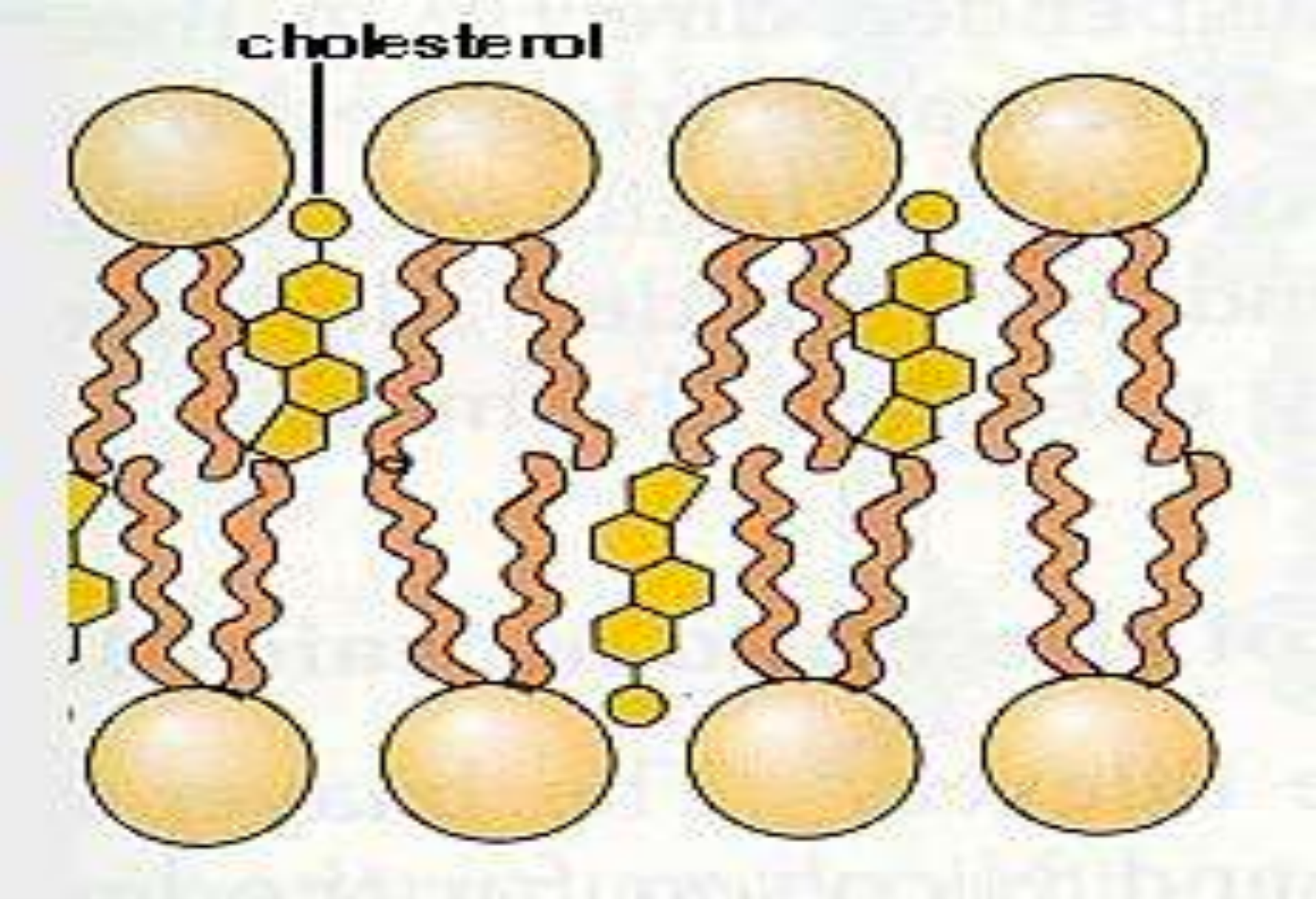
- Immobilize first few hydrocarbons groups phospholipids molecules.
- Prevents crystallization of hydrocarbons & phase shift in membrane

NON - POLAR HYDROCARBON CHAIN



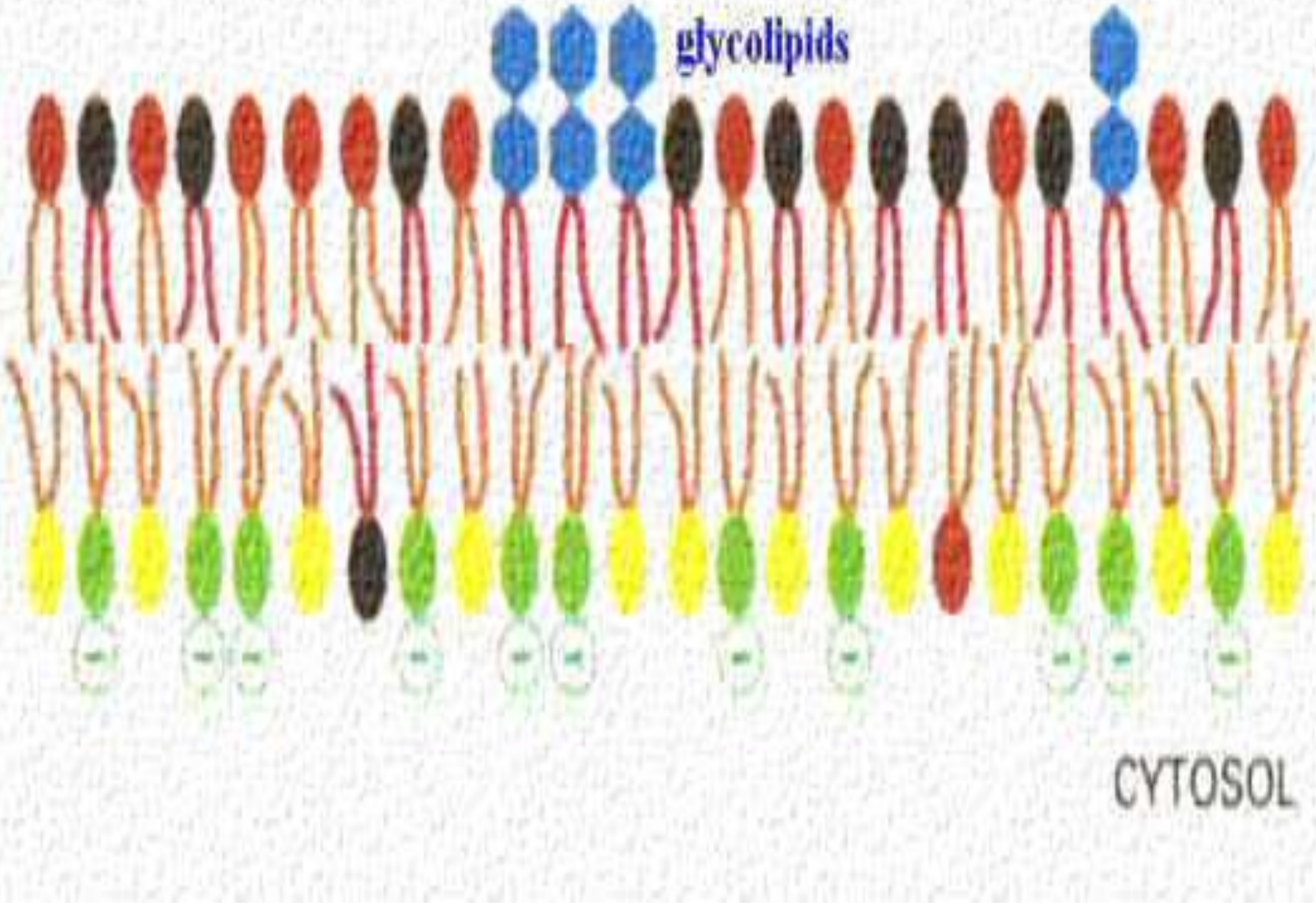
POLAR REGION

RIGID STEROID REGION

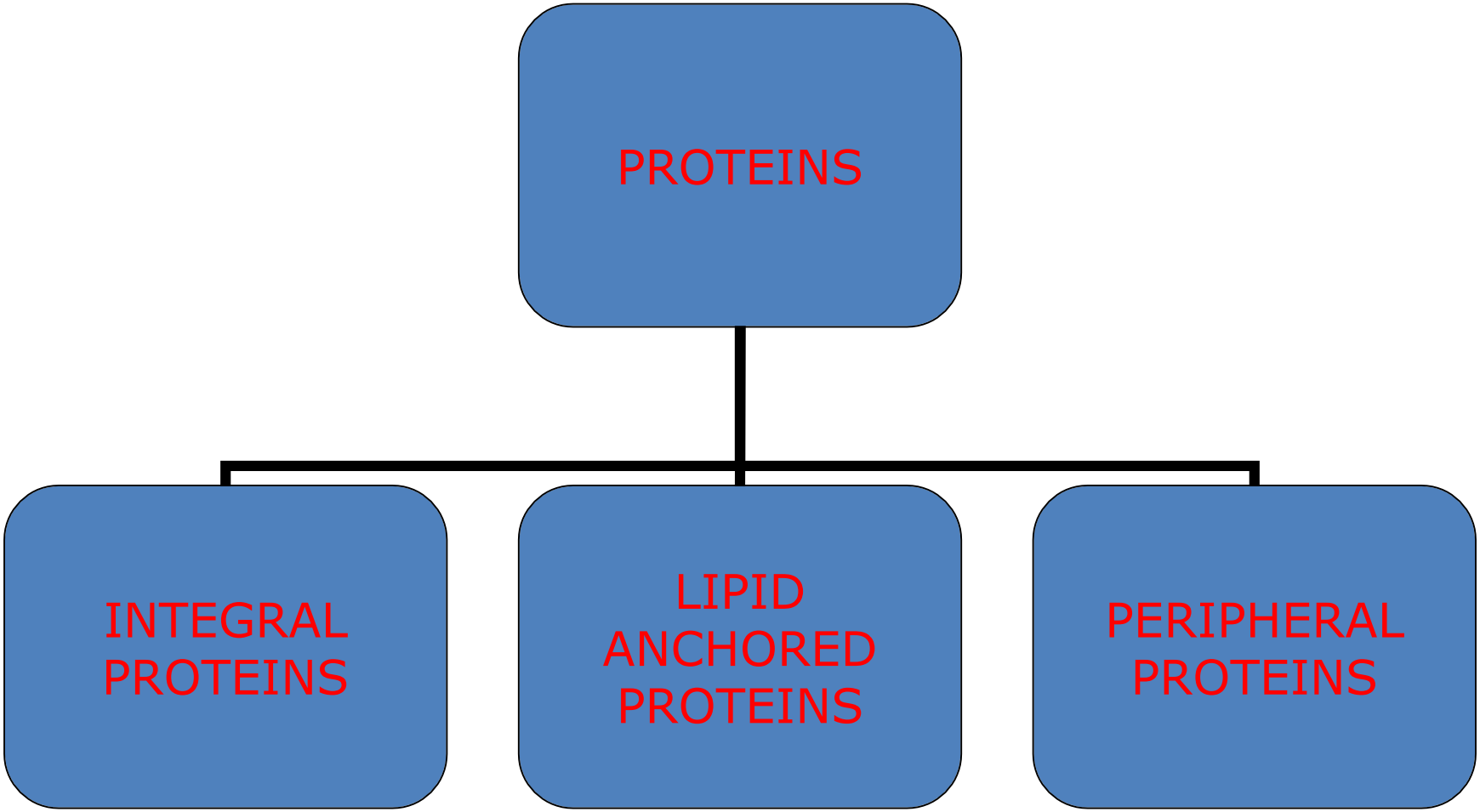

cholesterol

GLYCOLIPIDS

- Another component of membrane lipids present about 5 %.
- Carbohydrate groups form polar “head”.
- Fatty acids “tails” are non polar.
- Present in membrane layer that faces the extracellular fluid.
- This is one reason due to which bilayer is asymmetric.
- FUNCTIONS:
  Protective
  Insulator
  Site of receptor binding


glycolipids
CYTOSOL

COMPOSITION OF PROTEINS



INTEGRAL PROTEINS

- Also known as “Transmembrane protein”.
- Have hydrophilic and hydrophobic domain.
- Hydrophobic domain anchore within the cell membrane and hydrophilic domain interacts with external molecules.
- Hydrophobic domain consists of one, multiple or combination of α – helices and ß – sheets protein mofits.
- Ex. – Ion Channels, Proton pump, GPCR.

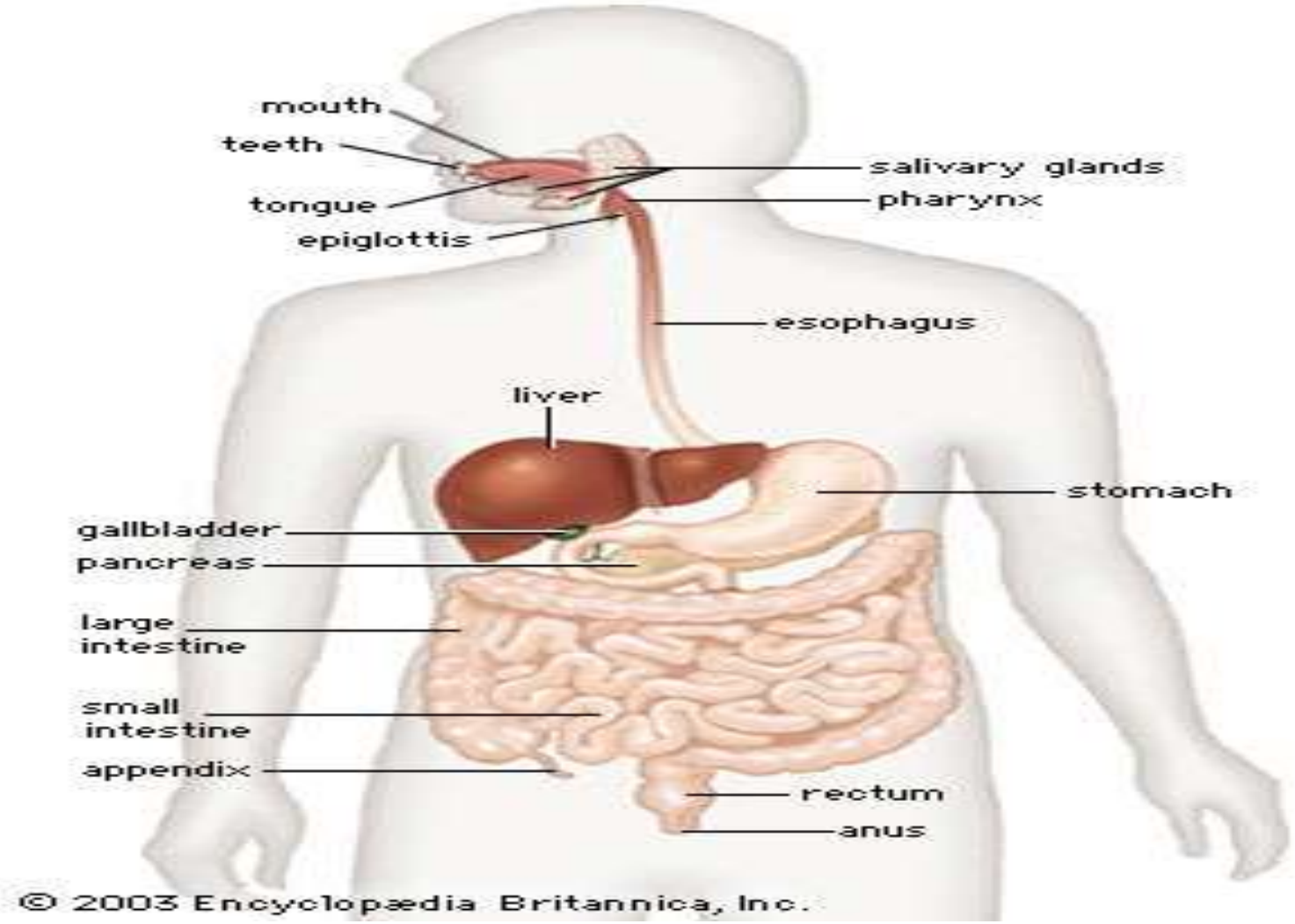
LIPID ANCHORED PROTEIN

- Covalently bound to single or multiple lipid molecules.
- Hydrophobically inert into cell membrane & anchor the protein.
- The protein itself is not in contact with membrane.
- Ex. – G Proteins.

PERIPHERAL PROTEINS

- Attached to integral membrane proteins OR associated with peripheral regions of lipid bilayer.
- Have only temporary interaction with biological membrane.
- Once reacted with molecule, dissociates to carry on its work in cytoplasm.
- Ex. – Some Enzyme, Some Hormone

GASTRO INTESTINAL ABSORPTION OF DRUGS



❖ Stomach :

- The surface area for absorption of drugs is relatively small in the stomach due to the absence of macrovilli & microvilli.
- Extent of drug absorption is affected by variation in the time it takes the stomach to empty, i.e., how long the dosage form is able to reside in stomach.
- Drugs which are acid labile must not be in contact with the acidic environment of the stomach.
- Stomach emptying applies more to the solid dosage forms because the drug has to dissolve in the GI fluid before it is available for absorption.
- Since solubility & dissolution rate of most drugs is a function of pH, it follows that, a delivery system carrying a drug that is predominantly absorbed from the stomach, must stay in the stomach for an extended period of time in order to assure maximum dissolution & therefore to extent of absorption.

❖ Small Intestine :

- The drugs which are predominantly absorbed through the small intestine, the transit time of a dosage form is the major determinant of extent of absorption.

- Various studies to determine transit time:

- Early studies using indirect methods placed the average normal transit time through the small intestine at about 7 hours.
- These studies were based on the detection of hydrogen after an oral dose of lactulose. (Fermentation of lactulose by colon bacteria yields hydrogen in the breath).

Small Intestine

- Newer studies suggest the transit time to be about 3 to 4 hours.
- Use gamma scintigraphy.

- Thus, if the transit time in small intestine for most healthy adults is between 3 to 4 hours, a drug may take about 4 to 8 hours to pass through the stomach & small intestine during fasting state.
- During the fed state, the small intestine transit time may take about 8 to 12 hours.

❖Large intestine :

- The major function of large intestine is to absorb water from ingestible food residues which are delivered to the large intestine in a fluid state, & eliminate them from the body as semi solid feces.

- Only a few drugs are absorbed in this region.

MECHANISM OF DRUG ABSORPTION

A. Transcellular/ Intracellular Transport
B. Paracellular/ Intercellular Transport
C. Vesicular Transport

A. Transcellular Transport Processes

1. Passive Transport Processes
   - Passive Diffusion Transport
   - Pore Transport
   - Ion Pair Transport
   - Facilitataed or mediated Transport
2. Active Transport Processes
   - Primary Active Transport
   - Secondary Active Transport
     (Symport & Antiport)

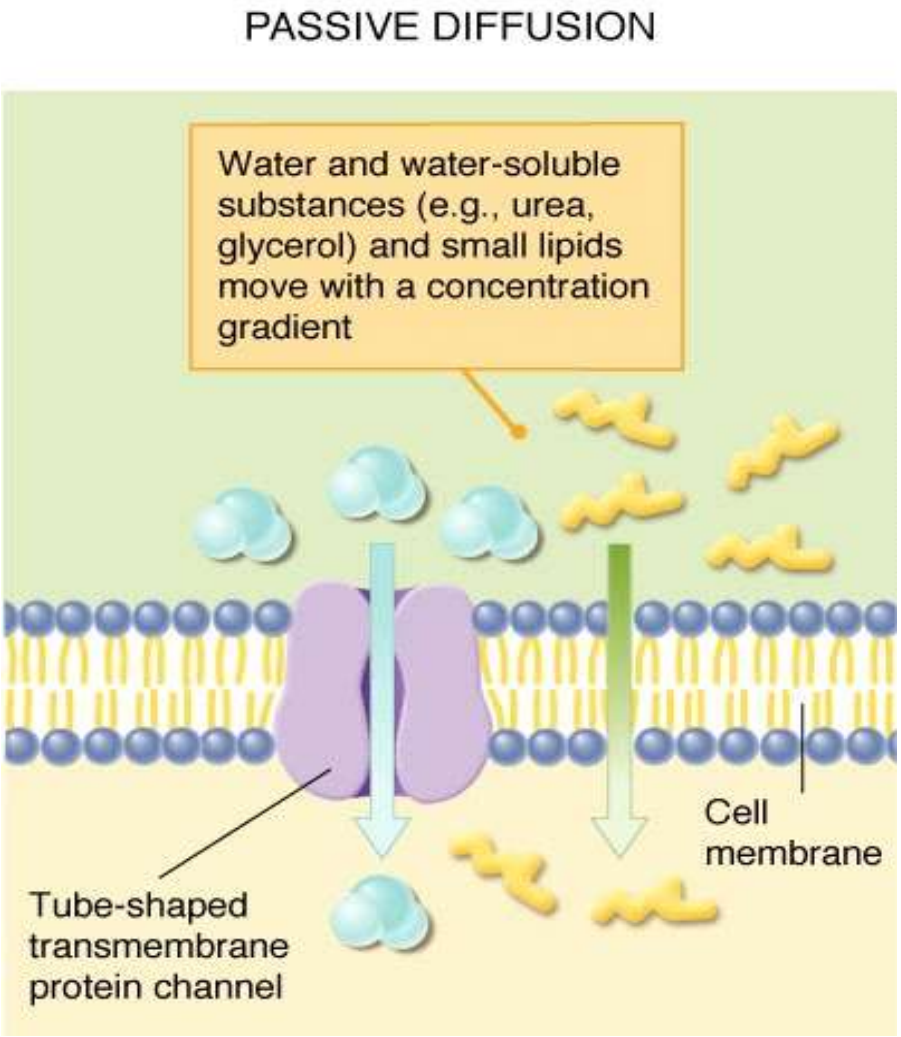
2. Paracellular Transport

1. Permeation through tight junctions of epithelial cells
2. Persorption

C. Vesicular Transport

1. Phagocytosis
2. Pinocytosis
3. Transcytosis

PASSIVE DIFFUSION



- Also known as non-ionic diffusion.
- It is defined as the difference in the drug concentration on either side of the membrane.
- Absorption of 90% of drugs.
- The driving force for this process is the concentration or electrochemical gradient.

- Passive diffusion is best expressed by Fick's first law of diffusion which states that the drug molecules diffuse from a region of higher concentration to one of lower concentration until equilibrium is attained & the rate of diffusion is directly proportional to the concentration gradient across the membrane.

$$\frac{dQ}{dt} = \frac{D\ A\ K_{m/w}}{h}(C_{GIT} - C)$$

- ➢ Certain characteristic of passive diffusion can be generalized.

a) Down hill transport

b) Greater the surface area & lesser the thickness of the membrane, faster the diffusion.

c) Equilibrium is attained when the concentration on either side of the membrane become equal.

d) Greater the membrane/ water partition coefficient of drug, faster the absorption.

- Passive diffusion process is energy independent process
- The mol. Wt. of the most drugs lie between 100 to 400 Daltons which can be effectively absorbed passively.

Pore transport

- Also known as convective transport, bulk flow or filtration.
- Important in the absorption of low mol. Wt. (less than 100). Low molecular size (smaller than the diameter of the pore) & generally water-soluble drugs through narrow, aqueous filled channels or pores in the membrane structure.

  e.g. urea, water & sugars.
- The driving force for the passage of the drugs is the hydrostatic or the osmotic pressure difference across the membrane.

- The rate of absorption via pore transport depends on the number & size of the pores, & given as follows:

$$\frac{dc}{dt} = \frac{N.\ R^2.\ A\ .\ \Delta C}{(\eta)\ (h)}$$

where,

$\frac{dc}{dt}$ = rate of the absorption.

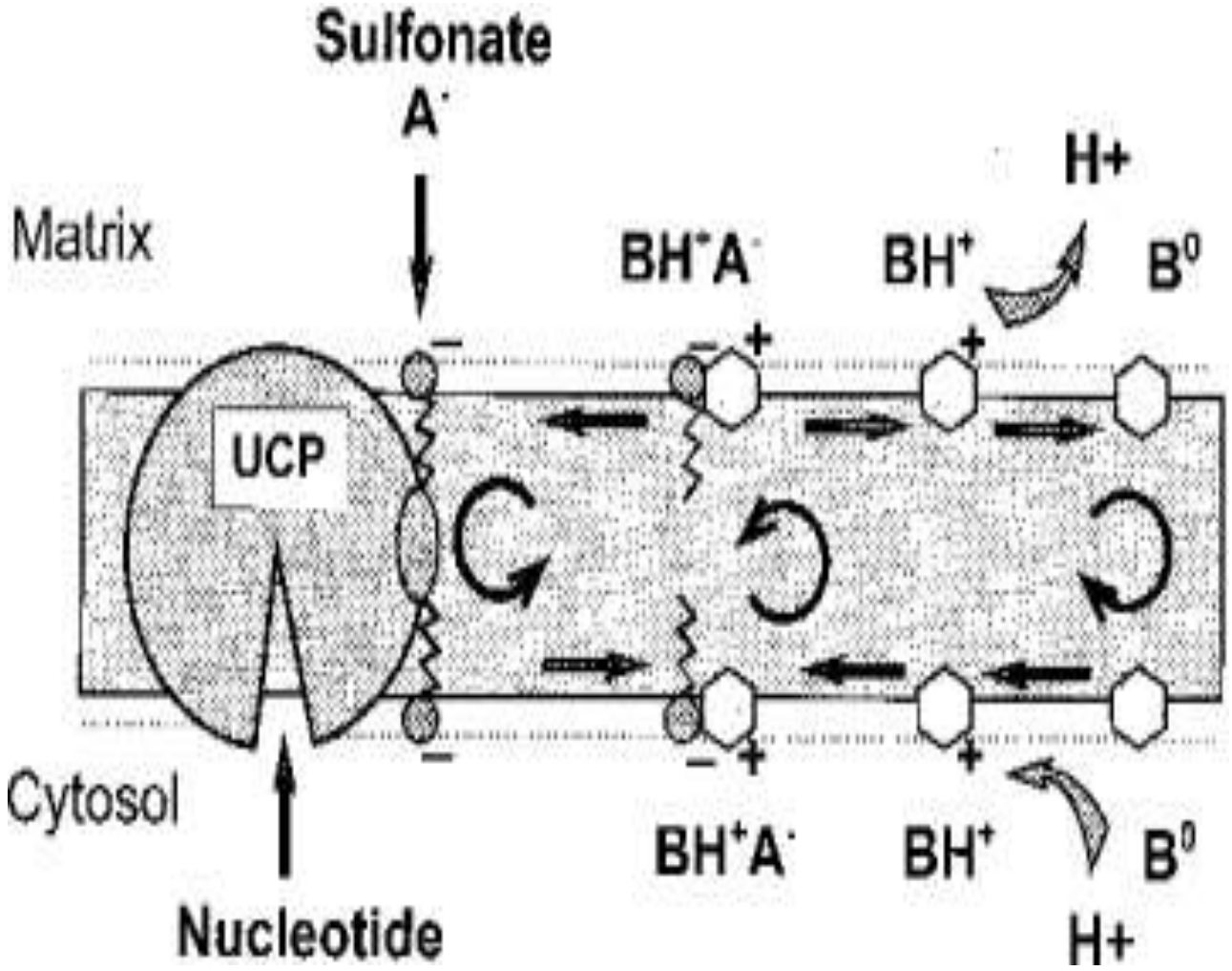
N = number of pores

R = radius of pores

ΔC = concentration gradient

η = viscosity of fluid in the pores

ION PAIR TRANSPORT

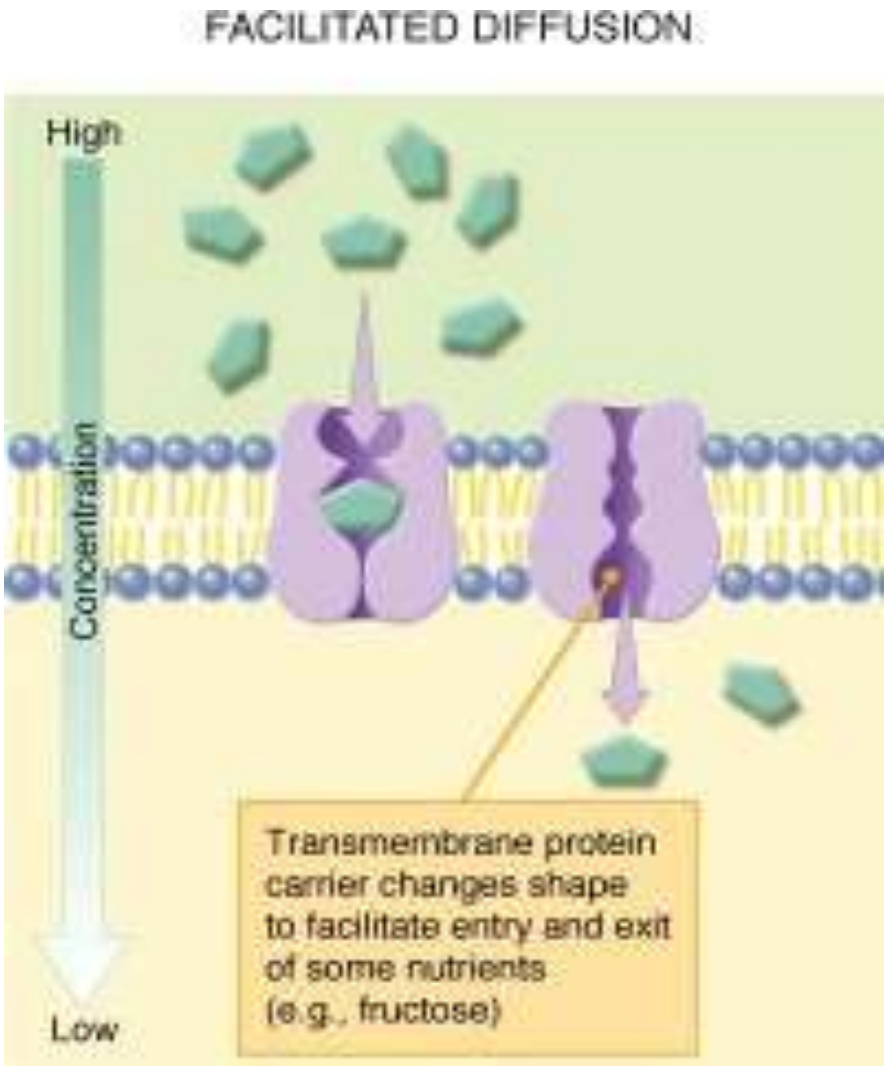


- It is another mechanism is able to explain the absorption of such drugs which ionize at all pH condition.

- Transport of charged molecules due to the formation of a neutral complex with another charged molecule carrying an opposite charge.
- Drugs have low o/w partition coefficient values, yet these penetrate the membrane by forming reversible neutral complexes with endogenous ions.

  e.g. mucin of GIT.
- Such neutral complexes have both the required lipophilicity as well as aqueous solubility for passive diffusion.
- This phenomenon is known as ion-pair transport.

Facilitated diffusion



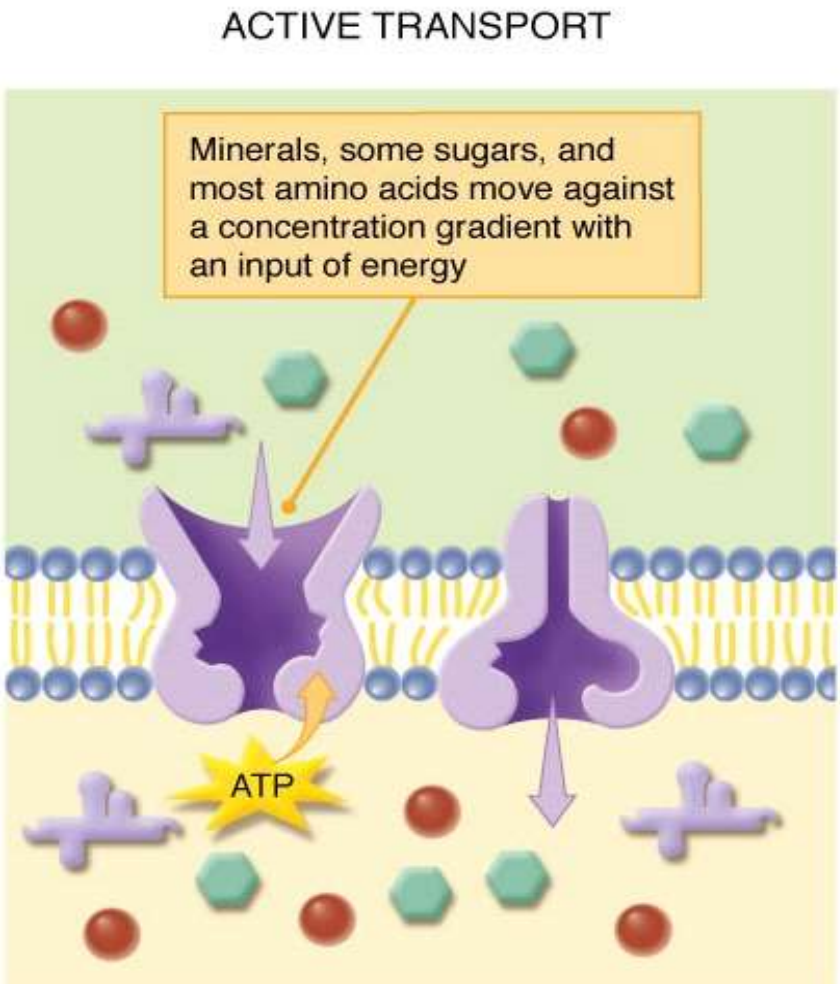
- This mechanism involves the driving force is concentration gradient.
- In this system, no expenditure of energy is involved (down-hill transport), therefore the process is not inhibited by metabolic poisons that interfere with energy production.

- Limited importance in the absorption of drugs.

  e.g. Such a transport system include entry of glucose into RBCs & intestinal absorption of vitamins B_1 & B_2.

- A classical example of passive facilitated diffusion is the gastro-intestinal absorption of vitamin B_{12}.
- An intrinsic factor (IF), a glycoprotein produced by the gastric parietal cells, forms a complex with vitamin B_{12} which is then transported across the intestinal membrane by a carrier system.

Active transport



- More important process than facilitated diffusion.
- The driving force is against the concentration gradient or uphill transport.
- Since the process is uphill, energy is required in the work done by the barrier.
- As the process requires expenditure of energy, it can be inhibited by metabolic poisons that interfere with energy production.

- If drugs (especially used in cancer) have structural similarities to such agents, they are absorbed actively.
- A good example of competitive inhibition of drug absorption via active transport is the impaired absorption of levodopa when ingested with meals rich in proteins.

- The rate of absorption by active transport can be determined by applying the equation used for Michalies-menten kinetics:

$$\frac{dc}{dt} = \frac{[C].(dc/dt)_{max}}{Km + [C]}$$

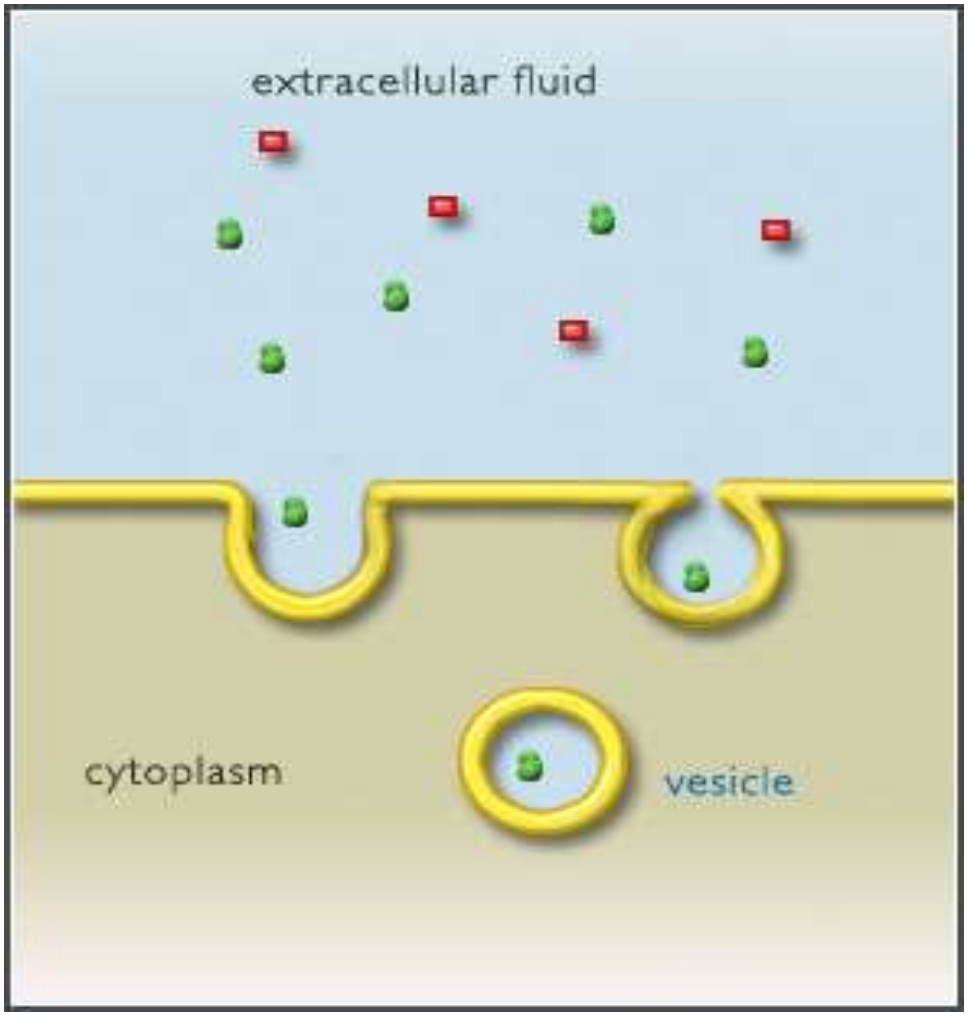
Where,

$(dc/dt)_{max}$ = maximal rate of drug absorption at high drug concentration.

[C] = concentration of drug available for absorption

Km = affinity constant of drug for the barrier.

ENDOCYTOSIS



- It involves engulfing extracellular materials within a segment of the cell membrane to form a saccule or a vesicle (hence also called as corpuscular or vesicular transport) which is then pinched off intracellularly.

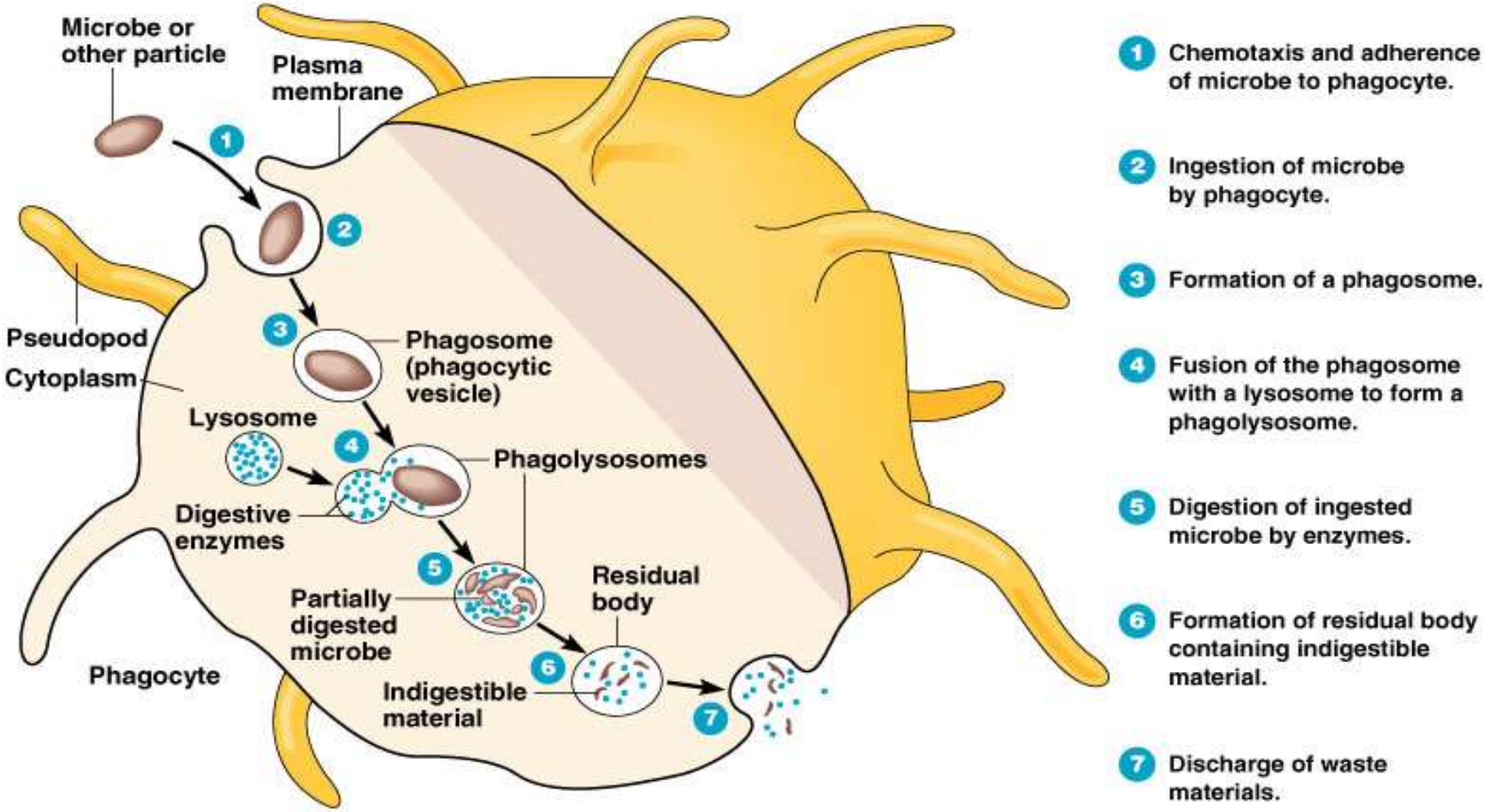
- In endocytosis, there are three process:

A) Phagocytosis

B) Pinocytosis

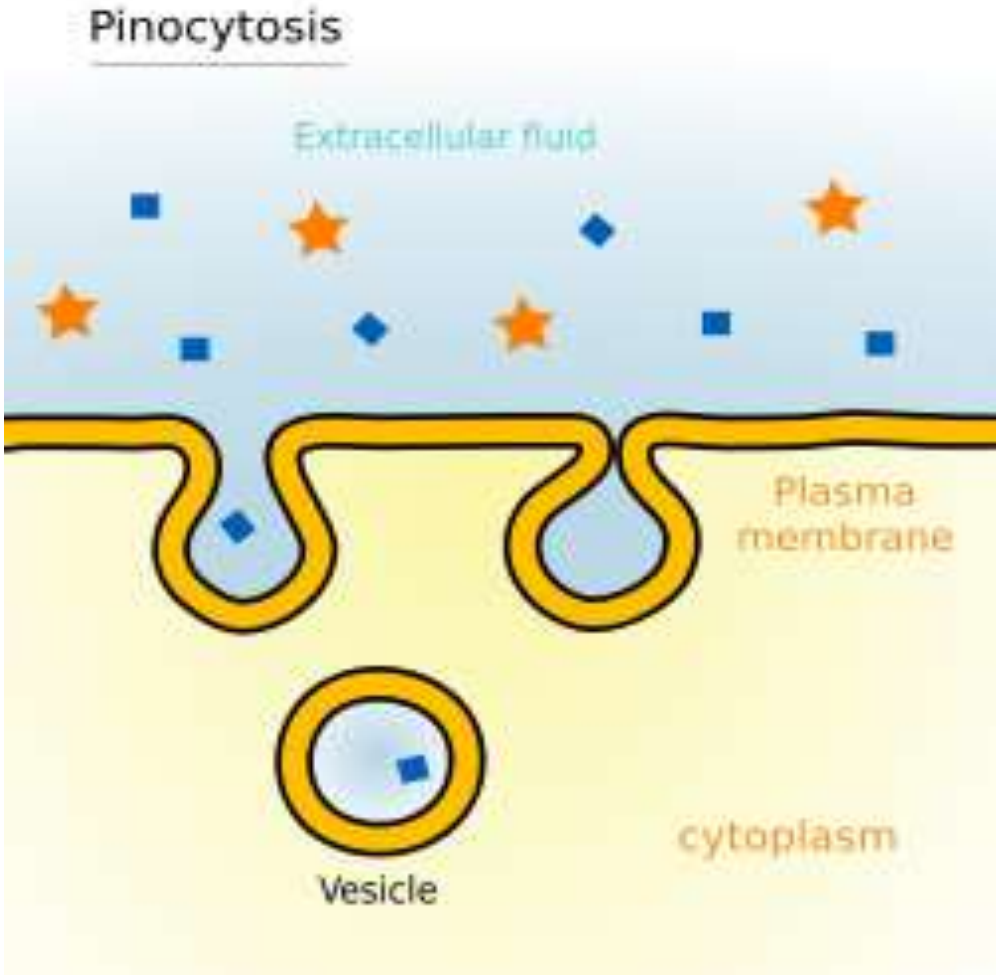
C) Transcytosis

A) Phagocytosis



(a) Phases of phagocytosis

Pinocytosis



- This process is important in the absorption of oil soluble vitamins & in the uptake of nutrients.

C) Transcytosis

- It is a phenomenon in which endocytic vesicle is transferred from one extracellular compartment to another.

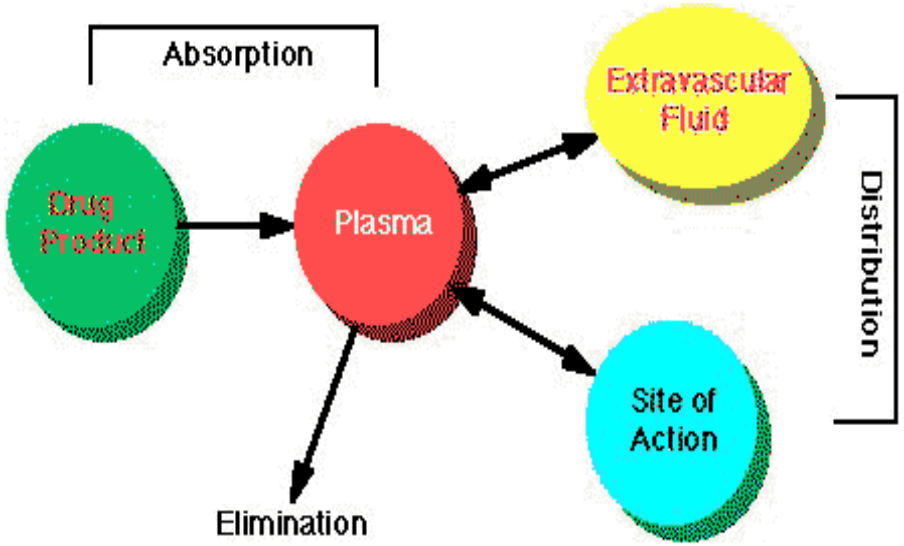
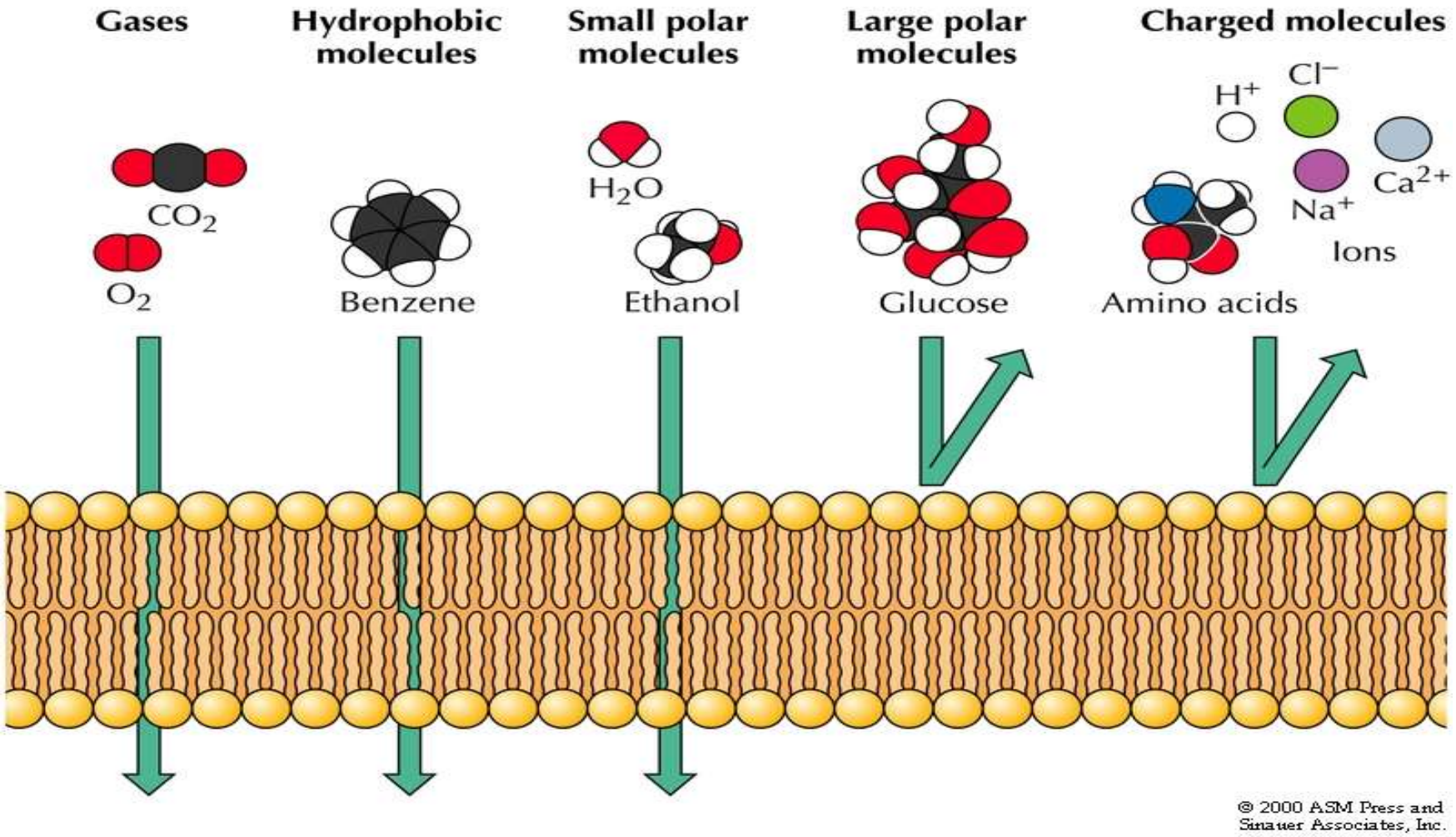


Diagram Representing Absorption, Distribution, Metabolism and Excretion

The ultimate goal is to have the drug reach the site of action in a concentration which produces a pharmacological effect. No matter how the drug is given (other than IV) it must pass through a number of biological membranes before it reaches the site of action.

MOVEMENT OF SUBSTANCES ACROSS CELL MEMBRANES



Factors affecting absorption:

A. Pharmaceutical factors:

1. Physicochemical properties of drug
   a. Drug solubility and dissolution rate
   b. Particle size and effective surface area
   c. Polymorphism and amorphism
   d. Pseudopolymorphism(hydrates or solvates)
   e. Salt form of the drug
   f. Lipophilicity of the drug
   g. Drug stability
   h. Stereochemical nature of the drug

2. Formulation factors:

a. disintegration time
b. manufacturing variables
c. nature and type of dosage form
d. pharmaceutical ingredients (excepients)
e. product age and storage conditions