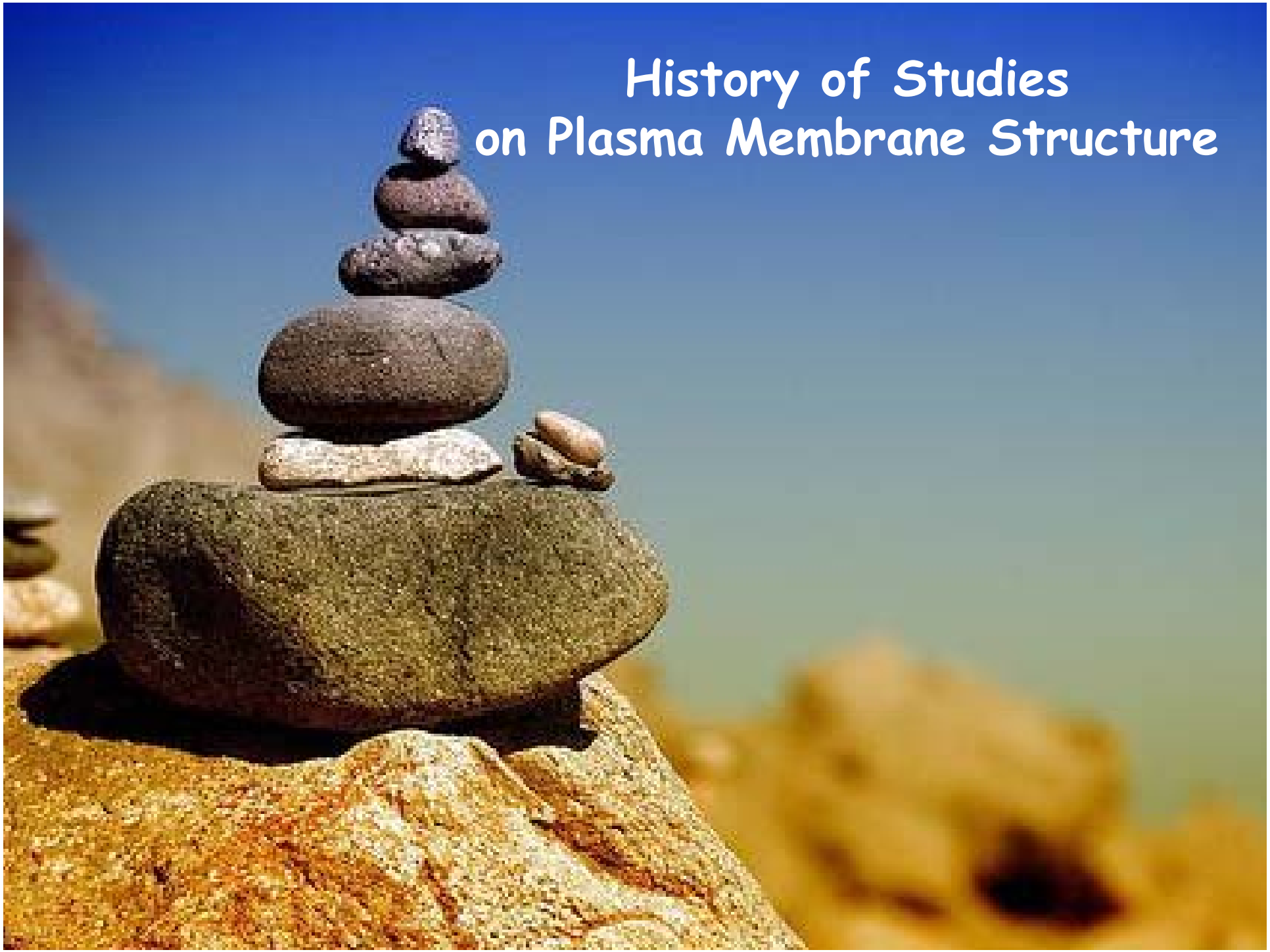
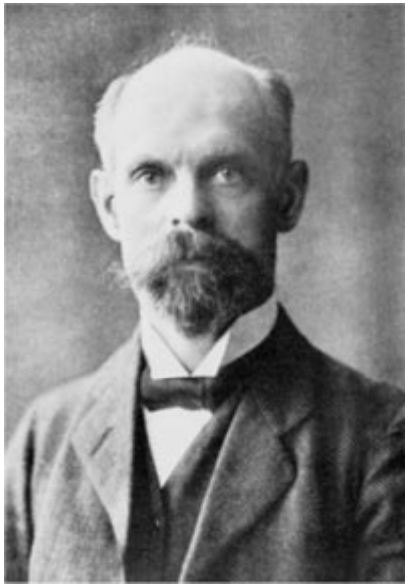
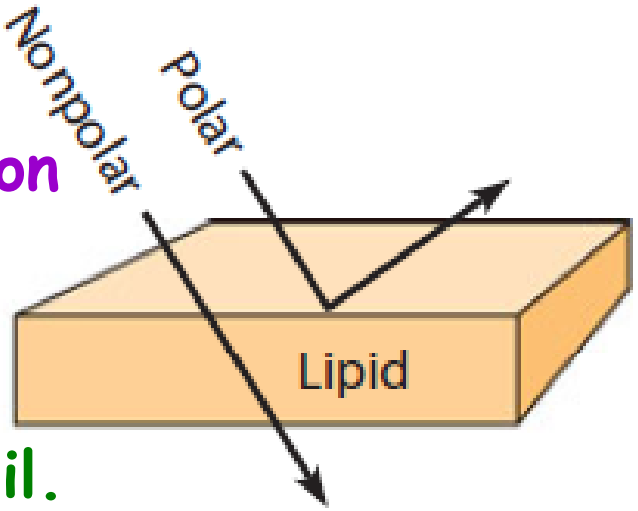

History of Studies
on Plasma Membrane Structure

C. E. Overton - Lipid Nature of Membrane



- ✓ German scientist -
  Charles Ernest Overton (1890)
- ✓ first insights into the chemical nature cell membrane
- ✓ In root hair cells, he observed that lipid-soluble substances penetrate readily into cells, whereas water-soluble substances do not
- ✓ he concluded that lipids are present on the cell surface as a "coat"
- ✓ the dissolving power of the cell membrane matched that of a fatty oil.

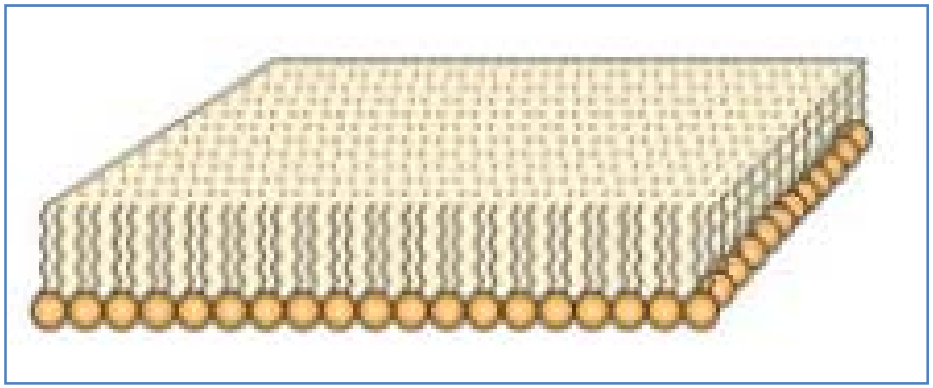


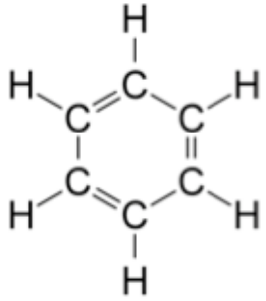
Irving Langmuir - Lipid Monolayer Concept

- ✓ In 1905

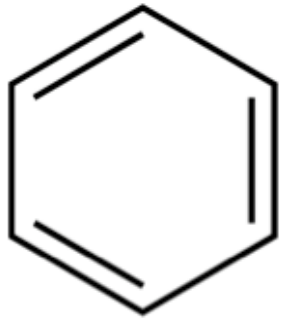
- ✓ He studied the behavior of purified phospholipids by dissolving them in benzene and layering samples of the benzene-lipid solution onto a water surface.

- ✓ As the benzene evaporated, the molecules were left as a lipid film one molecule thick, i.e., a "monolayer."

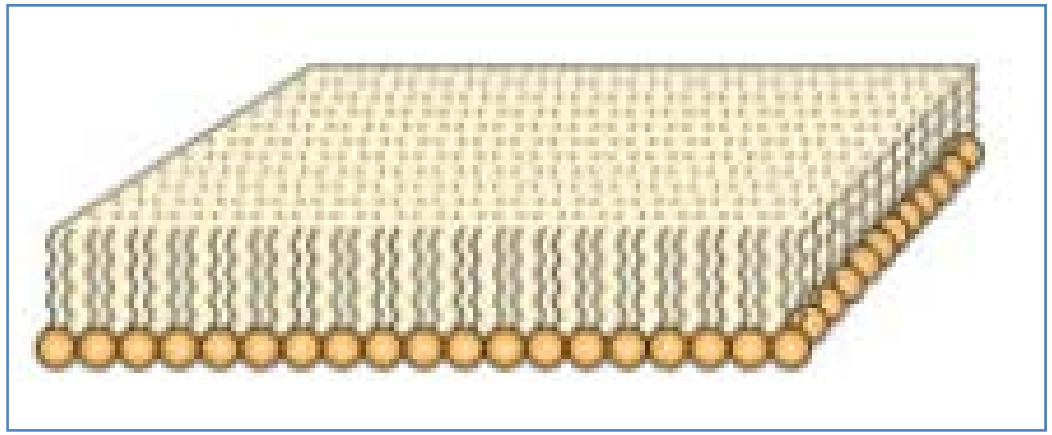




Benzene: C_6H_6



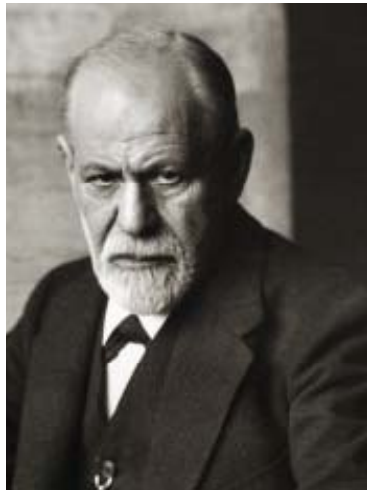
- ✓ the phospholipids orient themselves on water such that their hydrophilic heads face the water and their hydrophobic tails protrude away from the water.

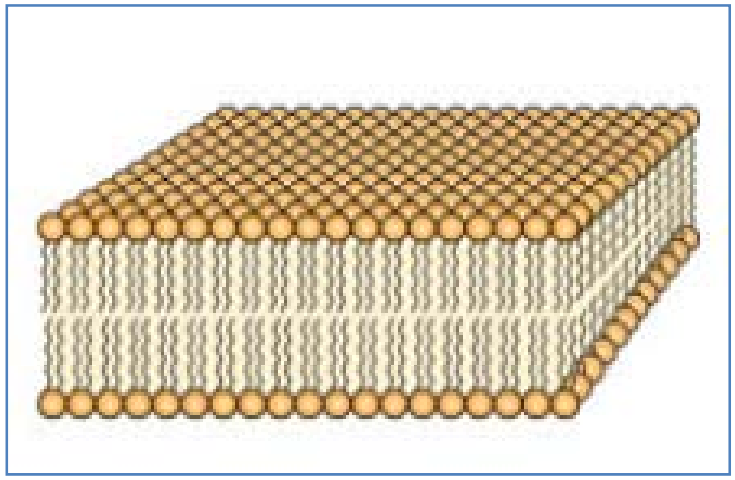


- ✓ Langmuir's lipid monolayer became the basis for further thought about membrane structure in the early years of the twentieth century...

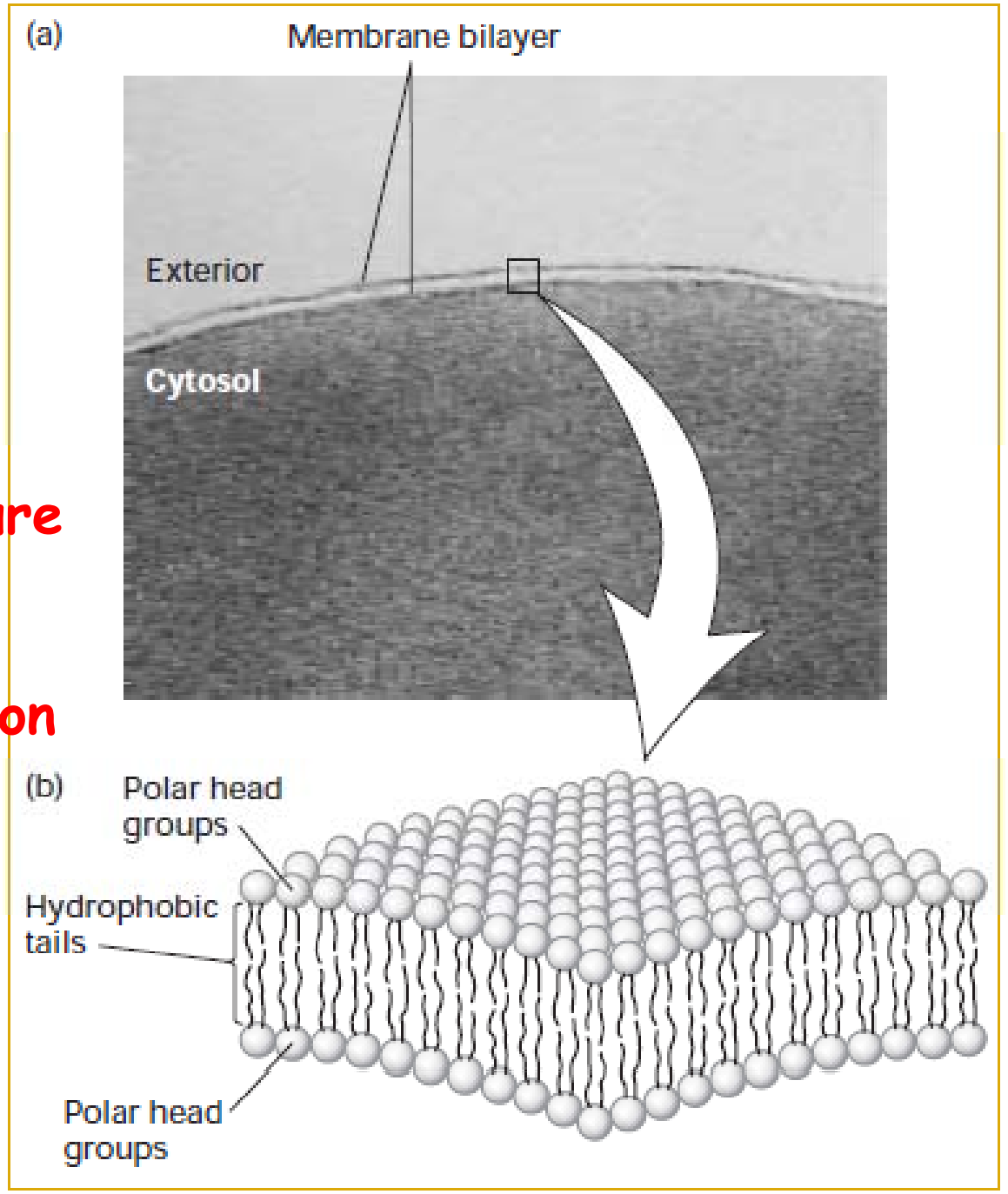
Gorter and Grendel - Lipid Bilayer Concept

- ✓ In 1925 two Dutch physiologists, Evert Gorter and F. Grendel, conducted the Langmuir's experiment using RBC.
- ✓ They found that the area of the lipid film on the water was about twice the estimated total surface area of the erythrocyte.
- ✓ Therefore, they concluded that the erythrocyte plasma membrane consists of not one but two layers of lipids.

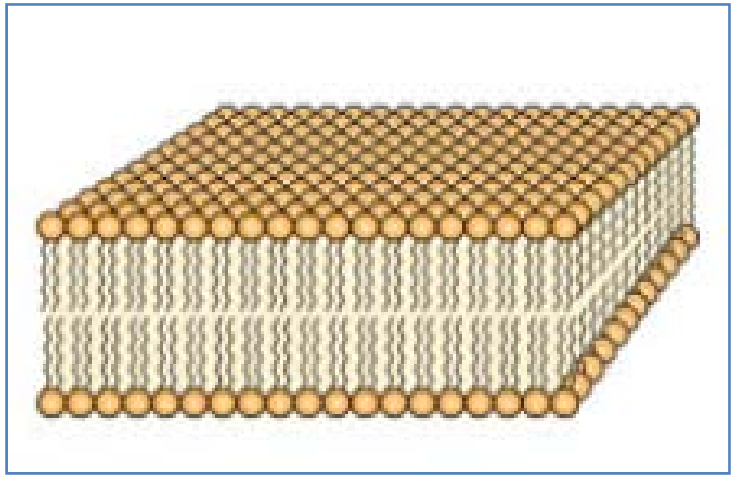




- **The bilayer structure would be the thermodynamically more stable condition in cells**



Gorter and Grendel's experiment and their conclusion was a major breakthrough in the study of plasma membrane.



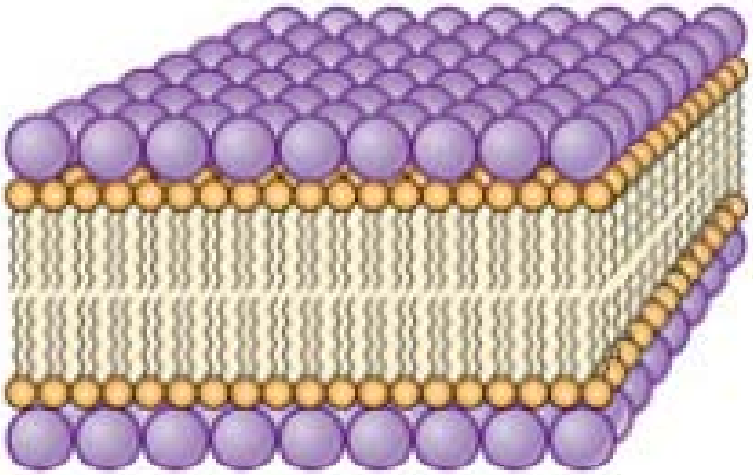
Davson and Danielli - Sandwich Model

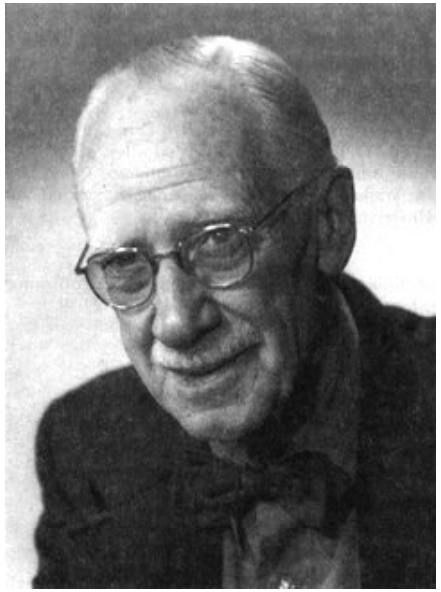
- ✓ In 1925, it became clear that a simple lipid bilayer, could not explain all the properties of membranes.
- ✓ Properties such as surface tension, solute permeability, electrical conductivity, and movement of water, solutes & ions.

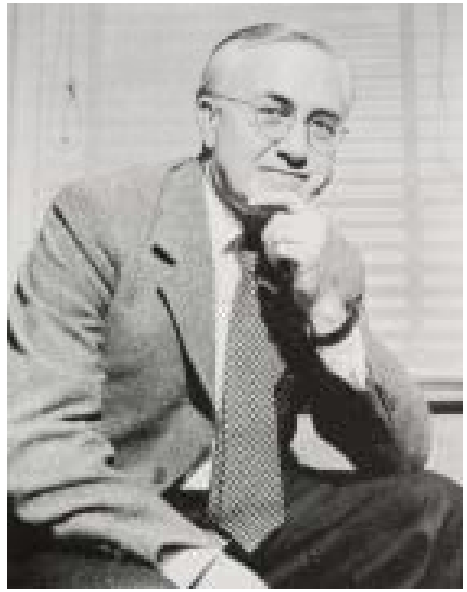
Example

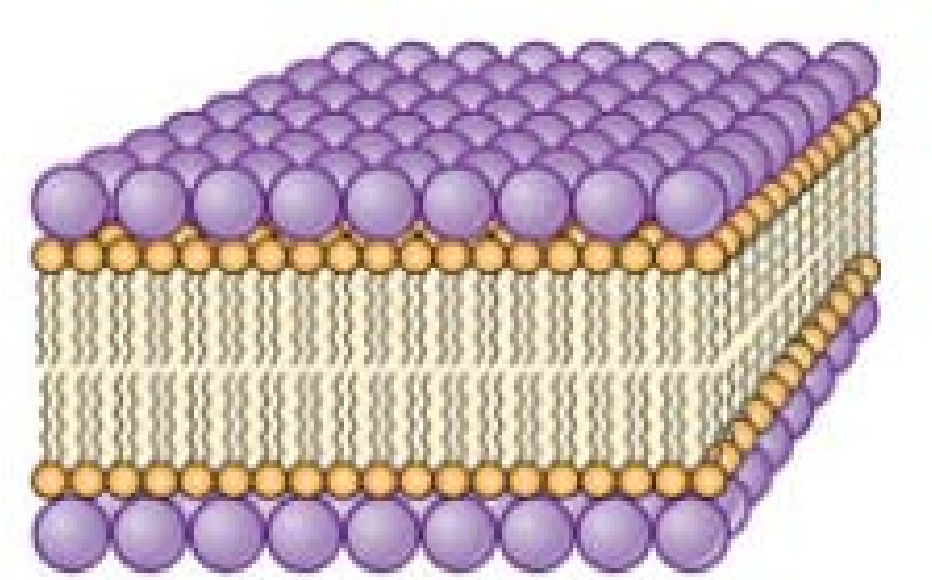
- ✓ the surface tension of a lipid film was significantly higher than that of cellular membranes but could be lowered by adding protein to the lipid film.
- ✓ sugars, ions, and other hydrophilic solutes readily moved into and out of cells even though pure lipid bilayers are nearly impermeable to water-soluble substances.

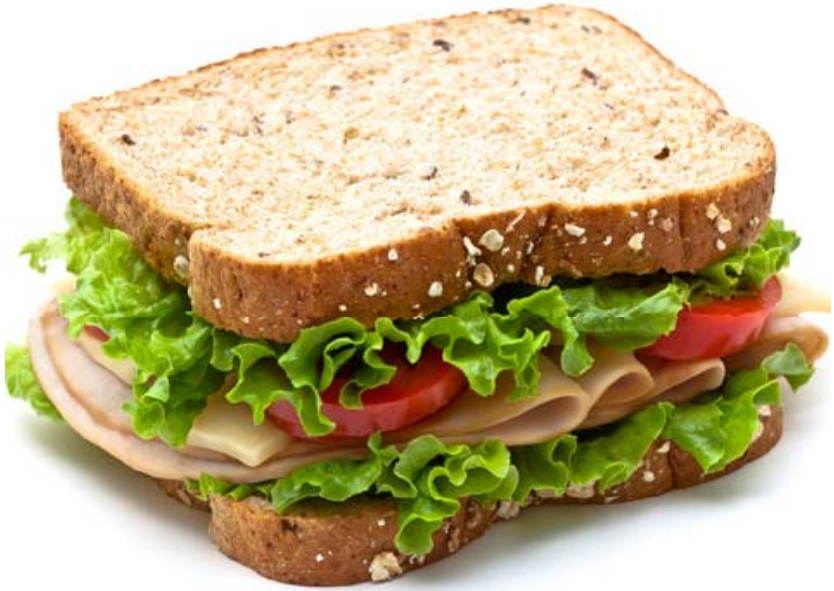
- ✓ To explain such properties, in 1935 Hugh Davson and James Danielli proposed the "sandwich" model.
- ✓ They suggested that proteins are present on membrane as a layer
- ✓ the lipid bilayers are coated on both sides with thin sheets of proteins- results in a protein-lipid-protein structure; known as sandwich model







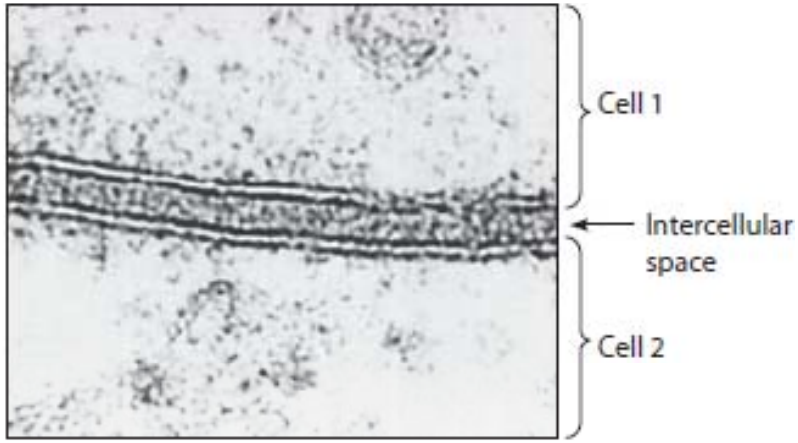


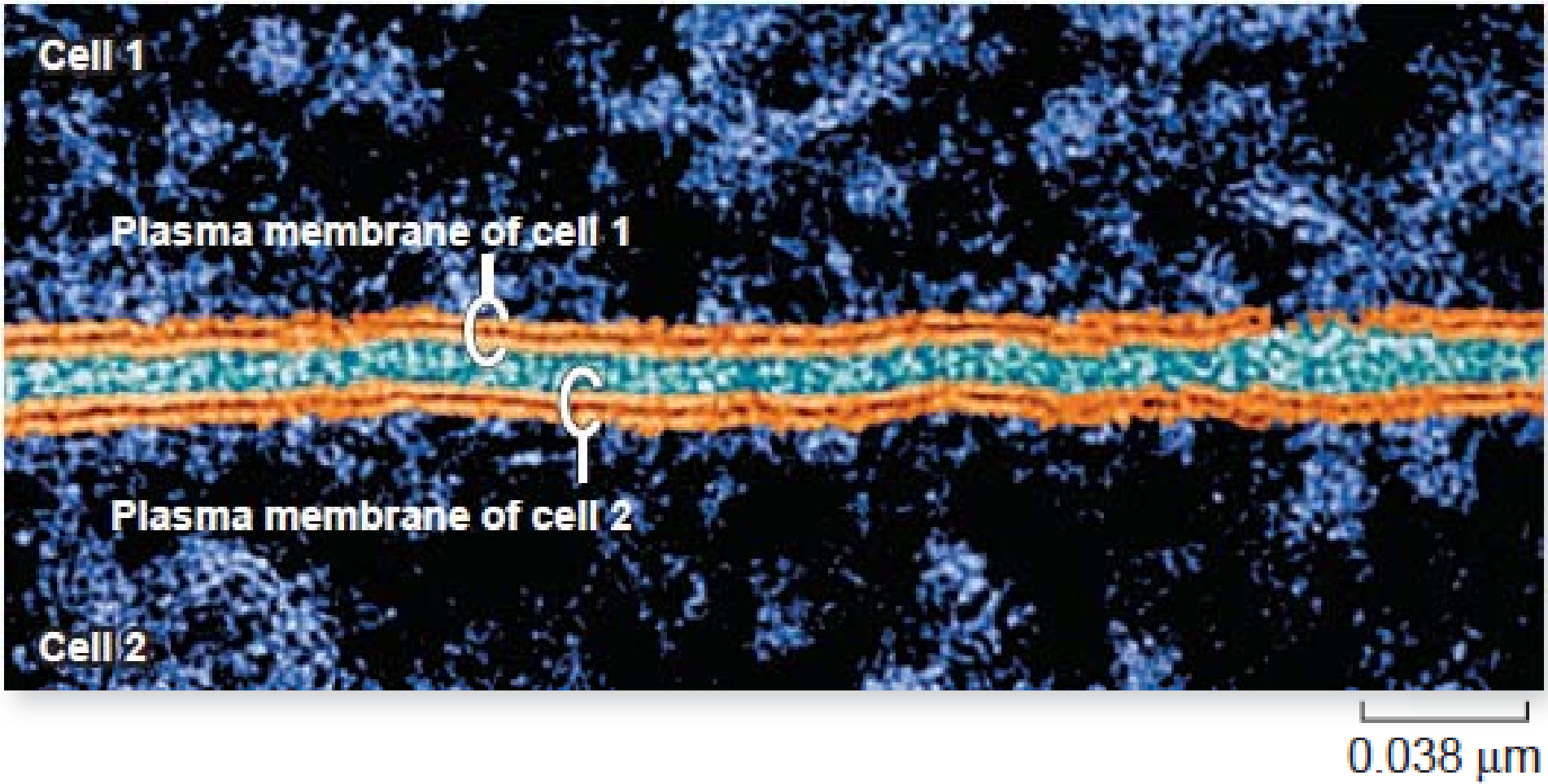


Robertson - Unit Membrane Model

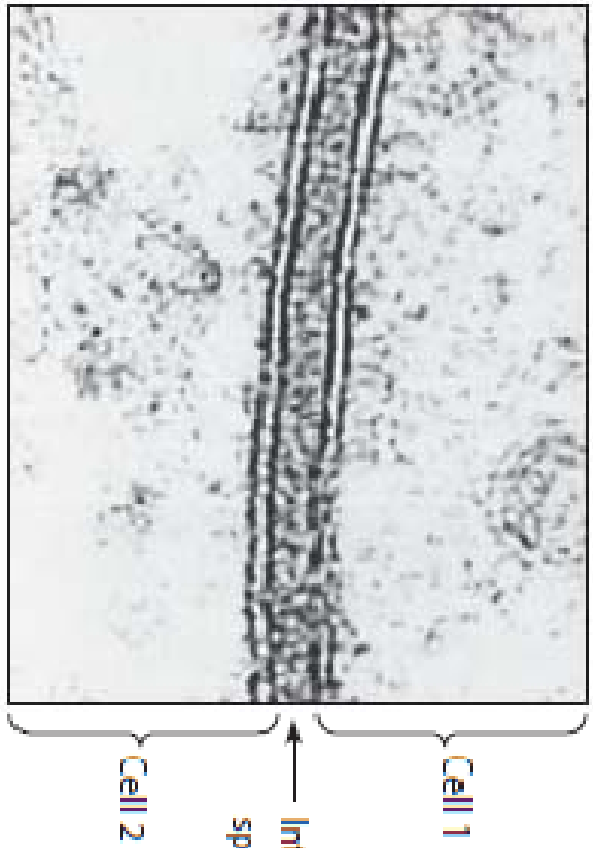
- ✓ J. David Robertson proposed this model in 1960
- ✓ When membranes were stained with osmium (heavy metal), and examined with electron microscope, he was found to have extensive regions of "railroad track" structure that appeared as two dark lines separated by a lightly stained central zone, with an overall thickness of 6–8 nm.

- ✓ This pattern is seen in the plasma membranes of two adjacent cells that are separated from each other by a thin intercellular space.




Cell 1
Plasma membrane of cell 1
Plasma membrane of cell 2
Cell 2
0.038 µm

- ✓ This same staining pattern was observed with many different kinds of cellular membranes.
- ✓ Thus Robertson suggested that all cellular membranes share a common underlying structure, which he called the unit membrane.
- ✓ The lightly stained space (between the two dark lines) contains the hydrophobic region of the lipid molecules; the two dark lines were represent phospholipid head groups and the thin sheets of protein bound to the membrane surfaces, which appear dark because of proteins affinity for heavy metal stains.



- ✓ the unit membrane structure seemed to agree remarkably well with the Davson–Danielli model

Further Studies... Questioning the Davson–Danielli Model

- ✓ The Davson–Danielli model encountered difficulties in the 1960s

1. Based on electron microscopy, most membranes were reported to be about 6–8 nm thick and, of this, the lipid bilayer accounted for about 4–5 nm.
   That left only about 1–2 nm of space on either surface of the bilayer for the membrane protein, a space that could at best accommodate a thin monolayer of protein.
   Yet after membrane proteins were isolated and studied, it became apparent that most of them were globular proteins with sizes and shapes that are inconsistent with the concept of thin sheets of protein on the two surfaces of the membrane.

2. With different types of cells, the membranes vary considerably in chemical composition and especially in the ratio of protein to lipid

Table 7-1 Protein, Lipid, and Carbohydrate Content of Biological Membranes

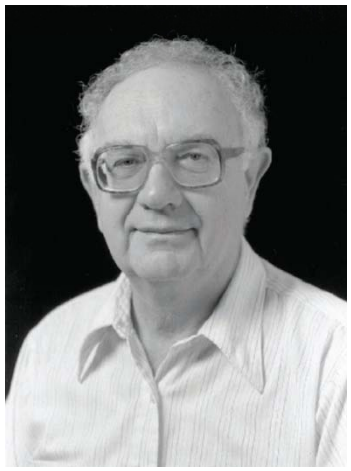
Membrane	Approximate Percentage by Weight			
	Protein	Lipid	Carbohydrate	Protein/Lipid Ratio
Plasma membrane				
Human erythrocyte	49	43	8	1.14
Mammalian liver cell	54	36	10	1.50
Amoeba	54	42	4	1.29
Myelin sheath of nerve axon	18	79	3	0.23
Nuclear envelope	66	32	2	2.06
Endoplasmic reticulum	63	27	10	2.33
Golgi complex	64	26	10	2.46
Chloroplast thylakoids	70	30	0	2.33
Mitochondrial outer membrane	55	45	0	1.22
Mitochondrial inner membrane	78	22	0	3.54
Gram-positive bacterium	75	25	0	3.00

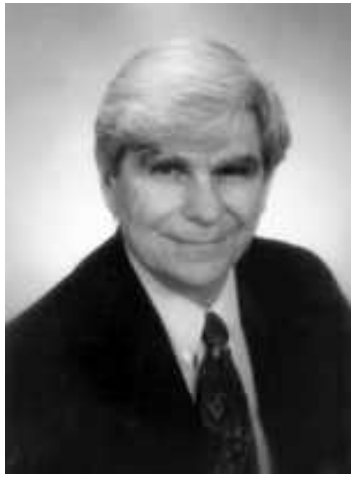
3. According to the model, the hydrophilic head groups of membrane lipids should be covered by a layer of protein and therefore protected from phospholipase digestion. However, up to 75% of the membrane phospholipid can be degraded when the membrane is exposed to phospholipases, suggesting that many of the phospholipid head groups are exposed at the membrane surface and not covered by a layer of protein.

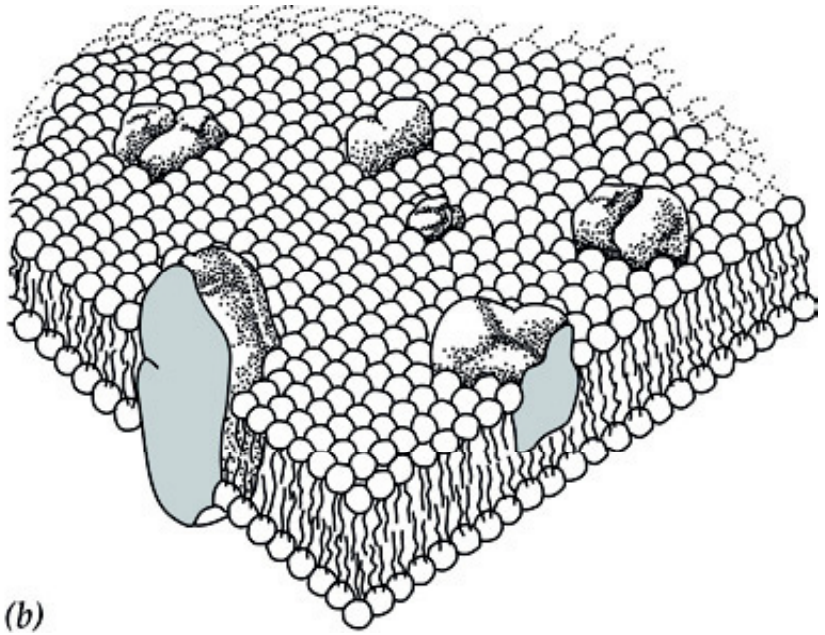
4. The surface localization of membrane proteins specified by the Davson–Danielli model was not supported by the experience of scientists who tried to isolate such proteins. Most membrane proteins turned out to be quite insoluble in water and could be extracted only by using organic solvents or detergents. These observations indicated that many membrane proteins are hydrophobic (or at least amphipathic) and suggested that they are located, at least partially, within the hydrophobic interior of the membrane rather than on either of its surfaces.

Singer and Nicolson: Fluid-mosaic model

- ✓ The "fluid-mosaic model" was proposed in 1972 by S. Jonathan Singer and Garth Nicolson of the University of California, San Diego.
- ✓ This model is considered as the "central dogma" of membrane biology





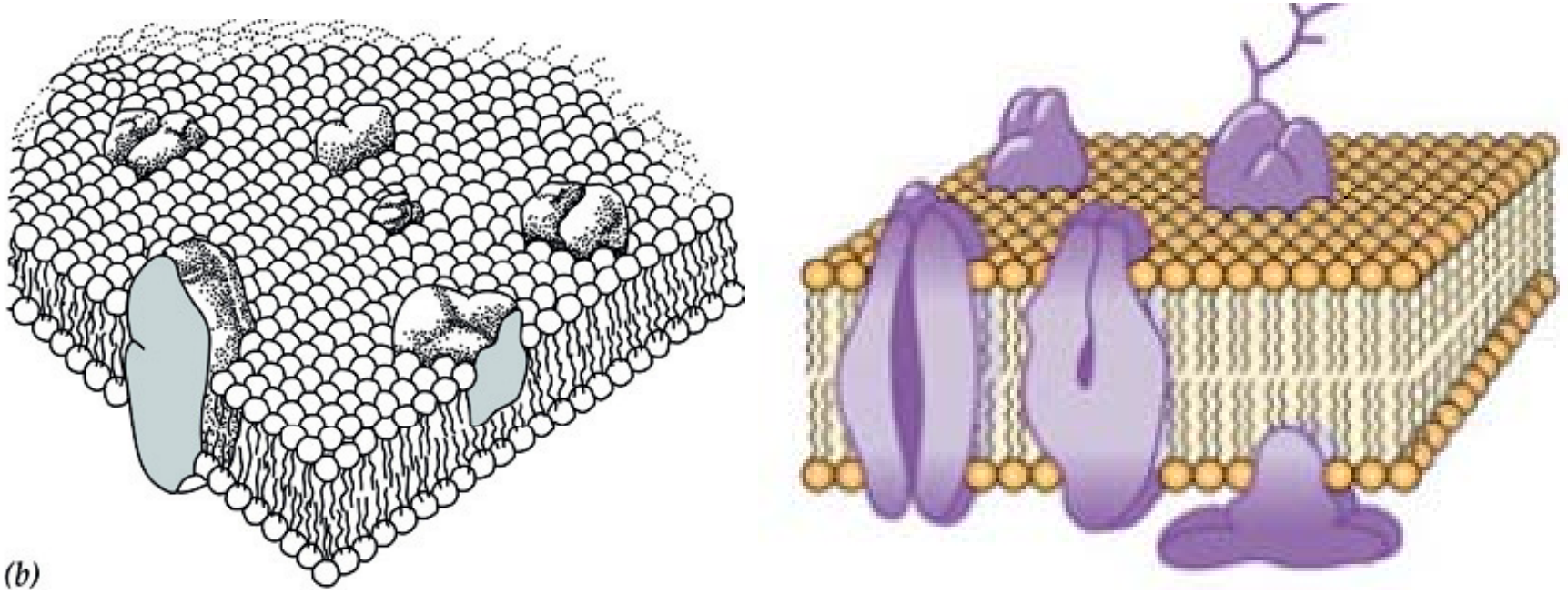


(b)

Two key features:

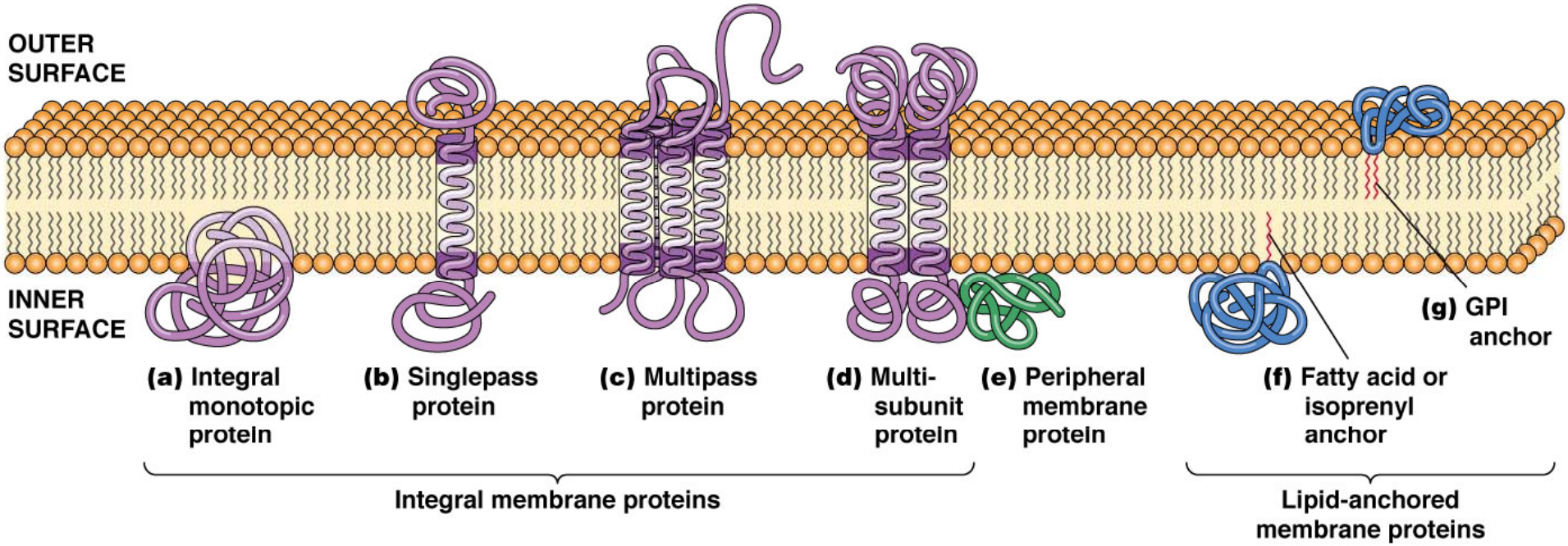
1. Physical state of the lipid; i.e., the fluid nature of lipid bilayer &
2. Proteins occur as a "mosaic" of discontinuous particles that penetrate the lipid sheet

The model envisions a membrane as a mosaic of proteins embedded in, or at least attached to, a fluid lipid bilayer.



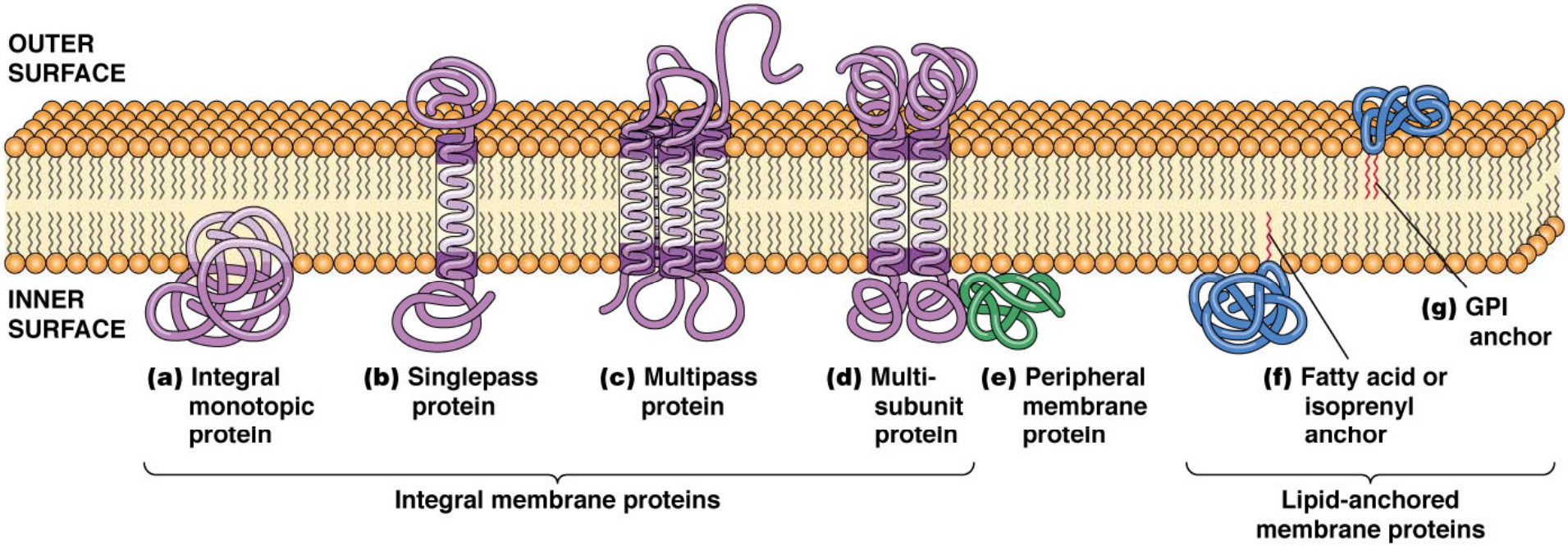
(b)

proteins were not viewed as thin sheets on the membrane surface but as discrete globular associated with the lipid bilayer

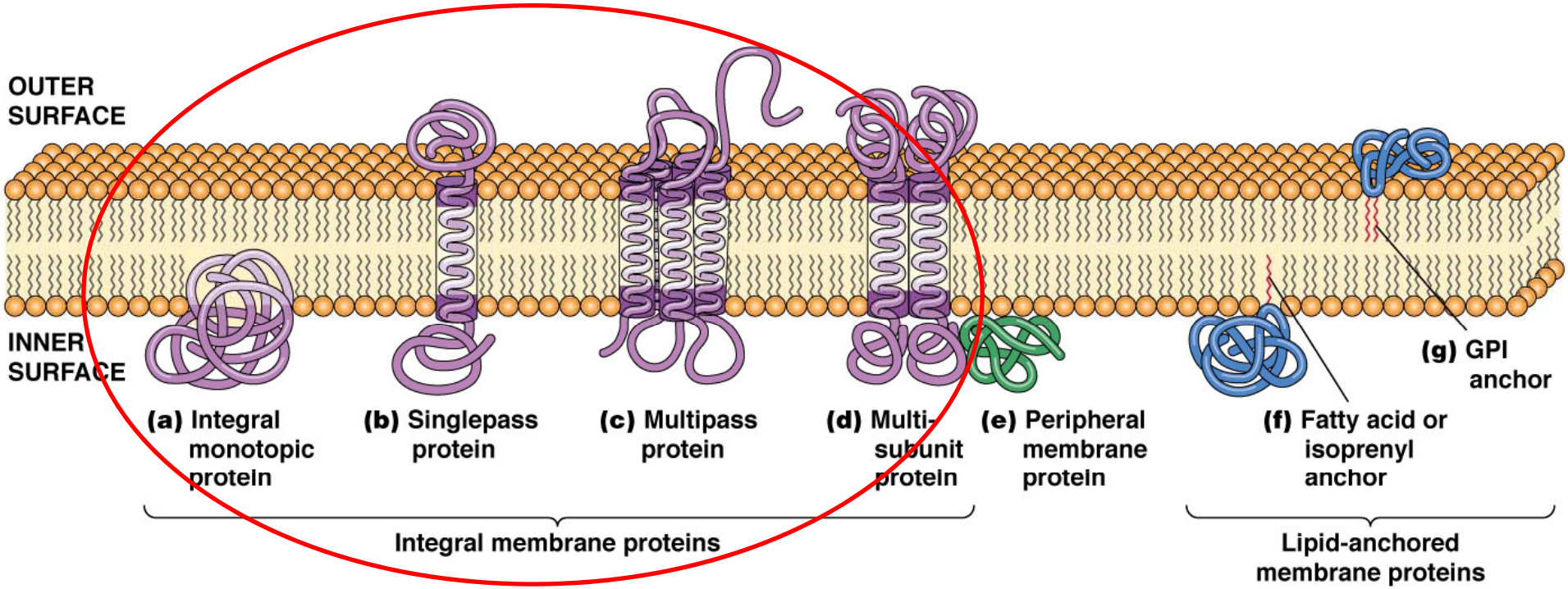


three classes of membrane proteins were recognized based on differences in how the proteins are linked to the bilayer.

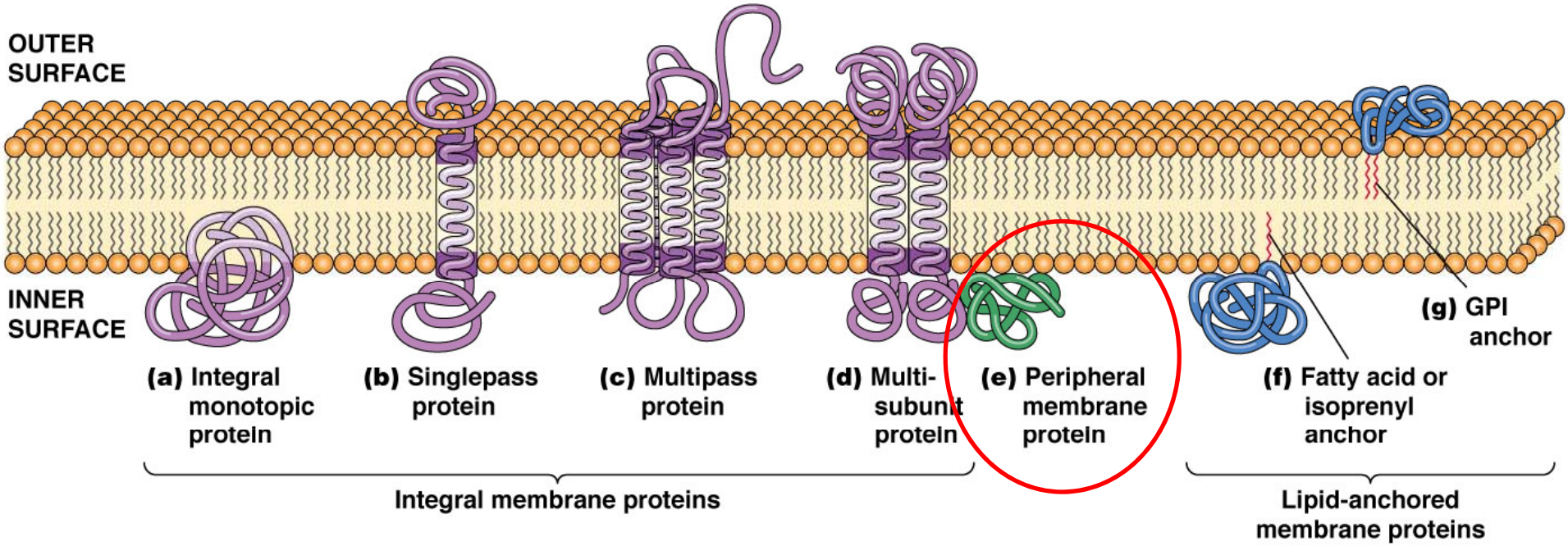
1. Integral membrane proteins,
2. Peripheral membrane proteins &
3. Lipid-anchored proteins



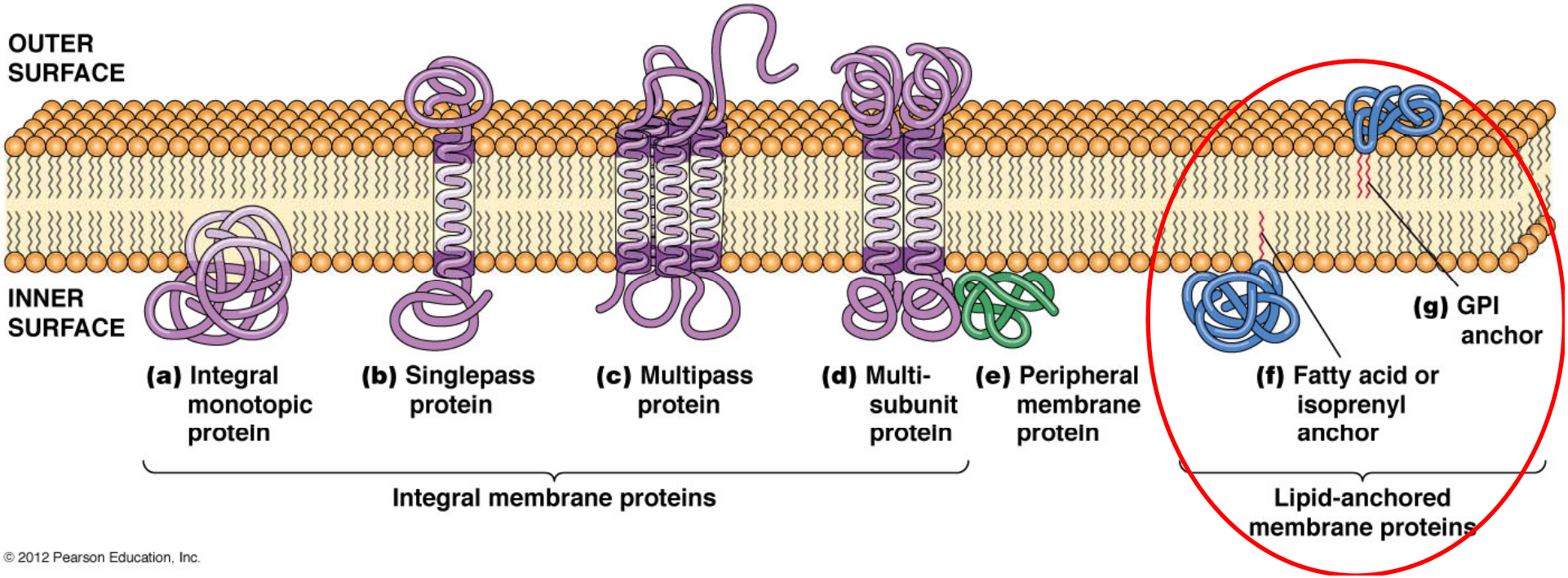
Integral membrane proteins: proteins embedded within the lipid bilayer, they are held in place by the affinity of hydrophobic segments of the protein for the hydrophobic interior of the lipid bilayer.



Peripheral proteins: proteins are more hydrophilic and are therefore located on the surface of the membrane, where they are linked noncovalently to the polar head groups of phospholipids and/or to the hydrophilic parts of other membrane proteins.



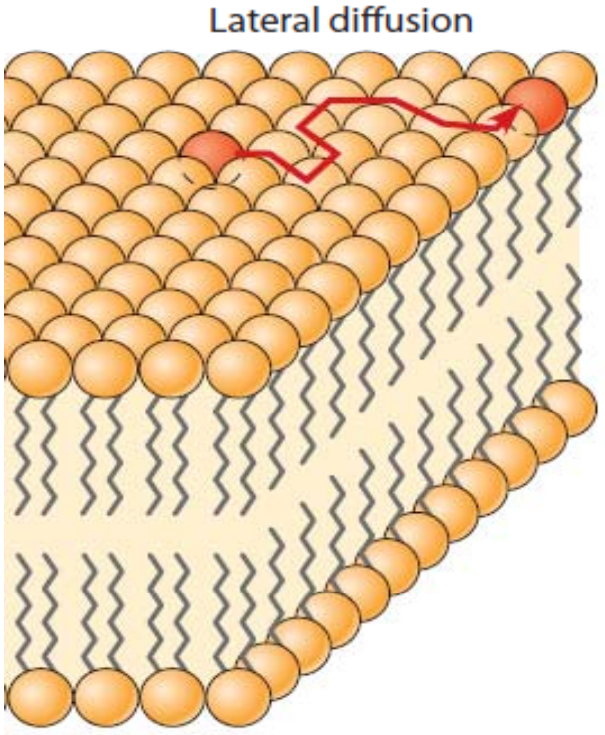
Lipid-anchored proteins: proteins are essentially hydrophilic proteins and therefore reside on membrane surfaces, but they are covalently attached to lipid molecules that are embedded within the bilayer



The fluid nature of the membrane is the second critical feature of this model.

- ✓ Rather than being rigidly locked in place, most of the lipid components of a membrane are in constant motion, capable of lateral mobility
- ✓ Many membrane proteins are also able to move laterally within the membrane

the bilayer of a fluid-mosaic membrane is present in a fluid state, and individual lipid molecules can move laterally within the plane of the membrane.

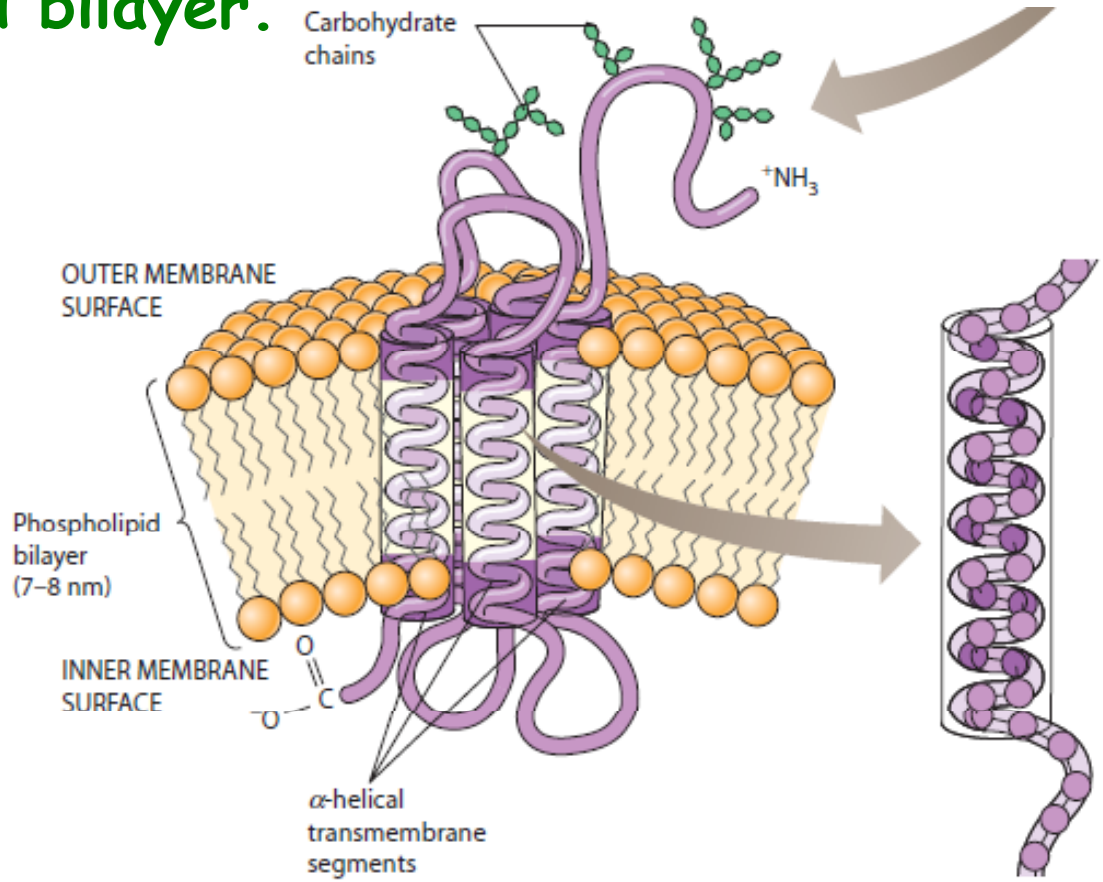


The fluid-mosaic model presents cellular membranes as dynamic structures in which the components are mobile and capable of coming together to engage in various types of transient or semipermanent interactions.

The major strength of the fluid mosaic model is that it readily explains most of the criticisms (proteins distribution, protein-lipid ratio, phospholipase action, etc) of the Davson–Danielli model.

Unwin and Henderson- Structure of integral membrane proteins

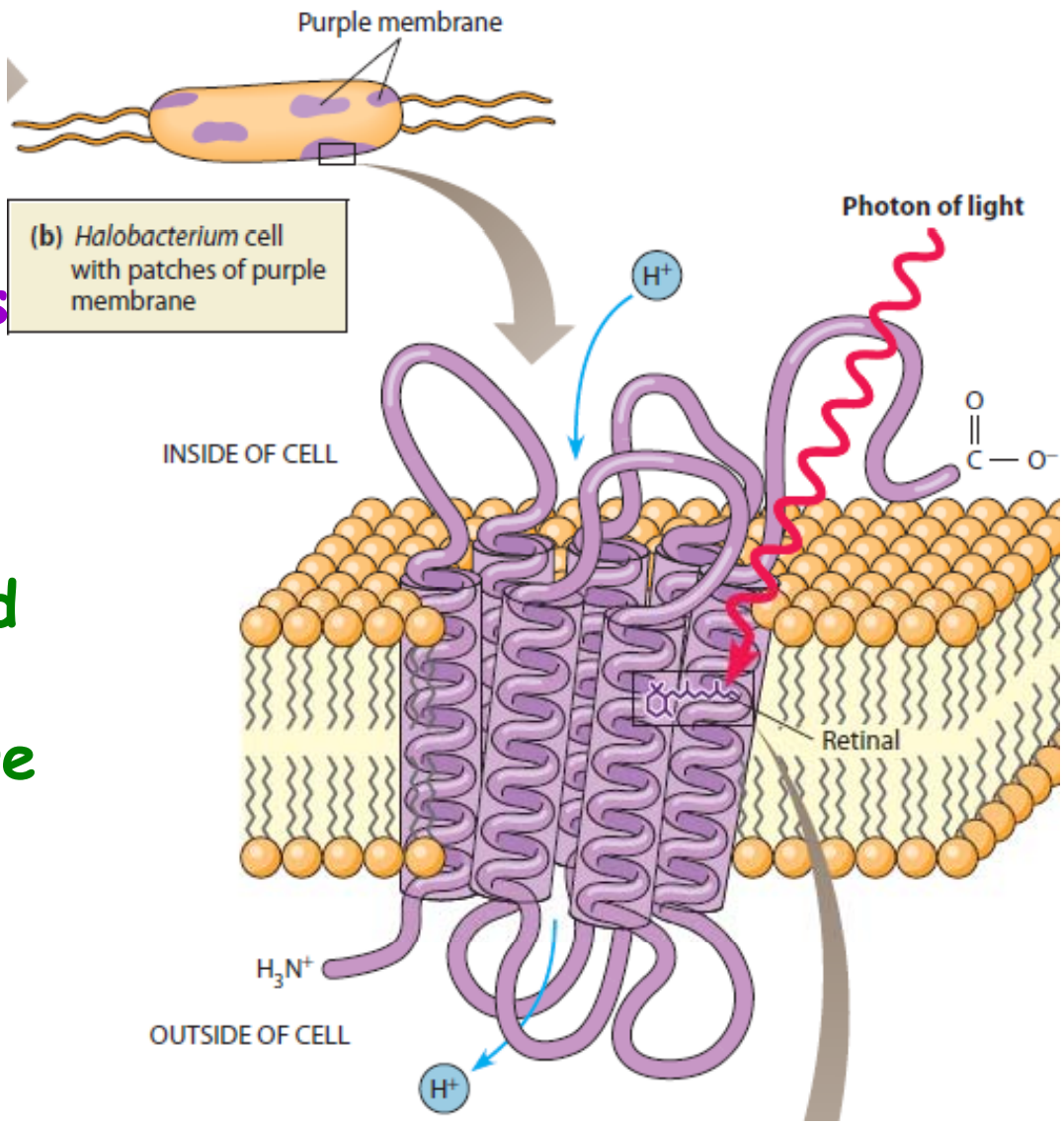
- ✓ Integral membrane proteins has secondary structural domains that span the lipid bilayer
- ✓ These transmembrane segments anchor the protein to the membrane and hold it in proper alignment within the lipid bilayer.



first studied
in Bacteriorhodopsin

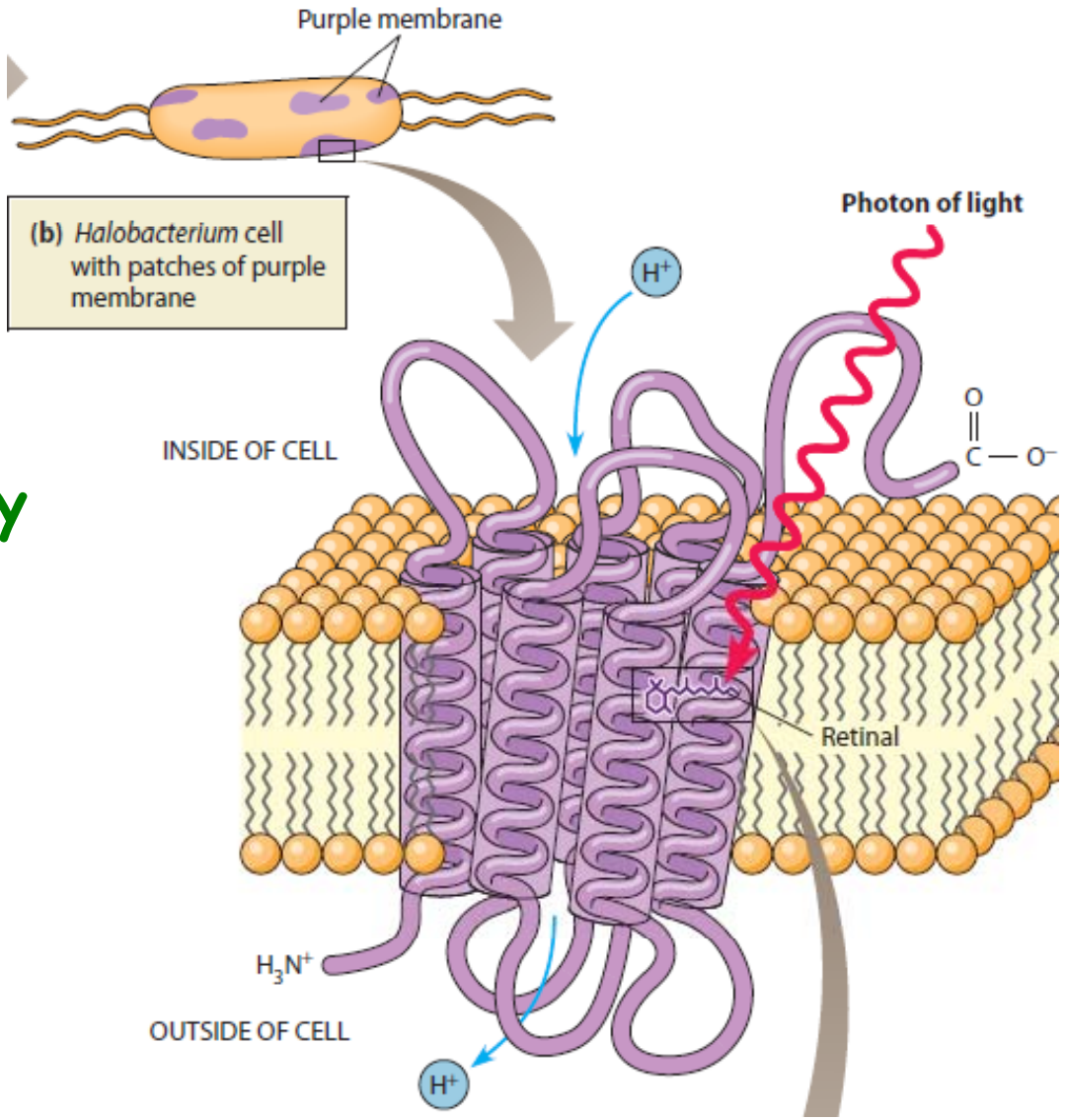
Bacteriorhodopsin is a plasma membrane protein found in the genus Halobacterium (archaea), where its presence allows cells to obtain energy directly from sunlight.

In 1975, Nigel Unwin and Richard Henderson studied the 3-D structure of bacteriorhodopsin to reveal its orientation in the membrane.



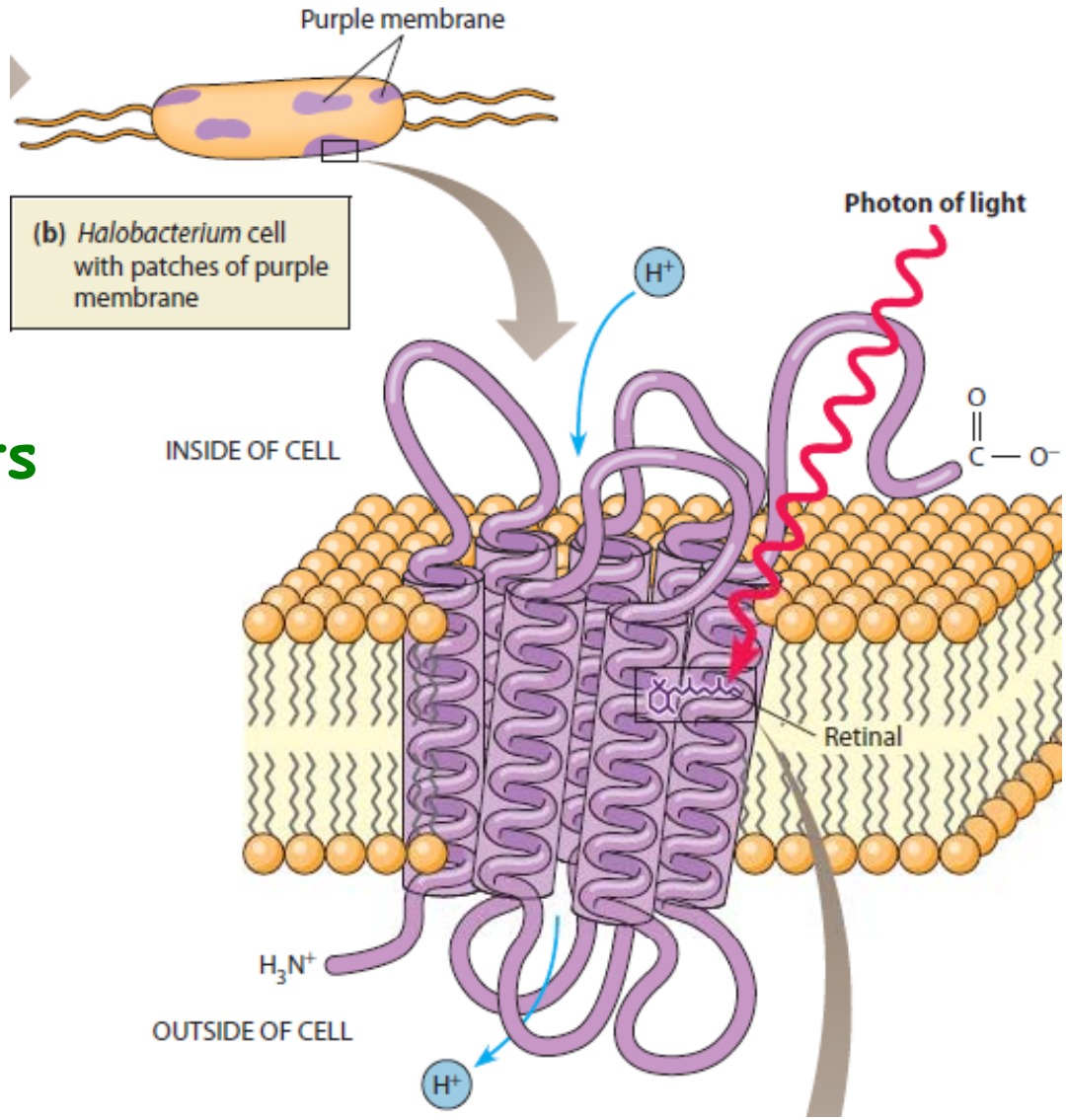
Bacteriorhodopsin consists of a single peptide chain folded back and forth across the lipid bilayer a total of seven times.

Each of the seven transmembrane segments of the protein is a closely packed α-helix composed mainly of hydrophobic amino acids.



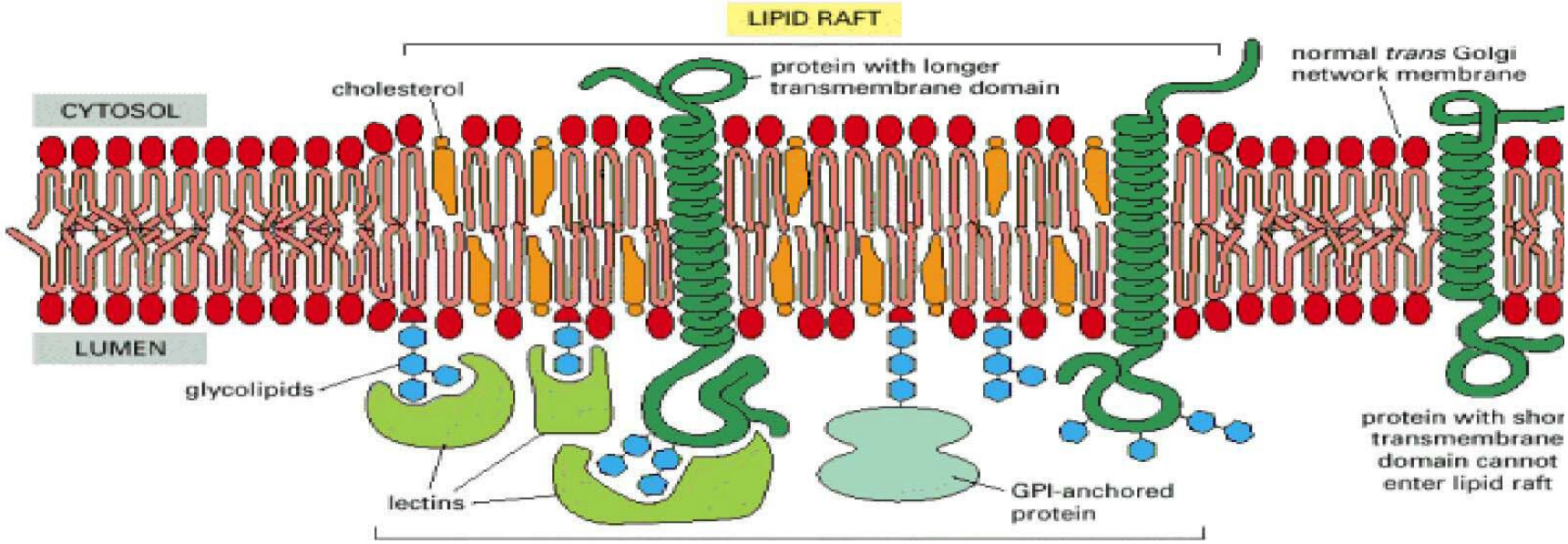
Successive transmembrane segments are linked to each other by short loops of hydrophilic amino acids

Based on subsequent work, membrane biologists currently believe that all transmembrane proteins are anchored in the lipid bilayer by one or more transmembrane segments

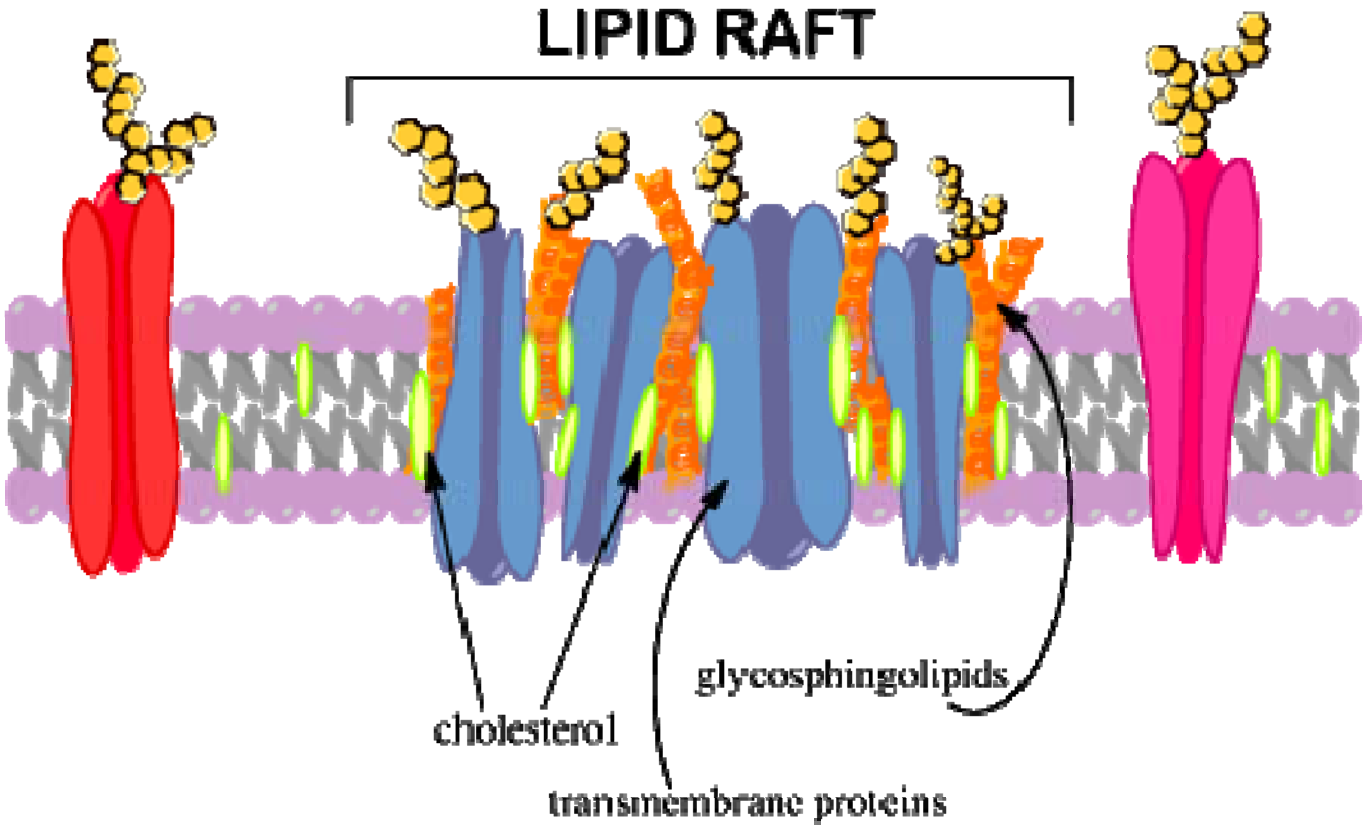


Recent studies...- Lipid Raft

- ✓ Recent developments emphasize the concept that not all regions of membranes are homogenous.
- ✓ The plasma membranes of cells contain combinations of glyco-lipids, glyco-proteins and protein receptors organized in microdomains termed lipid rafts.
- ✓ Both lipids and proteins are ordered within membranes, and this ordering often occurs in dynamic microdomains known as lipid rafts.



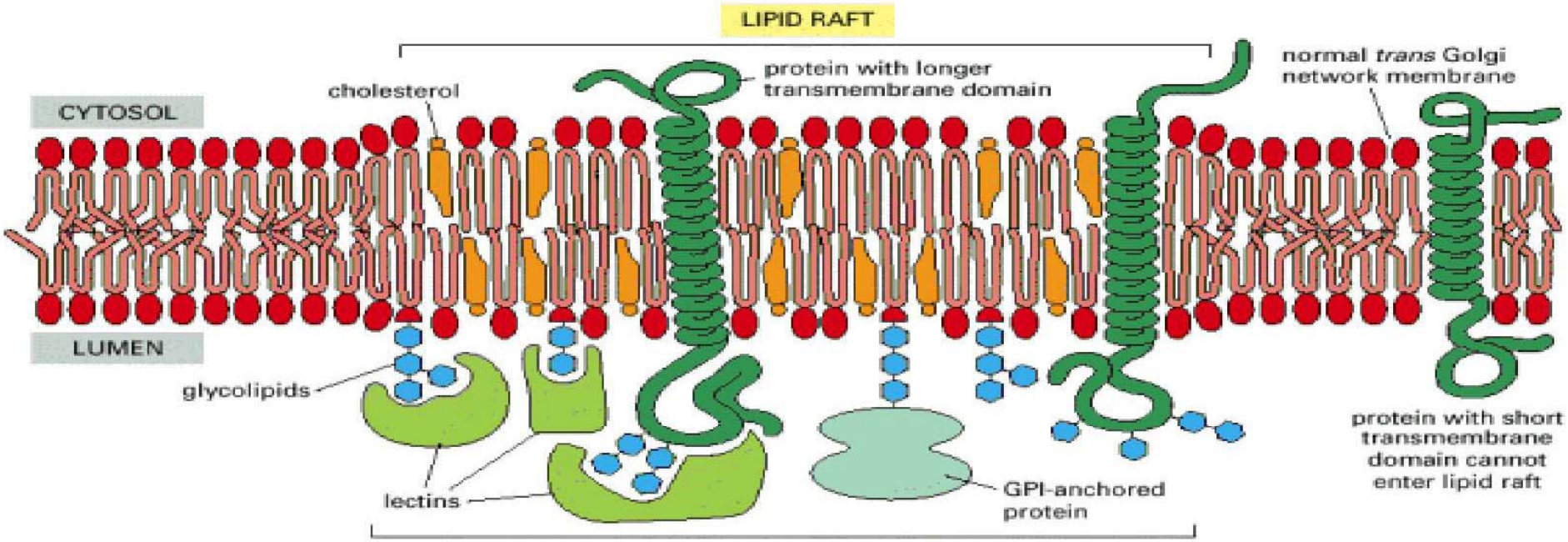
Lipid rafts are more ordered and tightly packed than the surrounding bilayer, but float freely in the membrane bilayer.

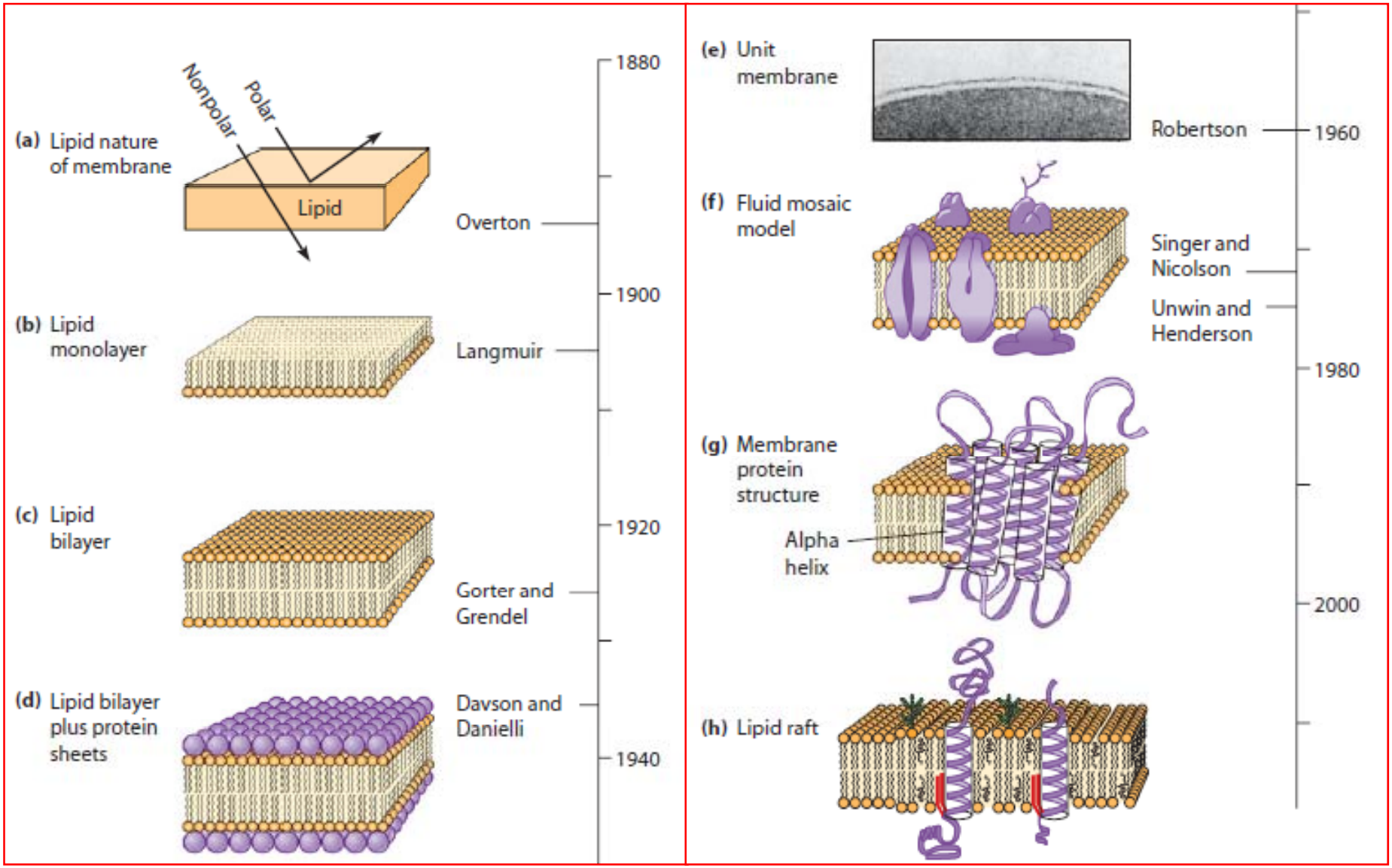


most cellular processes that involve membranes depend critically on these specific structural complexes.

Functions:

1. organizing centers for the assembly of signaling molecules and receptors,
2. influencing membrane fluidity,
3. membrane protein trafficking, and
4. regulating neurotransmission.




(a) Lipid nature of membrane
Nonpolar
Polar
Lipid
(b) Lipid monolayer
(c) Lipid bilayer
(d) Lipid bilayer plus protein sheets
1880
Overton
1900
Langmuir
1920
Gorter and Grendel
Davson and Danielli
1940
(e) Unit membrane
Robertson
1960
(f) Fluid mosaic model
Singer and Nicolson
Unwin and Henderson
1980
(g) Membrane protein structure
Alpha helix
2000
(h) Lipid raft