MEMBRANES AND RECEPTORS MODULE

SESSION 1: LIPIDS, PROTEINS AND MEMBRANE STRUCTURE

LECTURE: 2

DURATION: 1hr

MEMBRANE PROTEINS, MEMBRANE ASYMMETRY AND THE CYTOSKELETON

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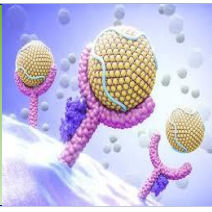
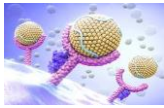
Harper's Illustrated Biochemistry, Thirtieth Edition Copyright © 2015 by The McGraw-Hill Education, ISBN 978-0-07-182534-4
Lehninger Principles of Biochemistry Sixth Edition (6th Edition) by David L. Nelson, Michael M. Cox, Hardcover, Published 2012, ISBN-13: 978-1-4292-4146



Learning objectives (LO)

1. The distribution and role of proteins in membrane structure.
2. The importance of an asymmetric distribution of membrane proteins .
3. Mechanisms for the correct insertion of membrane proteins into the lipid bilayer.
4. The structure of the erythrocyte cytoskeleton.

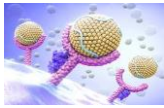


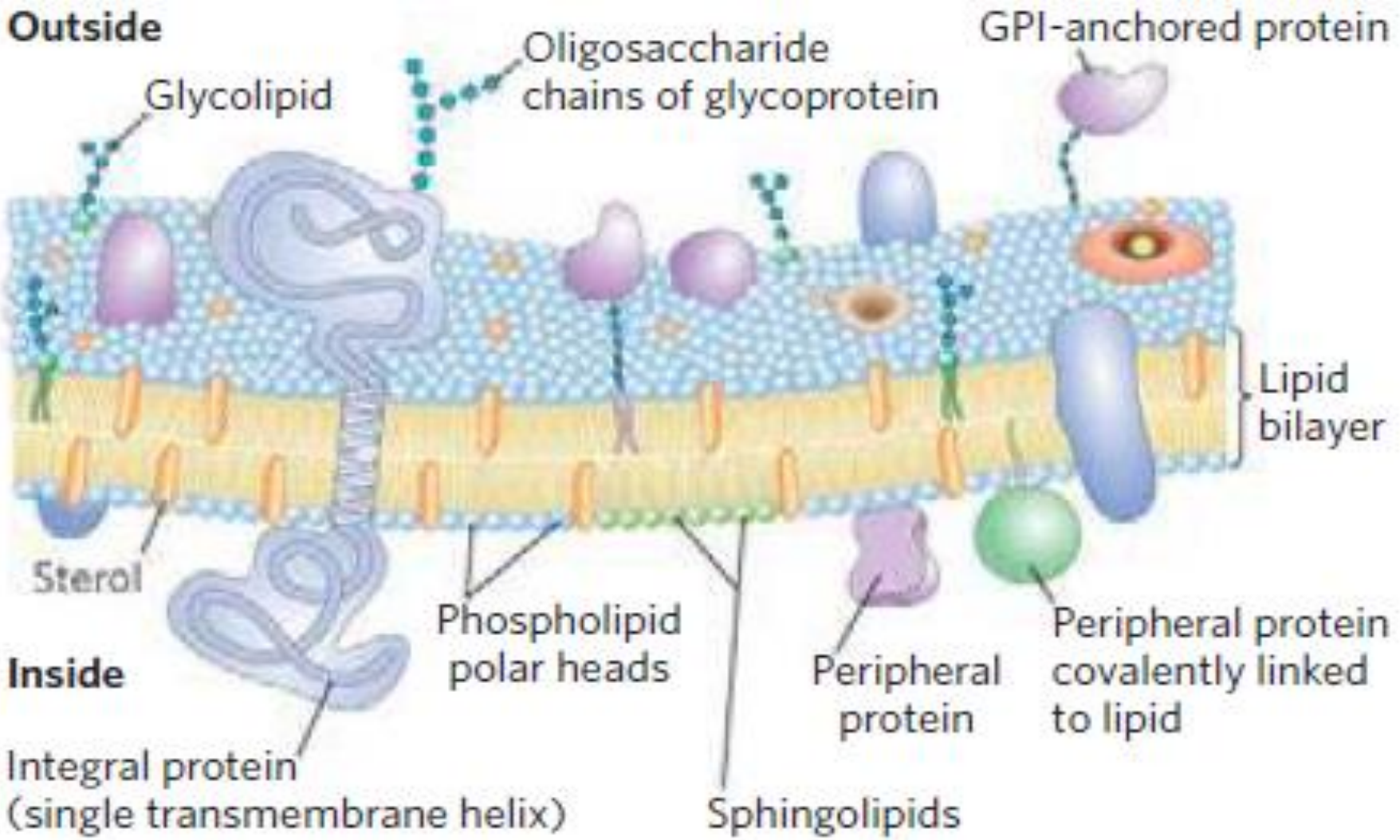
Lipid mosaic theory of membrane structure (Singer- Nicholson Model) LO.1

- The molecular components of membranes are:
  1. Polar lipids
  2. Proteins
  3. Carbohydrates, present as part of glycoproteins and glycolipids.
- The relative proportions of protein and lipid vary with the type of membrane.

E.g.

- Myelin sheath consists primarily of lipids.
- The membranes of mitochondria contain more protein than lipid.

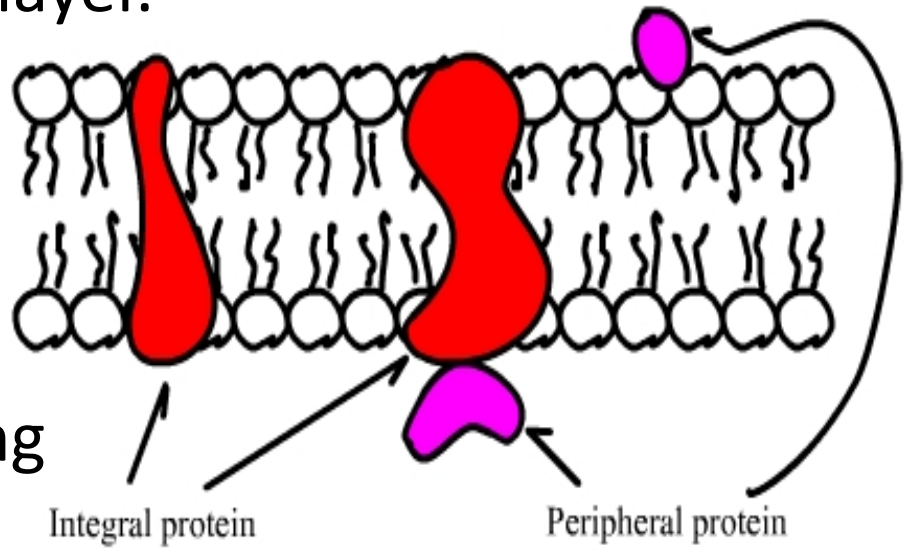



Outside
Glycolipid
Oligosaccharide chains of glycoprotein
GPI-anchored protein
Lipid bilayer
Sterol
Phospholipid polar heads
Peripheral protein
Peripheral protein covalently linked to lipid
Inside
Integral protein (single transmembrane helix)
Sphingolipids

Integral membrane proteins:

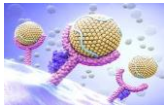
- They are anchored to membranes through a direct interaction with the lipid bilayer.

- They are amphipathic, consisting of two hydrophilic ends separated by an intervening hydrophobic region.



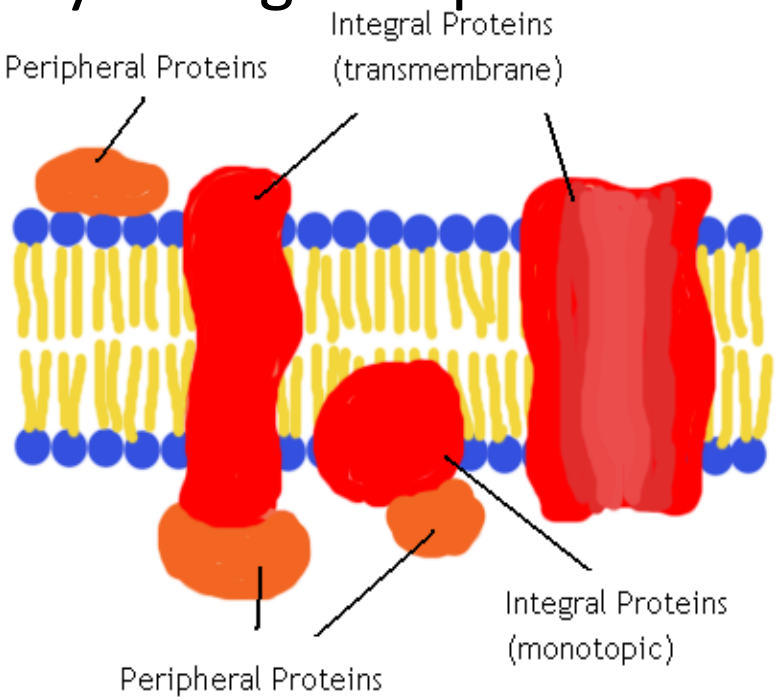
- They can remove by detergents and organic solvents .

- They are serve as channels, carriers (transporters), receptors and enzymes.

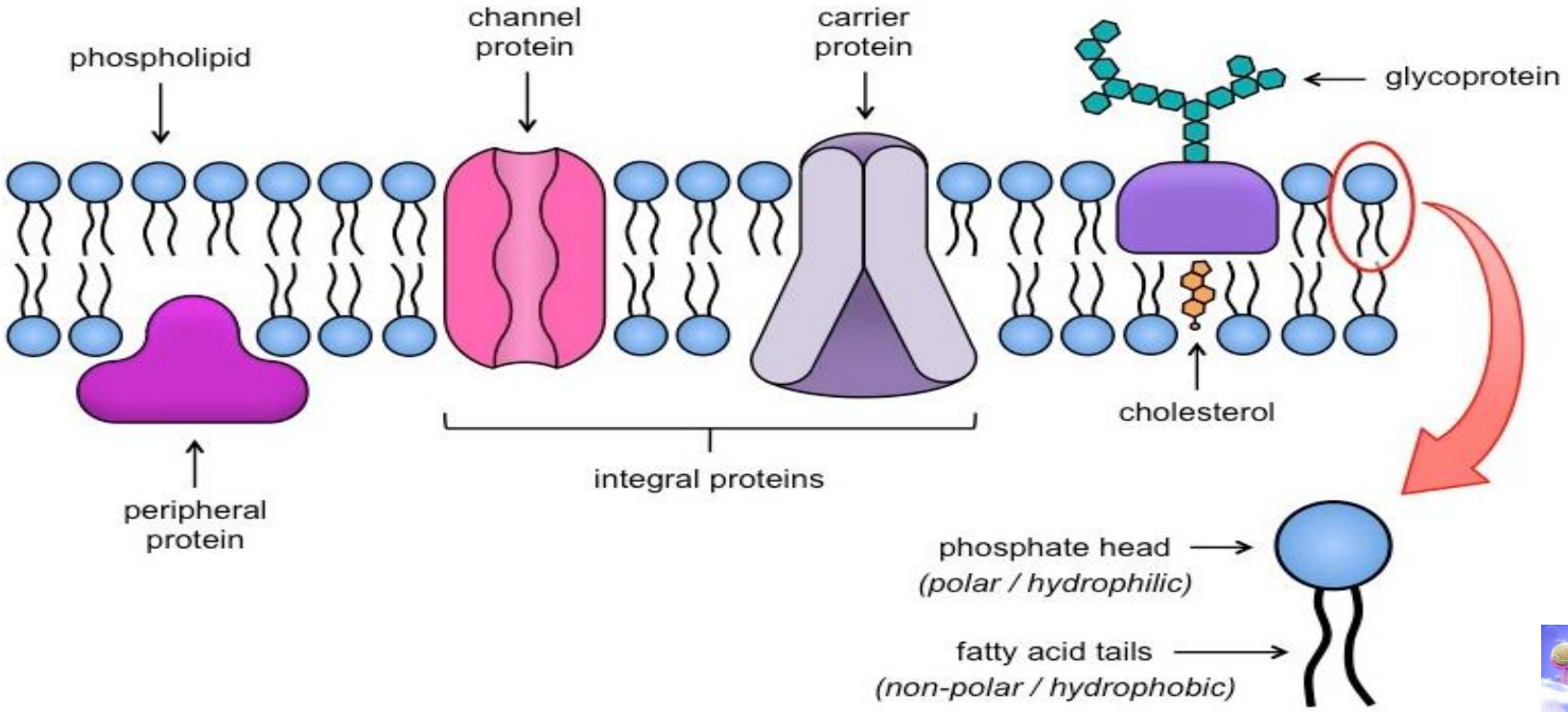


peripheral membrane proteins:

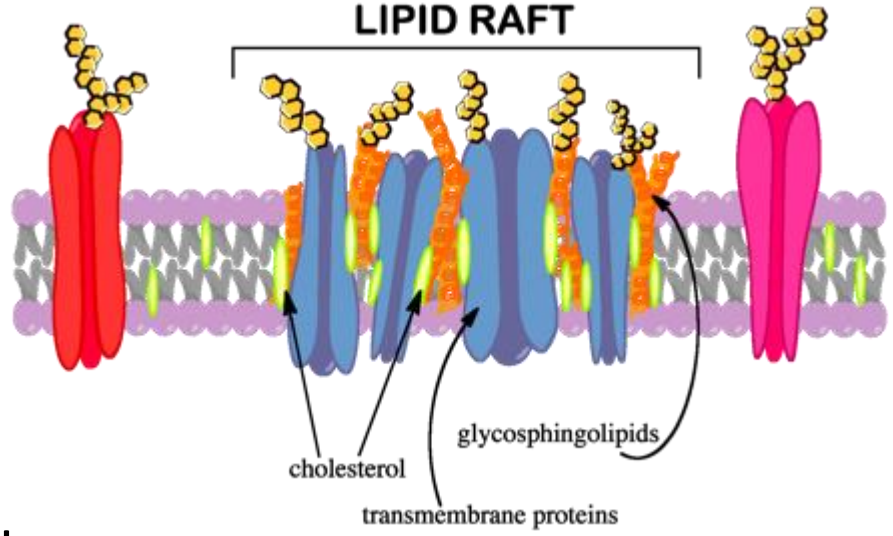
- They are located on both surfaces of the membrane.
- They are associated with integral proteins via electrostatic interactions.
- These proteins can be removed by changes in pH or ionic strength.
- They are serve as:
  1. Cell adhesion molecules (CAMs) that anchor cells to neighbouring cells.
  2. They also contribute to the cytoskeleton when present on the cytoplasmic side of the membrane.



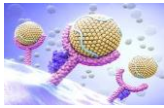
- The individual lipid, protein and carbohydrates units in a membrane form a **fluid mosaic model.**
- Because the **phospholipids** that form the cell membrane are a **fluid substance**, the membrane is also considered a fluid structure.



- The fluidity of the mosaic membrane is because weak (noncovalent) interactions among its components that enables individual lipid and protein molecules to move free laterally in the plane of the membrane.

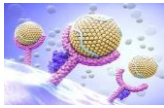


- This mobility is limited:
  1. by interactions of membrane proteins with internal cytoskeletal structures.
  2. interactions of lipids with lipid rafts (membrane microdomains enriched in cholesterol and sphingolipids)



Asymmetrical orientation of membrane proteins LO.2

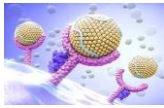
- Proteins have unique orientations in membranes, making the **outside surfaces different from the inside surfaces (sidedness)**.
- An **inside-outside asymmetry** is also provided by the external location of the carbohydrates attached to membrane proteins.
- This asymmetric orientation is conferred at the time of their insertion in the lipid bilayer during biosynthesis in the ER.

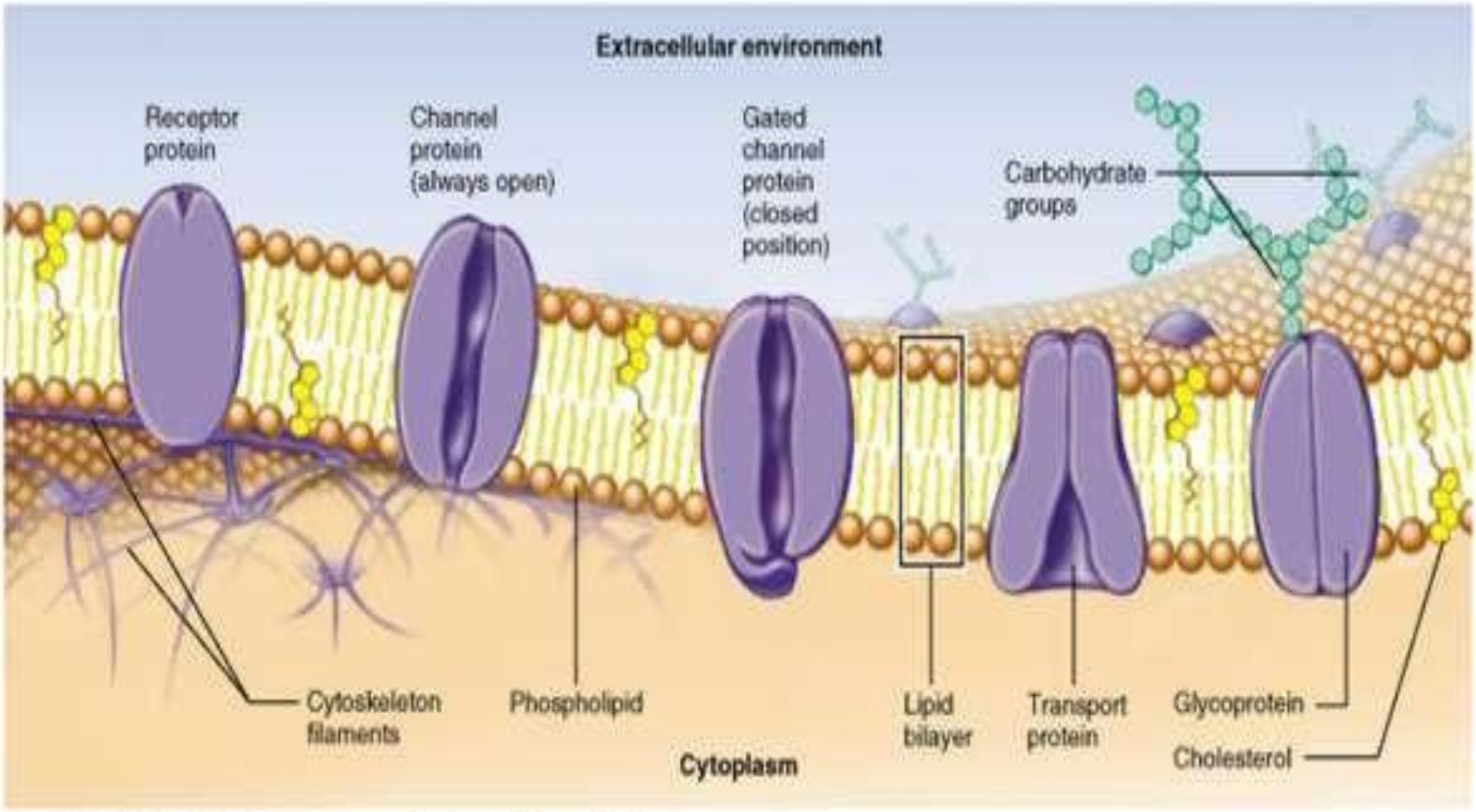


Asymmetrical orientation of membrane proteins

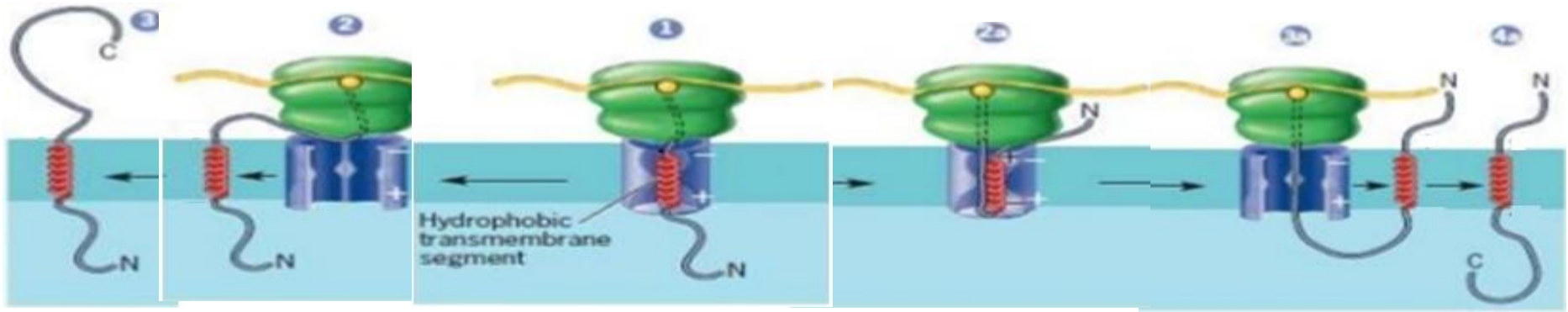
- Asymmetrical orientation of membrane proteins give rise to functional asymmetry.

E.g. transmembrane proteins in the plasma membrane are precisely oriented, with one cytosolic domain and one extracellular domain. This is very important for receptors that need to expose the recognition site to the extracellular space in order to recognize their ligands.





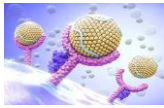
Synthesis of integral membrane protein L.O 3



Step 1. the nascent polypeptide enters the translocon, where transmembrane protein has been synthesized, the N-terminus is in the lumen of ER and C- terminus is in the cytosol.

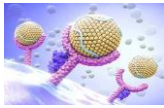
Step 2and 3. the translocon has opened laterally and expelled the transmembrane segment into the bilayer

Steps 2a-4a show the synthesis of transmembrane protein whose C- terminus is in the lumen and N-terminus is in the cytosol



The erythrocyte membrane- a model of plasma membrane (LO. 4)

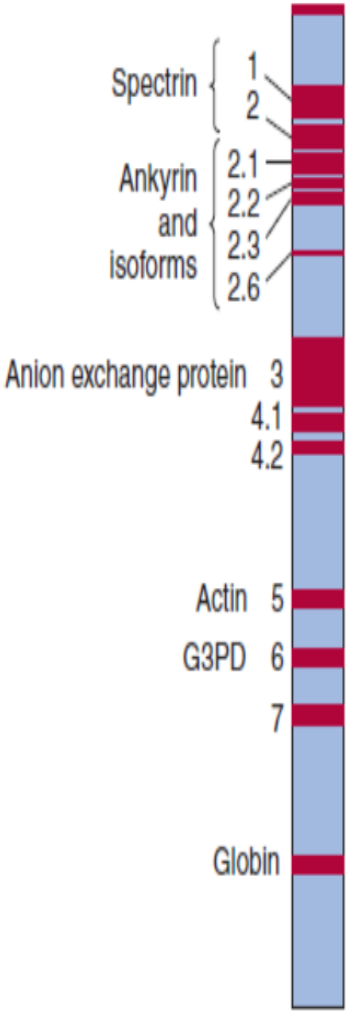
- Erythrocyte ghosts can be prepared by osmotic hemolysis to release cytoplasmic components.
- Analysis of ghost membranes by gel electrophoresis reveals over 10 major proteins based upon their migration.
- The slowest migrating (highest molecular mass) designated band 1 protein, also known as **spectrin**
- certain of these proteins are glycosylated and several span the membrane bilayer (integral membrane proteins), while others associate with its surface, generally via protein-protein interactions (peripheral membrane proteins).

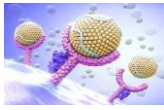


The erythrocyte membrane (LO. 4)

Principal Proteins of the Red Cell Membrane

Band Number[a]	Protein	Integral (I) or Peripheral (P)	Approximate Molecular Mass (kDa)
1	Spectrin (α)	P	240
2	Spectrin (β)	P	220
2.1	Ankyrin	P	210
2.2	Ankyrin	P	195
2.3	Ankyrin	P	175
2.6	Ankyrin	P	145
3	Anion exchange protein	I	100
4.1	Unnamed	P	80
5	Actin	P	43
6	Glyceraldehyde-3-phosphate dehydrogenase	P	35
7	Tropomyosin	P	29
8	Unnamed	P	23
	Glycophorins A, B, and C	I	31, 23, and 28

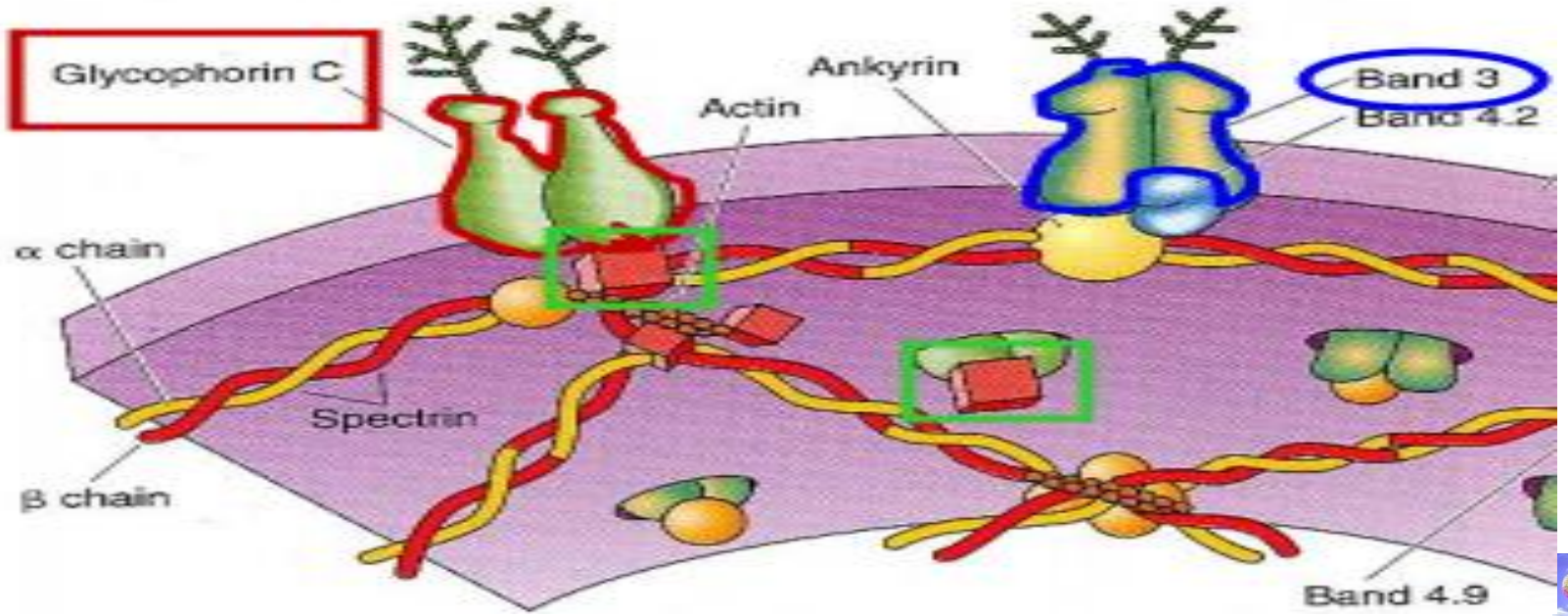




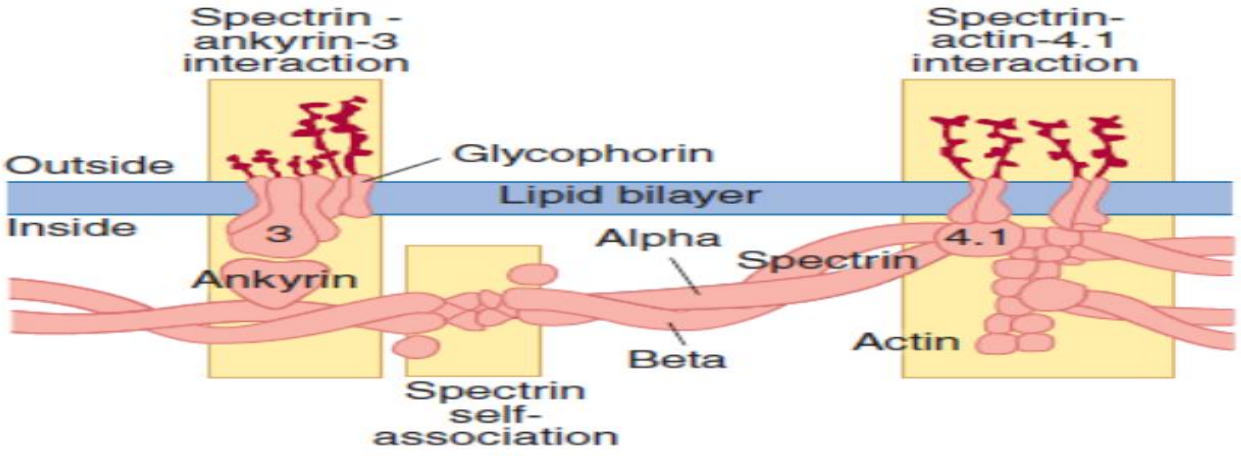
Cytoskeleton (Membrane skeleton)

A cellular protein structure like a skeleton, attached to the cell membrane of the cytoplasmic side and found in the cytoplasm.

- The erythrocyte cytoskeleton is a network of spectrin and actin molecules

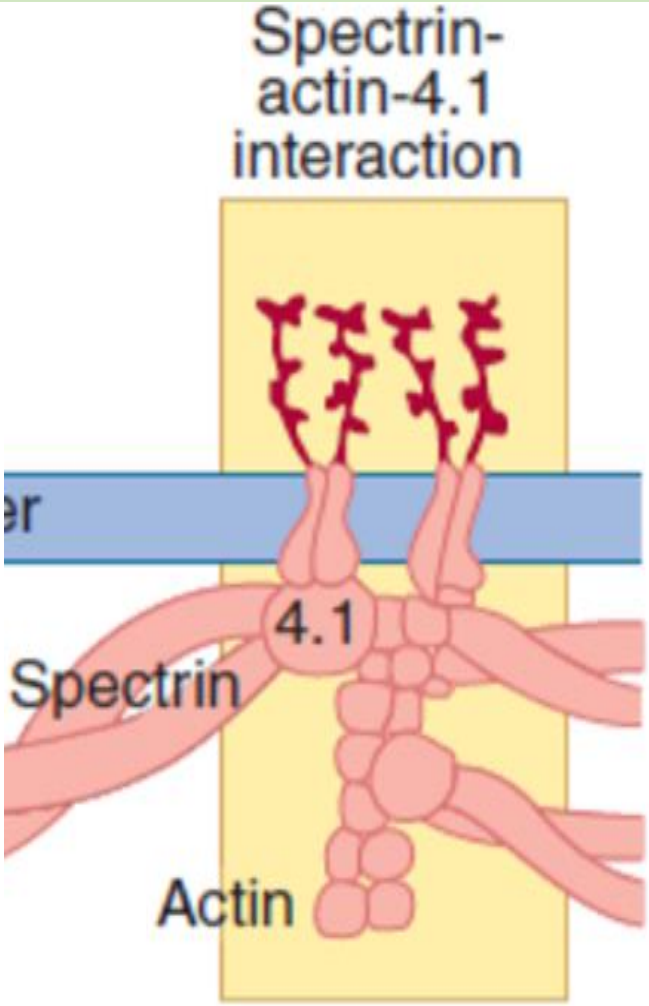


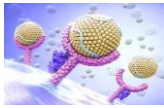
- Spectrin is a long, floppy rod-like molecule.
- α and β subunits are winding together to form an antiparallel heterodimer.
- The two heterodimers then form a head-to-head association to form a heterotetramer of α2β2.
- Ankyrin is a pyramid-shaped protein that binds spectrin.
- Ankyrin is sensitive to proteolysis.



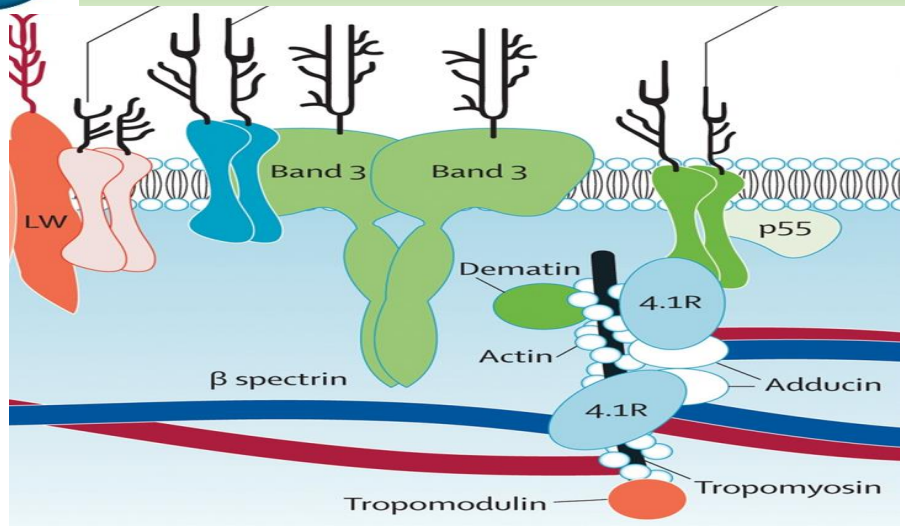
- Actin (band 5) exists in red blood cells as short, doublehelical filaments of F-actin.

- Protein 4.1, a globular protein, binds tightly to the tail end of spectrin, near the actin-binding site of the latter, and thus is part of a protein 4.1-spectrin-actin ternary complex

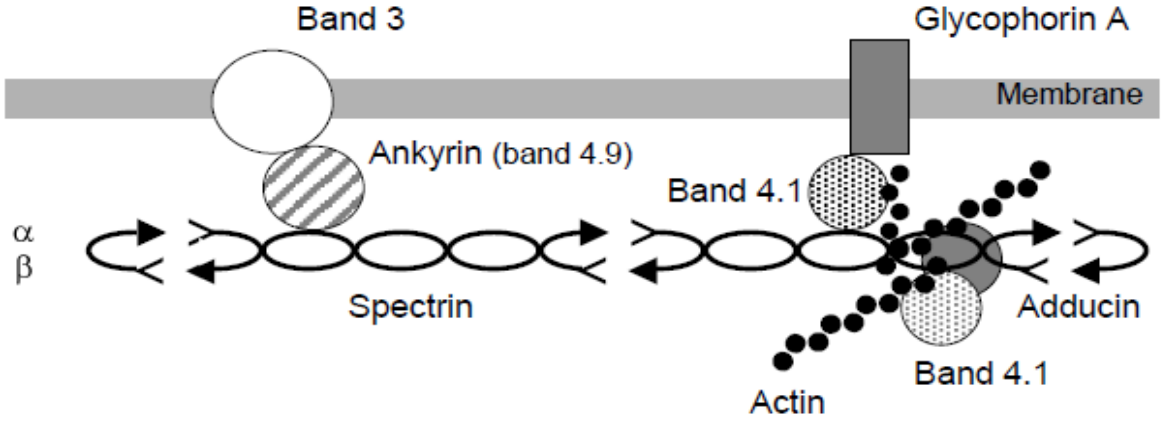


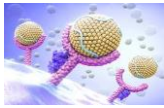


Adducin is an adaptor protein



Attachment of integral membrane proteins to the cytoskeleton restricts the lateral mobility of the membrane protein



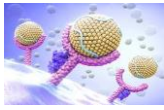


Haemolytic anaemia

- Membrane-specific factors that render red blood cells vulnerable to lysis include mutations that affect the cytoskeletal proteins.

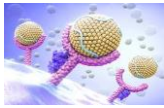
- The most important are

1. hereditary spherocytosis
2. hereditary elliptocytosis

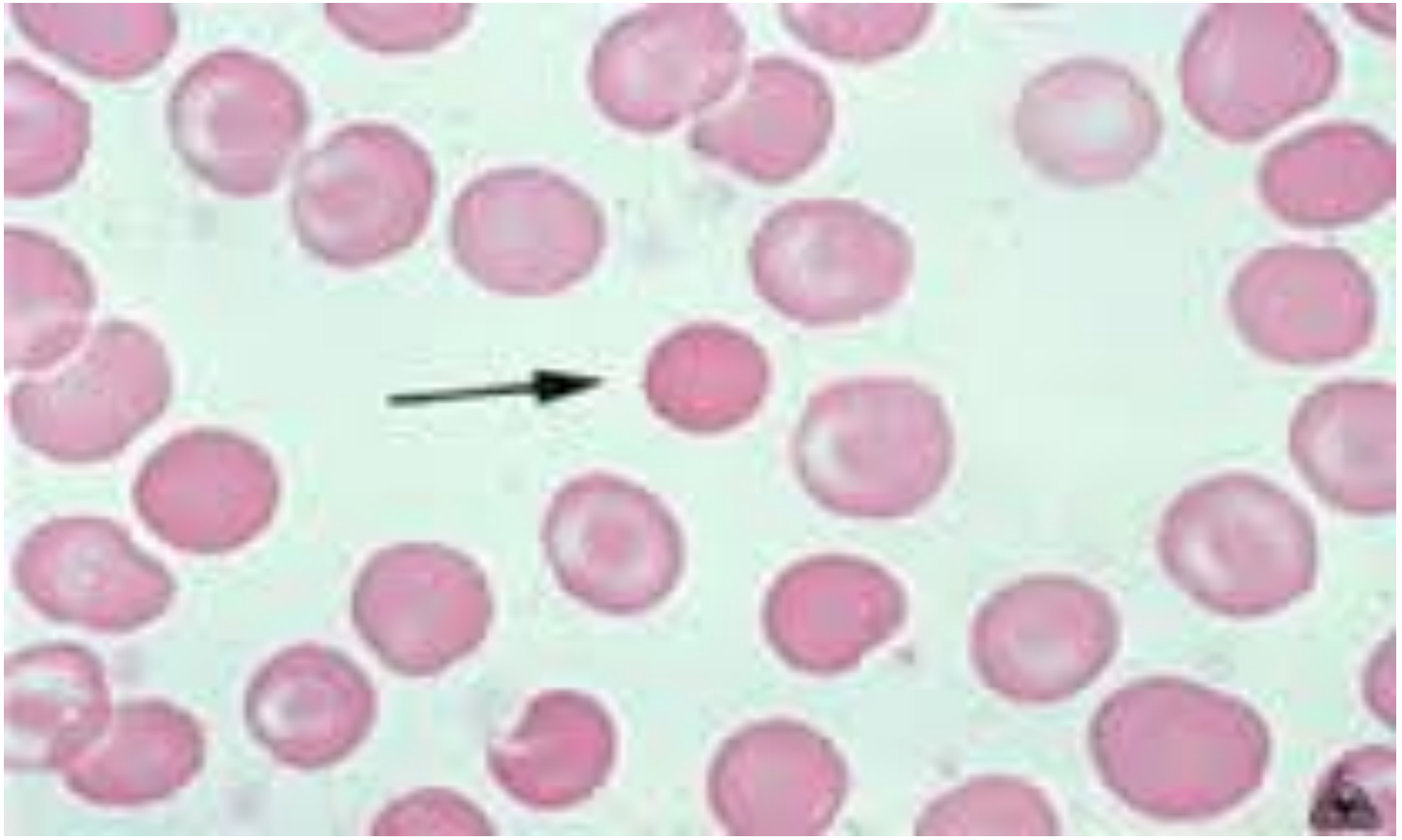


Hereditary spherocytosis

- Is a genetic disease transmitted as an autosomal dominant
- is caused by a deficiency in the amount of **spectrin** or mutations that produce abnormalities in **Ankyrin or in bands 3, 4.1, or 4.2.**
- It is characterized by the presence of spherocytes (spherical red blood cells).
- Spherocytes are more vulnerable to lysis when exposed to lower than normal osmotic pressure.

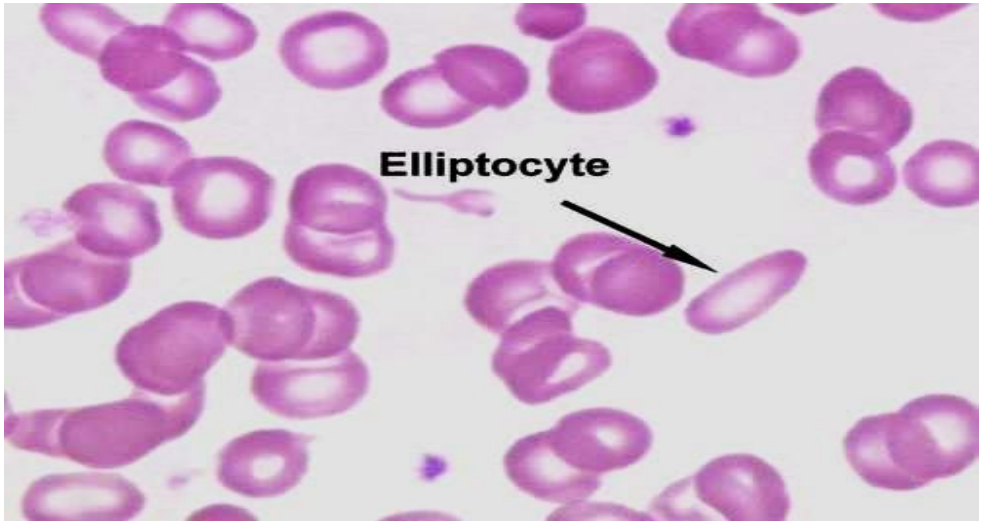


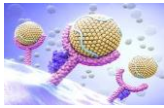
In spherocytosis RBC has a spherical shape in instead of the biconcave shape of normal RBC



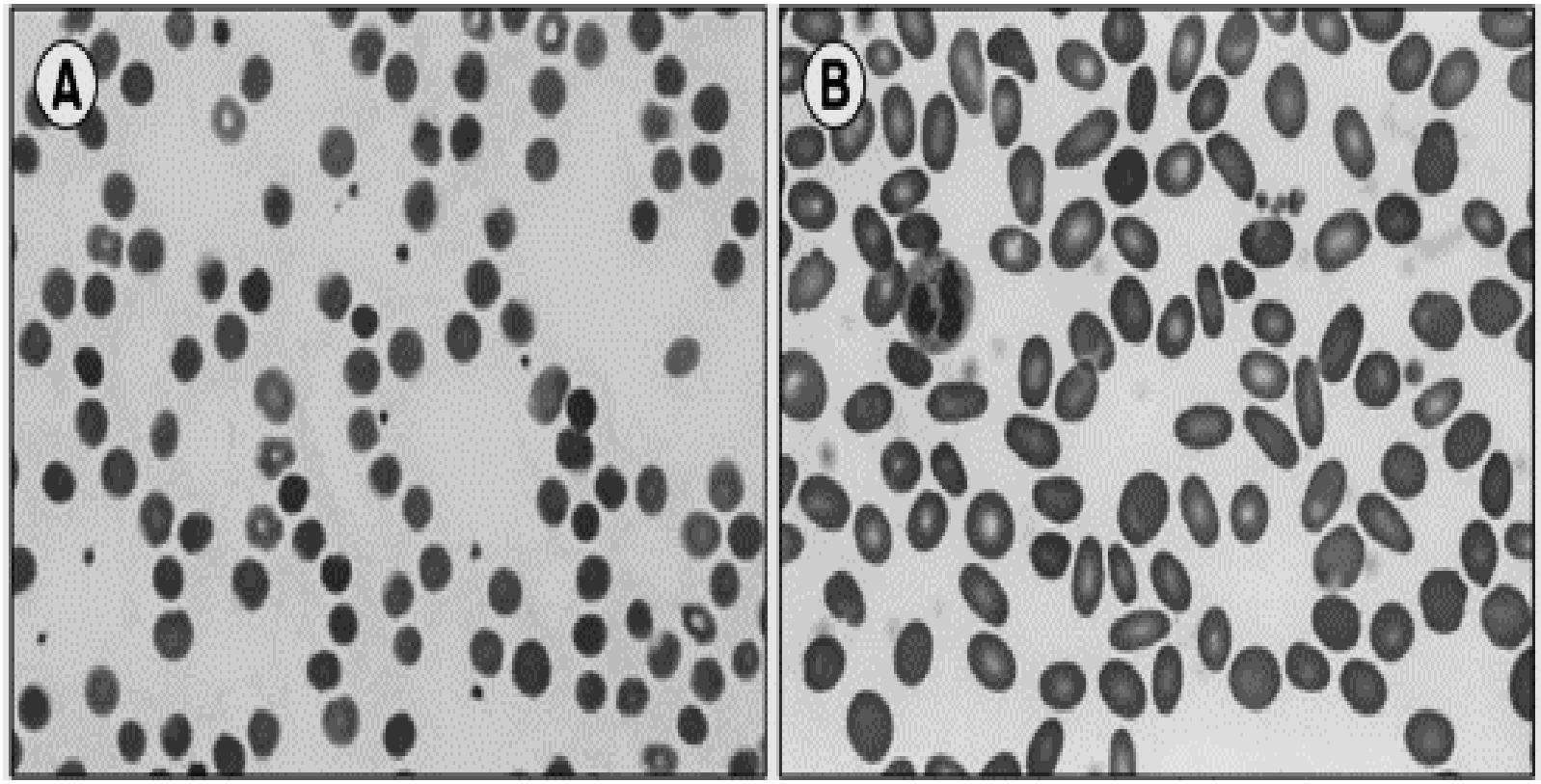
Hereditary elliptocytosis

- Is a genetic disorders
- That generate abnormalities in **spectrin** or, less frequently, in band **4.1 protein** .
- It can readily distinguished from hereditary spherocytosis by virtue of the fact that the affected red blood cells assume an elliptic disk-like shape.





Peripheral blood smear of inherited haemolytic anaemia.
(A) Hereditary spherocytosis, (B) hereditary elliptocytosis

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