Reading for Lectures 30-32: PKT Chapter 11 (skip Ch. 10)

3 μm

8 μm

capillary

This is an image of a human red blood cell.

The red cell is a specialized cell, whose job it is to transport oxygen via hemoglobin.
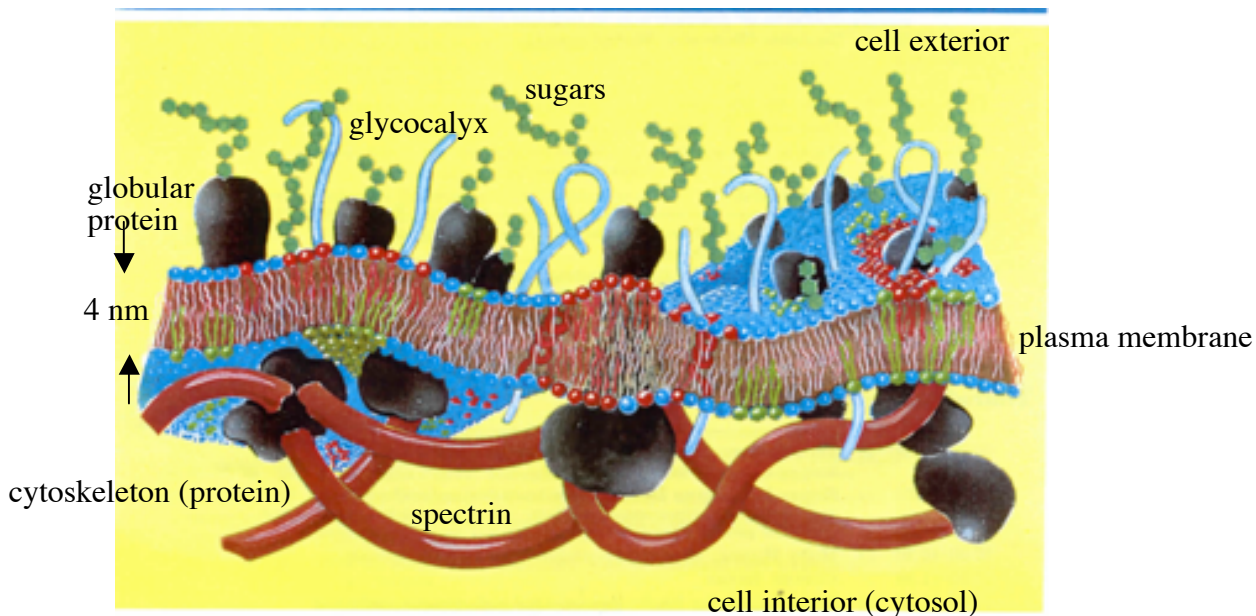
Unlike most cells, its interior is basically nothing but a concentrated solution of hemoglobin. There is no nucleus and very little by way of cellular machinery.

Red cells are produced in the bone marrow as nucleated cells. When they are ready, they are extruded from the marrow into the blood stream, a process during which they lose their nucleus.

They are initially rather "crinkled up in shape; however, after a few days circulating in the bloodstream, they attain their "normal shape" (below), which is a flattened disk slightly indented at the poles, about 8 μm in diameter.

They circulate in this form in the blood stream for about 120 days, during which they make about 10^5 round trips through the heart and lungs, through a capillary bed, and back.

In this process they deform to get thru 3 μm-diameter capillaries (sausage shape) but spring back.

After that their store of materials is used up (no nucleus and other machinery to replenish supplies).

At this point, they are tagged and go to the spleen, where they are broken down and recycled.

cell exterior

sugars

glycocalyx

globular protein

4 nm

plasma membrane

cytoskeleton (protein)

spectrin

cell interior (cytosol)

From "In Search of a New Biomembrane Model," International Symposium held in Copenhagen, Aug. 13-16, 1997.

This is a cartoon of the human red-cell plasma membrane. It is one of the simplest membrane systems.
Every cell—animal and plant, yeast and bacterium-- has a plasma membrane.
Eukaryotic cells have extensive internal membranes surrounding important organelles.
The biological function of all these membranes is to separate chemically different environments.
And, then, to control those environments for specialized chemical reactions.
Membranes are one of the most common biological structures. It has been estimated that the human body contains $10 - 100$ km^2 of membrane.
Let's see how this estimate works: I'll do it two different ways.

1. Humans have a mass of, say, 75 kg and, thus, a volume of roughly $75\,\ell = 0.075\ m^3$.

A typical cell has a dimension of, say, $1\,\mu m = 10^{-6}\ m$, so it has a volume of $\sim 10^{-18}\ m^3$. Thus, the number of cells in the human body is roughly $\dfrac{7.5 \times 10^{-2}}{10^{-18}} \sim 7.5 \times 10^{16}$.

Each cell has an area of $6 \times \left(10^{-6}\right)^2 = 6 \times 10^{-12}\ m^2$.

So the total plasma membrane (only) area is $\left(7.5 \times 10^{16}\right)\left(6 \times 10^{-12}\right) \sim 5 \times 10^5\ m^2 = 0.5\ km^2$.

But, for every m^2 of plasma membrane there might be $10 - 100$ m^2 of internal membranes, so we arrive at an estimate of $5 - 50\ km^2$.

Note: Wikipedia claims that there are only about 10^{14} cells in the human body, which would reduce this estimate significantly.

2. Given the very "crowded" interior of a typical cell, we could get another estimate by saying that, say, one half of all the material in your body is membrane. That would be, say, 40 liters $= 0.04$ m^3.
A typical membrane has a thickness of 4 nm, so the total area of this volume of membrane would be $\dfrac{0.04}{4 \times 10^{-9}} = 10^7\ m^2 = 10\ km^2$.

Membranes are very diverse in detail. This membrane will be our "model" system.
Membranes are made up of lipids and proteins.
It is a composite object:
- Plasma membrane (pm) (lipids+protein): chemical encapsulation
    pm is a 2D fluid
    This model of the pm is called the Singer-Nicholson fluid-mosaic model (1972)
- Cytoskeleton or membrane skelton: mechanical stability, toughness.
    Note: The rbc cytoskeleton is unusual in that it is only a thin flexible layer anchored into the pm. In most cells the cytoskelton runs throughout the cell.
- Glycocalxy mediates contact with the outside world, signaling

I will talk mainly about the plasma membrane as a lipid structure.

Here is a cartoon of a section of pure-lipid membrane:
The interior is a "spaghetti" of hydrocarbon chains (no water, "waterproof"). Highly hydrophobic, they are concentrated in this way to hide them from exposure to water.
The exterior is studded with polar groups, which like water exposure.

These structures form spontaneously when the lipid is put into the water. They are "self-assembling." The driving force is the hydrophobic effect.
In the form in which they occur most commonly biologically, they are 2D fluids, so they form the "solvent" of a 2D environment in which other molecules can diffuse around and reactions can take place. "2D reaction medium"
Membrane proteins are specialized to this environment by having hydrophobic amino acid residues in a 4 nm "band" or "belt". (But, how do they insert?)
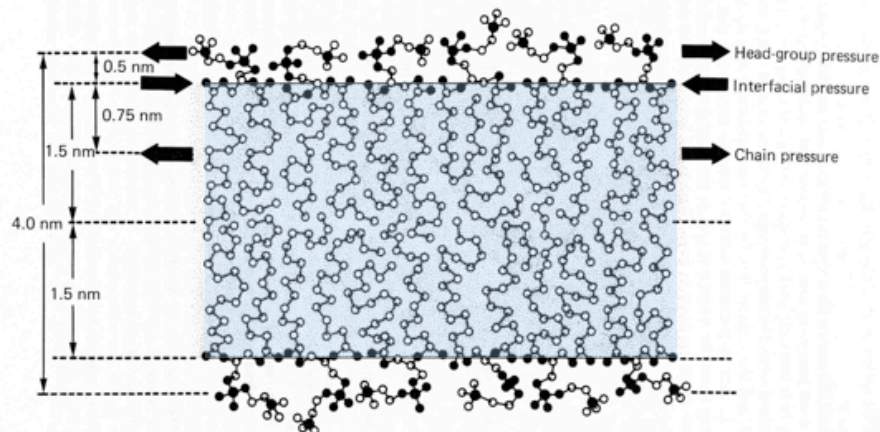
Fig. 17.4. Lecithin bilayer drawn to scale. The lipid bilayer is the basic structure of biological membranes, and most membrane lipids contain two hydrocarbon chains. The lipids diffuse rapidly in the plane of the bilayer, covering a distance of about 1 μm in 1 s. They also cross the bilayer from one side to the other ('flip-flop'), as well as exchange with lipids in the solution, but at much slower rates, of the order of hours (cf. the lifetime of single-chained surfactants in micelles of 10^{-5} to 10^{-3} s). (From Israelachvili et al., 1980a.)

Isrealachvili, Intermolecular and Surface Forces, p. 376

The plasma membrane is made up mainly of lipids. What is a lipid?

The basic lipid molecule is composed of two parts: A polar head-group attached via a short "backbone" to (typically) two hydrocarbon chains (hydrophobic). "di-acyl"

Such molecules are called "amphiphilic" or "amphipathic", meaning that they are partly hydrophobic and partly hydrophilic.
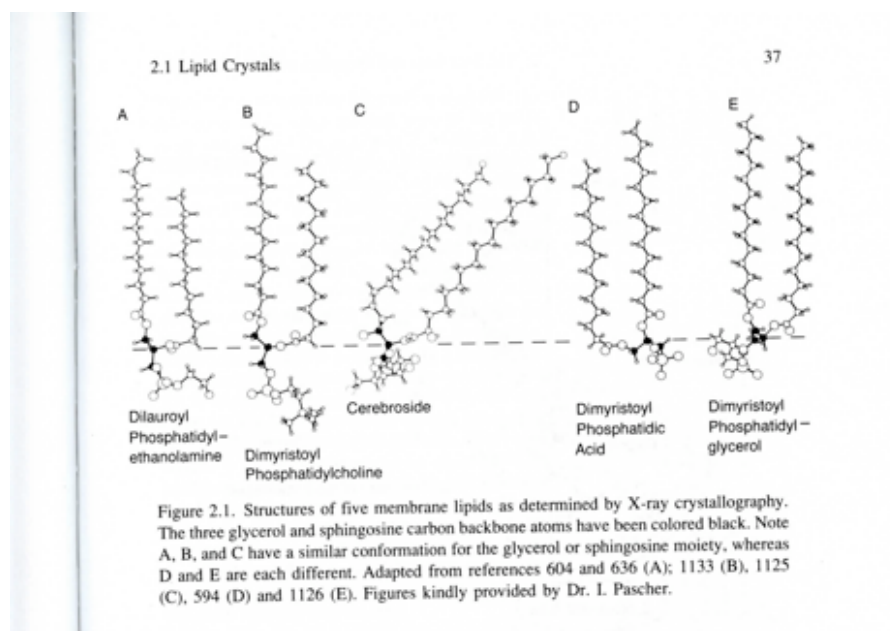
Individually, these molecules are very insoluble in water because of the long (typically 12—16 carbon) chains.

However, collectively, they can form a variety of structures which are happy to be in water.

The key feature of these structures is that they "sequester" the hydrophobic chains away from the water and "coat" the exterior with the polar groups.

From our point of view, the most important structure is the bilayer membrane. Basically, it is a butter sandwich.

Here are some examples of such di-acyl lipids:

2.1 Lipid Crystals   37

Dilauroyl
Phosphatidyl—
ethanolamine   Dimyristoyl
              Phosphatidylcholine

Cerebroside

Dimyristoyl
Phosphatidic
Acid

Dimyristoyl
Phosphatidyl—
glycerol

Figure 2.1. Structures of five membrane lipids as determined by X-ray crystallography. The three glycerol and sphingosine carbon backbone atoms have been colored black. Note A, B, and C have a similar conformation for the glycerol or sphingosine moiety, whereas D and E are each different. Adapted from references 604 and 636 (A); 1133 (B), 1125 (C), 594 (D) and 1126 (E). Figures kindly provided by Dr. I. Pascher.

Generic structure of an important class of complex membrane lipids is: **30.4**

(note ester linkages)
There can be one or two tails.
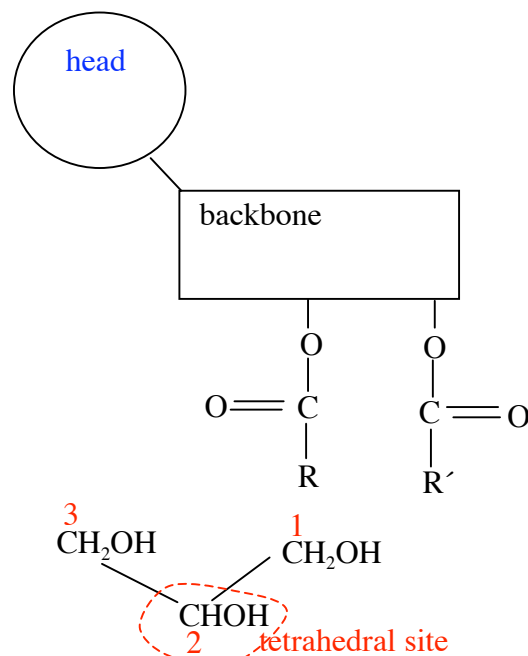With different backbones
Different fatty acid tails.
Different head groups
We will discuss these elements in turn:

Backbone:
Two biologically common backbones
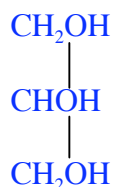(glycerol and sphingosine)

We will stick to glycerol:

Glycerol is a three-C alcohol based on propane:
And, choline is the alcohol $N(CH_3)_3-CH_2-CH_2OH$,
which is bonded through a phosphate bond.
There is stereochemistry about 2 (but not about 1 and 3) as soon as the two ends differ.

CH_2OH
|
$CHOH$
|
CH_2OH

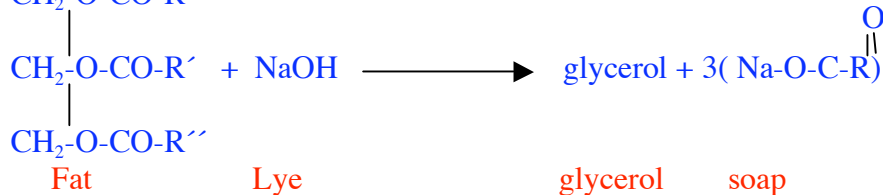You can attach fatty-acid chains to any and all of the carbons:
Three-chains glycerides are "fats" (called "triglycerides")
Common membrane lipids are all diglycerides.
Monoglycerides (with appropriate head groups) are called "lysolipids"
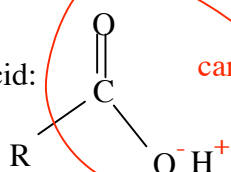
Comment: Close relation to soaps:
Triglycerides used biologically for energy storage

$CH_2-O-CO-R$
|
$CH_2-O-CO-R´$ + NaOH $\longrightarrow$ glycerol + 3(Na-O-C-R)
| $\overset{\displaystyle O}{\|}$
$CH_2-O-CO-R´´$

  Fat   Lye   glycerol   soap

Hydrocarbon Chains:
Many complex lipids of biological interest contain simple linear hydrocarbon chains, which
occur biologically in the form of "fatty acids."

Here's a generic fatty acid: carboxyl group

R-COOH , i.e.,   R—C(=O)O⁻H⁺   carboxyl group dissociates in water to give acid.

In the compounds we will be interested in the R group is a saturated or nearly saturated 30.5
hydrocarbon chain.

Thus, fully saturated chains (label by number of carbons):
N=1: H-COOH   formic acid (ants)
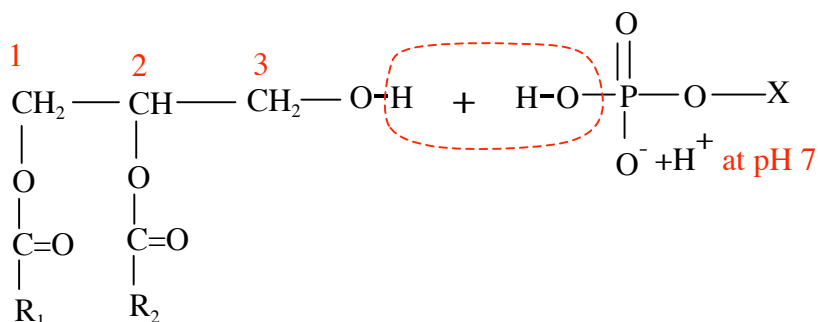N=2: CH_3-COOH   acetic acid (vinegar)
……
N=14: $CH_3(CH_2)_{12}$-COOH   myristic acid (nutmeg)
N=16: $CH_3(CH_2)_{14}$-COOH   palmitic acid (palm oil)
N=16: $CH_3(CH_2)_{16}$-COOH   stearic acid (beef)
In monounsaturated chains, you need to label position of double bond (counted from carboxyl
end) and whether it is cis or trans.

What about head groups?
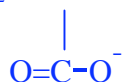Common head groups are phosphate-linked via condensation:

Such compounds are called "phosphoglycerides" or (di-acyl)-glycerophospholipids.

Common "X" groups include:

ethanol-amine: $-CH_2-CH_2-N^+H_3$, which gives phosphatidyl ethanolamine (PE)

**choline:** $-CH_2-CH_2-N^+(CH_3)_3$, which gives phosphatidylcholine (PC) lecithin (egg yoke)

serine: $-CH_2-CH-N^+H_3$, which gives phosphatidylserine (PS)
                        |
            $O=C-O^-$
There are many other possibilities, including lipo-proteins, etc.

Here is an important example of a complex lipid. Lipids like this are the dominant structural component of cell membranes, including the plasma membrane.
A generic "di-acyl-glycero-phospho-lipid"
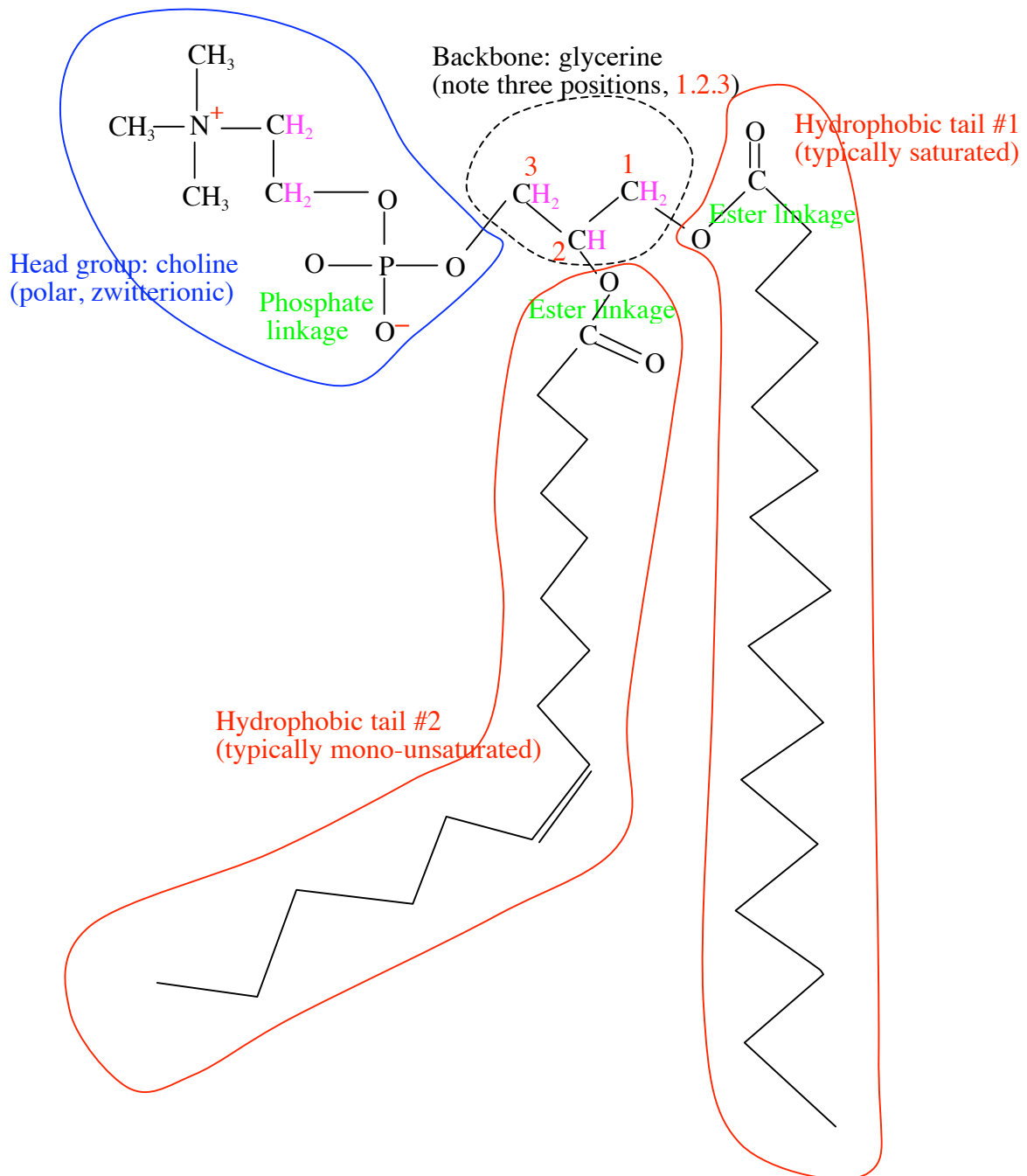
Technically, this is 1-palmitoyl-2-palmitoleoyl—sn-glycero-3-phosphatidyl choline.
Palmitate is a 16-carbon fully saturated fatty acid; palmitoleate is 16-carbon fatty acid with a cis double bond after the 9th C counting from the top.
Kink in tail #2 regulates membrane order and fluidity.
The saturated parts of the hydrocarbon chain have trans (straight) and gauche (bent) configurations. The trans configuration is lower energy; however, the trans-gauche energy difference is only about 5 k_BT, so under biological conditions, there can be several bends in each chain.

By contrast cholesterol is an important "simple" lipid:
Cholesterol is an important example of a simple lipid. Cholesterol occurs as a critical
component of the plasma membrane, contributing to its strength and fluidity.

Notes:
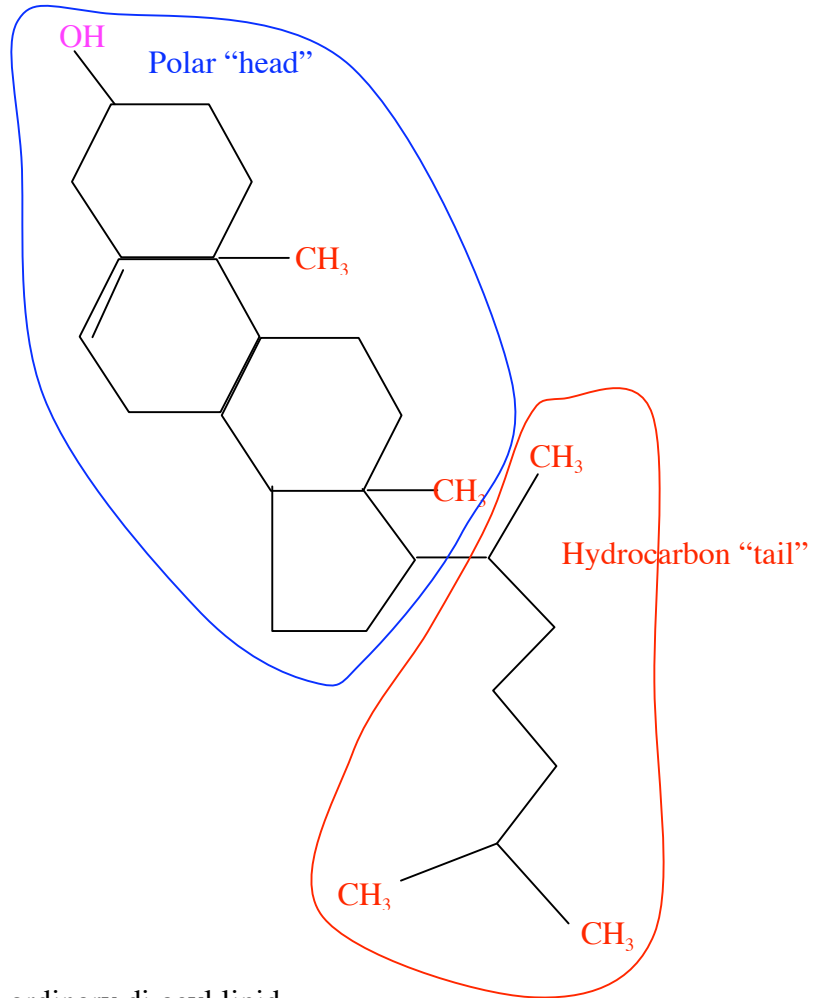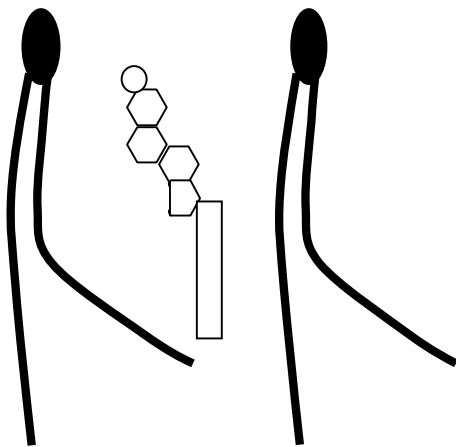This is amphipathic.
Common in animal pm,
e.g., 25% in human rbc.
(less common in organelle membranes)
Mono-acyl
Cholesterol is a sterol.
Regulates fluidity.

OH
Polar "head"

CH_3

CH_3
CH_2
Hydrocarbon "tail"

CH_3

CH_3
CH_3

Cholesterol:
- orients in the monolayer just like and ordinary di-acyl lipid.
- it regulates membrane fluidity by "stiffening" the near-head region
- it decreases the permeability of the membrane to small water-soluble molecules
- it increases flexibility and stability (cells without it lyse)
- it decreases membrane ordering (membranes without it would "freeze" into the gel phase)
- it can "flip-flop" relatively easily between the two leaves of the bilayer (see shape mechanics)

In the human red-cell plasma membrane, there is a lipid mixture including up to 1000 different kinds; however, five major groups predominate:

PC 25%
PE 22%
PS 10%
Sphingolipids 18%
Cholesterol 25%
Note: The two leaves of the bilayer differ significantly in composition.

Summary:
The plasma membrane is a fluid-phase self-assembled lipid-bilayer sheet about 4 nm thick.

It is:

- quite permeable to water
- impermeable to ions and large molecules (i.e. it is an osmotic barrier)
- it is a "soft" material
- it is quite "incompressible" (like water)
- it is easily bendable (important for rbc function)
- it has a large in-plane (fluid-phase) mobility (good 2D reaction medium)
- little or no exchange of lipids between leaves of the bilayer (flip-flop)
- little or no tail interdigitation, so leave slide freely
- self-sealing material

I want to focus next on where these properties come from.