Chemistry Review:
Lipids

Lecture 5

Objectives

- Know names of 3 lipid classes, their function and purpose
- Know the structure of the fatty acid & its chemistry and meaning of examples like C16:0 and C18:1
- What is an unsaturated and saturated fatty acid and how does it affect cell membrane fluidity
- What triglycerides are and role of glycerol
- What a phospholipid is: structure & function in cell membrane bilayer
- What is a micelle and liposome
- What cholesterol does in animal cell membranes

Objectives

- Lipoproteins: types (chylomicron, VLDL, …, HDL), structure & function/role in lipid metabolism, concept of density
- What atherosclerosis is and the theory on how it occurs

Lipids ("Fats")

Lipid classes

- Triglycerides: storage lipids
  - a nonpolar lipid used as "food"
  - catabolized to yield calories for ATP for other processes
- Phospholipids

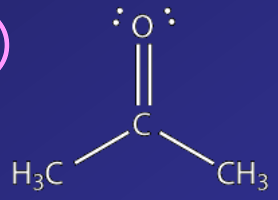
  a polar lipid which is the "skeleton" of cell membranes
- Glycolipids

  another polar lipid with special properties
- Steroids
  - help in membrane rigidity
  - many hormones derived
- Other lipids: terpenes, used to make vitamins

Terms / Definitions

- Lipophilic ("fat-loving") and Hydrophobic ("water-fearing) generally have the same meaning
- Lipids are insoluble in H_2O

  "oil and water do not mix"
- Lipids readily are soluble (dissolve in) organic solvents
  - alcohol (ethanol, CH_3CH_2OH, EtOH)
  - ether (diethyl ether, $CH_3CH_2{-}O{-}CH_2CH_3$)
  - acetone (2-propanone)



The Fatty Acid (FA)

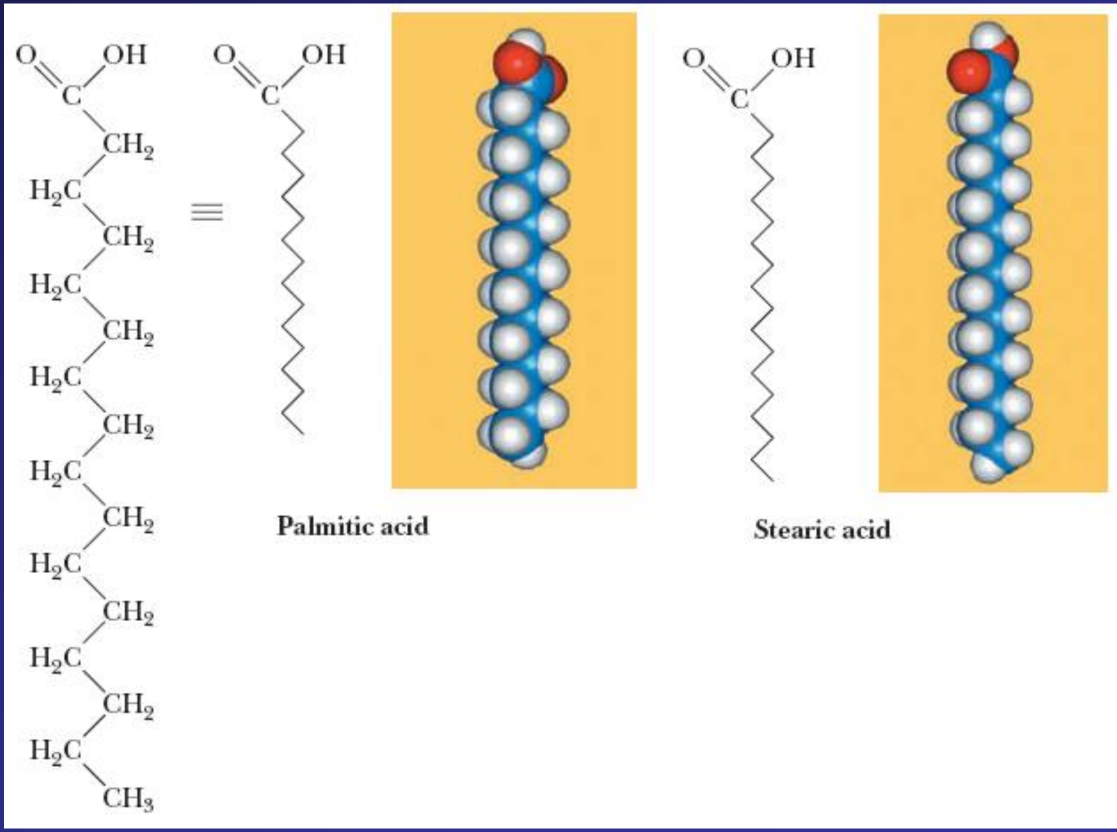
- Two parts in the chemical structure
  1. a long alkyl (–CH_2–) chain that is hydrophobic (lipophilic): doesn't interact with H_2O
  2. an acidic moiety that forms a negative (anionic) charge in water
- Structure is: $CH_3(CH_2)_nCOOH$ for the saturated fatty acids
- Saturated vs. Unsaturated Fatty Acids
  - Saturated means that all the hydrogen (H) atoms that can possibly bond to carbon (C) atom do bond
  - Unsaturated means that not all the possible H atom bonding is done to carbon, and this is indicated by double bonds between carbon atoms (C=C)

Saturated Fatty Acids

- C16:0
  Palmitic acid
- C18:0
  Stearic acid

- C12:0
  Lauric Acid
  C14:0
  Myristic Acid

C16:0 means
- total of 16 carbons
- 0 double bonds

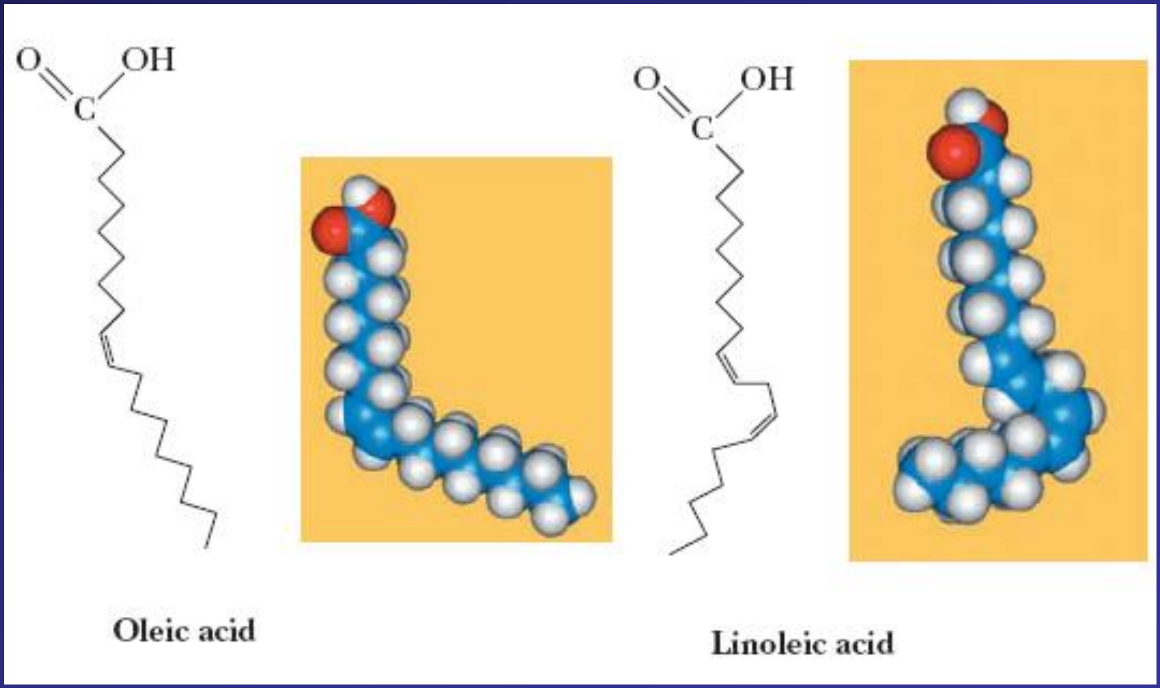


Unsaturated Fatty Acids

- C16:1 Δ^9
  Palmitioleic acid
- C18:1 Δ^9
  Oleic acid
- C18:2 $\Delta^{9,12}$
  Linoleic Acid
- C18:3 $\Delta^{9,12,15}$
  α-Linoleic Acid
- C20:4 $\Delta^{5,8,11,14}$
  Arachidonic Acid

Δ^9 means a double bond starts at carbon #9

With more than one C=C (carbon-carbon double bond), there is a single intervening carbon not involved in the double bond



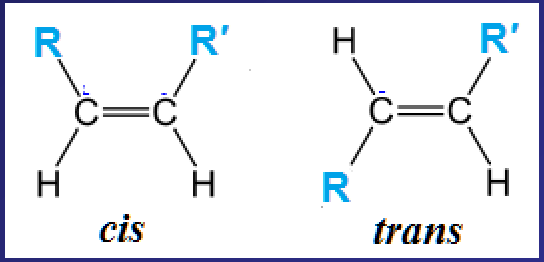
C=C Double Bonds: *cis* vs *trans*

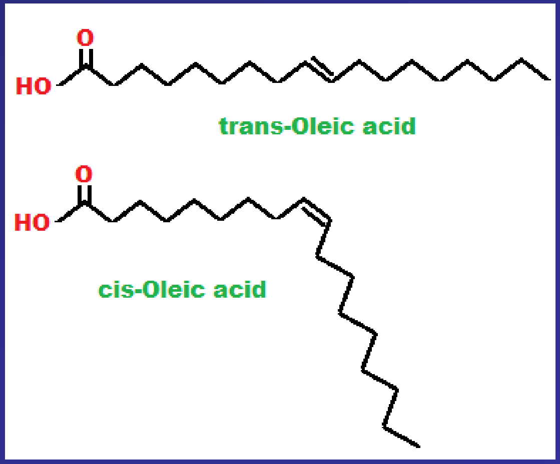
Carbon-carbon double bonds can have two possible geometries

- *cis*: the carbon chain continues on the "same side" of the double bond
- *trans*: the carbon chain continues on the "opposite side" of the double bond

In fatty acids, the C=C bond(s) is/are *cis*

the *cis* double bond can make the FA have a "kink" to it





Saturated vs Unsaturated

With saturated FAs (and also with "trans-" unsaturated FAs), these molecules can pack tightly together

- At low temperatures, they pack so well, they can form a solid (grease)

But with *cis*-unsaturated FAs in the mix, they don't pack to so well

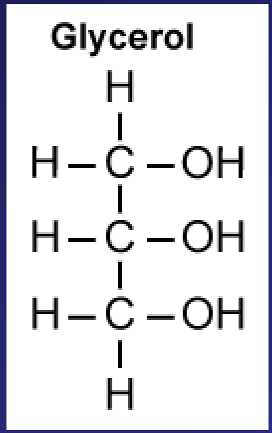
- At low temperatures, they keep the mixture liquid: an oil

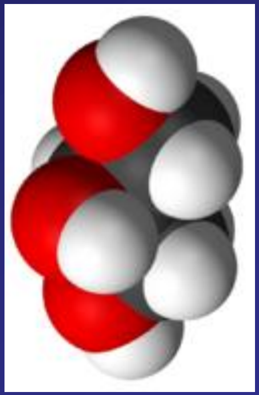
Plants generally make more unsaturated FAs for their lipids used in cell membranes to keep them fluid, because they don't have "body heat" like animals

Glycerol

- A 3-carbon polyhydroxy (poly-OH) alcohol that is fundamental in lipids important in biology
- In organic chemistry, an alcohol has the structure R-OH

  Glycerol has 3 R-OH groups
- Glycerol is found as an intermediate in many metabolic pathways, particularly in lipid metabolism (catabolism and biosynthesis)

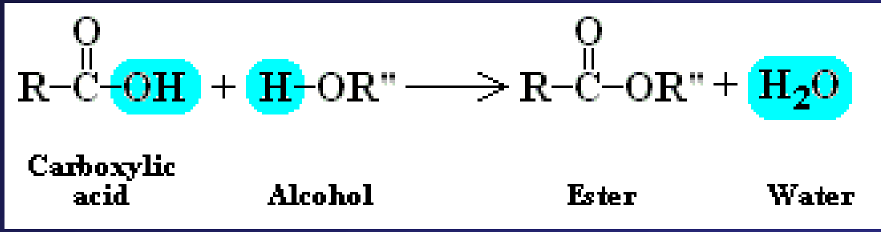




On the following slide, it is shown why glycerol was introduced

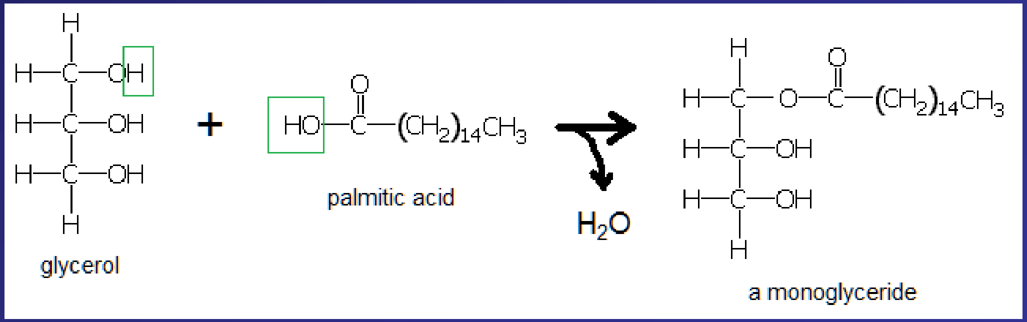
The Fatty Acid Ester

- In organic chemistry, the condensation of a carboxylic acid with an alcohol produces an ester



Condensation is the opposite of hydrolysis: H_2O is taken out

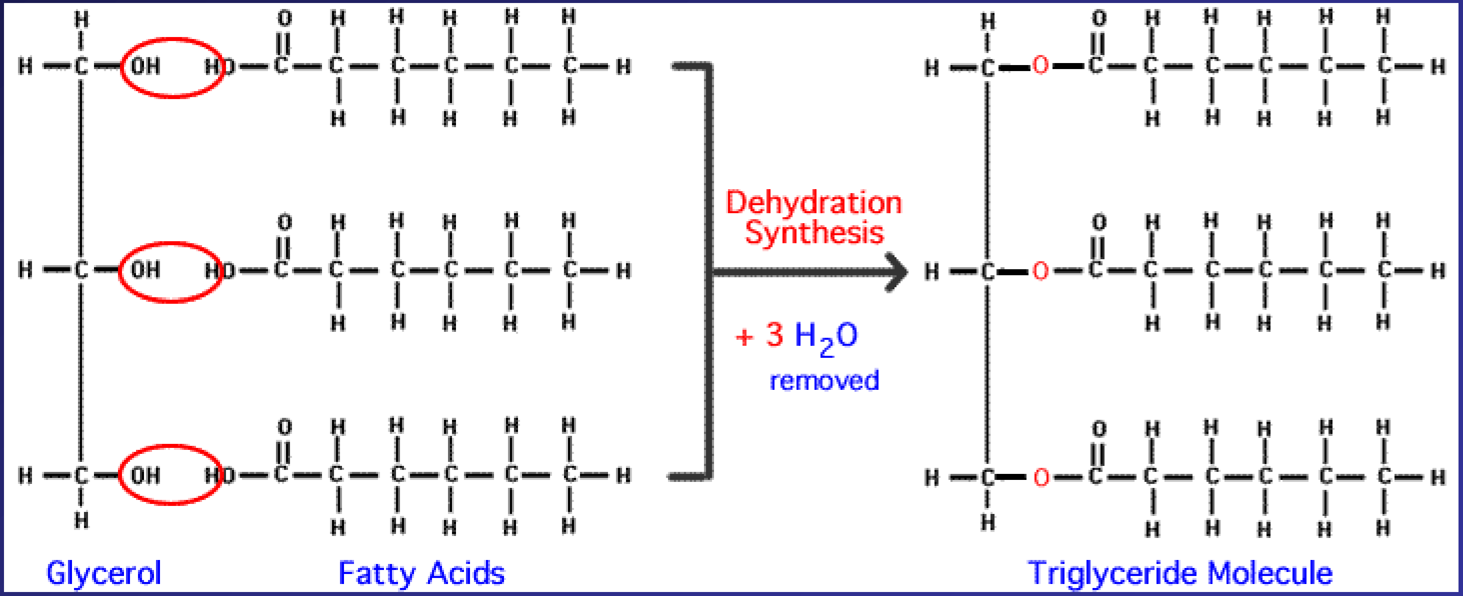
- A fatty acid (like palmitic acid) is a carboxylic acid
- Glycerol is an alcohol (has 3 –OH groups)
- Thus it forms an ester



Triglyceride Formation

- Now, repeat the process of esterifying two more fatty acids to the other two –OH groups on glycerol and …

you have a triglyceride



Triglycerides Role/Function

- These lipids are generally the storage form of fats for energy in metabolism
- They will be stored in cells of adipose tissue until mobilized in catabolic pathways

Polar Lipids

- Polar lipids means one part is polar: hydrophilic, prefers being around H_2O
- These would be molecules whose parts have –OH groups (especially large molecules like carbohydrates) or have charged groups $–COO^-$, $–NH_3^+$

- Phospholipids and glycolipids are among the major polar lipids
- Cholesterol has minor polarity

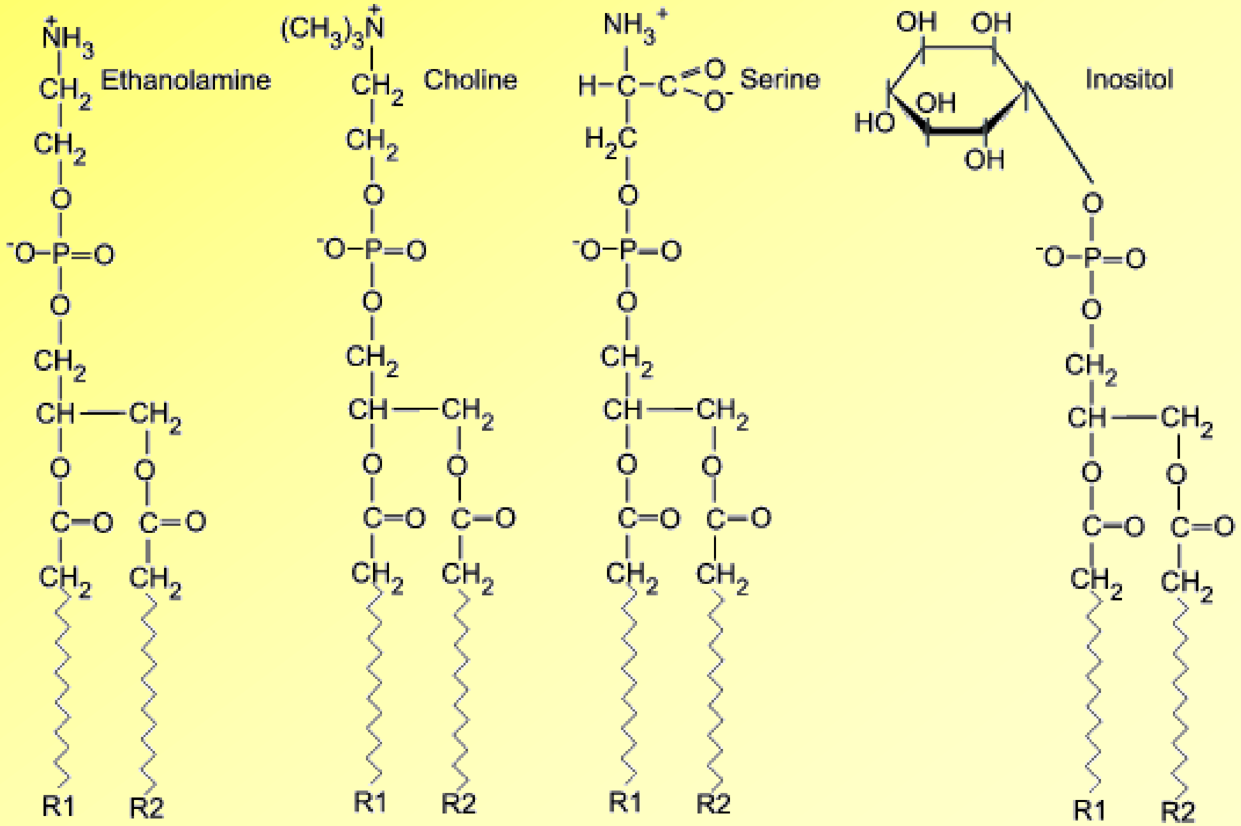
Phospholipids

- These differ from triglycerides (TGs) in that only two fatty acids are esterified to glycerol
- The other glycerol –OH is esterifed to a phosphate molecule (–OPO_3)
- Because the phosphate is negatively charged, if only a phosphate is on the molecule, the phospholipid will be negatively charged

Other Phospholipid Types

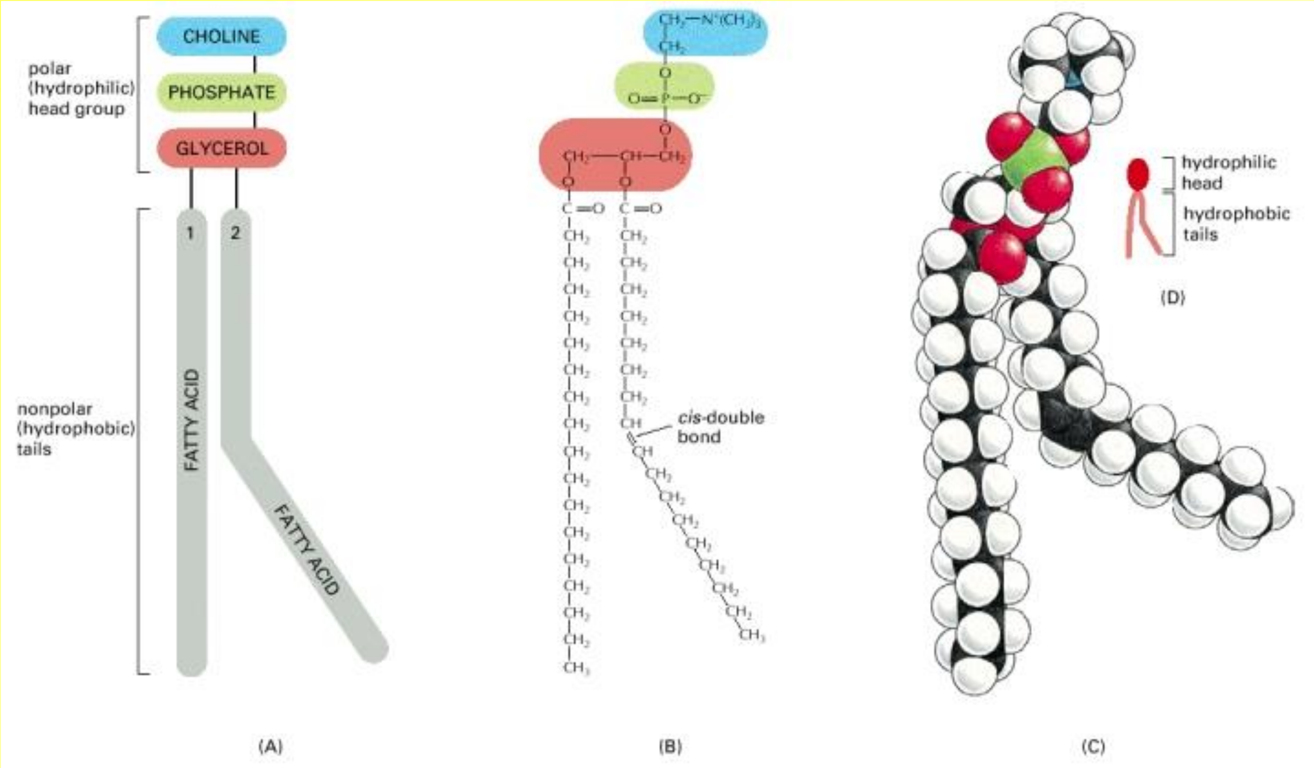
- But in fact, other groups are added to the $–OPO_2–$ group that is already attached to glycerol
- These are serine, choline, ethanolamine, inositol

Ethanolamine and choline mask the phosphate negative charge and puts a positive charge at the end
The serine still leaves a net negative charge, as does the inositol form. The inositol form is important precursor in calcium-regulated cell activation



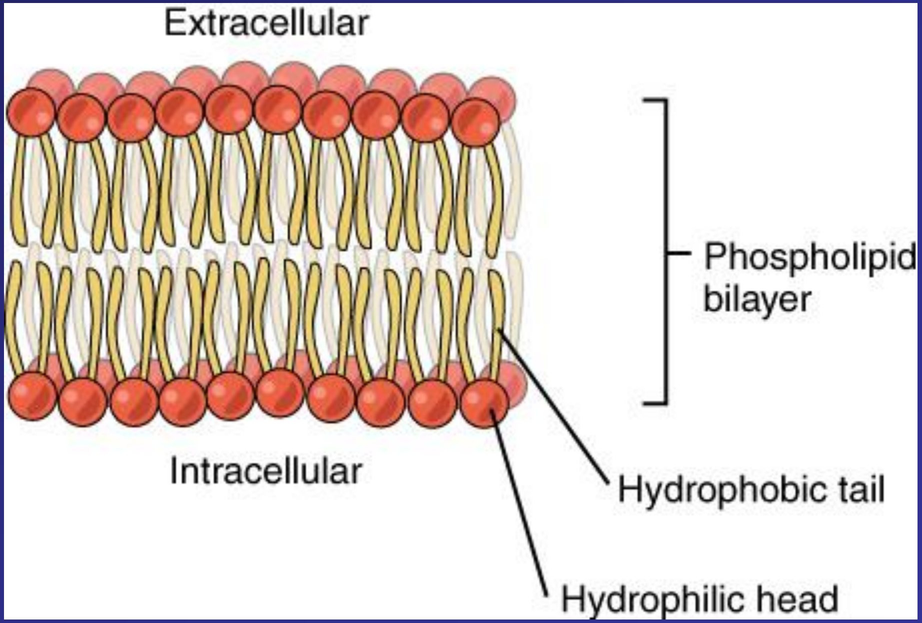
Phosphatidylcholine

- The figure below shows the phospholip phosphatidylcholine in three ways: schematic, chemical structure, and a space-filling model
- Notice how the cis-fatty acid would make it difficult for the membrane to pack tightly, giving it fluidity



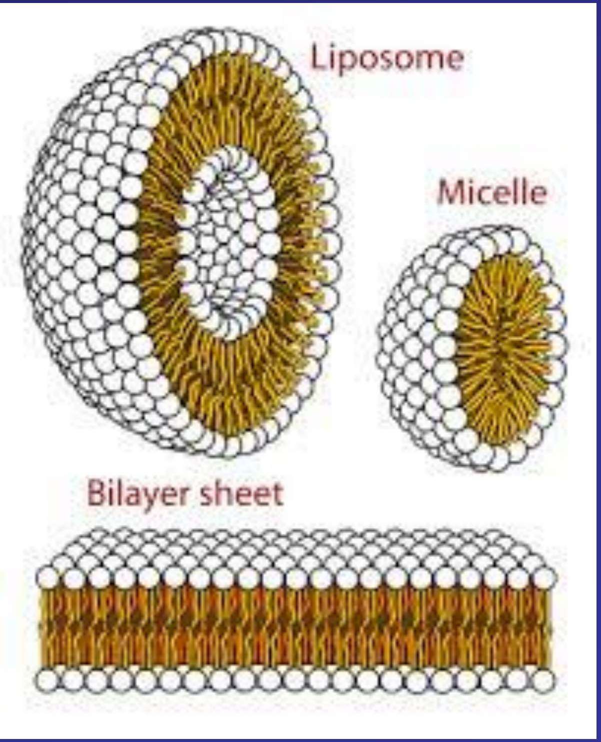
Phospholipid Bilayer

- The ability of the phosholipids to associate in opposite facing sheets (bilayer) makes them a natural chemical to form lipophilic membranes that compartmentalize aqueous solutions



Micelles & Liposomes

- Polar lipids (including phospholipids) can form micelles: spheres in which the hydrophobic tails are directed towards the center and the polar heads are oriented to the surface to make contact with water
- Liposomes are spheres where the phospholipid bilayer sheet forms a sphere with an interior that is composed of the outer solution during liposome formation



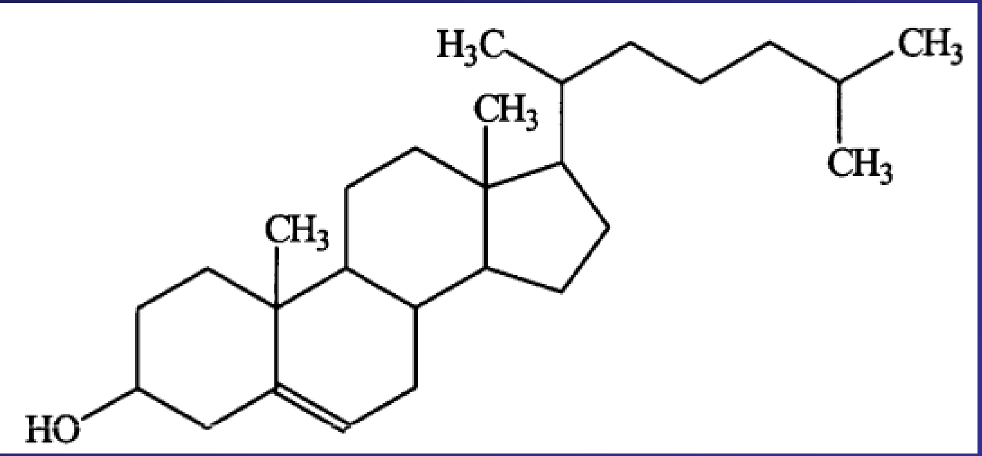
Liposomes can be formed by ultrasonication with a phospholipid solution containing a drug or useful toxicant, along with perhaps a membrane protein that targets a tissue or type of cell. They are then rinsed (dialyzed), then injected where they might dissolve/release their contents only at the target tissue or cells

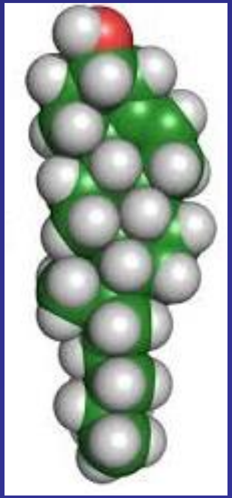
Sterols & Steroids

- Cholesterol
- Molecules derived from cholesterol
  - Mineralocorticoids
    - aldosterone
  - Glucocorticoids
    - cortisol
  - Sex Hormones
    - Testosterone
    - Estrogen

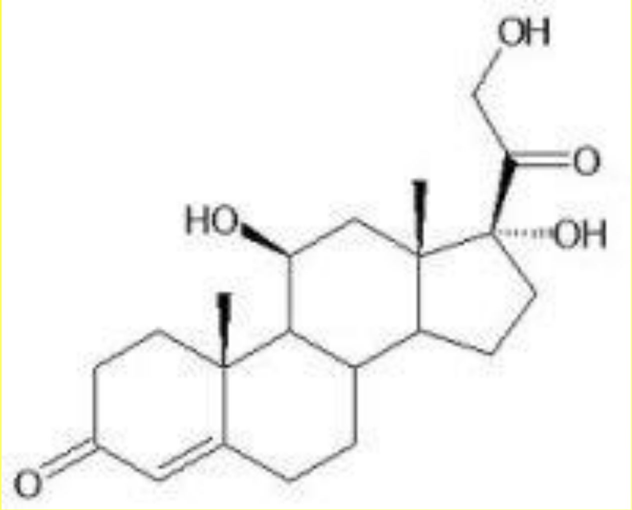
Cholesterol

- A 4-ringed molecule whose chemical structure is entirely hydrophobic except for a hydroxyl (–OH) group at the end of the molecule, which may extend out from the membrane interior
- Cholesterol is a fundamental component of cell membranes
- Starting point for biosynthesis of steroid hormones



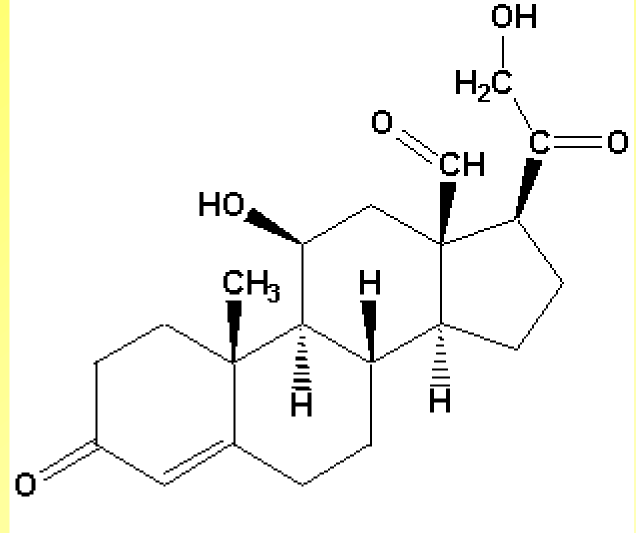


Steroids

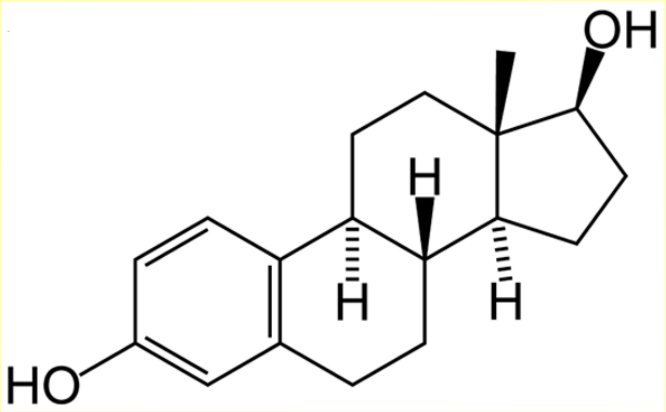


cortisol

Many of these structures differ by only one functional group or atom or slight arrangement of atoms. For example, cortisol and aldosterone differ in two ways structurally

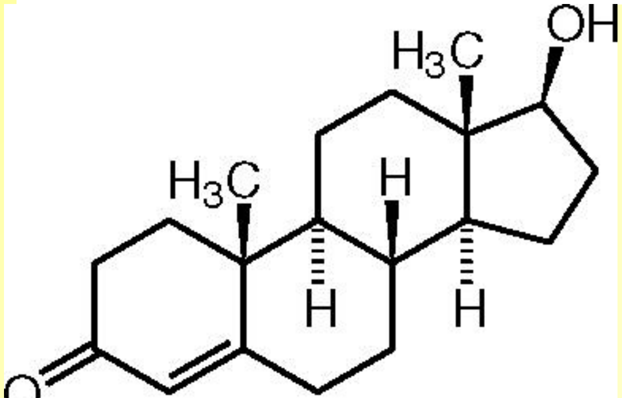


Aldosterone



estrogen

But this difference has a large effect physiologically: cortisol regulates glucose metabolism and aldosterone regulates electrolyte balance



testosterone

Lipid Transport In Blood

- Because "gobs of grease" do not mix with water in blood plasma, the body has a system for transporting lipids called lipoproteins
- Lipoproteins appear as 5 types:
  - Chylomicrons
  - Very Low-Density Lipoproteins (VLDLs)
  - Intermediate-Density Lipoprotein (IDLs)
  - Low-Density Lipoprotein (LDLs)
  - High-Density Lipoprotein Cholesterol (HDLs)

Note that in the past, they used to put "cholesterol" after the name: low-density lipoprotein cholesterol, and abbreviate it LDL. That's why it things are called "good" and "bad" cholestrol

Apolipoproteins

- The protein part of the lipoproteins are referred to as apolipoproteins
- The "apo" means that the protein is not assembled or bonded to other things that make it totally function or which identify it
- Apolipoprotein AI & AII

  these protein are associated with HDL in support of its function
- Apolipoprotein B
  - this protein is associated with all lipoprotein forms except HDL
  - It binds to cells with LDL receptors

Apolipoproteins

- Apolipoprotein C

  The protein moves to HDL when it has been a long time between meals and to chylomicrons and VLDL after a fatty meal

- Apolipoprotein E
  - Associates with chylomicrons and IDL
  - Very important in cholesterol regulation: mutations can cause hypocholesterolemia
  - Presence of an E4 variant indicates a high risk for Alzheimer's disease
- Apolipoprotein (a)
  - when part of LDL (bonded to ApoB), there is an abnormal metabolism of fats causing severe atherosclerosis

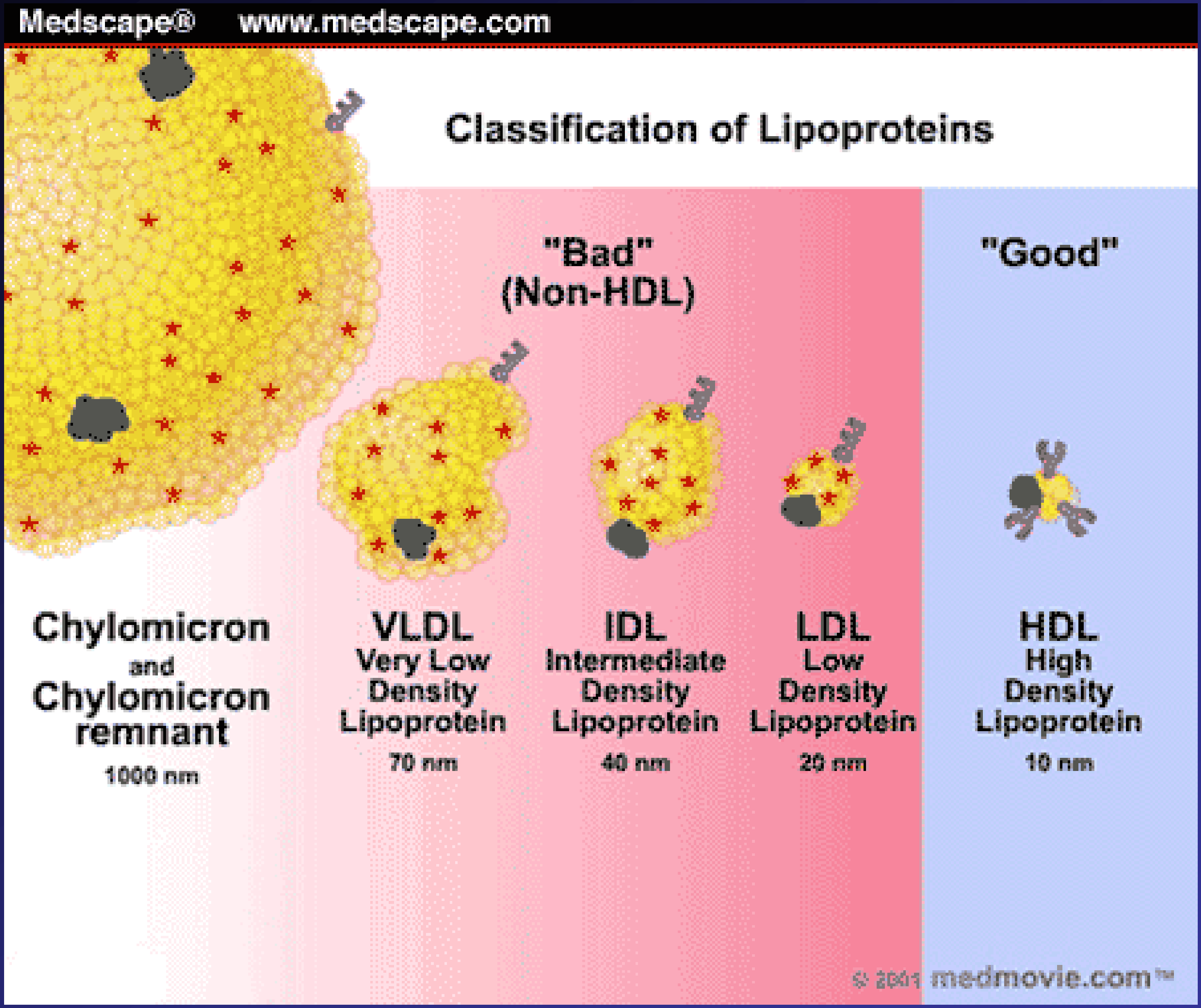
Density?

- Oil/fat floats on water: therefore it has a lower density than water
- When the amount of fat/lipid that makes up something increases, it lowers the density of that substance
- So the lower the of density a ball of cholesterol, fat, and protein, the more fat/lipid it has
- Look at the table below to see the relationship between lower density forms of lipoprotein and their lipid content

TABLE 24.1 Composition and Properties of Human Lipoproteins

Lipoprotein Class	Density (g/mL)	Diameter (nm)	Composition (% dry weight)			
			Protein	Cholesterol	Phospholipid	Triacylglycerol
HDL	1.063–1.21	5–15	33	30	29	8
LDL	1.019–1.063	18–28	25	50	21	4
IDL	1.006–1.019	25–50	18	29	22	31
VLDL	0.95–1.006	30–80	10	22	18	50
Chylomicrons	<0.95	100–500	1–2	8	7	84

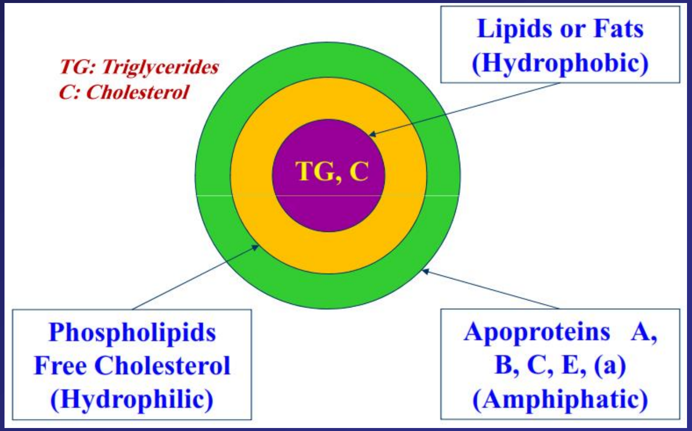
Adapted from Brown, M., and Goldstein, J., 1987. In Braunwald, E., et al., eds., *Harrison's Principles of Internal Medicine,* 11th ed. New York: McGraw-Hill; and Vance, D., and Vance, J., eds., 1985. *Biochemistry of Lipids and Membranes.* Menlo Park, CA: Benjamin/Cummings.

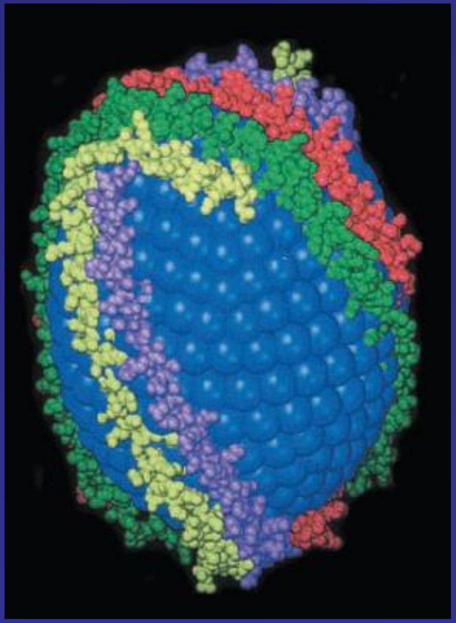

Medscape® www.medscape.com
Classification of Lipoproteins
"Bad"
(Non-HDL)
"Good"
Chylomicron
and
Chylomicron
remnant
1000 nm
VLDL
Very Low
Density
Lipoprotein
70 nm
IDL
Intermediate
Density
Lipoprotein
40 nm
LDL
Low
Density
Lipoprotein
20 nm
HDL
High
Density
Lipoprotein
10 nm
medmovie.com™

Lipoprotein Structure

- There are 3 layers to the spheroid that makes up lipoproteins

1. Innermost layer are the most lipophilic molecules: triglycerides and esterified cholesterol
2. Middle: Phospholipids and unesterified cholesterol, lipophilic parts oriented inward
3. Outermost layer are the proteins that contain the ball, and help it to be targeted to the right tissues in transport

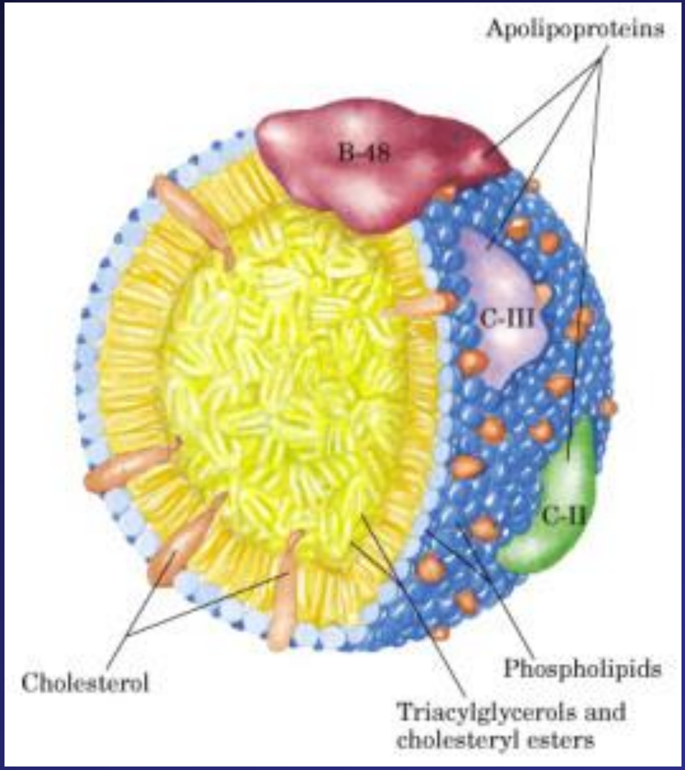




The bottom figure at right shows how the protein part (multi-colored) wraps around the middle layer

Chylomicrons

- These transport triglycerides after absorption in mucosa to the liver
- The liver will process these into VLDL



VLDL

- Made in the liver and exported from it, these travel in the blood
- During passage through the blood, the enzyme lipoprotein lipase on the surface of some cells removes fat (TGs) and cholesterol esters (along with some lipoproteins
- The VLDL particles become LDL by this process of trimming fat off VLDL

LDL

- LDL is made in the liver from chylomicron processing and exported for capture by body cells
- A receptor (the LDL receptor) must be on the surface of the cells for LDL to be imported into the cell
- Adipose tissue cells have lots of LDL receptors

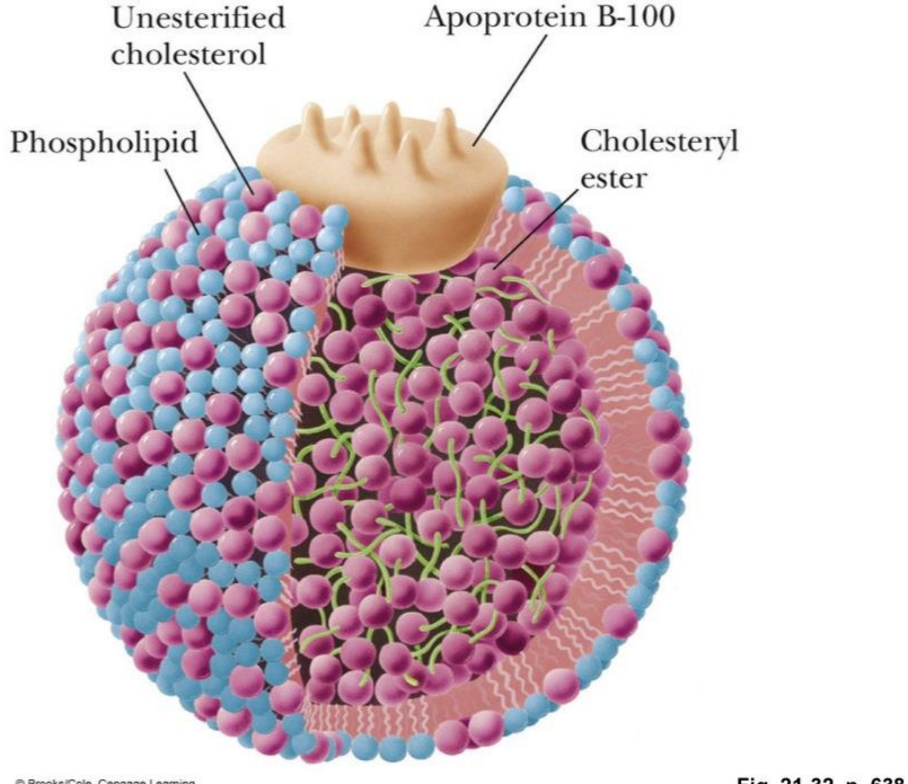
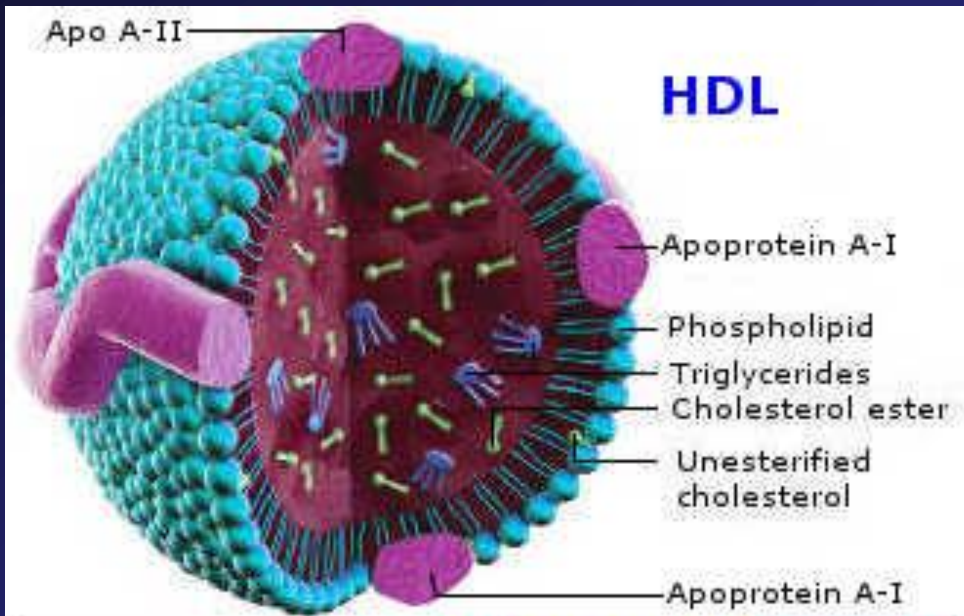


Fig. 21-32, p. 638

HDL

- HDL is synthesized in liver and intestine
- It plays a role in transporting cholesterol to the steroid-producing organs (gonads, adrenal cortex)



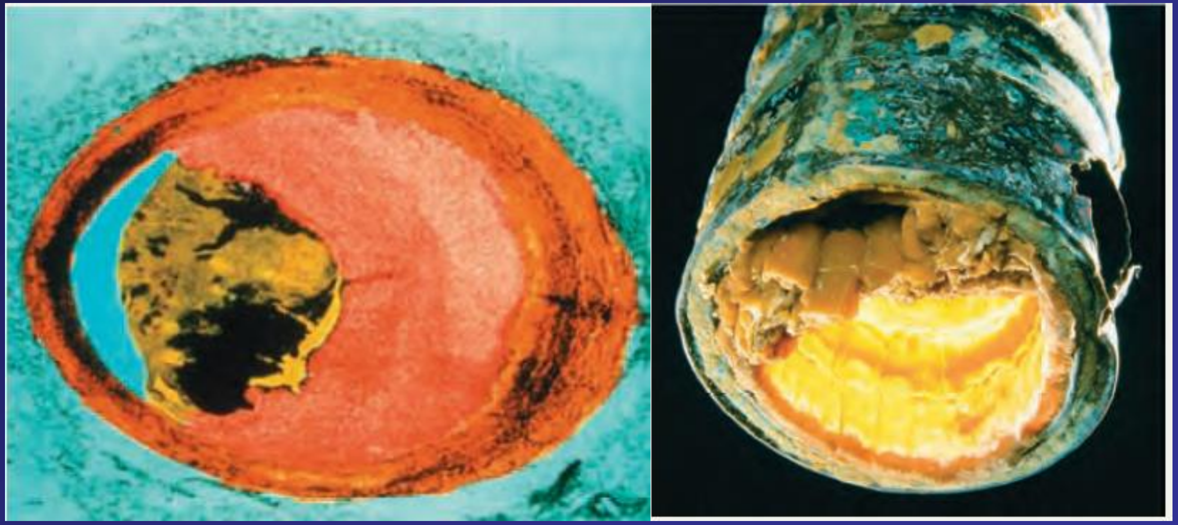
	High risk	Intermediate	Protective
HDL-C mg/dL	<40	40 - 60	>60
HDL-C mmol/dl	<1.03	1.03 – 1.55	>1.55

- More importantly, HDL collects excess lipids (TGs, cholesterol) from cells and the blood and transports them to the liver, where the liver excretes the excess into the bile

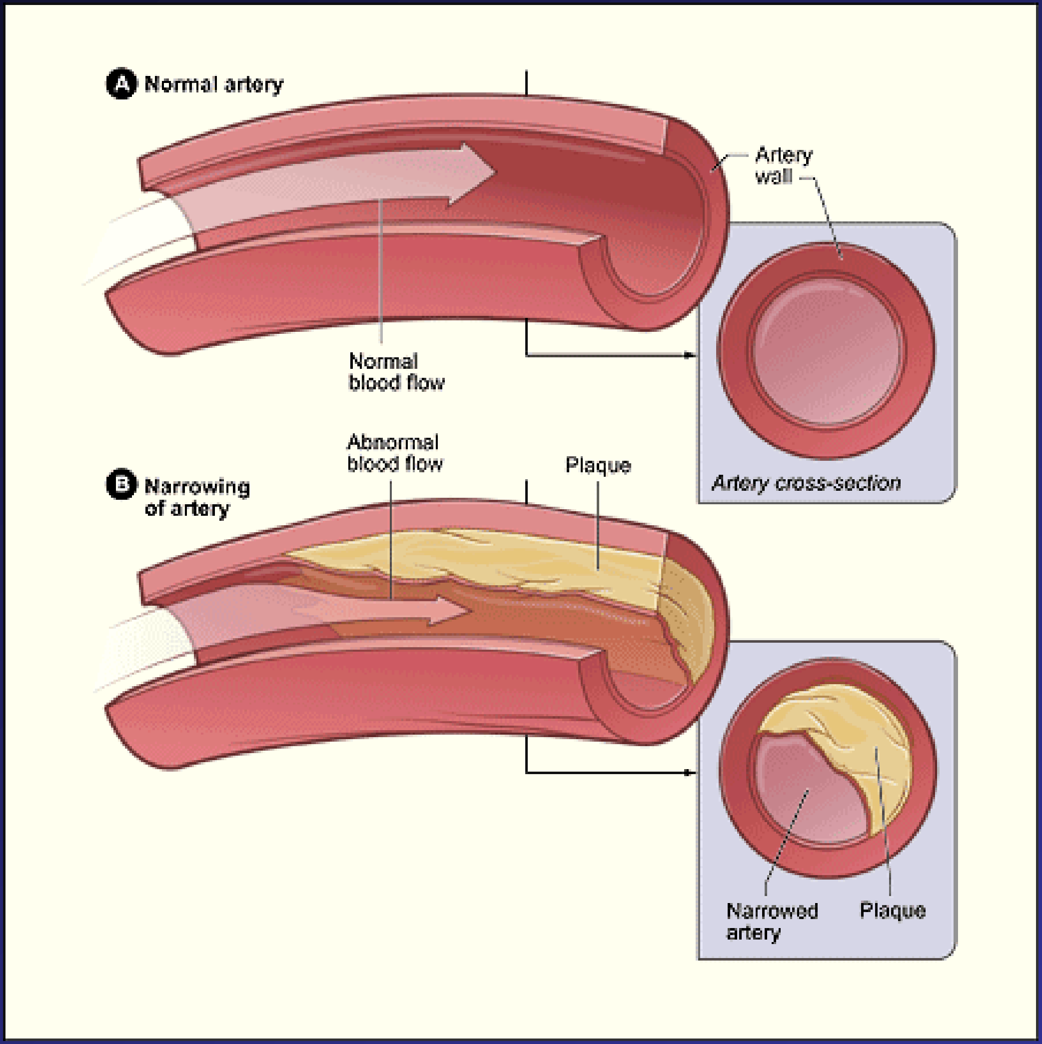
http://healthy-ojas.com/assets/chol/HDL.jpg

Atherosclerosis

- Atherosclerosis ("hardening of the arteries") is a cardiovascular disease that involves formation of a atheroma (plaque) in the walls of blood vessels
- Build up can block coronary blood flow to the heart (heart attack) or other places (ischemia), or plaques get loose and travel to brain blood vessels, causing a stroke



Which is the clogged drain/waste pipe from a sink, and which is the clogged artery?


A Normal artery
Artery wall
Normal blood flow
Artery cross-section
Abnormal blood flow
Plaque
B Narrowing of artery
Narrowed artery
Plaque

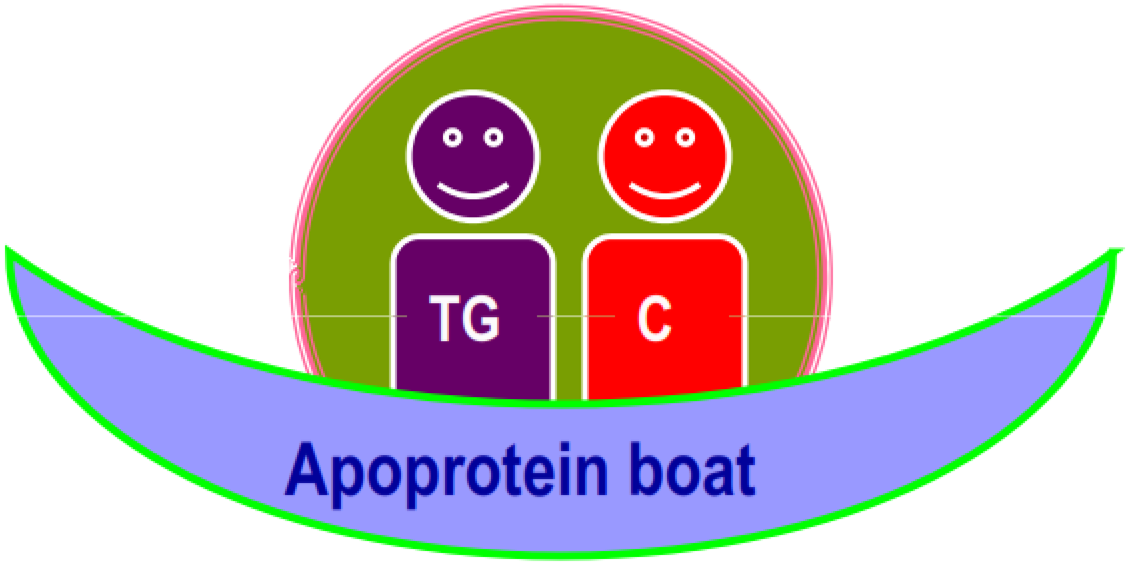
How It Works

1. Endothelial cells (they line the blood vessel wall) get "injured"
2. A bunch of repair cells along with immune cells come to the injury site. Immune cells tend to take the "burn it all down" approach (often how they work), releasing harsh chemicals (peroxides usually)
3. These peroxides react with everything, and especially LDL that is passing by constantly
4. So LDL gets oxidized and becomes abnormal
5. Its altered chemical state can cause it to adhere to the blood vessel wall

You can see where I'm going with the rest of this, right? This is called the injury hypothesis, by the way

Risking Atherosclerosis

- The risk of clogged arteries should be higher for those with higher levels of circulating LDL
- Diet and lifestyle have an effect on those circulating LDL levels
- If the diet is too high in fats (and saturated generally considered more "evil"), one risks that higher LDL level
- If one is too sedentary and not physically active or engaging in fitness activities, that too increases the risk of higher LDL levels
- To some degree, genetics also has something to say

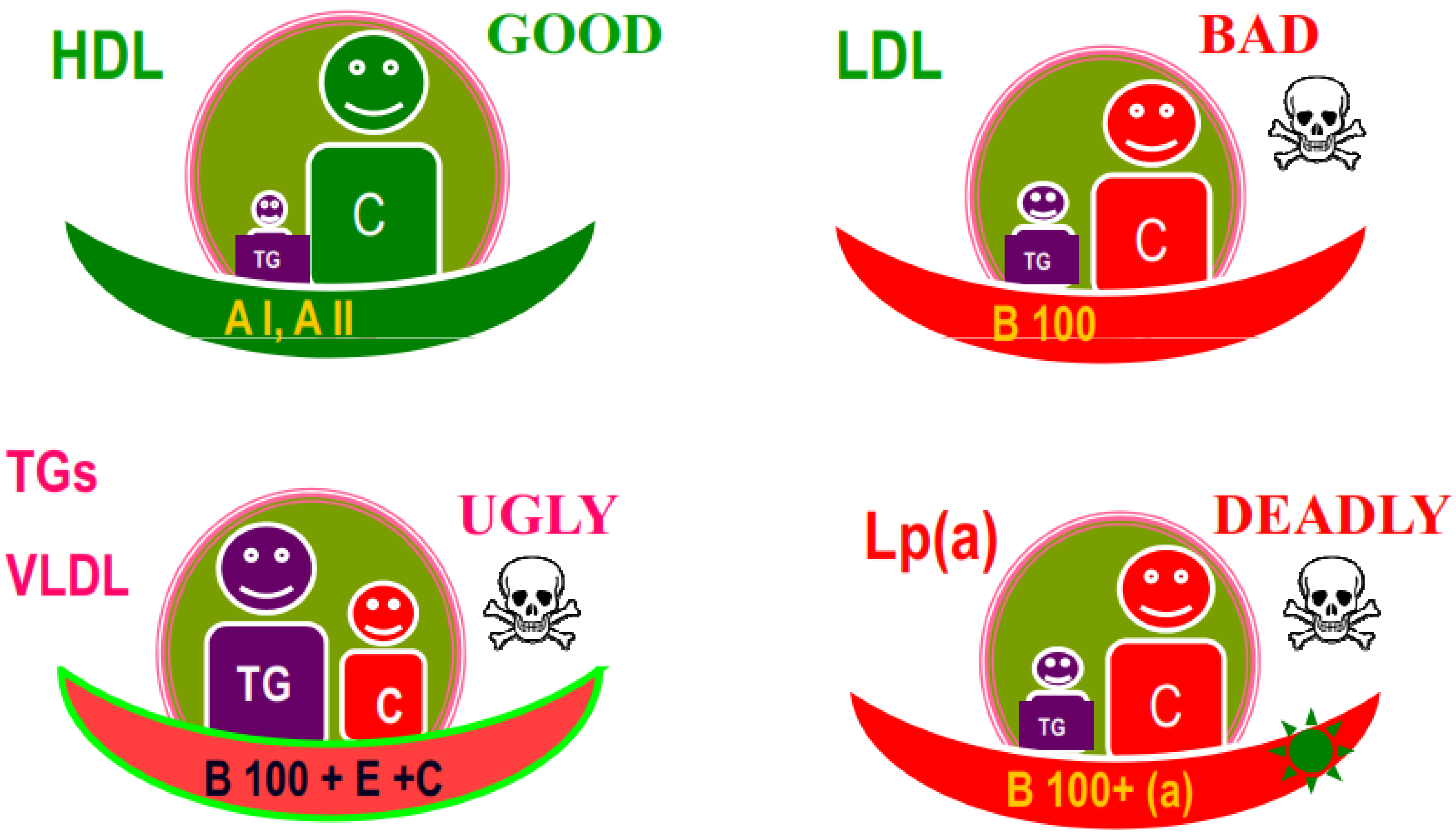


Apo A I and A II for HDL

Apo B100 for LDL

Apo B100+C+E for VLDL, IDL

Apo B100+Apo(a) for Lp(a)



Good, Bad, Ugly & Deadly

Reading (Sources)

- Marieb: Chapter 2: pp 45-49
- Becker's WotC: Chapter 3: pp 66-70
- Raven: Chap 3.5