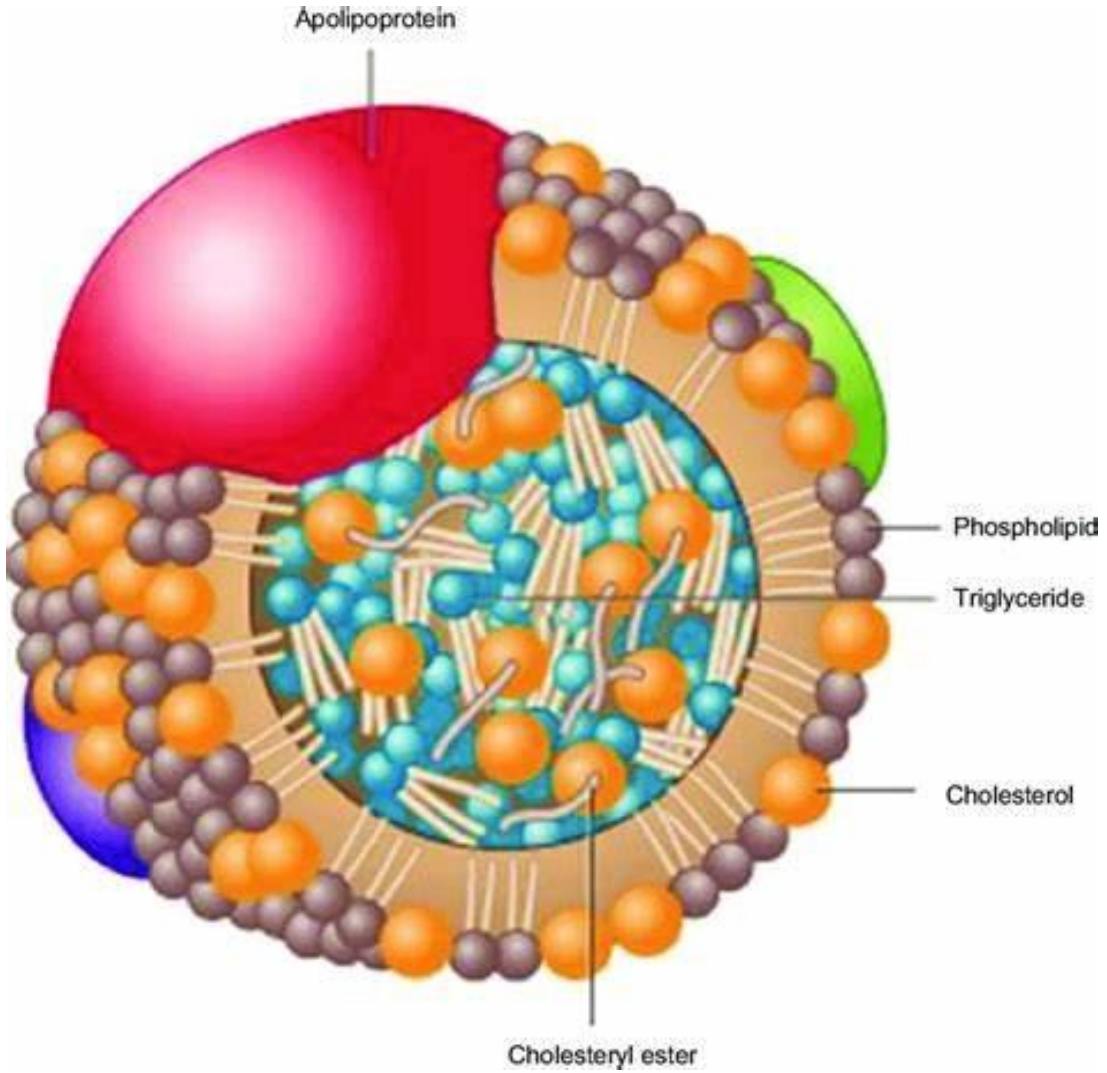
Metabolism of lipids:

Absorption and transport

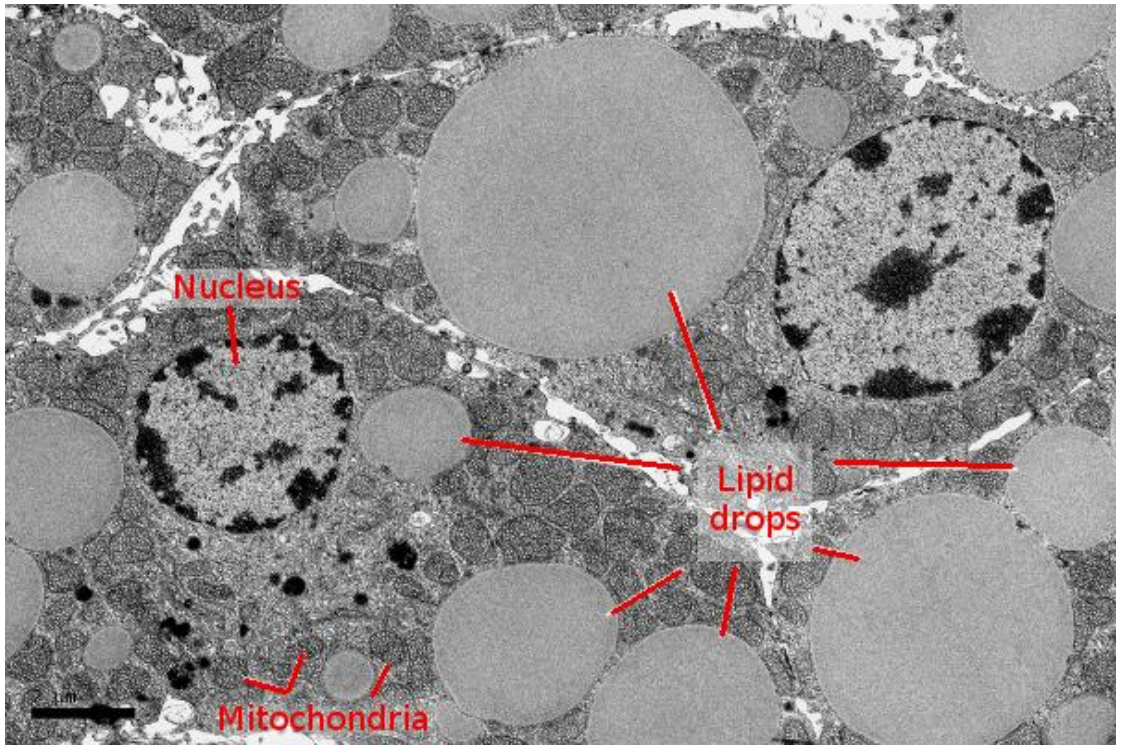
Dr. Diala Abu-Hassan

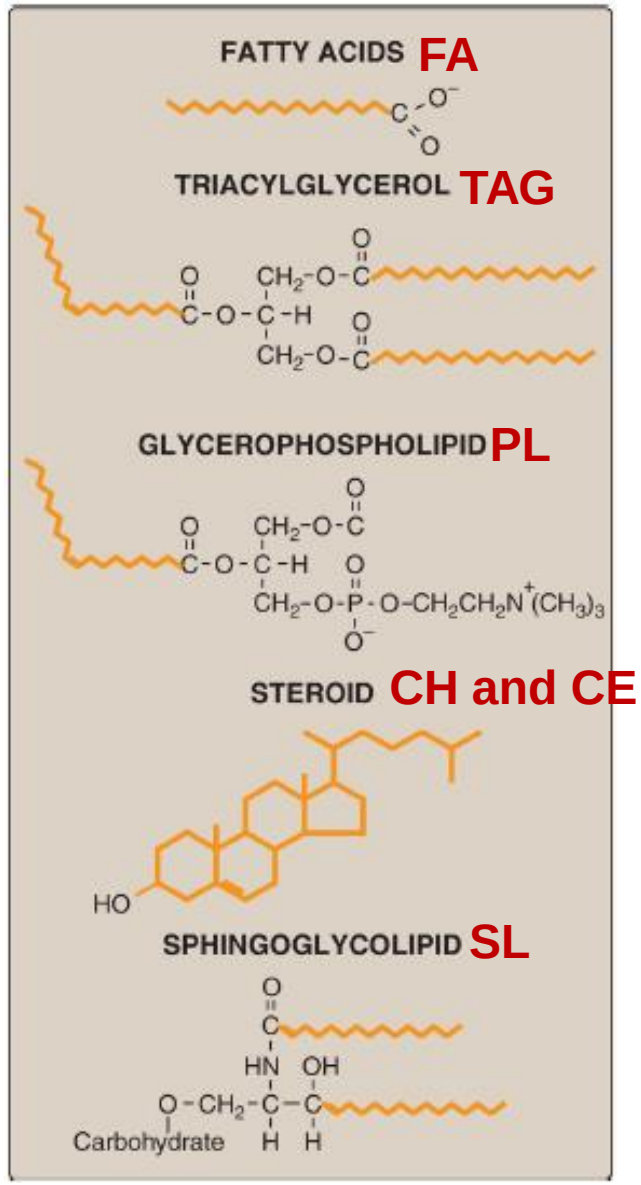


Lippincott's Biochemistry, Ch. 15

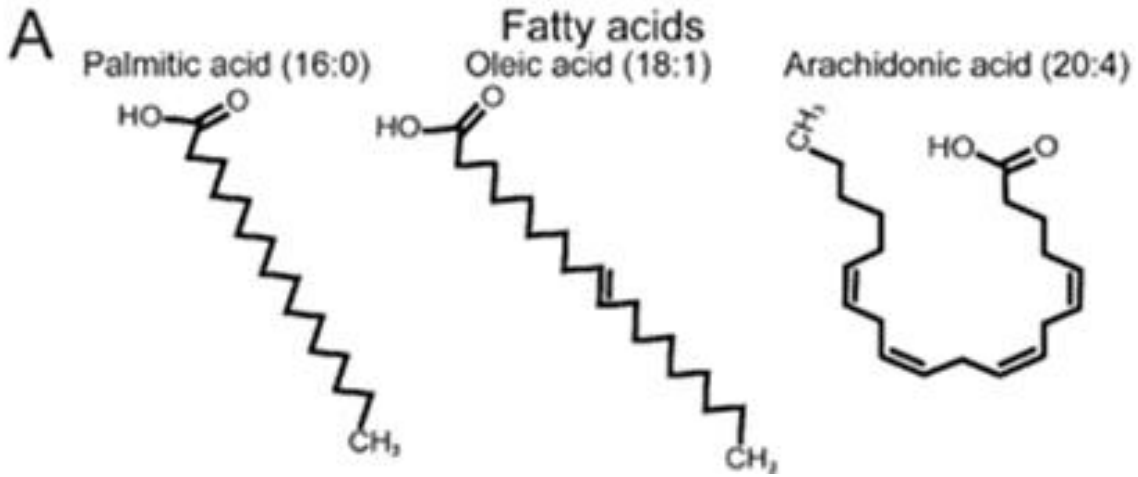
Lipids-review

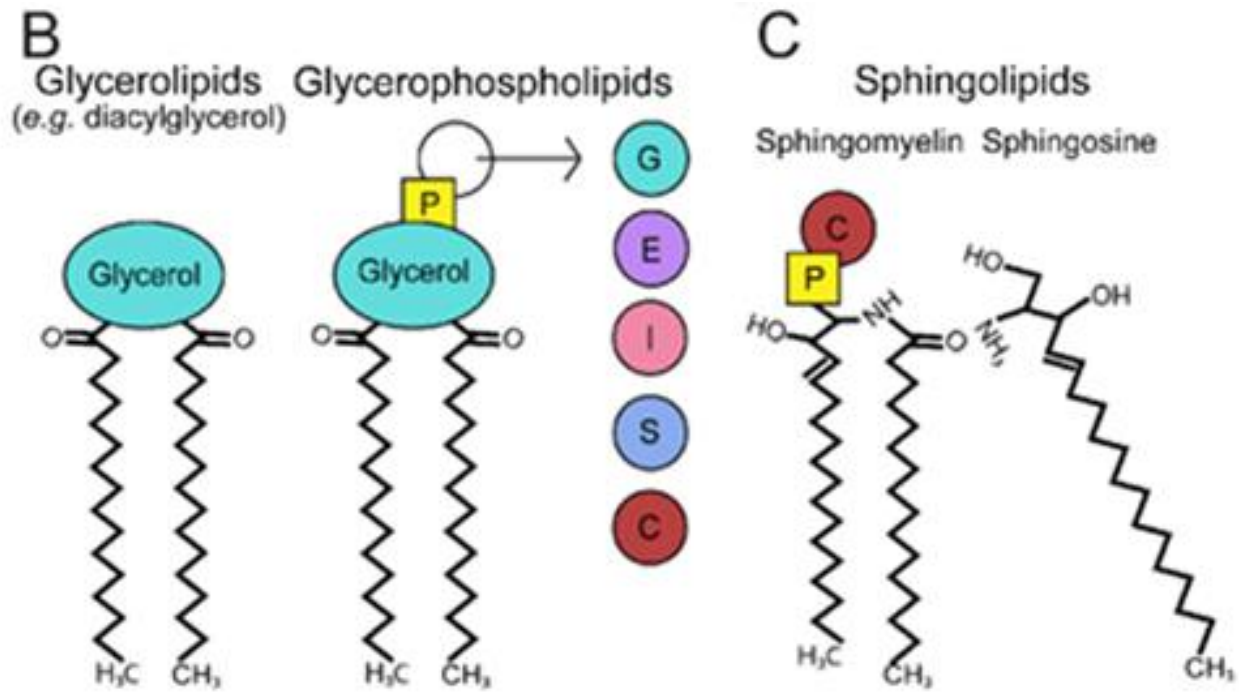
- Lipids are heterogeneous, hydrophobic, compartmentalized in membranes, as droplets of triacylglycerol (TAG), or in lipoprotein (LP) particles, or protein-bound.
- Functions: Energy, structures, molecular precursors (e.g., vitamins, signaling)
- The major dietary lipids are triacylglycerol, cholesterol, and phospholipids.

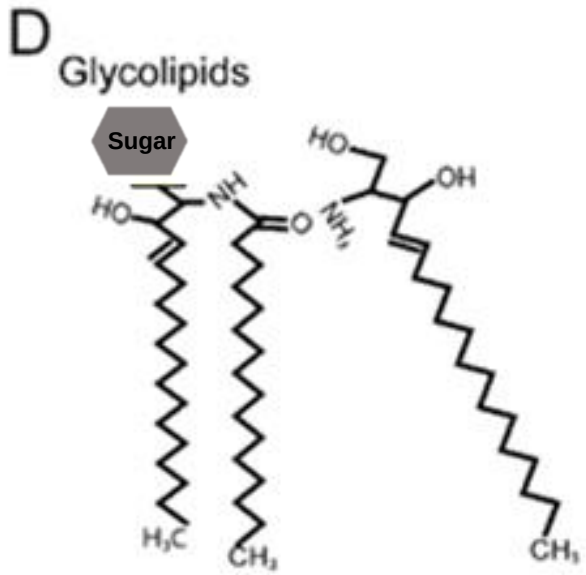


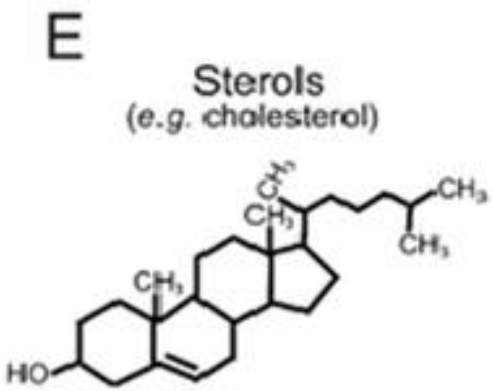


Structure and classification of lipids



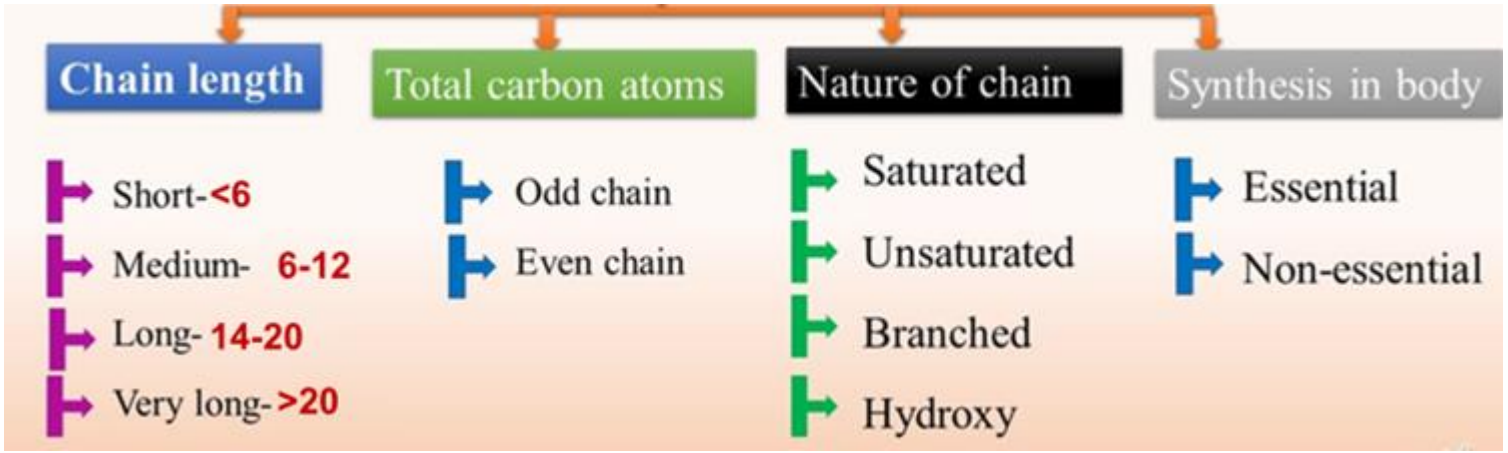


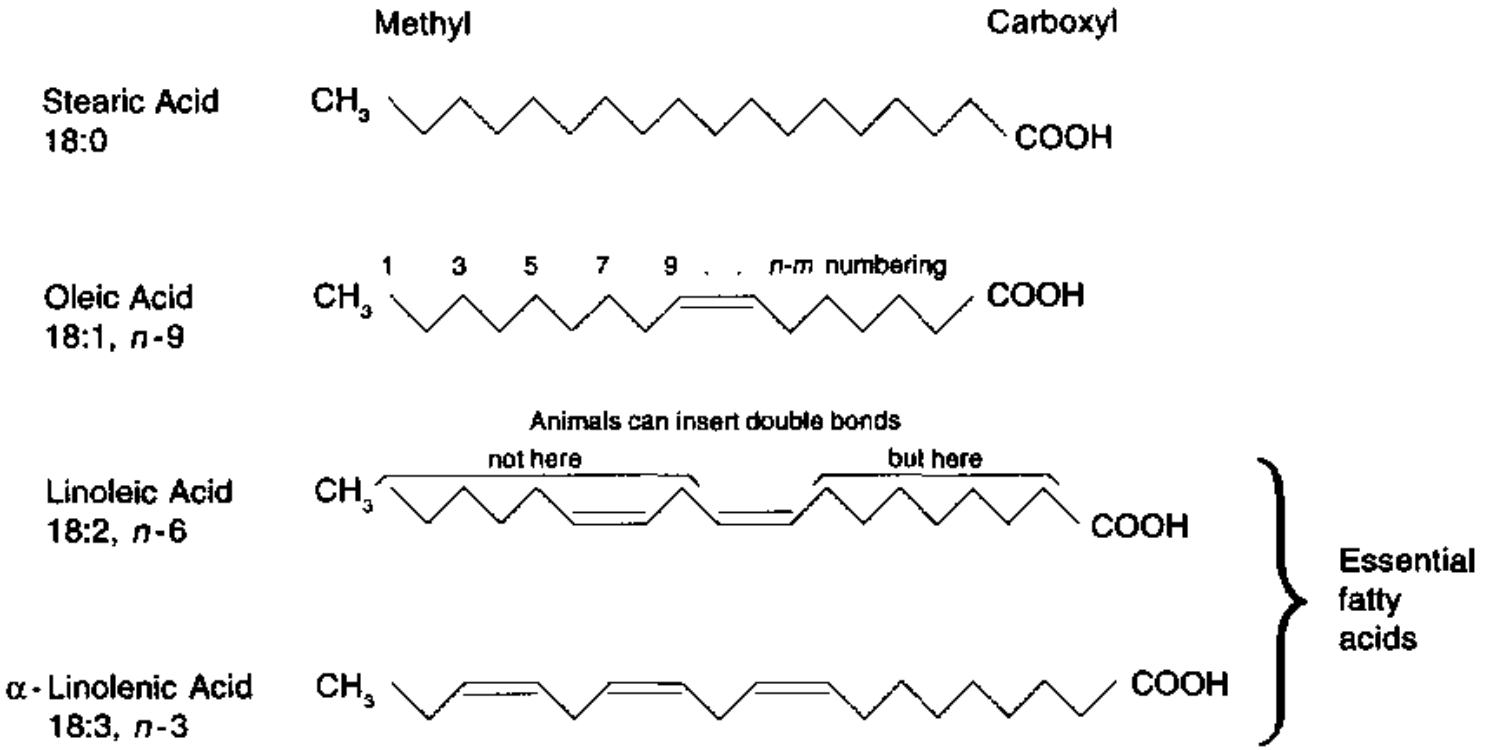




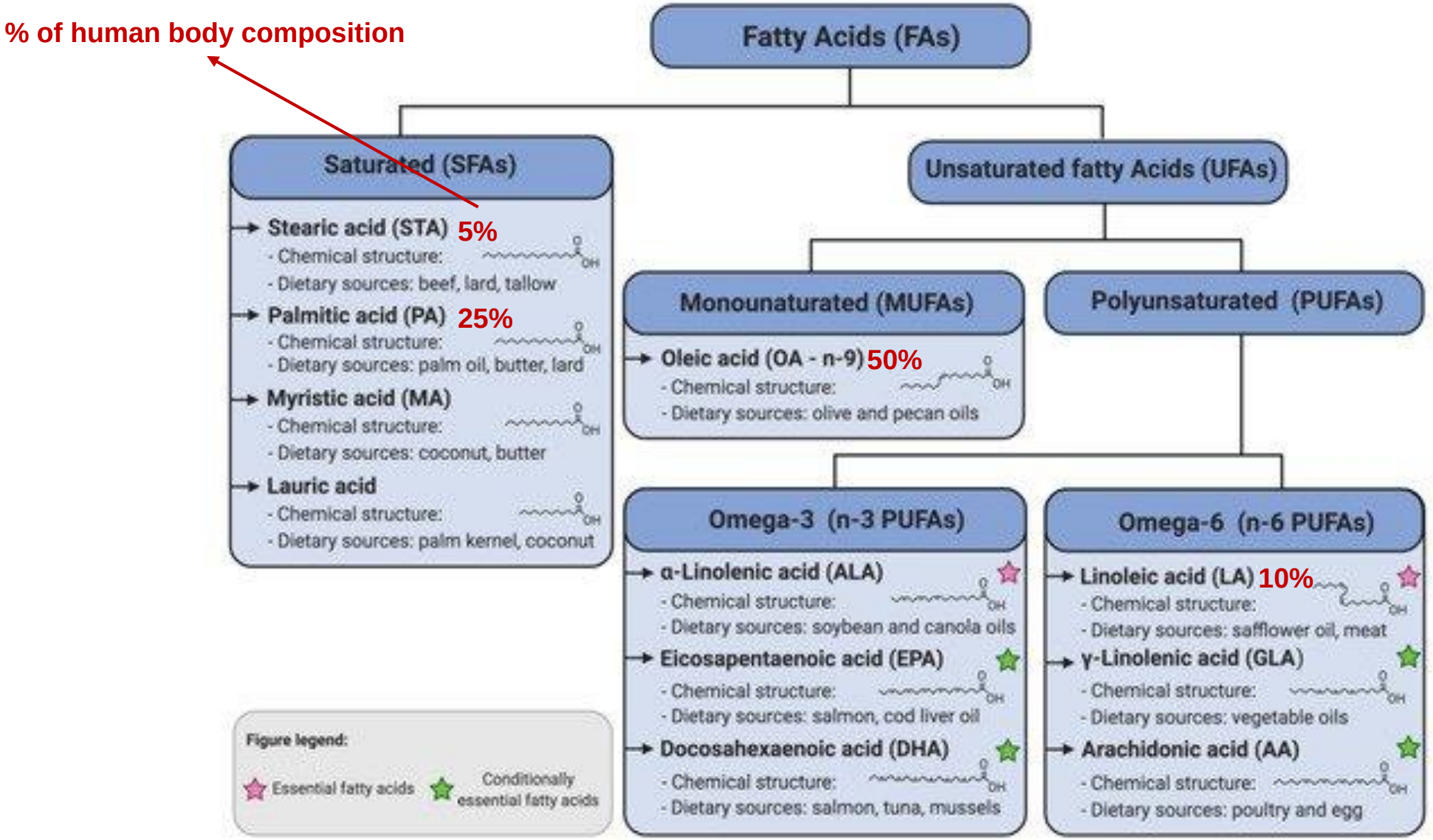
Fatty Acids

- Double bonds in FA are always spaced at three-carbon intervals.
- The addition of double bonds decreases the melting temperature (Tm) of a fatty acid.
- Increasing the chain's length increases the Tm.
- Membrane lipids typically contain unsaturated long-chain fatty acids (LCFA) to maintain fluidity.
- Fatty acids with double bonds beyond the 10th carbon are essential.





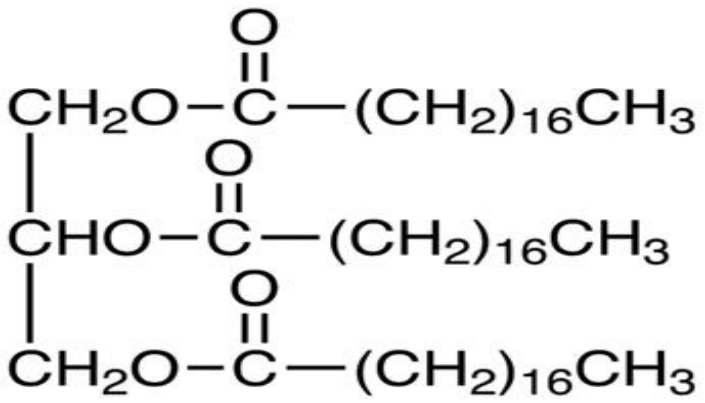
Fatty Acids


% of human body composition
Fatty Acids (FAs)
Saturated (SFAs)
Stearic acid (STA) 5%
- Chemical structure:
- Dietary sources: beef, lard, tallow
Palmitic acid (PA) 25%
- Chemical structure:
- Dietary sources: palm oil, butter, lard
Myristic acid (MA)
- Chemical structure:
- Dietary sources: coconut, butter
Lauric acid
- Chemical structure:
- Dietary sources: palm kernel, coconut
Unsaturated fatty Acids (UFAs)
Monounaturated (MUFAs)
Oleic acid (OA - n-9) 50%
- Chemical structure:
- Dietary sources: olive and pecan oils
Polyunsaturated (PUFAs)
Omega-3 (n-3 PUFAs)
α-Linolenic acid (ALA)
- Chemical structure:
- Dietary sources: soybean and canola oils
Eicosapentaenoic acid (EPA)
- Chemical structure:
- Dietary sources: salmon, cod liver oil
Docosahexaenoic acid (DHA)
- Chemical structure:
- Dietary sources: salmon, tuna, mussels
Omega-6 (n-6 PUFAs)
Linoleic acid (LA) 10%
- Chemical structure:
- Dietary sources: safflower oil, meat
γ-Linolenic acid (GLA)
- Chemical structure:
- Dietary sources: vegetable oils
Arachidonic acid (AA)
- Chemical structure:
- Dietary sources: poultry and egg
Figure legend:
Essential fatty acids
Conditionally essential fatty acids

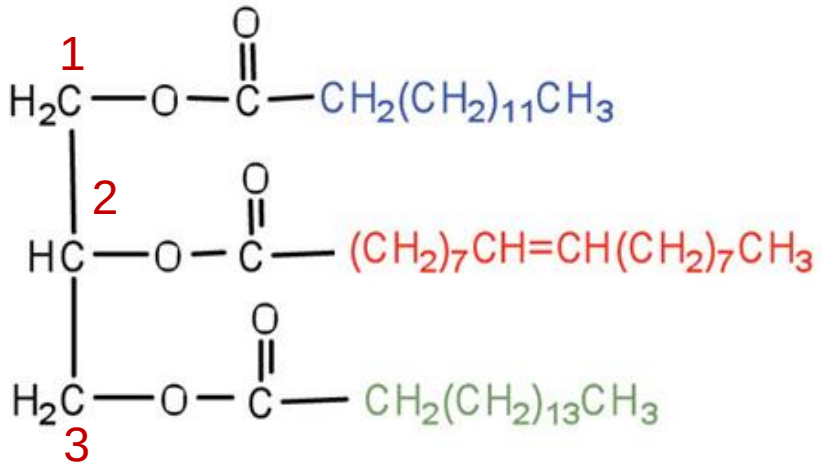
Forms of fatty acids

- **Free fatty acids** (FFA): occur in all tissues and in plasma (particularly during fasting).
  - >90% of the plasma fatty acids are in the form of fatty acid esters (primarily TAG, cholesteryl esters, and phospholipids) carried by circulating lipoprotein particles.
  - Plasma FFA are transported on albumin from adipose tissue to most tissues.
- FFA can be oxidized (broken up into acetyl CoA) in many tissues:
  - Liver and muscle, to provide energy
  - Liver to synthesize ketone body
- **Structural FA**: membrane lipids as phospholipids and glycolipids
- **Protein-associated FAs** facilitate membrane attachment.
- **FAs are precursors** of the hormone-like prostaglandins
- **Esterified FAs**: in the form of TAG stored in white adipose tissues as the major energy reserve of the body.

Triacylglycerol



Tristearin
a simple triglyceride



a mixed triglyceride

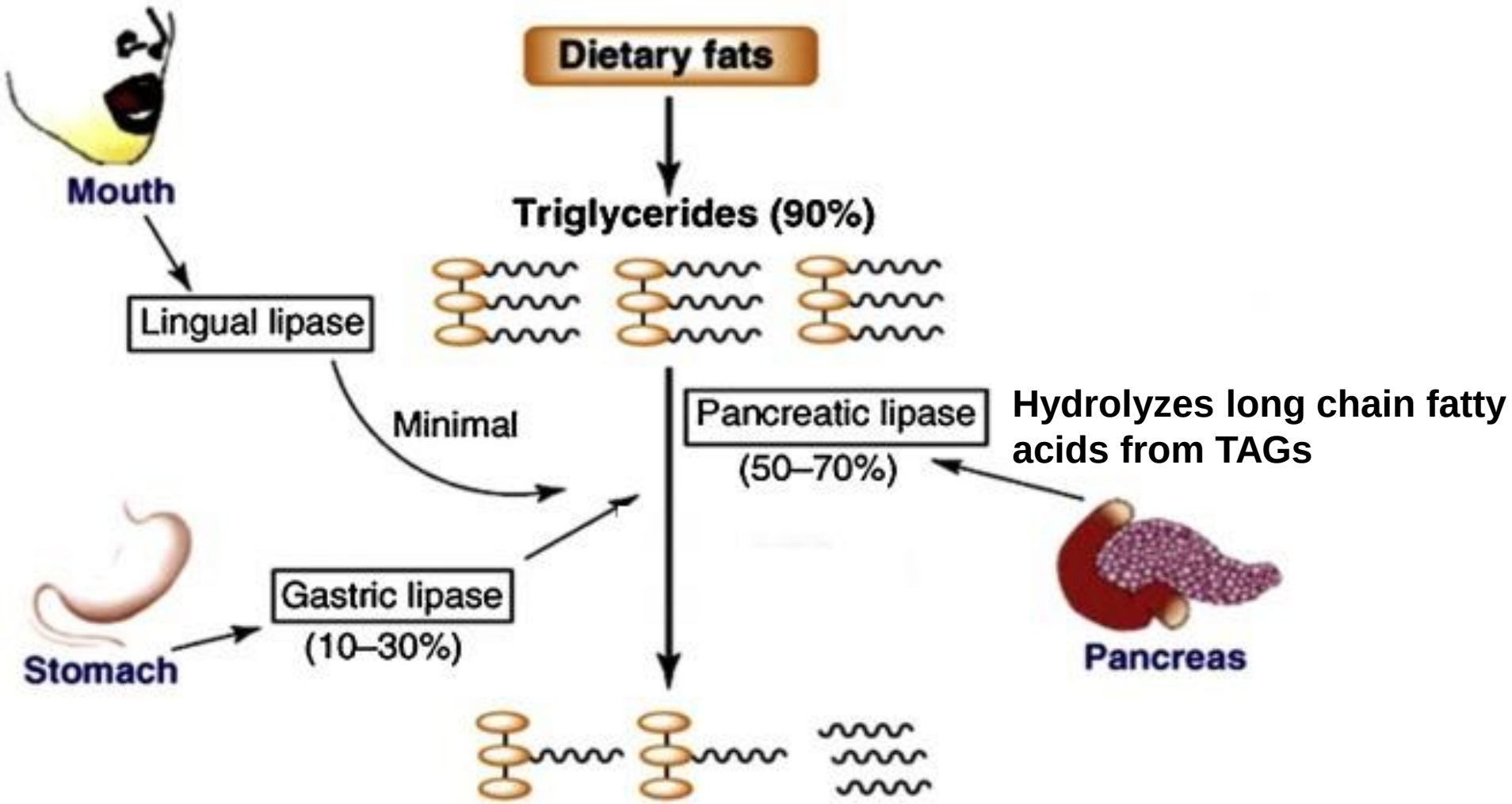
Usually, polyunsaturated FAs

Digestion of lipids in the stomach

- Acid-stable lipases: lingual lipase and gastric lipase (responsible for 30% of lipid hydrolysis)
- They have an optimum pH of 2.5 – 5.
- They do not require bile acid or colipase for optimal enzymatic activity.
- Gastric lipase will be stopped by long chain free fatty acids
- Main target: triacylglycerols with short- and medium-chain fatty acids (≤ 12 carbons)
- Significant in infants and patients with pancreatic lipase deficiency or pancreatic insufficiency (e.g., cystic fibrosis).
  - The action of lingual lipase is significant in newborn infants.
- Short- and medium-chain fatty are absorbed in the stomach.

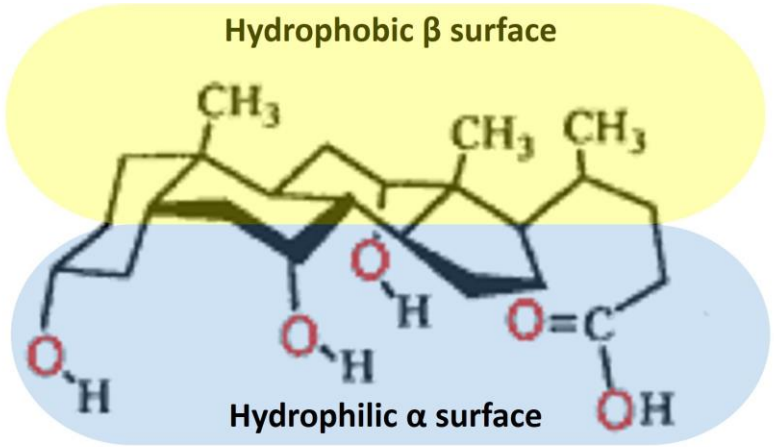
Fatty acids	*Human milk*[a] *%*
4:0	—
6:0	—
8:0	0.16
10:0	1.82
10:1 + 11:0	—
12:0	7.89
13:0	—
14:0	9.45
14:1 + 15:0 + 15:1	0.84
16:0	22.78
16:1 + 17:0 + 17:1	3.04
18:0	6.51
18:1 (*n*-9)	28.72
18:2 (*n*-6)	15.12
18:3 (*n*-6)	0.15
18:3 (*n*-3)	0.82
20:0	0.40
20:1	0.21
20:2	0.31
20:3 (*n*-6)	0.53
20:4 (*n*-6)	0.52
20:5 (*n*-3)	0.10
22:0	—
22:1	—
22:4 (*n*-6)	0.08
22:5 (*n*-6)	0.01
22:5 (*n*-3)	0.17
22:6 (*n*-3)	0.32
24:0	0.04

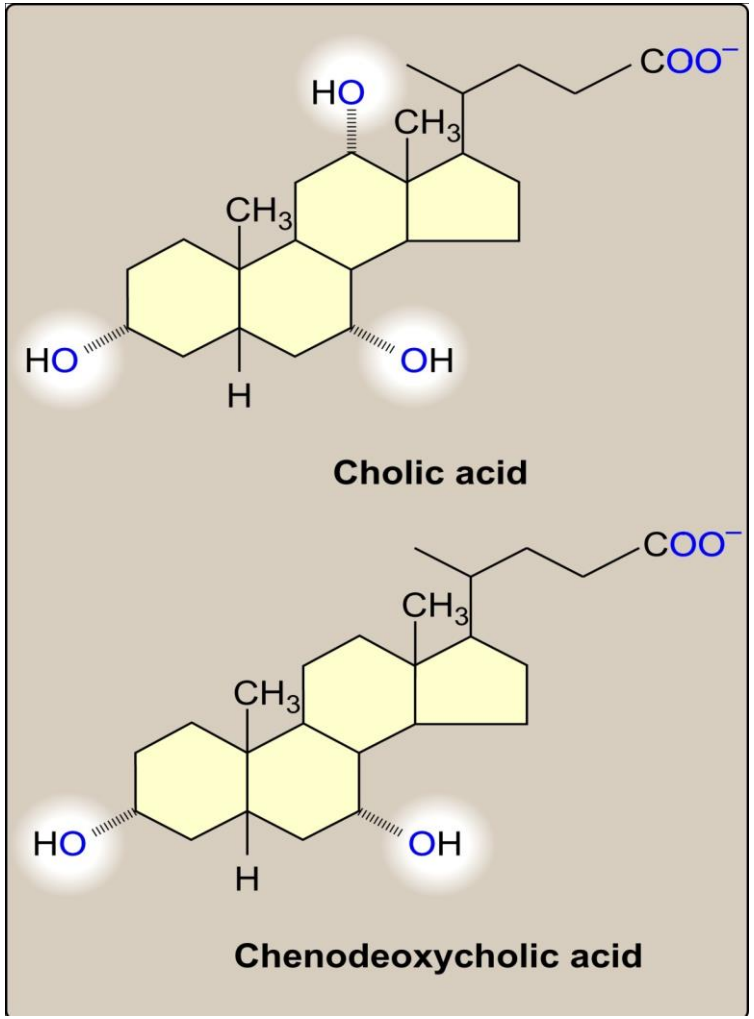
Degradation of triacylglycerol

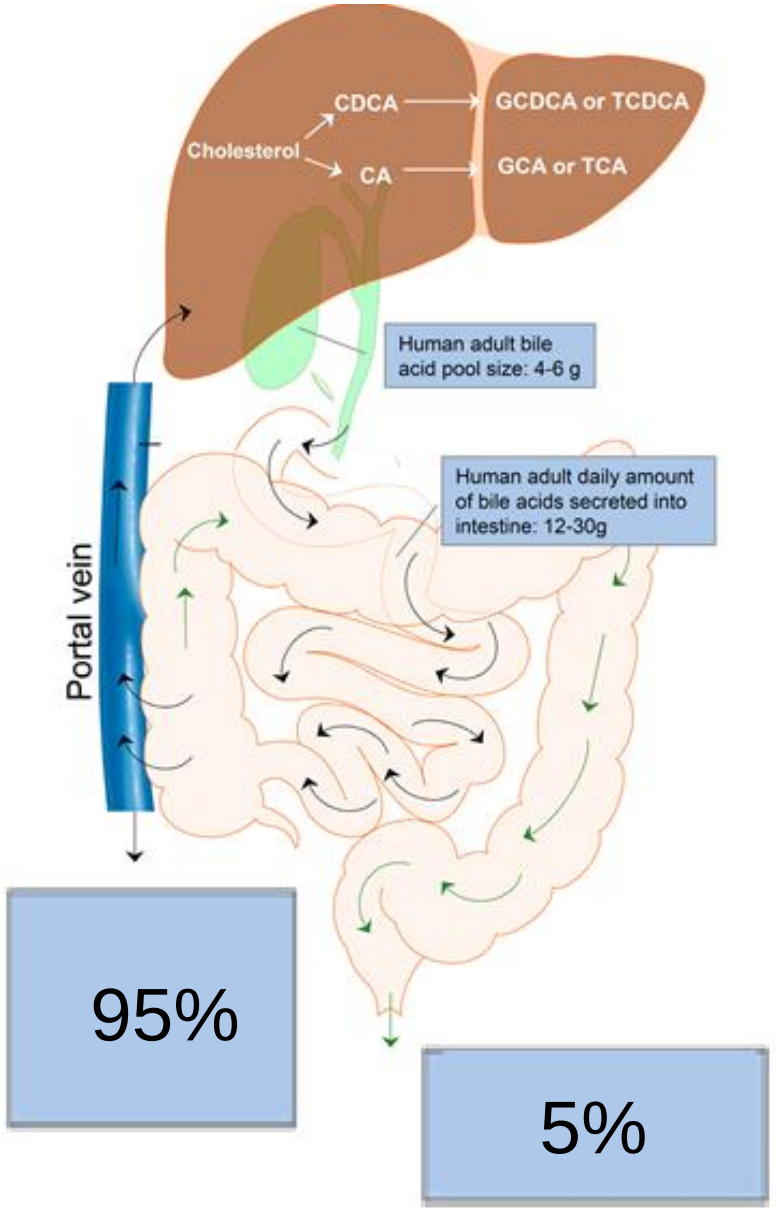


Emulsification: from drops to droplets

- Emulsification is defined as a process where one liquid is dispersed as small spherical droplets in a second immiscible (not homogeneous) liquid.
- Two mechanisms of emulsification in the duodenum:
  - Peristalsis : mechanical mixing leading to smaller droplets
  - Conjugated bile salts

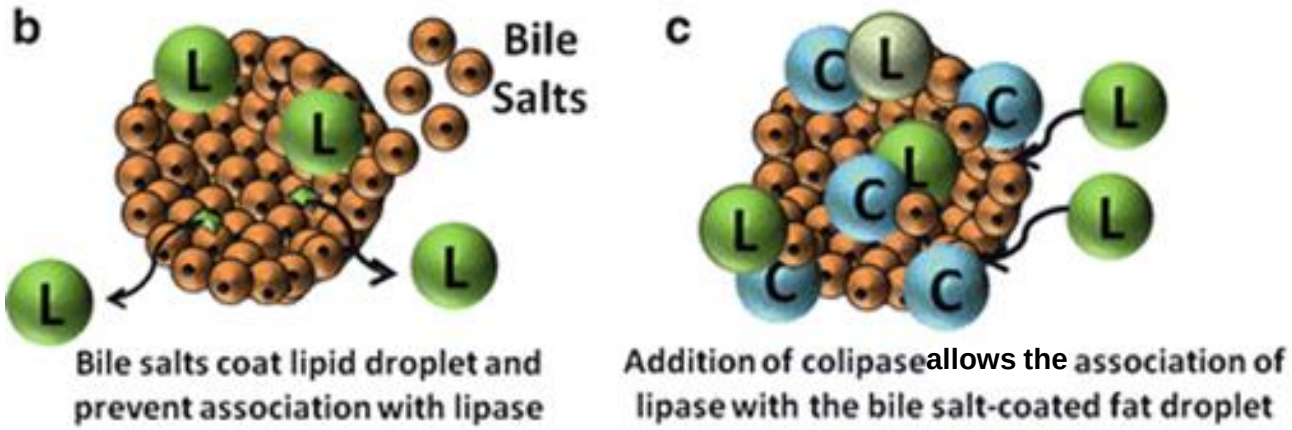


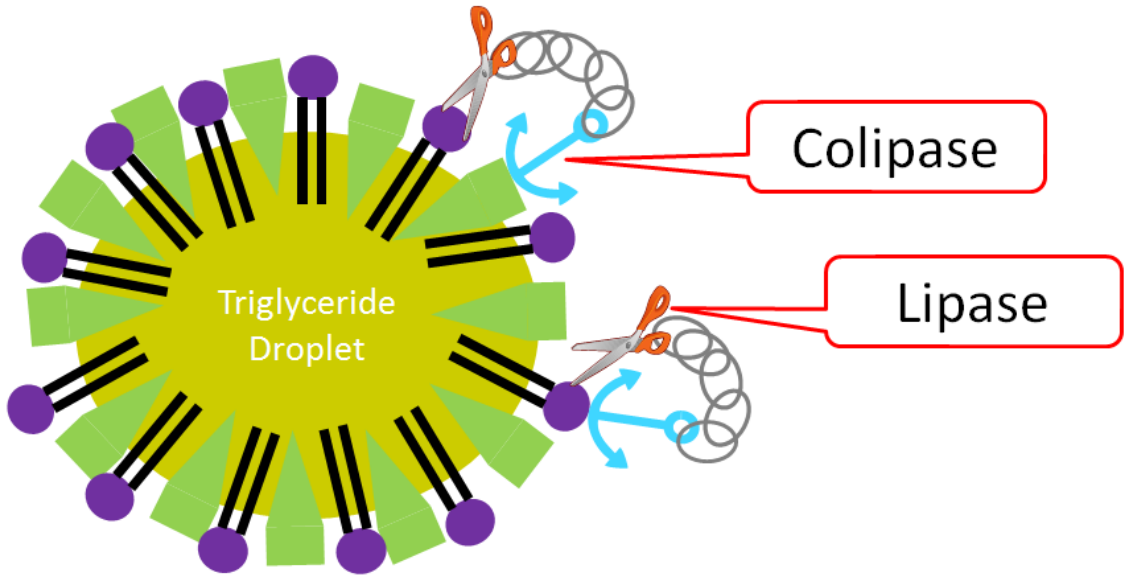




Pancreatic lipase: The significance of colipase

Pancreatic lipase is an interfacial enzyme that is most active at an oil-water interface



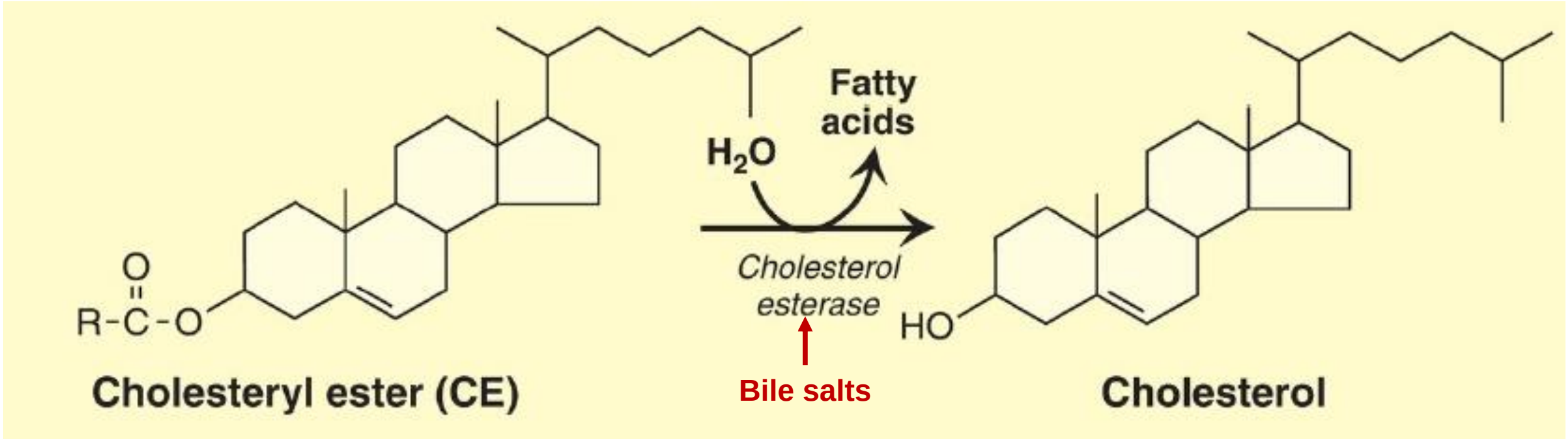


Combined pancreatic lipase-colipase deficiency is an orphan disease

Colipase:

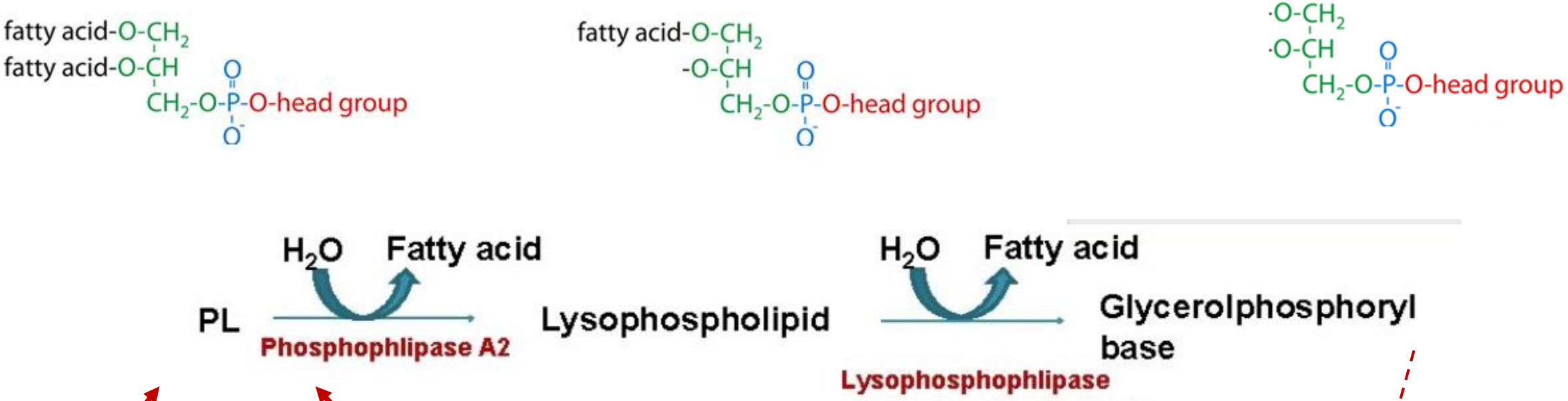
- Secreted as a zymogen from the pancreas
- Activated by trypsin
- Anchors lipase into the micelle interface at a ratio of 1:1
- Restores activity of lipase against inhibitors

Degradation of cholesterol esters



85-90%

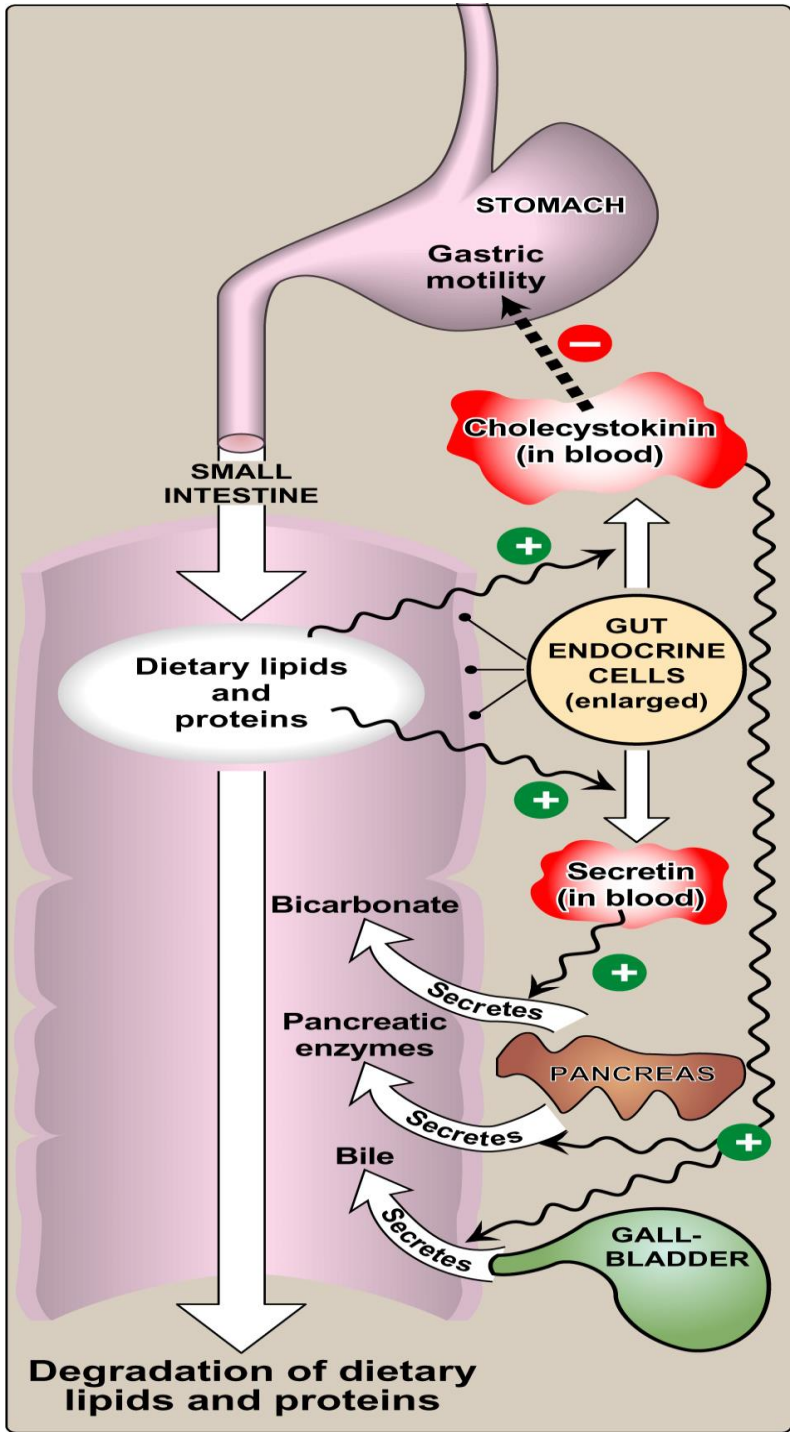
Degradation of phospholipids



- ***Excreted in the feces***
- ***Further degraded***
- ***Absorbed***

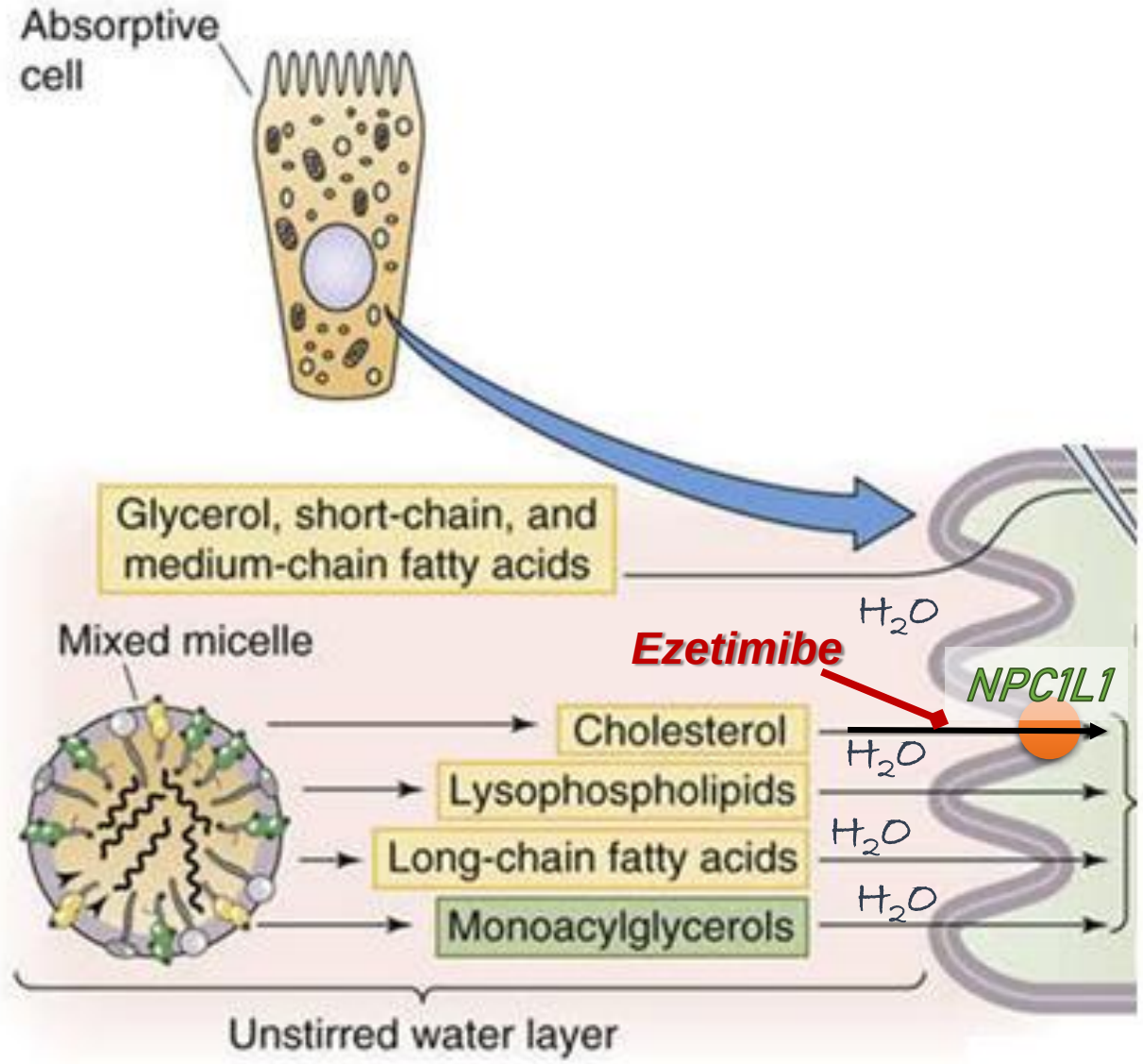
Hormonal control

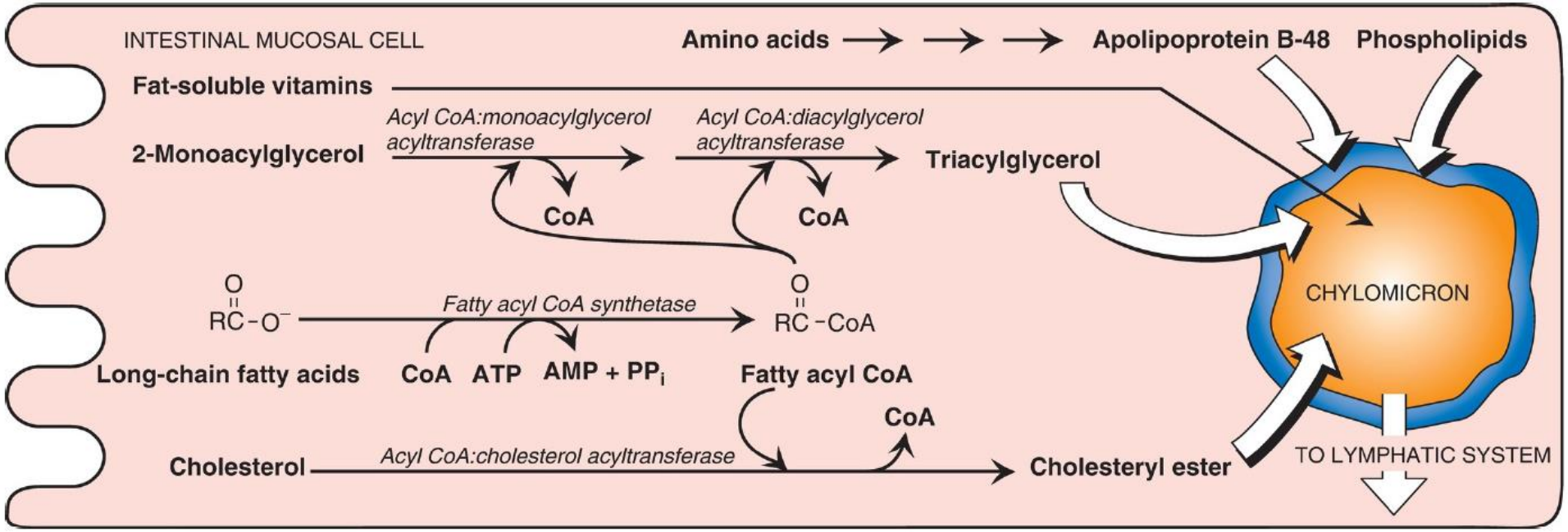
- Entry of food (chyme) induces the release **cholecystokinin** (CCK; a peptide hormone) from the duodenum and jejunum.
  - Induces contraction of the gallbladder to release bile (bile salts, phospholipids, and free cholesterol)
  - Acts on the exocrine pancreatic cells to release digestive enzymes
  - Decreases gastric motility to slow down the release of gastric contents
- The low pH of the chyme entering the intestine induces intestinal cells to produce **secretin** (a peptide hormone).
  - Causes the pancreas to release a bicarbonate-rich solution to neutralize the pH and make it optimal for the digestive pancreatic enzymes.
  - Inhibits gastric motility.



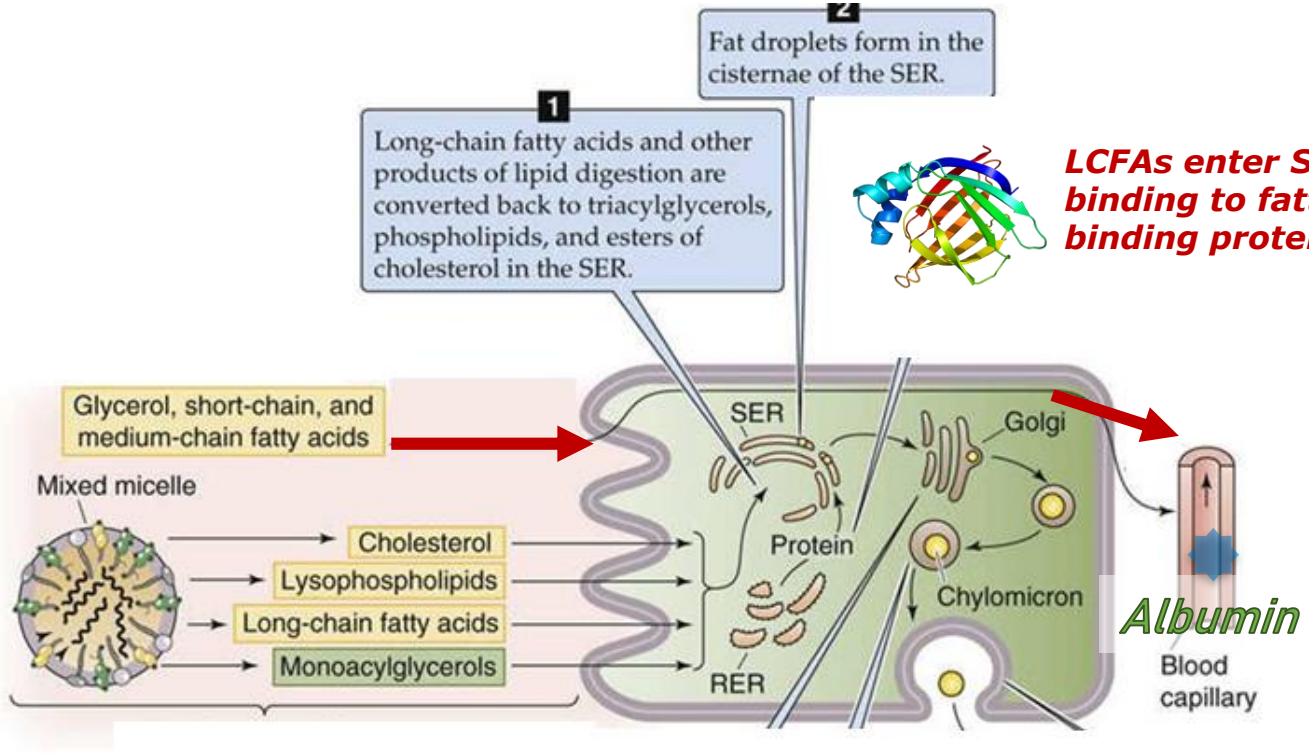
Absorption by enterocytes

- Mixed micelles are formed in the lumen from free fatty acids (FFA), monoacylglycerol, free cholesterol, bile salts, and fat-soluble vitamins.
- **Cholesterol absorption** is aided by an increase in dietary fat components and is hindered by high fiber content.
- The Niemann-Pick C1 like 1 protein (NPC1L1) is a sterol influx transporter (at the apical membrane) that facilitates the uptake of cholesterol via vesicular endocytosis
- Ezetimibe inhibits cholesterol absorption by suppressing the internalization of NPC1L1/cholesterol complex.
- The uptake of fatty acids across the enterocyte brush-border membrane occurs by passive diffusion and by protein–mediated mechanisms.
- Short- and medium-chain FAs are directly absorbed by passive diffusion.





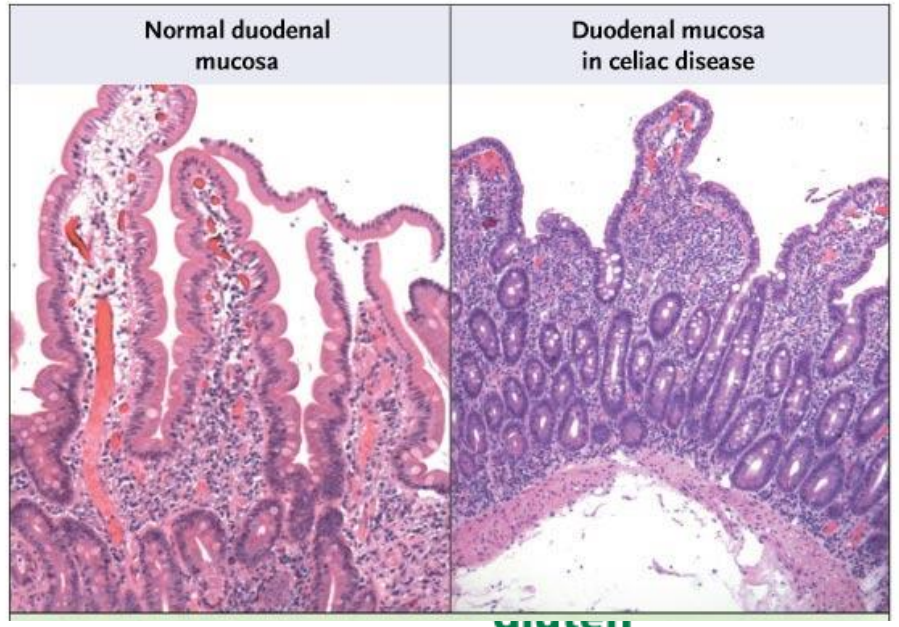
Reformation of complex lipids



LCFAs enter SER by binding to fatty acid–binding protein 2 (FABP2)

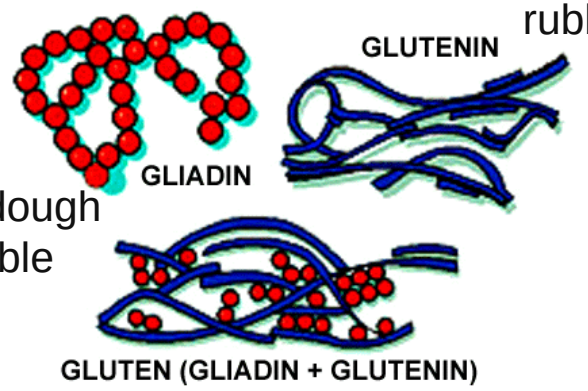
Celiac disease (CD)

- Fat malabsorption leading to steatorrhea (excess lipids in feces)
- It is an autoimmune response to gliadin, a peptide found in gluten (wheat, rye, and barley).
- Gliadin contains many proline (14%) and glutamine (40%) residues, making it resistant to digestion.
- Lab tests: the presence of anti-tissue transglutaminase (anti-tTG) antibodies.
- Tissue biopsy: absence of villous surface epithelial cells resulting in decreased nutrient absorption.



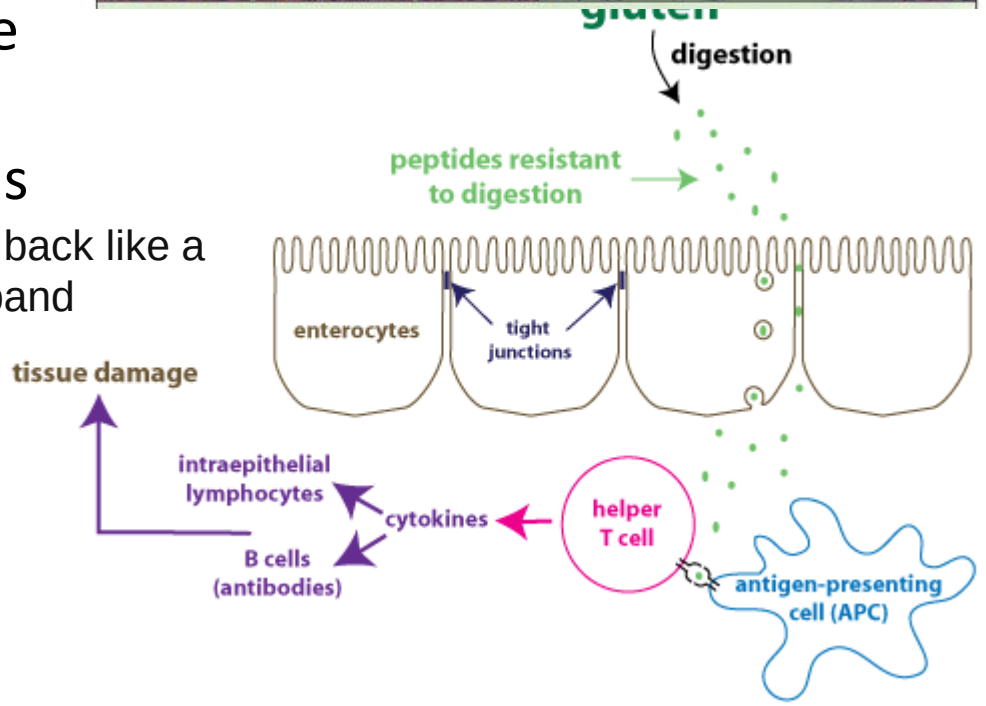
Principal causes of steatorrhea:

1. ***Short bowel disease***
2. ***Liver or biliary tract disease***
3. ***Pancreatic exocrine insufficiency***
4. ***Cystic fibrosis***



makes dough stretchable

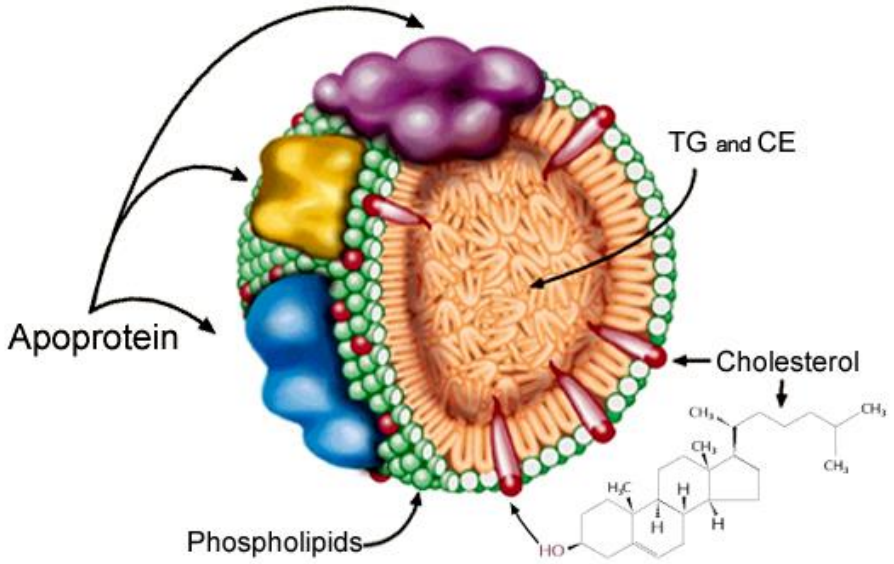
snaps it back like a rubber band

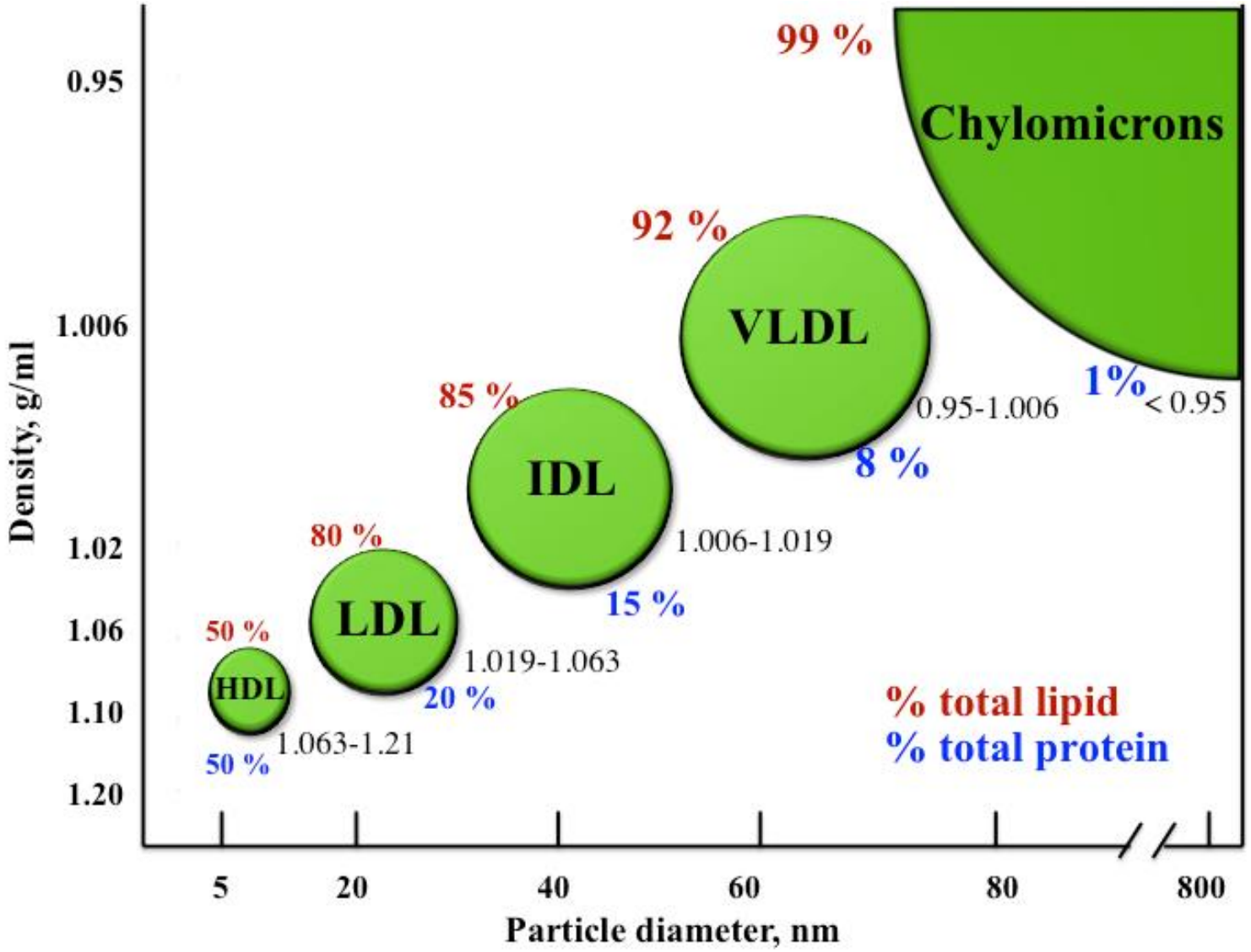


http://courses.washington.edu/pbio376/celiac/celiacdisease-376.html

Lipoproteins

Function: transport of lipids (cholesterol, cholesterol esters, phospholipids & triacylglycerols) in blood plasma.



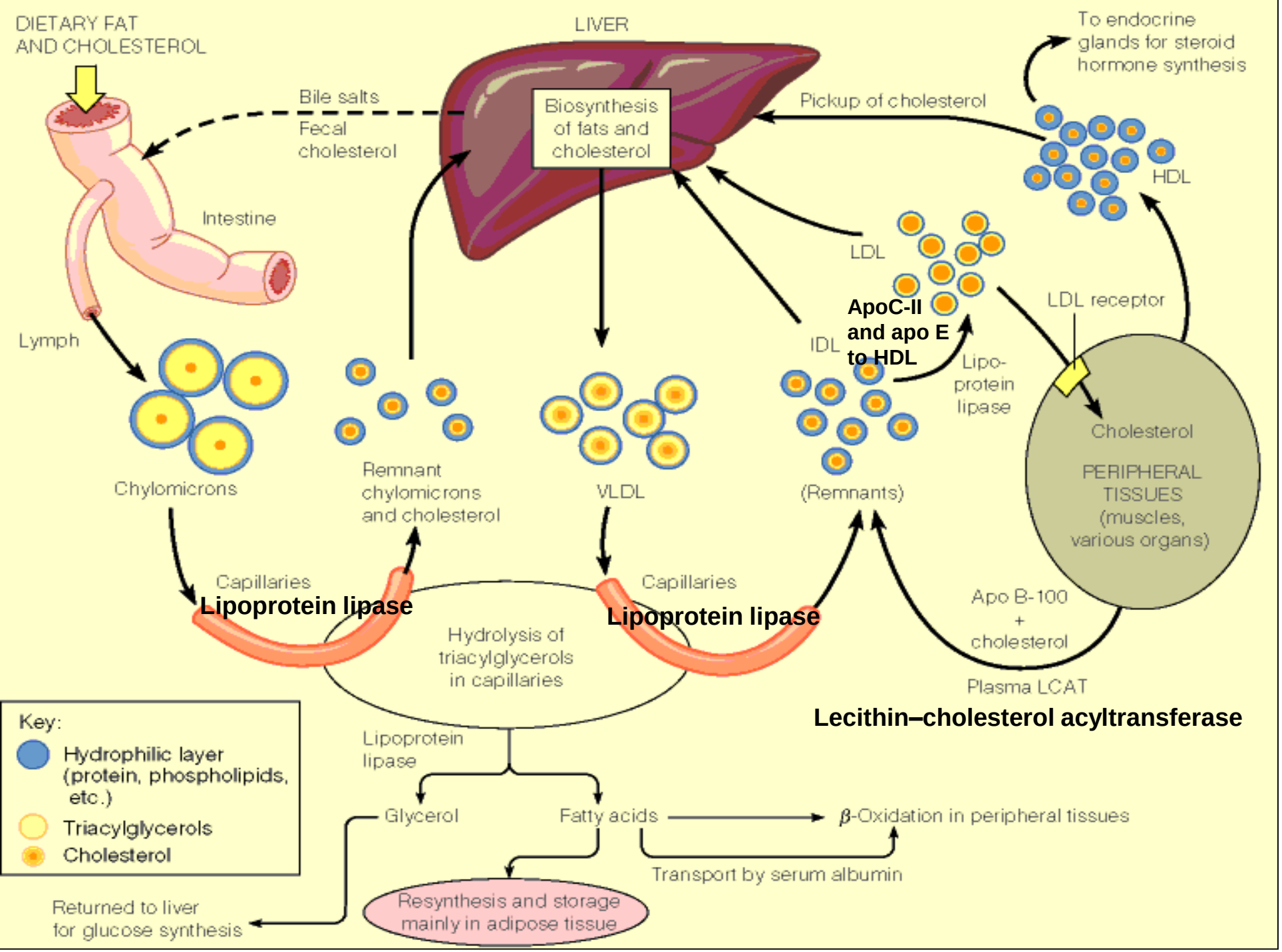


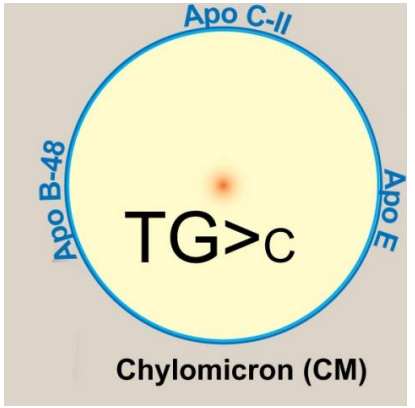
As lipid content increases, the density decreases

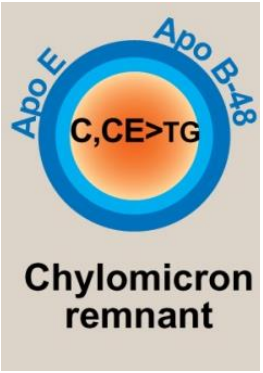
Composition of lipoproteins

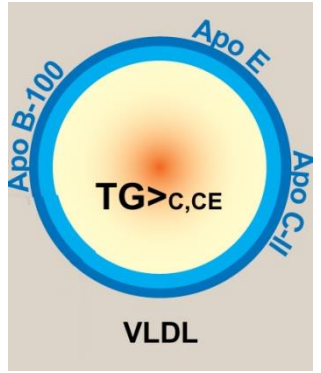
	Chylomicrons	VLDL	LDL	HDL
Density (g/ml)	< 0.94	0.94-1.006	1.006-1.063	1.063-1.210
Diameter (Å)	2000-6000	600	250	70-120
Site of synthesis	Intestine	Liver	Liver	Liver, intestine
Total lipid (wt%)	99	92	85	50
Triacylglycerols	85	55 Liver	10	6
Cholesterol esters	3	18	50 (bad)	40 (good)
Apolipoproteins	A, C, E, **B48**	C, **B100**, E	B100	A, C, E
Function	Transport of dietary TG to the liver	Transport of TG from the liver to peripheral tissues	Transport of cholesterol from the liver to peripheral tissues	Transport of cholesterol from peripheral tissues back to the liver (cholesterol scavengers)

Lipid transport



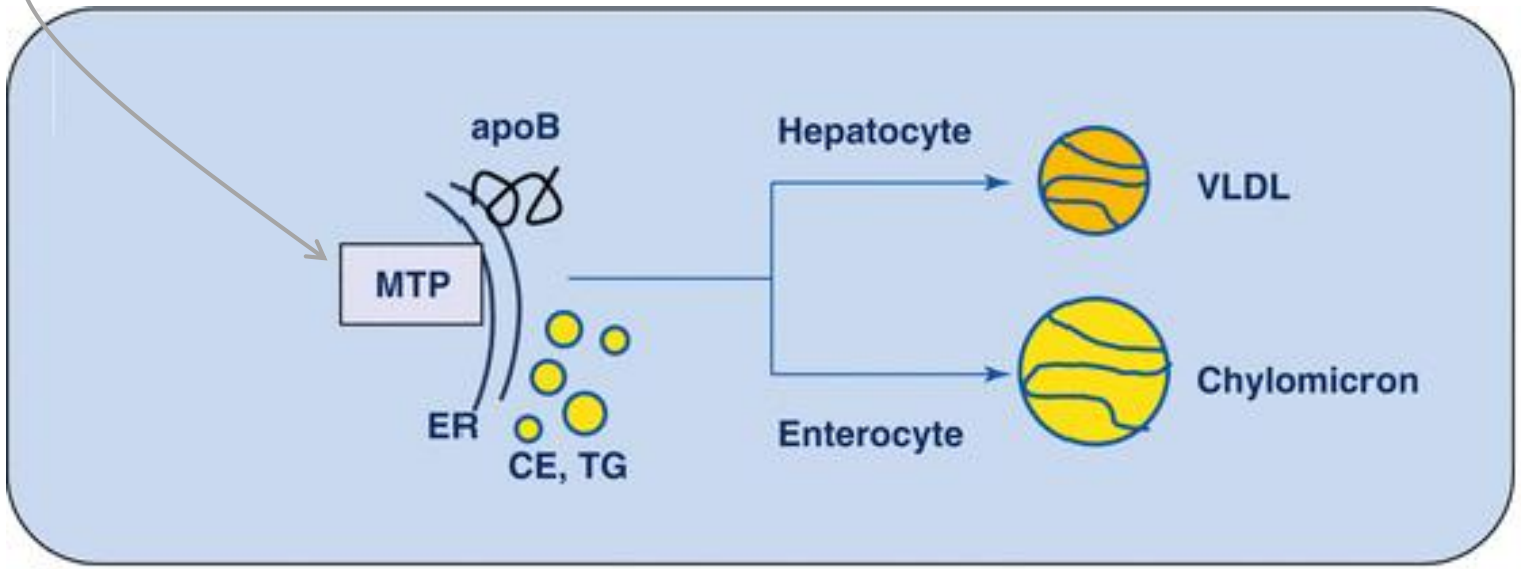


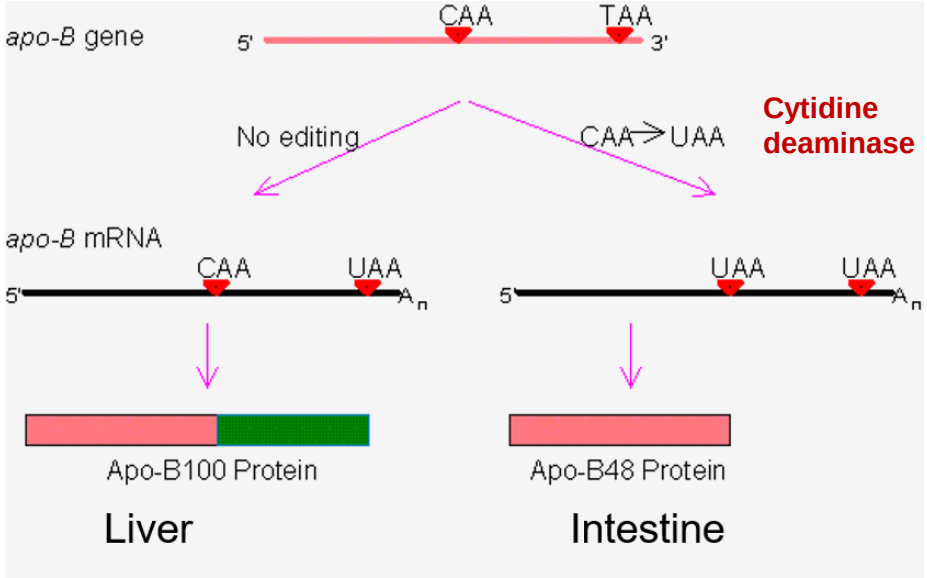




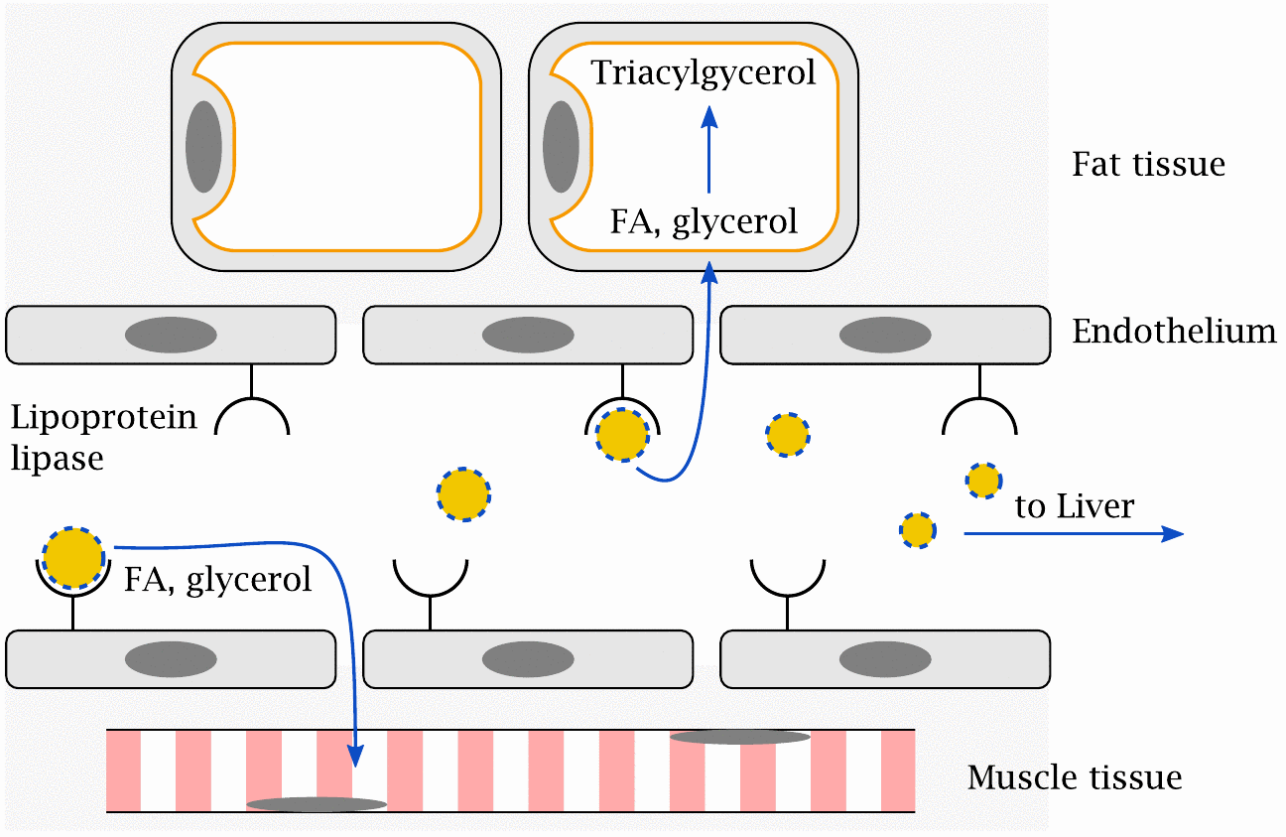
Formation and release of chylomicrons

- TAG and cholesteryl esters are packaged in chylomicrons made of phospholipids, non-esterified cholesterol, and apolipoprotein B-48.
- Microsomal triglyceride transfer protein (MTP) is essential for the assembly of all TAG-rich apoB-containing particles in the ER.





Fates of TAGs in chylomicrons



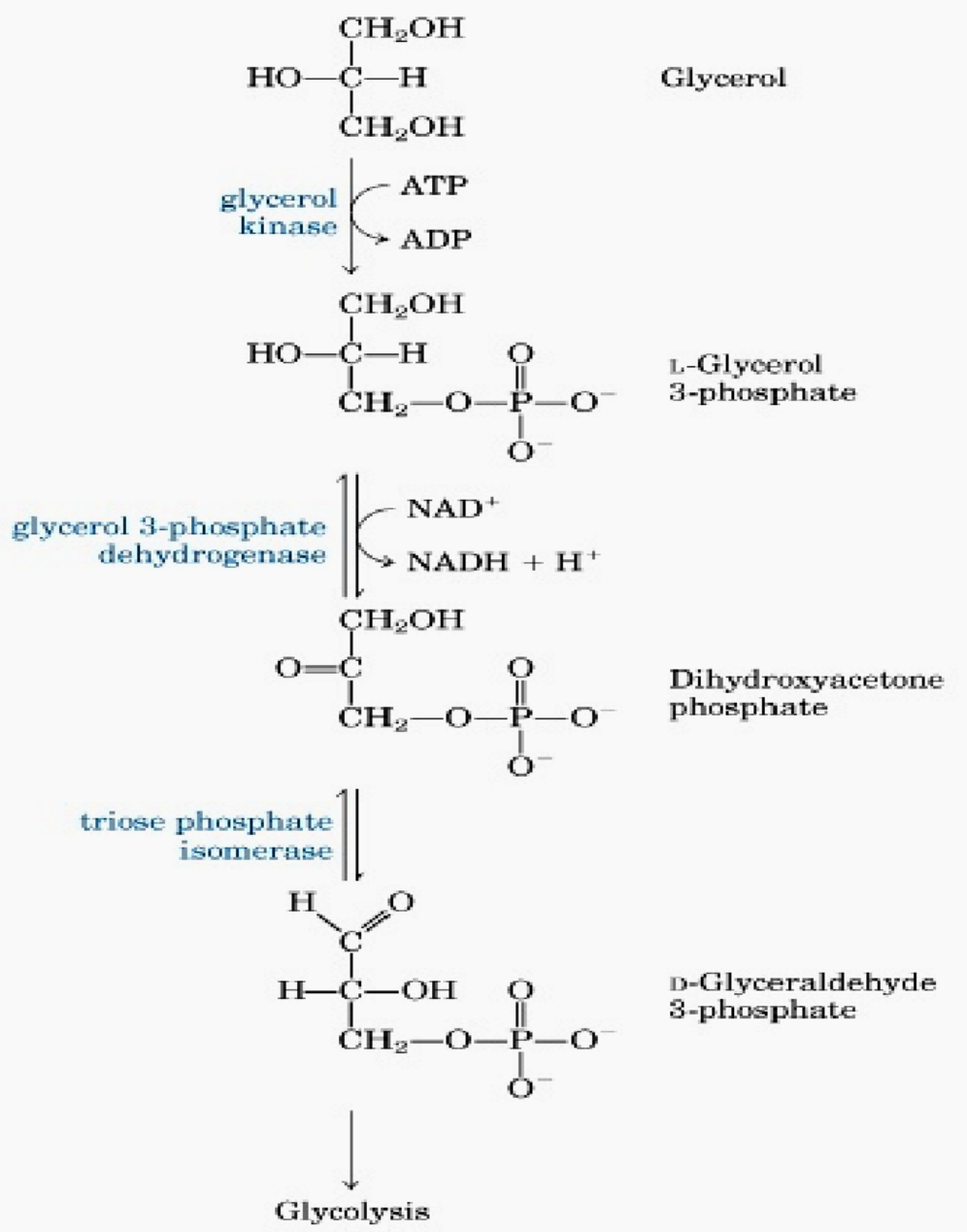
- TAGs in chylomicrons are hydrolyzed in the bloodstream by lipoprotein lipases that are anchored into the surface of endothelial cells.

- The resulting fatty acids have two possible fates:

(1) When energy is in good supply, they are converted back to TAGs for storage in adipose tissues.

(2) When cells need energy, the fatty acids are oxidized into acetyl-CoA.

Familial chylomicronemia (type I hyperlipoproteinemia) is a rare, autosomal-recessive disorder caused by a deficiency of LPL or its coenzyme apo C-II resulting in fasting chylomicronemia and severe hypertriacylglycerolemia, which can cause pancreatitis.



Fate of glycerol

- Glycerol is carried in the bloodstream to the liver or kidneys, where it is phosphorylated and then converted to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (DHAP) for either glycolysis or gluconeogenesis or synthesis of TAG.

Summary: What happens inside intestinal cells?