Metabolism of lipids I:

Absorption and transport

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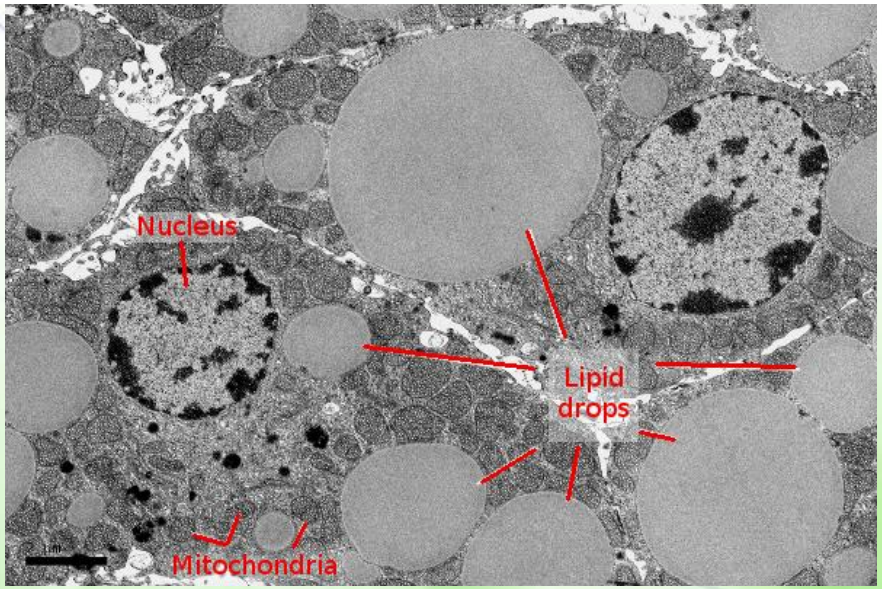
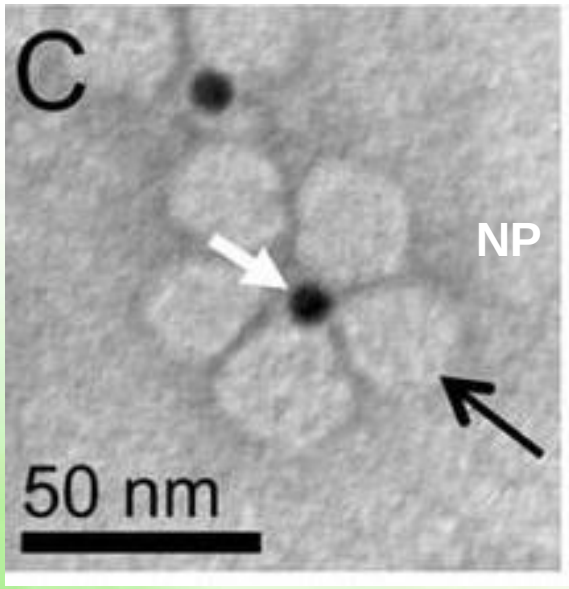
Resources

- This lecture
- Lippincott's Biochemistry, Ch. 15

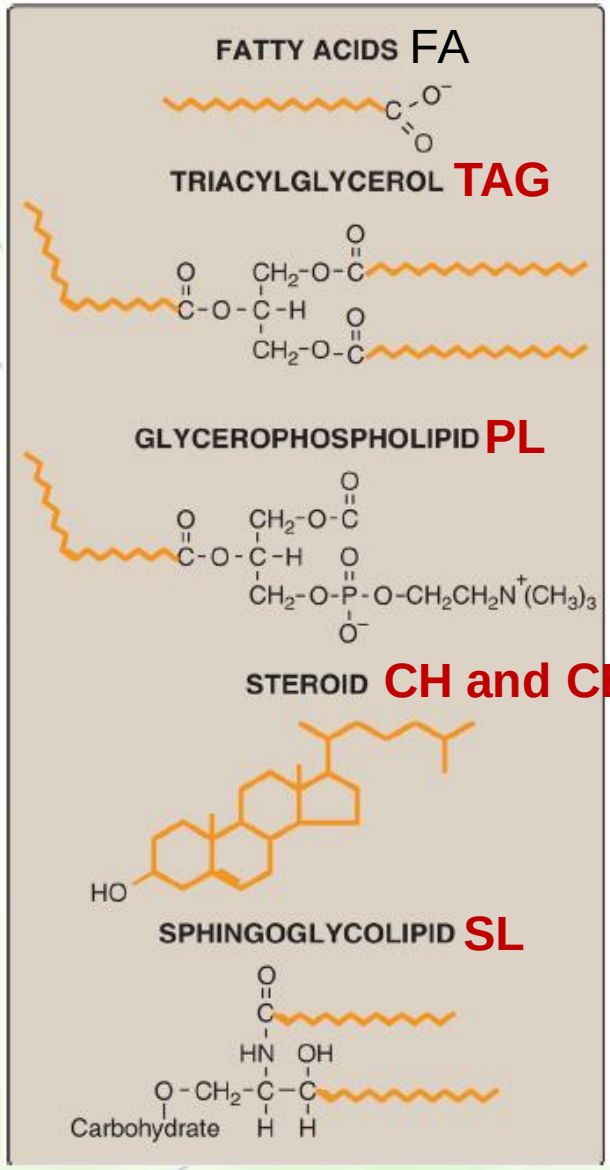
What are lipids?

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

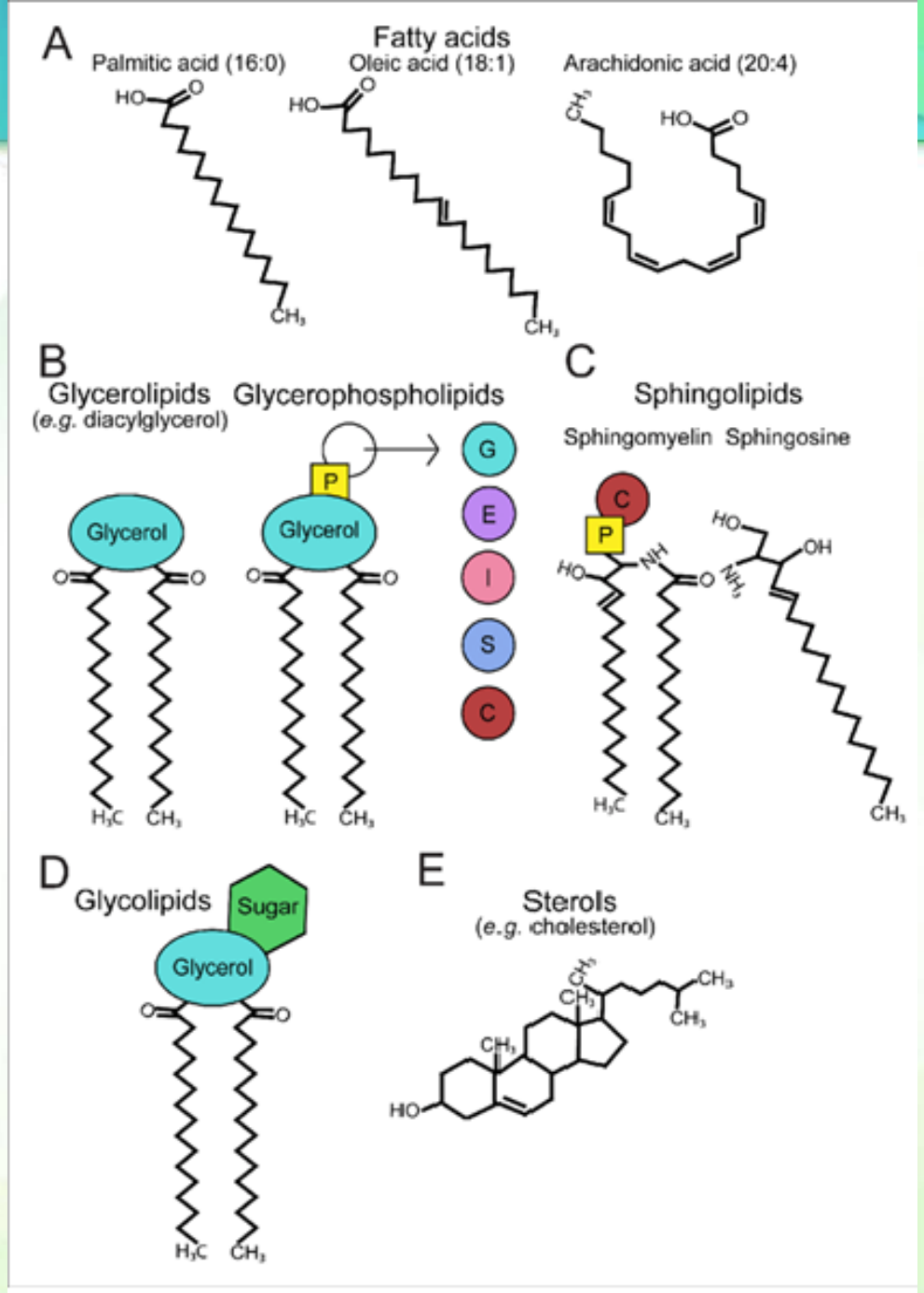




LDL



Structure and classification of lipids



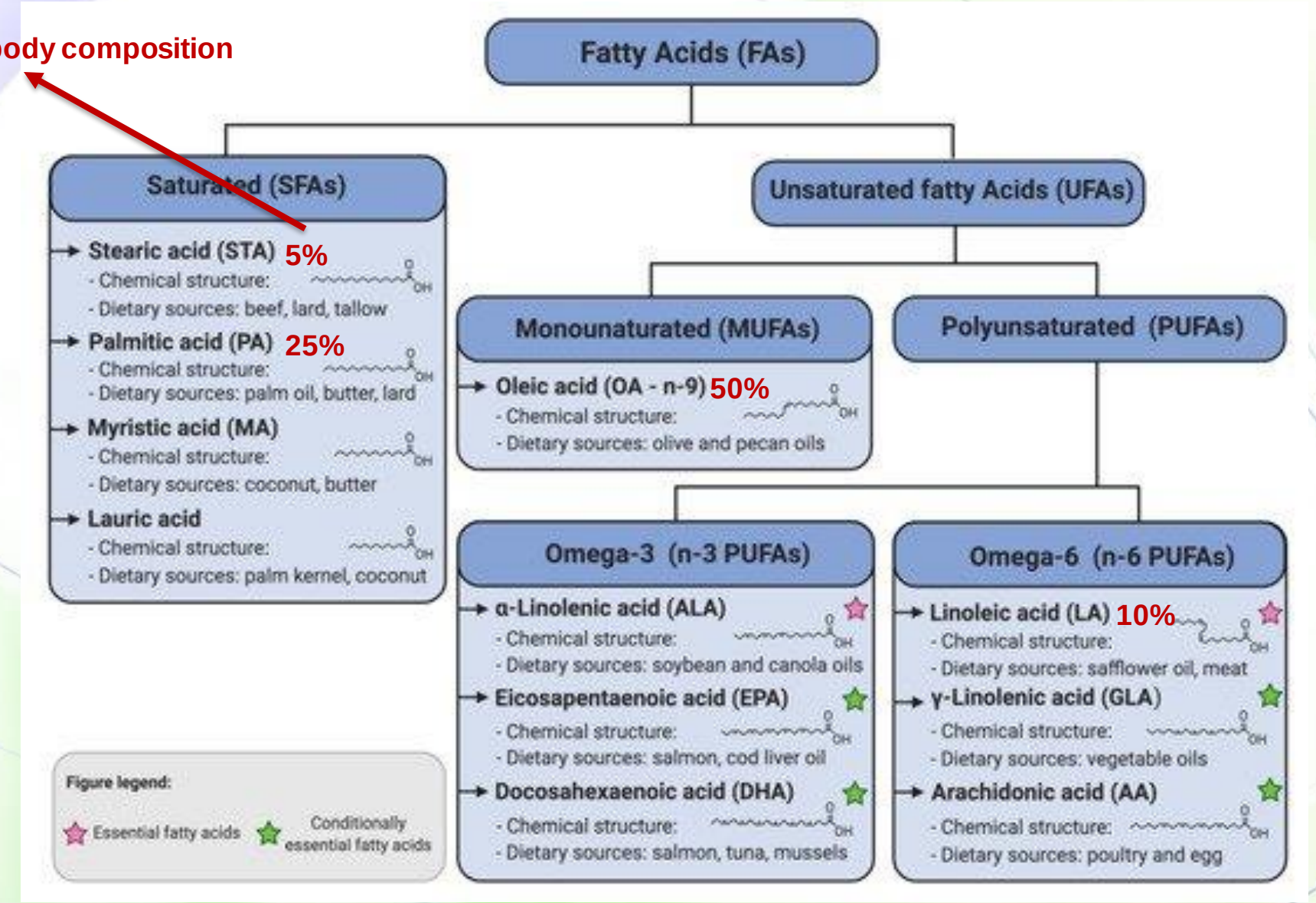
FATTY ACIDS

Classification

- **Chain length**
  - Short- **2-6**
  - Medium- **8-14**
  - Long- **14-24**
  - Very long- **>24**
- **Total carbon atoms**
  - Odd chain
  - Even chain
- **Nature of chain**
  - Saturated
  - Unsaturated
  - Branched
  - Hydroxy
- **Synthesis in body**
  - Essential
  - Non-essential

- 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 length increases the Tm.
- Membrane lipids typically contain unsaturated LCFA to maintain fluidity.

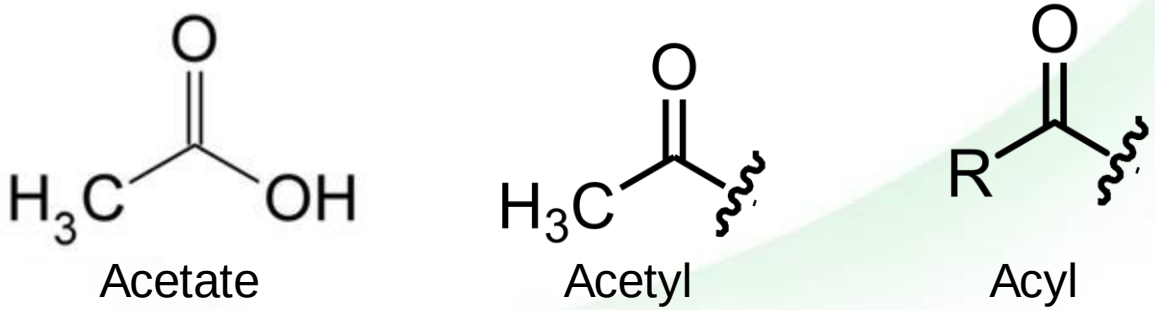
% of human body composition

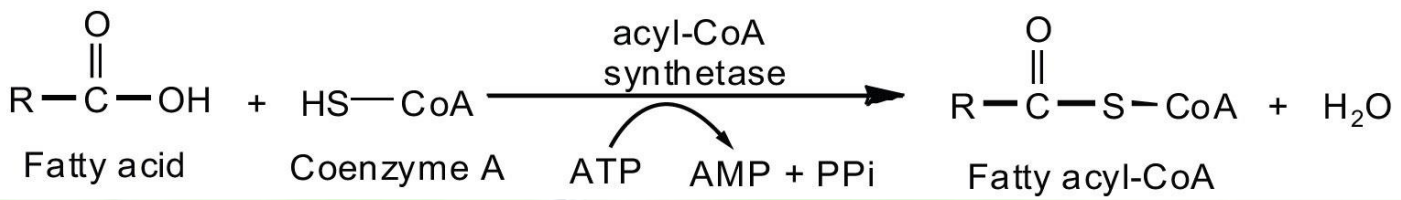


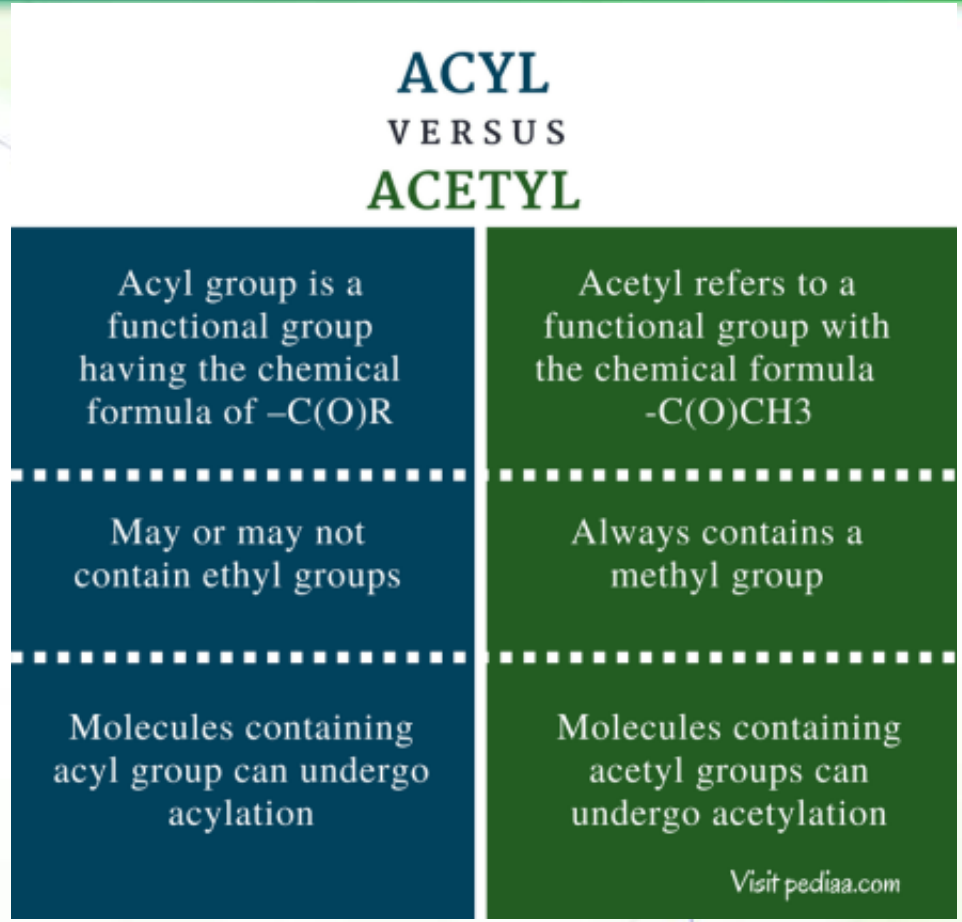
Forms of fatty acids

- Free fatty acids (FFA): occur in all tissues and plasma (particularly during fasting).
  - >90% of the plasma fatty acids are in the form of fatty acid esters (primarily TAG, cholesteryl esters, and phospholipids) contained in circulating lipoprotein particles.
  - Plasma FFA are transported on albumin from adipose tissue to most tissues.
- FFA can be oxidized by many tissues
  - Liver and muscle, to provide energy
  - Liver to synthesize ketone body
- Structural FA: membrane lipids as phospholipids and glycolipids
- Protein-associated FA 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.

Acetyl versus acyl

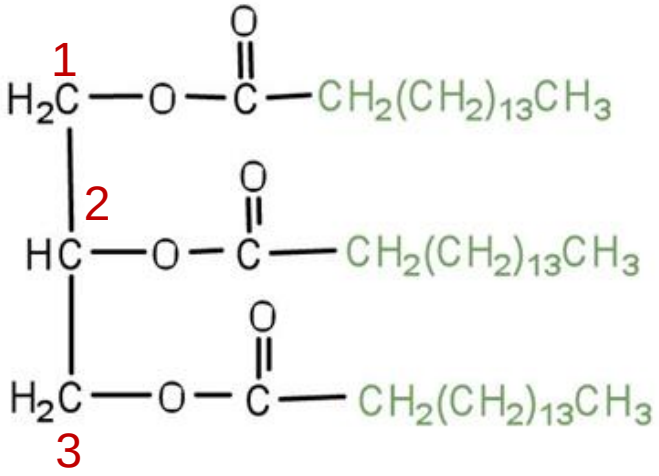




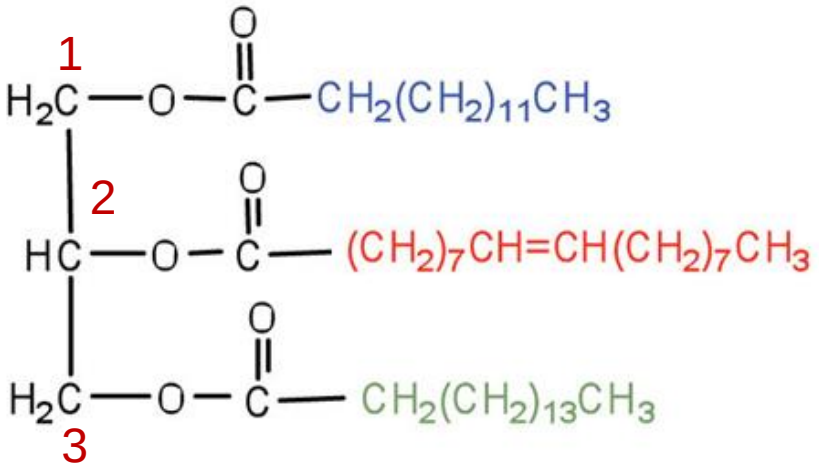


Both groups are composed of alkyl groups along with another group.

Triacyglycerol



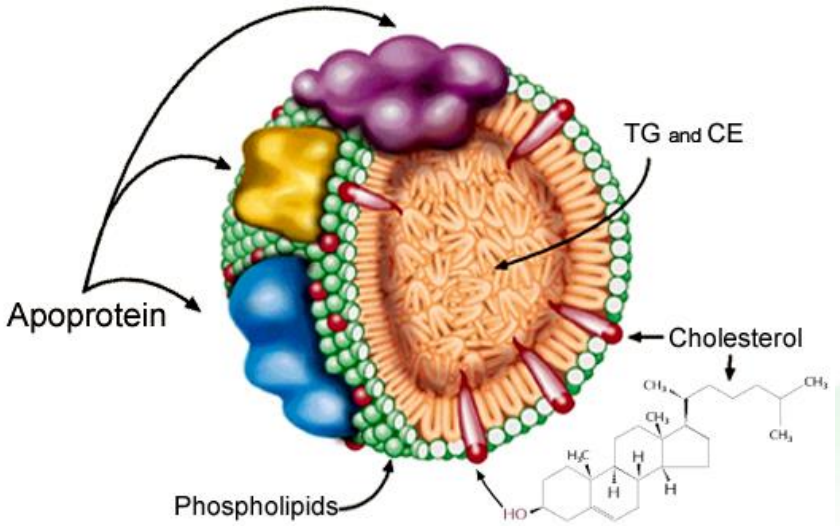
Tristearin
a simple triglyceride



a mixed triglyceride

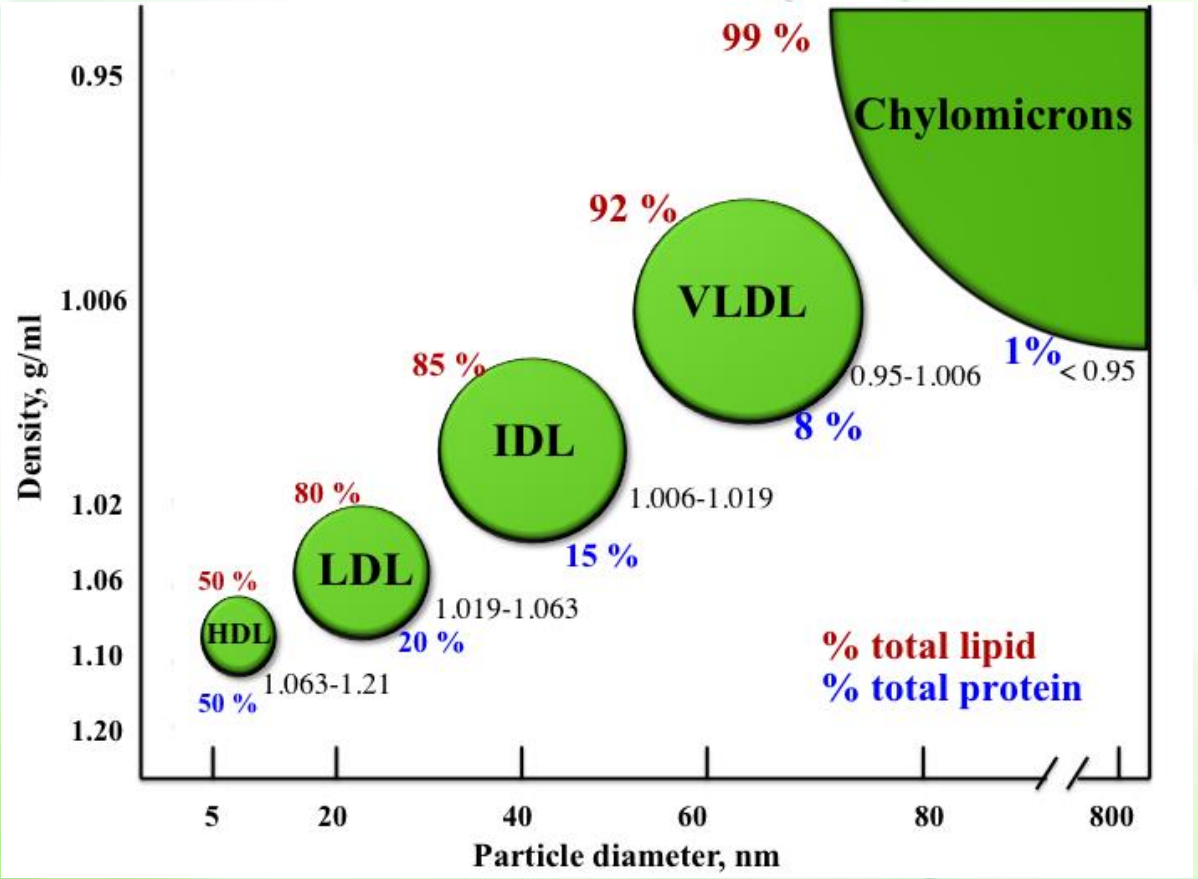
Usually, polyunsaturated FAs

Lipoproteins



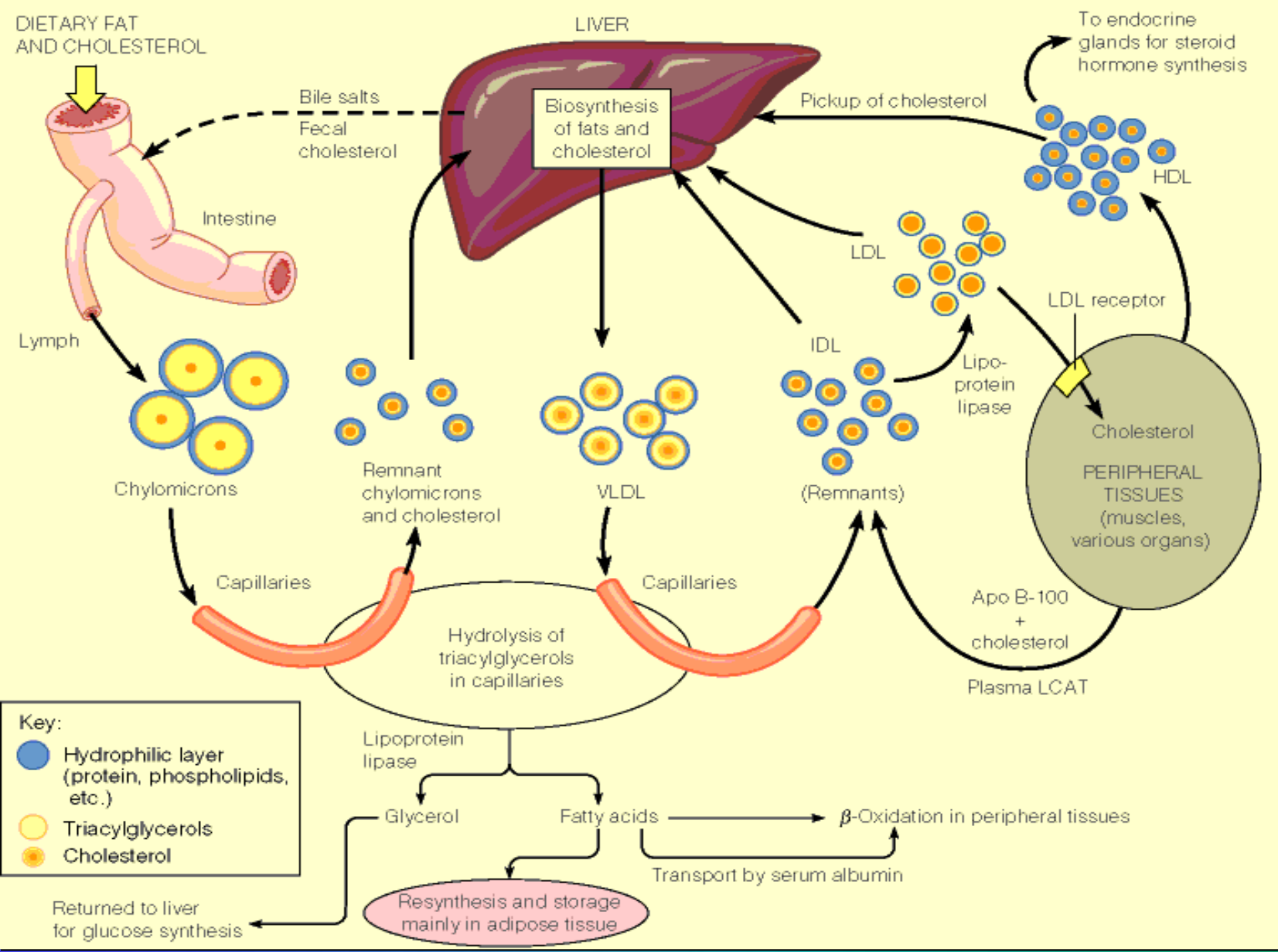
Function: transport of lipids (cholesterol, cholesterol esters, phospholipids & triacylglycerols) in blood plasma.

As lipid content increases, the density decreases



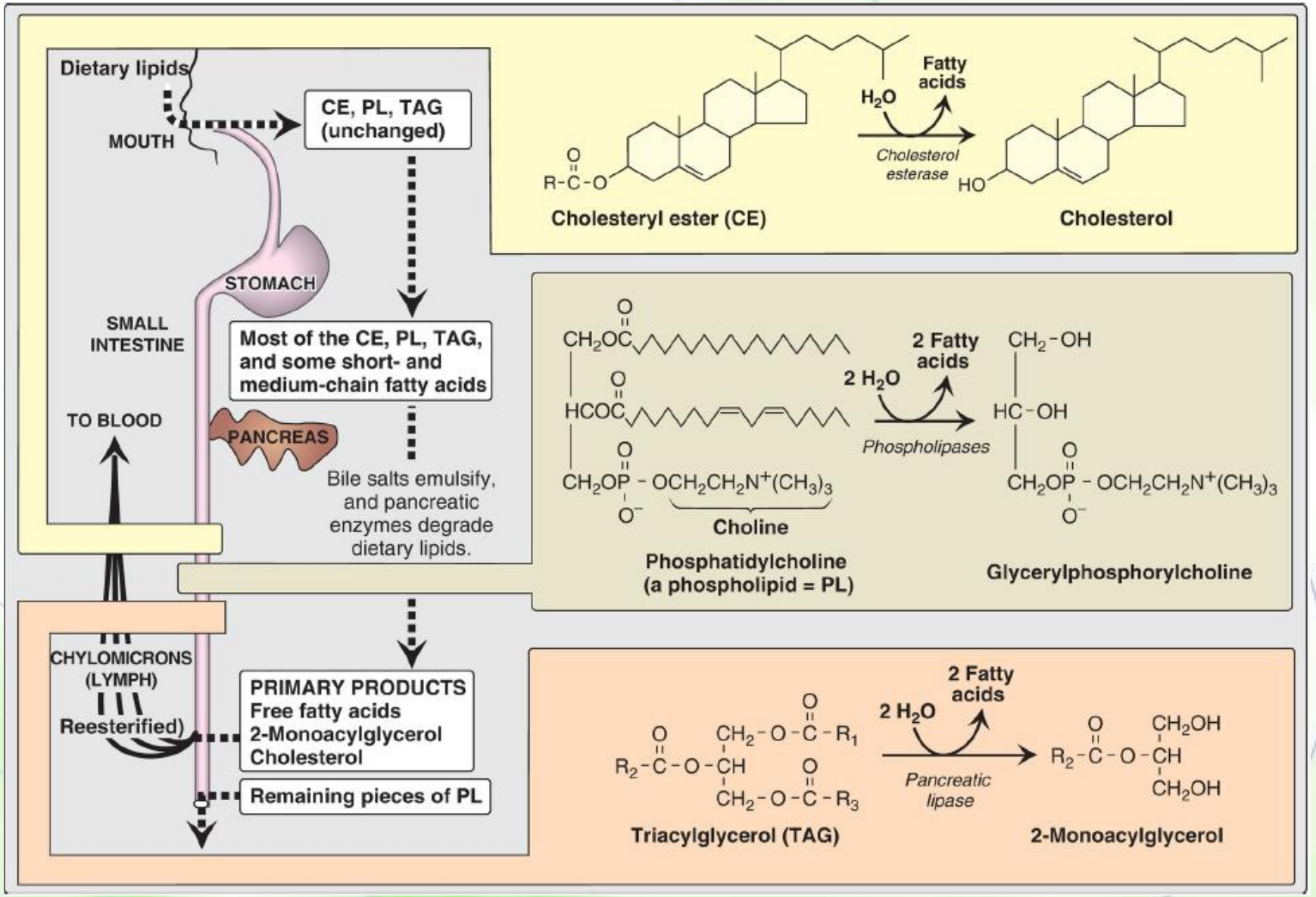
Composition of lipoproteins

	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	Transport of liver TG	Transport of cholesterol to peripheral tissues	Transport of cholesterol from peripheral tissues (cholesterol scavengers)



Lipid transport

Digestion of lipids

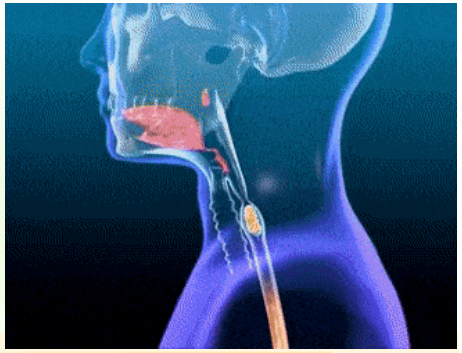


Digestion in the stomach

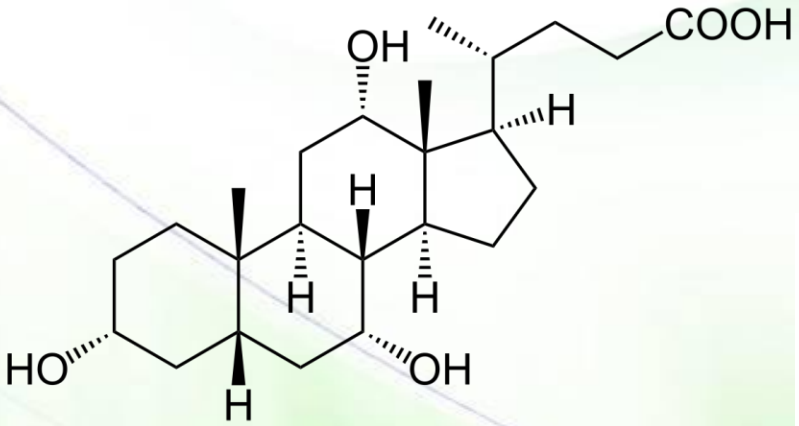
- Acid-stable lipases: lingual lipase and gastric lipase
- It has an optimum pH of 2.5 – 5.
- Main target: triacylglycerides with short- and medium-chain fatty acids (≤ 12 carbons)
- Significance: infants and patients of pancreatic lipase-deficiency or pancreatic insufficiency (e.g., cystic fibrosis).
- Short- and medium-chain fatty are absorbed in stomach.
- The action of lingual lipase is observed to be more significant in the newborn infants.

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

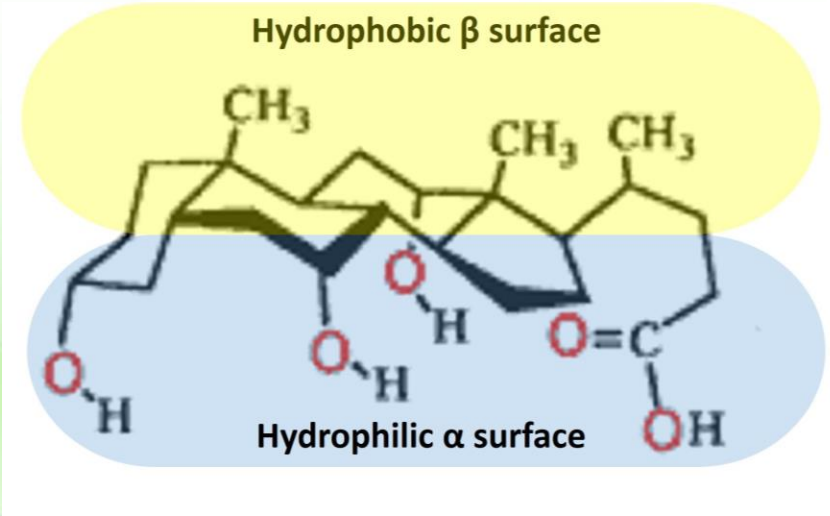
Emulsification in the small intestine

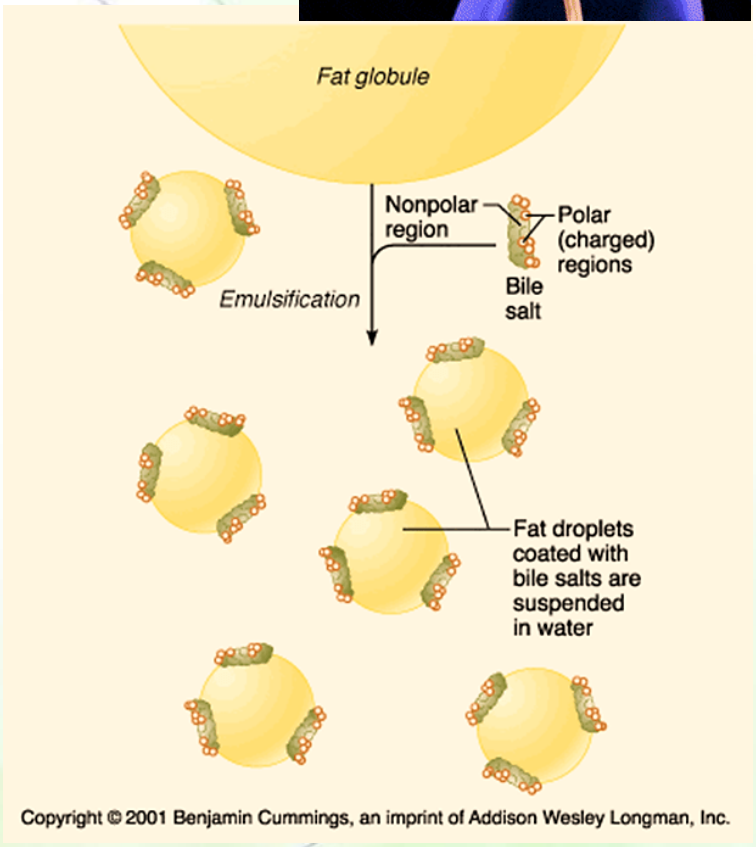


- Two mechanisms of emulsification in the duodenum:
  - Peristalsis : mechanical mixing leading to smaller droplets
  - Conjugated bile salts



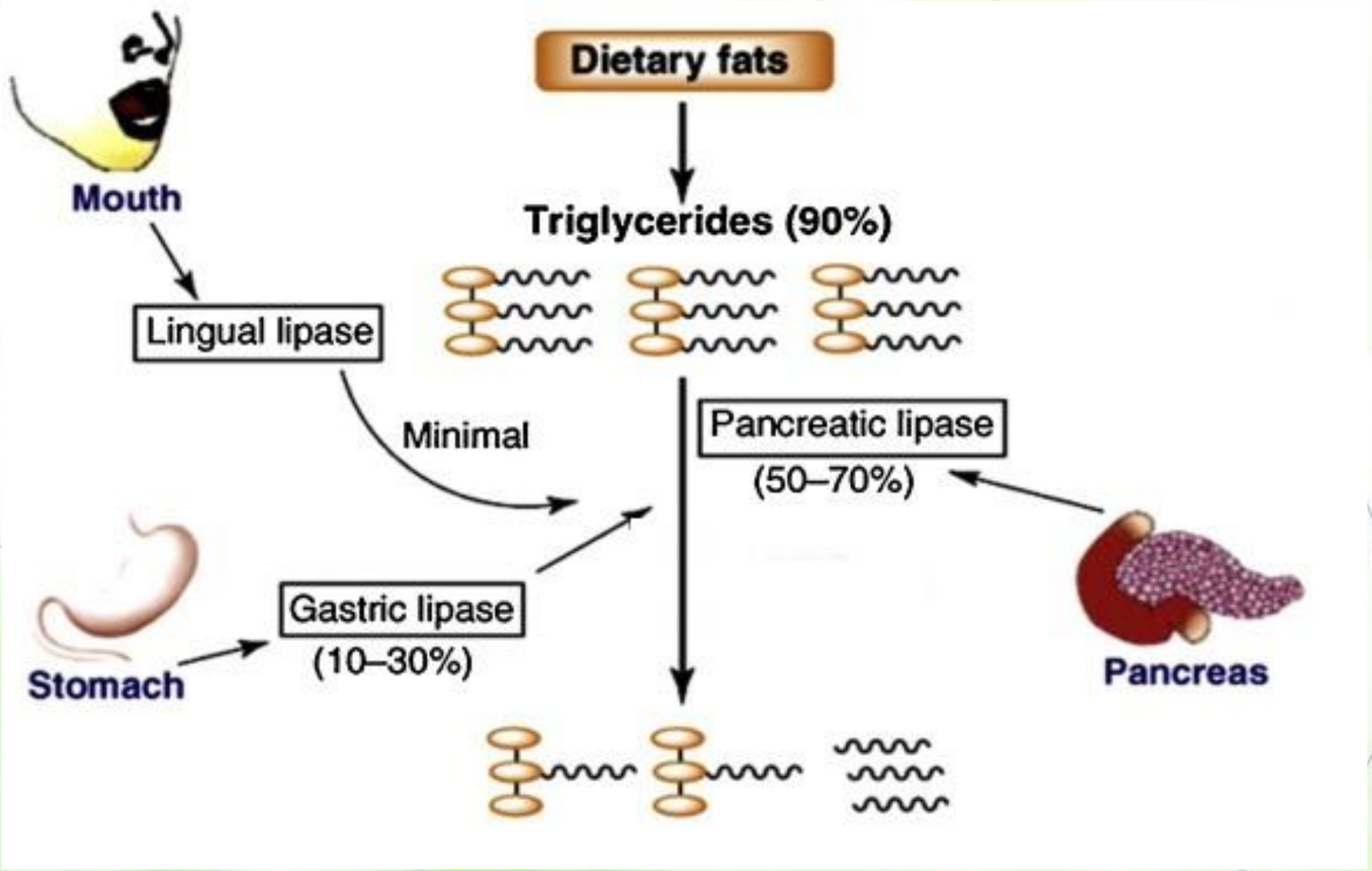
Cholic acid





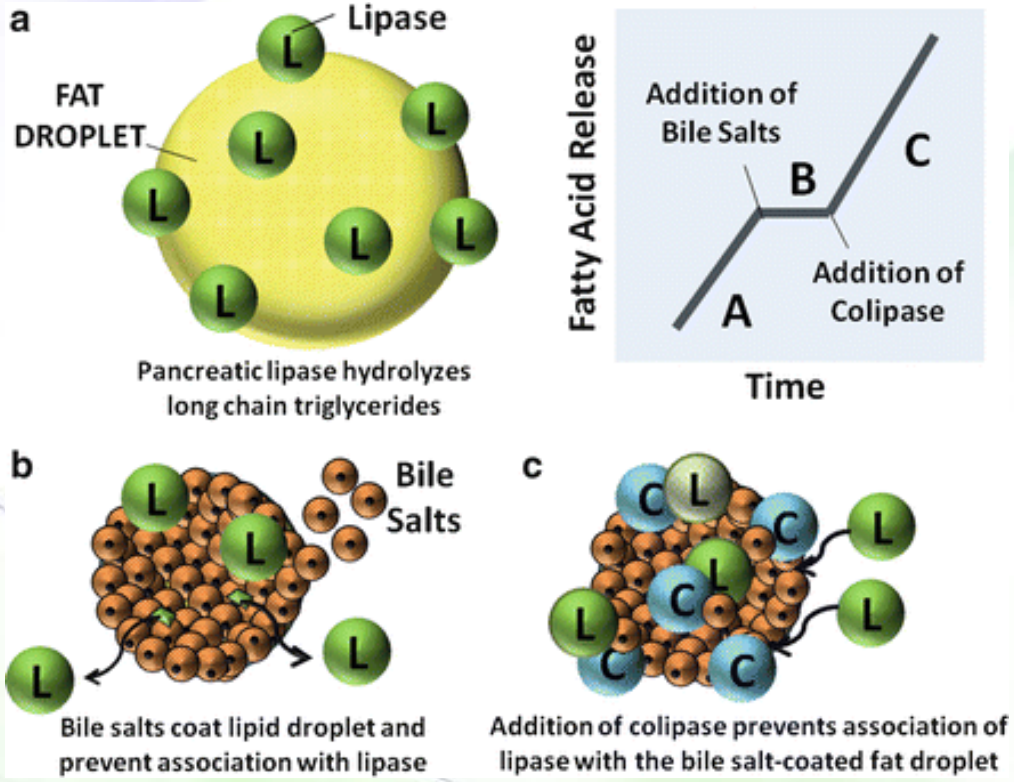
Degradation by pancreatic enzymes

Triacylglycerol degradation

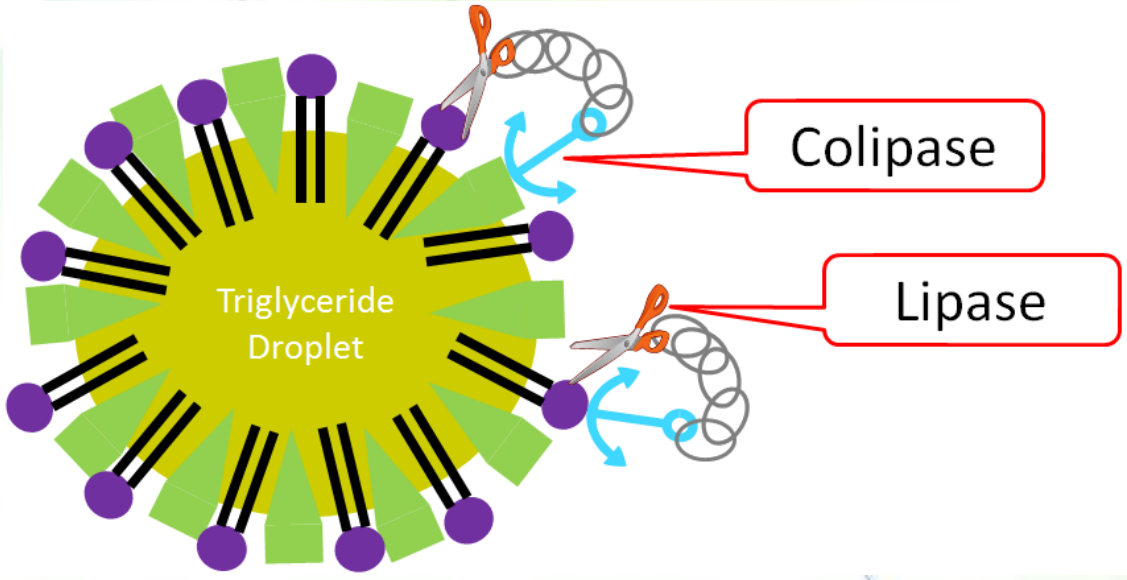


The significance of colipase

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



Combined pancreatic lipase-colipase deficiency is an orphan disease

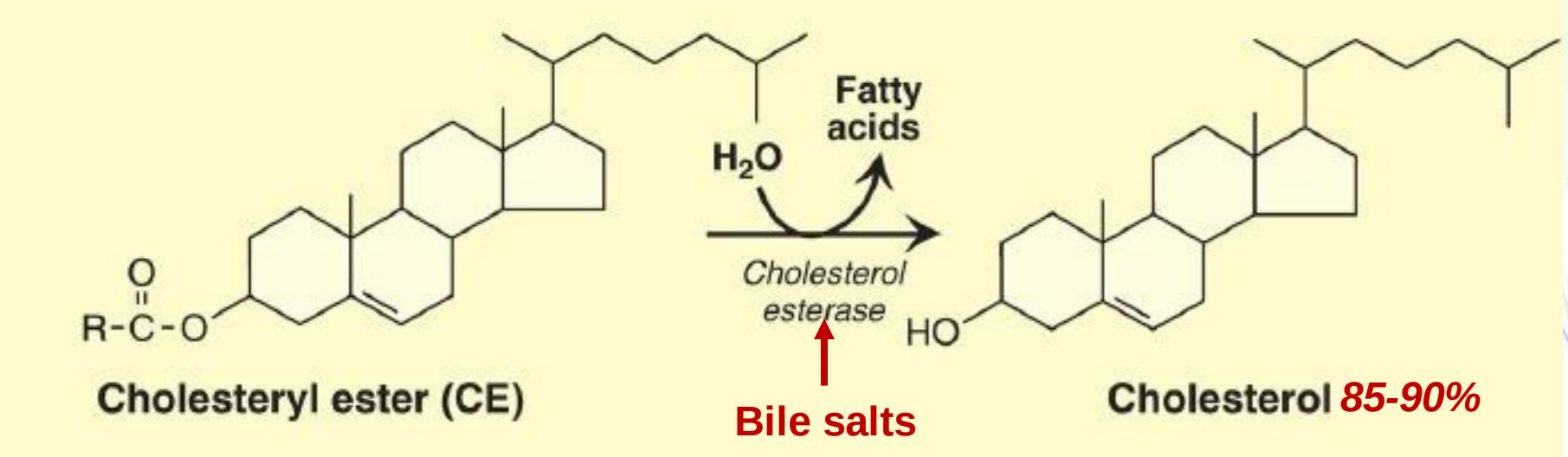


Colipase:

- 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

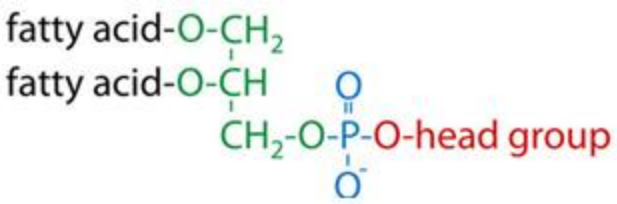
Degradation by pancreatic enzymes

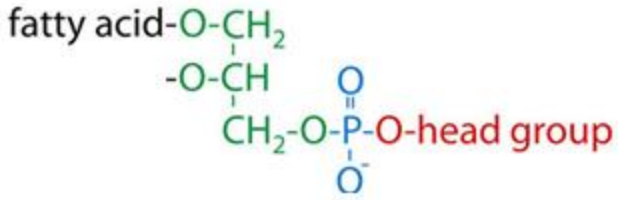
Degradation of cholesteryl ester

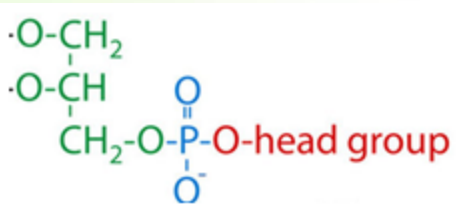


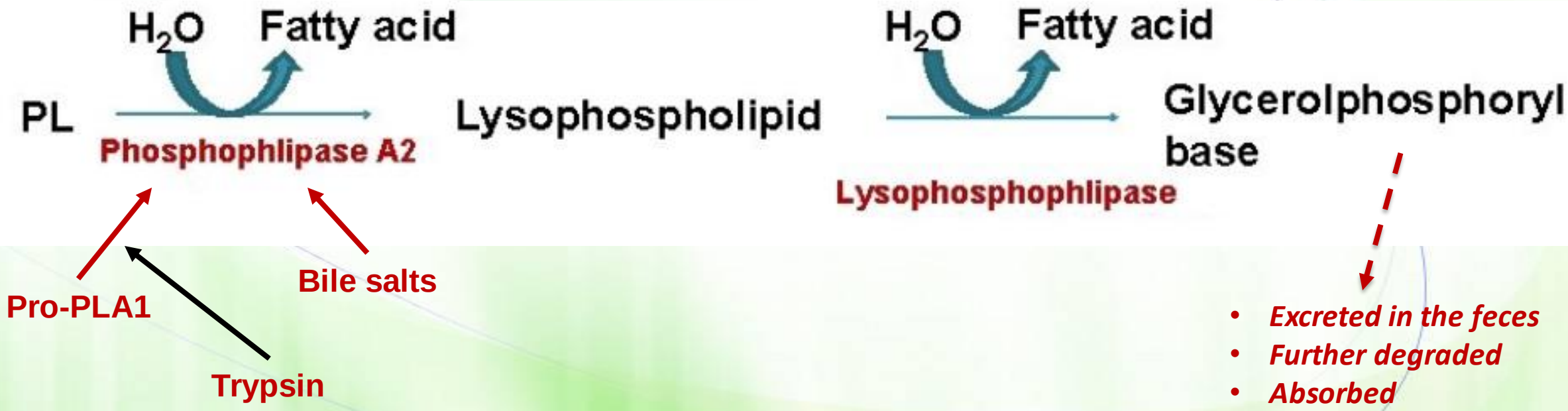
Degradation by pancreatic enzymes

Degradation of phospholipids



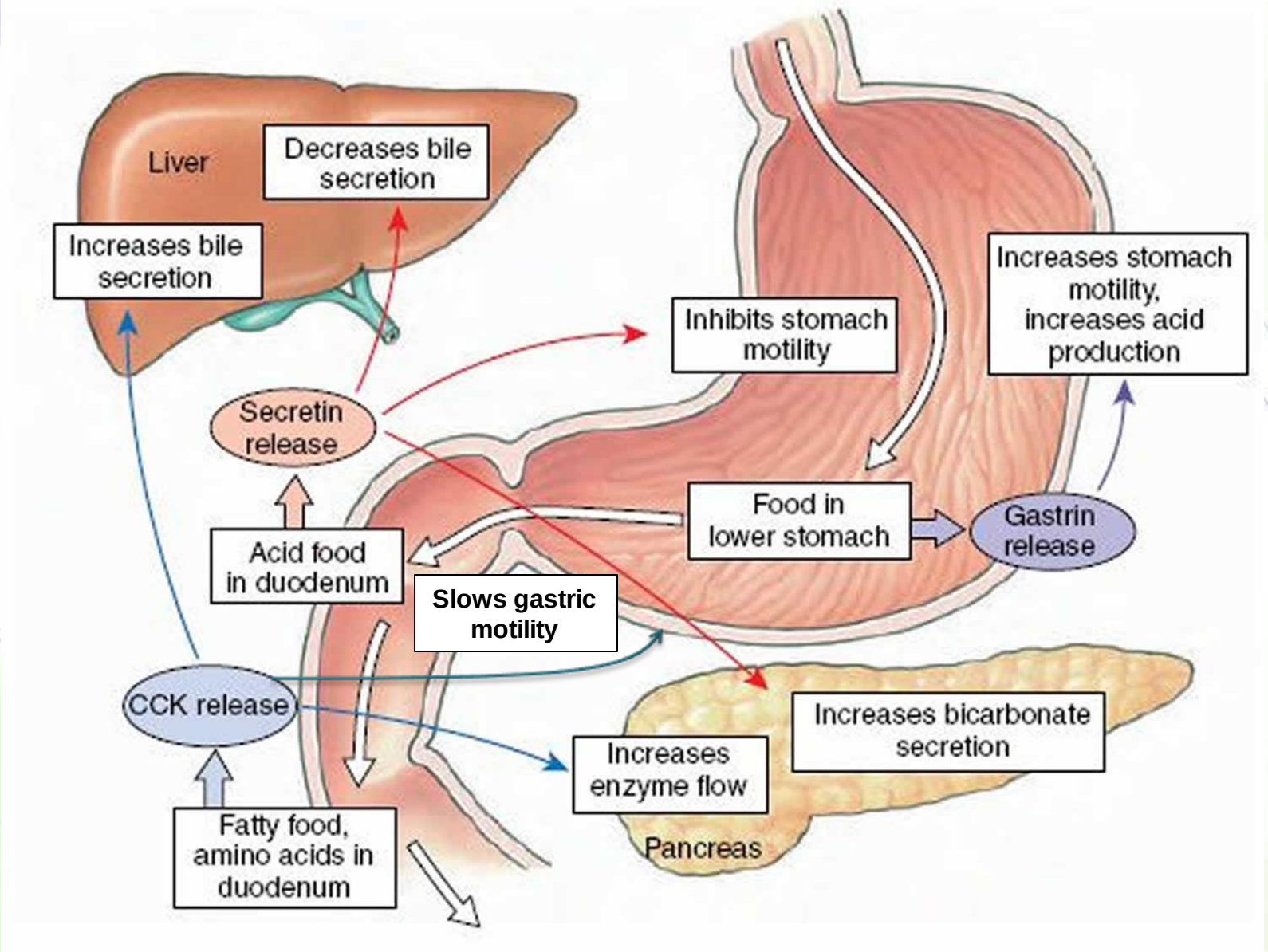






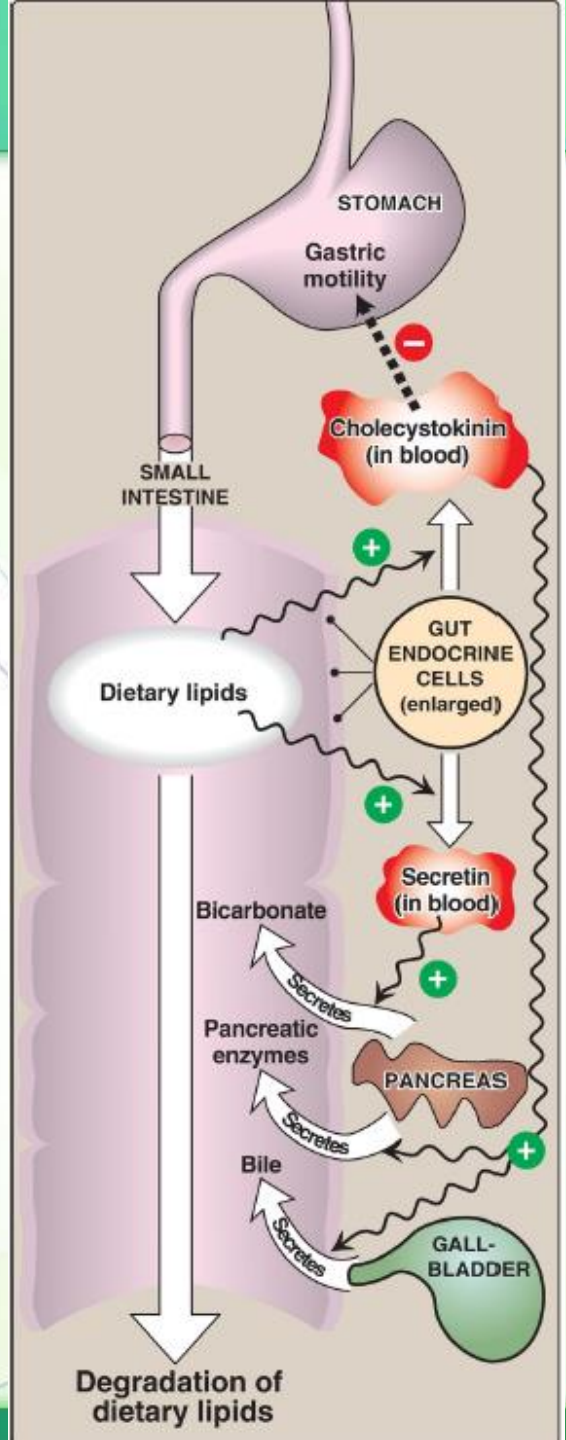
- *Excreted in the feces*
- *Further degraded*
- *Absorbed*

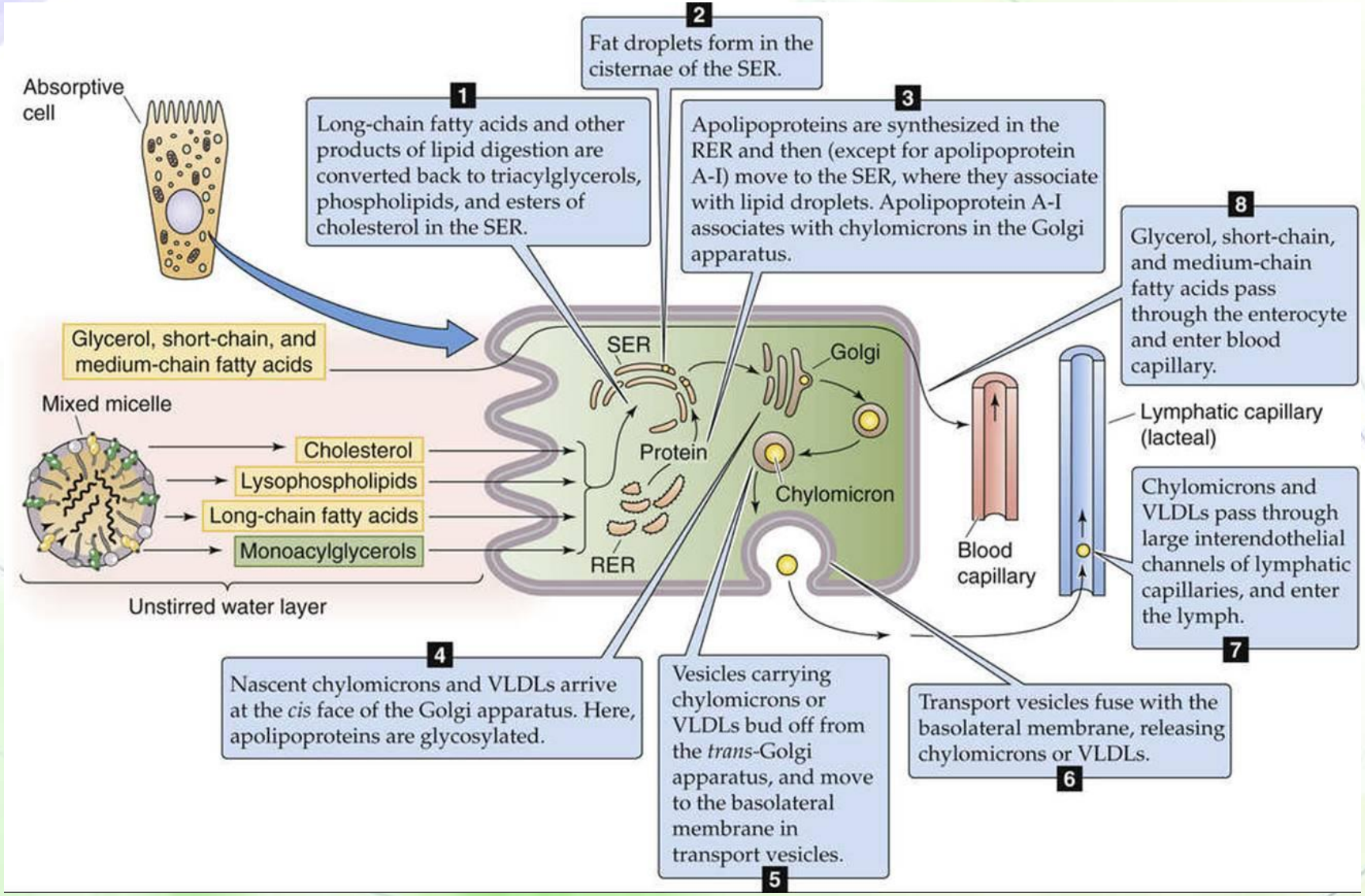
Hormonal control



Hormonal control

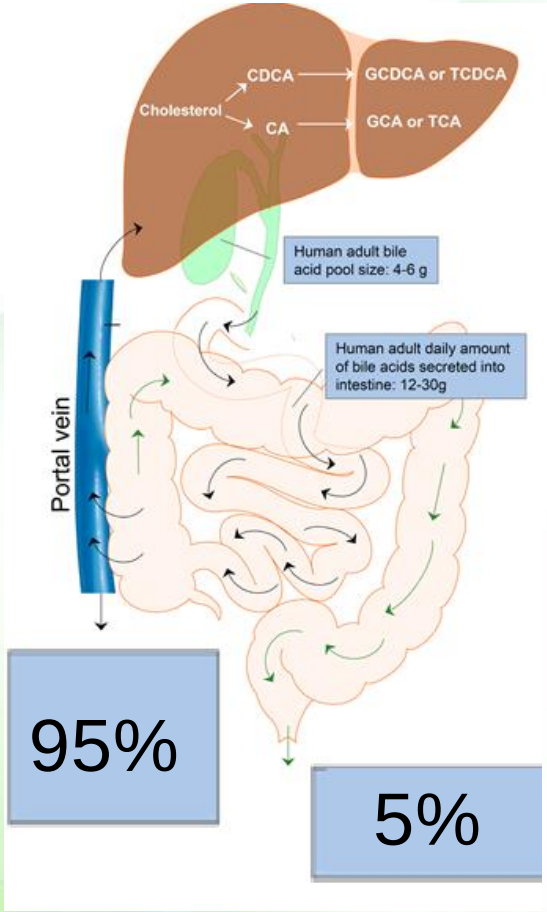
- Entry of food (chyme) induces the release cholecystokinin (CCK; a peptide hormone) from the duodenum and jejunum.
  - Induces contraction of the gallbladder to release bile (bile salts, phospholipids, and free cholesterol)
  - Acts on the exocrine pancreatic cells to release digestive enzymes
  - Decreases 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.

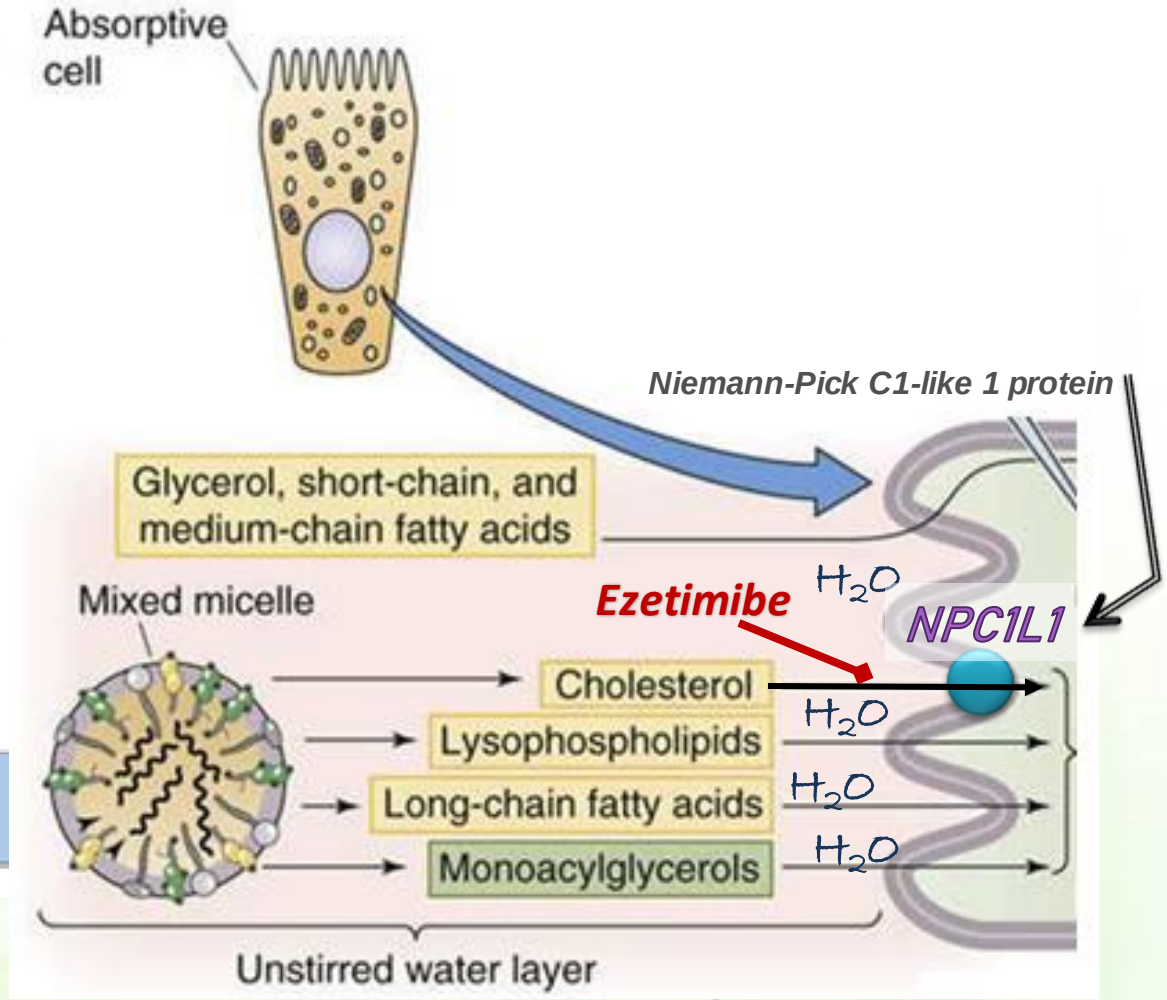



Absorptive cell
1
Long-chain fatty acids and other products of lipid digestion are converted back to triacylglycerols, phospholipids, and esters of cholesterol in the SER.
2
Fat droplets form in the cisternae of the SER.
3
Apolipoproteins are synthesized in the RER and then (except for apolipoprotein A-I) move to the SER, where they associate with lipid droplets. Apolipoprotein A-I associates with chylomicrons in the Golgi apparatus.
8
Glycerol, short-chain, and medium-chain fatty acids pass through the enterocyte and enter blood capillary.
Glycerol, short-chain, and medium-chain fatty acids
Mixed micelle
Cholesterol
Lysophospholipids
Long-chain fatty acids
Monoacylglycerols
Unstirred water layer
SER
Golgi
Protein
Chylomicron
RER
Blood capillary
Lymphatic capillary (lacteal)
Chylomicrons and VLDLs pass through large interendothelial channels of lymphatic capillaries, and enter the lymph.
7
4
Nascent chylomicrons and VLDLs arrive at the *cis* face of the Golgi apparatus. Here, apolipoproteins are glycosylated.
5
Vesicles carrying chylomicrons or VLDLs bud off from the *trans*-Golgi apparatus, and move to the basolateral membrane in transport vesicles.
6
Transport vesicles fuse with the basolateral membrane, releasing chylomicrons or VLDLs.

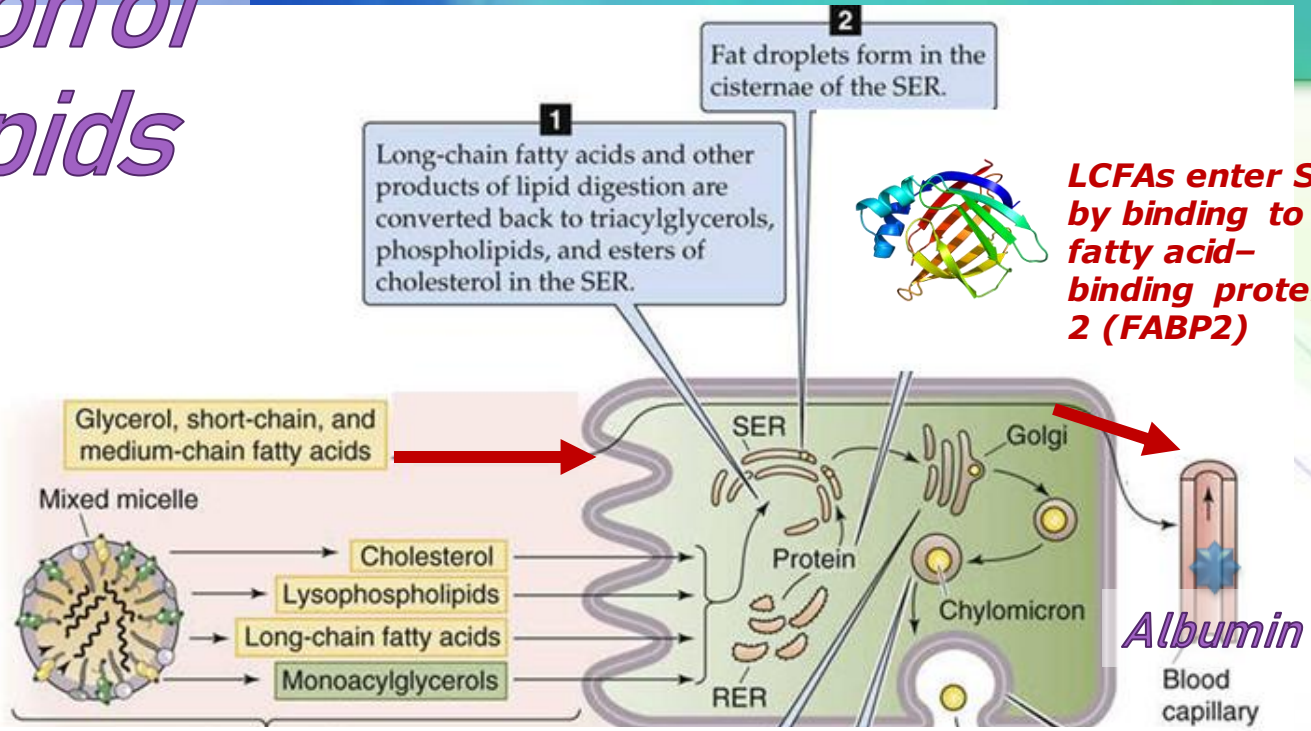
Absorption by enterocytes

- Mixed micelles are formed in the lumen from free fatty acids (FFA), monoacylglycerol, free cholesterol, bile salts, and fat-soluble vitamins.
- Cholesterol is poorly absorbed.
  - Note: it can be drug-targeted
- The uptake of fatty acids across the enterocyte brush-border membrane occurs by both passive diffusion and by protein–mediated mechanisms.
- Short- and medium-chain FAs are directly absorbed passive diffusion.

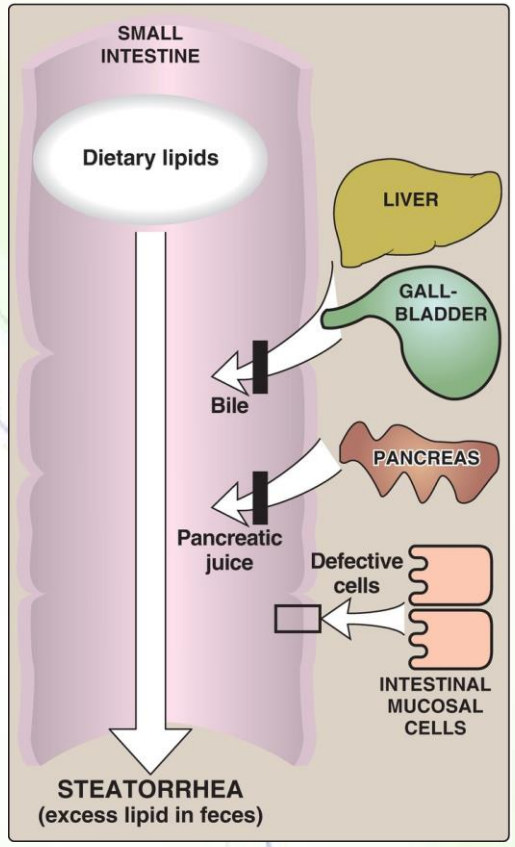


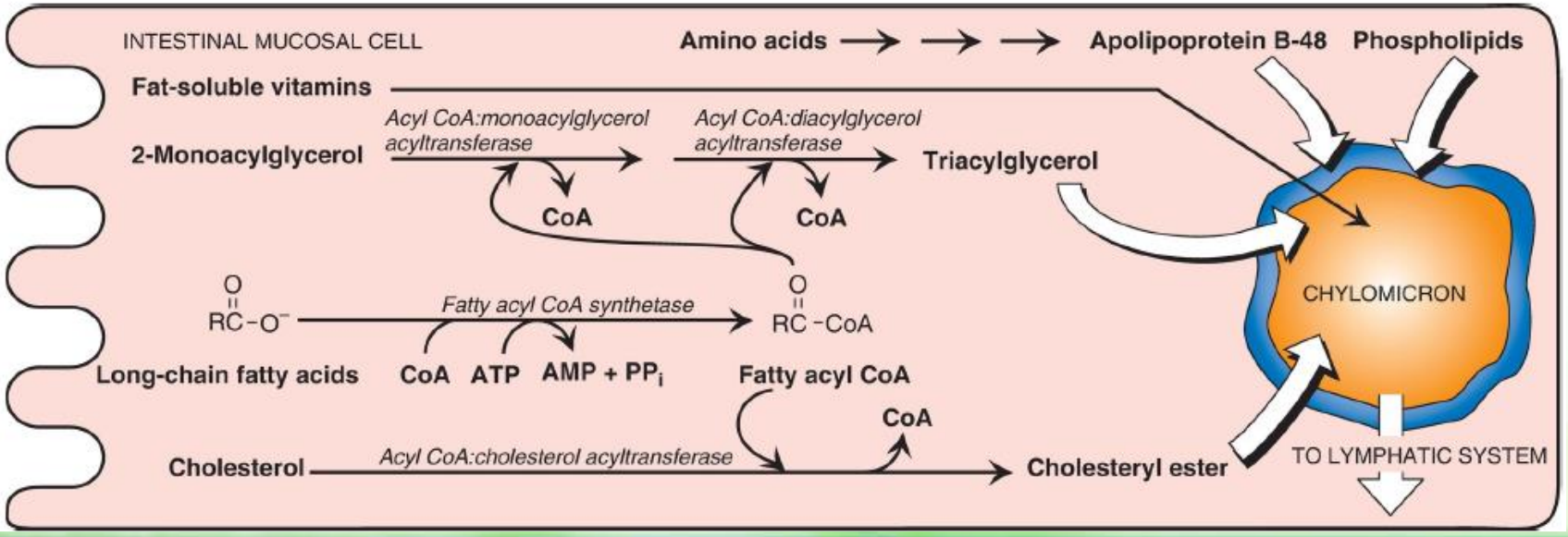


Reformation of complex lipids



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



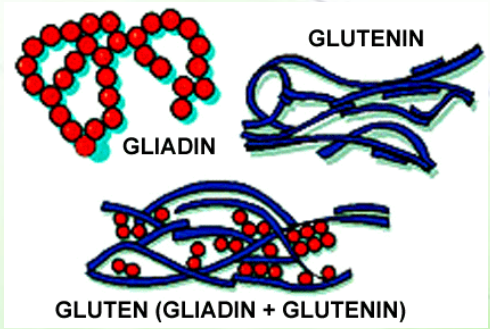


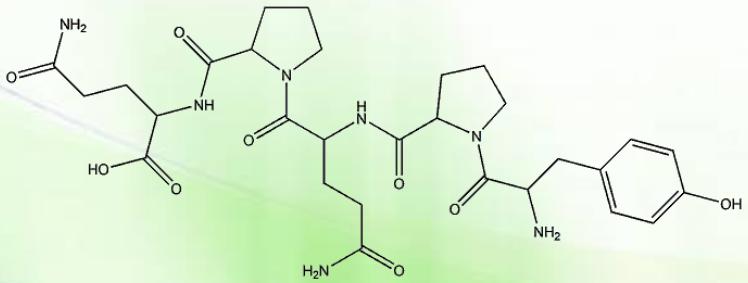
Principal causes of steatorrhea:

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

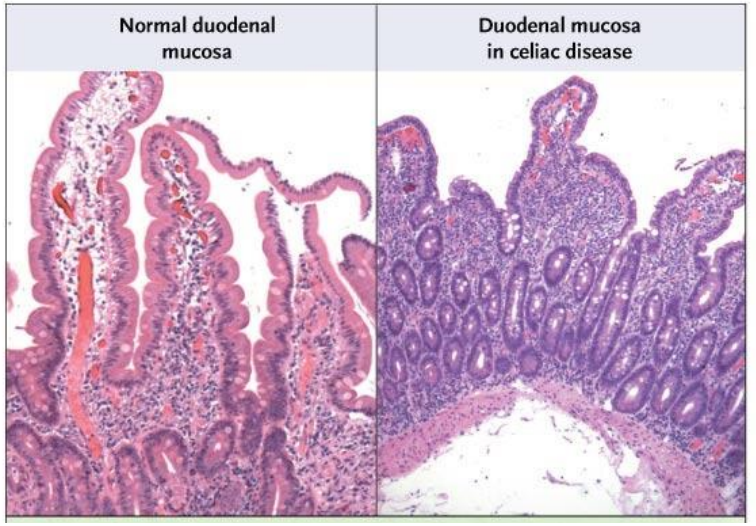
Celiac disease (CD)

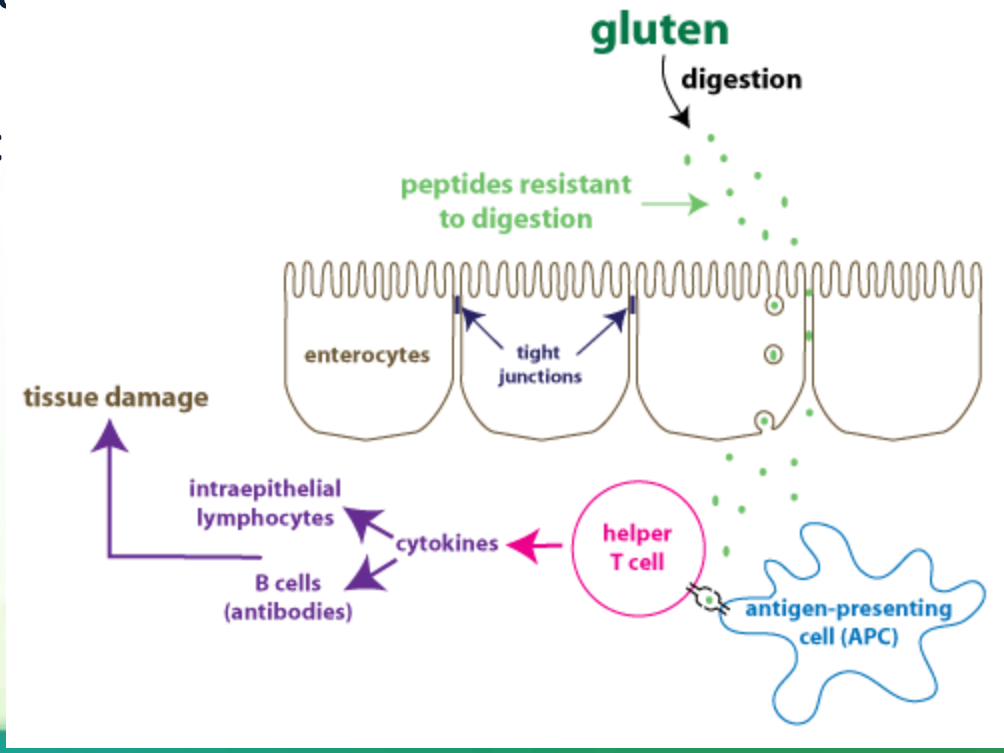
- Fat malabsorption leading to steatorrhea
- It is an autoimmune response to gliadin, a peptide found in gluten (wheat, rye, and barley).
- Gliadin contains many proline (14%) and glutamine (40%) residues, making it resistant to digestion.
- Lab tests: the presence of anti-tissue transglutaminase (anti-tTG)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





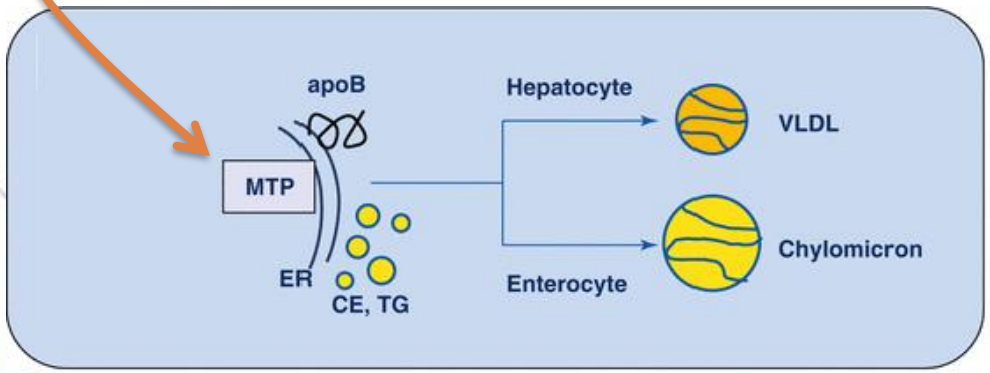
http://courses.washington.edu/pbio376/celiac/celiacdisease-376.html

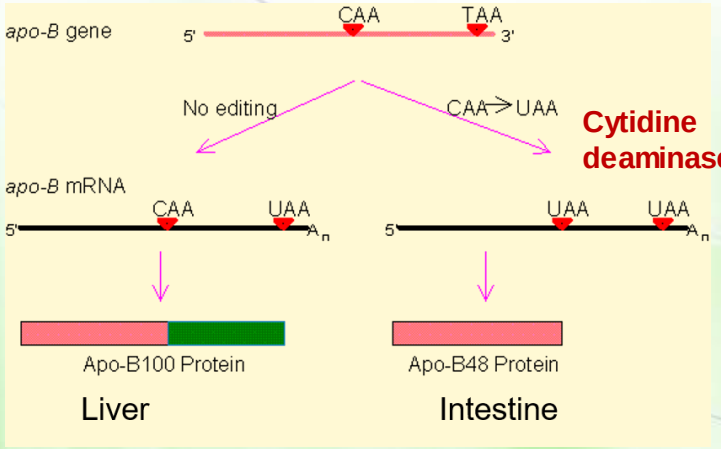


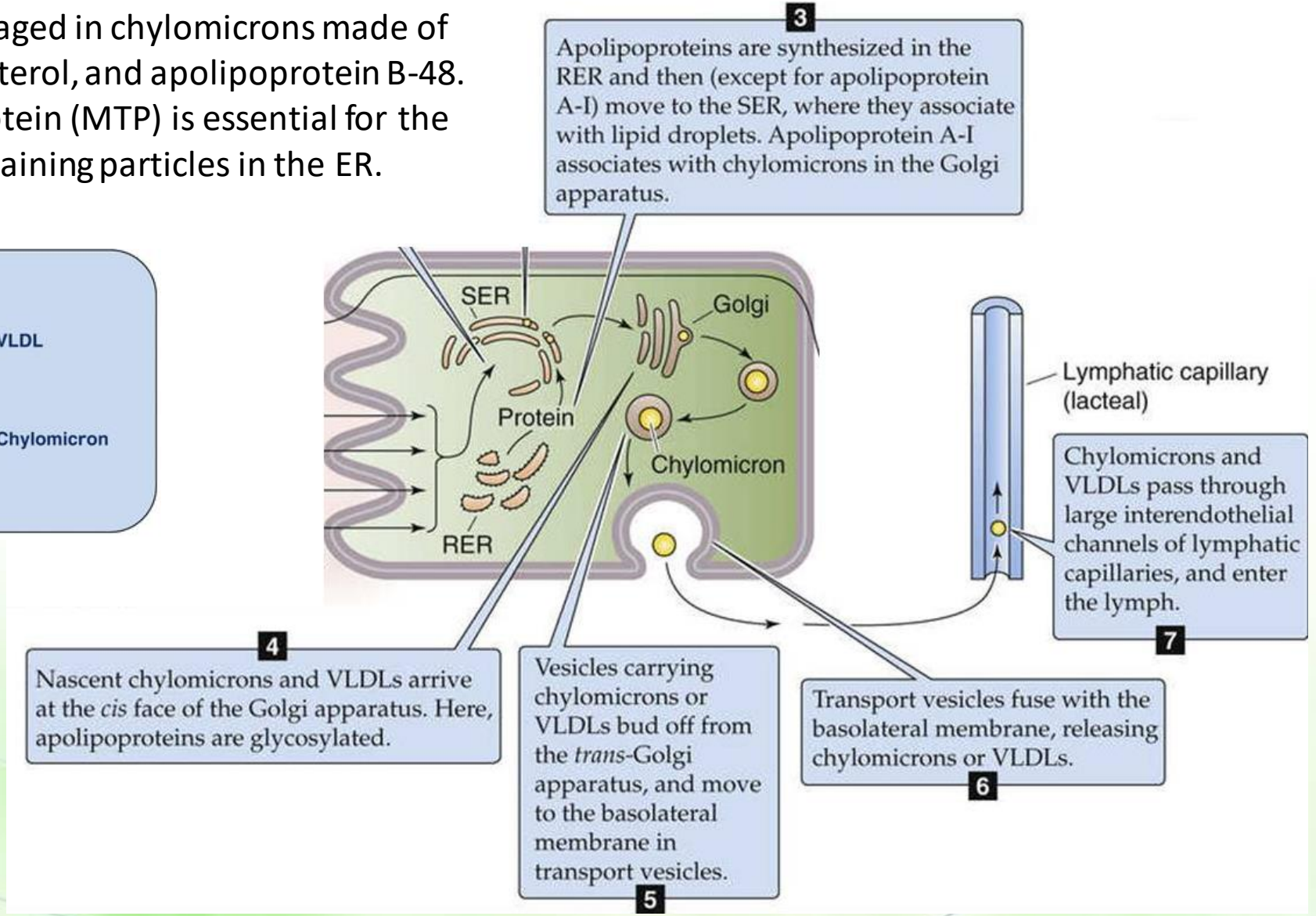


Formation and release of chylomicrons

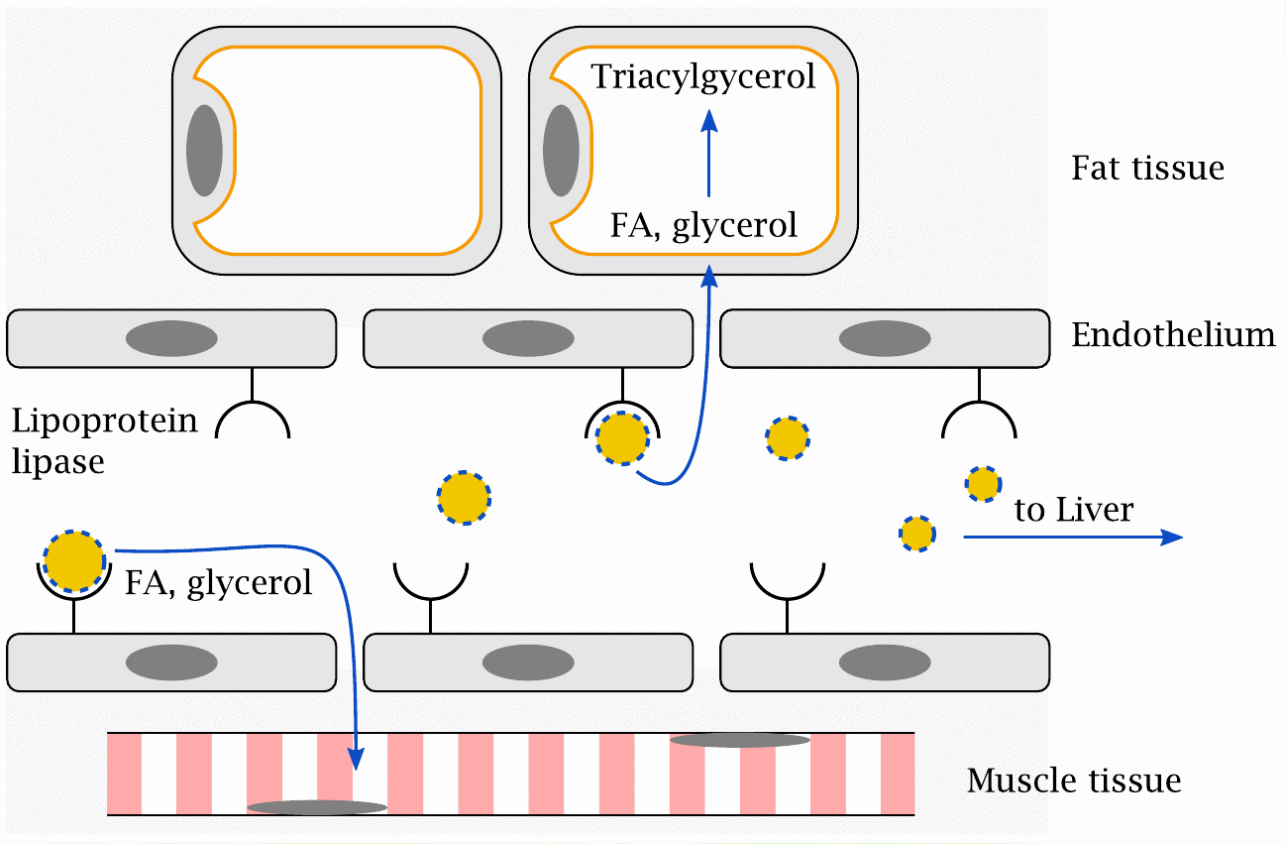
- TAG and cholesteryl esters are packaged in chylomicrons made of phospholipids, nonesterified cholesterol, and apolipoprotein B-48.
- Microsomal triglyceride transfer protein (MTP) is essential for the assembly of all TAG-rich apo B–containing particles in the ER.







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.

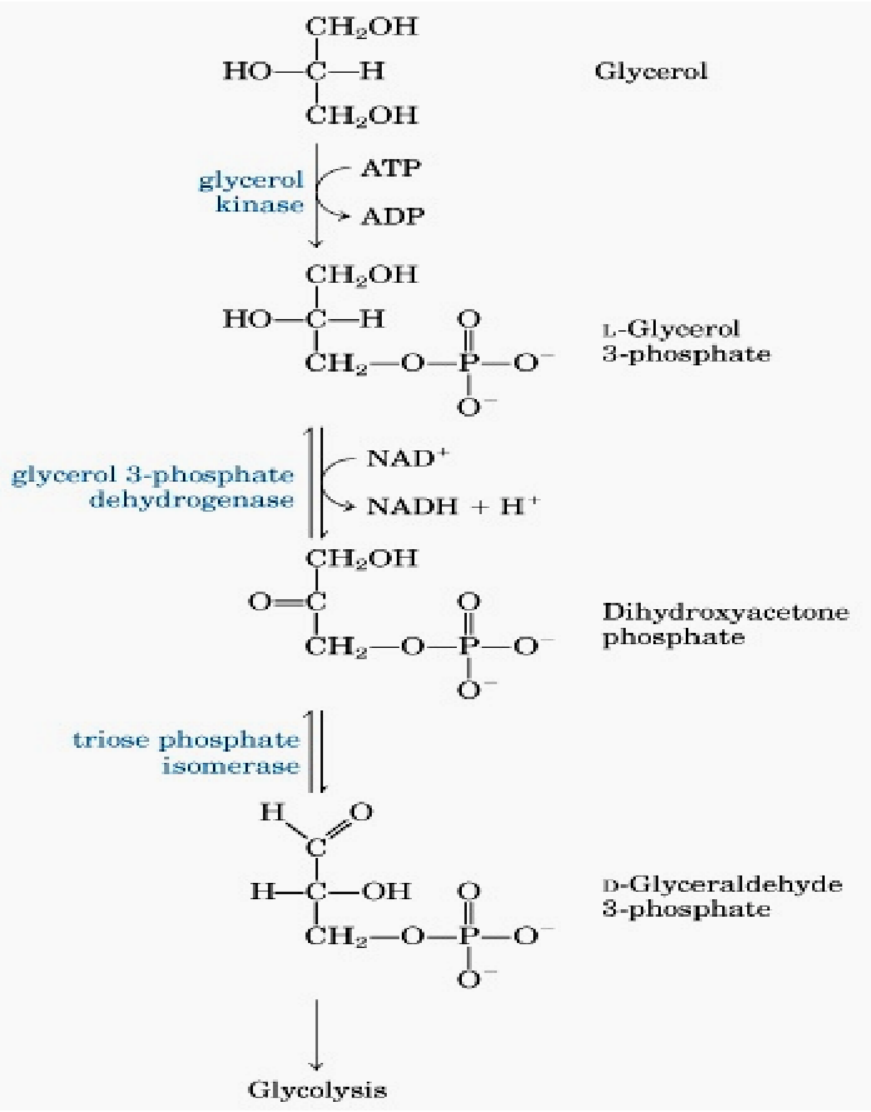
- The resulting fatty acids have two possible fates:

(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.

Fate of chylomicrons

- When TAGs are removed, chylomicron remnants would contain cholesteryl esters, phospholipids, apolipoproteins, fat-soluble vitamins, and a small amount of TAG).
- Chylomicron remnants bind to apoE receptors via their apoE and are endocytosed.
- ApoE receptor exists in the liver, skeletal muscles, and adipose tissues.
- The intracellular remnants are hydrolyzed to their component parts.

Type III hyperlipoproteinemia: mutations in apoE gene leading to decreased clearance of chylomicron remnants.