METABOLISM

بسم الله الرحمن الرحيم

Final – Lecture 4
Lipid digestion, absorption and transport (Pt.2)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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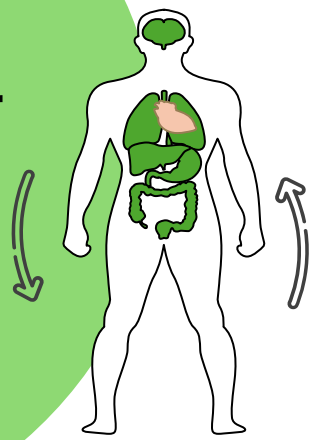


Quiz on the previous lecture

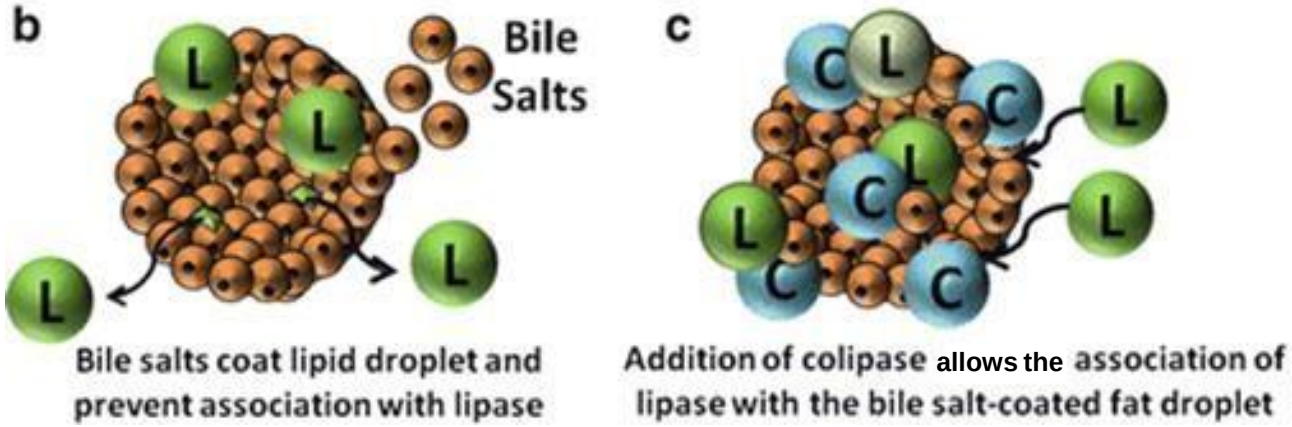
CLICK HERE!

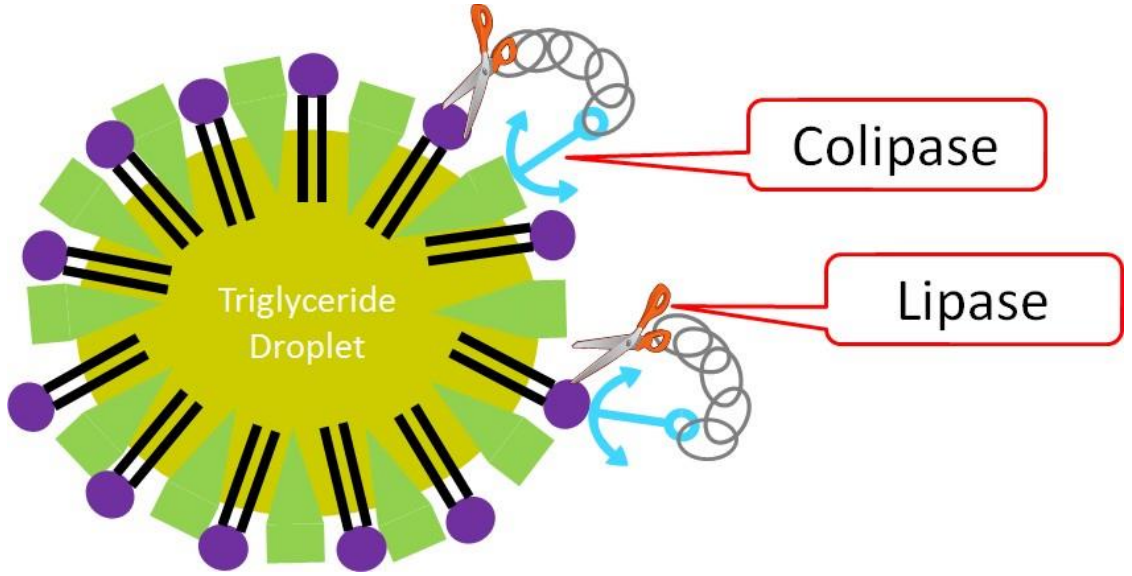
Quick Revision

- Lipid family consists of a heterogeneous compounds, which are hydrophobic (with small negligible polar part), meaning that their digestion is variable (due to heterogeneity) and complex as these compounds are hydrophobic making their adhesion to enzymes less efficient.
- The first stage in lipids digestion is on oral cavity by lingual lipase enzyme, and it hydrolyses ester bonds between short or medium-chain fatty acids and glycerol, but because of the low contact time it's not that effective.
- Secondly the previous enzyme and food is transported to the stomach where another one is introduced (gastric lipase) that works by the same mechanism alongside lingual lipase as both are stable at acidic conditions.
- At the last stage, after food particles with the enzymes and HCl from stomach to small intestines, where pancreatic enzymes are excreted to such as pancreatic lipase the one that hydrolase long-chain fatty acids, and due to the higher hydrophobicity of LCFAs, emulsifiers are needed (while in low and middle-chain fatty acids, we don't need them).

Pancreatic lipase: The significance of colipase

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





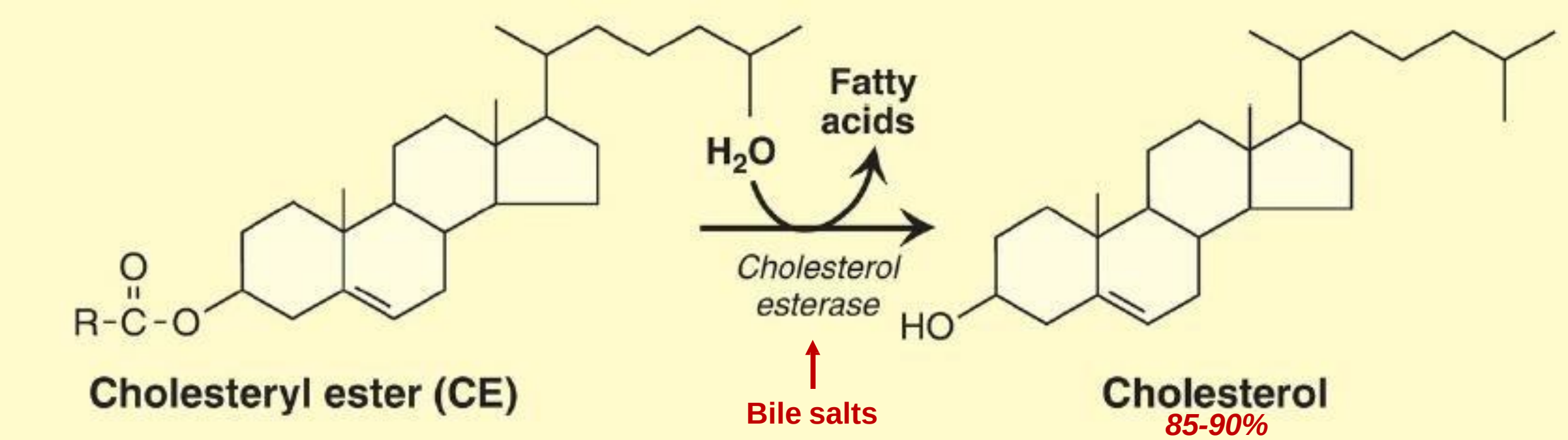
Combined pancreatic lipase-colipase deficiency is an orphan disease

- Emulsifiers (bile acids and salts) are made from cholesterol with a steroid nucleus in the center (big and rigid in structure) with the polar surface interacting with the enzyme and non-polar surface associated with fatty substrates.
- Colipase works by making a room for lipase to do hydrolysis, as it anchors lipase to a fat droplet which is covered with bile acids.

Colipase:

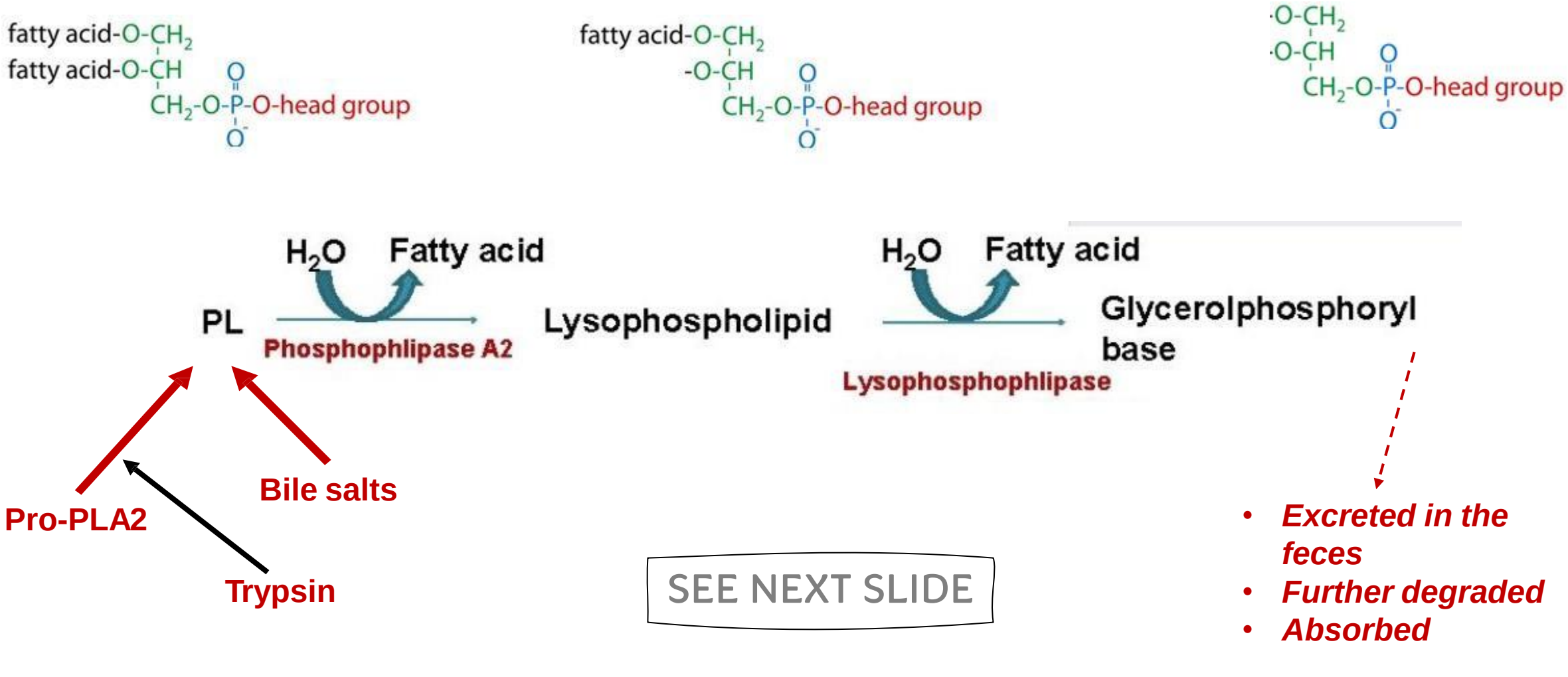
- Secreted as a zymogen (proenzyme) from the pancreas
- Activated by trypsin (By cleavage) in the small intestines
- Anchors lipase into the micelle interface at a ratio of 1:1
- Restores activity of lipase against inhibitors

Degradation of cholesterol esters



Lipids in food are mainly TAG from oils and fats, cholesterol or cholesterol esters and phospholipids. Cholesterol esters have lost the 'OH' of cholesterol and are highly hydrophobic; they thus need emulsifiers for their degradation (into cholesterol and fatty acid) by cholesterol esterase.

Degradation of phospholipids



SEE NEXT SLIDE

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

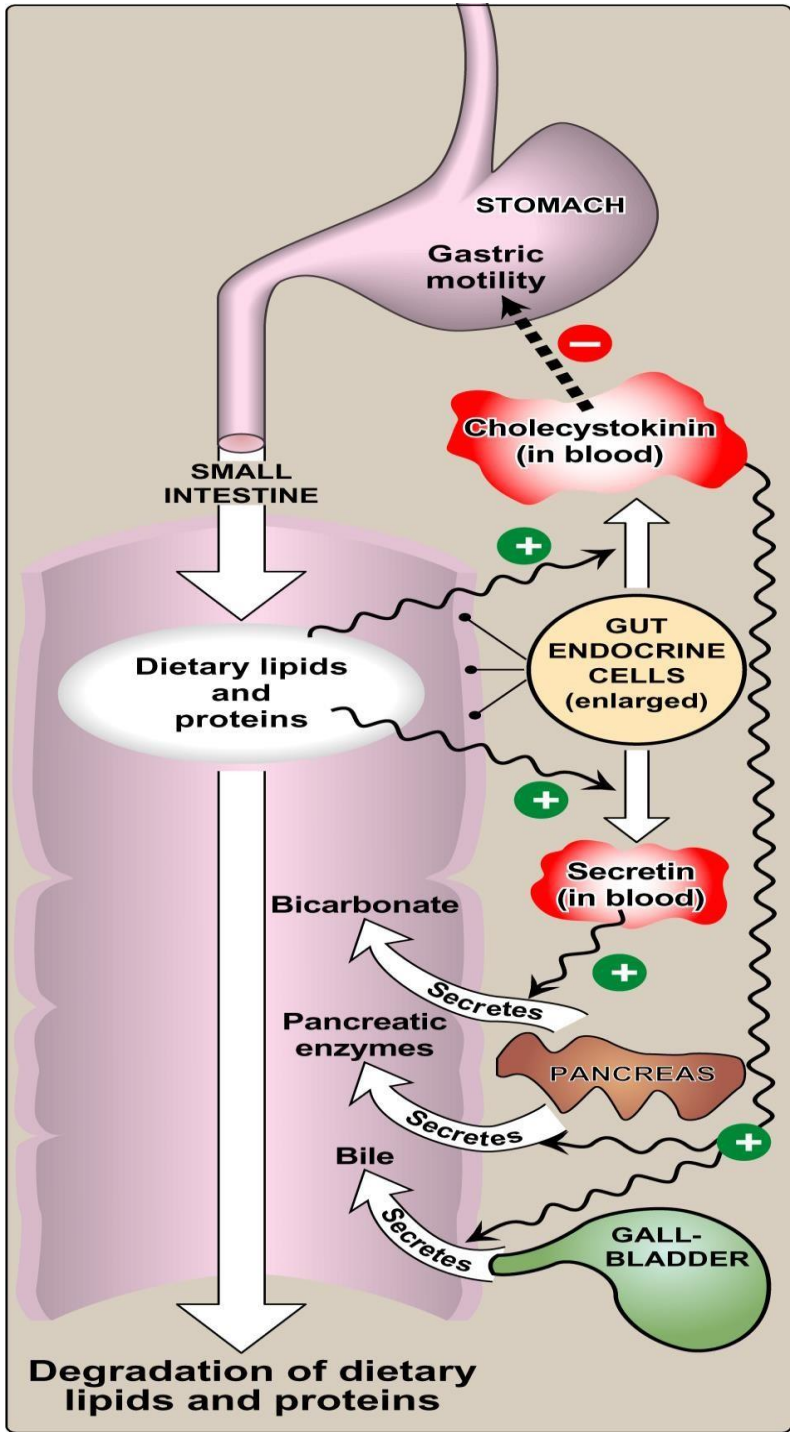
Regarding last slide:

- Phospholipids are degraded by **phospholipase A2**, an enzyme that
  - Is secreted as a proenzyme and cleaved by trypsin; gets activated.
  - Needs emulsifying bile acids and salts for its function
  - acts by hydrolyzing fatty acids on the second carbon, producing a lysophospholipid that continues the process and gets hydrolyzed by **lysophospholipase**, so the second fatty acid is stripped, producing a glycerophosphoryl base (glycerol and phosphate group associated with a head group), which has different fates:
    - excretion by feces
    - Absorption
    - further degradation to benefit from its components like glycerol, phosphate and head groups.

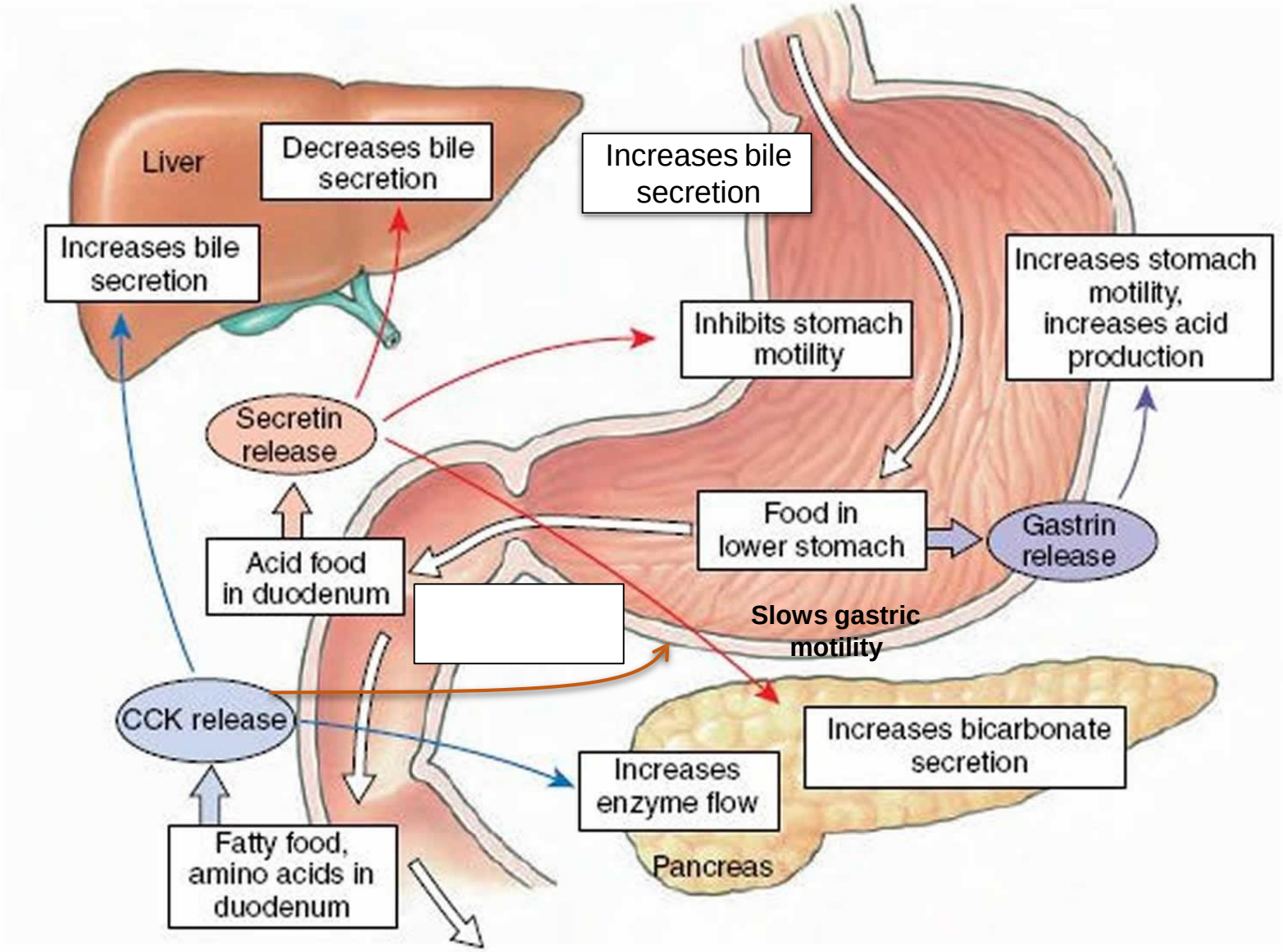
Phosphatidyl choline (lecithin) is the major phospholipid in our food.

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 Like lipase and colipase.
  - Decreases gastric motility to slow down the release of gastric contents So the release of fats is gradual and the process is more efficient, it's the reason why the digestion of fats takes a long time.
- 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.



Hormonal control

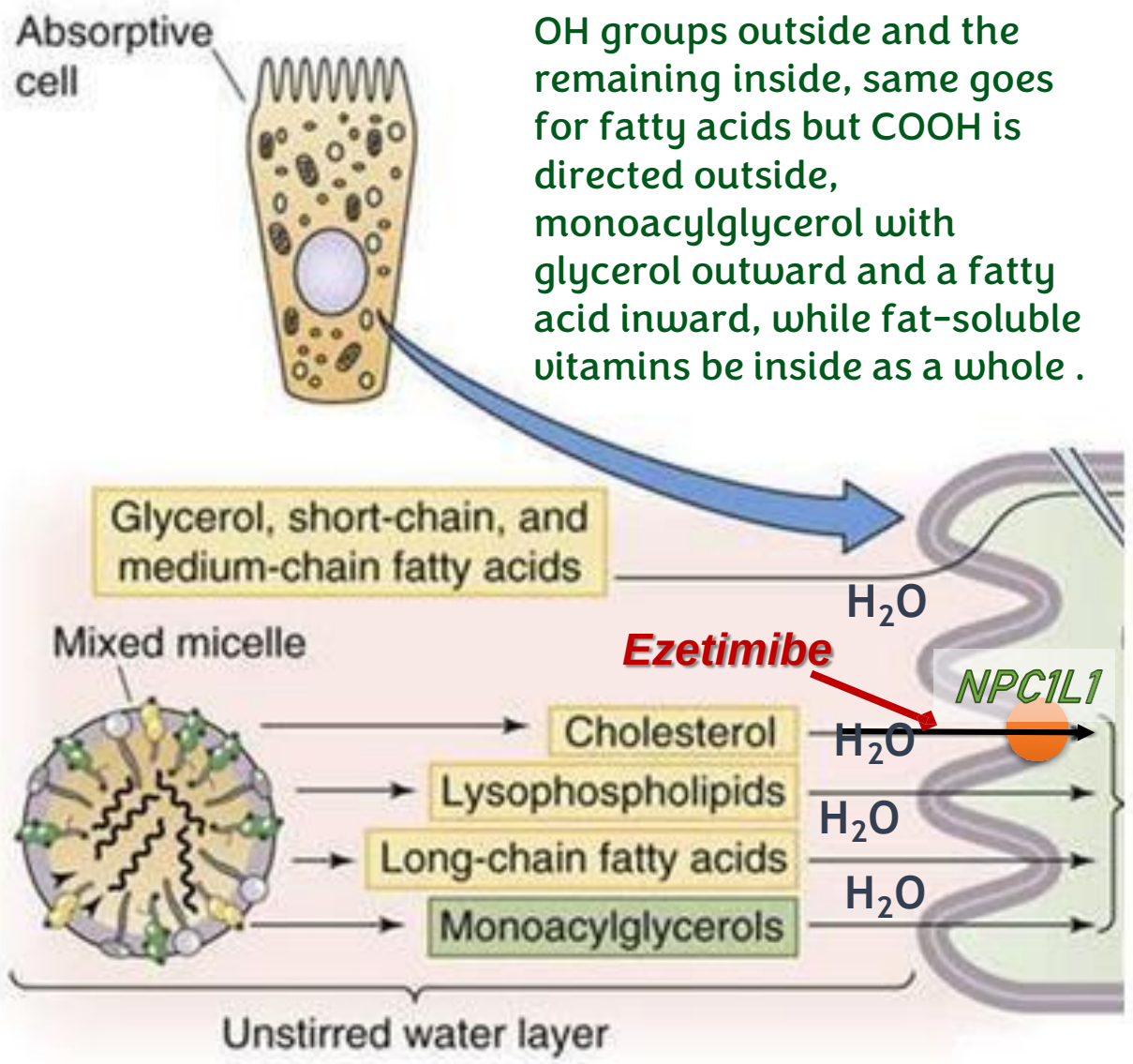


Bicarbonate is secreted by pancreas after induction by secretin, because when food is brought from stomach it's acidic which is not favored by pancreatic lipase, as a result bicarbonate works by neutralizing the acidity and creating an optimal pH.

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.

Micelles are polar outside and non-polar inside, meaning that cholesterols in it direct OH groups outside and the remaining inside, same goes for fatty acids but COOH is directed outside, monoacylglycerol with glycerol outward and a fatty acid inward, while fat-soluble vitamins be inside as a whole .

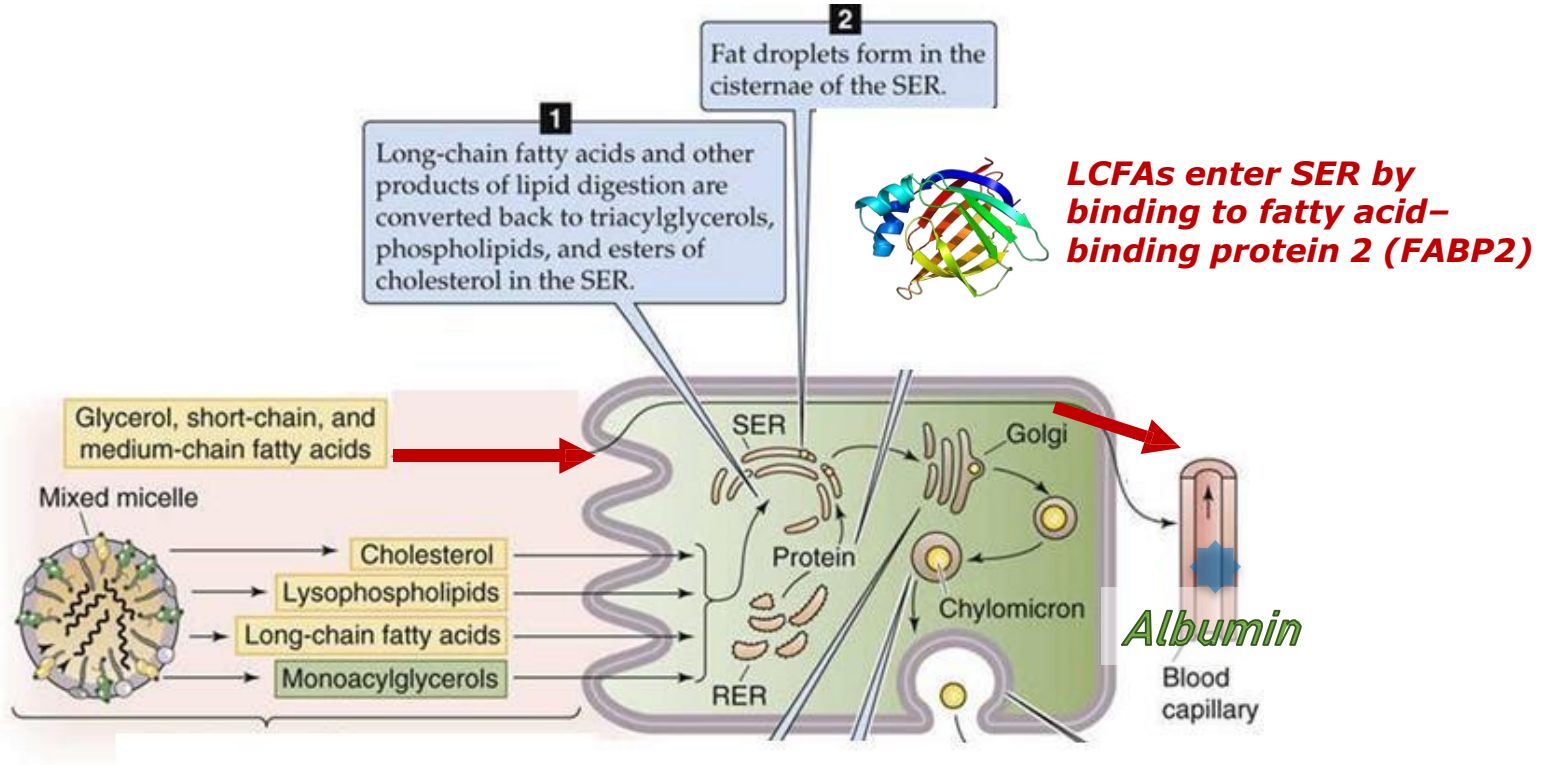


- After absorption, reverse processes are done in SER to reform complex fats (it were simplified only to permit absorption, but we need them as complex molecules to perform their biological functions in the body.

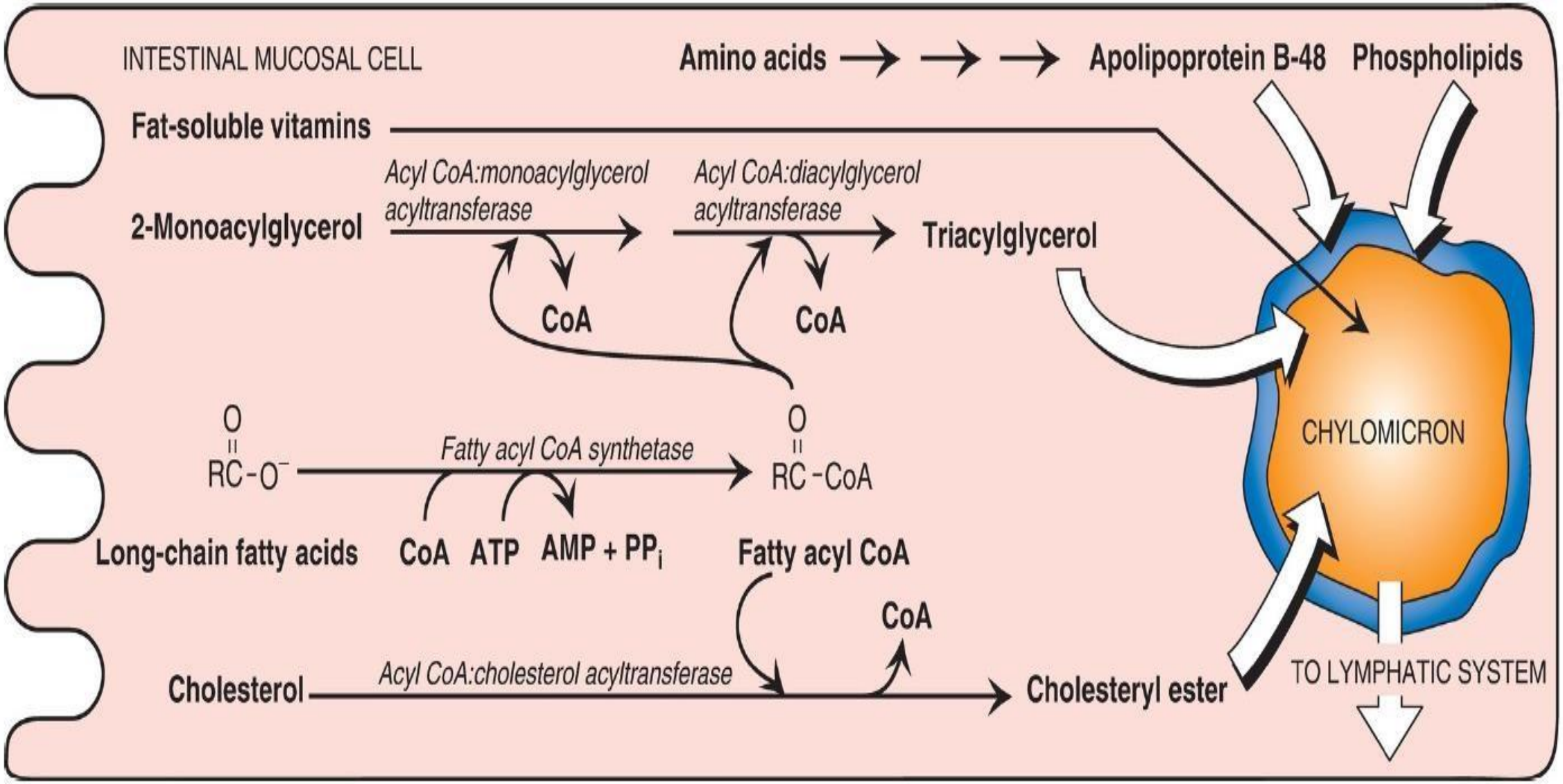
SEE next slide and focus on the synthetic pathways of cholesterol esters and TAGs.

- All of these lipids are combined to make chylomicrons, beside some proteins like apolipoprotein B48 (made at RER).
- Chylomicrons have a high percentage of TAGs and a lower one of cholesterol, and after its formation it goes to the basolateral surface going to the lymphatic system by lacteal capillary, then going to veins and entering circulation like portal circulation indirectly.

Reformation of complex lipids



YOU HAVE TO KNOW EVERYTHING ABOUT THIS FIGURE

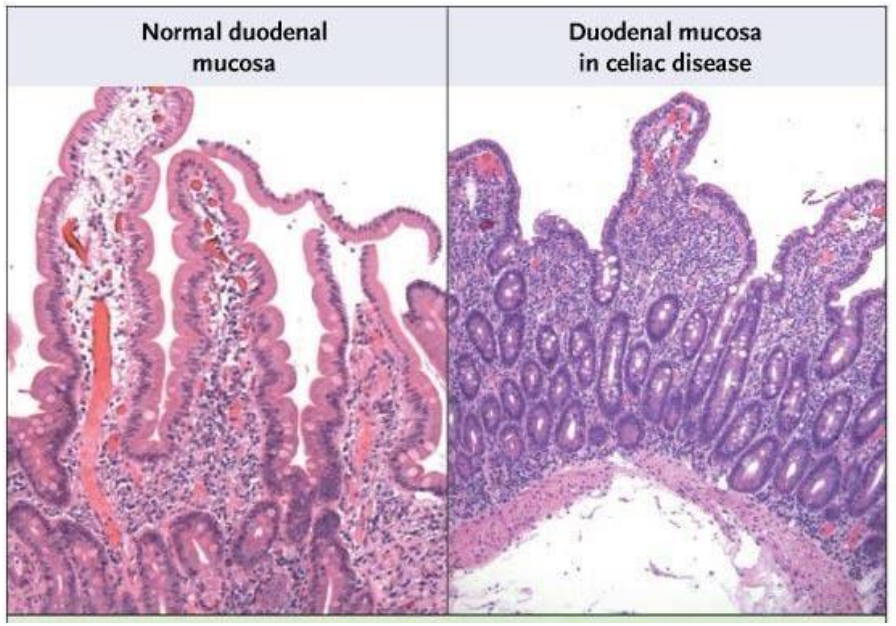


Celiac disease (CD)

- 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.

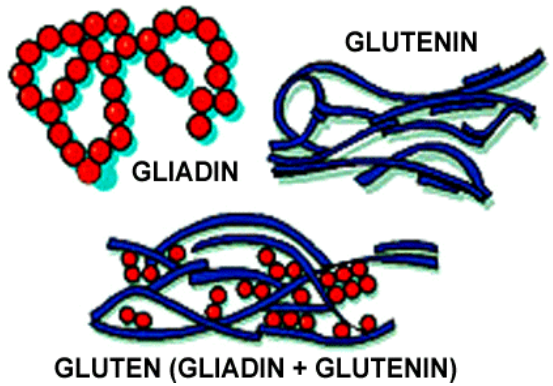
As a consequence of high proline content (relatively)

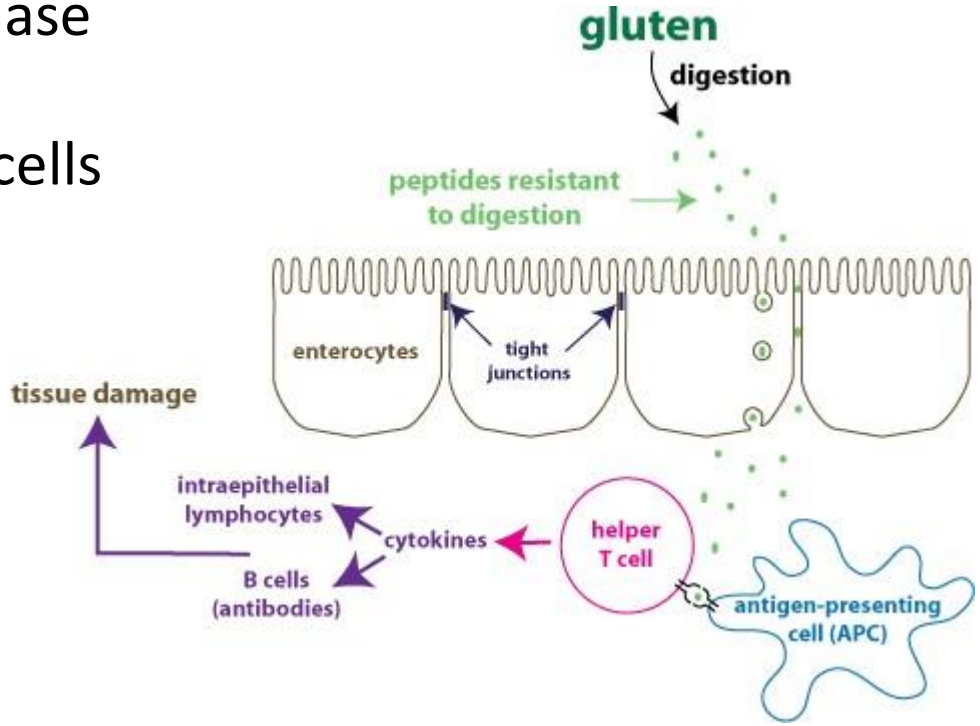
- Lab tests: the presence of anti-tissue transglutaminase (anti-tTG) antibodies.
- Tissue biopsy: absence of villous surface epithelial cells resulting in decreased nutrient absorption.



Principal causes of steatorrhea:

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

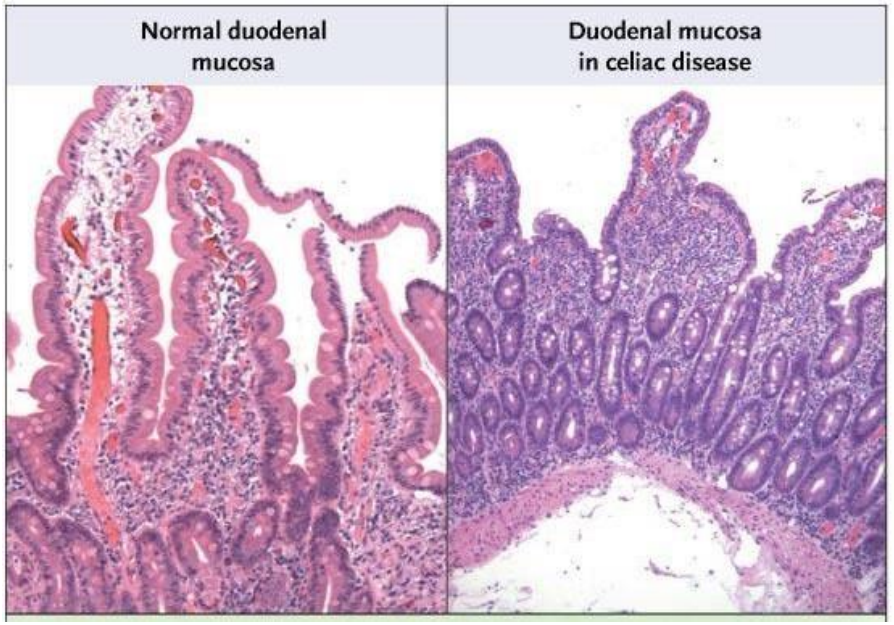




http://courses.washington.edu/pbio376/celiac/celiacdisease-376.html

Further notes

- Lipids are one of the easiest ways to detect GI digestion diseases as it's hydrophobic therefore it clusters and is visible macroscopically unlike proteins or carbohydrates.
- Lipids droplets in feces is called steatorrhea, which isn't congenital but rather an autoimmune disease.
- Gluten is composed of gliadin (high proline content) that impedes digestion.
- Gluten index is a quality indicator; the lower the better.

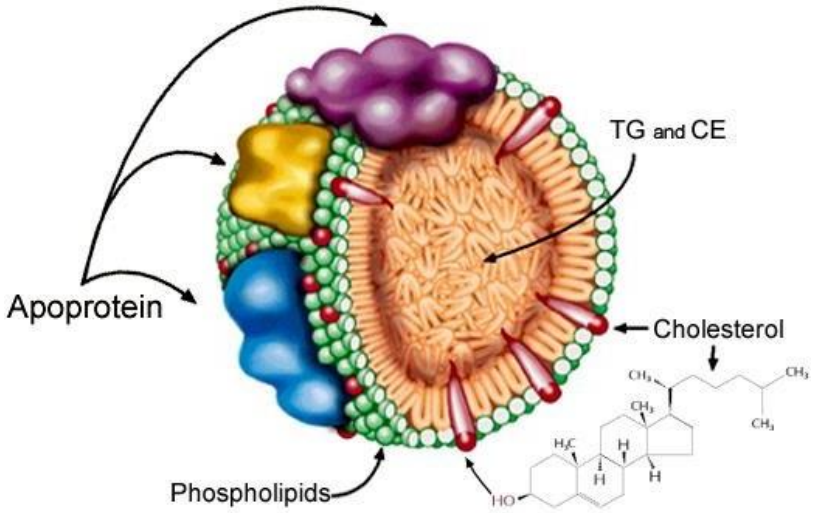


Purple color comes from inflammatory cells that invade the area, and surface area is lower due to lower cell number as a consequence of cellular damage.

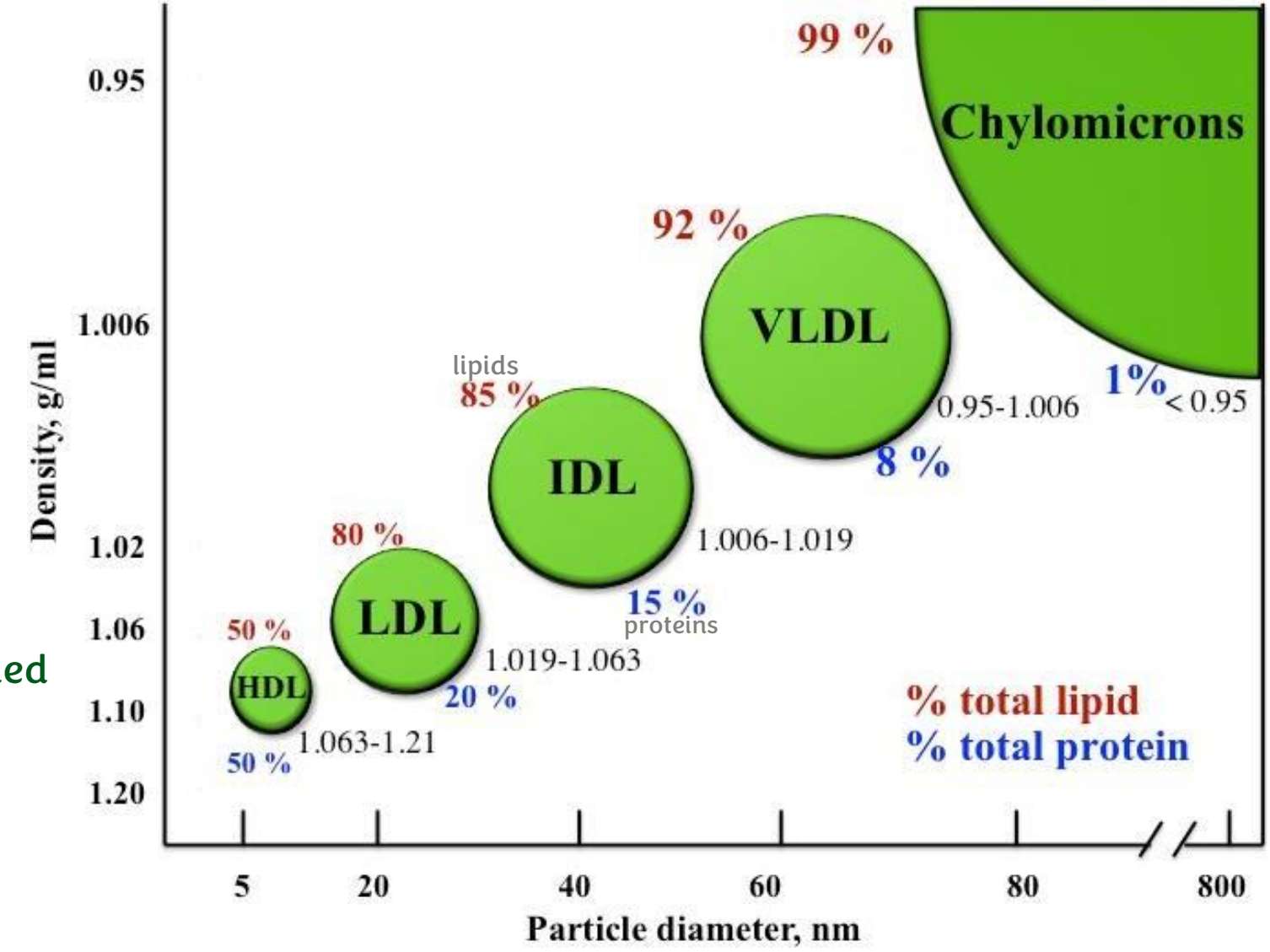
(here there is a chronic inflammation as a result of gluten allergy resulting in cellular death with time.)

Cystic fibrosis which is a congenital disease also leads to steatorrhea, it's more common in western countries especially for jews. In addition, its cause is a mutation in CFTR gene which codes for a chloride channel that affect water transport leading to thickness of exocrine secretions impeding its passage in respiratory and GI tract.

Lipoproteins



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



As lipid content increases, the density decreases

Chylomicrons are the first lipoproteins formed after the absorption process.
Due to their very high lipid content, chylomicrons have a large volume and the lowest density among lipoproteins.

These types of lipoproteins differ in the type and amount of lipids and proteins they contain, as well as in their functions.

Composition of lipoproteins

	Chylomicrons	VLDL Very low-density lipoproteins	LDL low-density lipoproteins	HDL High-density lipoproteins
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 Highest amount	55 Liver	10	6
Cholesterol esters	3	18	50 (bad)	40 (good)
Apolipoproteins	A, C, E, **B48** 1% only	C, **B100**, E 8%	B100 20%	A, C, E 50%
Function	Transport of <u>dietary</u> TAG to the liver	Transport of TAG 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)

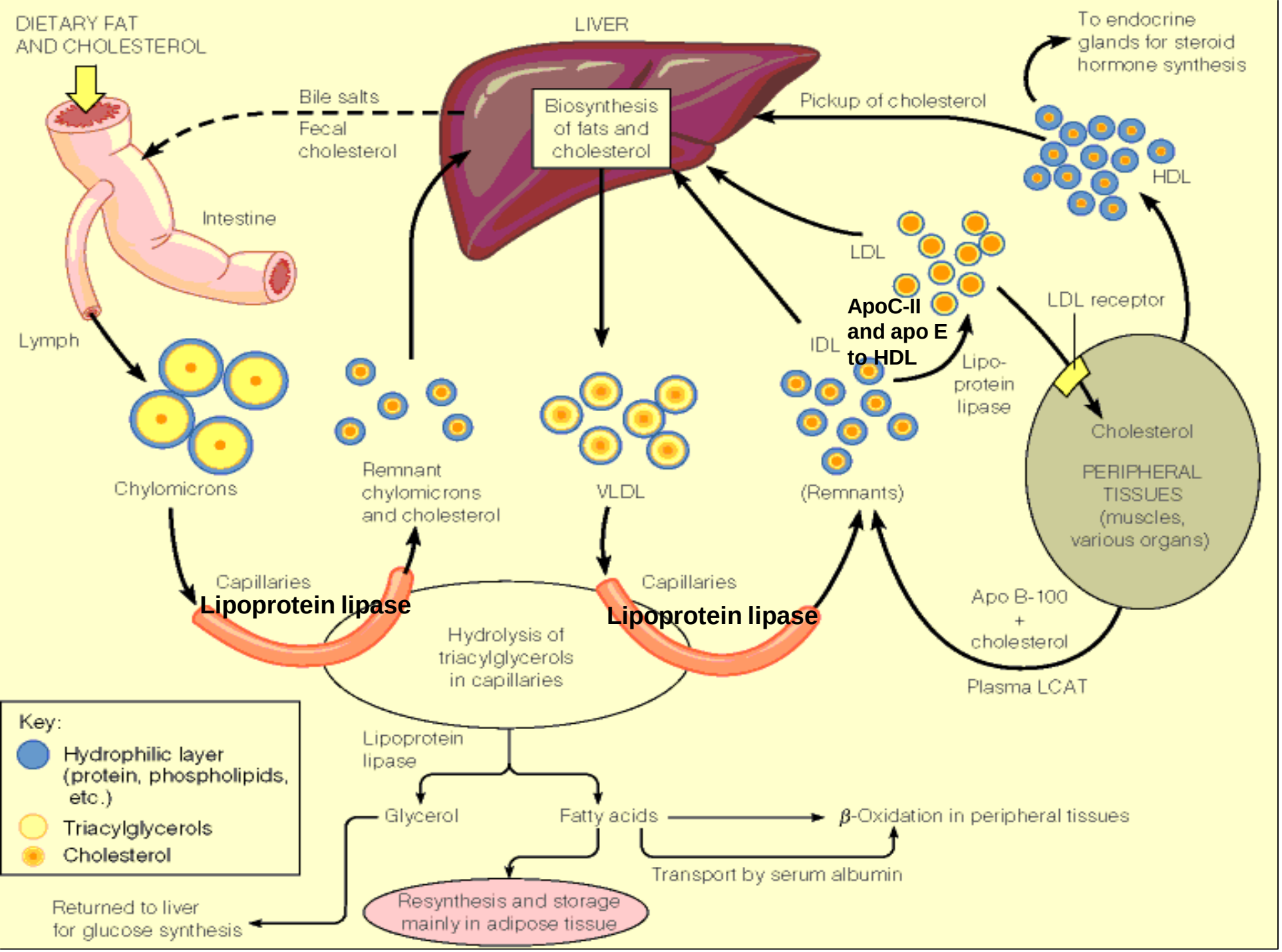
Reasons why HDL is beneficial:

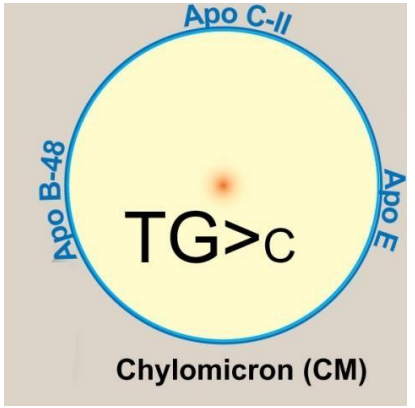
1- it contains more protein and less lipid compared to other lipoproteins.

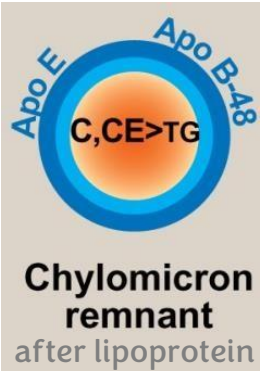
2- It facilitates the transport of lipids from peripheral tissues to the liver, where cholesterol is utilized to produce bile acids and vitamin D, reducing its levels in the body.

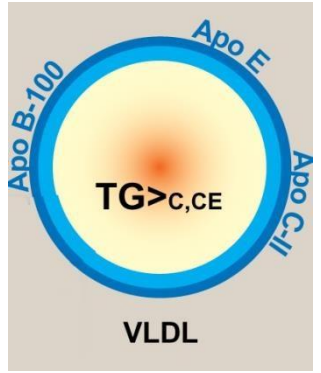
3- It transfers cholesterol to the testes and ovaries for hormone production and to the adrenal glands for cortisol synthesis.

Lipid transport



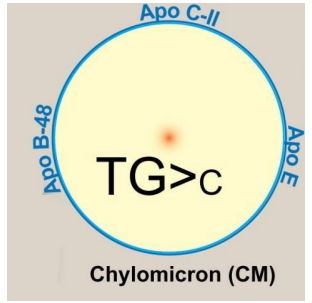




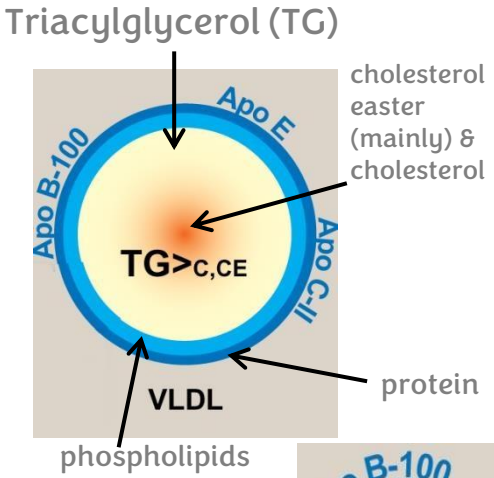


More explanation of the previous slide:

- I recommend to watch this section from the lecture min (34:35-38:36) https://youtu.be/TeM37YcCRp4?si=EpCLst4Y4I5aELuA

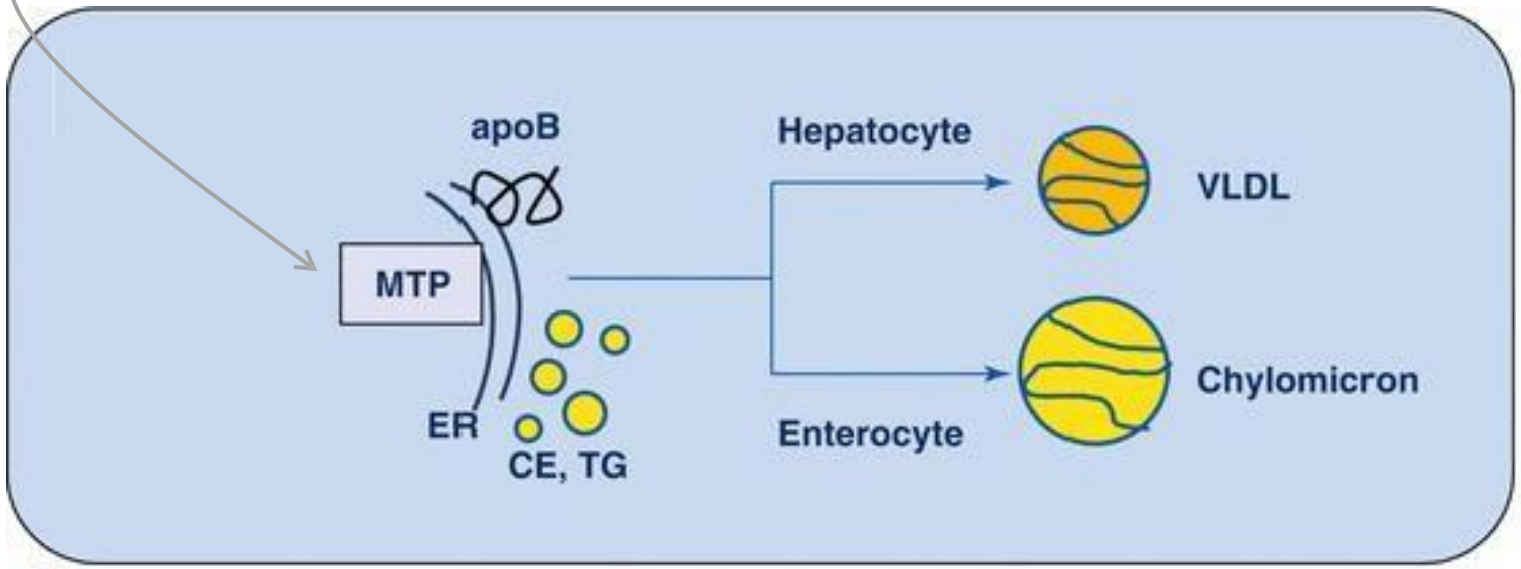


- Dietary fats enter the gastrointestinal tract (GIT) and are absorbed, leading to the formation of chylomicrons.
- During their movement through blood vessels, chylomicrons encounter **lipoprotein lipase**, a protein projected from endothelial cells into the lumen of blood vessels. Lipoprotein lipase hydrolyzes triacylglycerols, reducing their content in chylomicrons.
- The remnants chylomicrons are then taken up by the liver, which uses them to produce **(VLDL)**. As **VLDL** is transported from the liver to peripheral tissues, **lipoprotein lipase** continues to hydrolyze triglycerides, reducing their content and converting **VLDL** into **(IDL).** The apolipoproteins (apo C and E) are removed from IDL, leaving apo B-100, which results in the formation of **(LDL).** These removed apolipoproteins (C and E) are transferred to **(HDL).**
- The LDL formed is distributed to multiple cells by binding to receptors on their surfaces in peripheral tissues, while some LDL remains circulating in the bloodstream.

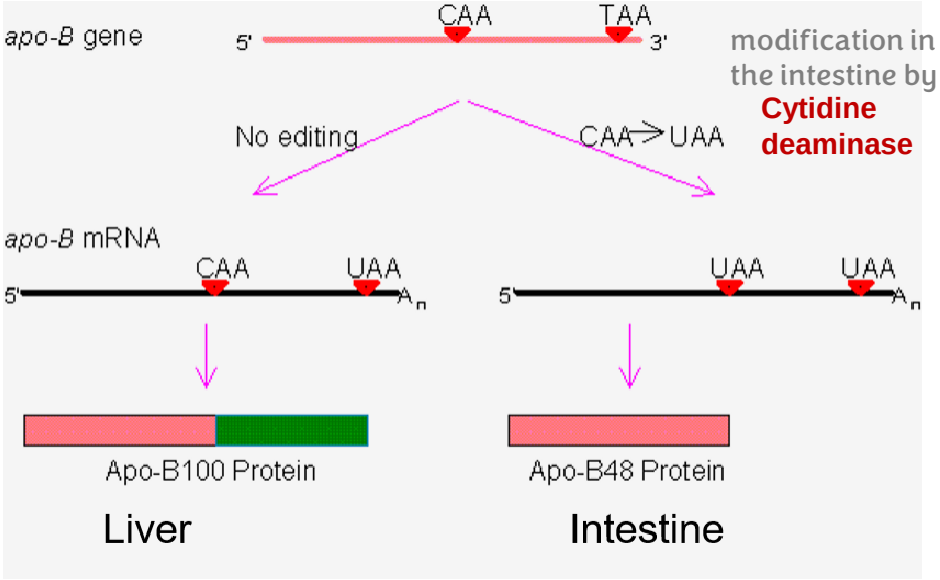


Formation and release of chylomicrons

- 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.

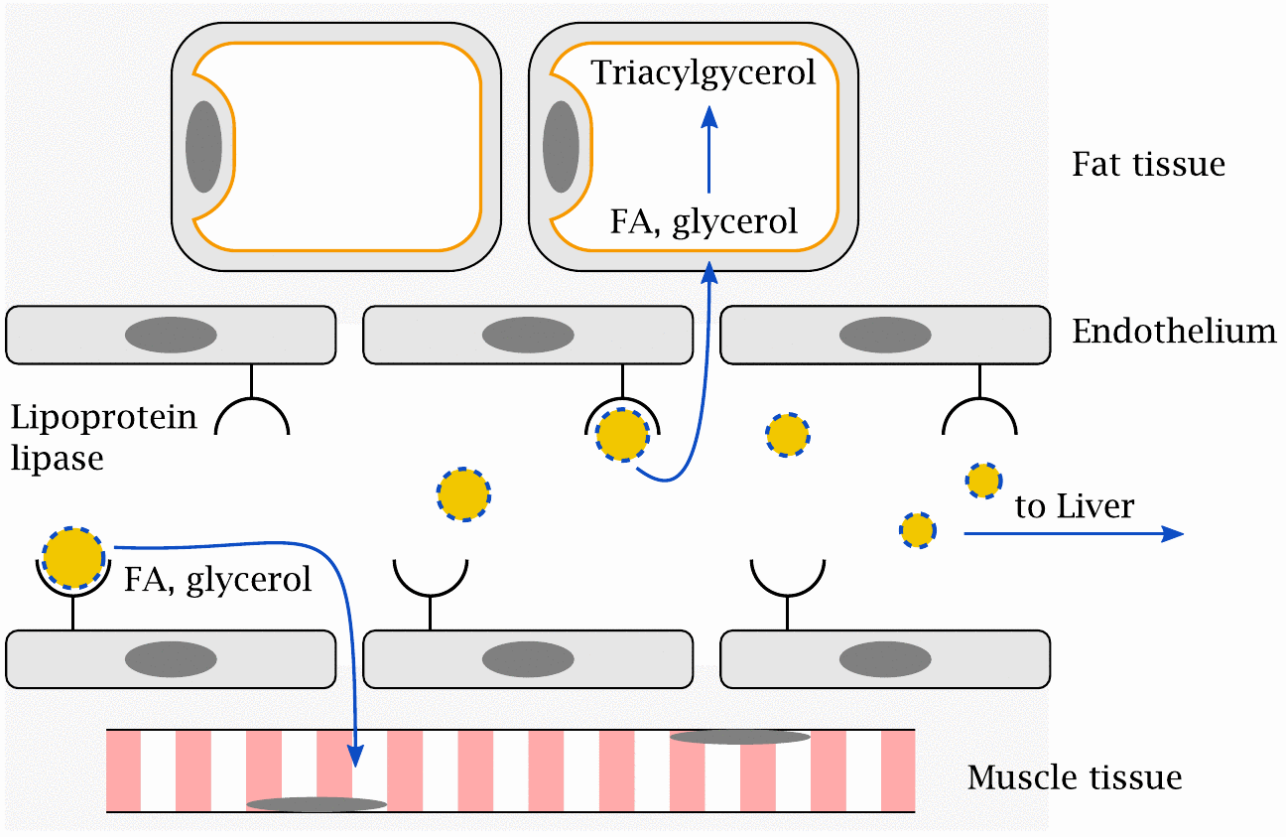


apolipoprotein B-48 and B-100 are encoded by the same gene



Cytidine deaminase functions in the intestine by removing the amino group from cytosine, converting it to uracil, which produces the UAA stop codon.

Fates of TAGs in chylomicrons



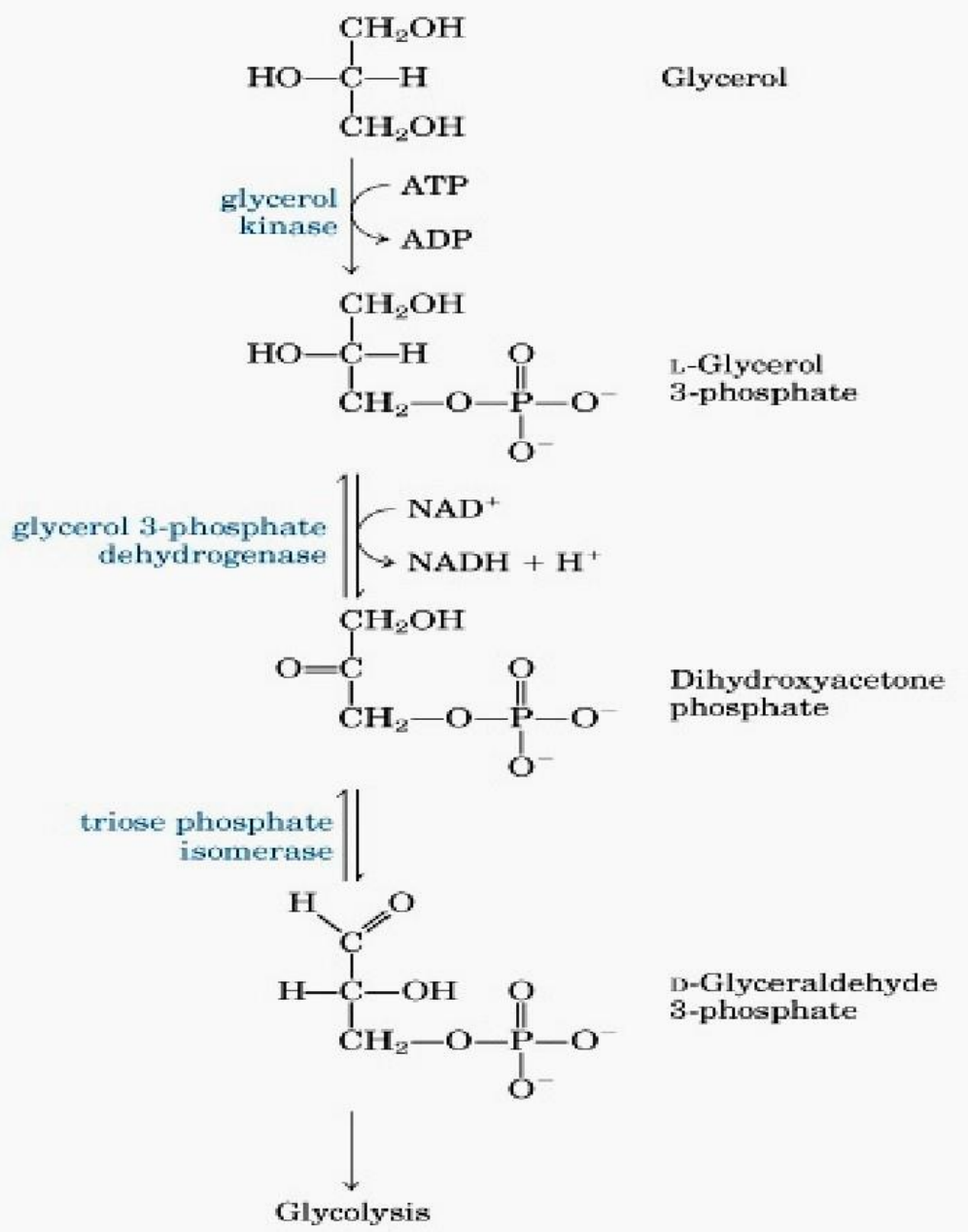
- TAGs in chylomicrons are hydrolyzed in the bloodstream by lipoprotein lipases that are anchored into the surface of endothelial cells.

- 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.

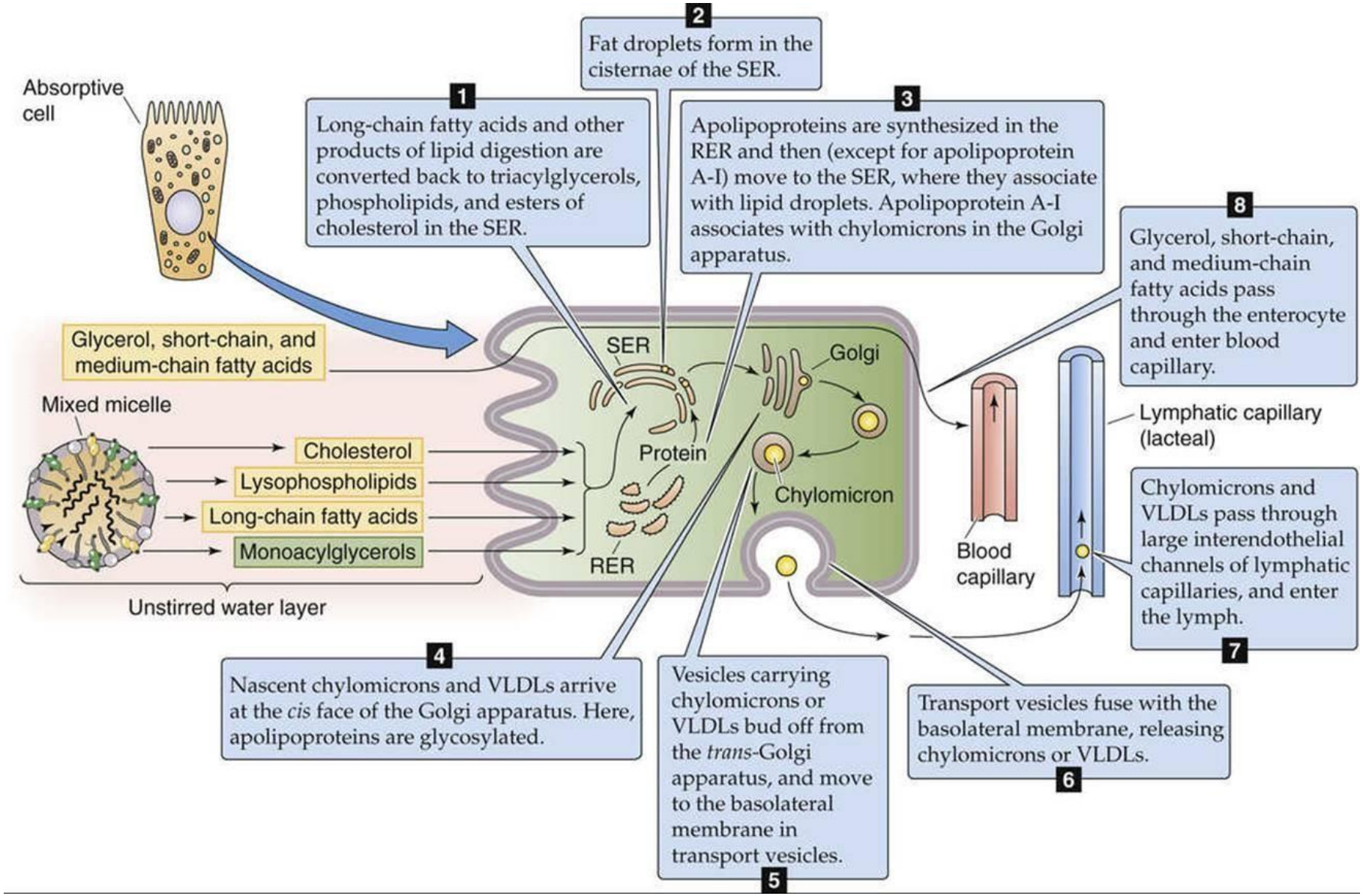
Familial chylomicronemia (type I hyperlipoproteinemia) is a rare, autosomal- recessive disorder caused by a deficiency of LPL or its coenzyme apo C-II resulting in fasting chylomicronemia and severe hypertriacylglycerolemia, which can cause pancreatitis.



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?



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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

رسالة من الفريق العلمي:

Additional Resources:

إلى زملائي الأعزاء،
قد تكون نتائج الامتحانات الأخيرة خالفت توقعاتنا وأحبطت البعض منا، ولكن دعونا نتذكر قول الله تعالى:
"وَعَسَىٰ أَن تَكْرَهُوا شَيْئًا وَهُوَ خَيْرٌ لَّكُمْ ۖ وَعَسَىٰ أَن تُحِبُّوا شَيْئًا وَهُوَ شَرٌّ لَّكُمْ ۗ وَٱللَّهُ يَعْلَمُ وَأَنتُمْ لَا تَعْلَمُونَ" *(البقرة: 216)*.

ما نمر به الآن قد يكون فرصة خفية لتحفيزنا على التعلم بشكل أعمق والعمل بجهد أكبر. أحيانًا تأتي الخيرات من حيث لا نتوقع، وحتى في العثرات يوجد دروس تصقلنا وتقوينا.

تذكروا أن هذا الامتحان مجرد خطوة صغيرة في رحلتنا الطويلة، فلا تيأسوا. القادم أفضل بإذن الله، ومع العمل والاجتهاد سندرك أحلامنا ونحقق طموحاتنا, و تذكروا أن مهمتكم ليست ورقةً تنالونها، وإنّما أمةً تحيونها.

دمتم متفائلين ومثابرين.