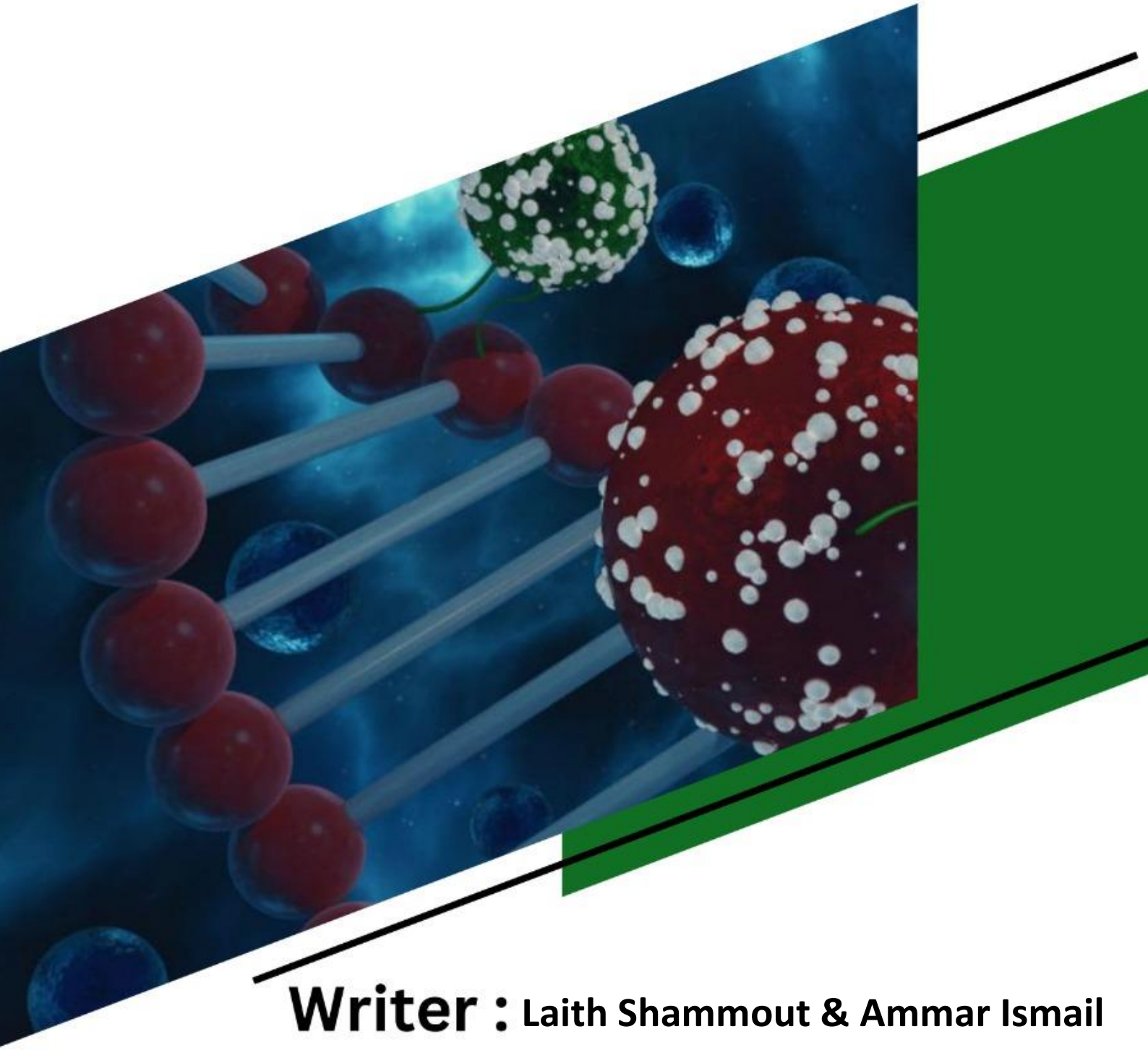
Doctor 021

METABOLISM

Sheet no. 20



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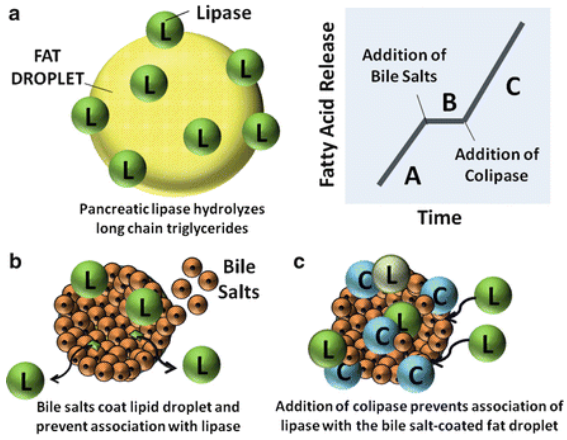
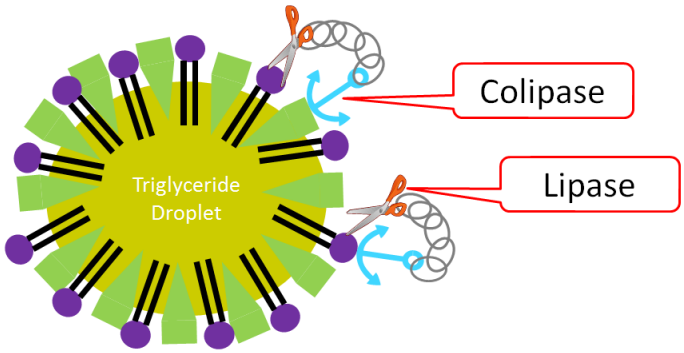
Doctor : Mamoun Ahram

METABOLISM OF LIPIDS I:
ABSORPTION AND TRANSPORT/ PART 2

THE SIGNIFICANCE OF COLIPASE

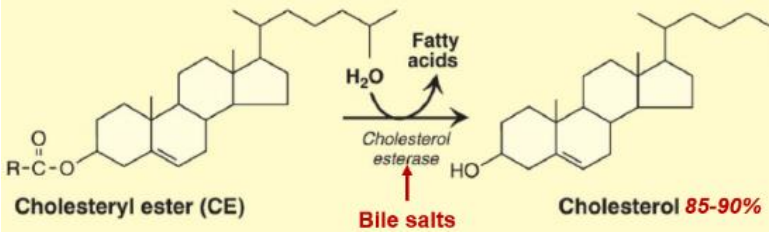




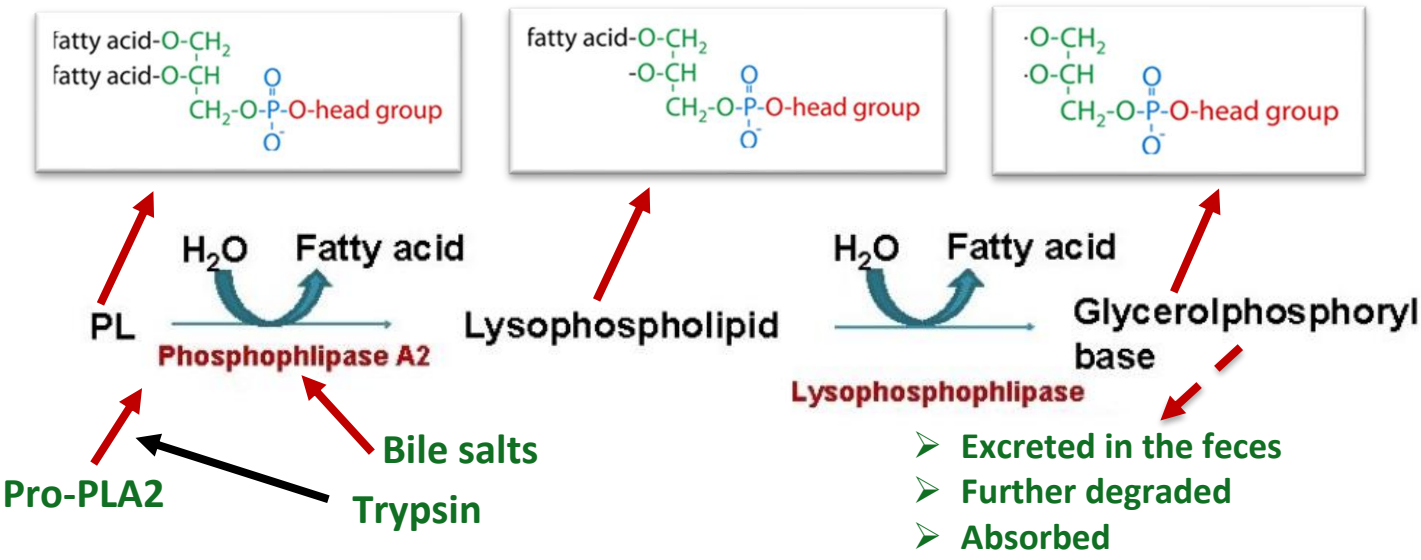
- Pancreatic lipase can't release fatty acids from TAGs because lipid molecules get encapsulated by bile salts. The enzyme then can't function on its own.
- **Pancreatic lipase is an interfacial enzyme that is most active at an oil-water interface,** meaning that it binds to bile salts, so it needs help.
- Lipase teams up with colipase, which is a small peptide that binds to bile salts and anchors lipase to them. Thus, it helps lipase to function.
- **Combined pancreatic lipase-colipase deficiency is an orphan disease.**
- Side note: orphan disease is any disease that affects only small percentage of people.
- **Colipase:**
  - **Secreted as a zymogen from the pancreas.**
  - Zymogen needs to be **activated** (cleaved) **by trypsin.**
  - **Anchors lipase into the micelle interface at a ratio of 1:1.**
  - **Restores activity of lipase against inhibitors.**

DEGRADATION BY PANCREATIC ENZYMES
1- DEGRADATION OF CHOLESTERYL ESTER

- Cholesterol esterase is activated by bile salts.
- Cholesteryl ester: cholesterol with fatty acids.
- Most of the cholesterol is free in intestines.



2- DEGRADATION OF PHOSPHOLIPIDS



- Phospholipase A2 is secreted as zymogen "Pro-PLA1". It is activated by trypsin and bile salts.
  1. **PLA2** releases **one** FA from carbon no. 2 to give lysophospholipid.
  2. **Lysophospholipase** releases **one** FA from carbon no. 1 to give glycerolphosphoryl base (glycerol with only one phosphate).

HORMONAL CONTROL

- When chyme (food) reaches the **stomach**, it stimulates it to release **gastrin** which increases the stomach motility, acid and trypsin secretion.

- When it reaches **intestine**, it stimulates releasing of two hormones:

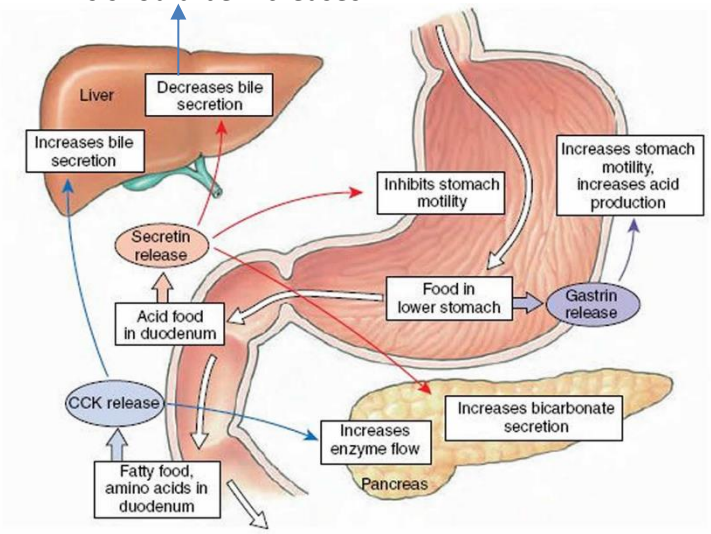
  1. CCK

  - Stomach: motility ↓
  - Liver: bile salts ↑
  - Pancreas: enzyme flow ↑

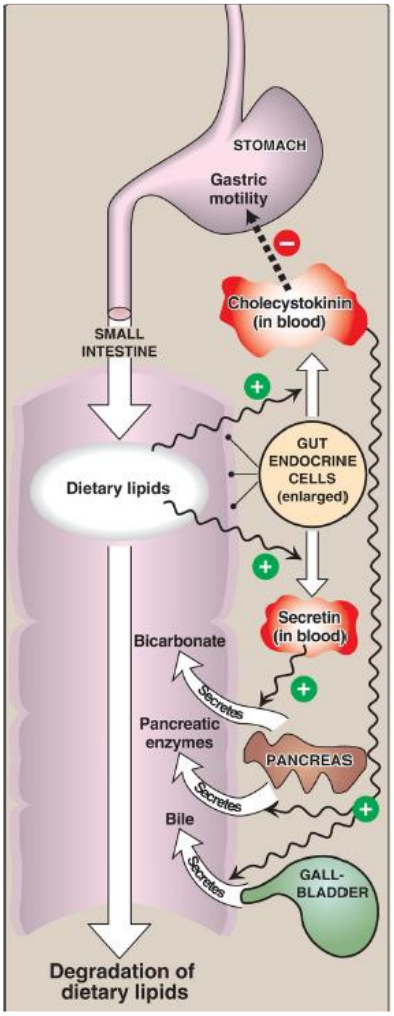
  2. Followed by **Secretin**

  - Stomach: motility ↓
  - Liver: bile salts ↑
  - Pancreas: bicarbonate ↑

This should be increases

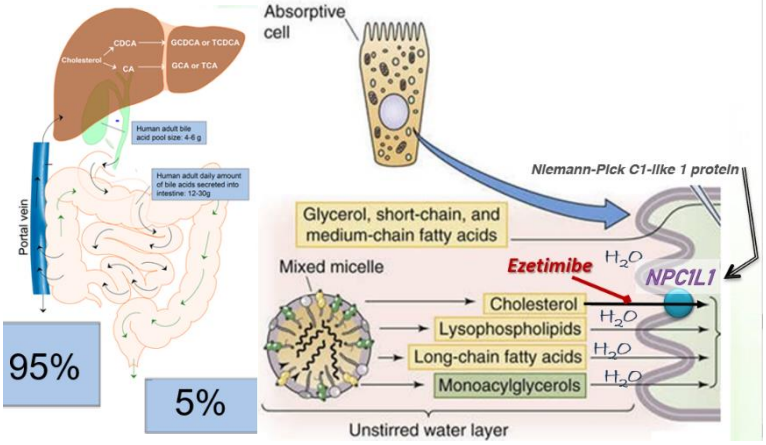


- **Entry of food (chyme) induces the release cholecystokinin (CCK; a peptide hormone) from the duodenum and jejunum.**
  - **Induces contraction of the gallbladder to release bile (bile salts, phospholipids, and free cholesterol).**
  - **Acts on the exocrine pancreatic cells to release digestive enzymes.**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

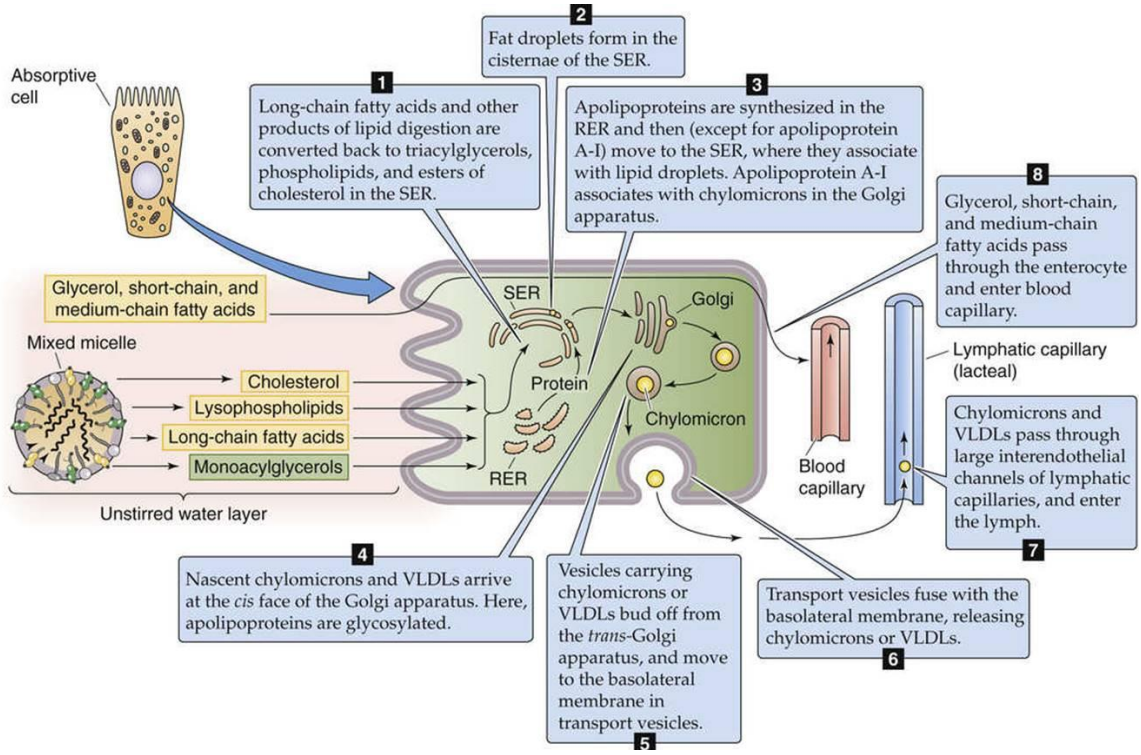


ABSORPTION BY ENTEROCYTES

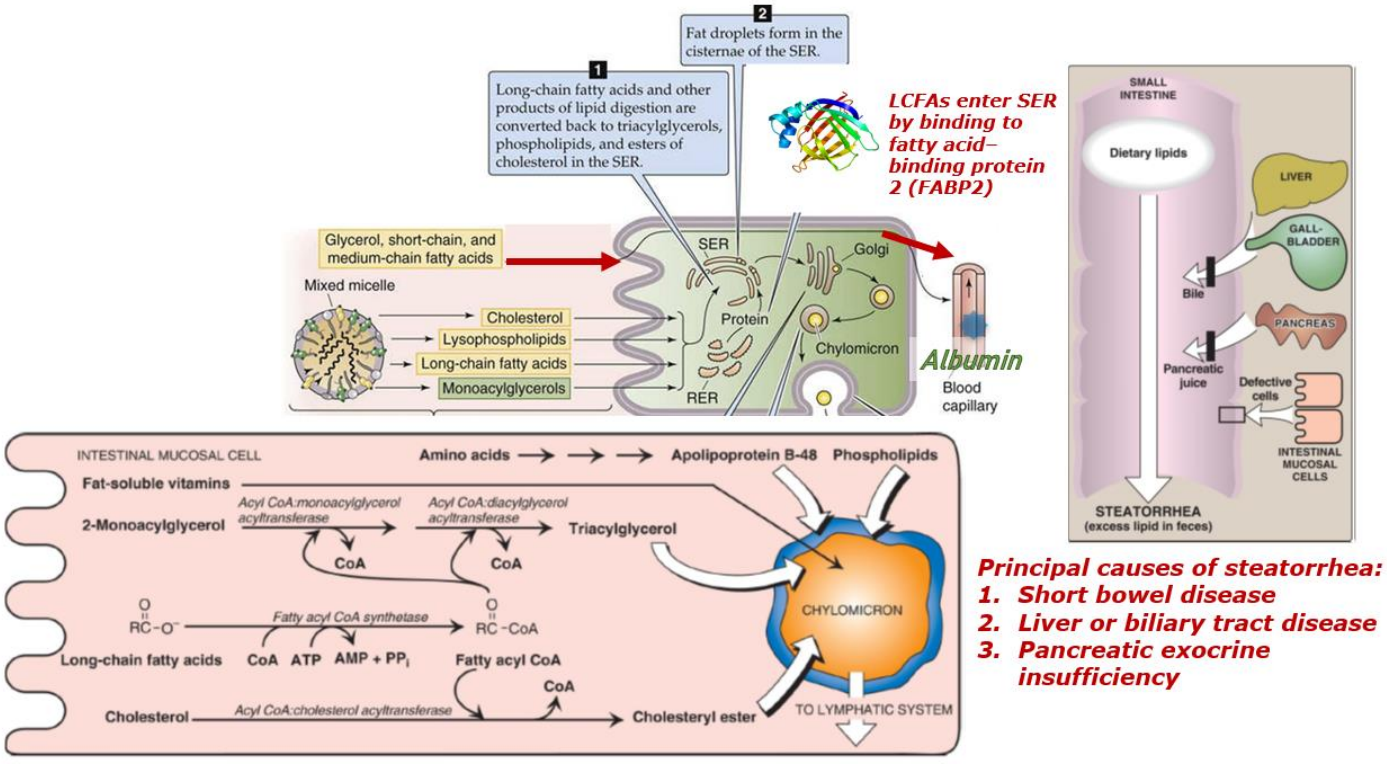
- **Mixed micelles are formed in the lumen from free fatty acids (FFA), monoacylglycerol, free cholesterol, bile salts, and fat-soluble vitamins.**
- **Cholesterol is poorly absorbed.**
  - **Note:** NPC1L1 (Nlemman-Pick C1-like 1 protein 'it's a carrier') **can be drug targeted** by **ezetimibe**, which lowers the absorption of cholesterol.
- **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 by passive diffusion** to the blood.



- Glycerol is moved to the blood directly too.
- 95% of bile salts are reabsorbed while 5% are excreted as feces.



REFORMATION OF COMPLEX LIPIDS



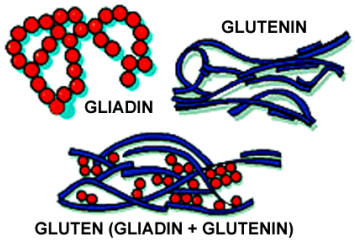
Principal causes of steatorrhea:

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

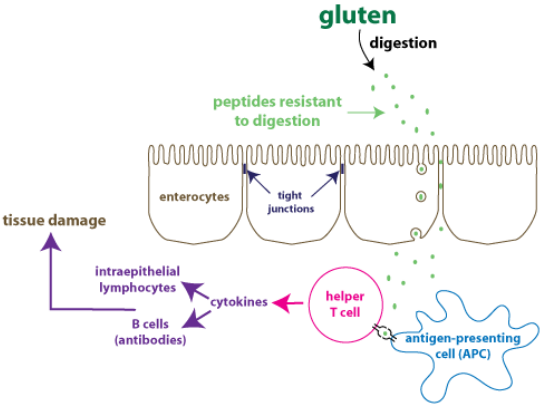
- **LCFAs enter SER by binding to fatty acid–binding protein 2 (FABP2),** LCFAs can:
  - **Forming TAG:** by acyltransferase, that attaches FAs to the free two carbons of MAG in a sequential manner, forming DAG, then TAG.
  - **Forming phospholipids.**
  - **Forming cholesteryl esters.**
- All the above are packed in chylomicrons.

- **Principal causes of steatorrhea** (too much fat in feces):
  1. **Short bowel disease** "having a short intestine; deficient absorption".
  2. **Liver or biliary tract disease** "deficiency in bile salts secretion".
  3. **Pancreatic exocrine insufficiency** "deficiency in pancreatic enzyme secretion".

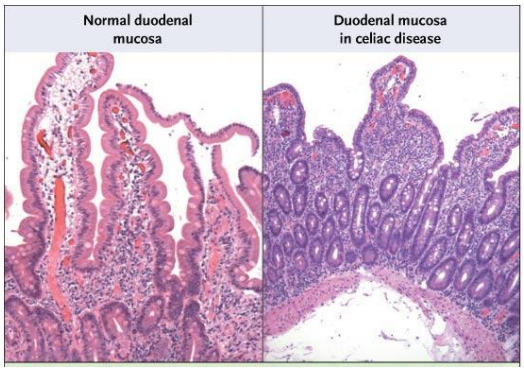
CELIAC DISEASE (CD)



- **It is an autoimmune response to gliadin, a peptide found in gluten (wheat, rye, and barley).**
- It causes **fat malabsorption leading to steatorrhea.**
- Wheat contains gluten, which is made of two peptides: gliadin and glutenin.
- **Gliadin contains many proline (14%) and glutamine (40%) residues, making it resistant to digestion.**

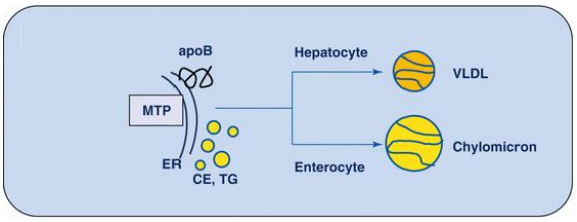


- Proline impairs cleaving by digestive enzymes, so gliadin can't be digested.
- **Lab tests: the presence of anti-tissue transglutaminase (anti-tTG) antibodies.**
- People with this disease form antibodies against gliadin, that damage intestine tissue.
- Gluten-free products are recommended to people with CD.
- **Tissue biopsy: absence of villous surface epithelial cells resulting in decreased nutrient absorption.**

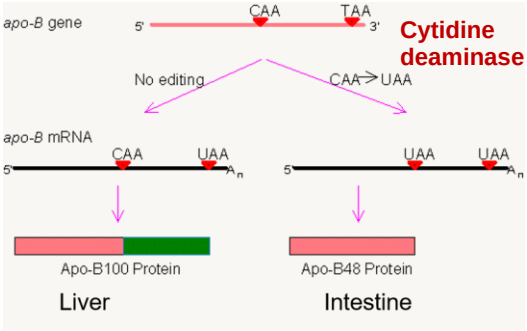


FORMATION AND RELEASE OF CHYLOMICRONS

- **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.**



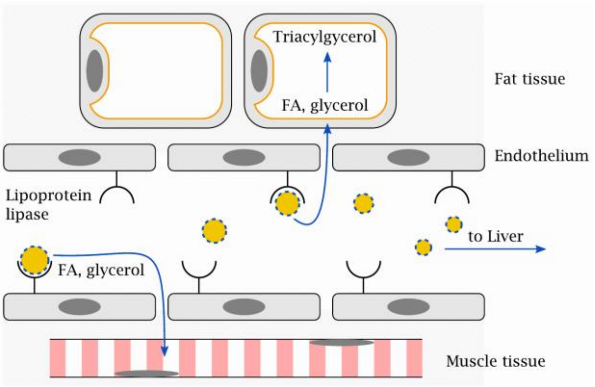
- Chylomicrons are synthesized inside intestinal cells by MTP.
- Apolipoprotein gene can be translated to make two proteins; B-100 and B-48 (the numbers stand for the molecular weight of each in kDa).
- The gene is transcribed into mRNA, this mRNA is modified in intestines by **cytidine deaminase**, it converts a C to U, leaving the mRNA with a UAA (a stop codon), so the intestine's copy is shorter than the liver's.



- B-100 is used in VLDL, while B-48 is used in chylomicrons.
- These chylomicrons are released into the lymphatic capillary.

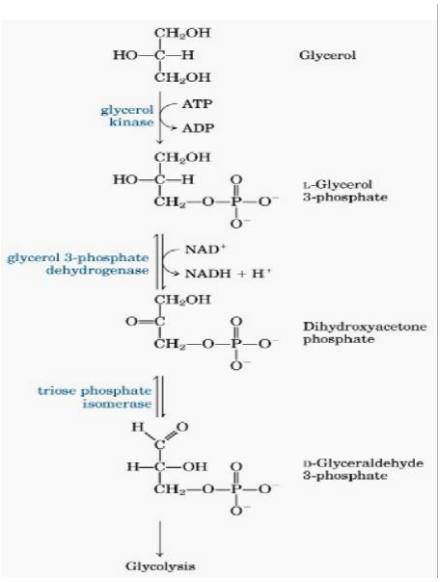
FATES OF TAGS IN CHYLOMICRONS

- Side note: after the lipids are done with the GI tract, they will be moved to the liver by capillaries.
- **TAGs in chylomicrons are hydrolyzed in the bloodstream by lipoprotein lipases that are anchored into the surface of endothelial cells.**



- Lipoprotein lipases (LPLs) only work on lipoproteins' lipids, not other lipids.
- **The resulting fatty acids have two possible fates:**
  - **When energy is in good supply, they are converted back to TAGs for storage in adipose tissues.**
  - **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** (high level of TAG in blood)**, which can cause pancreatitis.**
- This disease leads to deficiency in the formation of chylomicrons.
- Now, fatty acids are released from TAG, what about the glycerol?

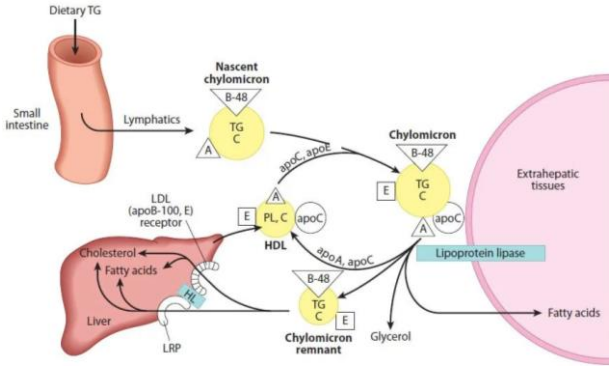
FATE OF GLYCEROL



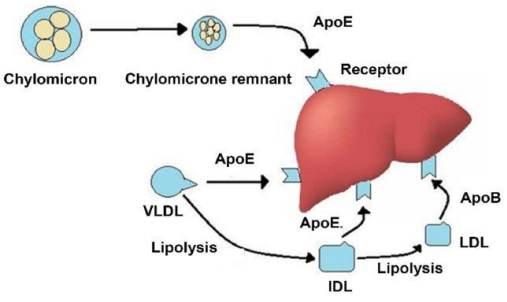
- **Glycerol is carried in the bloodstream to the liver or kidneys, where it is phosphorylated and then converted to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (DHAP) for either glycolysis or gluconeogenesis or synthesis of TAG** (depending on cell need).
- Glycerol is hydrophilic, it can move on its own in the blood and can enter cells.

FATE OF CHYLOMICRONS

- **When TAGs are removed, chylomicron remnants would contain cholesteryl esters, phospholipids, apolipoproteins, fat-soluble vitamins, and a small amount of TAG).**



- Chylomicrons are initially equipped with two proteins: **apoA** and **B-48**. As they move in the blood, they get **apoC** and **apoE** attached.
- **ApoC** is an activator for **LPL**.
- Chylomicrons, when finally drop off their TAGs and fatty acids, they cast away **apoC** and **apoA**. It's, therefore, a chylomicron remnant, with only **B-48** and **apoE**.
- **ApoE receptor exists in the liver, skeletal muscles, and adipose tissues.**
- **Chylomicron remnants bind to apoE receptors via their apoE and are endocytosed** (receptor-mediated endocytosis).



- **The intracellular remnants are hydrolyzed to their component parts** by releasing out cholesterol and proteins to be recycled.
- **Type III hyperlipoproteinemia: mutations in apoE gene leading to decreased clearance of chylomicron remnants.**

مَتى يَستَرِيحُ القَلبُ إِمّا مُجاوِرٌ حَزِينٌ وَإِمّا نازِحٌ يَتَذَكَّرُ

يَقولونَ كَم تَجري مَدامِعُ عَينِهِ لَها الدَهرَ دَمعٌ واكِفٌ يَتَحَدَّرُ

وَلَيسَ الَّذي يَجري مِنَ العَينِ ماؤُها وَلَكِنَّها نَفسٌ تَذوبُ وَتَقطُرُ

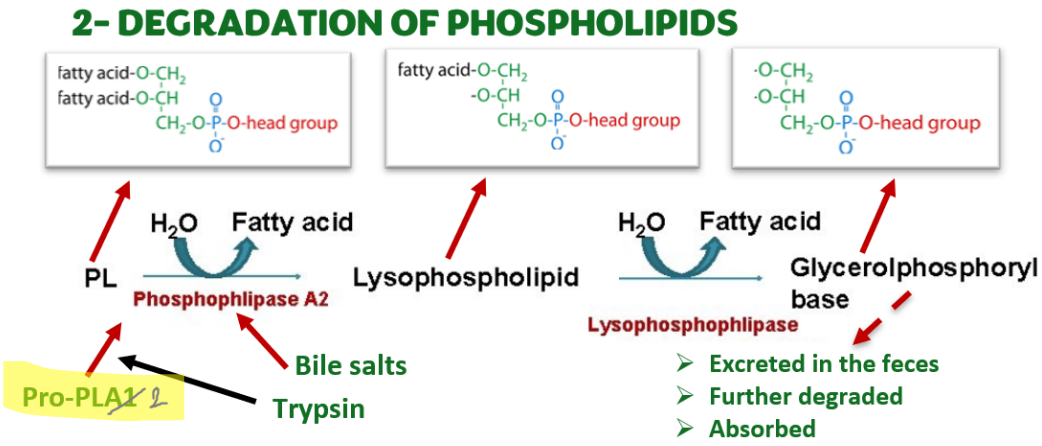
V2

- In V1, page 3, the picture in the slides is wrong, the doctor confirmed this.

2. Followed by **Secretin**

- Stomach: motility ↓
- Liver: bile salts ↓ **(this should be ↑ instead)**
- Pancreas: bicarbonate ↑

V3



This should be Pro-PLA2 instead.