Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

BIOCHEMICAL ASPECTS OF DIGESTION OF LIPIDS.

* Please check out this link to know if there are any changes or additions.

Revised by
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Color index: Important | Doctors notes | Further explanation.

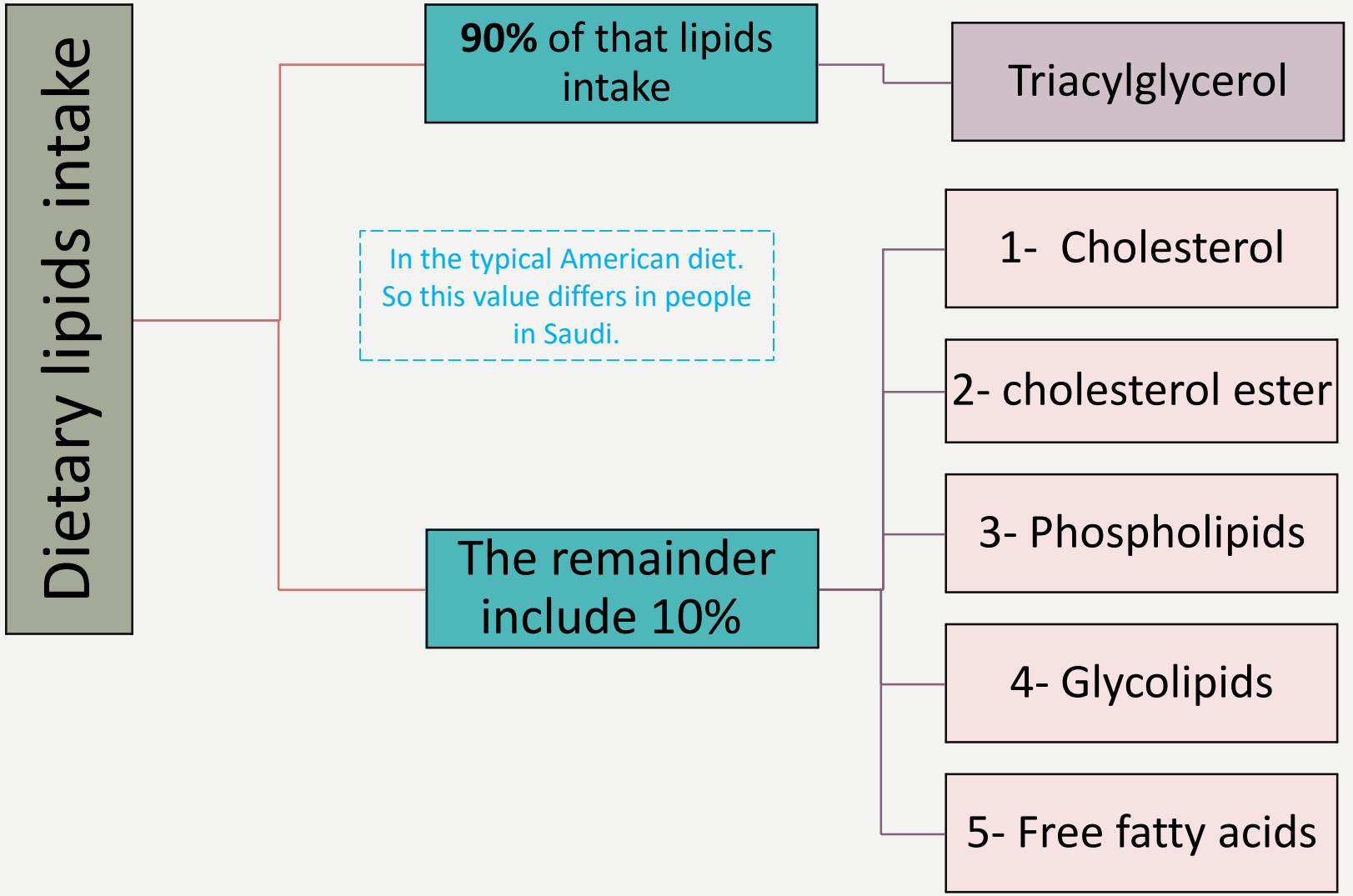
OBJECTIVES:

By the end of this lecture, the student should be able to understand:

- the process of digestion of dietary lipids including, the organs involved, the enzymes required, and the end products.
- the assembly (synthesis), metabolism and fate of chylomicrons.
- the clinical manifestations of diseases that involve defective lipid digestion and/or absorption (maldigestion and malabsorption syndromes).

Lipid Digestion

Dietary lipids intake is about 81 g/day.



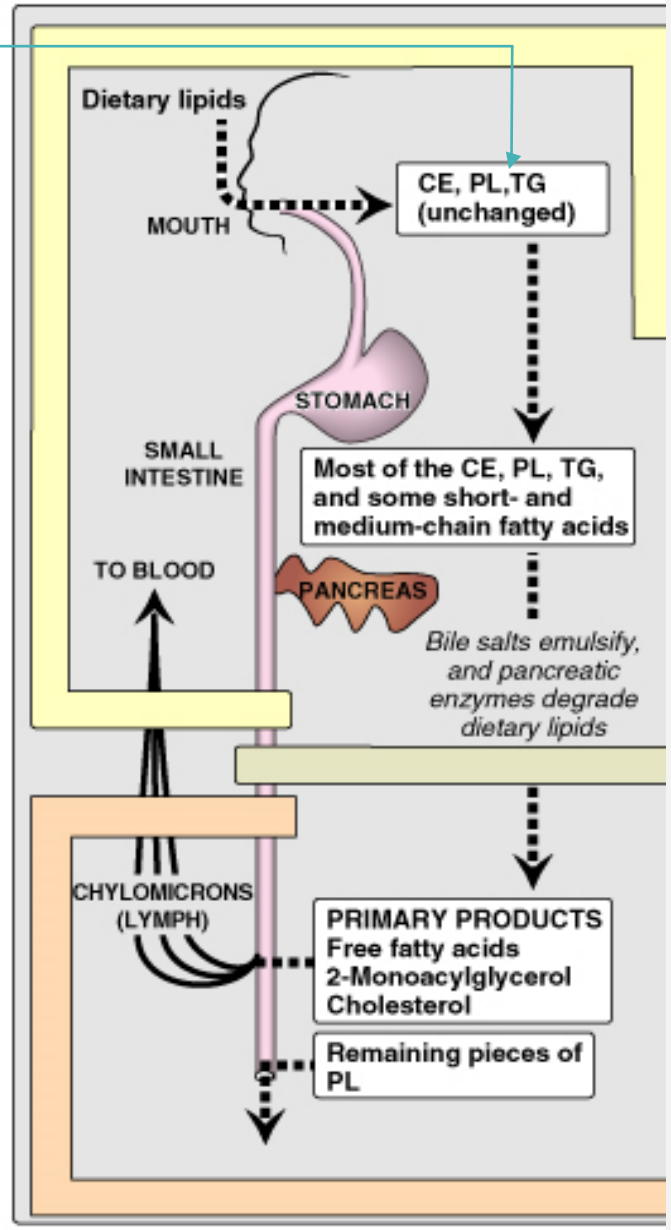
Lipid Digestion

"unchanged" here means partially digested.

Lipid digestion: organs and enzymes			
Site	Stomach (30% of digestion)		Small Intestines (70% of digestion)
Enzymes	**Lingual lipase**	**Gastric lipase**	Pancreatic enzymes "come from the pancreas" : 1- Lipase & co-lipase 2- Cholesterol esterase 3- Phospholipase A2 4- Lysophospholipase

Note that lingual lipase is produced at the back of the mouth BUT ACTS IN THE STOMACH!
Why doesn't this enzyme act in the mouth?
Because the pH optimum of this enzyme is the similar to the pH of the stomach

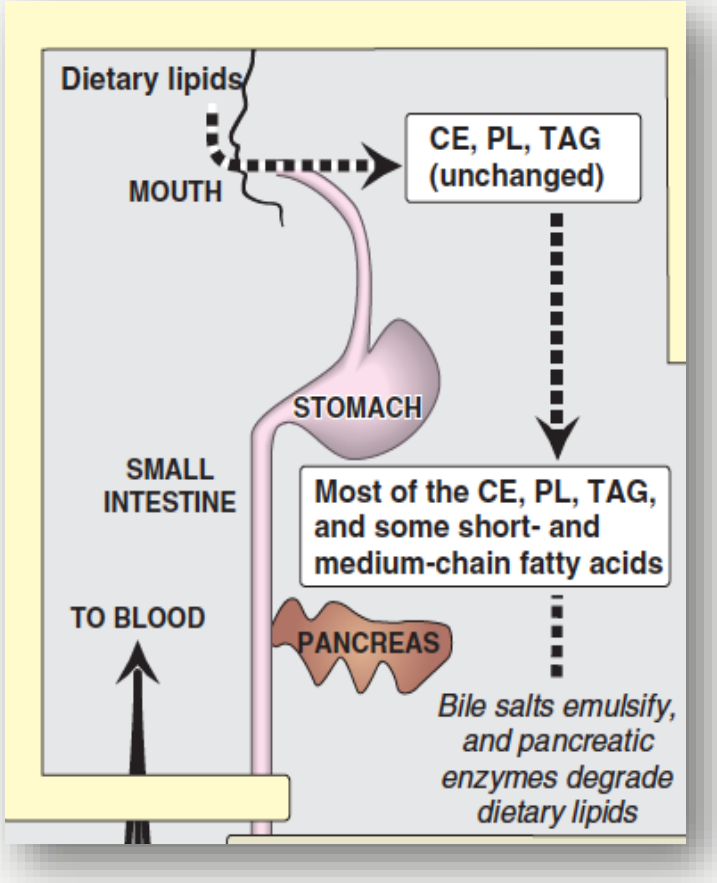
All of these enzymes will be explained in this lecture



Lipid digestion & absorption in the intestines (3:43)

1-Lipid Digestion in the stomach

Enzymes:	1- Lingual lipase:	2- Gastric lipase:
	Secreted under the tongue.	Secreted by the gastric mucosa.
Substrate:	Triacylglycerols (**TAGs**), particularly those containing fatty acids of short- or medium-chain length "such as found in milk".	
How they act on the substrate?	By **hydrolysis**.	
Important in:	1- **Neonates** for lipid "milk" digestion. 2- Patients with pancreatic insufficiency.	



Dr. Sumbul's explanation:

Cholesterol esters and **phospholipids**, **triacylglycerols** enter the mouth, and remain UNCHANGED!

These substances then go to the stomach and are acted upon by **gastric lipase** and **lingual lipase**:

So the following substances are found: still most of **cholesterol esters**, **TAG** ,**phospholipids** WITH some short and medium chain fatty acids.

Once these substances enter the small intestines, and the pancreas releases its digestive enzymes, and the gallbladder secretes bile (which are composed of bile salts).

These bile salts are required for the **emulsification** of the dietary lipids so that the enzymes are able to break them down.

2-Lipid Digestion in the small intestine

Digestion of lipids is preceded by a process called: **emulsification.**

Occurs in the duodenum

Increases surface area of lipid droplets

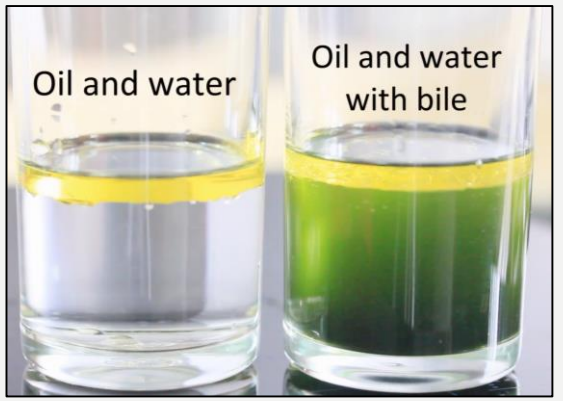
To **maximize** the effect of digestive enzymes, by two mechanisms:

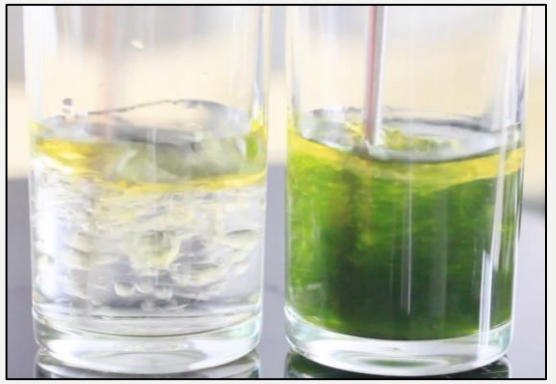
- Mechanical mixing by **peristalsis** (by smooth muscles).
  - Help in breaking the bonds
- Detergent properties of the **bile salts** in the bile.
  - "bile salts emulsify dietary lipids"
    - Bile salts help in keeping the bonds separated, by stabilizing the particles as they become smaller from peristalsis and preventing them from coalescing.

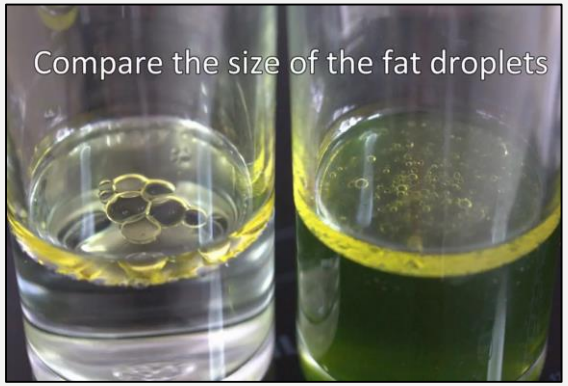
Emulsification: Dr sumbul's explanation

- The lipids are **water insoluble** while enzymes are **water soluble**, so how do we make them interact?
  - By **emulsification** which is aqueous and lipid interface.
- without emulsification, the hydrophobic lipids will stick to each other (coalesce), which is a problem because the enzymes cannot reach the lipids in the center of lipid ball. So only the lipids on the surface of the lipid ball will be acted upon by the enzymes (this impairs breakdown because the enzyme have a decreased surface area to work on).
- Emulsification solves all that by increasing the surface area of the substrate by breaking the bonds so that the enzyme can act on all the lipids to break them down.
- So in order to digest lipids in our bodies we need something that will break the bonds (which is mechanical mixing by peristalsis (by smooth muscles), and something that will keep the bonds separated (which is the bile salts).
- So when these bonds are separated ,enzymes are able to act on them.

In simple words: emulsification is a physical combination of water and lipids.







Lipid degradation by pancreatic enzymes

- Triacylglycerol degradation
- Cholesterol ester degradation
- Phospholipids digestion

❖ **Performed by:**

- **pancreatic lipase:**
  - ✓ Found in high conc. in pancreatic secretion (2-3% of total proteins) .
  - ✓ Inhibited by **Orlistat**, an antiobesity drug.

  It basically inhibits the enzyme pancreatic lipase, then no digestion of TAGs → inability to absorb them → they will be excreted in the feces! → weight loss!!

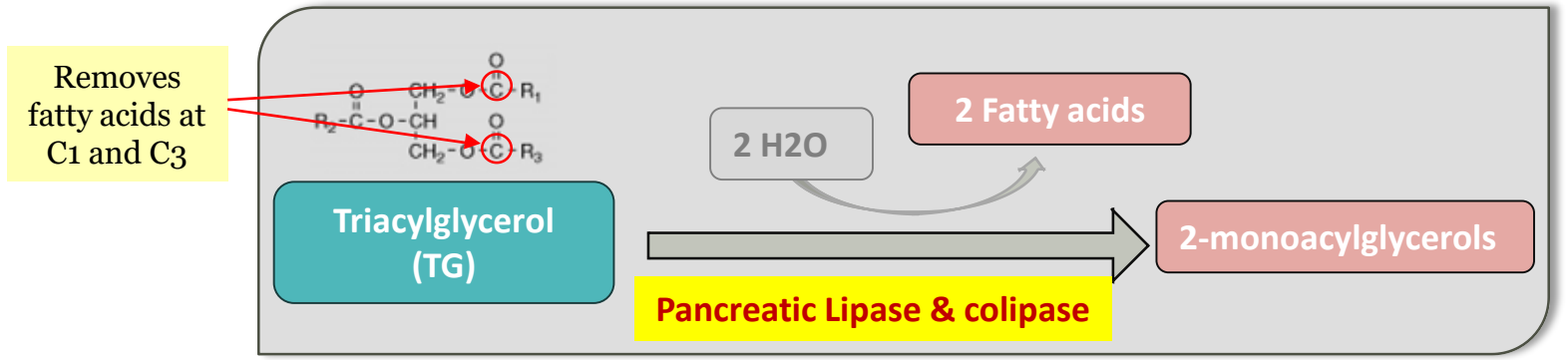
- **Colipase:** produced as a zymogen as procolipase which is then turned into colipase (how?) by biochemical modification done by trypsin. Then the active colipase attaches its self to pancreatic lipase which will cleave the fatty acids attached to the first and third carbons.

❖ **How does "pancreatic lipase" act on TAGs?**

- Removes fatty acids at **C1** and **C3.**

❖ **End products:**

- **2-monoacyglycerol** (this is a molecule with only ONE fatty acid chain attached to the second carbon!)
- **free fatty acids** (FFAs).

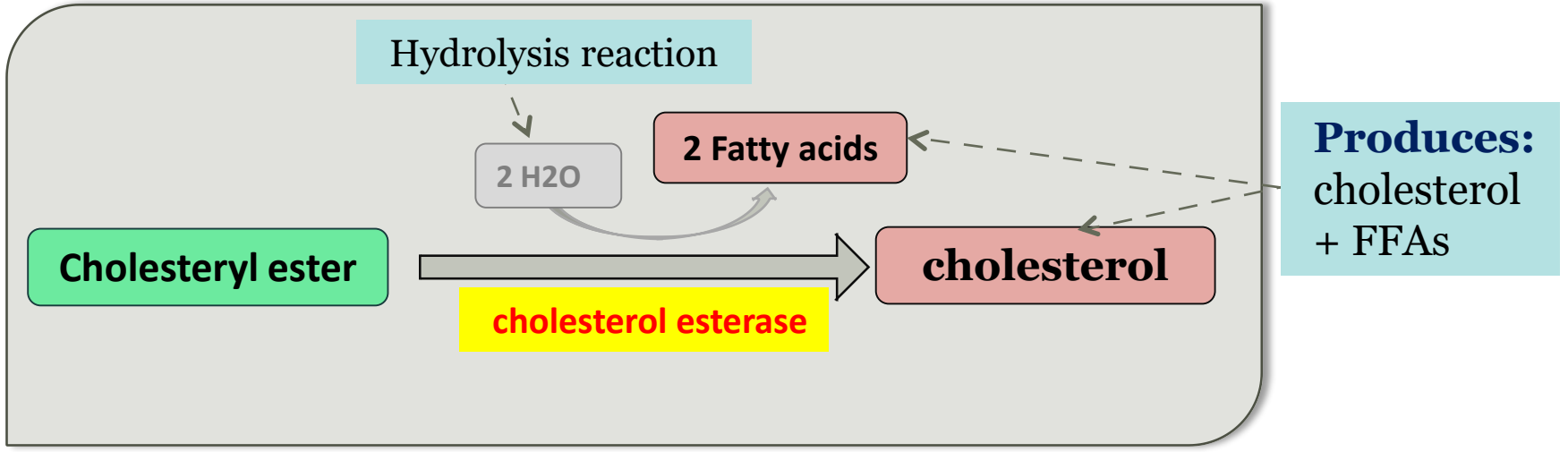


Lipid degradation by pancreatic enzymes

- Triacylglycerol degradation
- Cholesterol ester degradation
- Phospholipids digestion

Cholesteryl ester degradation:

- **Enzyme:** cholesterol esterase
- **Reaction type:** Hydrolysis
- **Produces:** cholesterol + FFAs.



Recall: **What is cholesterol ester?** It is basically a cholesterol bound with a fatty acid chain "esterified cholesterol".

- Cholesteryl esterase works by breaking the ester bond (removes the fatty acid chain so that you are left with cholesterol only)
- Note that pancreatic lipase is also considered an esterase enzyme because it breaks the ester bonds.

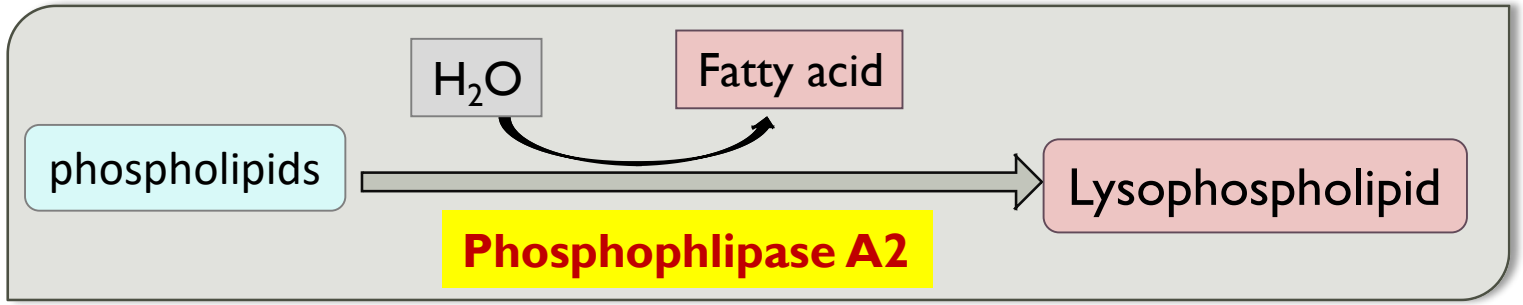
Lipid degradation by pancreatic enzymes

- Triacylglycerol degradation
- Cholesterol ester degradation
- Phospholipids digestion

Two enzymes are used in the phospholipids degradation:

- **phospholipase A2:** an enzyme that breaks the bond of the fatty acid attached to the carbon no. 2 in phospholipids (PL), resulting in releasing of lysophospholipids.
- **lysophospholipase:** an enzyme that breaks the remaining bond of lysophospholipid (which is a phospholipid with one fatty acid), and release glycerolphosphoryl (glycerol + phosphate).

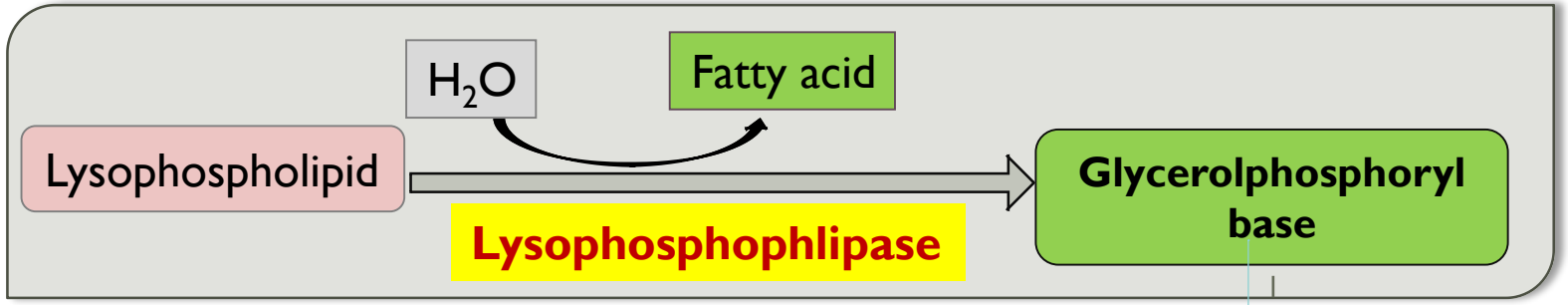
1-



* If phospholipase A2 is working in phosphotidylcholine ,then you will end up with lysophosphotidylcholine

* Or if it worked on phosphotidylserine , the end product will be lysophophotidylserine and so on…….

2-



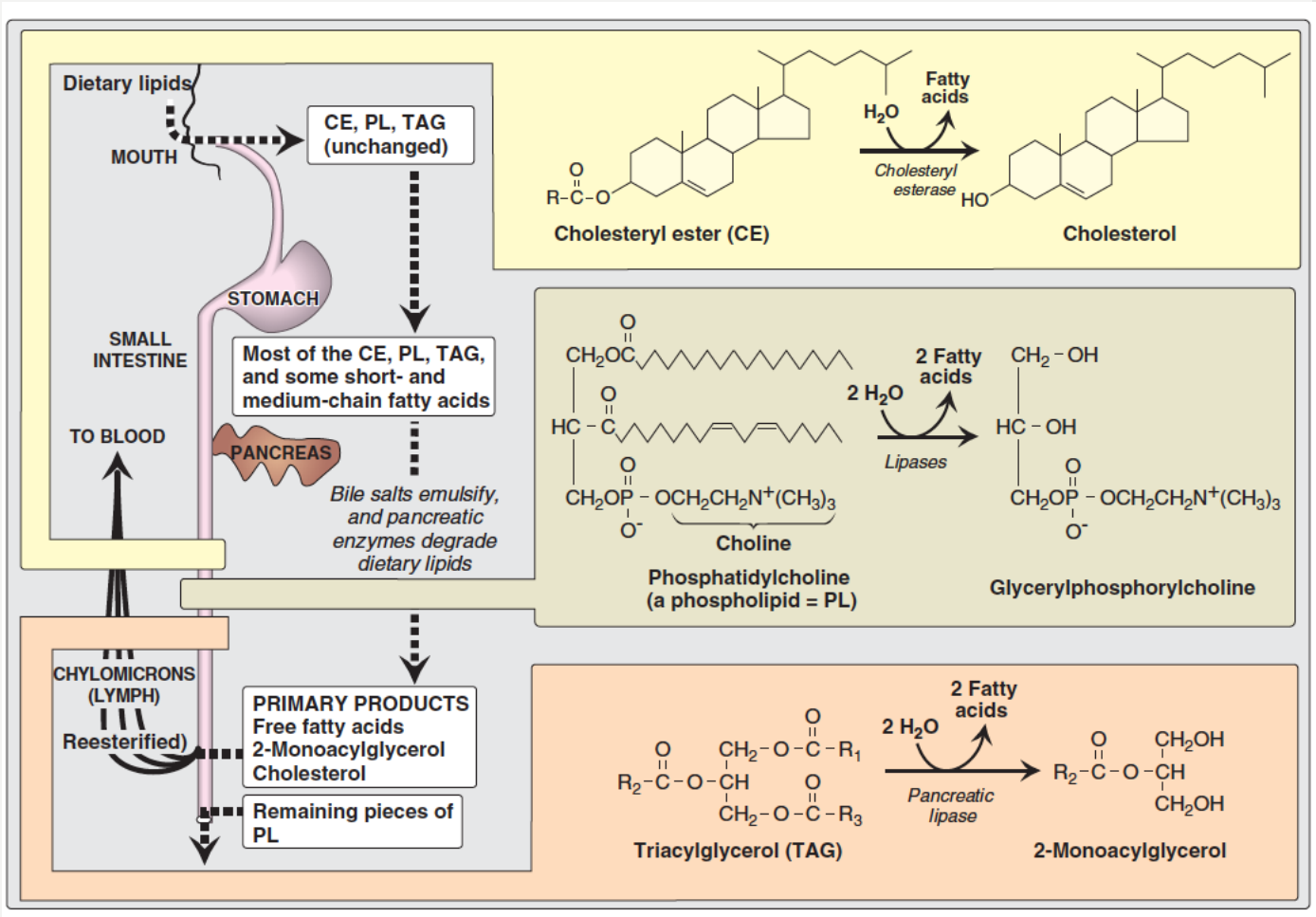
Any base that was attatched in first place (e.g. choline, serine.. etc).

Excreted in the feces, degraded or absorbed

What you need to know from this pic:

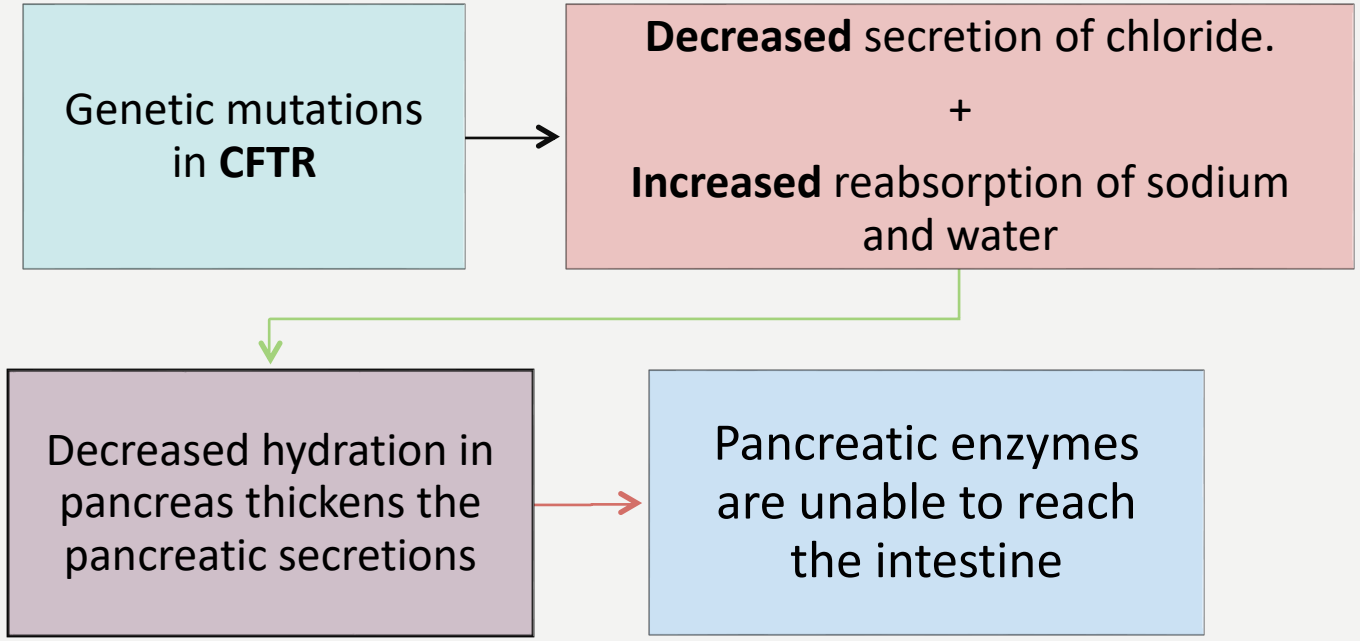
(this is basically a summary for all the past reactions)

1. Lipids are UNCHANGED **IN MOUTH**!
2. **In stomach: lingual lipase** and **gastric lipase** produce the following products: (TAGS , PL ,and cholesterol esters are still present in addition to short and intermediate chain fatty acids).
3. **Small intestines:**
   - **Pancreatic lipase** works on TAGS to give monoacylglycerols and fatty acids.
   -**Cholesteryl esterase** works on cholesterol ester to yield cholesterol + fatty acids.
   -**Phospholipase A2** works on phospholipids and yields lysophospholipids which are the converted into a glycerylphosphoryl BASE (generally speaking).



Pancreatic insufficiency in cystic fibrosis (CF)

- CF is an autosomal recessive caused by genetic mutations in **CFTR** (CF transmembrane conductance regulator protein)
  - **Functions as** chloride channel on epithelium.
- **Treatment: enzyme and fat-soluble vitamin supplementation**.



This channel normally functions in secreting chloride into the mucus

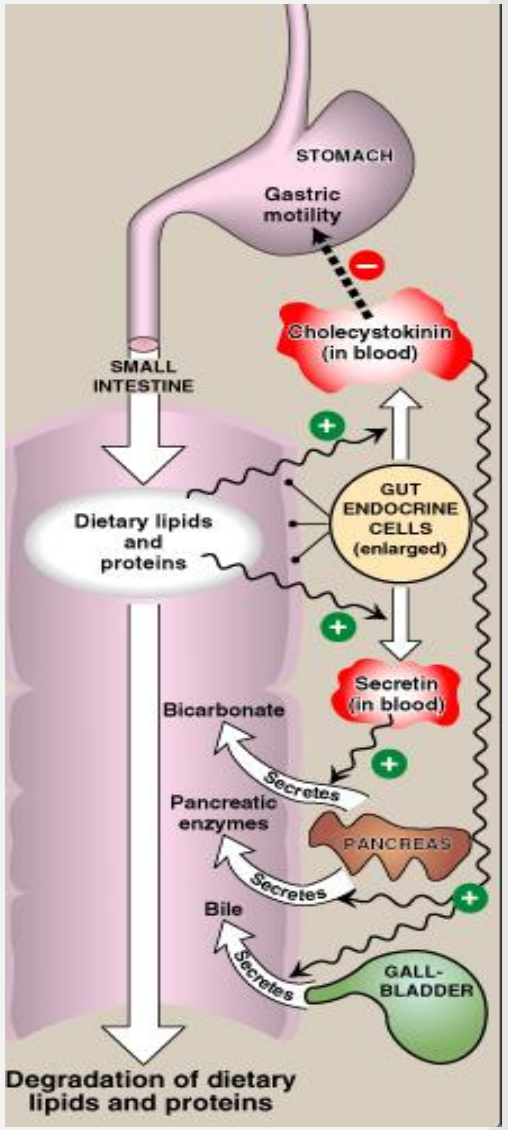
If this protein is defective, then chloride will not go out of epithelial cells, so the concentration of chloride will build up in the cells → the opening of ENAC channels which will lead the entry of **Na+** into the cells from the mucus → Sodium influx will result into osmosis (water has gone from the mucus into the epithelial cells) → thick mucus (because it lost its water) → impaired movement of cilia.

- If this occurs in the lung –> infection .and
- If it occurs in gut → blockage → pancreatic insufficiency.

Control of lipids digestion

these hormones are secreted by end of duodenum and jejunum .

Hormone:	Stimulus for secretion:	Effects:
Cholecystokinin (CCK)	Presence of partially digested Lipids + Proteins in the upper small intestine	- Acts on **pancreas** to release enzymes - Acts on **gallbladder** to release bile (by Stimulating the contraction of the gall bladder). - Decreases **gastric motility** that cause slower release of gastric contents into the small intestine (slowing down the emptying to maximize the digestion).
Secretin	Low pH of the chyme entering the intestine release in upper intestine	- Stimulates the pancreas and liver to release a watery solution rich in bicarbonate. - to neutralize the pH of the intestinal contents (to reach the optimum pH for digestive activity by pancreatic enzymes) before entering the small intestine.

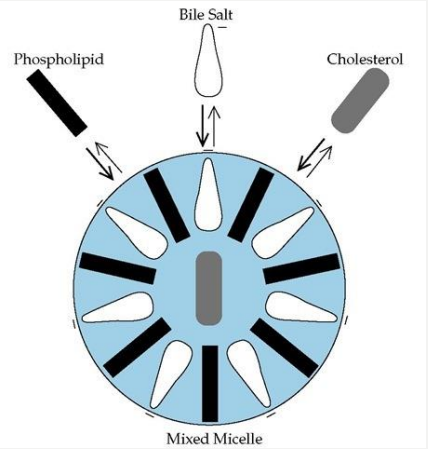


- Gut endocrine cells secrete cholecystokinin when undigested fats and proteins into the small intestines

- **why does secretin work on pancreas and liver to secrete bicarbonate?** So that the pancreatic enzymes can work (they need a neutral PH to act)

LIPID ABSORPTION BY ENTEROCYTES

- As we know lipids are water insoluble, so it will not be absorbed by the intestinal mucosal cells unless it forms the mixed micelles which are soluble in the aqueous environment of the intestinal lumen.
- Short- and medium-chain fatty acids **do not require** mixed micelle for absorption by intestinal cells, Because they are water soluble.



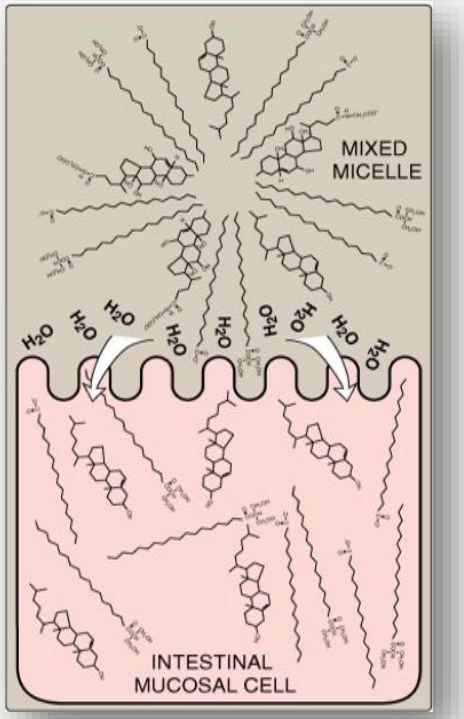
Mixed Micelles:

Mixed micelles include **Products of lipid digestion** (FFAs, free cholesterol, 2-monoacylglycerol) combine with bile salts and fat-soluble vitamins

Disc-shaped clusters of **amphipathic** lipids.
Consist of both hydrophobic and hydrophilic lipids.

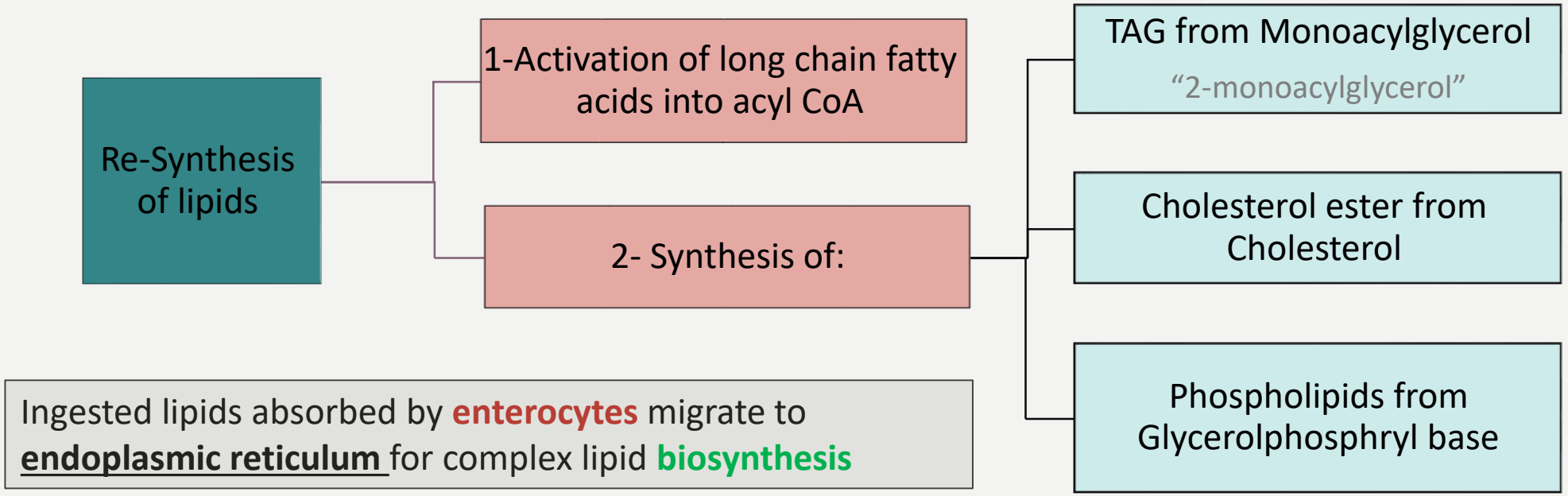
Arranged with their **hydrophobic groups** on the inside and their **hydrophilic groups** on the outside.
Mixed micelles have hydrophobic core, and hydrophilic surface facilitates the transport of the hydrophobic lipids through the water layer of the brush border membrane (of the mucosal cells) where they are absorbed.

absorbed by **brush border membrane** of enterocytes



RESYNTHESIS OF TAG / CHOLESTERYL ESTERS

Explanation in the next slide.....

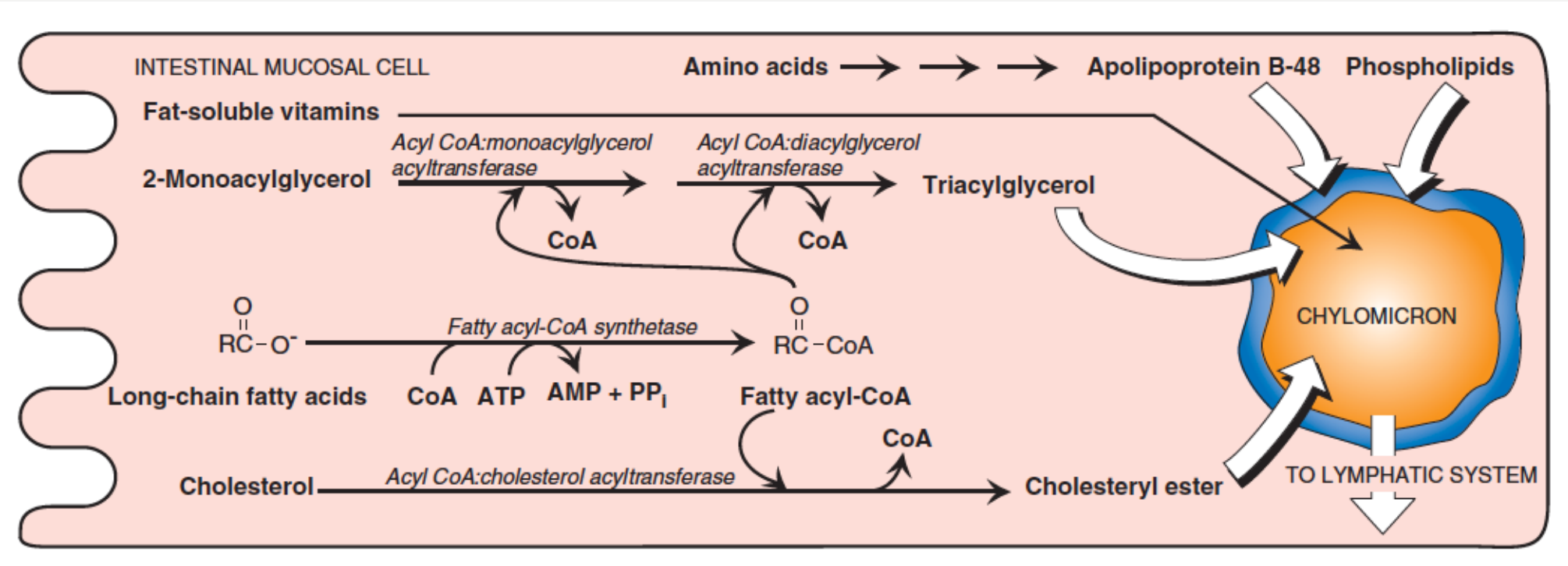


ASSEMBLY OF CHYLOMICRONS BY ENTEROCYTES

- Newly synthesized TAG and cholesterol ester are packaged as lipid droplets surrounded by thin layer of:
  - **Apolipoprotein B-48 (apo B-48)**
  - **Phospholipids**
  - **Free cholesterol**

Note: Assembly of this chylomicron requires an important enzyme : microsomal triglyceride transfer protein (MTTP) –not written in slides but was said by the DR

RE-SYNTHESIS OF LIPIDS AND ASSEMBLY OF CHYLOMICRONS BY INTESTINAL MUCOSAL CELLS



1. The long-chin length fatty acids are first converted into there activated form by fatty acyl-coenzyme A synthase.
2. Using the fatty acyl CoA derivatives the 2-Monoacylglycerols are converted to TAGs by Monoacylglycerol acyltransferase and Diacylglycerol acyltransferase .
3. Lysophospholipids are reacylated to form phospholipids by acyltransferases.
4. Cholesterol is esterified with a fatty acid by acyltransferase to form cholesteryl ester.
5. Amino acids will give Apolipoprotein B-48

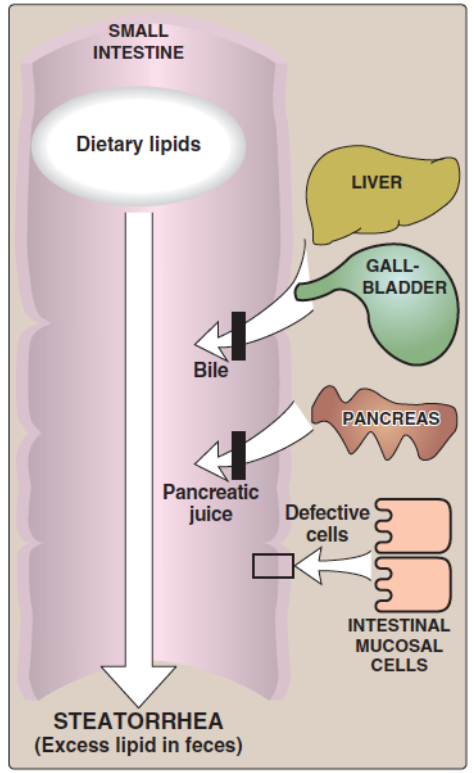
SECRETION OF CHYLOMICRONS BY ENTEROCYTES

Chylomicron will be secreted by **Exocytosis** from enterocytes → into the **lymphatic vessels** around villi of small intestine (lacteals) → then enter into **systemic circulation**. → **Milky-appearance** of serum after lipid-rich meal.

*In the picture, comparison between serum taken from fasting person (clear serum), and serum taken from person after lipid-rich meal (turbid serum).

LIPID MALABSORPTION

- **Increased excretion** of lipids, fat-soluble vitamins and essential FAs in the feces
- **Due to:** defects in lipid digestion or absorption
- Can be caused by: CF or shortened bowel



Lipid malabsorption, resulting in increase lipid in the feces this condition known as **STEATORRHEA**, can be caused by disturbances in lipid digestion and/or absorption such as: defect in the bile from the liver or gall bladder, pancreatic juices from pancreas or defective intestinal mucosal cells.

Check your understanding!

Q1: Where does most lipid digestion take place?

A. Stomach
B. Esophagus
C. Duodenum
D. Mouth

Q2: Which enzyme is the most important when digesting lipids?

A. Gastric Lipase
B. Lingual Lipase
C. A + B
D. Pancreatic Lipase

Q3: What is the effect of Orlistat on Pancreatic Lipase?

A. No effect on the enzyme
B. Inhibitory effect
C. Facilitatory effect
D. None of the Above

Q4: What is the primary role of Bile Salts in Lipid Digestion?

A. Quicker transport of lipids to the stomach
B. Emulsification of the lipids
C. Prevents digestion of lipids in the Stomach
D. Inhibits Secretin

Q5: Cholecystokinin (CCK) helps in digestion by…

A. Stimulating the release of pancreatic digestive enzymes
B. Stimulating the release of Bile
C. Decreasing Gastric Motility
D. All of the Above

Q6: The release of Secretin is stimulated by…

A. High pH
B. Low pH
C. Neither

1.C 2.D 3.B 4.B 5.D 6.B

Check your understanding!

Q1: Mixed Micelles are classified as…..

A. Hydrophilic
B. Hydrophobic
C. Amphipathic
D. Fat soluble

Q2: Apoprotein B-100 is found in….

A. VLDL's
B. HLDL's
C. Chylomicrons
D. All of the above

Q3: Steatorrhea is defined as:

A. Increased presence of Proteins in the feces
B. Increased presence of Lipids in the feces
C. Presence of Bile in the feces
D. Presence of Blood in the feces

Q4: Steatorrhea may be caused by:

A. Liver and Gallbladder diseases
B. Pancreatic insufficiency (Pancreatitis, Cystic Fibrosis, Pancreatic resection)
C. Intestinal Disorders (Intestinal resection)
D. All of the Above

1.C 2.C 3.B 4.D

Done by:

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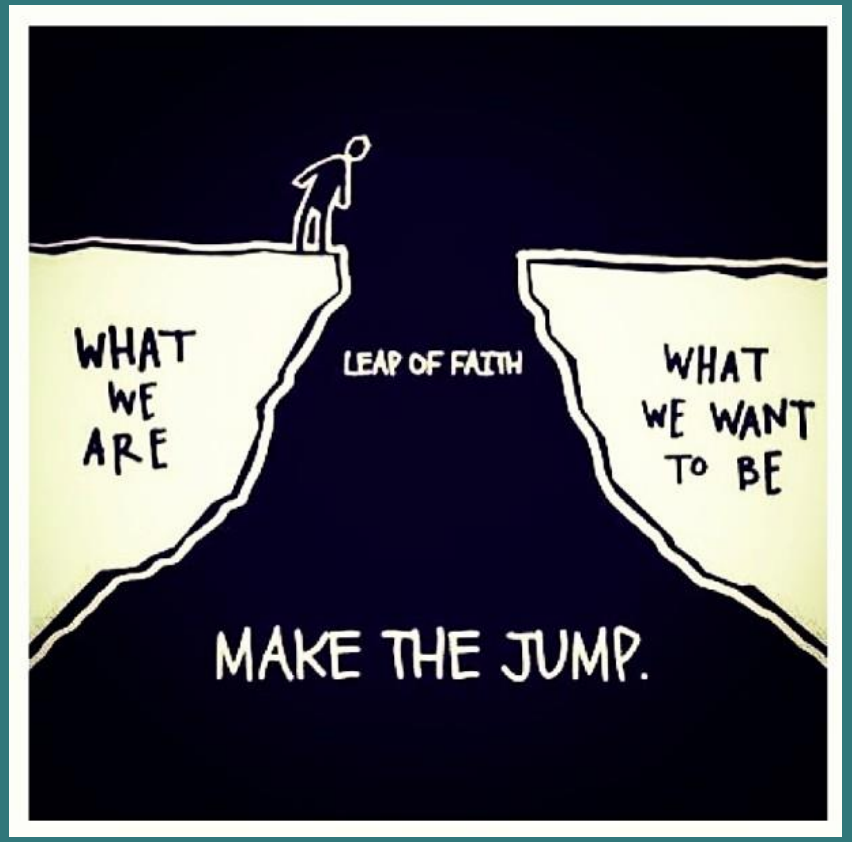
- ابراهيم الشايع.
- عبدالله الشنيفي
- رهف بن عباد.



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Resources:

- 435's slides and notes.
- Lippincott's illustrated reviews: Biochemistry – sixth edition.

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