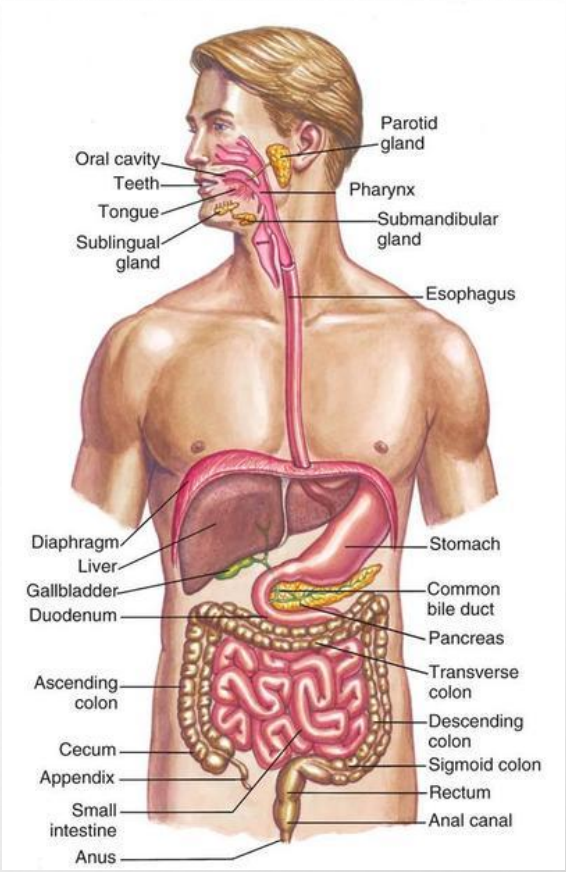
DIGESTION AND ABSORPTION OF LIPIDS



LIPIDS

- Lipids are heterogeneous group of water insoluble organic molecules (fats & oils) that are often considered culprits in the diet due to their association with cardiovascular diseases
- Major source of energy reserve for the body (triacylglycerols) also provide the hydrophobic barriers that permit partitioning of aqueous contents of cells and sub cellular structures (cholesterol & phospholipids).
- Fat soluble vitamins have regulatory or coenzyme role in the body.
- Prostaglandins and steroid hormones play major roles in the control of body's homeostasis.
- Give shape and contour to the body and protect internal organs by providing a cushioning effect.

DIETARY FAT COMPOSITION

- More than 95% are triglycerides, the other are
- Sterols (cholesterol)
- Phospholipids

DIETARY SOURCES OF LIPIDS

Animal sources

dairy products- meat, butter, ghee

meat and fish, pork, eggs

Vegetable sources

cooking oils- sun flower oil, mustard oil, ground nut oil

fats from other vegetable sources

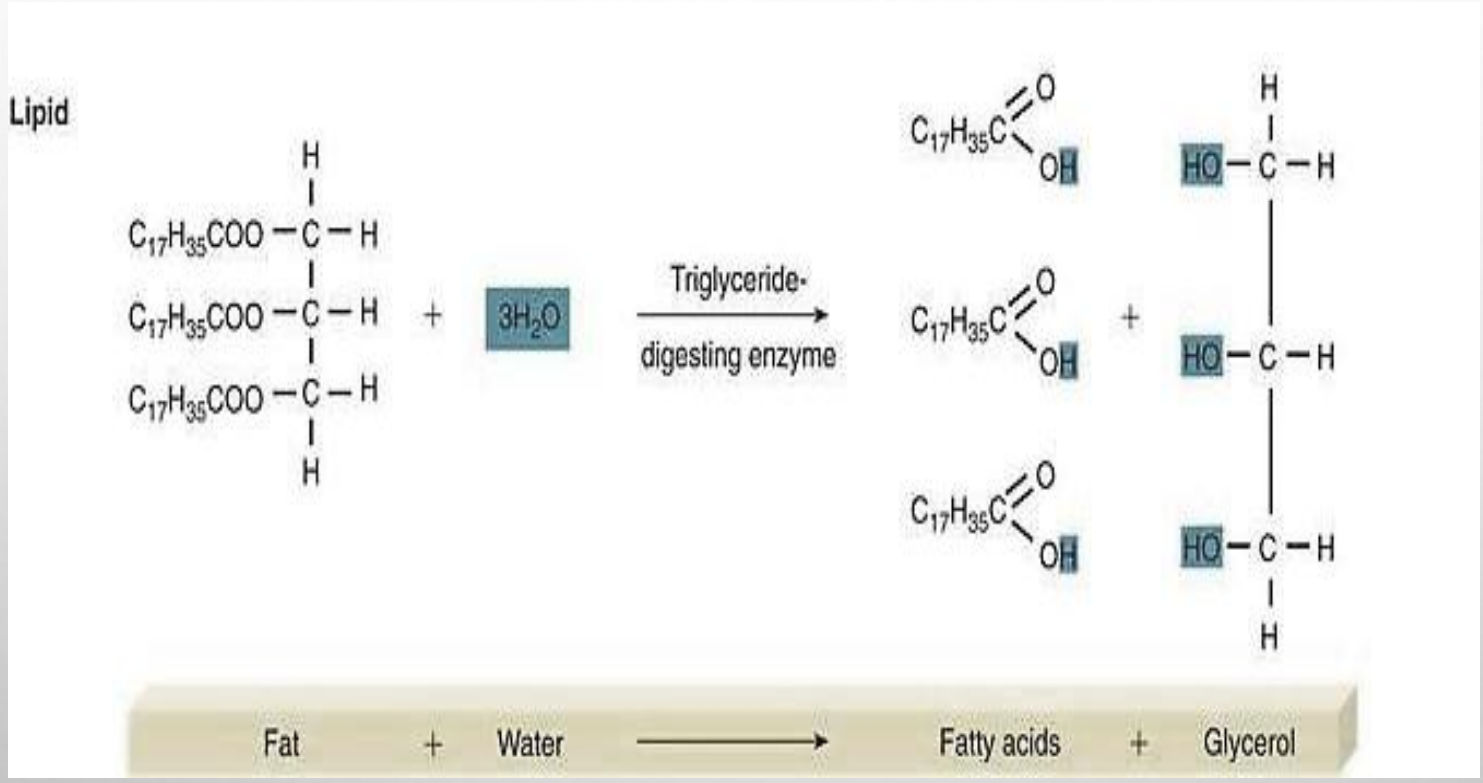
DIGESTION IN MOUTH

- hydrolysis of triacylglycerols is initiated by lingual and gastric lipases, which attack the *sn*-3 ester bond forming 1,2-diacylglycerols and free fatty acids, aiding emulsification.

Lingual lipase:

- Secreted by dorsal surface of tongue
- Active at low ph (ph 2.0 – 7.5)
- Optimum ph 4.0-4.5
- Ideal substrate-short chain tgs.
- Milk fat contains short chain fatty acids which are esterified at -3 position, thus it is the best substrate for lingual lipase enzymatic action continues in stomach
- Short chain fatty acids, released are absorbed directly from the stomach wall and enter the portal vein.

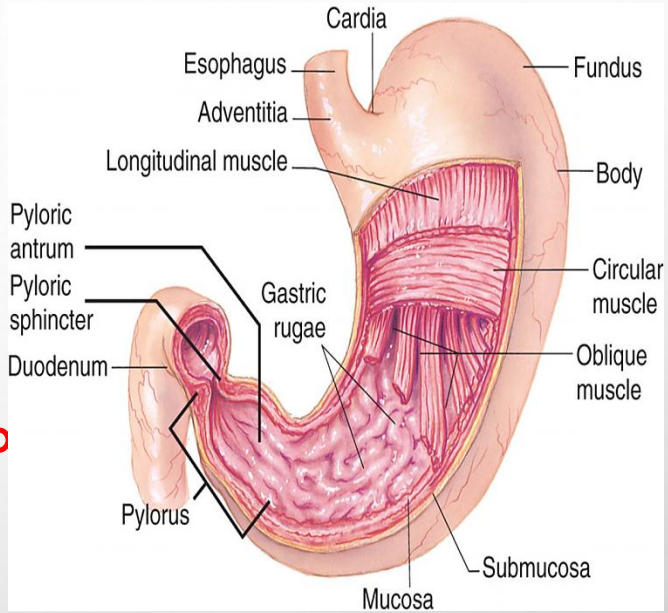
TRIGLYCERIDE DEGRADATION



TRIGLYCERIDES ARE DEGRADED BY LIPASES TO FORM FREE FATTY ACIDS AND GLYCEROL

DIGESTION IN STOMACH

- Gastric lipase- secreted in small quantities
- More effective at alkaline p h (average p h 7.8)
- Requires the presence of ca^{++}
- Less effective in stomach due to acidic p h except when intestinal contents are regurgitated in to the gastric lumen
- Not effective for long chain fatty acids, most effective for short and medium chain fatty acids
- Milk, egg yolk and fats containing short chain fatty acids are suitable substrates for its action



ROLE OF FATS IN GASTRIC EMPTYING

- Fats delay the rate of emptying of stomach
- Action is brought about by secretion of enterogastrone
- Enterogastrone inhibits gastric motility and retards the discharge of chyme of food from the stomach.
- Thus fats have a high satiety value.

SIGNIFICANCE OF LINGUAL AND GASTRIC LIPASES

- Play important role in lipid digestion in **neonates** since milk is the main source of energy
- Important digestive enzymes in pancreatic insufficiency such **as cystic fibrosis or other pancreatic disorders**
- Lingual and gastric lipases can degrade triglycerides with short and medium chain fatty acids in patients with pancreatic disorders despite a near or complete absence of pancreatic lipase

EMULSIFICATION AND DIGESTION

- Lipids are hydrophobic, and thus are poorly soluble in the aqueous environment of the digestive tract.
- The digestive enzyme, **lipase**, is water soluble and can only work at the surface of fat globules.
- Digestion is greatly aided by **emulsification**, the breaking up of fat globules into much smaller **emulsion droplets**.

EMULSIFICATION AND DIGESTION

- Triacylglycerol digestion occurs at lipid-water interfaces
- Rate of tag digestion depends on surface area of this interface which is increased by churning peristaltic movements of the intestine ,
- Combined with the emulsifying action of bile salts
- The critical process of emulsification takes place in the duodenum.

DIGESTION IN SMALL INTESTINE

Major site of fat digestion

- Effective digestion due to the presence of pancreatic lipase and bile salts. Bile salts act as effective emulsifying agents for fats
- Secretion of pancreatic juice is stimulated by-Passage of acid gastric contents in to the duodenum by secretion of secretin, cholecystokinin and pancreozymin, the gastro intestinal hormones

GASTRO INTESTINAL HORMONES

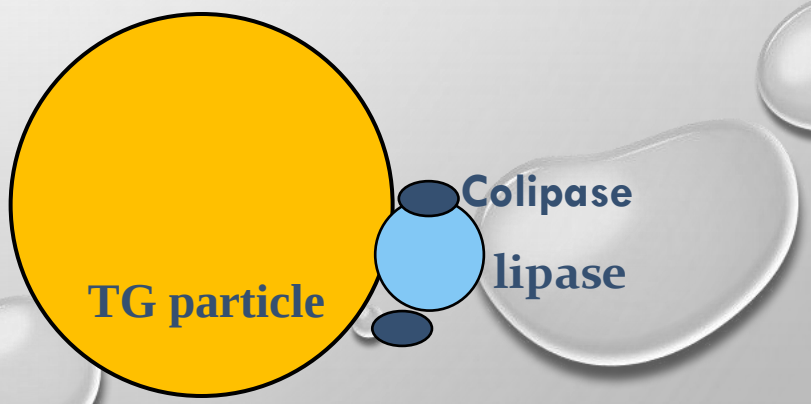
- **Secretin-** increases the secretion of electrolytes and fluid components of pancreatic juice
- **Pancreozymin of cck** -pz stimulates the secretion of the pancreatic enzymes
- **Cholecystokinin of cck-pz-** causes the contraction of the gall bladder and discharges the bile in to the duodenum.
- **Hepatocrinin-** released by intestinal mucosa, stimulates more bile formation which is relatively poor in bile acid content

CONTENTS OF PANCREATIC JUICE

- Pancreatic lipase- for the digestion of triglycerides
- Phospholipase A2- for the digestion of phospholipids
- Cholesterol esterase-for the digestion of cholesteryl esters

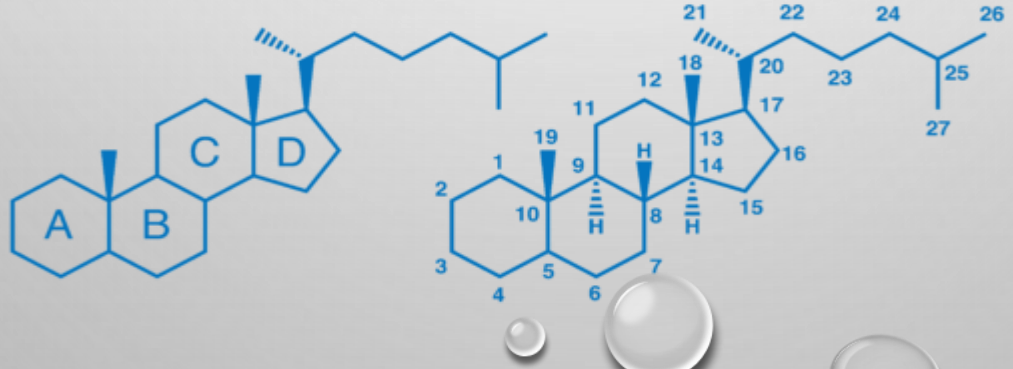
BILE SALTS

- Bile salts are required for the proper functioning of the pancreatic lipase enzyme
- Bile salts help in combination of lipase with two molecules of a small protein called as colipase. this combination enhances the lipase activity.
- Bile salts also help in the emulsification of fats



BILE SALTS

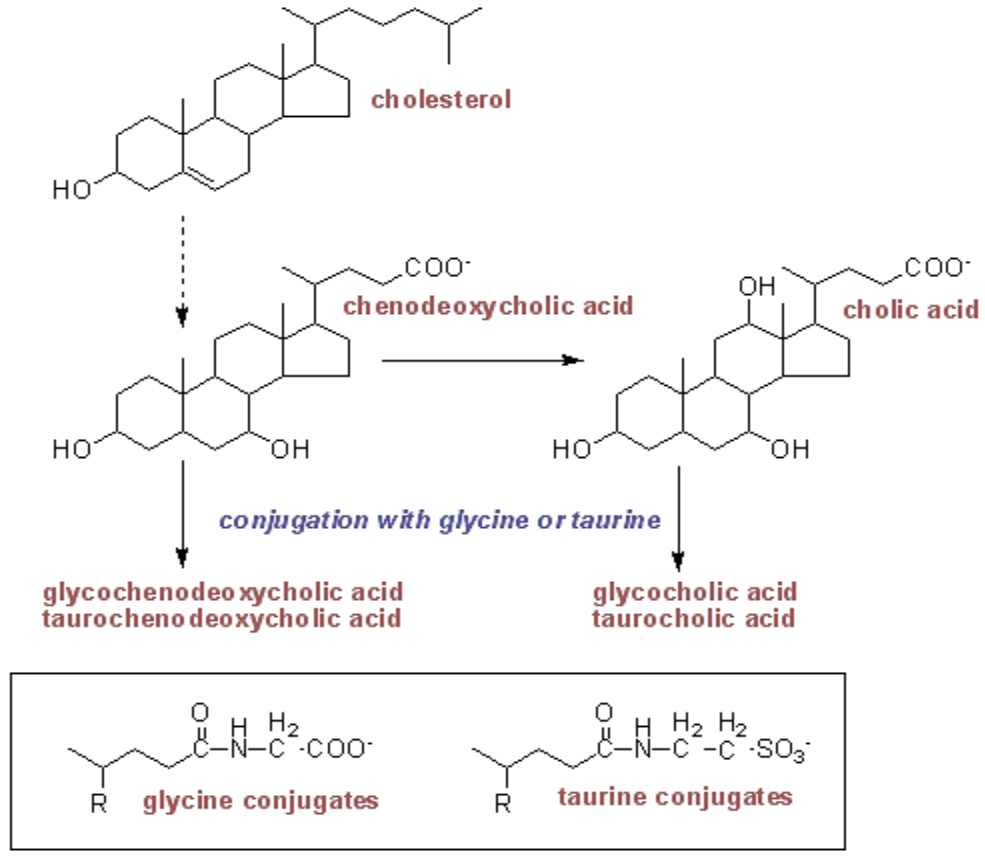
- Bile salts are synthesized in the liver and stored in the gall bladder
- They are derivatives of cholesterol
- They consist of a sterol ring structure with a side chain to which a molecule of glycine or taurine is covalently attached by an amide linkage



BILE SALTS

- Bile salts are formed from bile acids
- The **primary bile acids** are **cholic acid** (found in the largest amount) and **chenodeoxycholic acid** .
- The primary bile acids enter the bile as glycine or taurine conjugates.
- **In the alkaline bile, the bile acids and their conjugates are assumed to be in a salt form—hence the term "bile salts.“**

SYNTHESIS OF BILE SALTS



In humans, the ratio of the glycine to the taurine conjugates is normally 3:1.

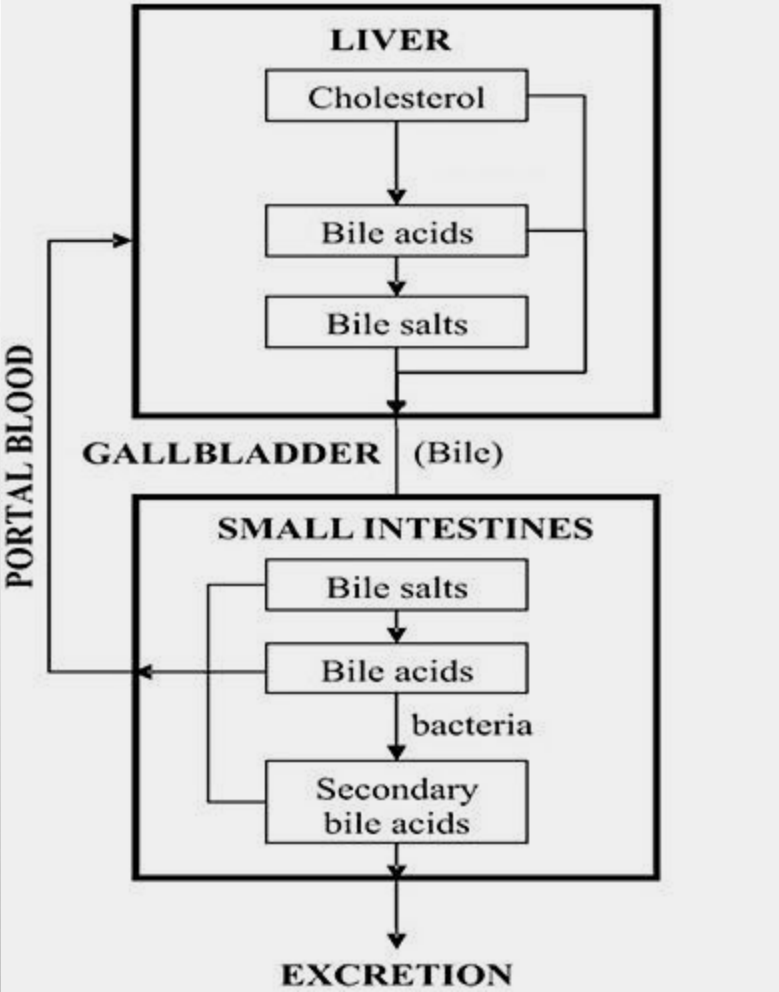
BILE SALTS

- A portion of the primary bile acids in the intestine is subjected to further changes by the activity of the intestinal bacteria.
- These include deconjugation and 7-alpha dehydroxylation, which produce the **secondary bile acids,** deoxycholic acid and lithocholic acid.

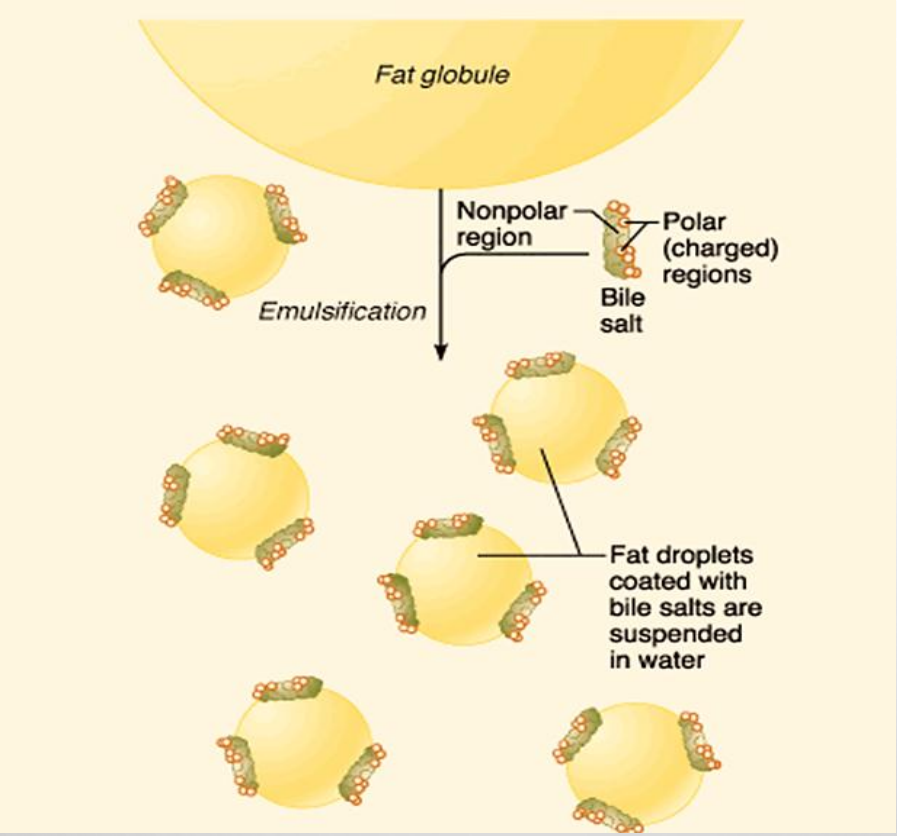
ENTEROHEPATIC CIRCULATION OF BILE SALTS

- The bile salts present in the body are not sufficient to fully process the fats in a typical meal, thus they need to be recycled.
- This is achieved by the **enterohepatic circulation**.
- Specific transporters in the **terminal ileum** move bile salts from the lumen of the digestive tract to the intestinal capillaries.
- They are then transported directly to the liver via the **hepatic portal vein**.
- Hepatocytes take up bile salts from the blood, and increase the secretion of bile salts into the **bile canaliculi**, small passage ways that convey bile into the larger bile ducts.
- 95% of the bile that is released to the small intestine is recycled via the enterohepatic circulation, while 5% of the bile salts are lost in the feces.

ENTEROHEPATIC CIRCULATION OF BILE SALTS



EMULSIFICATION BY BILE SALTS

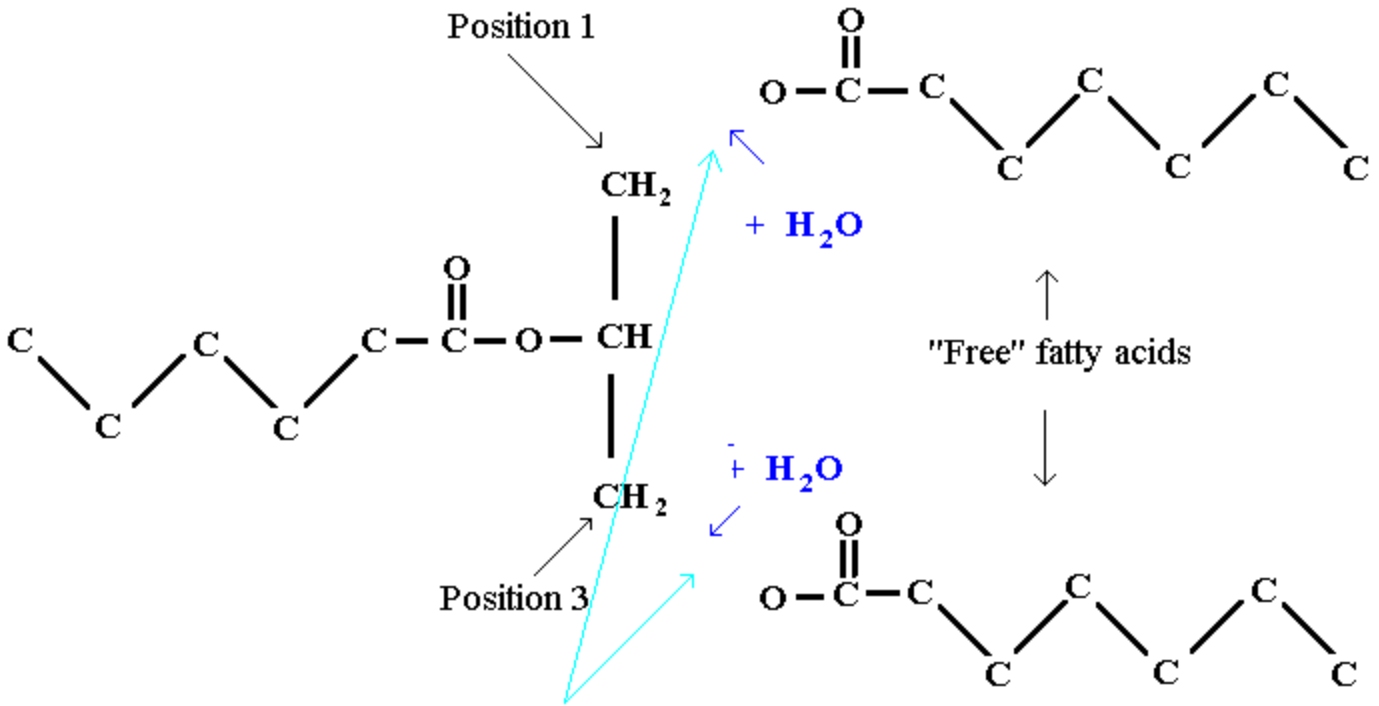


Bile salts as emulsifying agents interact with the dietary lipid particles and the aqueous duodenal contents, thereby stabilizing the lipid particles as they become smaller, and preventing them from coalescing.

TRIACYL GLYCEROL DEGRADATION BY PANCREATIC LIPASE

- Pancreatic lipase is specific for the hydrolysis of primary ester linkages(fatty acids present at position 1 and 3)
- It can not hydrolyze the ester linkages of position -2
- Digestion of triglycerides proceeds by removal of a terminal fatty acid to produce an α,β diglyceride.
- The other terminal fatty acid is then removed to produce β mono glyceride.

TRIACYL GLYCEROL DEGRADATION BY PANCREATIC LIPASE

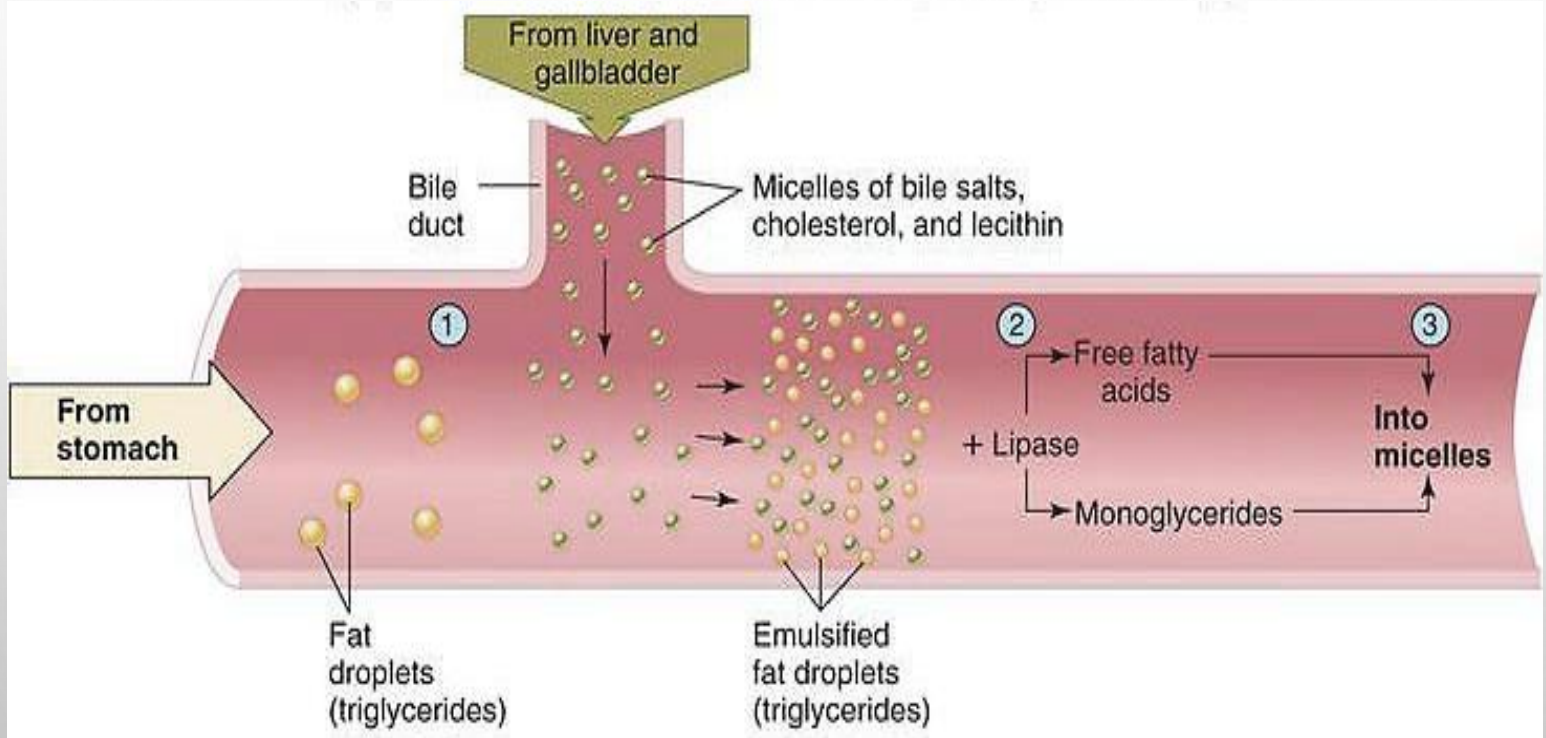


Pancreatic lipase is an enzyme that breaks the bonds between glycerol and the fatty acids at positions 1 and 3, liberating the 2 fatty acids.

TRIACYL GLYCEROL DEGRADATION BY PANCREATIC LIPASE

- The last fatty acid is linked by secondary ester group, hence can not be hydrolyzed by pancreatic lipase.
- β- mono acyl glycerol can be converted to α- mono acyl glycerol by isomerase enzyme and then hydrolyzed by pancreatic lipase.
- The primary product of hydrolysis are β- mono acyl glycerol (78%), α- mono acyl glycerol (6%) with free fatty acids and glycerol (14%)

EMULSIFICATION AND DIGESTION OF TRIGLYCERIDES



Step 1: Emulsification of fat droplets by bile salts

Step 2: Hydrolysis of triglycerides in emulsified fat droplets into fatty acid and monoglycerides

Step 3: Dissolving of fatty acids and monoglycerides into micelles to produce "mixed micelles"

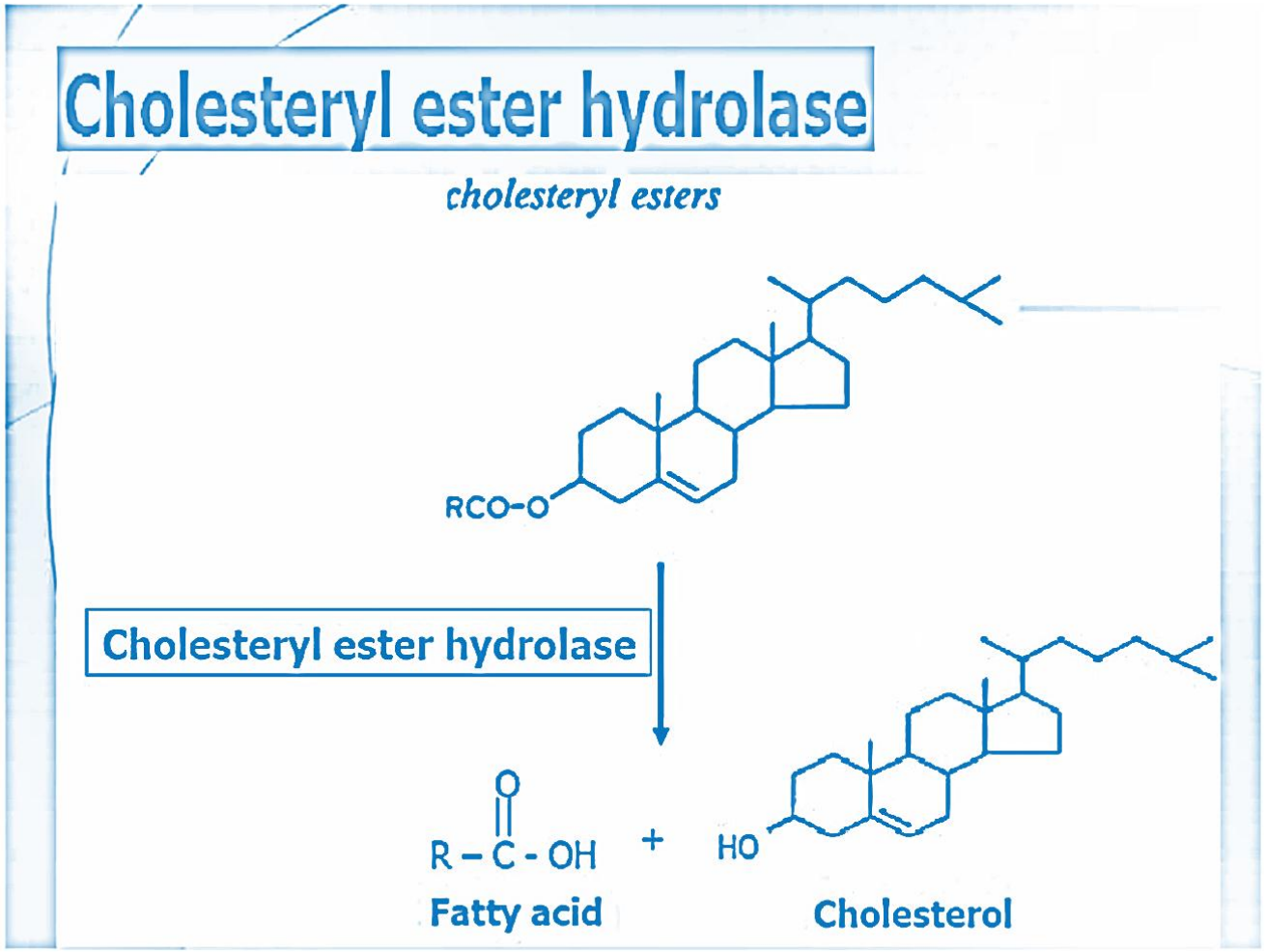
SIGNIFICANCE OF PANCREATIC LIPASE

- The enzyme is present in high concentration in pancreas. only very severe **pancreatic deficiency such as cystic fibrosis** results in malabsorption of fats due to impaired digestion.
- **Orlistat**, an antiobesity drug inhibits , gastric and pancreatic lipases, there by decreasing fat digestion and absorption resulting in weight loss.

CHOLESTERYL ESTER DEGRADATION

- Dietary cholesterol is mainly present in the free (non esterified) form
- Only 10-15% is present in the esterified form
- Cholesteryl esters are hydrolyzed by pancreatic cholesteryl esterase (cholesterol ester hydrolase) to produce cholesterol and free fatty acid
- The enzymatic activity is greatly increased in the presence of bile salts.

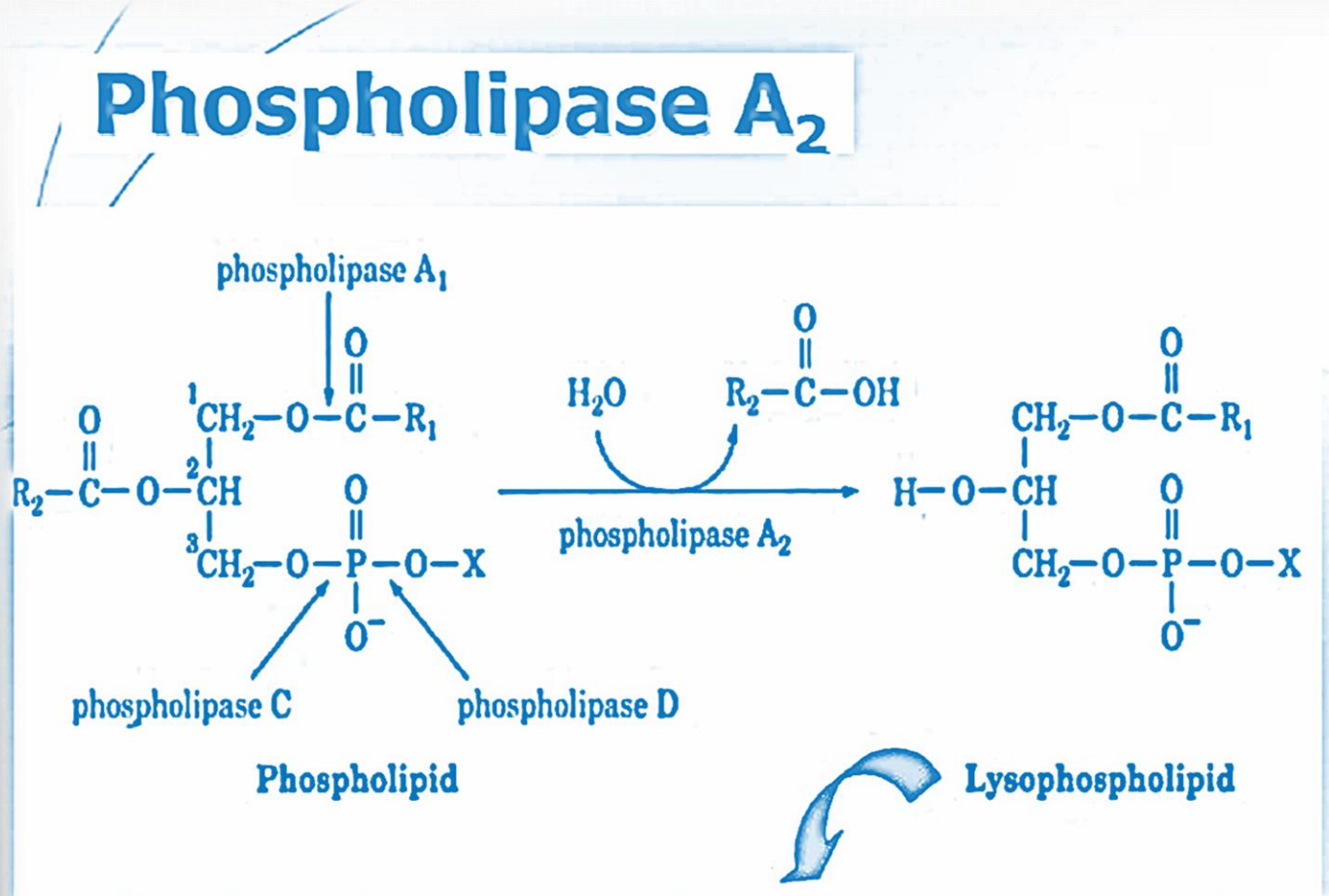
CHOLESTERYL ESTER DEGRADATION



PHOSPHOLIPID DEGRADATION

- The enzyme – phospholipase A_2 requires bile salts for optimum activity.
- Removes one fatty acid from carbon 2 of phospholipid to form lysophospholipid.
- The remaining fatty acid at position 1 can be removed by lysophospholipase , leaving a glycerylphosphoryl base that may be excreted in the feces, further degraded or absorbed.

PHOSPHOLIPID DEGRADATION

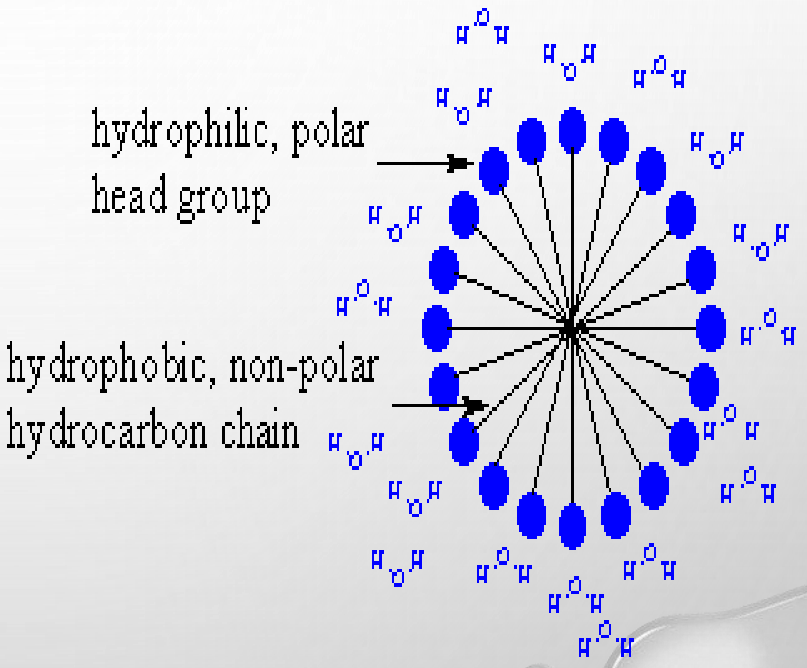


ABSORPTION OF LIPIDS

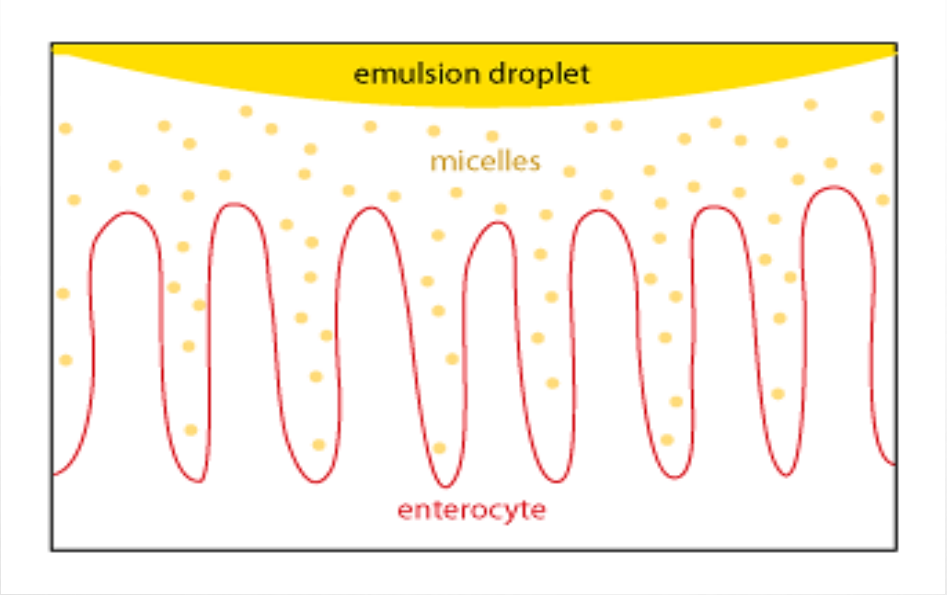
- Glycerol, short and medium chain fatty acids (chain length less than 14 carbons) are directly absorbed from the intestinal lumen in to the portal vein and taken to liver for further utilization.
- Long chain fatty acids, free cholesterol and β- acyl glycerol together with bile salts form mixed micelles.

MICELLES

- Micelles are disk shaped clusters of amphipathic lipids that coalesce with their hydrophobic groups on the inside and their hydrophilic groups on the outside of clusters
- Mixed micelles are soluble in the aqueous environment of the intestinal lumen
- The micelles approach the brush border membrane of the enterocytes



MICELLES



- Micelles constantly break down and re-form,
- It is the monoglycerides and fatty acids that are free in solution that are absorbed, not the micelles.
- Because of their nonpolar nature, monoglycerides and fatty acids can just diffuse across the plasma membrane of the enterocyte.
- Some absorption may be facilitated by specific transport proteins

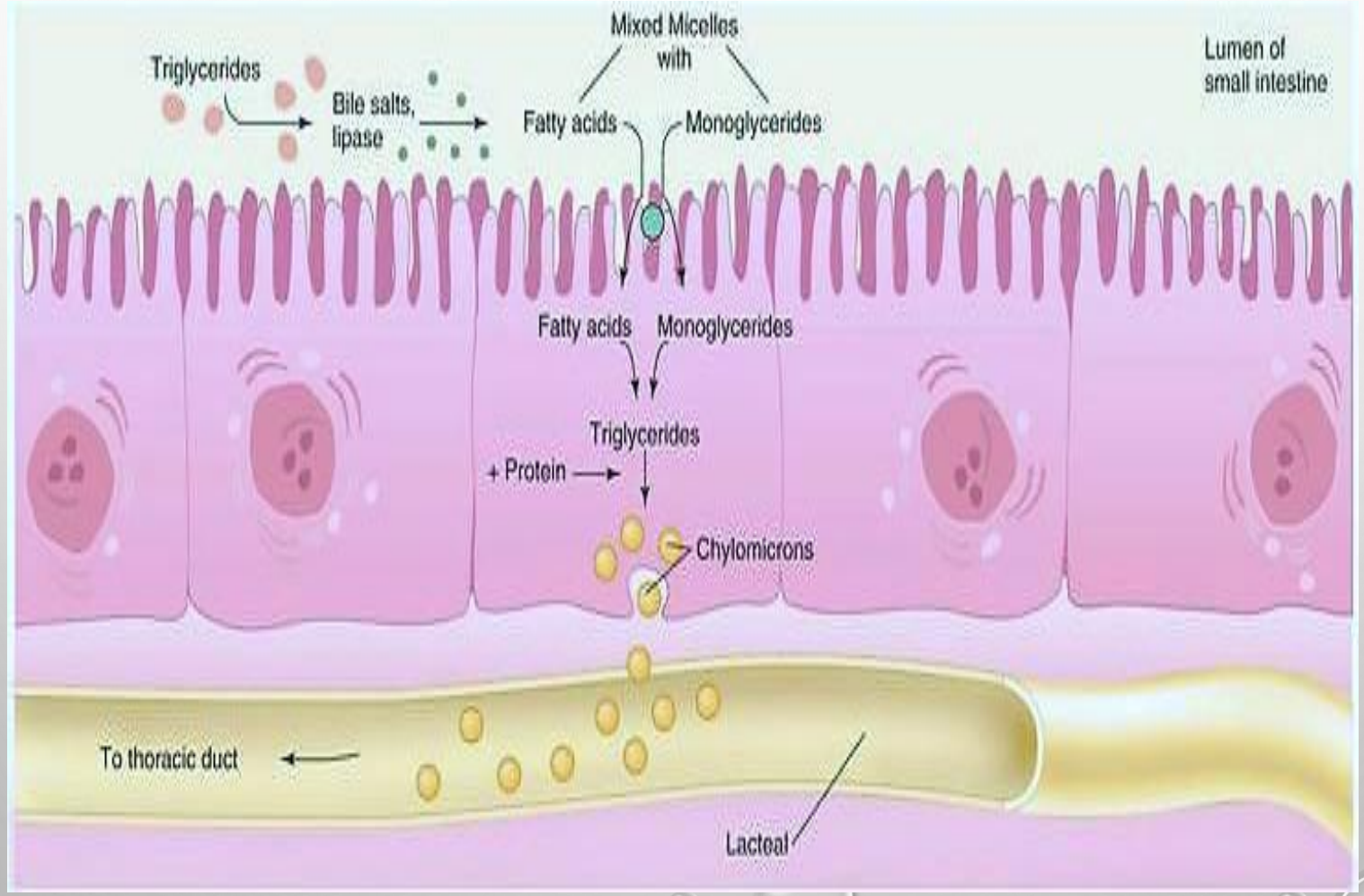
CLINICAL SIGNIFICANCE OF CHOLESTEROL ABSORPTION

- The drug **ezetimibe** blocks a protein that specifically mediates cholesterol transport across the apical plasma membrane of enterocytes.
- Ezetimibe has been shown to be effective at reducing levels of LDL cholesterol, particularly when combined with a **statin**, a drug that inhibits cholesterol synthesis in the liver.
- However, several clinical trials have shown that further cholesterol lowering with ezetimibe does not improve measures of atherosclerotic plaque.
- Clinical trials are in progress to determine whether ezetimibe (alone or combined with a statin) is beneficial for preventing cardiovascular events.

RESYNTHESIS OF TRIACYL GLYCEROL AND CHOLESTERYL ESTERS

- Within the intestinal epithelium, 1-monoacyglycerols are hydrolyzed to fatty acids and glycerol and 2-monoacylglycerols are re-acylated to triacylglycerols via the **monoacylglycerol pathway.**
- Lysophospholipids are recycled to form phospholipids.
- Cholesterol is re acylated to form cholesteryl esters
- Long chain fatty acids are used for esterification to form tgs, phospholipids and cholesteyl esters.
- Short and medium chain fatty acid are released in to the portal circulation and are carried by serum albumin to liver.

FORMATION AND TRANSPORTATION OF CHYLOMICRONS



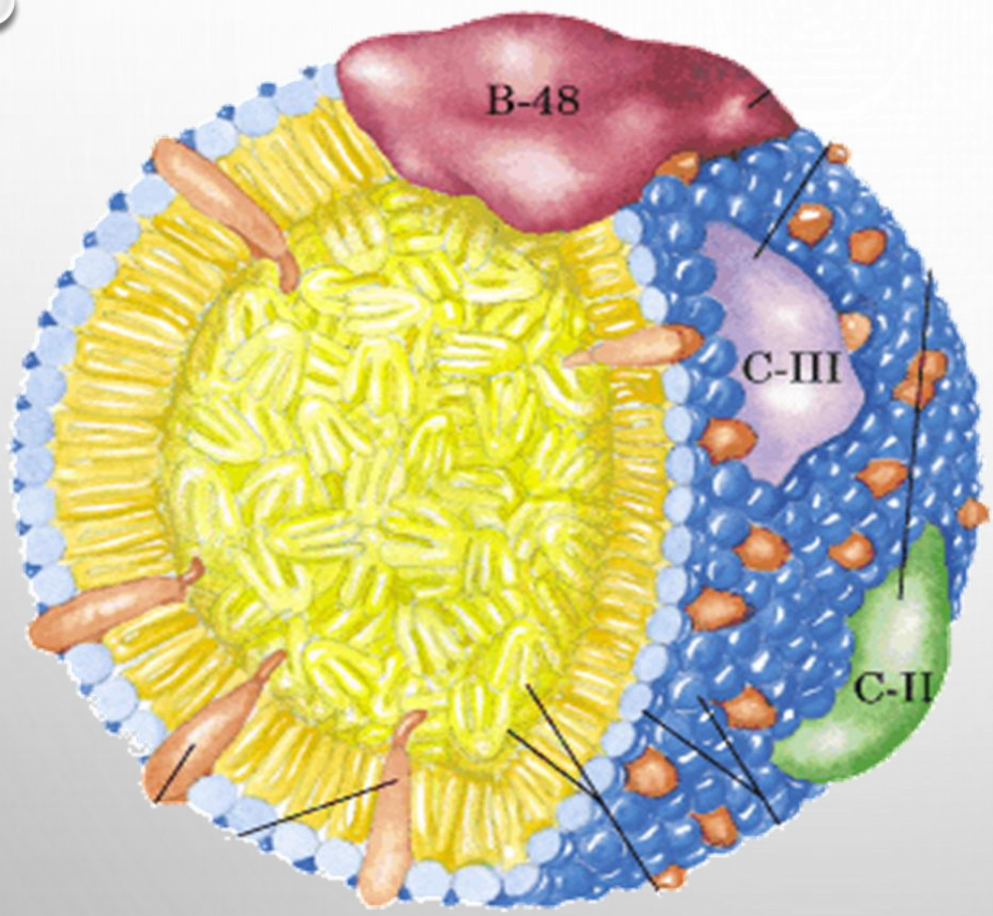
LIPID MALABSORPTION(STEATORRHEA)

- Lipid malabsorption results in increased lipids including fat soluble vitamins a,d e and k in the feces.
- Cause may be pancreatic insufficiency, including cystic fibrosis , chronic diseases of pancreas or surgical removal of pancreas
- Shortened bowel, celiac diseases, sprue or crohn's disease may be bile duct obstruction due to gall stones, tumor of head of pancreas, enlarged lymph nodes etc.
- Milk and coconut oil are used therapeutically since they contain medium chain fatty acids.

SECRETION OF LIPIDS FROM ENTEROCYTES

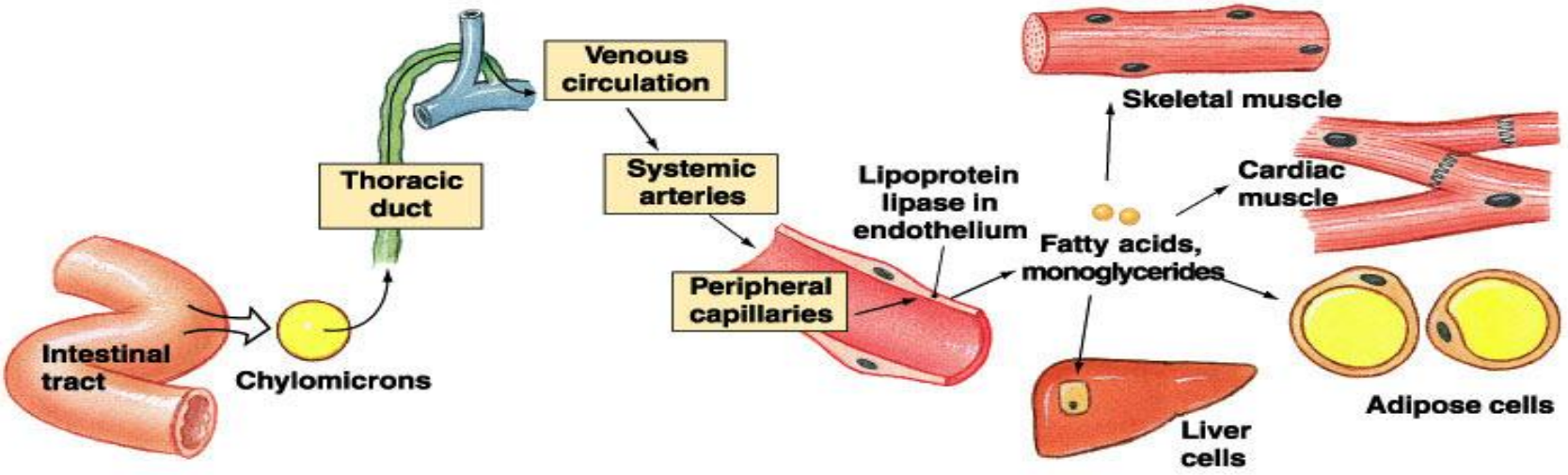
- Once inside the enterocyte, monoglycerides and fatty acids are re-synthesized into tag.
- The tag is packaged, along with cholesterol and fat soluble vitamins, into **chylomicrons**.
- Chylomicrons are **lipoproteins,** special particles that are designed for the transport of lipids in the circulation.
- Chylomicrons are released by exocytosis at the basolateral surface of the enterocytes. because they are particles, they are too large to enter typical capillaries.
- Instead they enter **lacteals**, lymphatic capillaries that poke up into the center of each villus.
- Chylomicrons then flow into the circulation via lymphatic vessels.

STRUCTURE OF CHYLOMICRON



- *size:* 0.1–1 µm
- *Average composition*
  - Tg (84%)
  - Cholesterol(2%)
  - Ester cholesterol (4%)
  - Phospholipid (8%)
  - Apo lipoproteins (2%)

TRANSPORT AND UTILIZATION OF CHYLOMICRONS



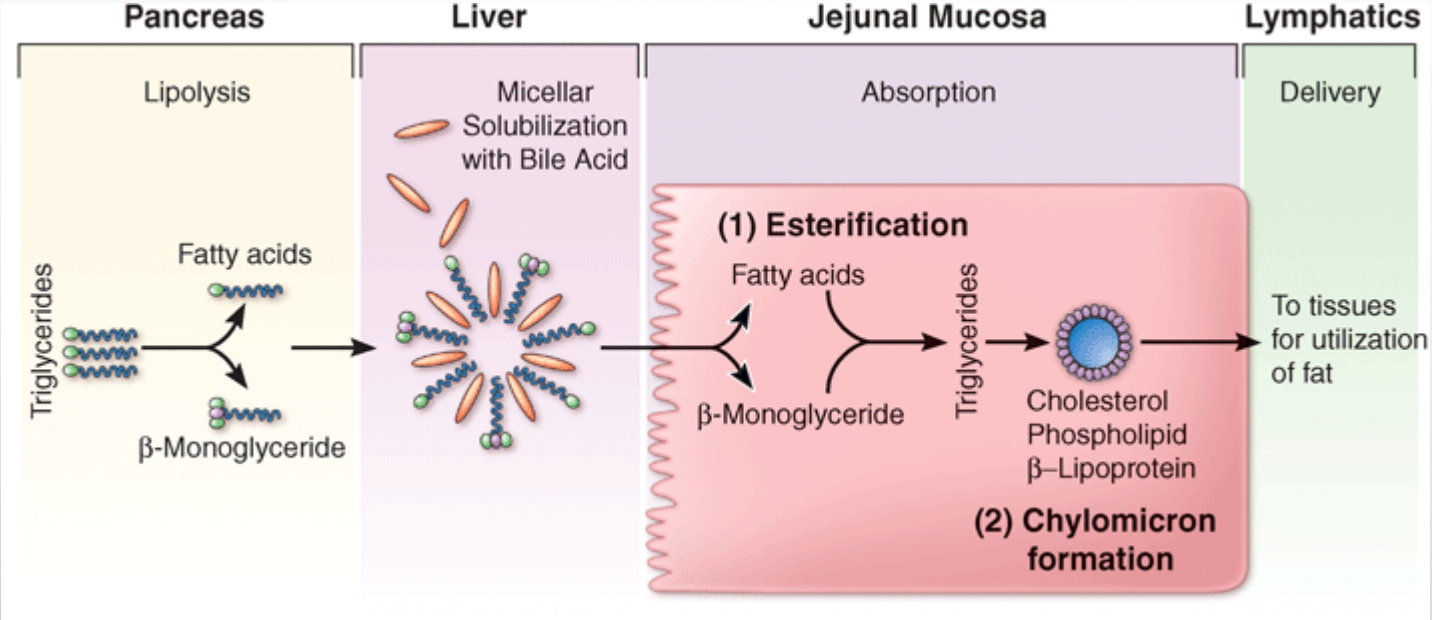
CLINICAL SIGNIFICANCE OF CHYLOMICRON SYNTHESIS AND UTILIZATION

- **Defective synthesis-** due to deficiency of apo-b 48 protein. the triglyceride may accumulate in intestinal cells.
- **Chyluria-** due to an abnormal connection between urinary tract and lymphatic drainage system of the intestines, forming chylous fistula. characterized by passage of milky urine.
- **Chylothorax-** there is an abnormal connection between pleural space and the lymphatic drainage of small intestine resulting in accumulation of lymph in pleural cavity giving milky pleural effusion

PHYSIOLOGICALLY IMPORTANT LIPASES

Lipase	Site of action	Preferred substrate	Product(s)
Lingual / acid stable lipase	Mouth , stomach	TAGs with medium chain FAs	FFA+DAG
Pancreatic lipase + co-lipase	Small intestine	TAGs with long chain FAs	FFA+2MAG
Intestinal lipase with bile acids	Small intestine	TAGs with medium chain FAs	2FFA+glycerol
Phospholipase A_2 + bile acids	Small intestine	PLs with unsat. FA at position 2	Unsat FFA lysolecithin
Lipoprotein lipase insulin (+)	Capillary walls	TAGs in chylomicron or VLDL	FFA+ glycerol
Hormone sensitive lipase	Adipose cell	TAG stored in adipose cells	FFA+ glycerol

SUMMARY OF LIPID DIGESTION AND ABSORPTION



Chylomicrons deliver absorbed tag to the body's cells. tag in chylomicrons and other lipoproteins are hydrolyzed by **lipoprotein lipase,** an enzyme that is found in capillary endothelial cells. monoglycerides and fatty acids released from digestion of tag then diffuse into cells.

Absorption of lipids through the intestinal wall