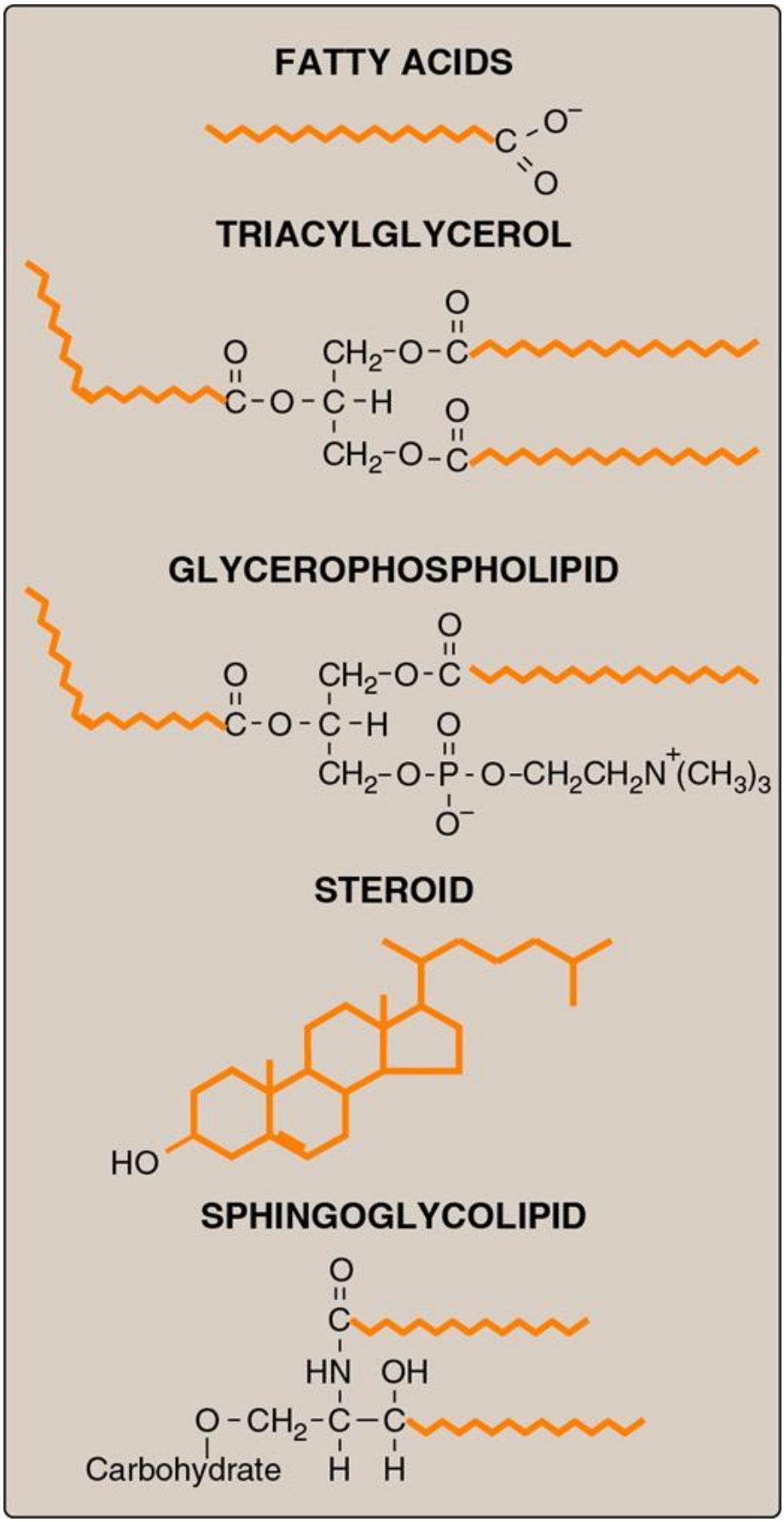
# 15: Dietary Lipid Metabolism

## Overview



Lipids are a heterogeneous group of water-insoluble (hydrophobic) organic molecules (Fig. 15.1). Because of their insolubility in aqueous solutions, body lipids are generally found compartmentalized, as in the case of membrane-associated lipids or droplets of triacylglycerol (TAG) in adipocytes, or transported in blood in association with protein, as in lipoprotein particles or on albumin. Lipids are a major source of energy for the body, and they also provide the hydrophobic barrier that permits partitioning of the aqueous contents of cells and subcellular structures. Lipids serve additional functions in the body (e.g., some fat-soluble vitamins have regulatory or coenzyme functions, and the prostaglandins and steroid hormones play major roles in the control of the body's homeostasis). Deficiencies or imbalances of lipid metabolism can lead to some of the major clinical problems encountered by physicians, such as atherosclerosis, diabetes, and obesity.

**FIGURE 15.1**




## Digestion, Absorption, Secretion, and Utilization

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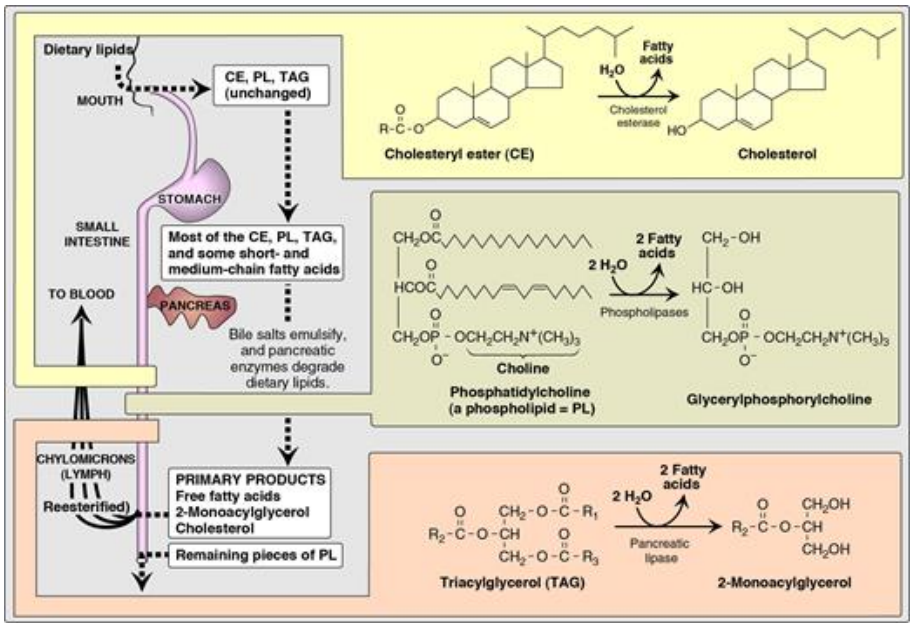
The average daily intake of lipids by U.S. adults is ~78 g, of which >90% is TAG, also known as triglyceride (TG), that consists of three fatty acids (FA) esterified to a glycerol backbone (see Fig. 15.1). The remainder of the dietary lipids consists primarily of cholesterol, cholesteryl esters, phospholipids, and nonesterified (free) FA (FFA). The digestion of dietary lipids begins in the stomach and is completed in the small intestine. The process is summarized in Figure 15.2.

**FIGURE 15.2**




## Digestion in the stomach

Lipid digestion in the stomach is limited. It is catalyzed by lingual lipase that originates from glands at the back of the tongue and gastric lipase that is secreted by the gastric mucosa. Both enzymes are relatively acid stable, with optimal pH values of 4 to 6. These acid lipases hydrolyze FA from TAG molecules, particularly those containing short- or medium-chain-length (≤12 carbons) FA such as are found in milk fat. Consequently, these lipases play a particularly important role in lipid digestion in infants for whom milk fat is the primary source of calories. They also become important digestive enzymes in individuals with pancreatic insufficiency such as those with cystic fibrosis (CF). Lingual and gastric lipases aid these patients in degrading TAG molecules (especially those with short- to medium-chain FA) despite a near or complete absence of pancreatic lipase (see Section D.1. below).

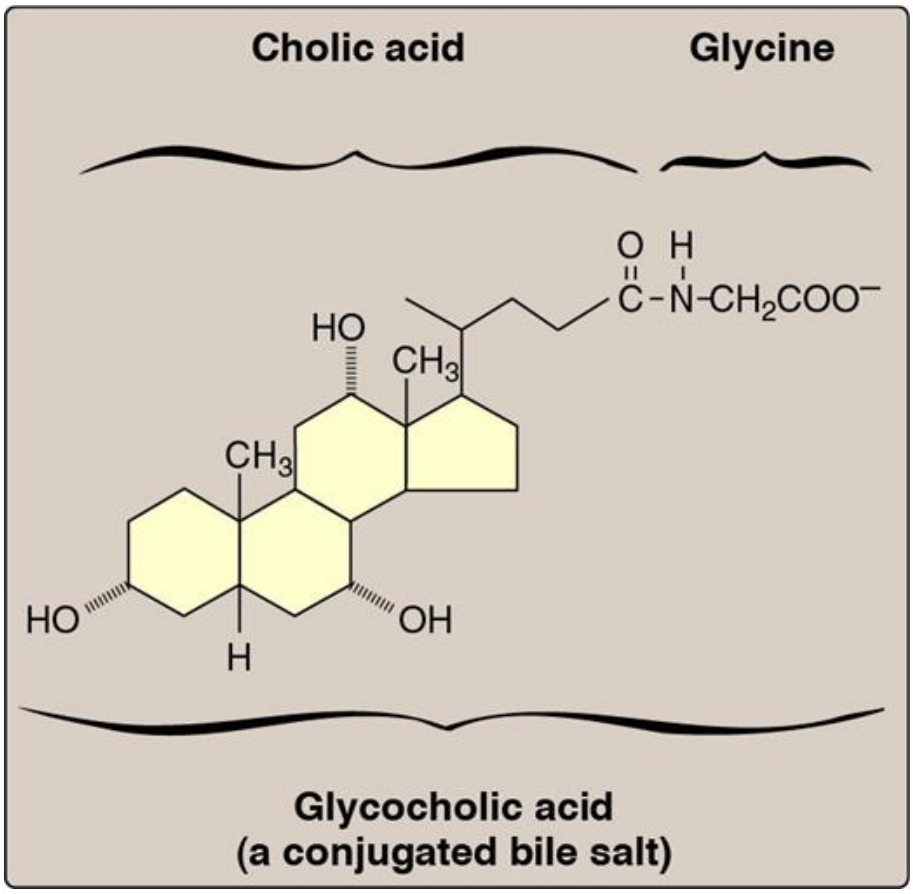
## Cystic fibrosis

CF is the most common lethal genetic disease in Caucasians of Northern European ancestry and has a prevalence of ~1:3,300 births in the United States. CF is an autosomal-recessive disorder caused by mutations to the gene for the CF transmembrane conductance regulator (CFTR) protein that functions as a chloride channel on epithelium in the pancreas, lungs, testes, and sweat glands. Defective CFTR results in decreased secretion of chloride and increased uptake of sodium and water. In the pancreas, the depletion of water on the cell surface results in thickened mucus that clogs the pancreatic ducts, preventing pancreatic enzymes from reaching the intestine, thereby leading to pancreatic insufficiency. Treatment includes replacement of these enzymes and supplementation with fat-soluble vitamins. (Note: CF also causes chronic lung infections with progressive pulmonary disease and male infertility.)

## Emulsification in the small intestine

The critical process of dietary lipid emulsification occurs in the duodenum. Emulsification increases the surface area of the hydrophobic lipid droplets so that the digestive enzymes, which work at the interface of the droplet and the surrounding aqueous solution, can act effectively. Emulsification is accomplished by two complementary mechanisms, namely, use of the detergent properties of the conjugated bile salts and mechanical mixing due to peristalsis. Bile salts, made in the liver and stored in the gallbladder, are amphipathic derivatives of cholesterol. Conjugated bile salts consist of a hydroxylated sterol ring structure with a side chain to which a molecule of glycine or taurine is covalently attached by an amide linkage (Fig. 15.3). These emulsifying agents interact with the dietary lipid droplets and the aqueous duodenal contents, thereby stabilizing the droplets as they become smaller from peristalsis and preventing them from coalescing. (Note: See Chapter 18 for a more complete discussion of bile salt metabolism.)

**FIGURE 15.3**




## Degradation by pancreatic enzymes

The dietary TAG, cholesteryl esters, and phospholipids are enzymatically degraded (digested) in the small intestine by pancreatic enzymes, whose secretion is hormonally controlled.

### Triacylglycerol degradation

TAG molecules are too large to be taken up efficiently by the mucosal cells (enterocytes) of the intestinal villi. Therefore, they are hydrolyzed by an esterase, pancreatic lipase, which preferentially removes the FA at carbons 1 and 3. The primary products of hydrolysis are, thus, a mixture of 2-monoacylglycerol (2-MAG) and FFA (see Fig. 15.2). (Note: Pancreatic lipase is found in high concentrations in pancreatic secretions [2% to 3% of the total protein present], and it is highly efficient catalytically, thus ensuring that only severe pancreatic deficiency, such as that seen in CF, results in significant malabsorption of fat.) A second protein, colipase, also secreted by the pancreas, binds the lipase at a ratio of 1:1 and anchors it at the lipid–aqueous interface. Colipase restores activity to lipase in the presence of inhibitory substances like bile salts that bind the micelles. (Note: Colipase is secreted as the zymogen, procolipase, which is activated in the intestine by trypsin.) Orlistat, an antiobesity drug, inhibits gastric and pancreatic lipases, thereby decreasing fat absorption, resulting in weight loss.

### Cholesteryl ester degradation

Most dietary cholesterol is present in the free (nonesterified) form, with 10% to 15% present in the esterified form. Cholesteryl esters are hydrolyzed by pancreatic cholesteryl ester hydrolase (cholesterol esterase), which produces cholesterol plus FFA (see Fig. 15.2). Activity of this enzyme is greatly increased in the presence of bile salts.

### Phospholipid degradation

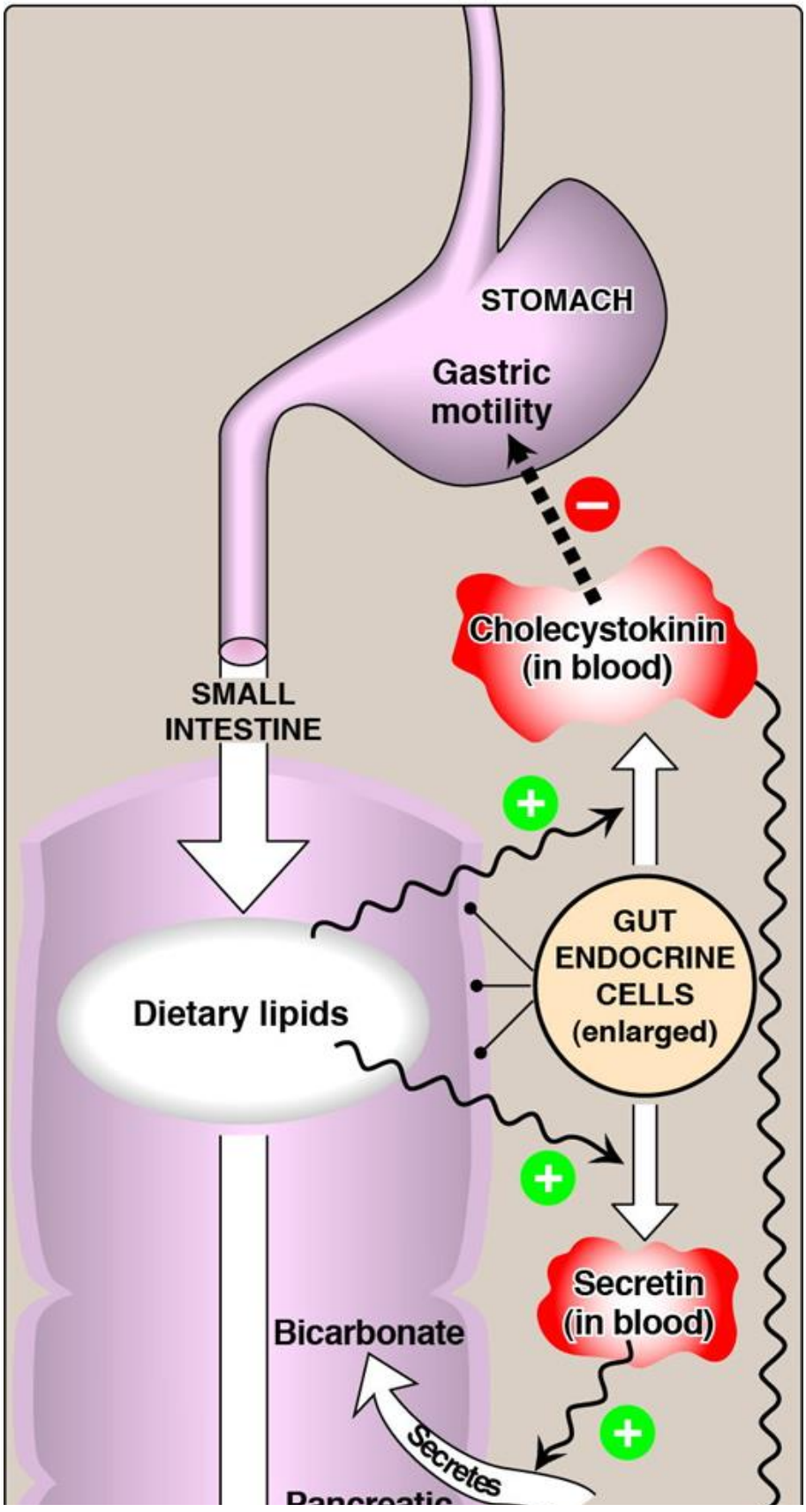
Pancreatic juice is rich in the proenzyme of phospholipase $A_2$ that, like procolipase, is activated by trypsin and, like cholesteryl ester hydrolase, requires bile salts for optimum activity. Phospholipase $A_2$ removes one FA from carbon 2 of a phospholipid, leaving a lysophospholipid. For example, phosphatidylcholine (the predominant phospholipid of digestion) becomes lysophosphatidylcholine. The remaining FA at carbon 1 can be removed by lysophospholipase, leaving a glycerylphosphoryl base (e.g., glycerylphosphorylcholine, see Fig. 15.2) that may be excreted in the feces, further degraded, or absorbed.

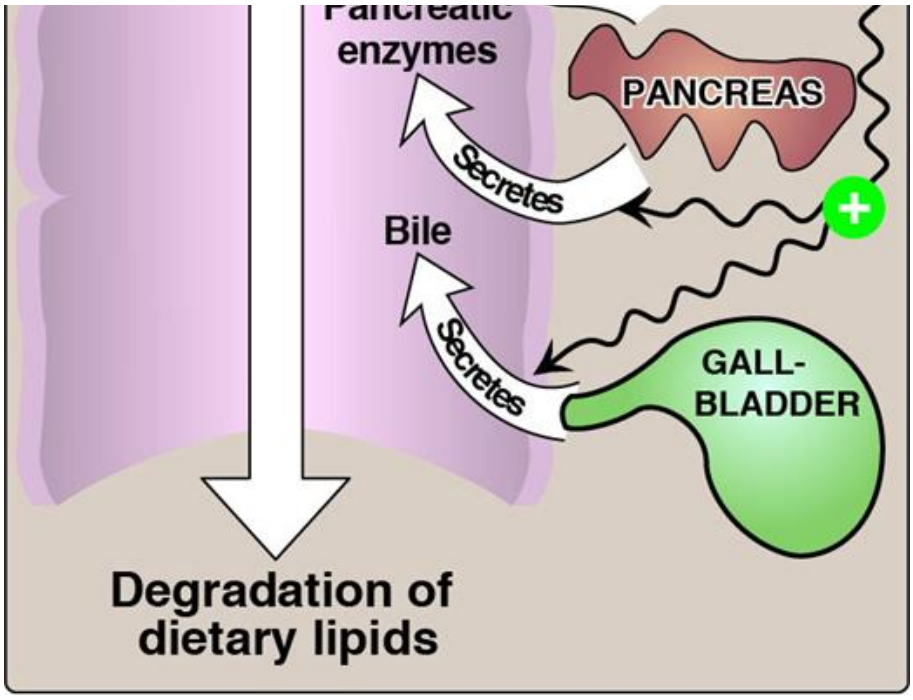
### Control

Pancreatic secretion of the hydrolytic enzymes that degrade dietary lipids in the small intestine is hormonally controlled (Fig. 15.4). Enteroendocrine cells found throughout the small intestine secrete several hormones such as cholecystokinin (CCK) and secretin. Enteroendocrine I cells in the mucosa of the lower duodenum and jejunum produce the peptide hormone CCK, in response to the presence of lipids and partially digested proteins entering these regions of the upper small intestine. CCK acts on the gallbladder (causing it to contract and release bile, a mixture of bile salts, phospholipids, and free cholesterol) and on the exocrine cells of the pancreas (causing them to release digestive enzymes). It also decreases gastric motility, resulting in a slower release of gastric contents into the small intestine. Enteroendocrine S cells produce another peptide hormone, secretin, in response to the low pH of the chyme entering the intestine from the stomach. Secretin causes the pancreas to release a solution rich in bicarbonate that helps neutralize the pH of the intestinal contents, bringing them to the appropriate pH for digestive activity by pancreatic enzymes.

**FIGURE 15.4**

per 5%], the jejunum, and the ileum

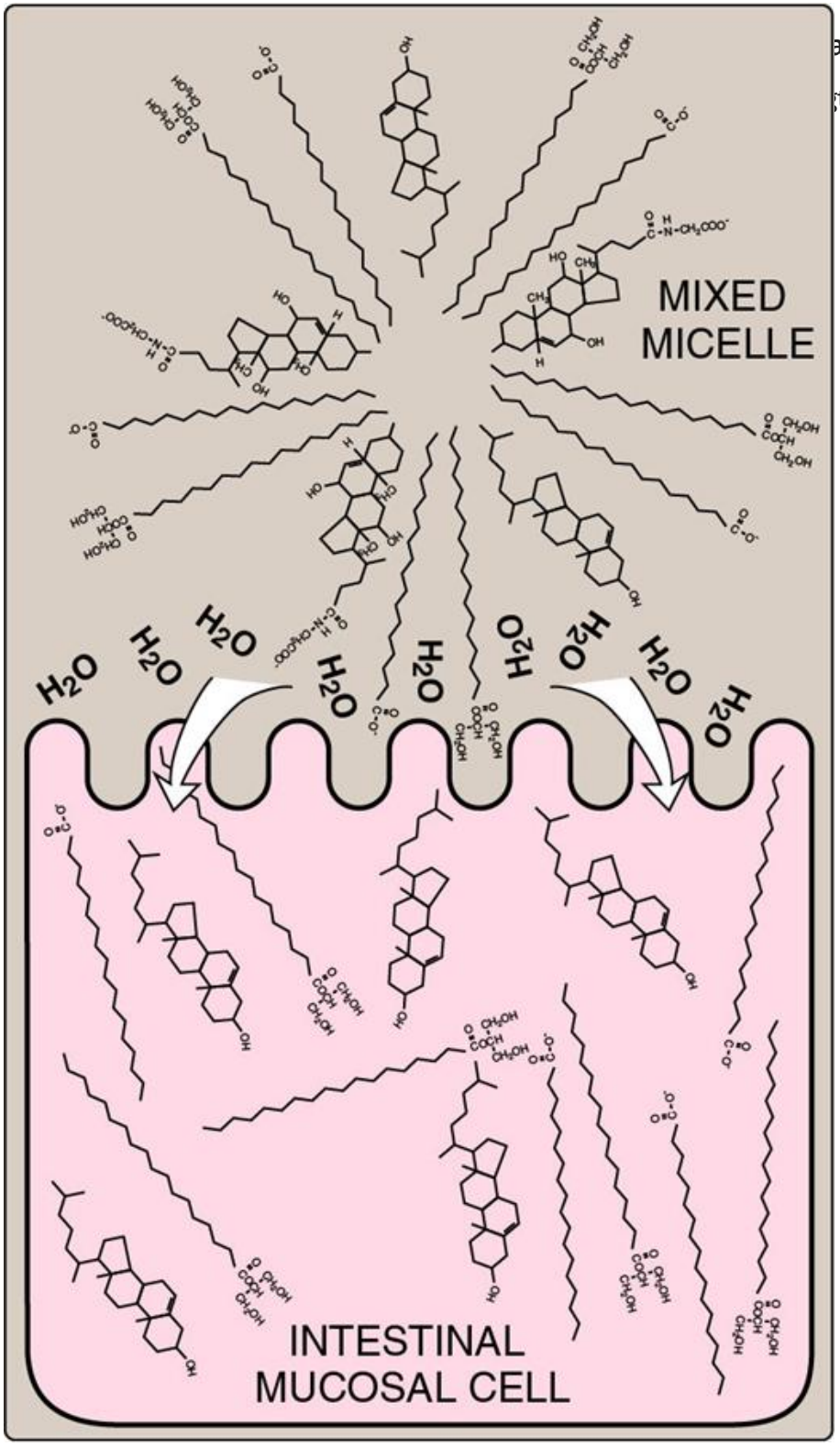





## Absorption by enterocytes

FFA, free cholesterol, and 2-MAG are the primary products of lipid digestion in the jejunum. These, plus bile salts and fat-soluble vitamins (A, D, E, and K), form mixed micelles (i.e., disc-shaped clusters of a mixture of amphipathic lipids that coalesce with their hydrophobic groups on the inside and their hydrophilic groups on the outside). Therefore, mixed micelles are soluble in the aqueous environment of the intestinal lumen (Fig. 15.5). These particles approach the primary site of lipid absorption, the brush border membrane of the enterocytes. This microvilli-rich apical membrane is separated from the liquid contents of the intestinal lumen by an unstirred water layer that mixes poorly with the bulk fluid. The hydrophilic surface of the micelles facilitates the transport of the hydrophobic lipids through the unstirred water layer to the brush border membrane where they are absorbed. Bile salts are absorbed in the terminal ileum, with <5% being lost in the feces. (Note: Cholesterol and plant sterols are taken up by the enterocytes through the Niemann-Pick C1-like 1 (NPC1L1) protein in the brush border cells. Ezetimibe, a cholesterol-lowering drug, inhibits NPC1L1 reducing cholesterol absorption in the small intestine.) Because short- and medium-chain FA are water soluble, they do not require the assistance of mixed micelles for absorption by the intestinal mucosa.

**FIGURE 15.5**

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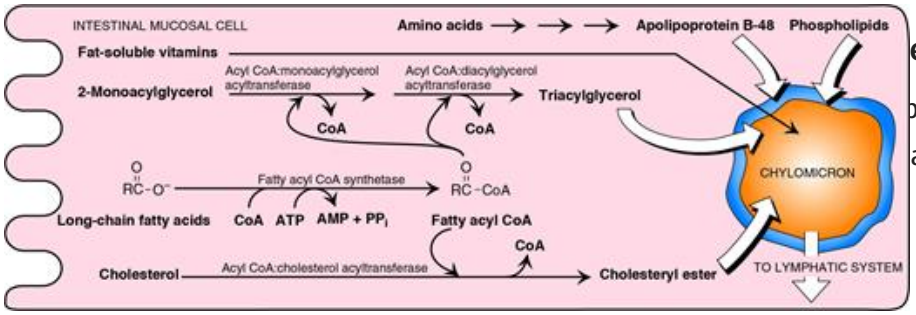
## Triacylglycerol and cholesteryl ester resynthesis

The mixture of lipids absorbed by the enterocytes migrates to the smooth endoplasmic reticulum (SER) where biosynthesis of complex lipids takes place. The long-chain FA are first converted into their activated form by fatty acyl coenzyme A (CoA) synthetase (thiokinase), as shown in Figure 15.6. Using the fatty acyl CoA derivatives, the 2-MAG absorbed by the enterocytes are converted to TAG through sequential reacylations by two acyltransferases, acyl CoA: MAG acyltransferase and acyl CoA:diacylglycerol acyltransferase. Lysophospholipids are reacylated to form phospholipids by a family of acyltransferases, and cholesterol is acylated primarily by acyl CoA:cholesterol acyltransferase. (Note: Virtually all long-chain FA entering the enterocytes are used in this fashion to form TAG, phospholipids, and cholesteryl esters. Short- and medium-chain FA are not converted to their CoA derivatives and are not reesterified to 2-MAG. Instead, they are released into the portal circulation, where they are carried by serum albumin to the liver.)

**FIGURE 15.6**




**ells.**

oration into chylomicrons and directly

ate; $PP_i$ = pyrophosphate.

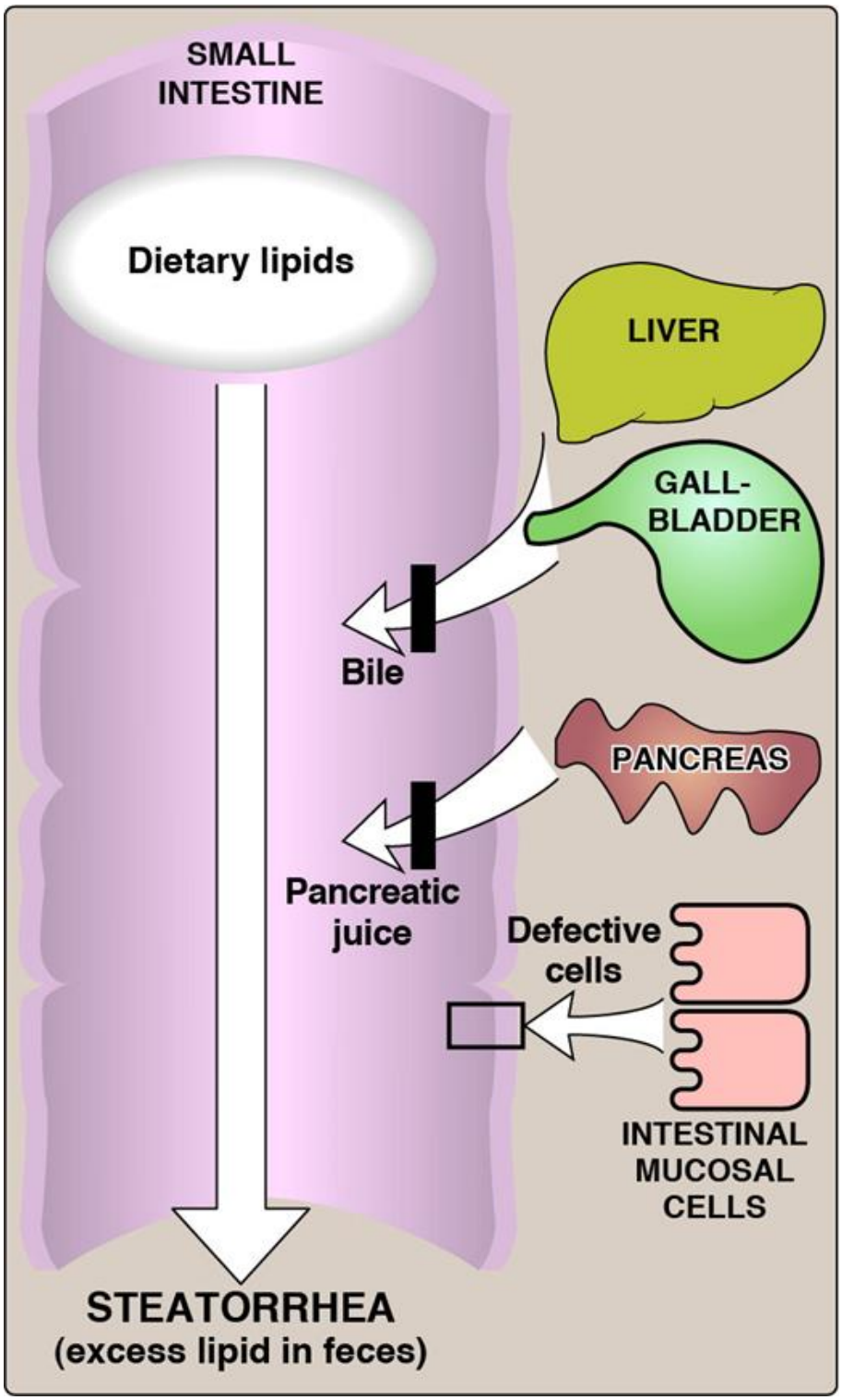
## Secretion from enterocytes

The newly resynthesized TAG and cholesteryl esters are very hydrophobic and aggregate in an aqueous environment. Therefore, they must be packaged as particles of lipid droplets surrounded by a thin layer composed of phospholipids, nonesterified cholesterol, and a molecule of the protein apolipoprotein (apo) B-48. This layer stabilizes the particle and increases its solubility, thereby preventing multiple particles from coalescing. (Note: Microsomal TG transfer protein is essential for the assembly of all TAG-rich apo B–containing particles in the ER.) The lipoprotein particles are released by exocytosis from enterocytes into the lacteals (lymphatic vessels in the villi of the small intestine). The presence of these particles in the lymph after a lipid-rich meal gives it a milky appearance. This lymph is called chyle (as opposed to chyme, the name given to the semifluid mass of partially digested food that passes from the stomach to the duodenum), and the particles are named chylomicrons. Chylomicrons follow the lymphatic system to the thoracic duct and are then conveyed to the left subclavian vein, where they enter the blood. The steps in the production of chylomicrons are summarized in Figure 15.6. (Note: Once released into blood, the nascent [immature] chylomicrons pick up apolipoproteins E and C-II from high-density lipoproteins and mature. [For a more detailed description of chylomicron structure and metabolism, see Chapter 18.])

## Lipid malabsorption

Lipid malabsorption, resulting in increased lipid (including the fat-soluble vitamins and essential FA, see Chapter 16) in the feces, a condition known as steatorrhea, can be caused by disturbances in lipid digestion and/or absorption (Fig. 15.7). Such disturbances can result from several conditions, including CF (causing poor digestion), short bowel syndrome (causing decreased absorption), and bariatric surgery (insufficient secretion of pancreatic enzymes).

**FIGURE 15.7**



The ability of short- and medium-chain FA to be taken up by enterocytes without the aid of mixed micelles has made them important in medical nutrition therapy for individuals with malabsorption disorders.

### Use by the tissues

Most of the TAG contained in chylomicrons is broken down in the capillary beds of skeletal and cardiac muscle and adipose tissue. The TAG is degraded to FFA and glycerol by lipoprotein lipase (LPL). This enzyme is synthesized and secreted primarily by adipocytes and muscle cells. Secreted LPL is anchored to the luminal surface of endothelial cells in the capillaries of muscle and adipose tissues. LPL is activated when bound to the cofactor, ApoCII which resides on the circulating lipoprotein particles. (Note: Familial chylomicronemia [type I Hyperlipoproteinemia] is a rare, autosomal-recessive disorder caused by a deficiency of LPL or its coenzyme apo C-II [see Chapter 18]. The result is fasting chylomicronemia and severe hypertriacylglycerolemia, which can cause pancreatitis.)

#### Fate of free fatty acids

The FFA derived from the hydrolysis of TAG may either directly enter adjacent muscle cells and adipocytes or be transported in the blood in association with serum albumin until they are taken up by cells. (Note: Human serum albumin is a large protein secreted by the liver. It transports a number of primarily hydrophobic compounds in the circulation, including FFA and some drugs.) Most cells can oxidize FA to produce energy. Adipocytes can also reesterify FFA to produce TAG molecules, which are stored until the FA are needed by the body.

#### Fate of glycerol

Glycerol released from TAG is taken up from the blood and phosphorylated by hepatic glycerol kinase to produce glycerol 3-phosphate, which can enter either glycolysis or gluconeogenesis by oxidation to dihydroxyacetone phosphate or be used in TAG synthesis (see Chapter 16).

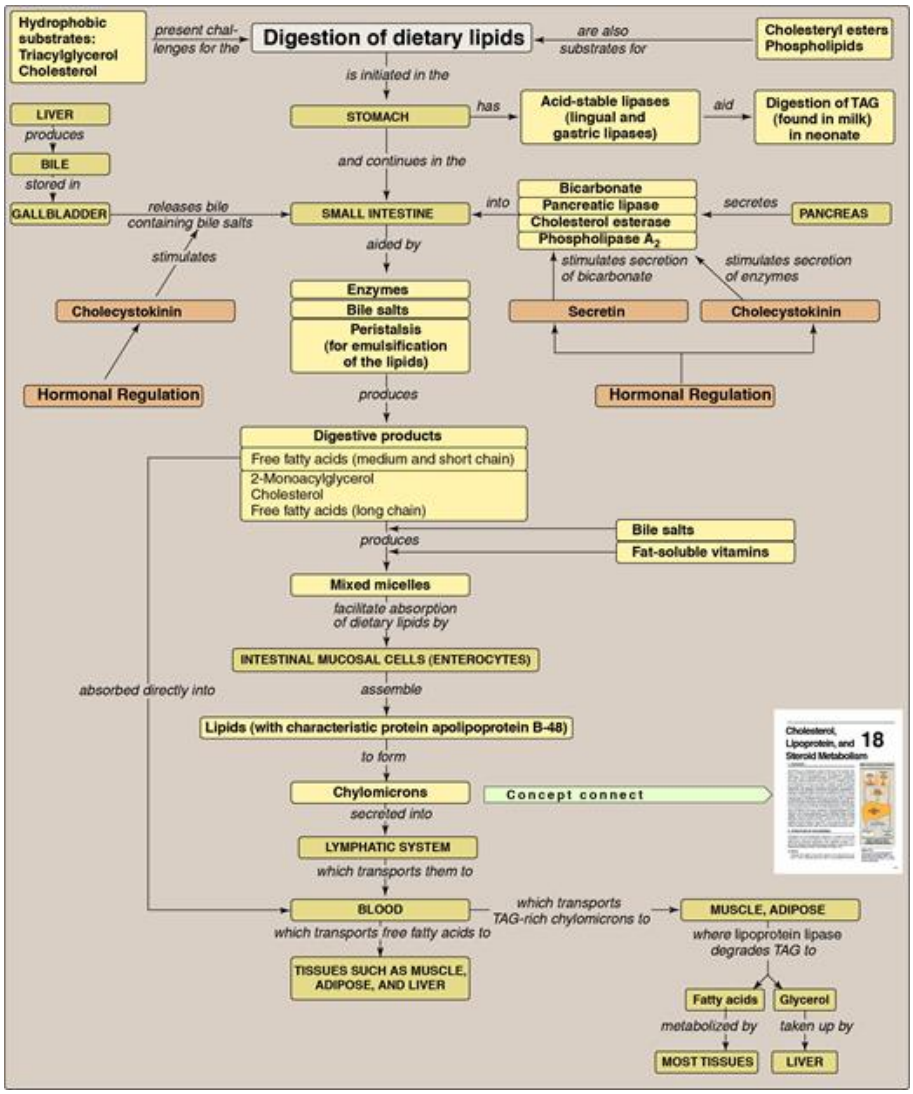
#### Fate of chylomicron remnants

After most of the TAG has been removed, the chylomicron remnants (which contain cholesteryl esters, phospholipids, apolipoproteins, fat-soluble vitamins, and a small amount of TAG) bind to receptors on the liver (apo E is the ligand; see Chapter 18) and are endocytosed. The intracellular remnants are hydrolyzed to their component parts. Cholesterol and the nitrogenous bases of phospholipids (e.g., choline) can be recycled by the body. (Note: If removal of remnants by the liver is decreased because of impaired binding to their receptor, they accumulate in the plasma. This is seen in the rare type III hyperlipoproteinemia [also called familial dysbetalipoproteinemia or broad beta disease].)

## Chapter Summary

- **Dietary lipid digestion** begins in the stomach and continues in the small intestine (Fig. 15.8).

**FIGURE 15.8**




- **Cholesteryl esters**, **phospholipids**, and **TAG** containing **long-chain-length FA** are degraded in the **small intestine** by **pancreatic enzymes**. The most important of these enzymes are **cholesterol esterase**, **phospholipase $A_2$**, and **pancreatic lipase**. In **CF**, thickened mucus prevents these enzymes reaching the intestine.
- TAGs in **milk fat** contain **short-** to **medium-chain-length FA** and are degraded in the **stomach** by **acid lipases** (**lingual lipase** and **gastric lipase**).
- The **hydrophobic** nature of lipids requires that dietary lipids be **emulsified** for efficient degradation. Emulsification occurs in the small intestine using **peristaltic action** (mechanical mixing) and **bile salts** (detergents).
- The primary products of dietary lipid degradation are **2-MAG**, nonesterified (free) **cholesterol**, and **free FA**. These compounds, plus the **fat-soluble vitamins**, form **mixed micelles** that facilitate dietary lipid absorption by **intestinal mucosal cells** (**enterocytes**). These cells use activated long-chain FA to regenerate TAG and

cholesteryl esters and also synthesize protein **apo B-48**, all of which are then assembled with the fat-soluble vitamins into **lipoprotein particles** called **chylomicrons**. Short- and medium-chain FA enter blood directly.

- Chylomicrons are first released into the **lymph** and then enter the **blood**, where their lipid core is degraded by **LPL** (with **apo C-II** as the coenzyme) in the **capillaries** of **muscle** and **adipose** tissues. Thus, dietary lipids are made available to the peripheral tissues.
- A deficiency in the ability to degrade chylomicron components, or remove chylomicron remnants after TAG has been degraded, results in accumulation of these particles in blood.
- **Fat maldigestion** or malabsorption causes **steatorrhea** (lipid in the feces).

## Study Questions

Listen

**Choose the ONE best answer.**

**15.1. Which one of the following statements about lipid digestion is correct?**

A. Large lipid droplets are emulsified (have their surface area increased) in the mouth through the act of chewing (mastication).

B. The enzyme colipase facilitates the binding of bile salts to mixed micelles, maximizing the activity of pancreatic lipase.

C. The peptide hormone secretin causes the gallbladder to contract and release bile.

D. Patients with cystic fibrosis have difficulties with digestion because their pancreatic secretions are less able to reach the small intestine, the primary site of lipid digestion.

E. Formation of triacylglycerol-rich chylomicrons is independent of protein synthesis in the intestinal mucosa.

Correct answer = D. Patients with cystic fibrosis, a genetic disease resulting in a deficiency of a functional chloride transporter, have thickened mucus that impedes the flow of pancreatic enzymes into the duodenum. Emulsification occurs through peristalsis, which provides mechanical mixing, and bile salts that function as detergents. Colipase restores activity to pancreatic lipase in the presence of inhibitory bile salts that bind the micelles. Cholecystokinin is the hormone that causes contraction of the gallbladder and release of stored bile, and secretin causes release of bicarbonate. Chylomicron formation requires synthesis of apolipoprotein B-48.

**15.2. Which one of the following statements about lipid absorption from the intestine is correct?**

A. Dietary triacylglycerol must be completely hydrolyzed to free fatty acids and glycerol before absorption.

B. The triacylglycerol carried by chylomicrons is degraded by lipoprotein lipase, producing fatty acids that are taken up by muscle and adipose tissues and glycerol that is taken up by the liver.

C. Fatty acids that contain ≤12 carbon atoms are absorbed and enter the circulation primarily via the lymphatic system.

D. Deficiencies in the ability to absorb fat result in excessive amounts of chylomicrons in the blood.

Correct answer = B. The triacylglycerols (TAG) in chylomicrons are degraded to fatty acids (FA) and glycerol by lipoprotein lipase on capillary endothelial surfaces in muscle and adipose tissue, thus providing a source of FA to these tissues for degradation or storage and providing glycerol for hepatic metabolism. In the duodenum, TAG are degraded to one 2-monoacylglycerol + two free FA that get absorbed. Medium- and short-chain FA enter directly into blood (not lymph), and they neither require micelles nor get packaged into chylomicrons. Because chylomicrons contain dietary lipids that were digested and absorbed, a defect in fat absorption would result in decreased production of chylomicrons.

**15.3. A 2-year-old female is brought to the physician because of recurrent respiratory tract infections, weight loss, and foul-smelling diarrhea. This patient most likely has a defective secretion in which of the following?**

A. Cholecystokinin

B. Pancreatic enzymes

C. Chylomicron

D. Secretin

Correct answer: B. This patient most likely has cystic fibrosis (CF) which causes defective secretion of pancreatic enzymes such as lipase and colipase due to mutations in the cystic fibrosis transmembrane conductance receptor (CFTR). These enzymes are important for digestion and absorption of lipids. Cholecystokinin and secretin are released from enteroendocrine cells. Although they are important for lipid digestion and absorption, they are not defective in CF. Chylomicron formation and release into lymphatic system is not affected in CF.

**15.4. A 45-year-old female is brought to the emergency department due to acute pain, nausea, and vomiting. Computed tomography indicates acute pancreatitis that leads to an increased activation of trypsin. Which of the following is most likely activated in this condition?**

A. Gastric lipase

B. Pancreatic lipase

C. Lysophospholipase

D. Colipase

Correct answer: D. Colipase is secreted as the zymogen, procolipase, which is activated in the intestine by trypsin. Colipase is important for pancreatic lipase for hydrolyzing triacylglycerols. Gastric lipase hydrolyze short and medium chain fatty acids in milk, especially important for infants and patients with pancreatic insufficiency. Lysophospholipase is important for the digestion of phospholipids.

**15.5. A 22-month-old child is brought to the physician by her parents because of refusal to feed, chronic diarrhea, abdominal distension, and weight loss. She is diagnosed with chylomicron retention disease, which prevents the release chylomicrons into the lymphatics. This patient most likely has a deficiency in which of the following vitamins?**

A. Ascorbic acid

B. Beta-carotene

C. Folate

D. Pyridoxine

Correct answer: B. Chylomicron is important for the absorption of fat-soluble vitamins: vitamin A, D, E, and K. Beta-carotene is a provitamin A that is packaged into chylomicron before its release into the lymphatics. Ascorbic acid is vitamin C, folate is vitamin B9, and pyridoxine is vitamin B6. These three vitamins are water soluble.