Absorption of Lipids

The bulk of dietary lipid is neutral fat or triglyceride, composed of a glycerol backbone with each carbon linked to a fatty acid. Foodstuffs typically also contain phospholipids, sterols like cholesterol and many minor lipids, including fat-soluble vitamins. Finally, small intestinal contents contain lipids from sloughed epithelial cells and considerable cholesterol delivered in bile.

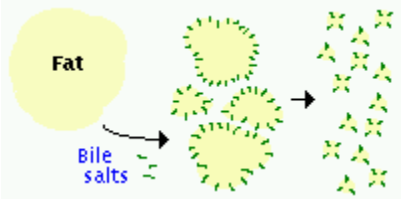
In order for the triglyceride to be absorbed, two processes must occur:

- Large aggregates of dietary triglyceride, which are virtually insoluble in an aqueous environment, must be broken down physically and held in suspension - a process called emulsification.
- Triglyceride molecules must be enzymatically digested to yield monoglyceride and fatty acids, both of which can efficiently diffuse or be transported into the enterocyte

The key players in these two transformations are *bile acids* and *pancreatic lipase*, both of which are mixed with chyme and act in the lumen of the small intestine. Bile acids are also necessary to solubilize other lipids, including cholesterol.

Emulsification, Hydrolysis and Micelle Formation

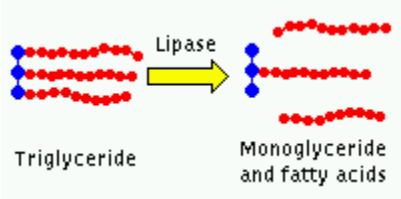
Bile acids play their first critical role in lipid assimilation by promoting emulsification. As derivatives of cholesterol, bile acids have both hydrophilic and hydrophobic domains (i.e. they are amphipathic). On exposure to a large aggregate of triglyceride, the hydrophobic portions of bile acids intercalate into the lipid, with the hydrophilic domains remaining at the surface. Such coating with bile acids aids in breakdown of large aggregates or droplets into smaller and smaller droplets.



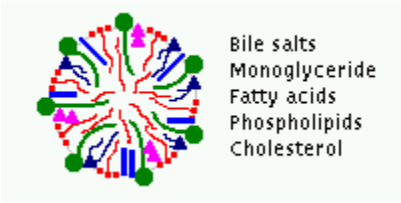
Hydrolysis of triglyceride into monoglyceride and free fatty acids is accomplished predominantly by pancreatic lipase. The activity of this enzyme is to clip the fatty acids at positions 1 and 3 of the triglyceride, leaving two free fatty acids and a 2-monoglyceride.

Lipase is a water-soluble enzyme, and with a little imagination, it's easy to understand why emulsification is a necessary prelude to its efficient activity. Shortly after a meal, lipase is present within the small intestine in rather huge quantities, but can act only on the surface of triglyeride droplets. For a given volume of lipid, the smaller the droplet size, the greater the surface area, which means more lipase molecules can get to work.

The drug orlistat (Xenical) that is promoted for treatment of obesity works by inhibiting pancreatic lipase, thereby reducing the digestion and absorption of fat in the small intestine.



As monoglycerides and fatty acids are liberated through the action of lipase, they retain their association with bile acids and complex with other lipids to form structures called **micelles**. Micelles are essentially small aggregates (4-8 nm in diameter) of mixed lipids and bile acids suspended within the ingesta. As the ingesta is mixed, micelles bump into the brush border of small intestinal enterocytes, and the lipids, including monoglyceride and fatty acids, are taken up into the epithelial cells.



Absorption and Transport into Blood

The major products of lipid digestion - fatty acids and 2-monoglycerides - enter the enterocyte by simple diffusion across the plasma membrane. A considerable fraction of the fatty acids also enter the enterocyte via a specific fatty acid transporter protein in the membrane.

Lipids are transported from the enterocyte into blood by a mechanism distinctly different from what we've seen for monosaccharides and amino acids.

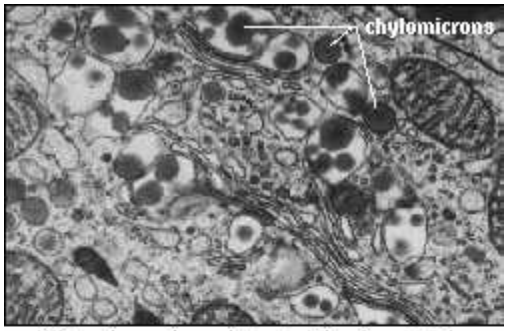
Once inside the enterocyte, fatty acids and monoglyceride are transported into the endoplasmic reticulum, where they are used to synthesize triglyeride. Beginning in the endoplasmic reticulum and continuing in the Golgi, triglyceride is packaged with cholesterol, lipoproteins and other lipids into particles called **chylomicrons**. *Remember where this is occurring - in the absorptive enterocyte of the small intestine.*

Chylomicrons are extruded from the Golgi into exocytotic vesicles, which are transported to the basolateral aspect of the enterocyte. The vesicles fuse with the plasma membrane and undergo exocytosis, dumping the chylomicrons into the space outside the cells.

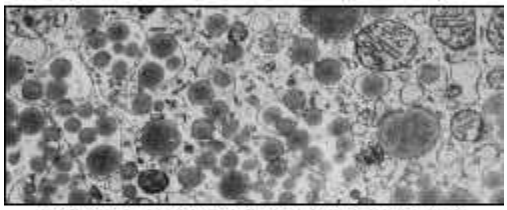
Because chylomicrons are particles, virtually all steps in this pathway can be visualized using an electron microscope, as the montage of images to the right demonstrates.

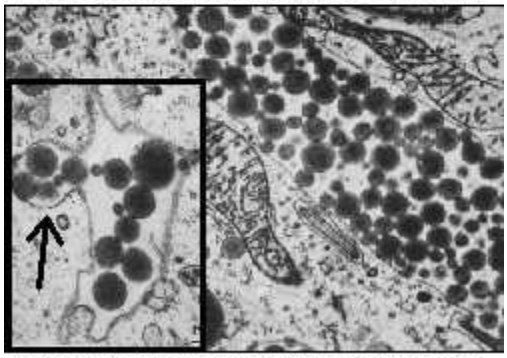
Transport of lipids into the circulation is also different from what occurs with sugars and amino acids. Instead of being absorbed directly into capillary blood, chylomicrons are transported first into the lymphatic vessel that penetrates into each villus. Chylomicron-

rich lymph then drains into the system lymphatic system, which rapidly flows into blood. Blood-borne chylomicrons are rapidly disassembled and their constitutent lipids utilized throughout the body.

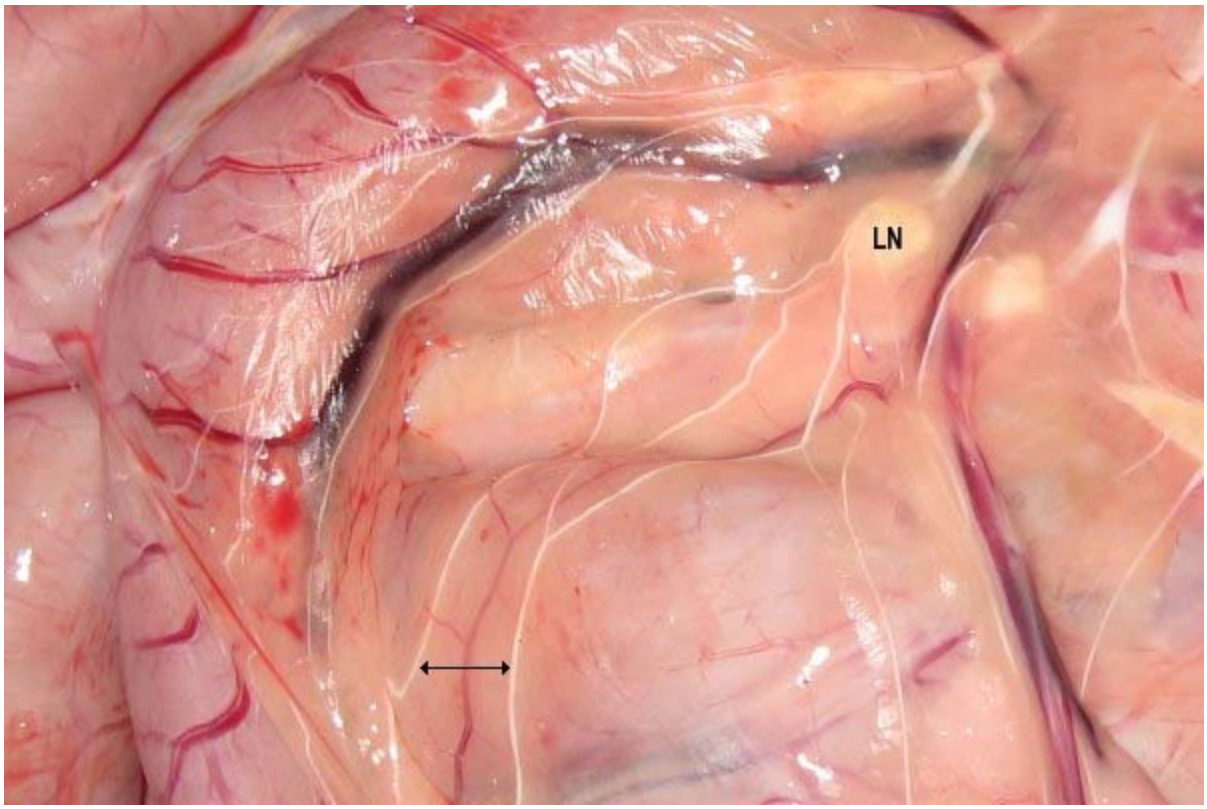


Chylomicrons in vesicles budding from Golgi


Secretory vesicles packed with chylomicrons


Intercellular space between adjacent enterocytes packed with chylomicrons. Inset shows exocytosis of chylomicrons (arrow).

When large numbers of chylomicrons are being absorbed, the lymph draining from the small intestine appears milky and the lymphatics are easy to see. In the image below, of abdominal contents from a coyote, the fine white lines (arrows) are intestinal lymphatics packed with chylomicrons. That lymph passes through mesenteric lymph nodes (LN) and then into larger lymphatics.



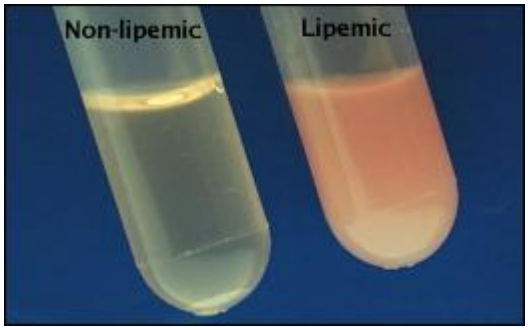
Another lipid of importance that is absorbed in the small intestine is cholesterol. Cholesterol homeostatis results from a balance of cholestrol synthesis, absorption of dietary cholesterol, and elimination of cholesterol by excretion in bile. Years ago it was shown that cholesterol, but not plant sterols, is readily absorbed in the intestine. More recently, a specific transport protein (NPC1L1) has been identified that ferries cholesterol from the intestinal lumen into the enterocyte. From there, a bulk of the cholesterol is esterified, incorporated into chylomicrons and shuttled into blood by the mechanisms described above.

If you are interested in confirming for yourself at least some of the processes described above, you should perform the following experiment:

- Consume a cup of rich cream or a sack of fast-food French fries.
- Do something productive like studying for about 30 minutes.
- Draw a blood sample from yourself (a capillary tube is enough) - use an anticoagulant to prevent clotting.

Centrifuge the blood sample to separate cells and plasma.

When you examine your plasma it will look distinctly milky due to the presence of billions of light-reflecting chylomicrons (the condition is called *lipemia*). If you want extra credit, continue the blood sampling every 15 minutes until your plasma clears, then plot your results on graph paper. Alternatively, you can simply examine the image to the right to see what dog serum looks like after several hours of fasting in comparison to lipemic serum collected shortly after a meal of puppy chow.


Non-lipemic
Lipemic