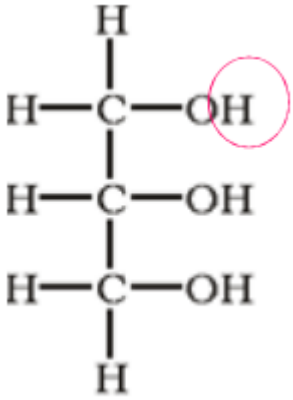
◉Sheet ○Slides

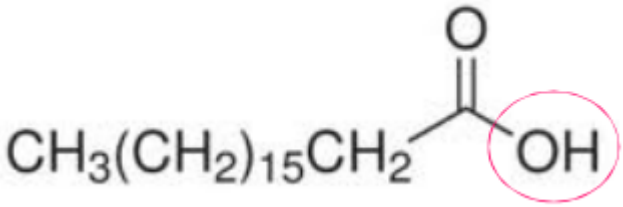
Subject :	**Digestion and Transport of TAG by Plasma Lipoproteins**
Done and corrected by :	**Qusai Zureikat and Basel Baniatta**
Number :	**26**

Transport of TAG by Plasma Lipoproteins

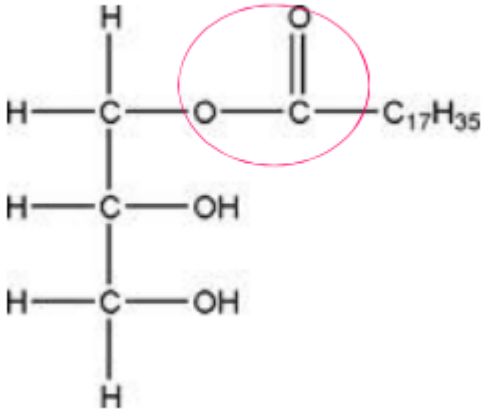
Refer to Lippincott's Illustrated Review Biochemistry Chapter 15 and 18



Glycerol has 3 hydroxyl groups that are responsible for its solubility in water.



The hydrocarbon chain of the **fatty acid** is highly non-polar and therefore water insoluble.

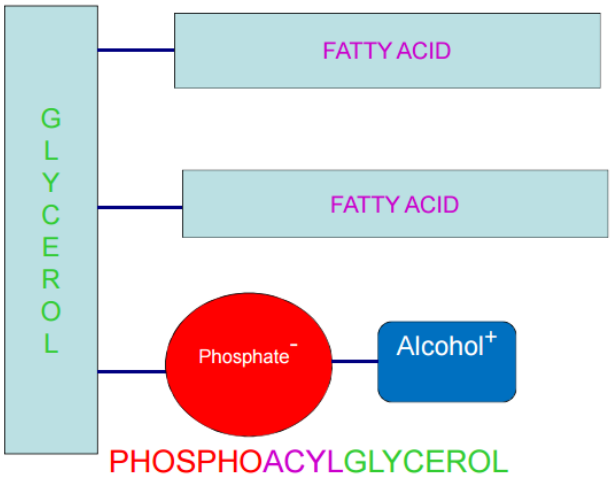


Monoacylglycerols are composed of a molecule of glycerol linked to a fatty acid via an ester bond, thus it no longer has the properties of hydroxyl and carboxyl groups so it becomes very insoluble in water.

-The only common relation between all lipids is their hydrophobic nature (water insoluble) as there is no direct chemical relationship between them.

-Lipids have to be transported from the liver to various tissues by using **Phosphoacylglycerols**, which are amphipathic molecules that can form micelles and thus enhance the solubility of fat (TAG).

-Lipoproteins are multimolecular complexes of lipids and proteins. Unlike, glycoproteins which are composed of a carbohydrate and protein part, Lipoproteins are an *aggregate* of large amounts of lipids and proteins.



-Lipoproteins are found in the plasma of the blood, which is mainly composed of water (90%), and function in the transport of lipids which are insoluble in water.

-The lipids of lipoproteins include:
1) TAG – Triacylglycerol
2) CE – Cholesterol esters
3) CH – Cholesterol
4) PL – Phospholipids

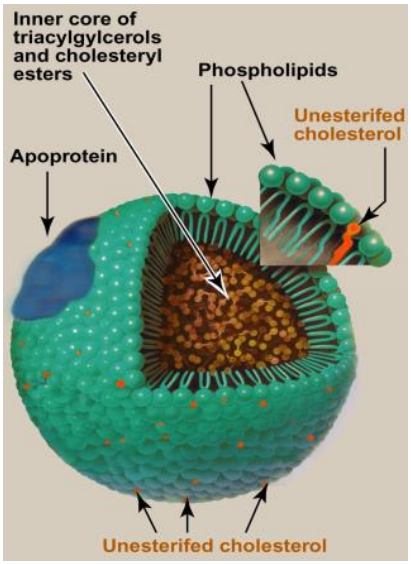
-TAGs and Cholesterol esters → **Insoluble**
-Cholesterol and Phospholipids → **amphipathic**

Apolipoproteins (Apoproteins)

-The protein portion of lipoproteins is called Apo-lipoprotein.
-*Apo* prefix means a protein lacking a non-proteinous part.
-Amphipathic
-Includes several classes Apo A, Apo B-48, Apo E..etc.
-It serves:
1) A structural role by maintaining the structure of lipoproteins
2) A regulatory role
3) In facilitating the binding to cell surface receptors

<u>Structure of Lipoproteins:</u>

1) **A Core (Interior)** : contains TAG and Cholesterol esters because they are none polar(hydrophobic)
2) **Surface Component (Exterior)** : contains phospholipids, unesterified cholesterol and proteins.



Classification of Lipoproteins:
1) According to the type of lipoprotein
2) According to the density (Most commonly used)

-Based on their density, Lipoproteins are classified into:

1- **Chylomicrons**
2- **VLDL** (Very Low Density Lipoproteins)
3- **IDL** (Intermediate Density Lipoproteins)
4- **LDL** (Low Density Lipoproteins)
5- **HDL** (High Density Lipoproteins)

Classes of Lipoproteins

Lipoprotein	Density	Protein	Major Lipid
Chylomicrons	<0.95	2 %	TAG (85%)
VLDL	0.95- 1.006	9%	TAG (55%)
IDL	1.006-1.019	11%	TAG (26%) CE (30%)
LDL	1.019- 1.063	20%	CE (35%)
HDL	1.063- 1.21	45%	PL (25%)

-Each class of lipoproteins has a range of densities (not a fixed density) since they will undergo many changes in the plasma of the blood and accordingly undergo changes in density.

- Density= mass **(g)**/ volume (**cm^3**). The density of water equals 1 g/cm^3.
-Anything that has a density above 1 will sink, and anything that has a density below 1 will float, so Chylomicrons which have a density lower than that of water float.

-The density increases as we go from Chylomicrons (<0.95) to HDL (1.063-1.21)

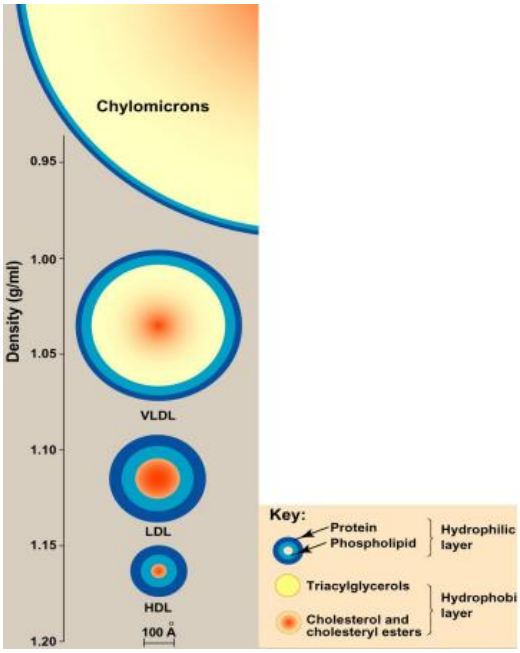
What determines the density of Lipoproteins?
-The ratio of proteins and lipids.

- Higher percentage of Proteins → Higher Density
- Higher percentage of Lipids → Lower Density

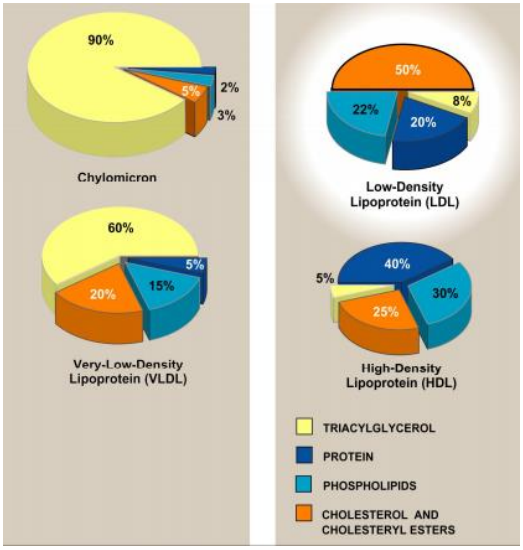
-The major lipid component of Chylomicrons and VLDLs are TAGs whereas in HDL, the major lipid component is phospholipids, which make up 25% of HDL.
- Phospholipids and proteins make up the surface of lipoproteins, which in the case of HDL is (45%+25%=70%), so in conclusion, 70% of the components of HDL are surface components.

***When the percentage of the surface components is higher, the volume decreases.**

↑ Surface Area ↓Size



The picture to the left shows that the smaller the volume (e.g; HDL), the greater the surface component and the larger the volume (e,g; chylomicron), the lesser the surface component.

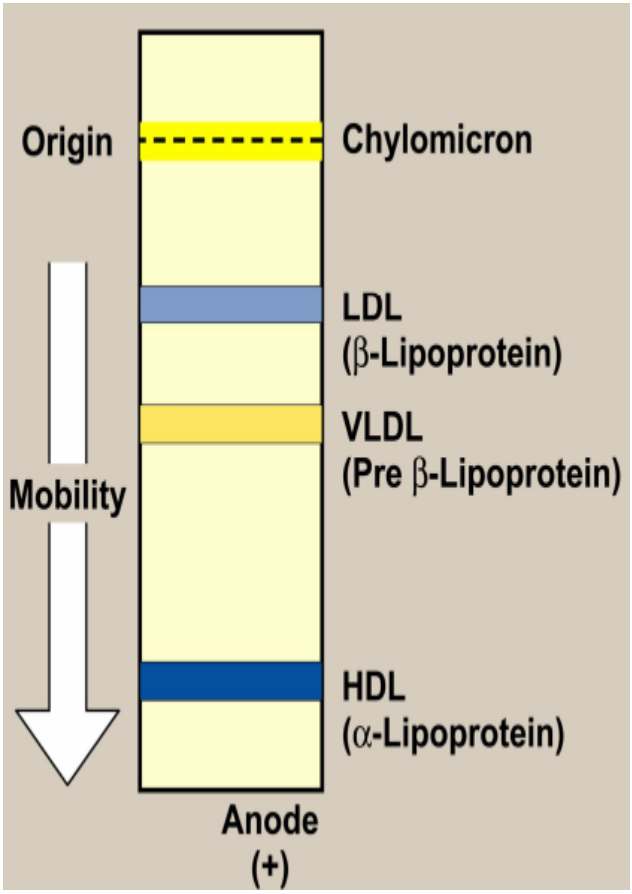


-TAG component of Chylomicron is predominant (90%)
-Protein and Phospholipid component of HDL is predominant (70%).
-Chylomicron is Larger in size and has a smaller surface component than HDL.

Lipoprotein	Apo Protein Types	
Chylomicrons	Apo B, Apo C, Apo E	Dietary Lipids
VLDL	Apo B, Apo C, Apo E	Endogenous TAG
IDL	Apo B, Apo E	
LDL	Apo **B**	Cholesterol
HDL	Apo **A**, Apo C, Apo E	Cholesterol Return to Liver

You should be familiar with the following:
-Apo A is only found in HDL
-LDL contains only Apo B
-Apo B is found in all lipoproteins except HDL

-We separate Lipoproteins by Ultracentrifugation, which is very expensive and not suitable for everyday use, so we resort to Electrophoresis



Under the influence of an electrical field, Proteins in the serum sample migrate from the origin to the Anode (since at high pH, all proteins are negatively charged). A dye that binds to lipids is used so as we can keep track of the movement of lipoproteins.

-Chylomicron don't move due to their low protein content
-HDL (α -Lipoprotein) migrates the fastest and furthest due to their high protein content. They are called α -lipoproteins because they migrate with α -globulins (plasma proteins).
-VLDL (also called pre β-Lipoprotein): slower than HDL.
{Note: pre means in precedes the β lipoprotein}.
-LDL: slower than VLDL.

Note: Mobility is not totally based on density, since VLDL precedes LDL. It is based on charge/mass ratio (charge depends on the type of proteins in the lipoprotein).

Digestion of Dietary Lipids

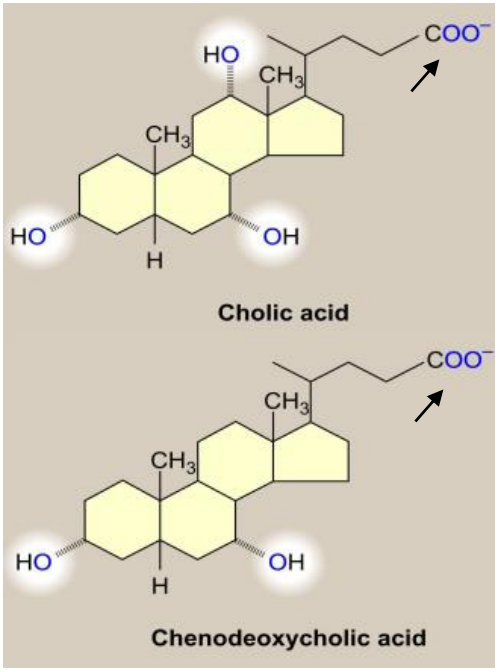
$$TAG + 2H_2O \longrightarrow 2\,FA + MAG$$

$$CE + H_2O \longrightarrow FA + Cholesterol$$

-Digestion of dietary lipids occurs in the GI tract, and then they are absorbed into the intestinal cells. 2 out of the 3 ester bonds in TAG are hydrolyzed forming 2 fatty acids and Monoacylglycerol, whereas the digestion of Cholesterol esters produces 1 fatty acid and 1 cholesterol.

-But we are left facing a solubility problem with the previous reactions, TAG and CE cannot mix with water and in order to solve this problem, we use emulsifying agents (substances that are soluble in both fat and water and enable fat to be uniformly dispersed in water as an emulsion)
-Examples of emulsifying agents: Phospholipids, Cholic acid and Chenodeoxycholic acid. The latter two are strong emulsifying agents.

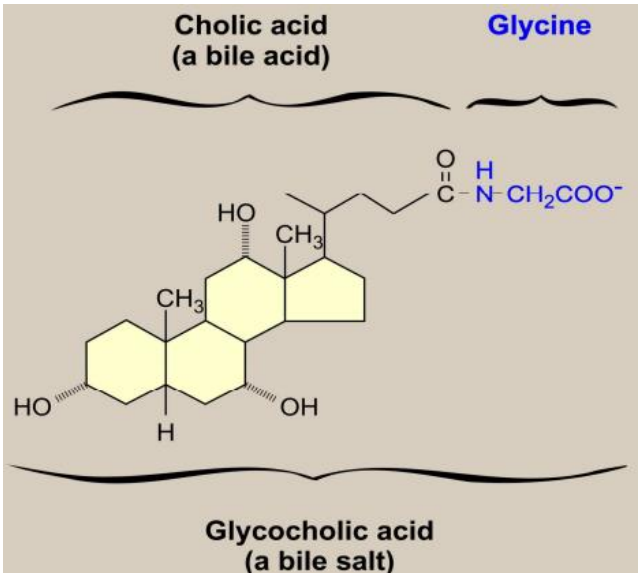
-Cholic and Chenodeoxycholic acid are structurally similar to cholesterol; the only difference is the presence of hydroxyl and carboxyl groups, therefore cholesterol is not considered an acid.



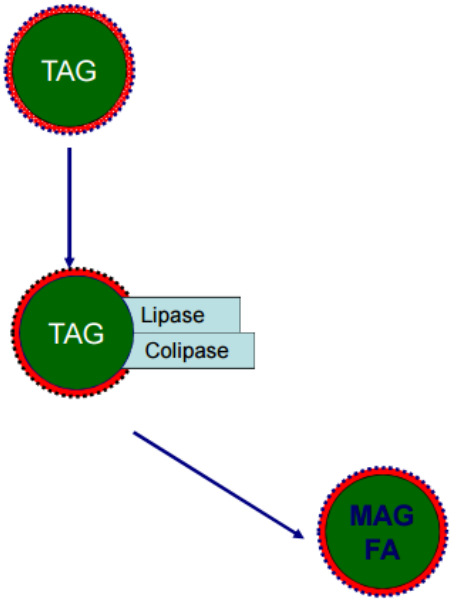
-Cholesterol is converted to bile acid in order to help in solubilization of fats.

-Bile acid binds to amino acids, like glycine, forming a conjugated bile salt called glycocholic acid, which has lower pKa thus stronger acidity. (It is present only in the form of salt)

-There is another sulfur containing amino acid called Taurine which binds to cholic acid forming a strong bile salt.



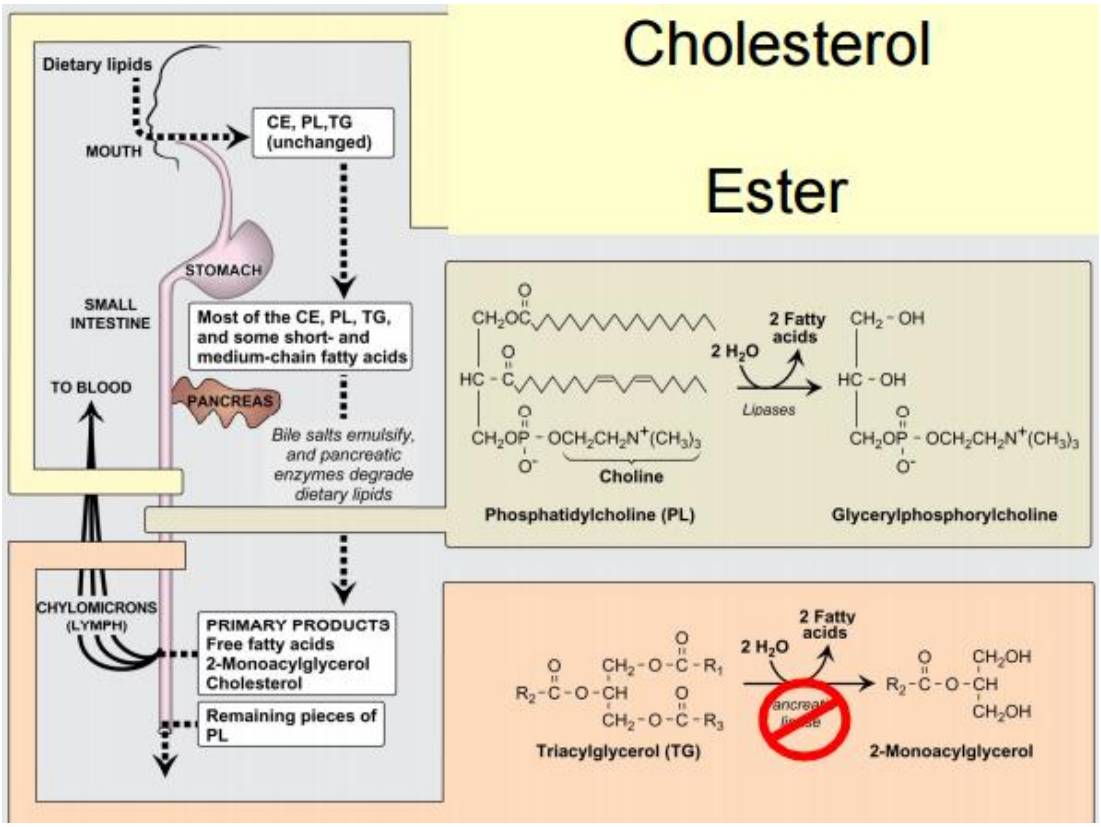
-TAG and bile acids mix in the small intestine to form micelles. The surface of micelles contains phospholipids and bile acids, whereas the interior contains TAG. These are very small particles, so their surface area is large and so they bind to enzymes called lipases (Lipases need another enzyme



called co-lipase in order to function). The two enzymes interact with micelles and this allows the hydrolysis process to occur producing MAG and FA. This is why hydrolysis of TAG requires bile acid.

-Lipases are pancreatic enzymes secreted into the small intestine. Bile acids are produced in liver and are stored in the gall bladder. When fatty food enters the duodenum, the gall bladder contracts, releasing the bile acids. If bile duct is blocked, the digestion of TAG is terminated.

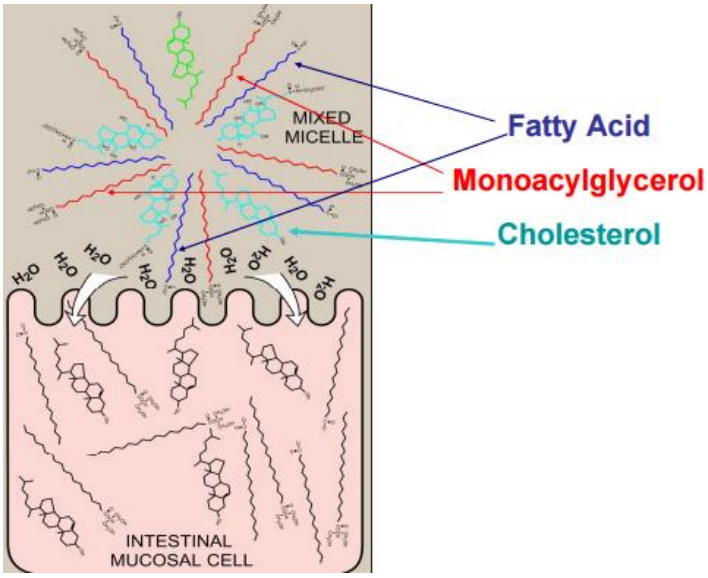
Study this diagram well



-Cholesterol esterase breaks down Cholesterol esters into Cholesterol and Fatty acids

-If there is a deficiency in pancreatic lipases, the digestion of TAGs will stop and so they will not be absorbed.

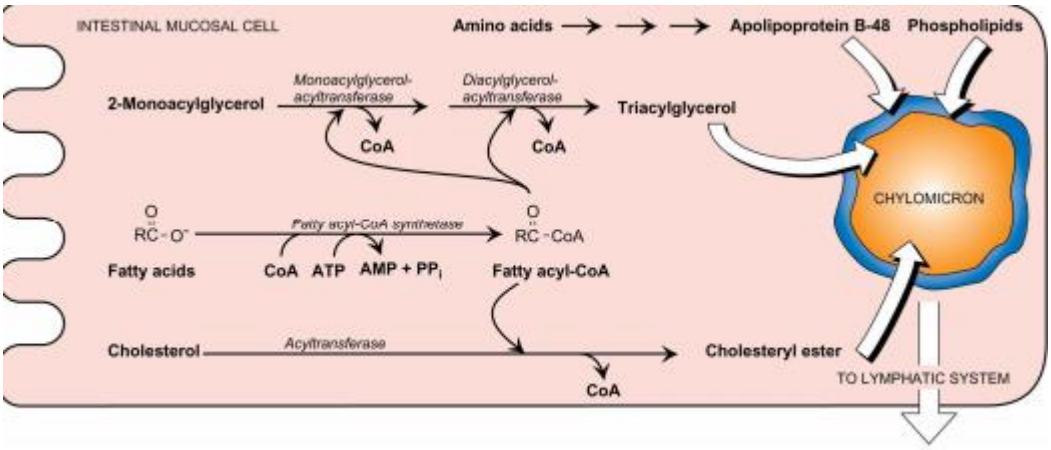
After digestion of Mixed Micelles, MAG and fatty acids and cholesterol are produced. The micelles can come into contact with intestinal mucosal cell and these substances diffuse into the intestinal mucosal cell. Absorption occurs by diffusion without the need of transporters.



Digestion of TAGs *consisting of short or medium chain fatty acids* begins in the stomach. The tongue secretes a lipase called lingual lipase and the gastric mucosa also secretes a lipase. They are stable and can work with the high acidity of the stomach, this is significant in pancreatic insufficiency and in the neonates; they feed on milk and require fast digestion. Milk has short and medium chain fatty acids that can be digested in the stomach and thus can get fatty acids more rapidly than normal sized TAGs.

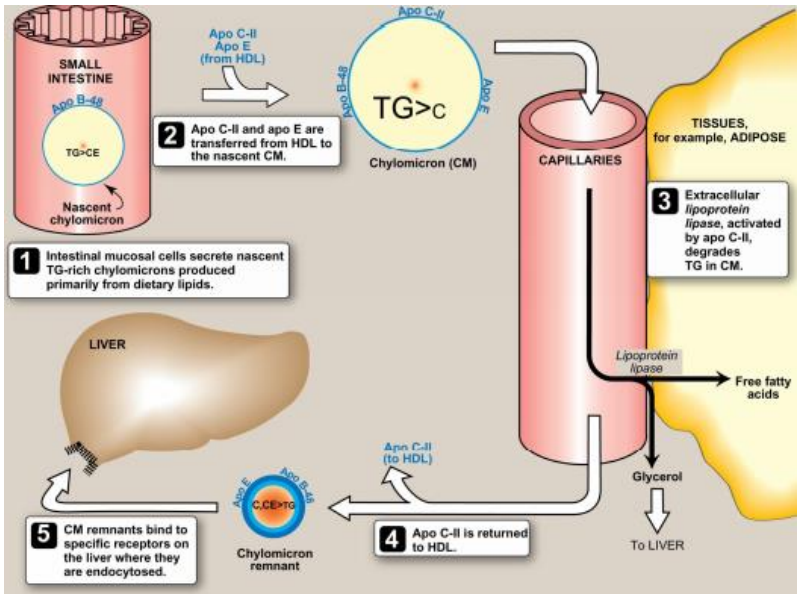
What happens in the small intestinal cells?

-Fatty Acids are activated forming fatty acyl CoA
-Fatty acyl CoA reacts with cholesterol to form cholesterol esters
-Fatty acyl CoA binds with MAG forming DAG which binds to another fatty acyl CoA forming TAG.



-TAG and CE that are digested outside the cell are resynthesized again inside the cell, this occurs in the Endoplasmic Reticulum.
-TAG and CE are incorporated with a protein called Apolipoprotein B-48 and phospholipids to form a large structure called Chylomicron.
-It leaves the cell by exocytosis, by fusing with the cell membrane and then it gets released into the lymph (not into the capillary).
-Digestion of carbohydrates produces sugars that are released into the capillary directly whereas Chylomicrons cannot be released into the capillary directly because the capillary is very small/narrow.
-If large amounts of Chylomicrons enter the capillary directly, the blood flow will be blocked, thus they migrate into the lymphatic vessels and enter the blood through the subclavian vein.

What happens in the blood?



-In the blood Apo C-II and Apo E are transferred from HDL to the nascent Chylomicrons.

-Chylomicrons enter the capillaries of various tissues, where they are digested by lipoprotein lipase (that exists on the surface of endothelial cells with extracellular enzyme) to produce to 3 Fatty acids and glycerol.

-Fatty Acids are taken by various tissues and glycerol is taken to the liver.
-The size of the Chylomicrons becomes much smaller and are now known as Chylomicrons remnants.

-Apo C-II is an activator of lipoprotein lipase.

-Apo E is important for the binding of Chylomicrons remnants to the liver cells so as to be taken by endocytosis.