Medical Committee
The University of Jordan

SLIDE SHEET

LECTURE#: 20

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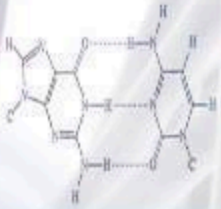
Biochemistry



Majida Al-Foqaraa'

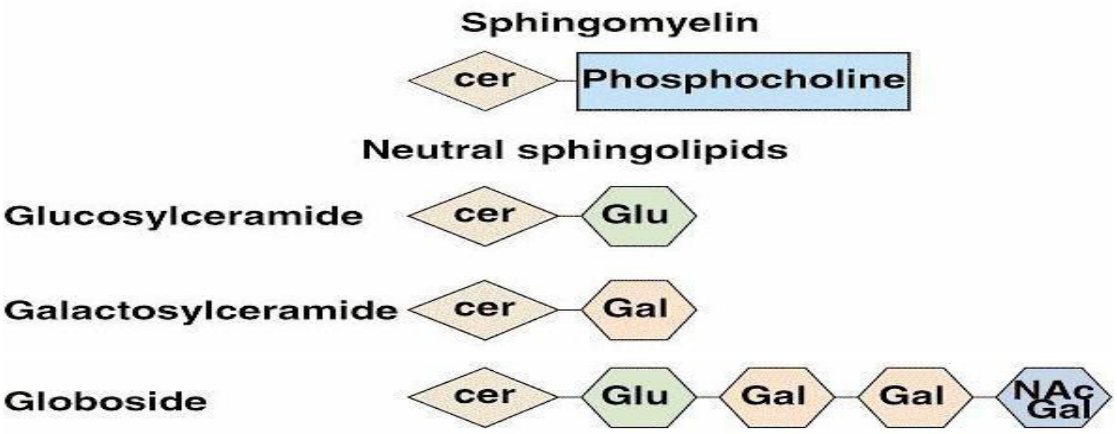
Glycosphingolipids and Lipoproteins

Glycosphingolipids (Glycolipids):

they differ from sphingomyelin(sphingophospholipids) in that they do not contain phosphate group, they are composed of a ceramide attached to a sugar, they differ in name according to the sugar attached:

A-neutral glycosphingolipids

1. if a single sugar is added, it's named sugarcerebroside as in addition of glucose gives glucucerebroside and addition of galactose gives galactocerebroside (the name ose indicates the presence of a sugar)
2. If an oligosaccharide (small number of monomers 3-9), its name is globoside.



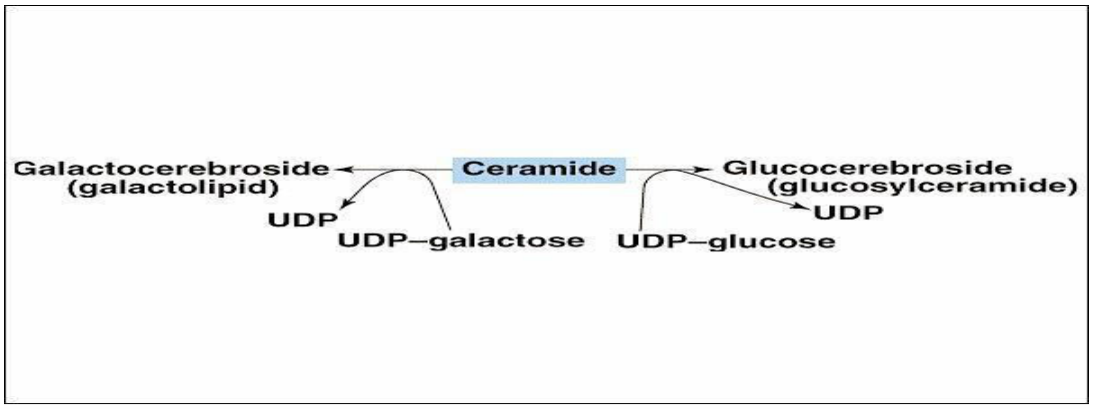
B-acidic glycosphingolipids (because they are charged):

1. **Gangliosides:** and are charged by N-acetylneuraminic acid (NANA) they are named G which indicates **g**anglioside then M D T or Q which indicates the number of NANA molecules, M is mono D is di T is tri and Q is quarto, followed by a number which indicates the sequence of carbohydrates attached to the ceramide,

So the final name would look like Gm1 or Gm2.
The sequence of carbohydrates has a big significance, because these molecules serve in cell-cell interaction/recognition and they are made during development so they give identity to the cell, blood groups for example which are made by different sequence of these molecules *very small difference in sequence gives you different blood group*

Synthesis:

synthesis occurs by sequential addition of sugars (1 at a time), glucose is not added as glucose molecule for example; it should be in the active form which is UDP-glucose if we're talking about glucose or UDP-galactose in the case of galactose. (UDP-sugar; which is the activated form of sugar). The mechanism is similar to the synthesis of glycoproteins and synthesis of glycogen,



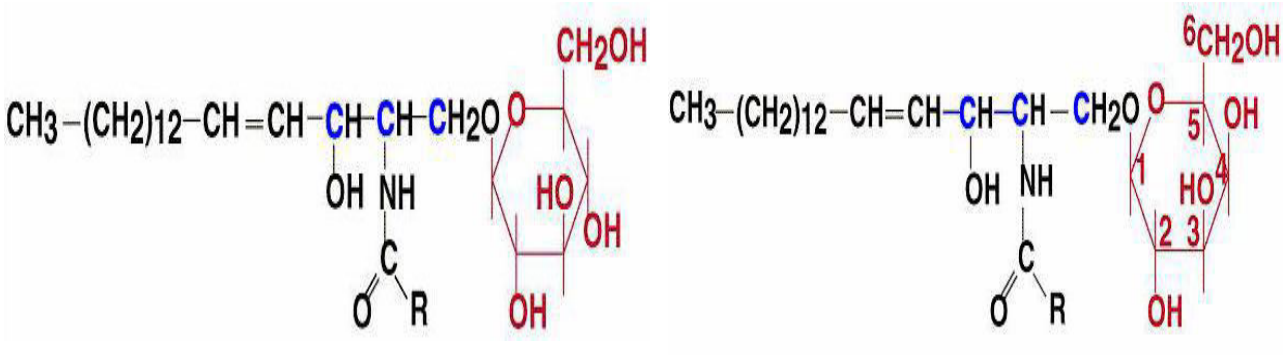
however every rule has an exception, in the case of N-acetylneuraminic acid it's not attached to a UDP molecule, but it's attached to a CMP (cytidine monophosphate) so the final donor is CMP-NANA.

Synthesis occurs by specific enzymes called glycosyl transferases because they transfer sugars from the active donor form to the ceramide, for example, if galactosyltransferase is found, galactose will be added to the ceramide, whereas if a different enzyme is found for example glucosyltransferase glucose will be added, so the sequence is determined by the presence or absence of a specific enzyme, moreover these enzymes are specific to the sugar molecule that's added in addition to the molecule to which the sugar molecule is added, in other words the enzymes are

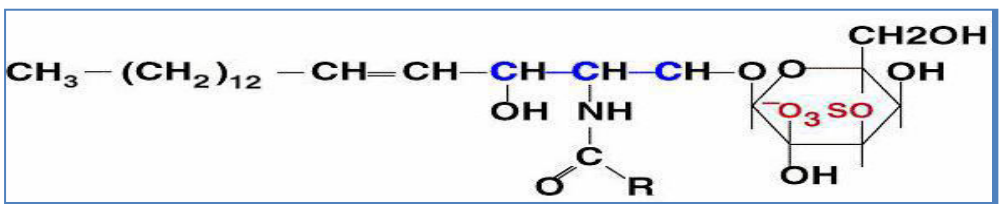
specific to both the donor and acceptor, as a result they are highly specific.

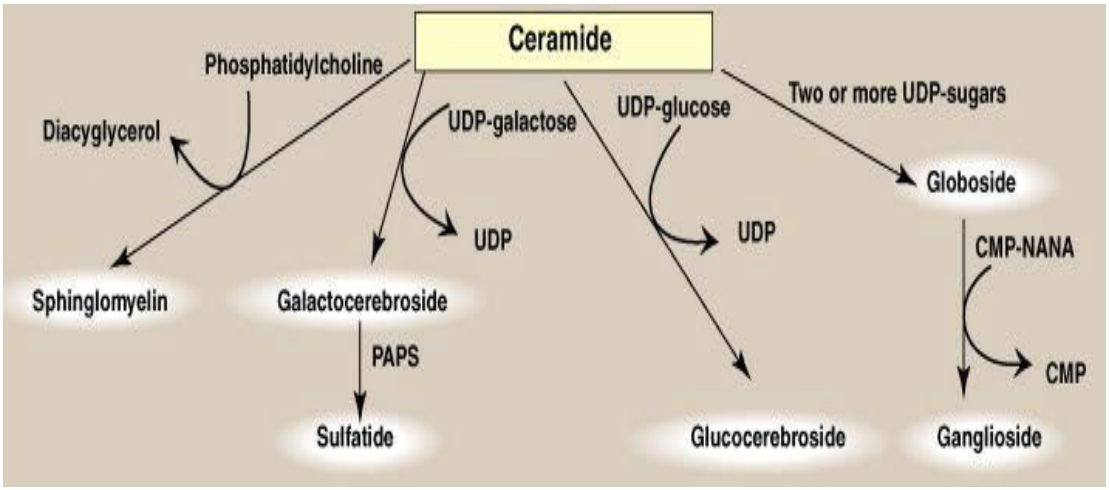
So why to have so many enzymes to make a molecule with 4 or 5 sugars? Actually because they carry important information about the protein and about the interaction as we said.

Galactocerebroside and Glucocerebroside are very similar in shape, the only difference is the OH group which is attached to the 4th carbon, therefore they are epimers, and although being very similar structure-wise they have different identities. *to emphasize the importance of having different sugars* to the right it's Galactocerebroside and to the left it's Glucocerebroside.



2. **Sulfatides**: are charged by sulfate groups. Transfer of sulfate group which is found on galactose, it carries negative charge, the sulfate group is added to galactocerebroside to produce sulfatide. The donor of sulfate group is 3 Phosphoadenosine 5 Phosphosulfate PAPS (it has adenine, ribose, sulfate, phosphate) it's similar to ADP but the group is phosphosulfate rather than pyrophosphate, so it's the donor of sulfate, it also acts in the synthesis of glycosaminoglycans which have sulfated sugar.





This figure is from the book, it illustrates the formation of glycosphingolipids

Note: addition of two or more UDP-sugars to Ceramide gives Globoside (sugars are added one at a time), then addition of CMP-NANA (NANA group) converts globoside ganglioside.

Actually synthesis isn't important from a clinical point of view because any defect in synthesis will yield an individual that is not consistent with life, whereas defects in degradation is important clinically because any problem will yield a family of disease called Lipid Storage Diseases which we will discuss later in the lecture.

Degradation of glycosphingolipids:

It occurs by hydrolytic enzymes they are also specific for each sugar, they have specifity, usually these glycosphingolipids are found on the outer leaflet of the cell, on the outer surface of the plasma membrane, therefore they are taken in by endocytosis, so they are internalized into endocytic vesicles which then fuses with lysosomes for degradation by sequential removal of sugars(1 by 1 again just like synthesis)
From the name of the enzyme you can know the substrate, for example β -galactosidase it removes galactose which is linked by β configuration, whereas α-galactosidase it removes galactose which is linked by α

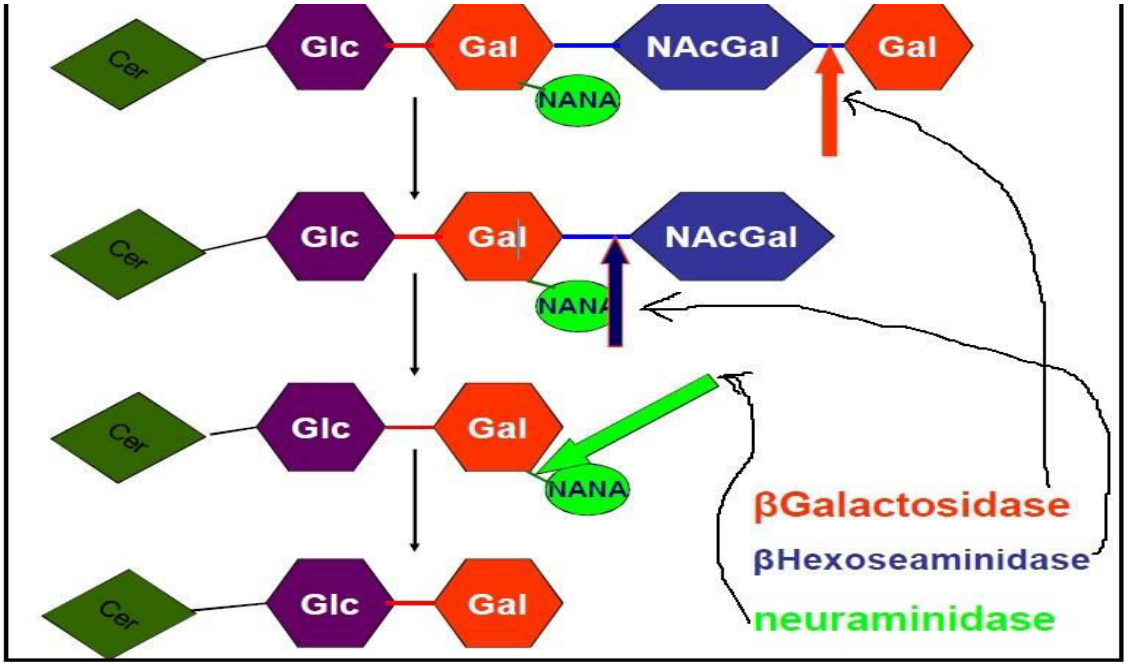
configuration, also neuraminidase removes neuraminic acid, also hexosaminidase removes hexose amine, for example, galactose amine.

All of these enzymes are found in the lysosome, so they are for degrading the turnover of the cell, always all molecules undergo turnover, and there is synthesis and degradation in our cell, however normally they are balanced.

These enzymes are firmly bound to lysosomal membrane and are not free to leave into the cell; otherwise they would destroy the cell components.

The pH inside the lysosome is acidic, optimally between 3.5-5.5 which is optimal for enzymatic activity, so even if these enzymes leave into the cell they won't work effectively because their enzymatic activity decrease at neutral pH.

Here in degradation, the last one (sugar) to be synthesized (added) in synthesis is the first one to be degraded and vice versa. For example Cer-Gal-Gal-Gal-**Glc**, the last one to be synthesized here is Glucose therefore it will be the first one to be degraded, and the first to be synthesized is the galactose therefore it is the last to be degraded.



When dealing with gangliosides there is not a single enzyme that degrades the whole molecule, each enzyme removes one sugar at a time (sequential process).

Gm1, Gm2 and Gm3 are therefore named according to the degradation process and size, Gm3 is the first molecule, degrading it gives Gm2, and degrading Gm2 gives Gm1, therefore Gm1 is shorter than Gm2 which is shorter than Gm3. Therefore size wise Gm3>Gm2>Gm1 **note each step is carried by a specific enzyme**

Sphingolipidoses (singular "sphingolipidosis"):

They are also called lipid storage diseases, they result from the defect of one enzyme, therefore deficiency of this enzyme yields to accumulation of the substrate.

These diseases are inherited as **autosomal recessive** (both genes are defect) diseases, what does this mean? Let's talk some genetics:

Recessive means that both genes should be defective for the disease to appear. If the person is Heterozygous (he has normal gene and the other gene is abnormal) the phenotype would be normal.

Homozygous vs. Heterozygous:

Homozygous means both genes are the same *either both dominant or both recessive* while in heterozygous the genes are different one dominant and one recessive.
So in other words Homozygous is either WW or ww
and heterozygous is Ww.

Homozygous recessive vs. Homozygous dominant:
homozygous recessive means both genes are recessive which is ww and homozygous dominant means both gens are dominant which is WW.

Let's get back to biochemistry, since these diseases are considered autosomal recessive diseases, therefore they only occur in homozygous recessive individuals, why is that? Because these enzymes are highly

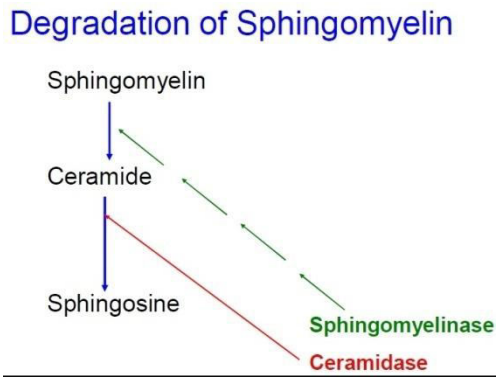
active, so even if 10% of the enzymes are working, they are enough for degradation. So a heterozygous would have 50% enzymatic activity and will be normal, what if 2 heterozygotes mate? They will have a 25% chance for each child to be homozygous recessive (the doctor said some of their children will be homozygous recessive but I don't find "some" accurate) the child will inherit 2 defective genes and the activity of the enzyme would be zero.

So in homozygous recessive the enzymatic activity is almost zero and there will be an accumulation of the specific lipid which is the substrate of that enzyme, and therefore the cell will be engorged with abnormal amounts of that lipid that will not be degraded.

Therefore the brain is mostly affected while the skin, for example, isn't. Even though the lipids are found everywhere, they are rich in nervous tissue and because the nervous tissue has low regenerative capability it will not be replaced if damaged. So these storage diseases will mostly affect the brain. It will cause brain damage, mental retardation, cerebral palsy, etc. The child will be born normal, but gradually he will suffer from the disease. Sometimes in the early childhood, others in the late childhood phase.

The extent of enzyme deficiency is the same in all tissues, because the enzyme is deficient everywhere. To diagnose the disease they usually take tissue from the fibroblast or the leukocyte & measure the enzymatic activity, so the activity is the same but the brain is the most affected.

Degradation of Sphingomyelin:



Sphingomyelin is degraded by the enzyme Sphingomyelinase that cleaves the phosphocholine, producing ceramide, if it's defective this leads to accumulation of Sphingomyelin and the disease here is NIEMANN-PICK disease. Ceramide is degraded by Ceramide into sphingosine and fatty acid. This is the normal process of degradation of Sphingomyelin.

From all of these diseases we are required to know only 3; also we aren't required to know the lipid which accumulates. Please refer to the picture for details (*picture from slide or book*) about each disease:

1-TAY-SACHS disease: affects Jewish people more (Polish/Swedish/Czech these different group are most likely to suffer), it results from the accumulation of gangliosides, and it causes: I) rapid, progressive and fatal neurodegeneration II) Blindness III) Cherry-red macula IV) Muscular weakness V) Seizures.

2-GAUCHER disease: which also affects Jewish people more, it results from the accumulation of glucocerebrosides, it is the most common lysosomal storage disease, and it causes: I) hepatosplenomegaly II)osteoporosis of long bones III) CNS involvement in rare infantile and juvenile forms

3-NIEMANN-PICK disease: Phosphorylcholine-Cer (sphingomyelin) is degraded by sphingomyelinase to Choline-Phosphate and Ceramide, if sphingomyelinase is defected, sphingomyelin will accumulate, which causes: I) Hepatosplenomegaly II) Neurodegenerative course (Type A antigen) III) Cherry-red macula.

Transport and digestion of TAG by Lipoproteins:

- **Lipoproteins:**

The doctor talks about glycerol and fatty acid and talks about monoacylglycerol, diacylglycerol and triacylglycerol in brief, mono is 1 fatty acid + glycerol bound by 1 ester bond, di is 2 fatty acids +glycerol bound by 2 ester bonds and tri is 3 fatty acids + glycerol bound by 3 ester bonds.

TAG (and di or mono) is highly hydrophobic and non-polar, while phosphoacylglycerol is very similar in structure to TAG but has a

negative and positive charge, which makes it an amphipathic molecule which can dissolve in water, and they are considered solubilizing agents.

How can we transport TAG? In the form of lipoproteins!

Lipoproteins are not like glycoproteins, glycoproteins are 1 molecule which has a protein and a carbohydrate covalently attached, while in lipoproteins the lipids and proteins aren't covalently attached, it is not one molecule it is actually large numbers of molecules that interact together to form particles that are soluble therefore they are for transport of lipids in the plasma (in order to transport lipids within the plasma like TAG for example we should have it in the soluble form). Because plasma is 90% water (aqueous) and lipids are hydrophobic they need transporters (which makes lipids in the soluble form) to move them from 1 region to the other within the plasma.

Lipids that are transported in the lipoproteins are TAG, Cholesterol (free Cholesterol), Cholesterol esters and phospholipids.

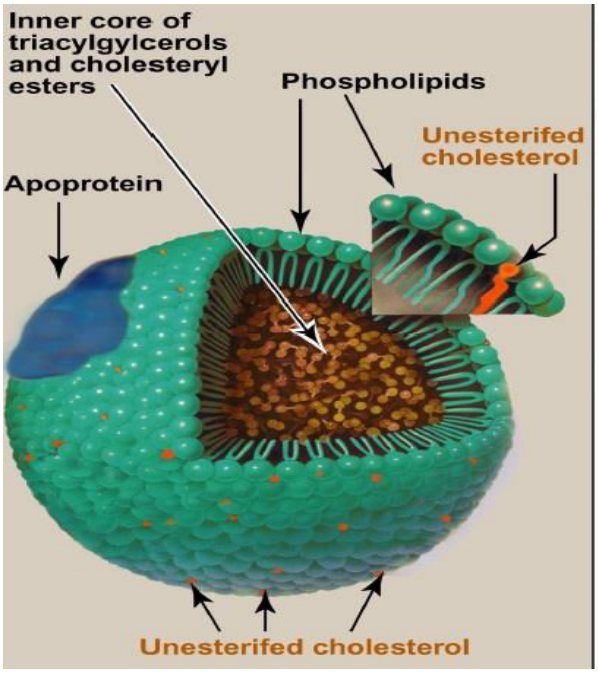
The protein part of the lipoprotein is the Apolipoprotein, wherever you find Apoprotein you know that you have a protein that can bind to something else. So the free form of the protein is called the Apolipoprotein, they are amphipathic, part binds to the lipids which is non-polar and another part that is polar which interacts with the plasma.

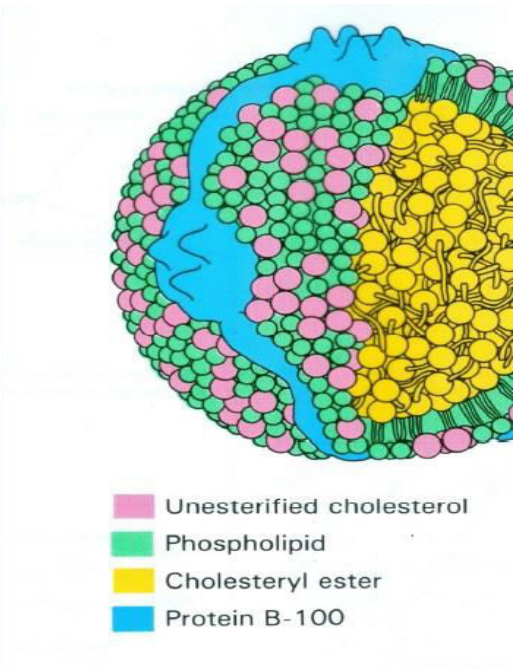
These proteins fit into classes: Apo-A, Apo-B48, Apo-E etc.

The apolipoproteins have different roles:

1. Structural role: by maintaining the integrity of the lipoprotein
2. regulatory role: by regulating the enzymes that act on these
3. binding role: by binding to cell-surface receptors (interact with cells)

The interior is made of TAGs and cholesteryl esters, while the surface is made of phospholipids, unesterified cholesterol and apoproteins.





The density is the mass of one unit of volume (mass/volume)

*density of water is 1g/cm^3

We can classify lipoproteins according to their densities.

Going from smallest to largest:
Chylomicrons→VLDL→IDL→LDL→HDL.

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%)

Chylomicrons has lower density than water (0.95), therefore chylomicrons in plasma will float on top, to test if plasma has large amounts of chylomicrons we leave plasma in the refrigerator for 24hours you will find them floating on top of the plasma

HDL has the highest density.

You are not expected to memorize numbers and densities, you should know which one is denser for example you should know how to compare between them.

What determines the density of the lipoproteins?

Simply put the ratio of proteins to lipids in the lipoprotein, the larger the ratio of proteins to lipids the greater the density, just like how oil floats on top of water and meat or cheese sinks. In conclusion the higher the lipid the less the density, the higher the protein the more the density and vice versa. We aren't required to memorize the ratio of protein to lipids in each chylomicron.

Based on the above we can conclude that HDL has the highest protein % and that's true from the numbers which indicates 45% proteins, and the lowest protein % is in chylomicrons which is in fact 1-2%.

The major lipid in chylomicrons is TAG (90%), while in HDL it's phospholipids (25%)

Notice that in HDL phospholipids as we mentioned earlier are found in the outer surface of the lipoprotein, and also the proteins are found in the surface, therefore the HDL relatively has a higher surface component, therefore its relative size is small.

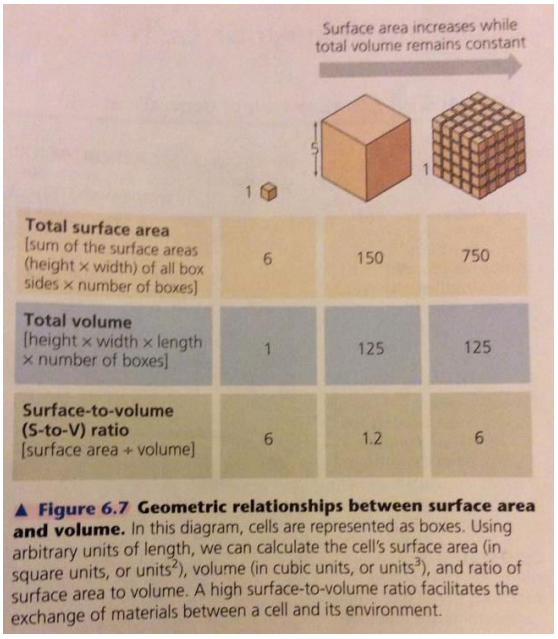
The higher the % of surface component the smaller the size. (the increase in surface area means small size)

Here we are talking about the relative size which means the volume compared to the surface area, the higher the surface area the lower the relative size.

The doctor mentioned the watermelon example here, if we have 1 large watermelon which weighs 12kg and 4 smaller watermelons each weighing 3kg, both cases have 12kg. So if we peel the watermelons, we'll find that the 4 small will produce more peel, therefore more surface area, so as the relative mass decrease the surface area increase and vice versa. The doctor gave another example about the surface area of adults and babies, which has a higher relative surface area, the answer is the baby because he has a lower volume/mass.

The following wasn't mentioned from the doctor, but because not many students got what the doctor said, I figured I would try to explain it in another 2 ways: (if you understood the above feel free to skip this explanation):

1- This explanation (the image on the right) is from the biology 101 book explaining the same point but in cell absorption.
2- The math point of view:
since the volume of the sphere = $4/3*\pi*r^3$
while the surface area $=4\ \pi\ r^2$
doing the math $S.A/V = 3/r$
so as r increases the ratio of S.A to V decreases and vice versa.



▲ **Figure 6.7 Geometric relationships between surface area and volume.** In this diagram, cells are represented as boxes. Using arbitrary units of length, we can calculate the cell's surface area (in square units, or units^2), volume (in cubic units, or units^3), and ratio of surface area to volume. A high surface-to-volume ratio facilitates the exchange of materials between a cell and its environment.

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

Apolipoproteins (Apo-A, Apo-B, Apo-C, Apo-E) etc, each has a different function, notice that Apo-B is found in all lipoproteins except HDL, also Apo-A is only found in the HDL, we will understand this table later on.

Don't memorize numbers!

According to relative sizes, Chylomicron has the largest size (it has 1% proteins and 10% phospholipids) the surface component is only 10% that's why it's very large, it's full of TAGs in the core.
HDL on the other hand has the smallest size because most of its component is made of surface component (Proteins and phospholipids)

There you have it!

"Reserving judgments is a matter of infinite hope."