Biochemistry - I

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Lecture-14
Lipids and membranes - II

We continue our discussion on lipids and membranes and in the last class we learnt what comprises lipid of the membranes. We learnt that we can have a glycerophospholipids or a spingolipids that will look or could assemble into basically bilayers. Now we are going to look at the properties of the lipid bilayer and see how it forms and what are the basic physical and chemical properties of this bilayer? We will learn about the transportation later on from one end of the cell to the other.

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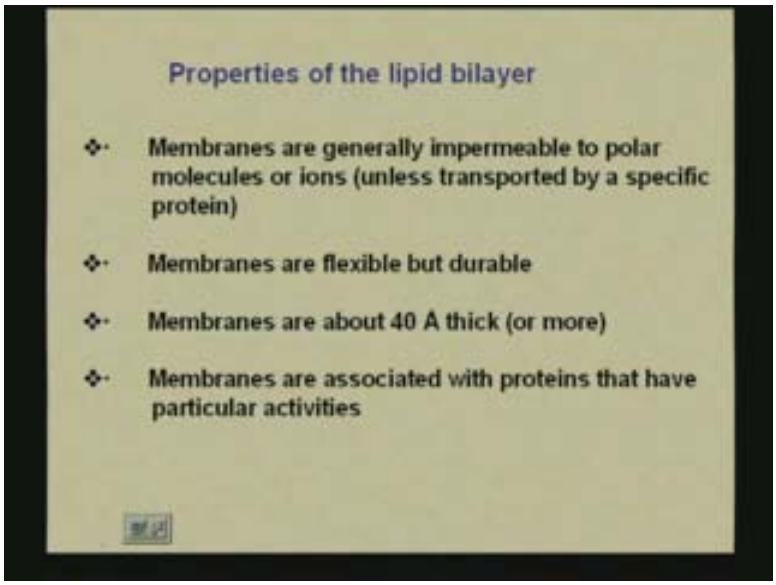

If you look at the properties of the lipid bilayer they are usually impermeable to polar molecules or ions. You understand why that is so because you have the polar head groups on the surface only and if we have to have a transportation from the inside of the cell to the outside or from the outside of the cell to the inside then it is not possible because of the hydrophobic chains that are present in traversing the whole membrane. Normally the membranes are impermeable to the polar molecules or ions unless we have some specific proteins that facilitate the transfer. We will see how we can have active transport or passive transport. The membranes themselves are flexible but they are very strong and they are durable. They do not just rupture. The membranes can be about 40 A thick or even more than that and membranes are associated with specific proteins that have definite activities. The basic properties of the bilayer are that they do not allow the

transport of the ions unless assisted by a protein. They are flexible; they are quite thick 40 A and they are associated with proteins that have specific activity associated with it. When we speak of the interior of the lipid bilayer it means we are speaking about the hydrophobic tails. That is what the interior of the bilayer is. The exterior of the bilayer is the polar portion, the polar head groups that forms the inside and the outside and the interior is highly fluid and we will see how that fluidity occurs, why it occurs and what its usefulness is.

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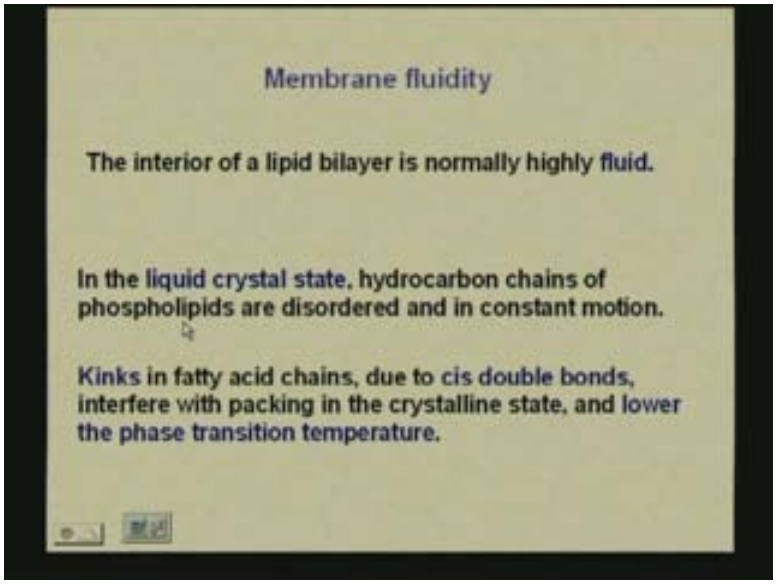

In the liquid crystal state, the hydrocarbon chains of the phospholipids are disordered. They are in constant motion because they are suspended. The cells are suspended in the plasma. There is a cytosol to it there is an extra cellular matrix to it. So they are all suspended. Because of their constant movement they are in constant motion and they are highly disordered as well. The kinks we saw in the last class that are there in the fatty acid chains are due to the cis double bond and they interfere with packing in the crystalline state and they lower what is called the phase transition temperatures. What is this phase transition temperature?

When we consider membrane fluidity if we have straight chains we can form what is called a gel or a liquid crystal sort of a thing. We have a liquid crystal here and a gel. What we have in a gel is a perfect ordering of the chains. When this is heated there is a lot of disruption that can occur. This disruption occurs because there is a lot of possible rotation about the single bonds in these chains. Because of this we can have what is called a transition temperature that is going to take us from the perfectly ordered form to a liquid crystal form where we have a transition. What is this transition due to? The transition is due to the flexibility of the single bonds that we see here and if we had a kink in the structure due to the presence of the cis double bonds then this at some point would set into a specific form that would give on heating a transition that would result in a crystal structure, a liquid crystal structure.

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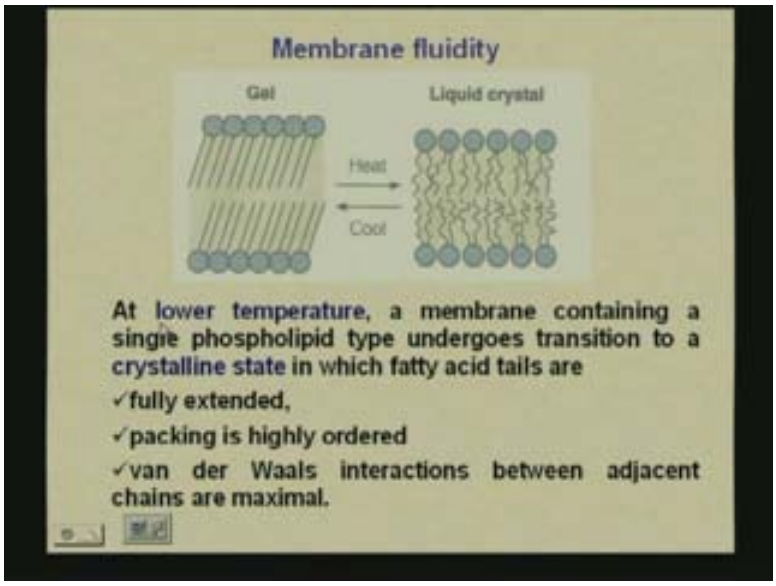

At lower temperature a membrane that contains a single phospholipid type would undergo a transition to a crystalline state. This would be our crystalline state where we would have the fatty acid tails perfectly ordered, perfectly packed, fully extended with the maximum possible Vanderwall's interactions between the chains. We are talking about the single type of phospholipid attached to the polar head groups. Even if we have one fatty acid chain here have a cis double bond to it, it would on the formation of the crystalline state set into a perfect format where it would probably not be completely straight but it would set into what it could form in its crystalline form. We would have it set if it had the single type of phospholipids. But as soon as we have different types of phospholipids it arises not only to a single transition temperature but we have a range where this gradation or this graduation from one to the other gradually takes place. The transition in that case gradually occurs.

What we have for the fluidity of membranes is the introduction of steroids; sterols particularly. We will see what these are and what the roles of these are? Steroids as you probably know are complex hydrophobic molecules that have 4 fused rings and they have a short aliphatic tail. This is the component or this is the structure of any steroid. At a particular position of the steroid when one of these groups is transferred to an -OH we call it a sterol and we have cholesterol, sterols of plants and fungi, steroid hormones and bile salts that help in digestion are all derivatives of these cholesterols which is why you probably have heard of gallstones. There are a lot of gallstones that are made of cholesterol and a combination of these bile salts and cholesterols.

What are the roles of cholesterols in mammals? You know that fat is good for you. All cholesterol is not bad. You need some fat. You need some cholesterol also. The role of cholesterol in the mammals is that they act as structural components of the plasma

membrane and they modulate membrane fluidity and they also form a precursor of steroid hormones and bile acids.
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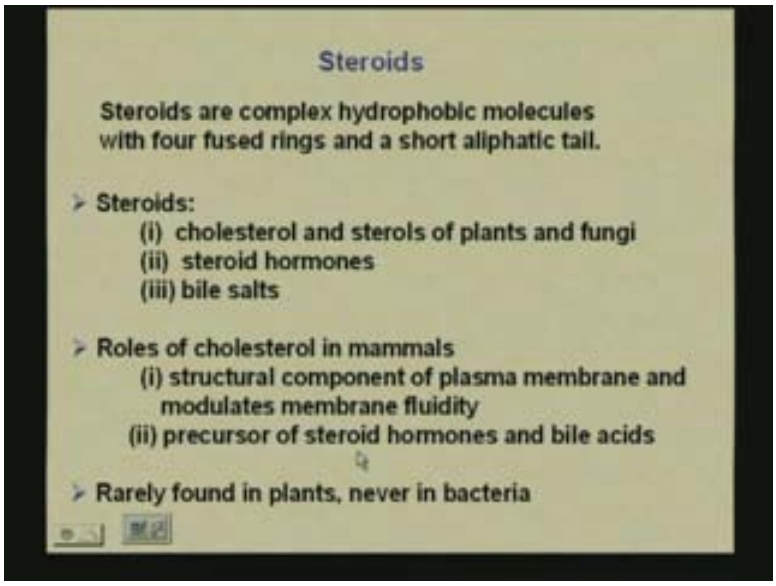

The bile acids are extremely important for digestion. So you have to have sufficient cholesterol for the formation of steroid hormones and for the formation of bile acids and the cholesterol is not found in plants. There is another form that is found in plants called stigma sterol which we will see in the next slide. The uses of this cholesterol are in the modulation of membrane fluidity and also as a structural component in the plasma membrane. This is the structure of cholesterol. This is where the steroid becomes the sterol. It is -OH.

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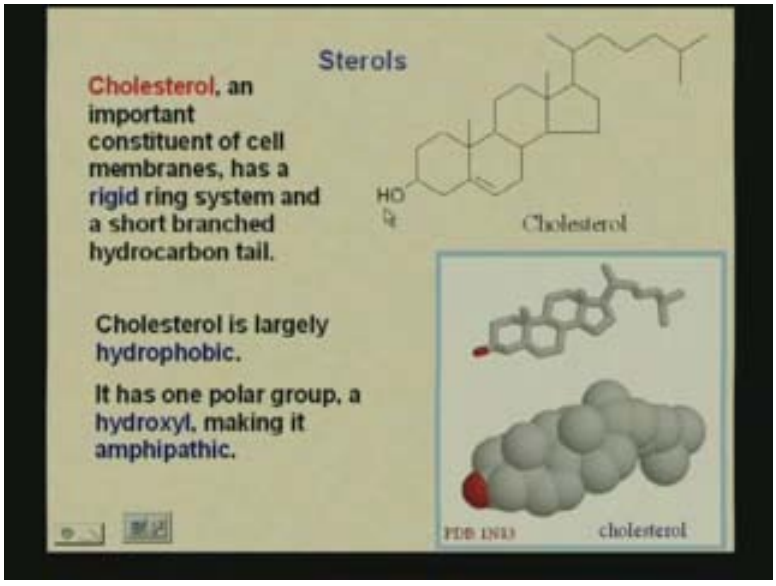

It has in it a rigid ring system, a short branched hydrocarbon tail which we can see in the stick structure that I have here. What is this red one? The red one is the oxygen and this is the rigid hydrophobic structure, the rigid ring structure and this is a short aliphatic hydrocarbon tail that is attached to it. We see that we have a hydrocarbon part and we have a polar part to it. So cholesterol is largely hydrophobic in nature. But it has one hydroxyl, this hydroxyl that makes it amphipathic in nature. So if this were to be also incorporated into the lipid bilayer, it would be this part that would interact with the hydrocarbon chain the fatty acid chain part of the lipid and it would be this -OH that would interact with the polar head group of the lipids.

This is the numbering scheme for cholesterol. It is the three position that has an -OH attached to it. We have four fused rings A, B, C, D.

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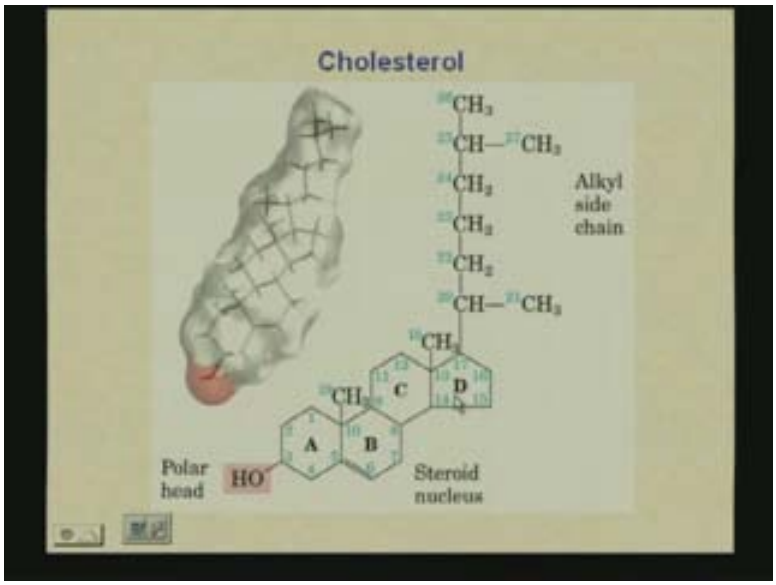

There are three 6 membered rings and the D is a 5 membered ring fused with ring C. This is the polar head, the -OH and the rest is the alkyl side chain and steroid nucleus. This forms the part of every steroid. This is the steroid nucleus. The changes are in the alkyl side chain. Any bile salt or any other sterol that we will see will have a difference in the alkyl side chain, a difference here also but this steroid nucleus remains intact. The numbering starts from ring A in 1, 2, 3, where the -OH is attached to 3; 4, 5. Then it goes the ring B. There is double bond between 5 and 6. So it forms 5, 6, 7, 8, 9 and 10. So that forms rings A and B. The numbering then begins at ring C where we have 11, 12, 13 and 14. At ring D 15, 16, 17. Then we have two methyl groups attached one to carbon 13 and one to carbon 10. Number 18 is the one that is attached to 13 and 19 is the one that is attached to 10. Then we have the alkyl side chain where we have a methyl group attached to the first carbon atom and a methyl group attached to the last carbon atom in the alkyl side chain. So this is the structure of cholesterol and what we have to recognize here is that this whole part is hydrophobic in nature and this -OH part is a polar part in nature

that is going to help in the fluidity of the membranes and we will see how it can help in the fluidity.

As I mentioned before plant cells do not have cholesterol. They have what is called stigmasterol.

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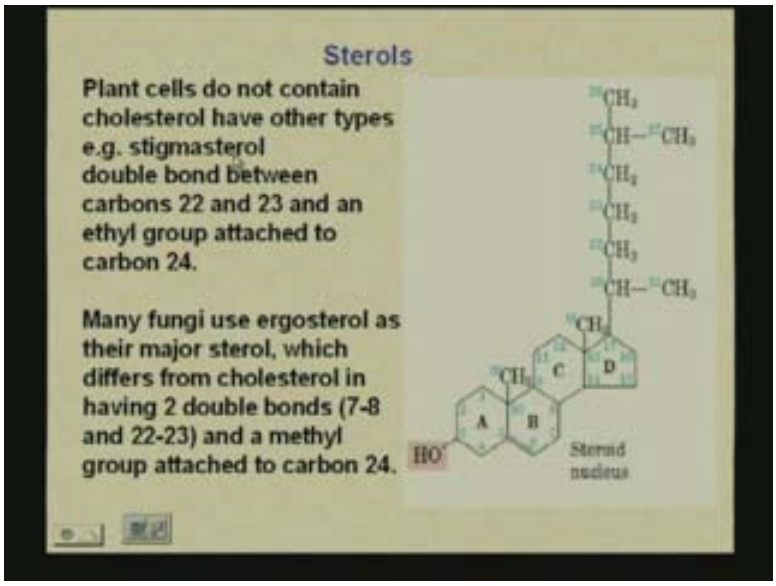

The difference there is that there is a double bond between carbons 22 and 23. So 22 and 23 have a double bond and there is an additional ethyl group attached to carbon 24. So this is the basic structure of the cholesterol that I showed in the previous slide and the difference between cholesterol and what plants have, which is called stigmasterol, is that there is double bond between 22 and 23 and an ethyl group attached to 24. In fungi we have ergosterol which is their major sterol. This again differs from cholesterol in having two double bonds one again here in the B ring between 7 and 8 and again between 22 and 23 like stigmasterol and instead of the ethyl group that was attached in stigmasterol we have a methyl group attached in ergosterol. So these are the different types of sterols that are commonly known. We have plant sterols, fungi sterols and cholesterol. This is the basic structure of cholesterol that has a steroid nucleus to it. Because we call it a sterol it means it has -OH attached to it. The -OH is attached at the 3 position and we have an alkyl chain here and all of these still have the alkyl chain. What we do have is just some saturation and additional alkyl chains attached. The basic structure is still a hydrophobic part and a polar head group.

This is our cholesterol. The cholesterol will insert into the bilayer membrane with its hydroxyl group oriented towards the aqueous phase associated with the polar head groups of the lipid bilayer and the hydrophobic ring system would be adjacent to the fatty acids in the glycerol of the sphingosine and the -OH group of the cholesterol will form hydrogen bonds with the polar phospholipid head groups.

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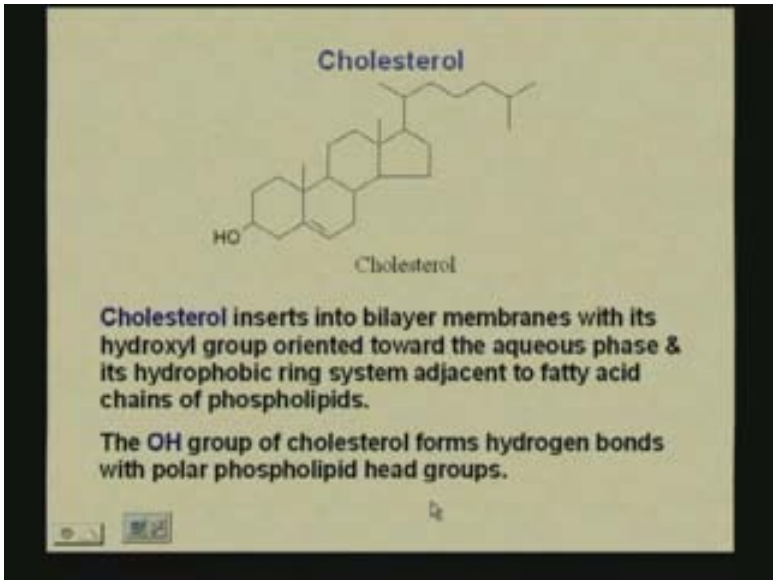

In what we call the phospholipid bilayer, we have the cholesterol embedded in it and because the cholesterol has this rigid structure and the alkyl chain, it is this part that is going to interact with fatty acids, and it is this part that is going to interact with the polar head groups, but it is this that is going to give the membrane some fluidity. It is going to allow some movement. Now what happens is the interaction with the relatively rigid cholesterol, rigid because of the fused steroid nucleus, decreases the mobility of the hydrocarbon tail of the phospholipids.

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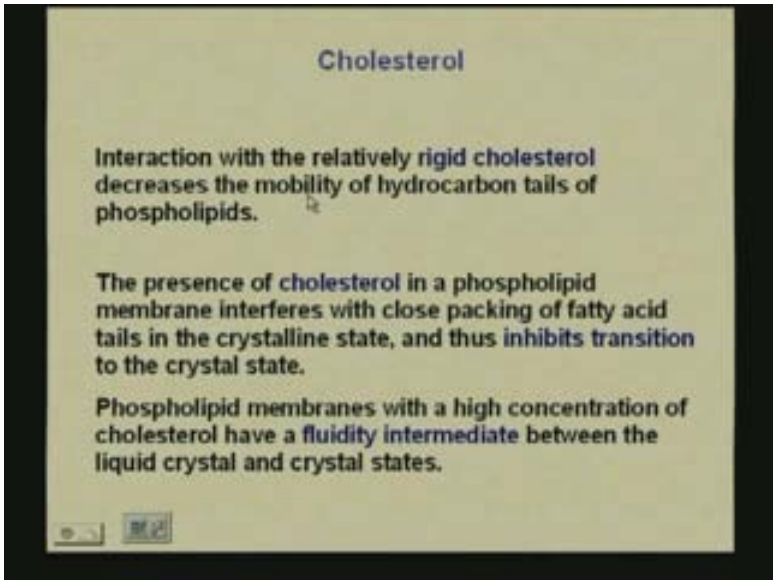

You recognize that the long fatty acid chain have a lot of single bonds to them. The single bonds are free to move and they are flexible. But if the cholesterol is sitting beside it which has a very rigid steroid nucleus to it, the flexibility is not allowed in the hydrocarbon tails as such. But the presence of cholesterol in a phospholipid membrane interferes with the close packing of the fatty acids. So normally the way that the fatty acids would be packed would change with the presence of cholesterol. If we had a single type of phospholipids attached we would have perfect orientation to our chains. Now when I heat this, it is going to form something like this. Now what happens if I have something sitting here? It will be sitting here also. So that is where the cholesterol comes into the picture. It will not allow it to form this complete perfect crystalline state because it disrupts the packing. The presence of the cholesterol is going to interfere with the close packing of the fatty acid tails and it is going to inhibit the transition to the crystal state. So the phospholipid membrane with the high concentration of cholesterol has a fluidity that is intermediate between the liquid crystals and the crystal state. So it imparts in a sense rigidity but at the same time it does not allow a close packing that is there in the crystal state. So it sort of gives it a fluid feature, a fluid intermediate that is between this liquid crystal and the crystal states. It is due to the rigid crystal structure of cholesterol and the rigidity is because of the fused rings of the steroid and it is this part that is interacting with the hydrocarbon chain.

We have the formation of our lipid bilayer. We have here now a glycolipid.

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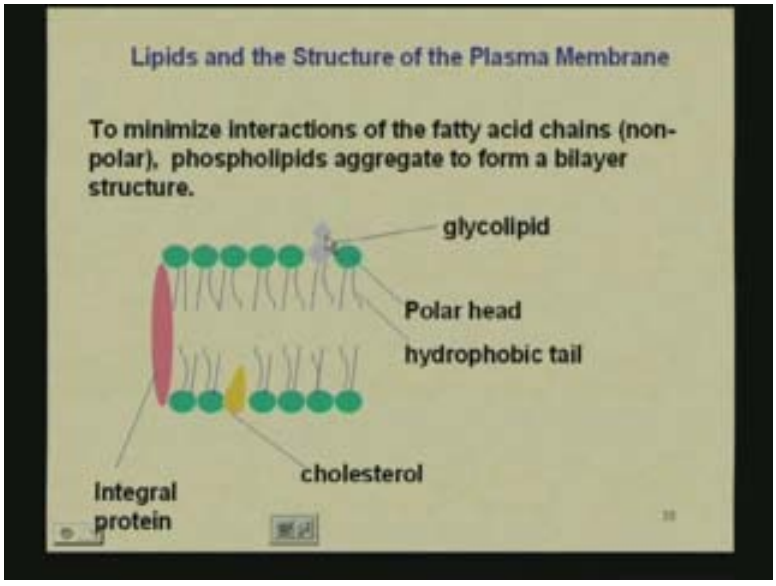

What is a glycolipid? Something that has a sugar attached to it. All the green spheres are polar heads; all the blue lines here are hydrophobic tails. In here we have cholesterol. This cholesterol is there to impart some fluidity to the membrane so that it does not be rigid. Here we have a protein molecule. Now we are going to see how these protein molecules actually help in the transport. We have these phospholipids aggregate to form this bilayer structure. We have already looked at the different types of phospholipids that

we can have including a glycolipid type where we have a sugar ring attached like we would have in a cerebroside or a ganglioside. We speak of the gel to the liquid crystal transition. What does the gel mean? the complete crystal form where all the hydrocarbon tails are perfectly oriented.

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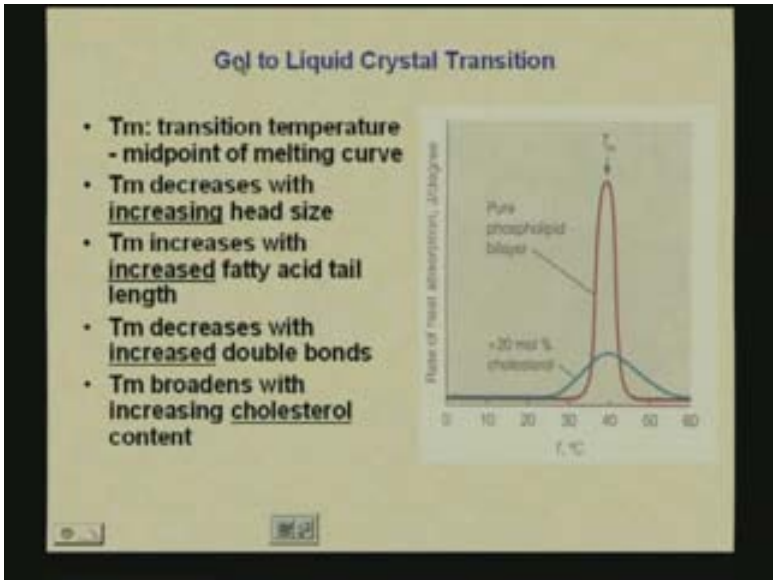

We have what is called the transition temperature. What is this transition temperature? It is sort of a melting point. A melting curve that we get and the midpoint of this melting curve is going to be the transition from the perfectly ordered form to a disordered form. We are going to look at the features that are going to result in differences in this transition temperature. When we look at the heat absorption, we have temperature along the x-axis here. When the temperature is low everything is ordered. All the fatty acid chains are ordered in some fashion and at some point it moves over to the liquid crystal state because of the disruption in the order. So the disruption in the order is going to give us a melting temperature that is the midpoint of the melting curve that is denoted as T_m.

What are the features that can change the T_m? If you have a pure phospholipid bilayer you are going to have a sharp transition. Why? All of them are perfectly ordered because you have pure phospholipid bilayer. The differences can arise where you will get a broader melting curve based on the differences of the fatty acid chains that the phospolipid is comprised of. If we have increasing head size you have lesser packing possible which is going to decrease the melting temperature. You have to recognize that a perfect crystal form or a perfect packing is being disrupted, is been broken. How do you break this packing? You can break the packing by having an increased head size because the increased head size will not allow a nice packing of the fatty acid chains. If you have an increased fatty acid chain length you will have increased hydrophobic interaction. You will have increased T_m because it will be harder to disrupt the ordering. You have to look at the feature and decide whether that ordering is easier to break or difficult to break. If it is easier to break, the T_m will decrease. If it is harder to break, the T_m will increase.

If you have an increased number of double bonds, larger number of kinks in the structure it disrupts the ordering, T_m will decrease. In the presence of cholesterol what happens is the T_m broadens. So you have basically a flatter T_m, a flatter curve because the cholesterol is now embedded in it and you do not have a sharp transition from a perfectly ordered gel state or a crystal state to a liquid crystal state. Let us just go over this once more. We are looking at a phospholipid bilayer and we are looking at the transition from an ordered state to a disordered state. We know that the lipid bilayer is comprised of different lipids, phospholipids and there are different properties of these lipids associated with different types of polar head groups and different types of fatty acid chains. That's the difference. If we have any property that is going to disrupt the structure we will have a lower T_m. So if we have increasing head size that is not going to allow a proper packing we are going to have decreased T_m. If we have long fatty acid chains then it is going to be harder to disrupt the fatty acid chain packing we will have a higher T_m. If we have increased double bonds we have increased number of kinks and increased disruption; T_m is going to decrease. With the presence of cholesterol there is an increase in the cholesterol content meaning that the T_m is going to broaden and the transition will not be sharp. We are going to have a broadened amount of melting because there is going to be gradual disruption in the structure amounting to a gradual curve. Not a sharp transition.

If we look at the times we are going to have these lipid movements. These lipid movements are actually what are causing some disruptions and some features specific features of the membranes.

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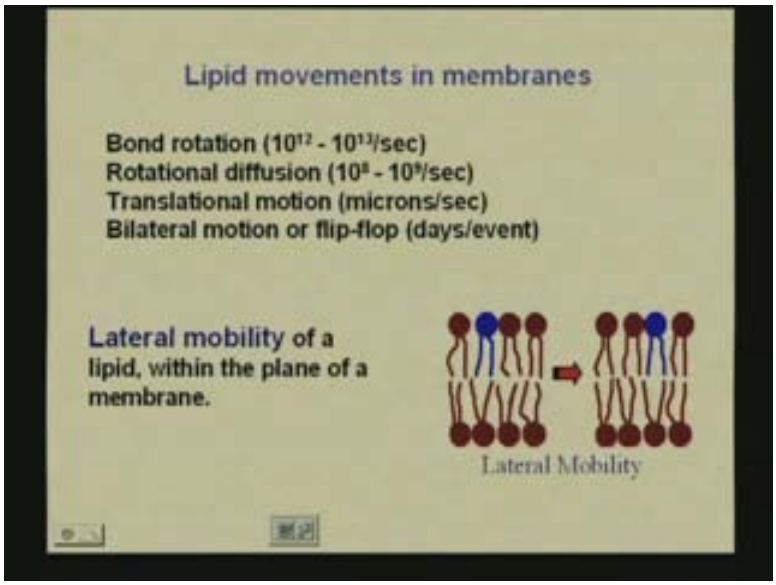

If we look at lipid movements in membranes, bond rotations occur at this level; 10 to the power 12 to 10 to the power 13 per second. The rotational diffusion is about 10 to the 8 to 10 to the power 9 per second. So you see how the lipid membranes, the bilayers are actually moving. We have a translational motion that can be measured in microns per second and we have bilateral motion some thing called flip flop that takes in the order of

days for one such event to occur. When you speak of the lateral mobility of the lipid within the plane of the membrane, we have the lipids actually moving around. So this blue lipid actually shifts. This is what is meant by lateral mobility. You have to realize that this lipid bilayer that is shown here is just a two dimensional representation. It is actually a surface. It is either going back or forth or left or right because you have a surface that you are speaking about. The two types of motion that can actually occur apart from bond rotation and rotational diffusion are translational motion that is lateral mobility and we will see how this lateral mobility is actually important because it would help the transport of any material inside to the outside or outside to the inside of the cell. We will see how that plays a role in a minute.

The other type is flip flop where this blue phospholipid instead of being in the top has come to the bottom of the membrane.

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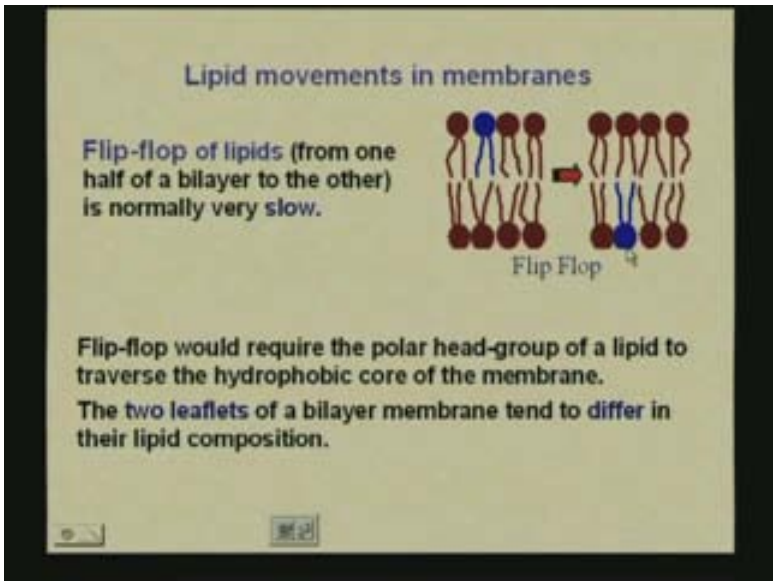

That is what is called the flip flop of the lipids where it moves from one half of the bilayer to the other half. This requires more time and is less probable because it is less probable than the lateral diffusion. This polar head group if it has come to this side, it has to traverse the hydrophobic chain. It has to go through this hydrophobic region which is unlikely for it to occur in the first place. When we consider the flip flop the lateral mobility is relatively easier for it to occur than the flip flop because here we are speaking of a lateral diffusion where the polar head groups remains in a polar environment. But in a flip flop case we have the lipid go from one bilayer to the other bilayer. So for this event to occur this would have to transverse the whole hydrobhopic core of the membrane which would be unlikely. If we consider the lipid bilayer and consider how it actually forms the cell, if we could just draw that here, considering a cell so if we have part of the cell wall this is inside and this is outside. We have a lipid bilayer. We have all the polar head groups sitting here. We have another set of polar groups sitting here. Each of these has their tails. So the membrane actually looks like this. This is what the

membrane actually looks like. This part and this part have different curvatures. These are what are called two leaflets. For this curvature to occur or to be different, the lipid bilayer has to be asymmetric. For this curvature to occur you cannot have the same types of lipids in the inner part and in the outer part.

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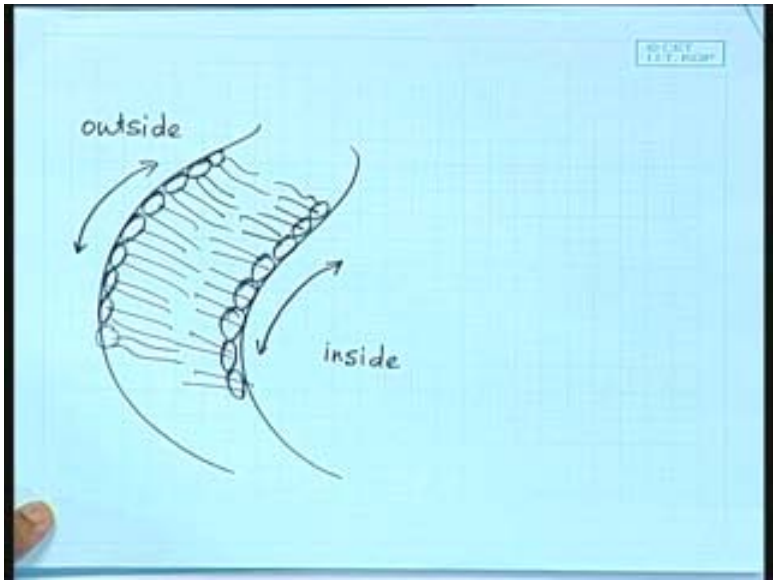

The lipid membrane is actually asymmetric in nature where the types of lipids on the outer surface are not the same as the types of lipids in the inner surface. That is what we mean by saying that the two leaflets of the bilayer membrane differ in their lipid composition. They have to differ in the lipid composition because their curvature is different. But we have the lipid bilayer asymmetry. The biological membranes are asymmetric.

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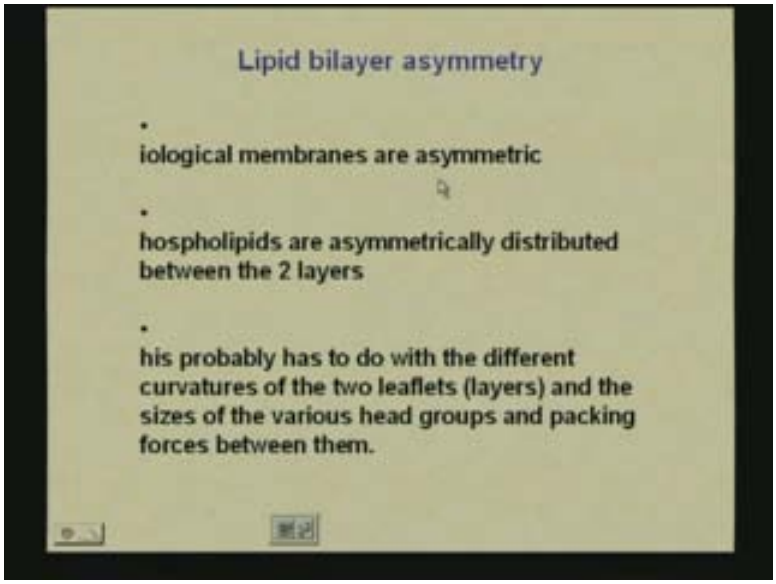

The phospholipids are asymmetrically distributed between the two layers and this is due to the curvature of the two leaflets or the two layers and how can we bring that about? By changing the type of fatty acid, changing the type of polar head groups - that is the way we can bring about a change in the curvature of the two layers by changing the size and by changing the packing. We change the packing by changing the fatty acids. So this is what we can do.

What we have here is the cytosol. What is the cytosol? It is inside the cell.

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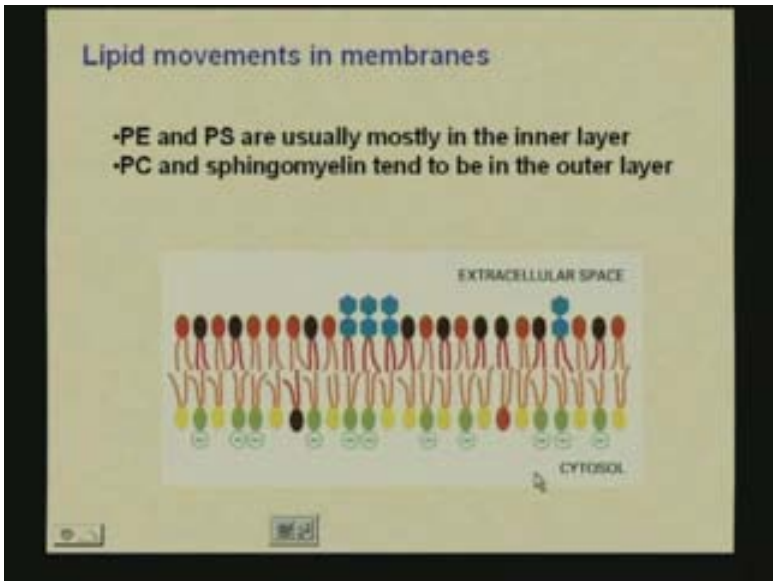

Extra cellular space means it is out side the cell. All these are different membranes. Red ones, the black ones and blue one with sugar attached to them are more preferred on the surface and a few red and black ones in the inner leaflets but populated more by green and yellow ones. We have different polar head groups. The green, the yellow, the blue and the black of the different polar head groups and the chains are also going to be different depending on the type of fatty acids that we have. Phosphatethyl ethanolamine that is PE and phosphatethyl serine are usually in the inner layer. So the ethanolamine type and the serine type are preferred in the inner layer and in the outer layer we have the sphingomyelin and the choline type, the phosphatethyl choline. We have more of the phosphatethyl choline and the sphingomyelin on the outside and more of the phosphatethyl ethanolamine and serine on the inside.

We have to look at membrane proteins. What are membrane proteins going to do?

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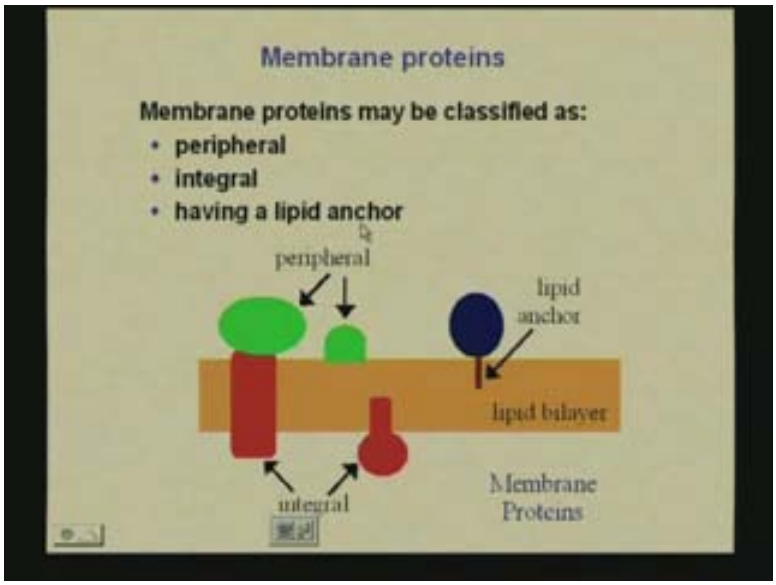

They are going to help in the transfer of ions. They are usually of three types. You can have peripheral proteins, integral proteins or ones that have a lipid anchor. The peripheral proteins are the ones that are marked in green here that are on the periphery of the membrane. The ones marked in red are integral proteins that are sort of embedded in the bilayer. The lipid anchor ones have a lipid chain attached to them that the lipid chain of which interacts with the hydrocarbon chains of the lipid fatty acids. These are the three types of membranes proteins that we can have and we will see the properties of the membrane proteins.

The peripheral proteins are on the membrane surface. They are water soluble and they have to be hydrophilic in nature so that they can interact with the polar head groups of the lipid bilayers. They are water soluble with mostly hydrophilic surfaces. You can just wash them off the membrane by adding specific chemicals or specific components that are going to disrupt the ionic and hydrogen bond interactions.

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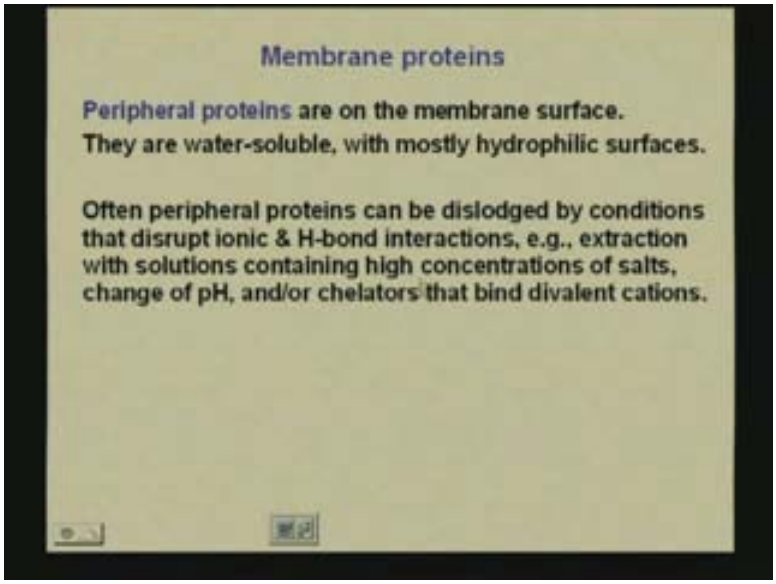

You can add urea, change the pH and extract the proteins that are on the periphery. But if you look at integral proteins they are not difficult to dislodge because they are traversing the membrane. So what are the properties of the integral membranes? They are embedded in the membrane. The segments that span the membrane are usually alpha helices.

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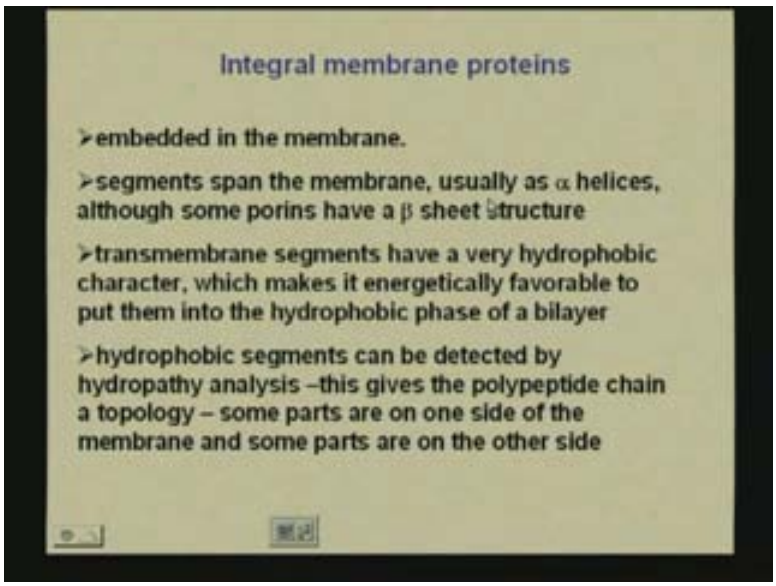

Remember in one of our very earlier classes we studied about hydropathy plots and there we identified transmembrane helices. This is where the transmembrane helices occur, in integral membrane proteins. There are some points that have a beta sheet structure to it. The transmembrane segments, we know from our previous classes, have a very

hydrophobic character so that there is an energetically favorable interaction with the hydrophobic chains of the lipid bilayer. The hydrophobic segments can be detected by hydropathy analysis and this gives the polypeptide chain a specific orientation, a specific topology where we have some parts on one side of the membrane and some parts on the other side of the membrane. So this is the property of the integral membrane proteins.

For the lipid bilayer with these proteins embedded in it, this is basically the structure. We have a movement, which is a bilateral movement, to the lipid bilayer and we have all these proteins on the structures. There has to be some model that denotes what this structure actually looks like. This was given in 1972 and is called the Fluid mosaic model.

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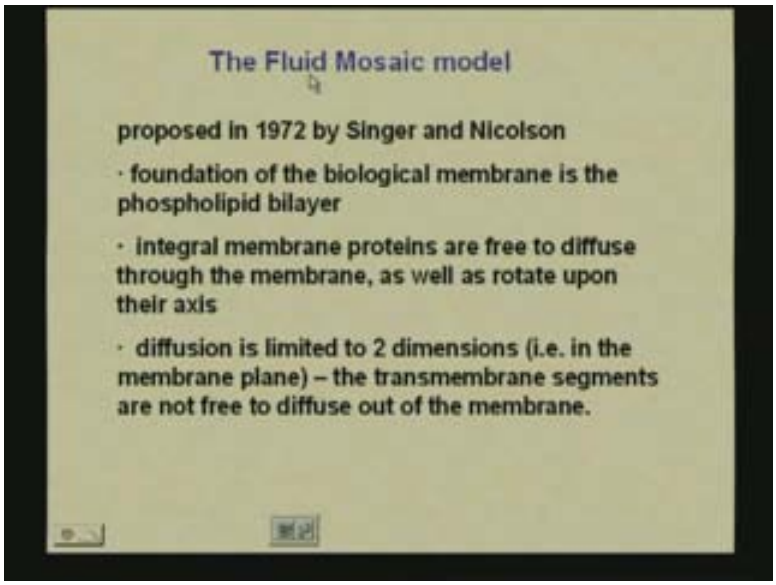

You can think of the lipid membrane like being a mosaic where you have some proteins. When you look at it from the top it will look like some polar head groups, different types of polar head groups, different types of proteins - integral proteins, peripheral proteins and the whole thing is sort of moving. So it is a fluid mosaic model. The basic thing is the phospholipid bilayer. The integral membrane proteins are free to diffuse through the membrane because they have that membrane channel to it and they can rotate about their axis because they have the lipid bilayer. The hydrocarbon chain is sticking out. You have the integral membrane protein that can rotate. Because the surface is hydrophobic in nature it will have a constant favorable interaction which is possible. Then the diffusion that you have is limited to two dimensions. The transmembrane segments do not flip flop. They remain as they are once they are embedded. We have some thing that looks like this. This is our fluid mosaic model. The blue groups that we see here are all the polar head groups of all the different types of lipids - the glycerophospholipids or sphingolipids that we can have. All these zig zag chains are the fatty acid chains, the yellow blobs are the cholesterols that have to be there imparting a fluidity.

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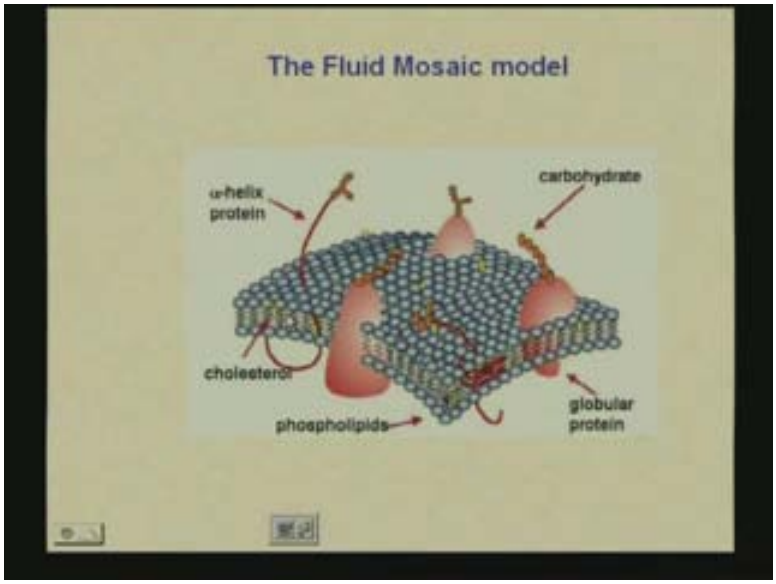

These are integral membrane proteins, the globular proteins and these are some carbohydrates attached to the proteins that are called glycopodines. We have an alpha helix protein that could be in there that could form a single helix. This would be what the lipid bilayer membrane would look like with the proteins embedded in it and since it is always moving and the proteins are rotating it is called a fluid mosaic model. This is the lipid bilayer and we have different types of proteins embedded in it.

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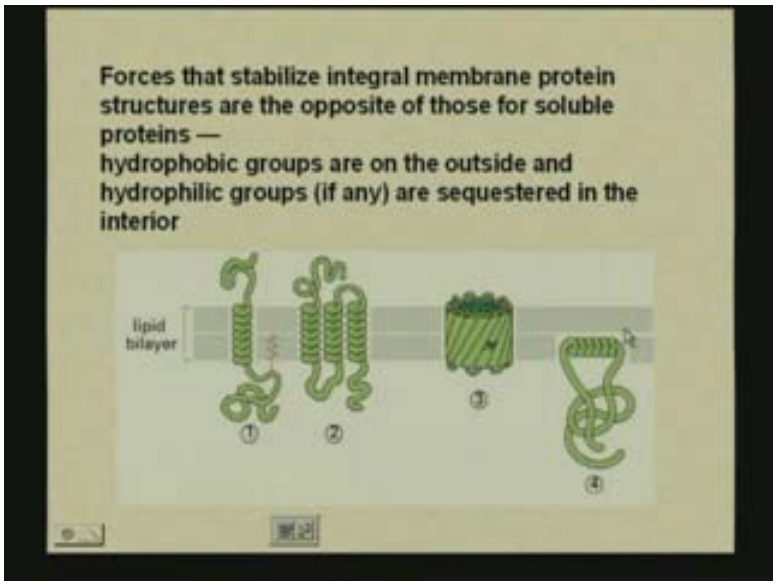

What are the different types of proteins? We can have a protein that looks like this, we can have a protein that has a large number of transmembrane segments or we could have

a protein that has a larger pore. These are porines that are formed not from alpha helices but from beta sheets. The beta sheets fold onto themselves and you have a large pore. When we studied the forces that stabilized these membrane proteins, we studied that it was these proteins that would have surface hydrophobic residues. Suppose we had like a bundle of helices, when we are looking at the top down to the membrane these are the helices. We have now our polar head groups. We are looking at the fluid mosaic model from the top. The blue one is the protein. These are hydrophobic groups that are going to interact with the fatty acid chains that are sticking out from these polar phospholipids. All the hydrophobic interactions that we see here are going to be down. The inner parts here are going to be polar. This has to be polar so that we form a channel. Once we form a channel, then this part is the surface say the outside and we have another part that is the inside. Once we have a channel formed here I can have transport.

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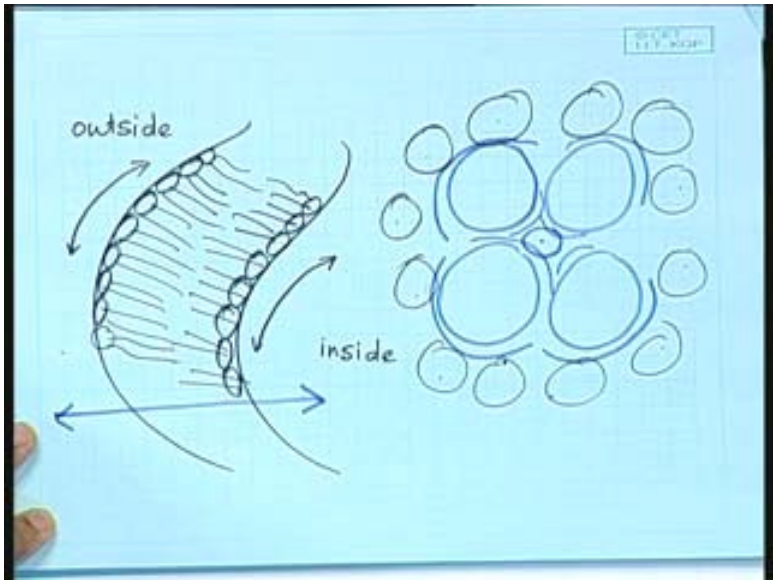

It is only through these membrane proteins that you will have ion channel pore formation and the transport either from the inside to the outside or from the outside to the inside. What we have here are the hydrophobic groups that are going be on the outside hydrophilic groups that are going to be on the inside. If we have this beta sheet structure here all the hydrophobic chains are going to be on the surface and all the hydrophilic chains are going to be in the centre and they are going to allow the movement. When would we need a porine? When we have to transfer of a large ionic part. Not just an $-OH^-$ or $-CN^-$ but when we have to transport a large hydrated ion, then we would need the formation of this pore. Do you remember how we are supposed to find out the transmembrane helices using the hydrophathic plot? What do we do for the hydropathy plot? There is a certain sequence of amino acids that we have. So we have amino acids 1, 2, 3, 4, say 5, 6, 7 and so on. For every amino acid there is a hydropathy scale. We consider the sequence along this axis and the average hydropathy index along the y-axis. How do we calculate it? We have a series of numbers for the amino acids and each of them has a specific scale. We use what is called a sliding window approach and we find

the average of say the first 7 or first 9. We usually use an odd number so that we can assign the average value to the middle residue. So we find the average of the scale of these 7 residues, assign it to the 4th residue and determine where it lies in the sequence in this plot. We continue this till we come to the end of the protein sequence and we determine regions of high hydrophobicity.

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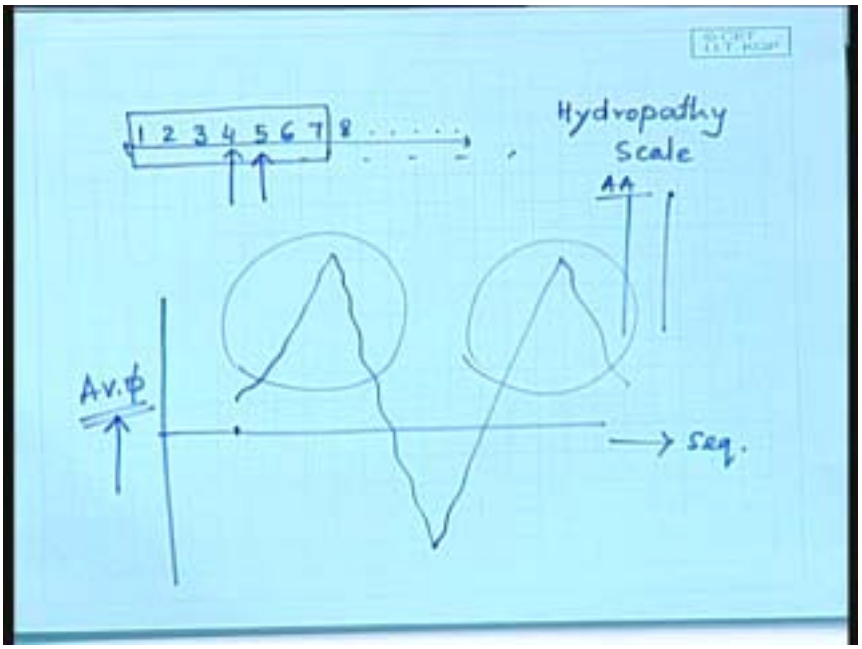

If we have high hydrophobic regions we consider those regions to be traversing the membrane and these hydropathy plots are used much more for membrane proteins than the depiction or the detection of any other sort of analyses of proteins. When we do these plots for say glycophorin in this case we consider here the hydropathy index that has a negative value here and a positive value here. We have this specific amino acid number along the x-axis. In this case there is one transmembrane segment.

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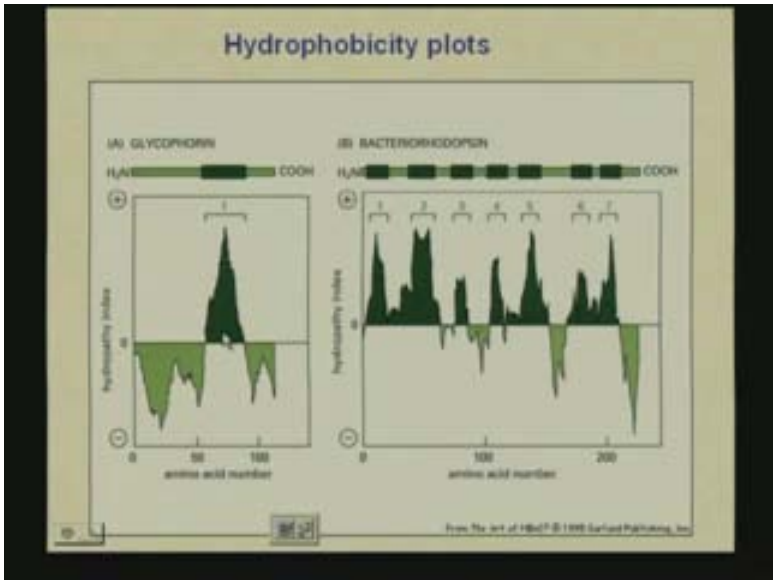

Single transmembrane segment is determined by the positive hydropathy index in this hydrophobicity plot. When we consider bacteriorhodopsin that has a large number of such transmembrane helices, we have 7 such possible helices that form bacteriorhodopsin and these can be identified again by the positive regions of the hydropathy index on the hydrophobicity plot that we see. If we go back to the fluid mosaic model, we have our polar head groups. The polar head groups that have the specific fatty acid chains, the globular proteins that are going to have transmembrane helices and the transmembrane helices are going to allow the transfer of ions from the outside of the cell to the inside of the cell.

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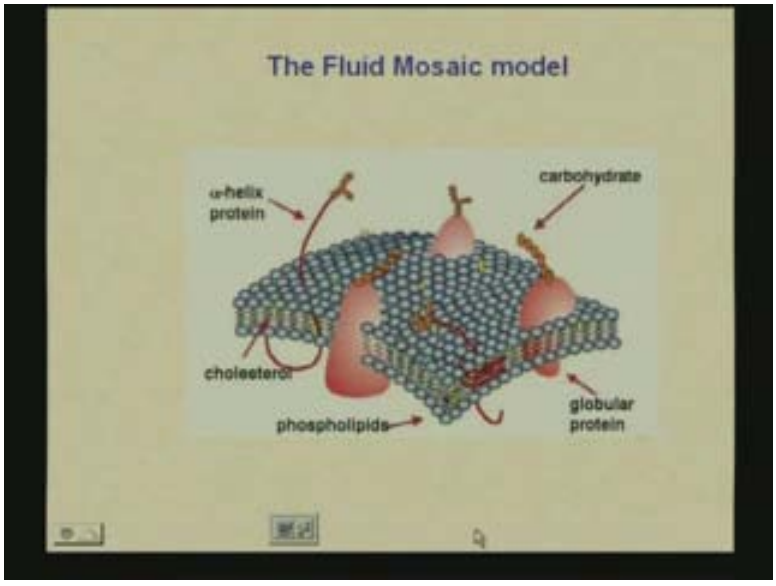

There is a specific curvature to the cell because the cell is globular in nature. It has to turn around to form a spherical moiety. If that has to happen then the composition of the phospholipids on the outer layer and the inner layer is different. The phospholipids composition of what is called lipid leaflets are different. So the lipid bilayer is basically a fluid portion, a fluid layer where we have constant movement, we have constant free rotation, some diffusion also and we have cholesterol embedded. The cholesterol structure is such that it has a large hydrophobic region to it and a polar -OH group to it. The polar -OH interacts with the polar head groups and it imparts some rigidity to the rigid steroid nucleus but it allows a disruption in the overall structure and the composition of the layers is going to result in a different curvature and the proteins are going to result in the transport. In our next class we will see how we have this membrane transport and how the specific ions are transported from the inside to the outside and outside to inside of the cell. Thank you!