Organic Chemistry In Biology And Drug Development

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Lecture – 02 NOTE VERSION
Biological Macromolecules and Small Molecules: Importance and Functions

Welcome back to this course on Organic Chemistry in Biology and Drug Design. Last time, we had a very basic understanding of the genesis of this course and then we started with what are the molecules that are essential for a living organism to have. Now, these essential molecules of life are actually proteins, nucleic acids, carbohydrates and lipids.

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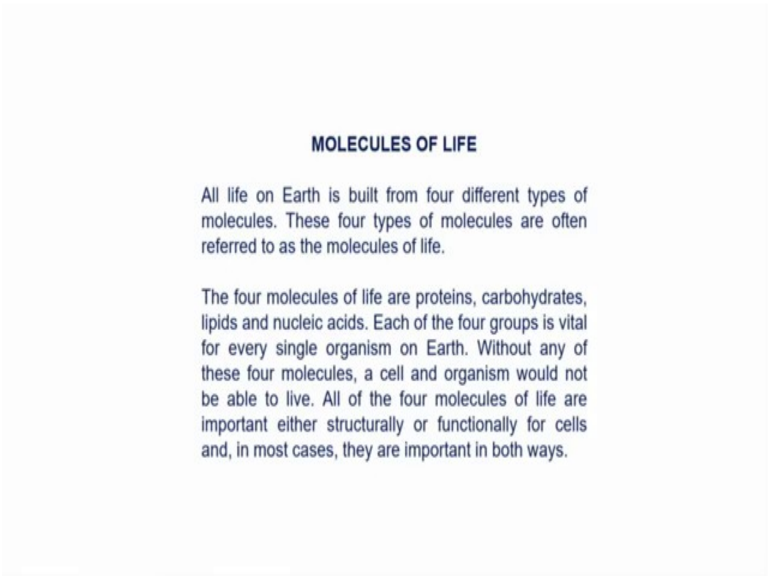

Now, these molecules are also called molecules of life, because without these molecules the living system cannot survive. Now, because most of these molecules are having very large molecular weight, unlike the small organic molecules; so, sometimes they are also called biological macromolecules, like proteins. They have a building block which combine with each other and finally, form the proteins. Same is true for nucleic acids.

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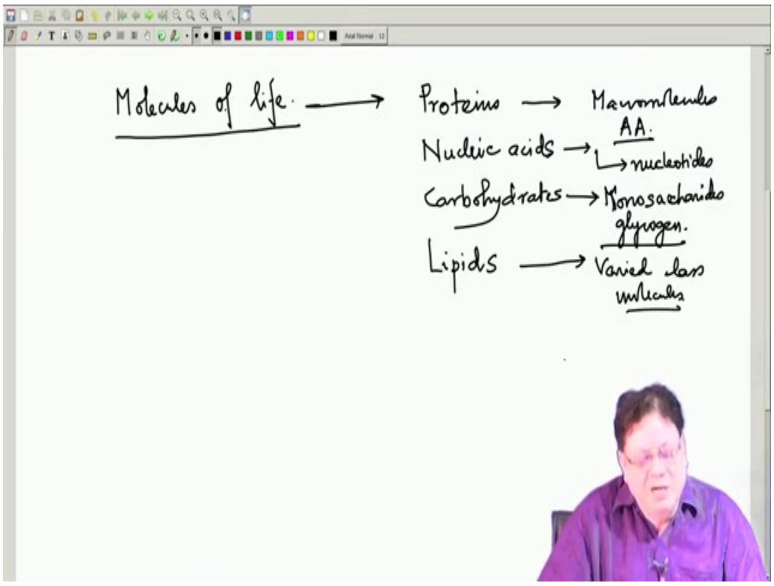

For carbohydrates, again we have building blocks which are called monosaccharides. These are the building blocks. For lipids, there are different types. There could be building blocks to make the lipids and or there could be a single molecule which is biosynthesized from very small starting materials like a derivative of acetic acid which is called acetyl coenzyme A. Lipids are slightly different from the other three categories. The other three categories are all macromolecules.

Protein is a macro molecule where the building blocks (we know) are amino acids. Nucleic acids, they are also macromolecules and their building blocks are nucleotides or deoxynucleotides. We will come back to these nucleic acids elaborately when we describe the DNA and the RNA molecules.

Carbohydrates are also made up of monosaccharides, but interestingly some of these carbohydrates are also present in the form of monosaccharides in the body. Like we measure their glucose level, we know that is a test that whether the person is suffering from diabetes or not. So, we measure the building blocks which are also present and having a biological function.

On the other hand, in carbohydrates, these building blocks are joined together and stored like what is starch in plants. So, these are also stored and this storage material is called glycogen in case of humans. This glycogen is nothing, but again combination of glucose through various glycosidic linkages. Only thing is that it is more branched than the starch. So, when glucose is in short supply, then we can break down this glycogen and get the monosaccharides which can be burnt later on to generate energy.

Lipids on the other hand are really a varied class of molecules. Now, the definition of lipids is basically the molecules which are not water soluble, they are called lipids. They are actually soluble in nonpolar solvents like the organic solvents, ok.

Now, there could be several molecules like that, some of the lipids are actually derivatives of fatty acids and some of the lipids could be steroids and there are many other molecules like terpenes in plants which are also soluble in organic solvents. They are all mostly made up of hydrophobic carbon chains, ok. Lot of carbons are usually there and functionalized carbons are much less in lipids.

I will show some structure of these molecules of life, but before that let me again point out something. That, last time we said that in addition to these large molecules, what we have are some small molecules which are also essential for the survival of living organisms. Like some molecules say coenzymes which are small molecules which assist the enzyme to perform their job, that means, to catalyze the reactions; there are neurotransmitters which performs the signal transduction; there are hormones.

So, these are the other small molecules, some of them could be lipids because they are insoluble (by definition they should be lipids because lipid is something which is insoluble in water). Some of them could be amino acids also; some of the neurotransmitters are amino acids like γ-amino butyric acid.

So, they are a different class that is the small molecule domain of biology and there is this large molecular domain of biology which consists of proteins, nucleic acids, carbohydrates and lipids. In this case lipids which we are talking about are fairly large molecules consisting of big fatty acid chains, ok. Now, let me show you some of these molecules of life, like proteins.

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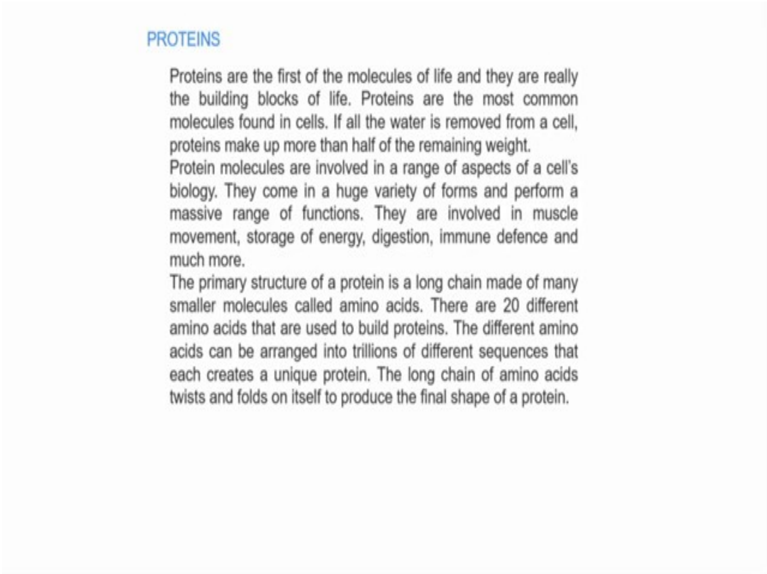

Now, proteins have building blocks as amino acids; Amino acids combine; when they combine, they expel a molecule of water and form a bond which is known as the amide bond in this case called a peptide bond because what you are making is a peptide.

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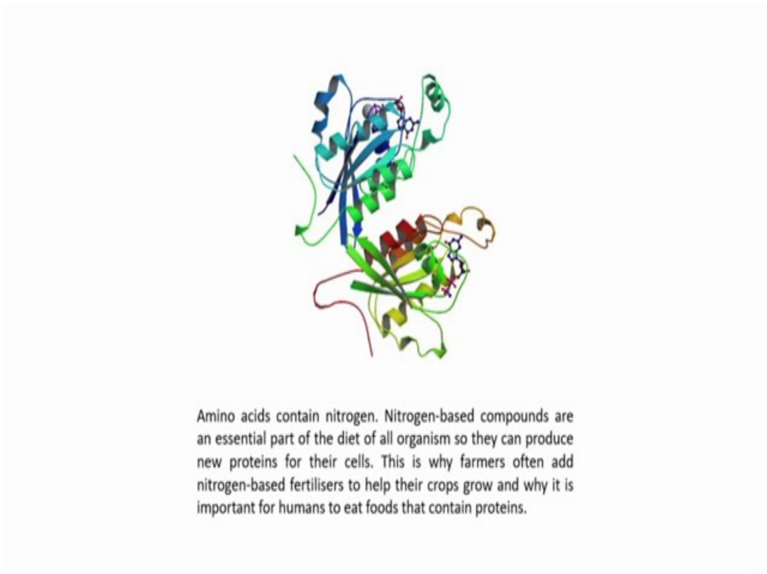

And ultimately how many amino acids will join that depends on the nature of the protein and the direction has to come from the nucleic acids. Because there is a hierarchical structure in biology, that although we have these proteins nucleic acids; that are there, but we have a hierarchical structure which means that the direction to make a particular protein it is given by the nucleic acid. So, from nucleic acids, the information flows up to proteins. This is also called the central dogma of biology.

We will also again come back when we discuss nucleic acids, because nucleic acids are also of two types- the ribonucleic acids the RNA and the deoxyribonucleic acid that is the DNA ok. The central dogma says that it is the deoxyribonucleic acid polymers are the ones which sends the signal via the RNA, which is called the messenger RNA, (they take the message) and then translate the message into the proteins.

And however, there are certain violations of this central dogma. Some viruses only have RNA (ribonucleic acids), they do not have that deoxyribonucleic acid. So, in that case the central dogma is not applicable. But anyway those are very special cases.

Now, let us show these molecules of life, what how do they look like, what is their three dimensional structure. This is a beautiful structure of a protein which has been crystallized and its crystal structure is what is shown here,.

So, you see there are lot of folding that has taken place because in this system, if you take the two terminals; and then stretch them, the length of the protein will be very long and it will be very difficult to have this protein ultimately fit into the small cell that we have. Because ultimately if you break down the biological system, according to the hierarchical order, at first it is the organs, then tissues and then from tissues it goes to the cells, then the internal structure of the cell.

So, cell has a definite dimension. So, the proteins cannot just have a linear straight chain. However, that is not the only reason why proteins will fold. It folds also in such a way that it generates certain pockets which are important to do whatever the function they are supposed to carry out. So, this is a crystal structure of a particular protein.

We see that this is composed of some helix. You see that the green one and the red ones. And then it has got certain portions which are called sheet structure and certain random loop structure, ok, some like this loop what we are seeing here. Now, that is the protein.

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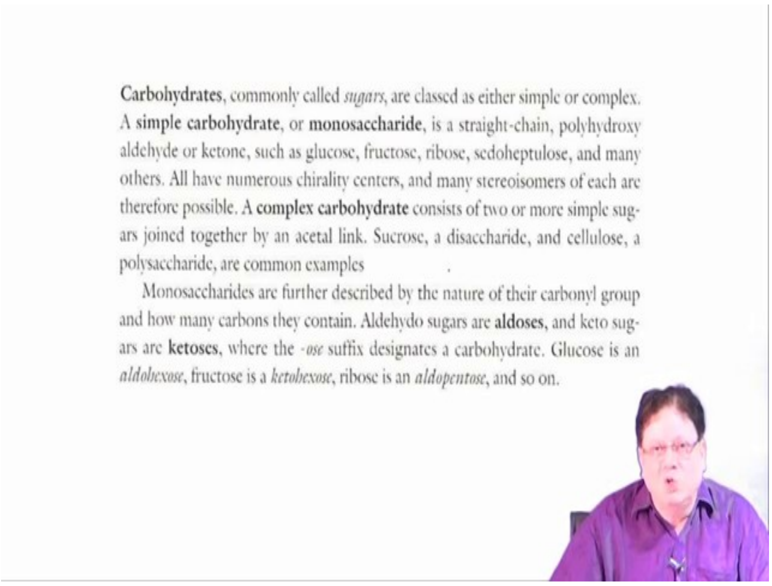

Now, next let us show some carbohydrates. Now, carbohydrates as I said are pretty interesting because we use the monomers; that means, the monosaccharides as well as we store that into the glycogen at the time of need, ok.

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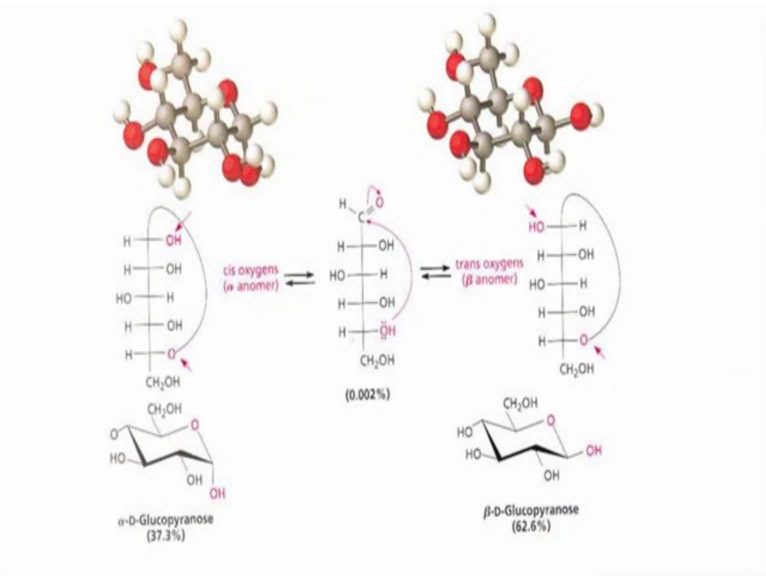

It all starts with the glucose molecule. Glucose molecule is shown here; this is the simple monosaccharide that we have. And glucose we know that it can be present in the α- form and the β- form; there are two forms of glucose which is shown here and we also know that if you take glucose and subject it to an amphoteric pH, then what happens? There will be a mutarotation. Amphoteric pH means both acid and base are present, then in that system, if you take α-glucose that isomerizes to β-glucose and vice versa, finally, an equilibrium takes place and this process is called mutarotation.

However, the point here is just to show some of the carbohydrates that we require in a biological system. Now, remember this is the monomer of the polymeric carbohydrate that we are talking about.

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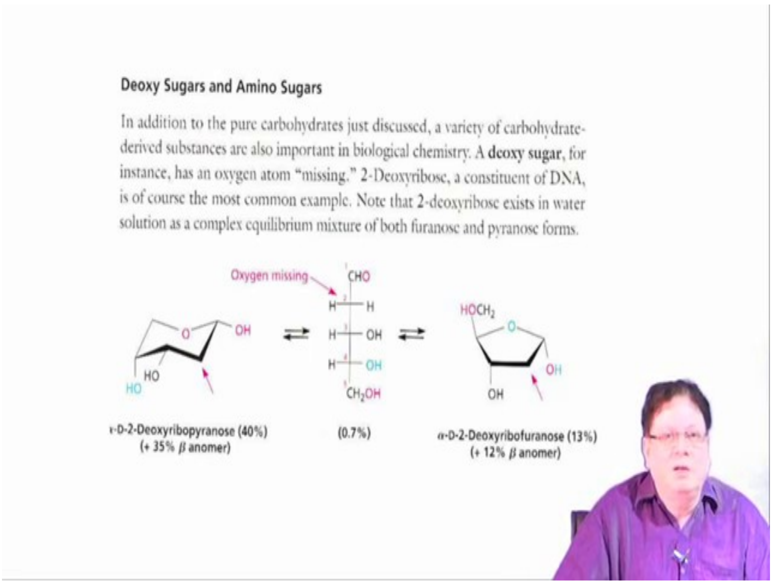

Now, usually sugars are polyhydroxy aldehydes or ketones. But sometimes in these biological systems, what we find that some of the carbon lacks the hydroxy unit then we call that as deoxy sugar. And this is a very vital step that is happening in biology because we know that ribonucleic acid has a sugar unit which is ribose and this ribose in RNA has all the hydroxy groups (what they are supposed to have). And in the deoxyribonucleic acid you lack the 2'- hydroxy, ok.

If you know the numbering (you must be knowing), we can again go back that the 2' is next to the anomeric carbon and that is missing in the DNA. Sice DNA is the fundamental molecule in our hierarchical biological system, so it must be a very important step. And there are 5 membered rings also. Apart from glucose we have ribose, ribose is the C5, 5 carbon containing molecule and the structure of ribose is shown here. It has got a furanose structure. By the way if you have a 6 membered ring that is called a pyranose structure and if you have a 5 membered ring that is called a furanose structure ok.

The ribose is present usually in the furanose structure. And here on the right-hand side it is shown in a furanose structure and it is also a deoxy. Precisely this is called α-D-2-deoxy ribofuranose. And the arrow points out where the deoxygenation that has taken place and why it is α? Because anomeric OH (which is adjacent to the ring oxygen) that is the anomeric carbon and the OH is alpha; that means, below the plane of the ring, the way it has been presented.

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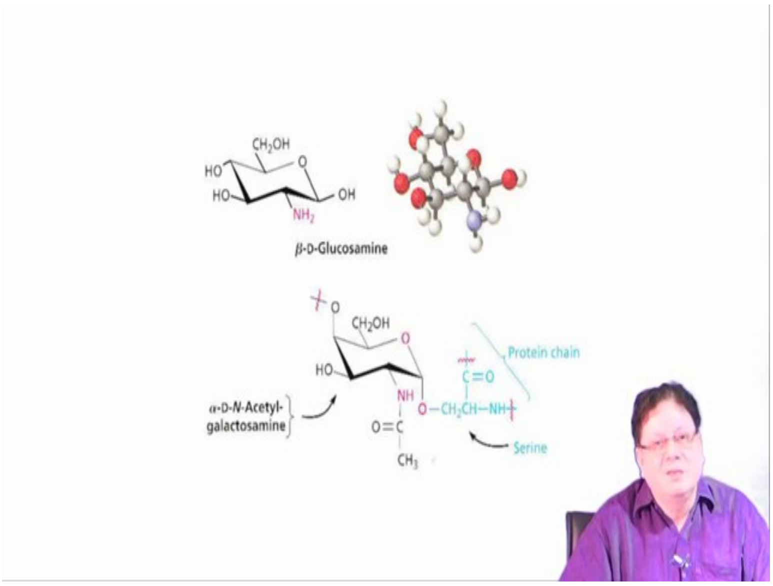

There are other forms of carbohydrates where the hydroxy group may be replaced by an NH_2 group. Like in this molecule, what we are seeing is that it is close to glucose molecule, but only one difference and that is the 2' carbon (of course, in glucose there is no prime). We are talking about this prime number in relation to a nucleic acid because in nucleic acid you have a base, you have a sugar and you have the phosphate.

And the nucleobase takes the numbering 1, 2, 3, 4; then the sugar gets the numbering 1', 2', 3'. But here it is only glucose, so we cannot technically say that this is a 2' position, we have to say 1, 2, 3, 4 because this is only the carbohydrate portion and not the nucleic acid.

So, this is basically 2-amino glucose, you can say; but it has got a name, it is called glucosamine. And this is β, you can see it is β; β because the anomeric OH is in the β orientation (above the average plane of the ring). And also, in the β form, this is in the equatorial position and the NH_2 is in the two position, that is α.

This is a very important molecule; we will see later on, the function of this glucosamine. This is a part of the unit which forms the cell wall of the bacteria. The cell wall which contains the bacterial material inside, the glucosamine is a constituent of that and which is a little bit shown here that the glucosamine ultimately goes to the acetyl form, the nitrogen is now acetylated as you see and then there is some serine, then there is a protein chain. So, this participates in the formation of the cell wall biosynthesis. But we will come back to that when we talk about the antibiotics and their action on bacterial cells.

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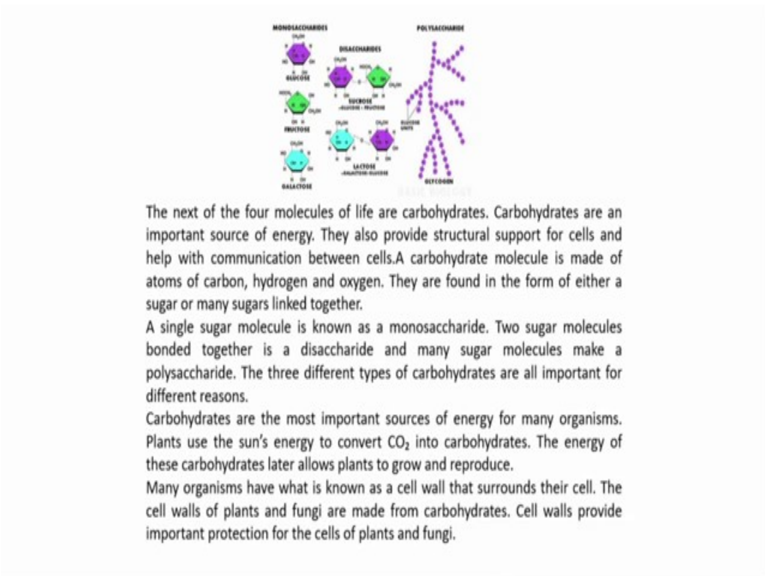

This is what I was talking about this glycogen. This dotted structure on the right, that is what is shown here as dotted structure (the branch structures) is glycogen, where each dot is representing a glucose unit, ok. As I said this is just a counterpart of starch which is present in the plants.

So, what is the function of carbohydrates? There are many functions, one is that the carbohydrates are the most important source of energy for many organisms like we also need carbohydrates, every day we eat starch to get the energy. Plants, however, use the sun's energy to convert carbon dioxide into carbohydrates, there is a difference. So, plants actually make the carbohydrates for us and then we eat the plants and get the starch from it.

The carbohydrates are also present in the cell wall which also has a very important role. So, carbohydrates have many important roles in our life or in the living system. They are the storage of energy, and it is a precursor of many biomolecules and then even it is a precursor of many fatty acids that we synthesize like palmitic acid, stearic acid those things and it is a component of the cell wall and it also gives the energy to the plants.

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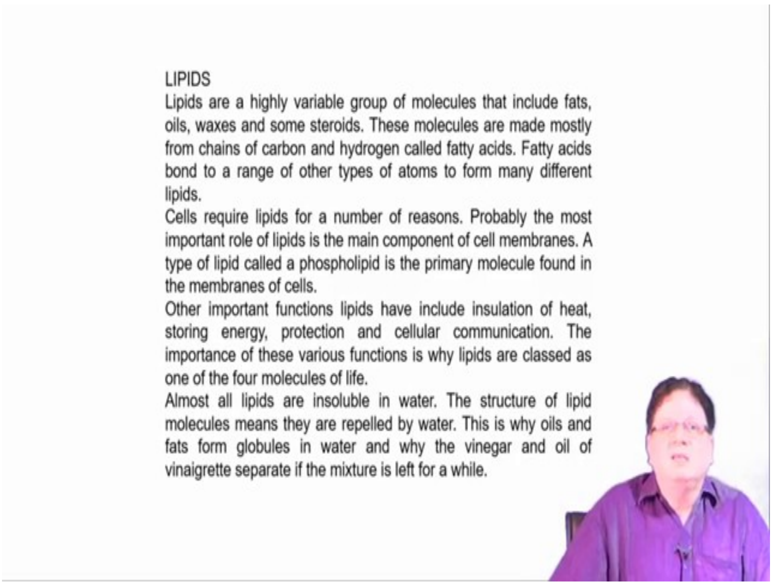

Now, let us go to the lipids. As I said lipids are the most variable group of molecules because the definition of lipid is not based on the structure, that is why we have a varied class. Lipids definition is something which is soluble in organic solvents and which is insoluble in water. So, there could be several different types of molecules, that is why we have different varieties of lipids. It could be fatty acids, it could be a steroid, it could be a terpene and I will show you some molecules which are lipids; the molecules are shown here, like this is.

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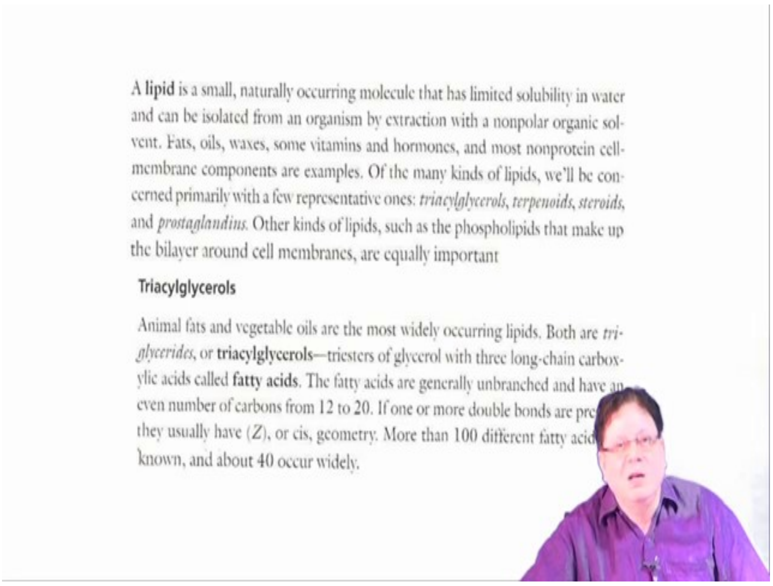

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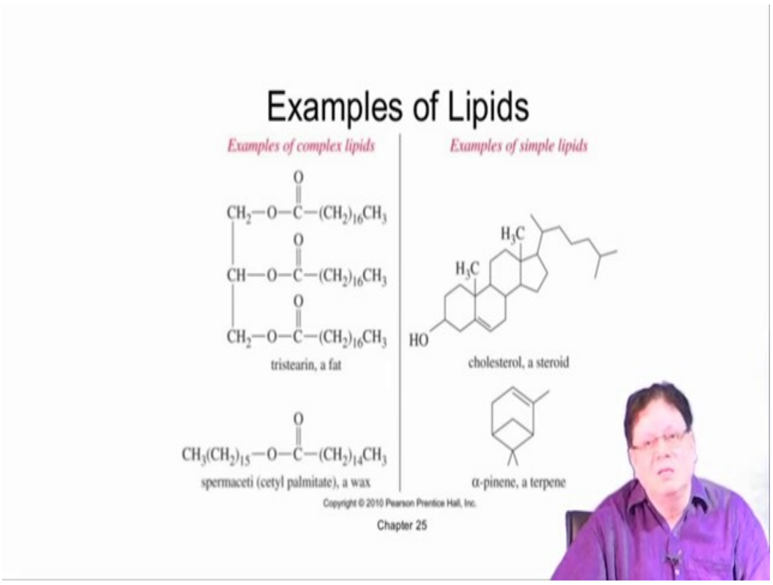

The first one is shown on the left that is called a tristearin. Actually, that is known as triglyceride in general, triglyceride is basically the triester of glycerol and the acid part is a fatty acid. So, in this case it is stearic acid because the acid comes from stearic acids. So, this is called tristearin. It is a fat, it is soluble in organic solvent. Then you have on the right-side, the cholesterol. Cholesterol is a steroid, and that is also a lipid because you see there is no functionality (in true sense) only there is a double bond and others are all carbons. So, in that way it is a very non-polar molecule (cholesterol).

Then you have other different types of esters like this (Refer Time: 21:05) cetyl palmitate, a wax kind of thing and then you have a terpene which is α pinene and it is shown on the right-side at the bottom left ok. So, these are some of the examples of lipids.

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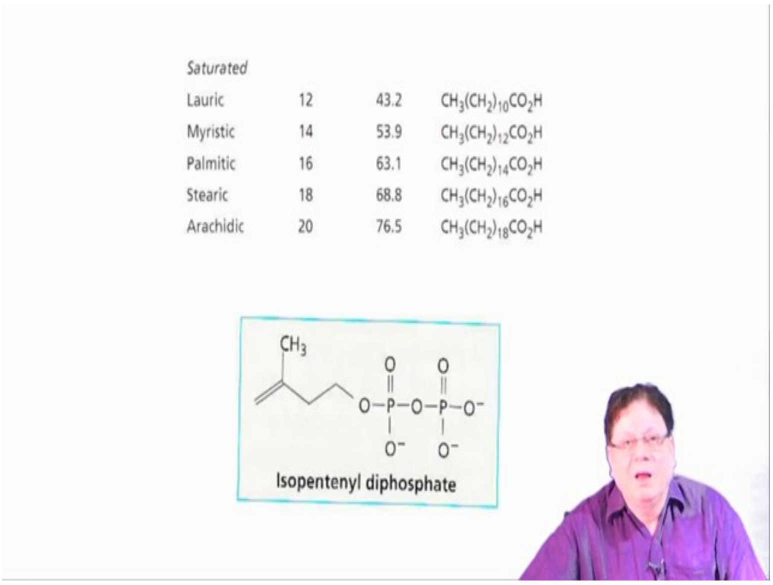

Different types of saturated and unsaturated fatty acids are present, and they can be biosynthesized. Usually the ones that dominate in the biological world are the lauric acid, that starts with C12; that means, 12 carbon atoms are present there, then myristic acid, palmitic acid, stearic acid and the C20 fatty acid which is called arachidonic acids or actually arachidic acid (that is the actual name), and the derivative that comes from this is called arachidonic acid.

On the bottom, there is a block which is a 5-carbon unit we can see, there are 5 carbons with a diphosphate. And this is called isopentenyl diphosphate. This this is one of the precursor, through which we make the steroids, we make the terpenes. And this also has a very interesting biochemical way of making, ok. Remember what I said when the synthesis takes place in biology, that is what is called biosynthesis.

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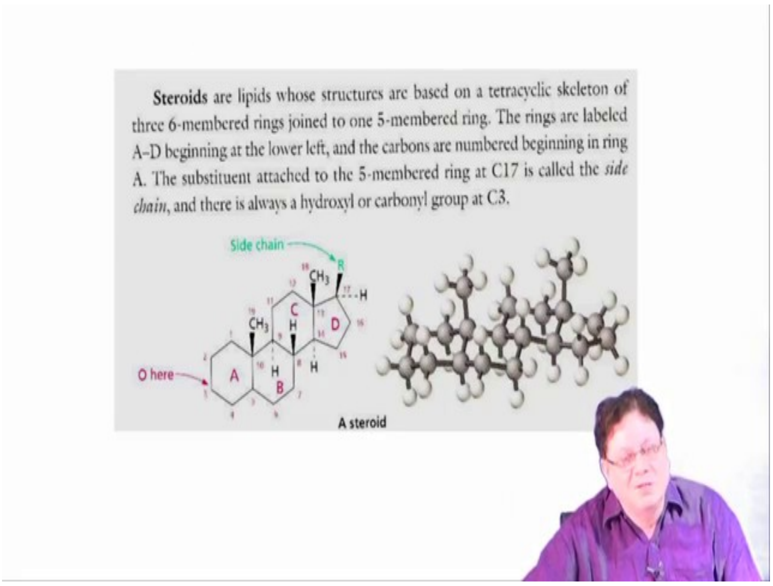

And when it takes place in the laboratory, we call it synthesis; organic synthesis is just plain synthesis that we call. And in biology whatever molecules we synthesize, that is called an anabolic process. Anabolic process means we make molecules and the reverse is also there, that is called catabolic process or catabolism where we break down molecules into smaller fragments. Both processes are essential in our body.

This is a steroid structure shown here and you see. What are steroids? By definition, the steroids are basically having these three 6-membered rings A B C and that is fused with a 5-membered ring which is shown as D. First of all this is a derivative of phenanthrene, but this is phenanthrene without any double bond. So, this is called perhydro phenanthrene. When you have angular fusion between three 6-membered rings, that is called phenanthrene. If it is linear, that is called anthracene. So, steroid is actually called cyclopentane perhydro phenanthrene, that is what is a steroid, ok.

And as I showed in the previous slide, that it was the isopentenyl pyrophosphate or diphosphate that acts as the precursor of a steroid ok. Through molecular modeling, there is a structure shown here, a model of this steroid and it seems that we have so many atoms crowding together, and in this molecule, there is no functionalized carbon.

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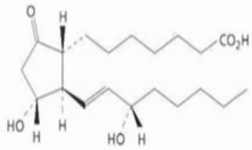
Prostaglandins and related compounds are a group of C_{20} carboxylic acids derived biologically from arachidonic acid (5,8,11,14-eicosatetraenoic acid) through a pathway we'll explore in **later sections** . The several dozen known prostaglandins have an extraordinary range of physiological effects, including an ability to lower blood pressure, affect blood clotting and kidney function, control inflammation, and stimulate uterine contractions during childbirth. Closely related compounds are involved in producing the asthmatic response.



Prostaglandin E_1

This is also another steroid molecule. This is called prostaglandins. I told you that there is a C20 carboxylic acid which if fully saturated then called arachidic acid, but if there are double bonds present in that, it is called arachidonic acid and from this C 20 arachidonic acid prostaglandins are biosynthesized in the body.

When they are biosynthesized, if you count the carbons it will be 20 carbon atoms including the carboxylic acid and you have different varieties of prostaglandins. But the definition is that it will have a 5-membered ring as is shown on the left side and along with two side chains, one side chain you have the carboxy terminus this is called prostaglandin E 1.

And depending on the different geometrics and the position of the double bond you have different prostaglandins. They are extremely important, they have extraordinary range of physiological effects including an ability to lower the blood pressure. So, they have a role in blood pressure, affect blood clotting, they also regulate the kidney function, they control inflammation. So, when we have inflammation, we have pain, then the medicines we take (they are mostly like aspirin) stop the biosynthesis of the prostaglandin. They also stimulate uterine contractions during childbirth. So, prostaglandin is also administered for that.

In 1970s, when prostaglandins were discovered, it was thought that prostaglandins will solve many of the diseases that we have. Yes, it has solved many of these problems.

They are anti-inflammatory agents, they are agents which help childbirth, they are agents which help in lowering of blood pressure. So, definitely they are extremely important but they cannot solve all the problems which was at that time over-hyped in 70s.

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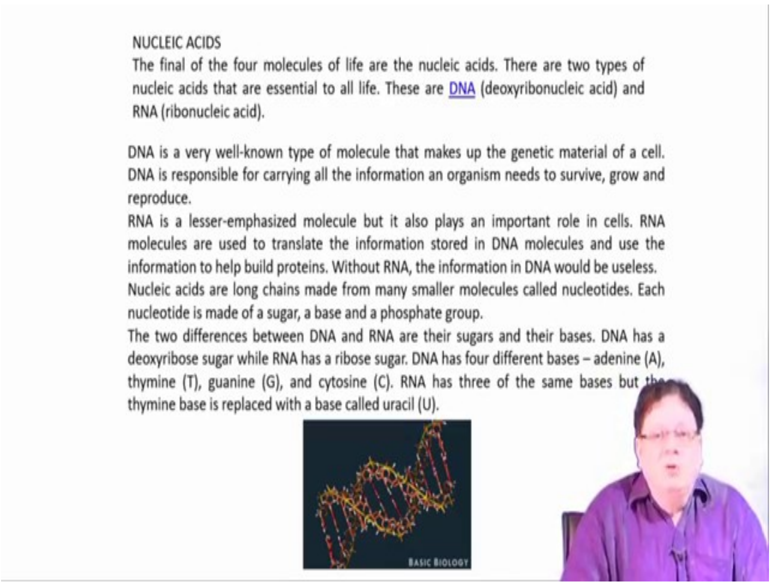

After this we come to the nucleic acids. Now, this is I tell you that these are very general topics, we are saying about these molecules of life. Nucleic acids are are basically polymers of nucleotides. Now, nucleotides are what? Nucleotides are basically having a phosphate, having a sugar and having a base. And they are linked one after another and that makes a strand of nucleic acids.

And there are different types of nucleic acids, broadly there are two types, deoxyribonucleic acid and then the ribonucleic acid. And if I say what is the genetic material of the normal eukaryotic cells like the higher organisms? Then DNA has to be the answer. There is no eukaryotic organism where DNA is not the genetic material. DNA is the genetic material in all eukaryotic cells.

This eukaryotic cells means the a higher level of organism because the organism it starts with unicellular systems and where there was basically only a cell, only a membrane and all cells are basically same in that case. Then the higher organisms started growing. So, we have a distinct class, prokaryotes and eukaryotes. Prokaryotes like the bacteria, They do not have actually compartmentalized cell cytosol; cytosol means what is present in the cell, but in eukaryotes we have compartmentalized systems. And there is a nucleus in a cell and in the nucleus this deoxyribonucleic acid is present.

Again, I repeat this is made up of the base, sugar, phosphate that is the building block called the nucleotide or deoxynucleotides (to be precise) if it is DNA. And the bases are of 4 different types, and in the RNA also there are 4 different bases, only there is a difference between DNA and RNA, that RNA has a base which is called uracil in DNA that uracil is replaced by what is called thymine. But this is just a very general slide that I am showing and in the bottom, the very famous three-dimensional structure which was proposed by Watson and Crick is shown and that is called the double helical structure of a DNA, ok.

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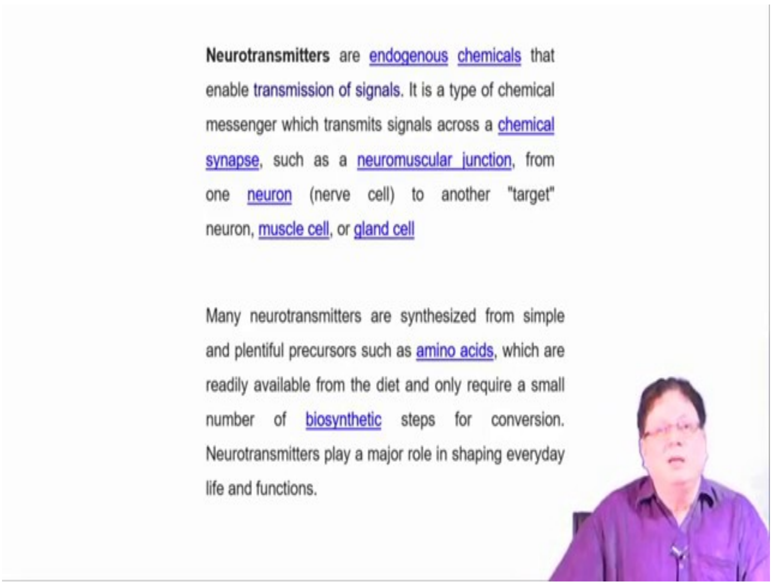

Then comes the other small molecules that we have talked about because the biological domain comprises of basically two parts, one is the large molecules another is the small molecules. The small molecules are also equally important. Equally important means like neurotransmitters, which gives the signals that what to do, when to do and when to stop. All these things are controlled by small molecules or sometimes large molecule-large molecule interactions are also possible, but the whole process is called signal transduction. This signal transduction is controlled by the central nervous system where we generate the neurotransmitters which are basically very small molecules, even amino acids are also neurotransmitters. I will show you some of the structure of neurotransmitters.

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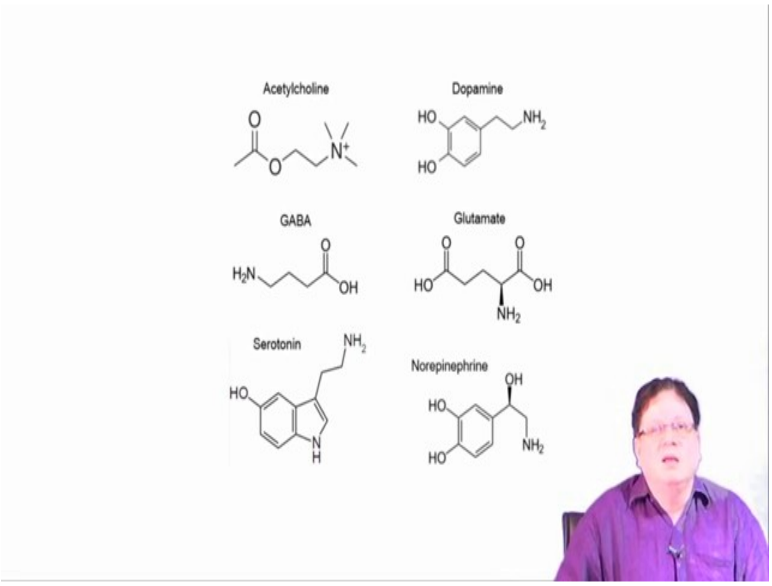

So, you see acetylcholine, has a so simple structure and its a very small molecule, but extremely essential. If we have acetylcholine which is not secreted properly and its level is not maintained properly, then we suffer from many diseases. In fact, there are drugs, which controls or lowers the acetylcholine to such a level that the organism dies, ok. Then we have dopamine that is also a very simple molecule. So, these are very simple, the simplest of the molecules that are again essential for the functioning of the biological system.

Remember, the biological system is made of macromolecules which are called molecules of life, 4 classes I have shown. But then once you have the structure, you know that it is like a house, that you build the house, but then the house has to be operational, you need electricity, you need water, you need so many things. And these small molecules are basically functioning like electricity, light, because without them, for the whole house and the persons who are living in the house, life will be miserable.

So, these cells are like that house. If we cannot maintain, if we cannot have these molecules in our body then our life will also become miserable. And at some point of time, there may be serious complications where people die out, they lose their memory, all these things can happen.

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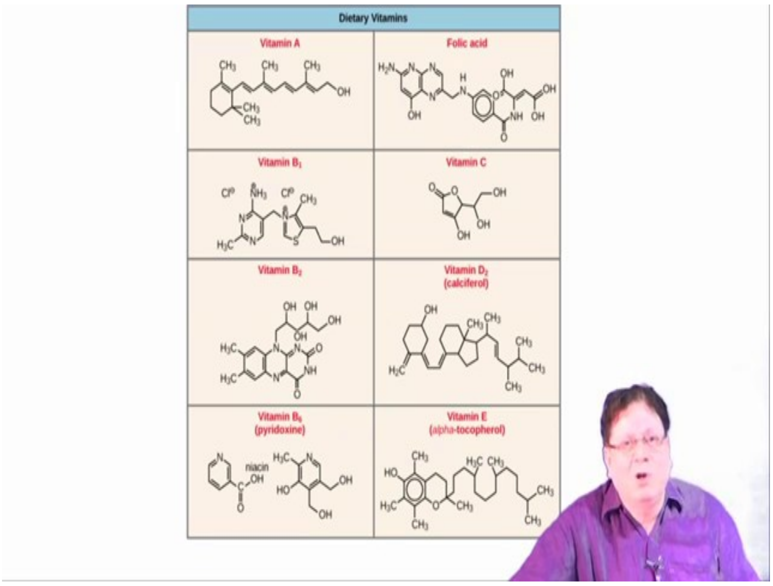

So, there are other different types of small molecules like these vitamins, we talk about vitamins; these are also extremely essential for making molecules, for catalyzing reactions, they help many enzymes to carry out the reactions that they are supposed to do.

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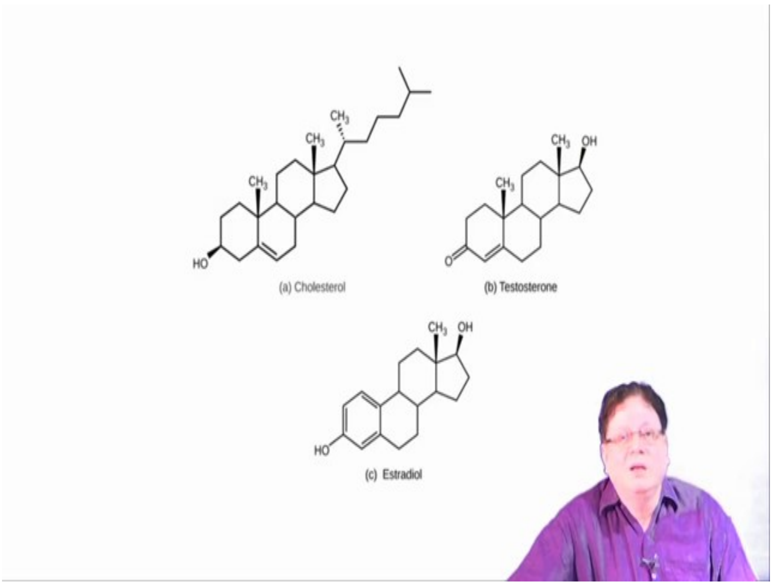

So, I think that basically; these are some of the molecules which are medium sized, means we have a small molecule we have large molecules.

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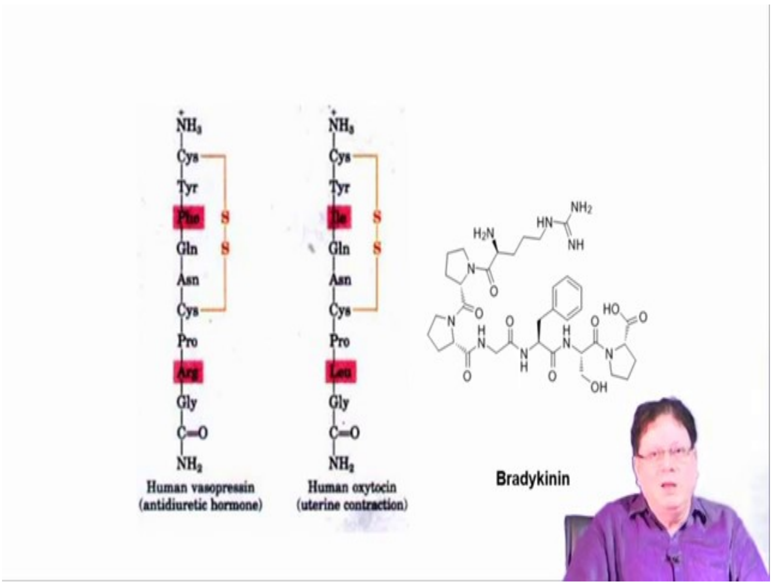

In between large and small sized molecules, on the interface, some molecules are there, which based on their molecular weight, you cannot classify them as macromolecules or classify them as very small molecules, ok. So, they are medium sized molecules. And I have shown 3 important molecules here, mostly they are made up of amino acids. Just I want to point out the one which is on the right side that is called bradykinin. This is a hormone which again controls the blood pressure. It is a vasodilator; that means, it dilates the blood vessel so that the blood flow can become smooth and that causes the blood pressure to drop.

So, now we have gone through all these different molecules that are involved in the biological world. This is a very miniscule number of molecules I have shown to you, there are thousands and thousands of molecules that are present in the biological system. But this is just now the introduction to the molecules whose chemistry we are going to describe in the subsequent lectures.

Thank you.